

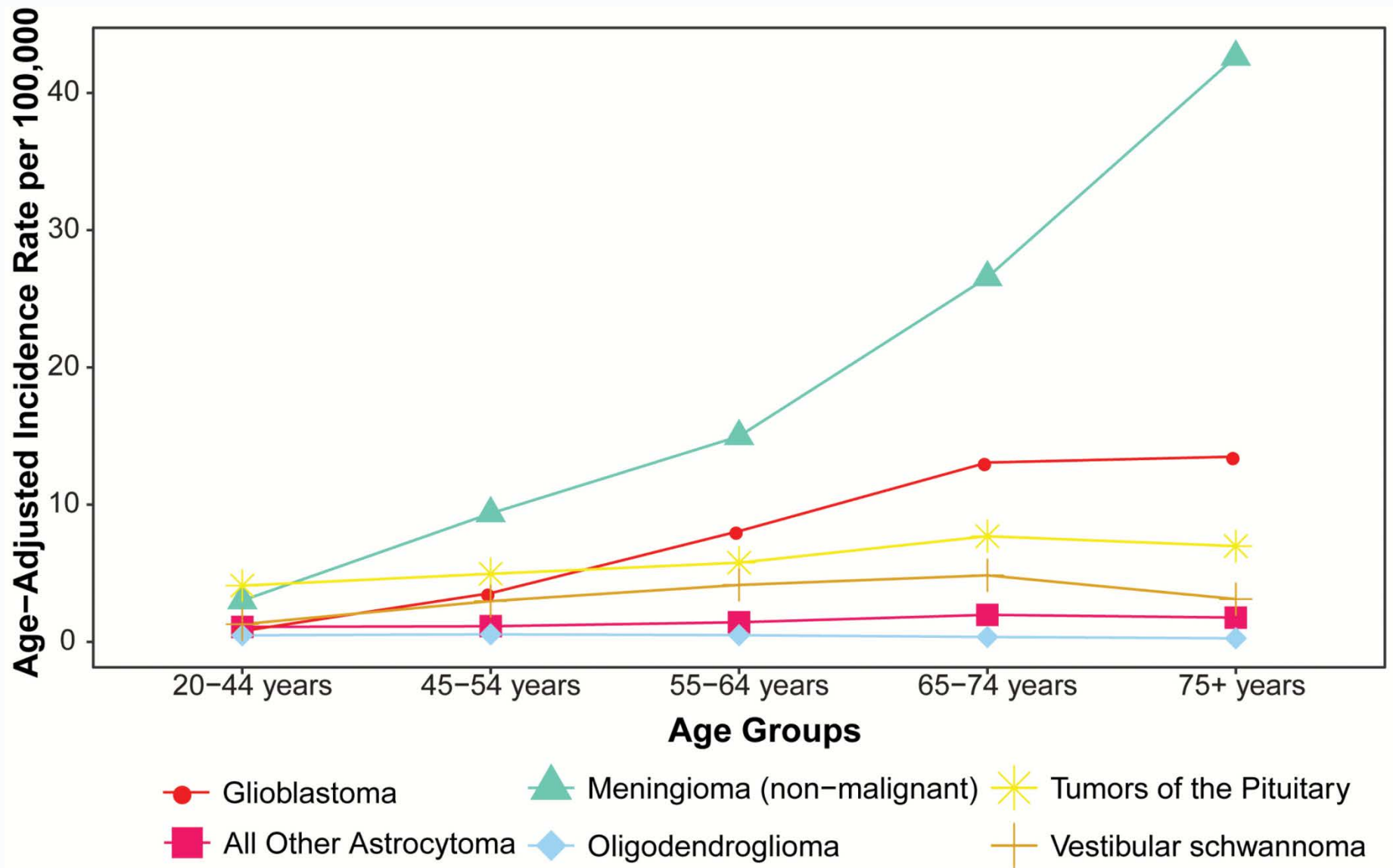
Brain and Spine Tumors Overview

Nicholas G. Avgeropoulos, M.D.

Director, Neuro-Oncology

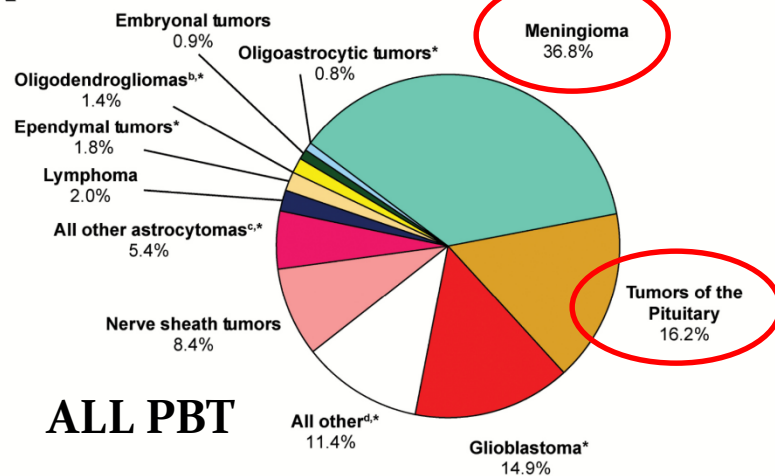
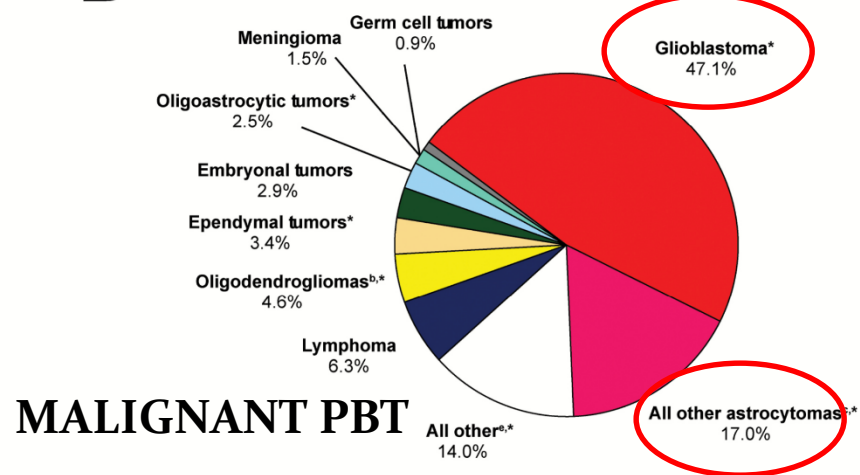
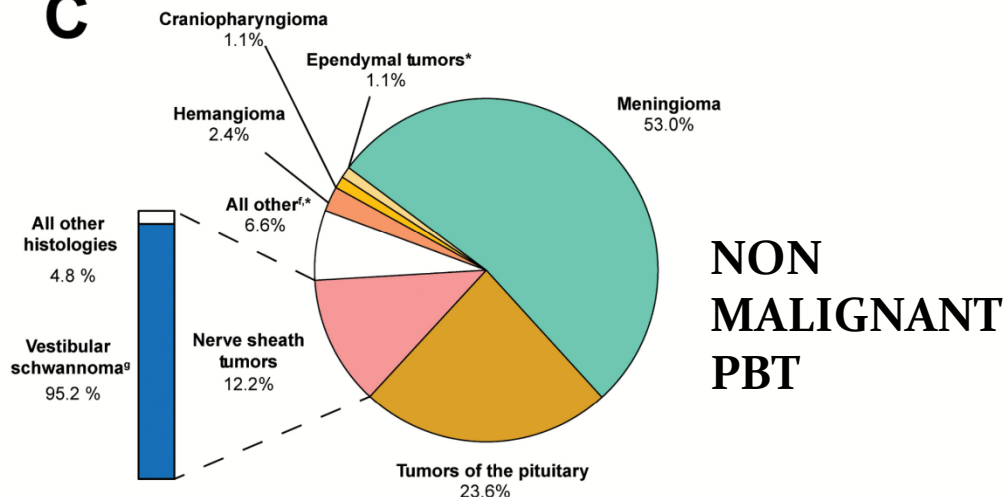
Co-Director, Brain and Spine Tumor Program
Orlando Health / UF Health Cancer Center

19 May 2018



† All or some of this histology are included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460 (Table 2a).

a. Rates per 100,000 and age-adjusted to the 2000 United States standard population. b. ICD-O-3 Histology Codes: 9381, 9384, 9424, 9400, 9401, 9410, 9411, 9420. c. ICD-O-3 Histology Codes: 945, 9451, 9460. d. ICD-O-3 Code: 9560. e. ICD-O-3 Histology Codes: 9530/0, 9530/1, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/1, 9539/1.

A**B****C**

* All or some of this histology is included in the CBRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460 (Table 2).

a. Percentages may not add up to 100% due to rounding;

b. Includes oligodendroglioma and anaplastic oligodendroglioma (Table 2);

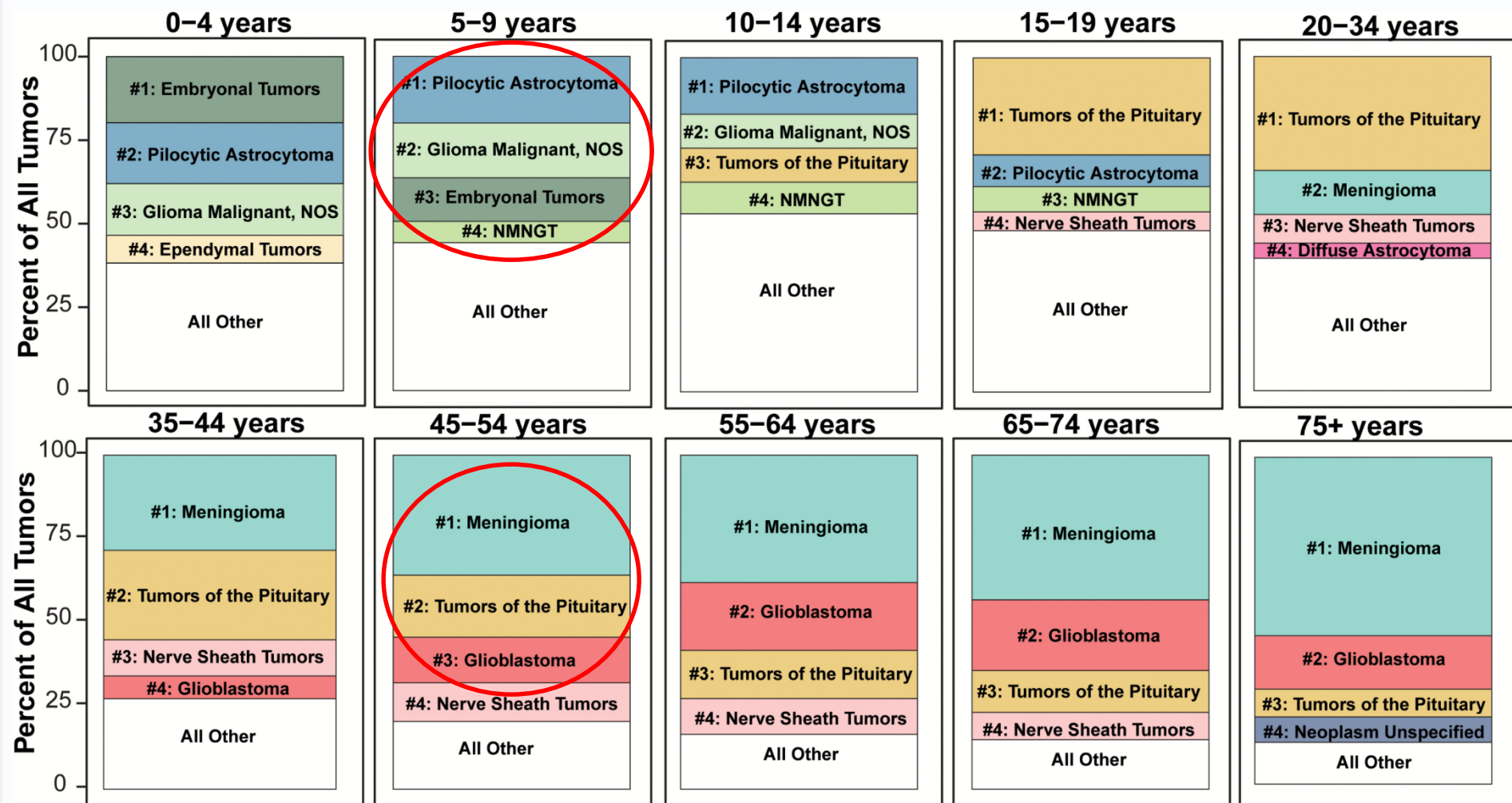
Include: s pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, and unique astrocytoma variants (Table 2);

d. Includes glioma malignant, NOS, choroid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, tumors of the pineal region, other tumors of cranial and spinal nerves, mesenchymal tumors, primary melanocytic lesions, other neoplasms related to the meninges, other hematopoietic neoplasms, hemangioma, neoplasm, unspecified, and all other (Table 2).

e. Includes glioma malignant, NOS, choroid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, tumors of the pineal region, nerve sheath tumors, other tumors of cranial and spinal nerves, mesenchymal tumors, primary melanocytic lesions, other neoplasms related to the meninges, other hematopoietic neoplasms, hemangioma, neoplasm, unspecified, and all other (Table 2);

f. Includes unique astrocytoma variants, choroid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, tumors of the pineal region, embryonal tumors, other tumors of cranial and spinal nerves, mesenchymal tumors, primary melanocytic lesions, other neoplasms related to the meninges, other hematopoietic neoplasms, germ cell tumors, neoplasm, unspecified, and all other (Table 2);

g. ICD-O-3 histology code 9560.



Abbreviations: NMNGT: Neuronal and mixed neuronal glial tumors

Survival Declines with Age

Age	5-Year Survival
0-19	72%
20-44	56%
45-54	31%
55-64	17%
65-74	11%
75+	6%

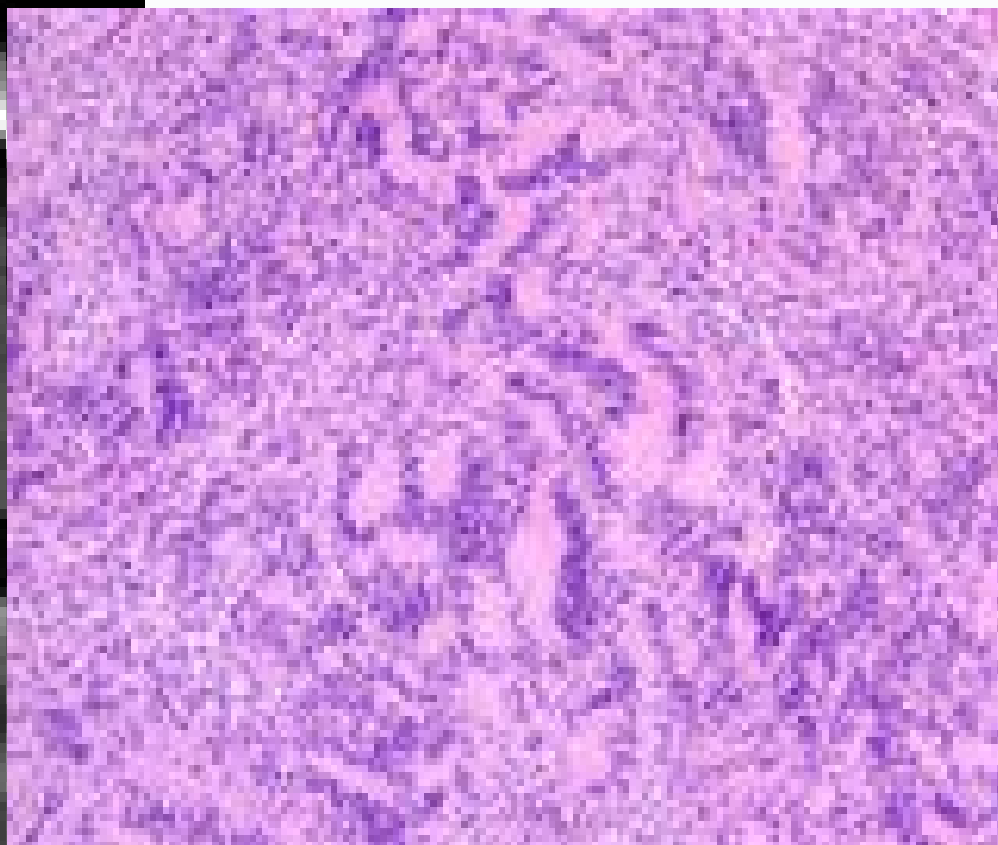
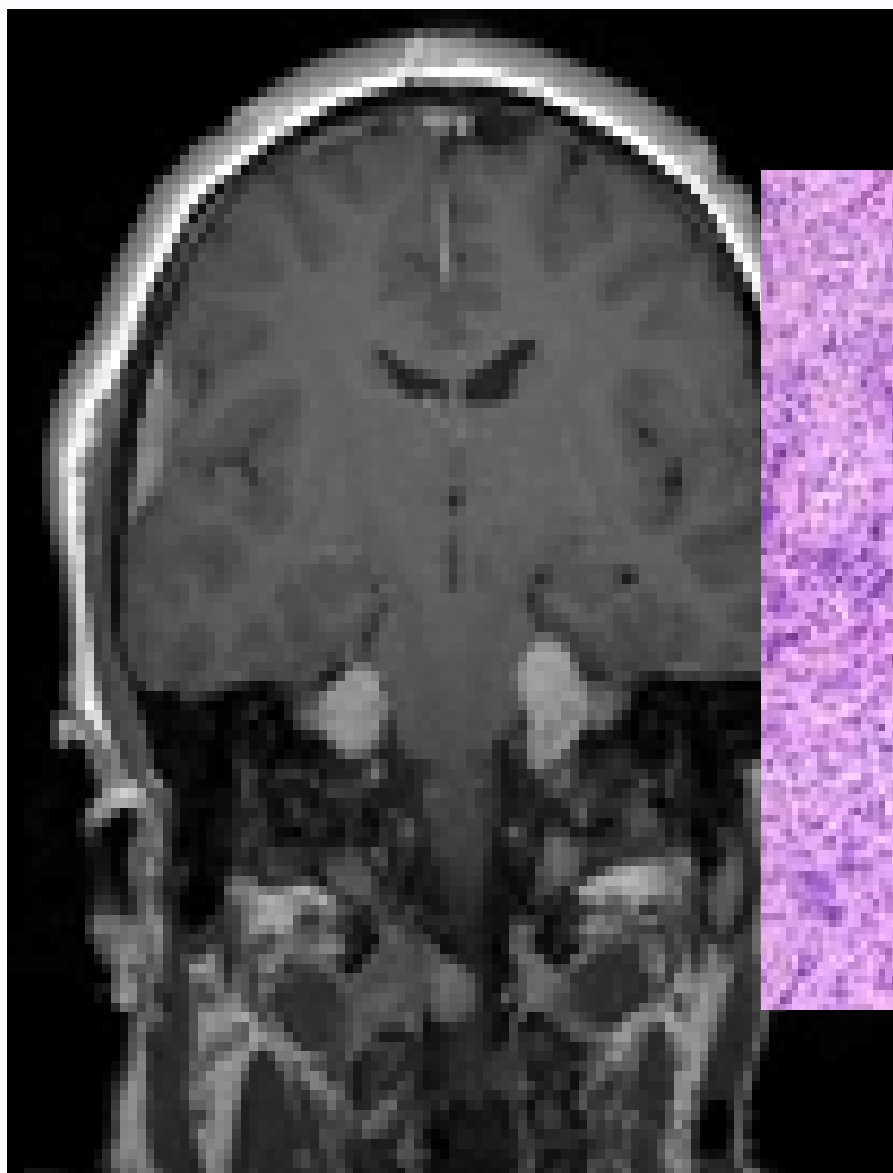
CBTRUS (2010). Statistical Report: Primary Brain Tumors in the U.S., 2004-2006.

Incidence of Primary Brain Tumors (PBT)

- ***Gliomas***, a broad term which includes all tumors arising from the supportive tissue of the brain, represent 26.5% of all primary brain tumors and 80.7% of all malignant tumors.
- ***Glioblastoma*** (astrocytoma grade 4) represents over half of all gliomas. Glioblastoma has the highest number of cases of all malignant tumors, with an estimated **12,760 new cases predicted in 2018**.
- ***Meningioma*** represents 36.3% of all primary brain tumors, making them **the most common primary brain tumor**. There will be an estimated **29,320 new cases in 2018**.
- ***Pituitary tumors*** represent nearly 16.2% of all primary brain tumors and rarely become malignant. There will be an estimated 13,210 new cases of pituitary tumors in 2018.

Genetic Syndromes

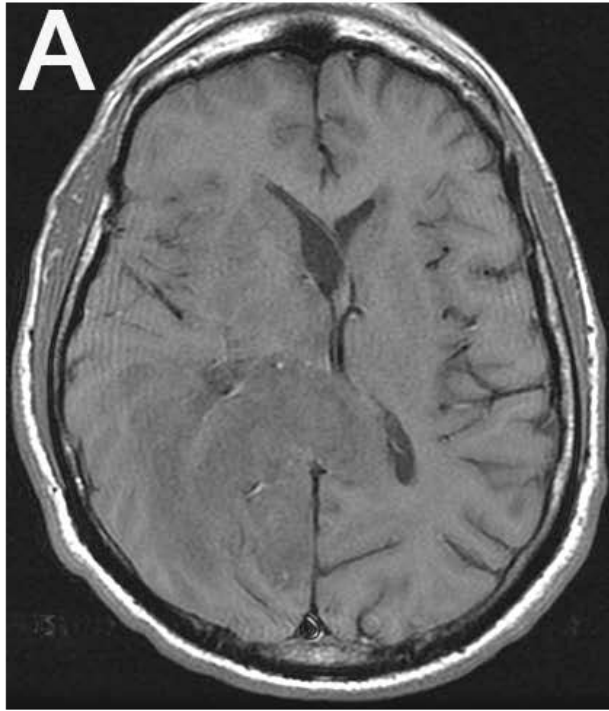
Syndrome	Gene/Protein	Classic Brain Tumors
NF1	<i>NF1</i> /Neurofibromin	Optic nerve gliomas
NF2	<i>NF2</i> /Merlin	BVS, meningiomas
vHL	<i>VHL</i>	Hemangioblastomas
Li-Fraumeni	<i>TP53</i>	Gliomas
Turcot's	<i>APC</i> , others	Medulloblastomas
Basal cell nevus (Gorlin's)	<i>PTCH</i>	Medulloblastomas



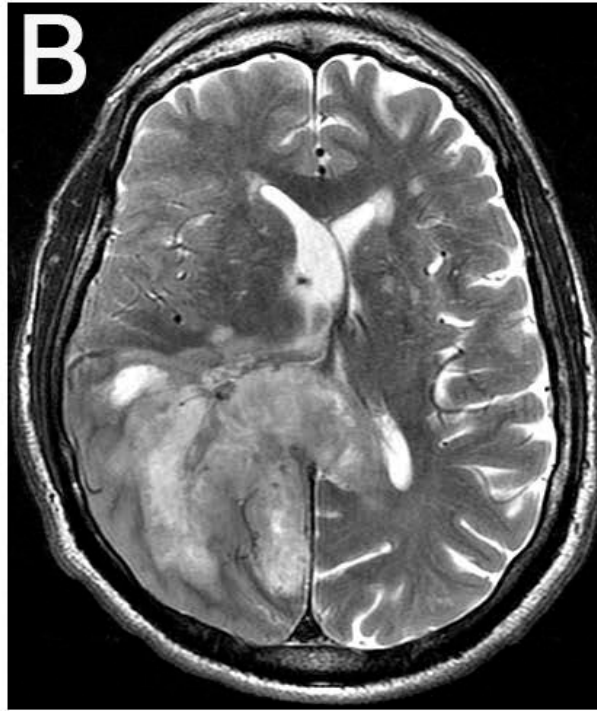
Clinical Presentation

- Symptomatology is protean
 - Headache is the presenting symptom in approx 1/3 patients with brain tumors and about 2/3 will experience headache through their clinical course
 - Cognitive disturbances are the initial symptom of brain tumor in 1/3 of patients with glioma and occur eventually in 1/2 of these patients
 - Quite common are weakness and AMS
 - 8% of patients with a brain tumor have papilledema
 - Seizure may confer better prognosis (ascertainment bias)

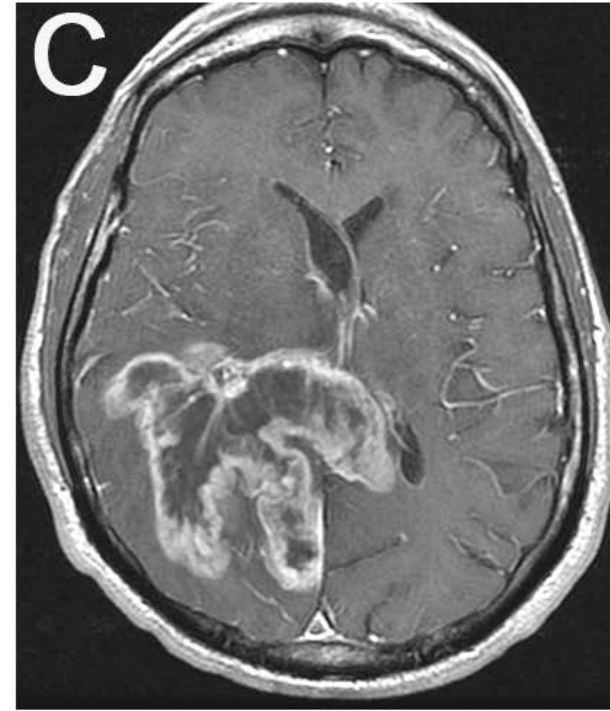
MRI: Diagnostic Relevance



T₁
pre-gadolinium

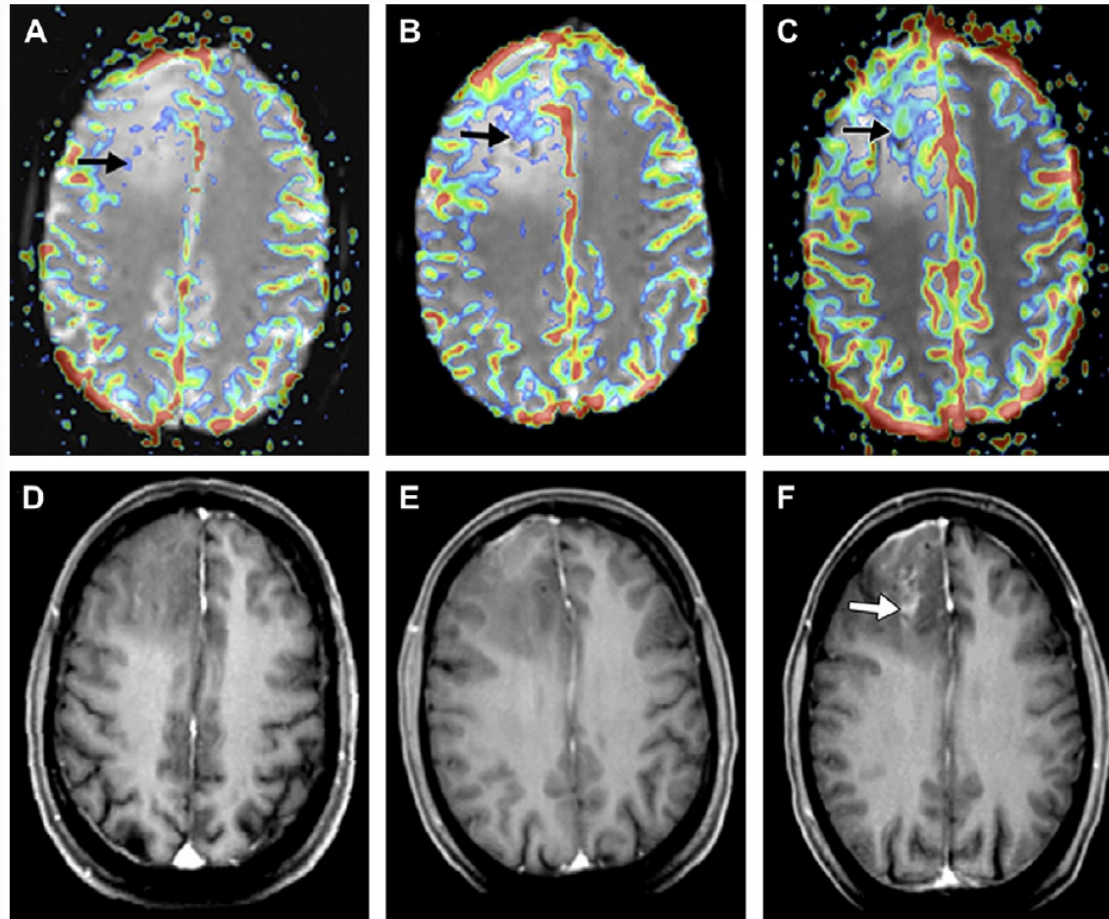


T₂



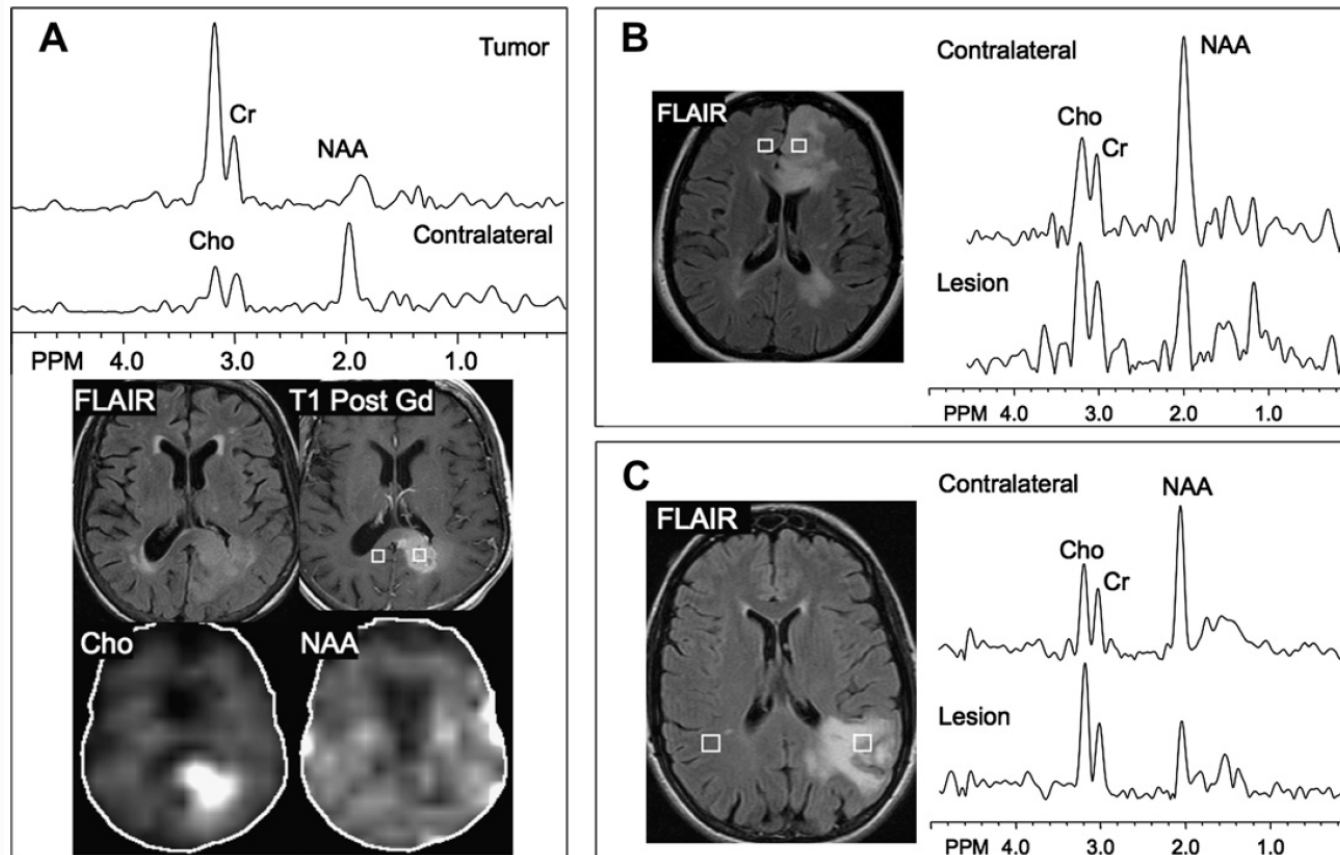
T₁
post-gadolinium

MR Perfusion



Thompson G, et al. Neuroimag Clin N Am 20 (2010) 337-353.

MR Spectroscopy



fMRI and DTI

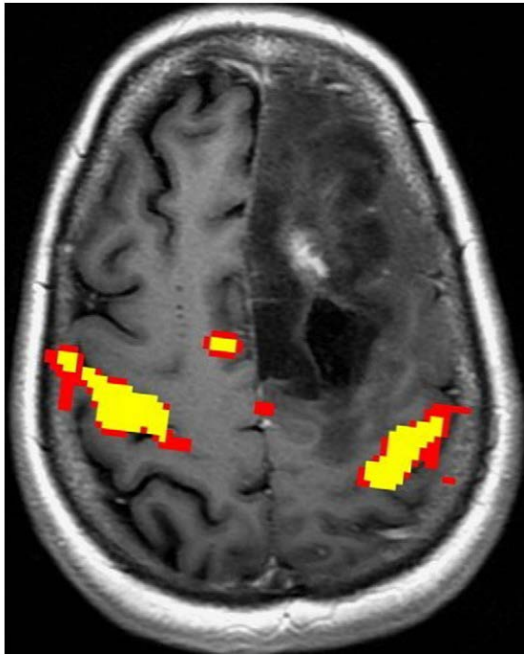
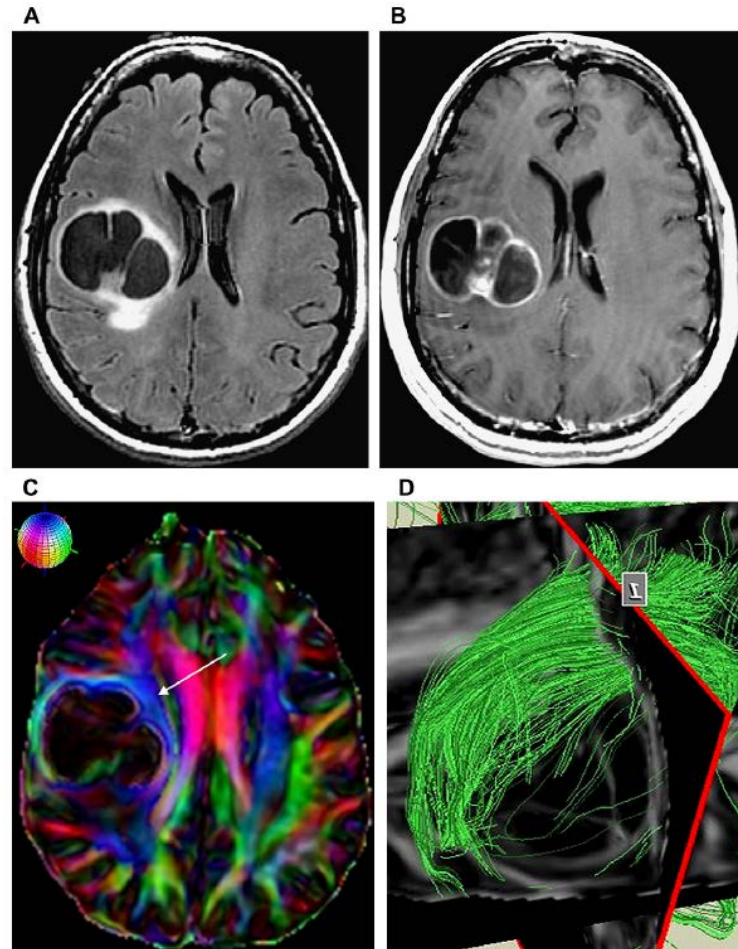
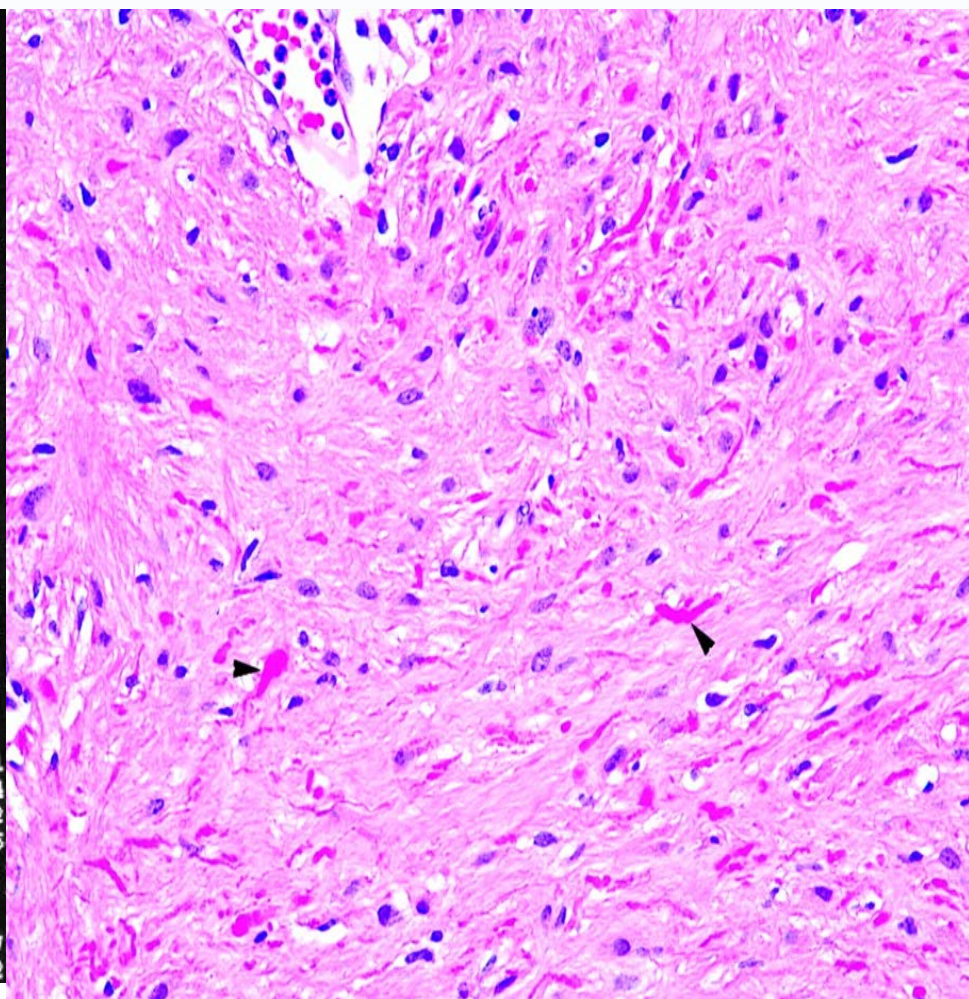
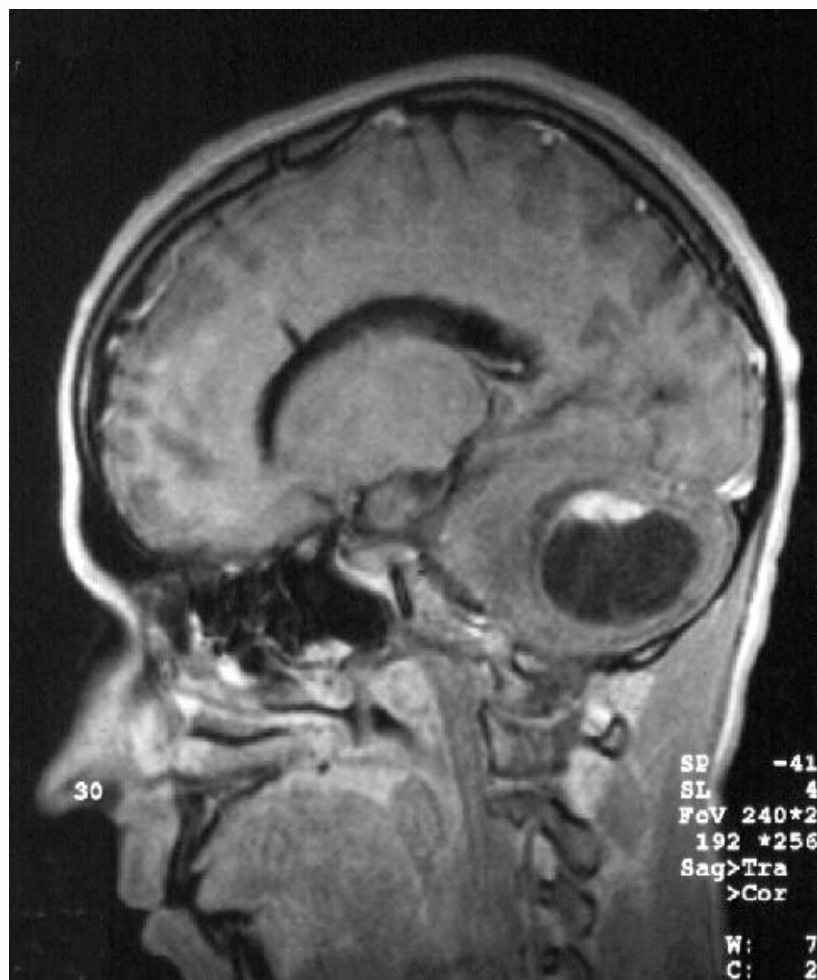


Fig. 1. Motor hand task, fMR imaging overlaid on contrast T1-weighted image. Activated voxels localize to the precentral gyri, with mild posterior displacement of the left precentral gyrus by the frontal lobe glioblastoma.



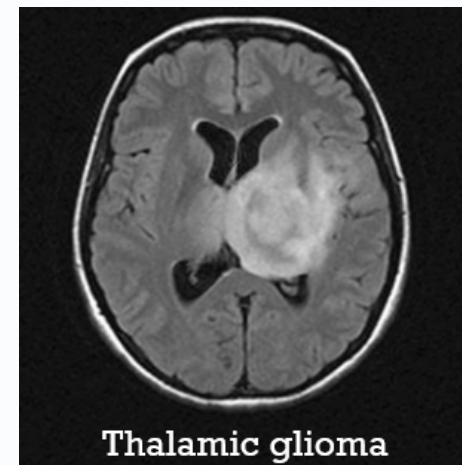
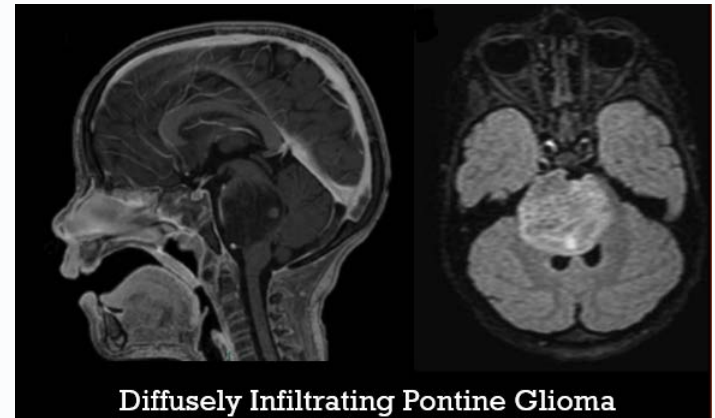


Pilocytic / Grade I Astrocytoma

- Prognosis tends to be excellent with total removal 10 year survival rates approaching 90+%. However, drop metastases and progressive growth can be seen
- WHO Grade I *** More likely to have a BRAF alteration
- Pleomorphic xantoastrocytoma (PXA) – also more prone to have a BRAF alteration
- Subependymal giant cell astrocytoma – more prone to have TSC1/TSC2 mutations

Major Changes in 2016 CNS WHO: Pediatric Diffuse Gliomas

- Recognition of diffuse midline glioma, H3 K27M-mutant: characterized by a diffuse growth pattern and a midline location (thalamus, brain stem and spinal cord).
- Arises in pons, thalamus or spinal cord.
- Typically present in children with median age at diagnosis 5-11 years.
- Poor prognosis, with a 2-year survival less than 10%.



Astrocytoma – Classic Neuropathology

Histologic diagnosis - 4 main parameters

Nuclear atypia

Mitoses

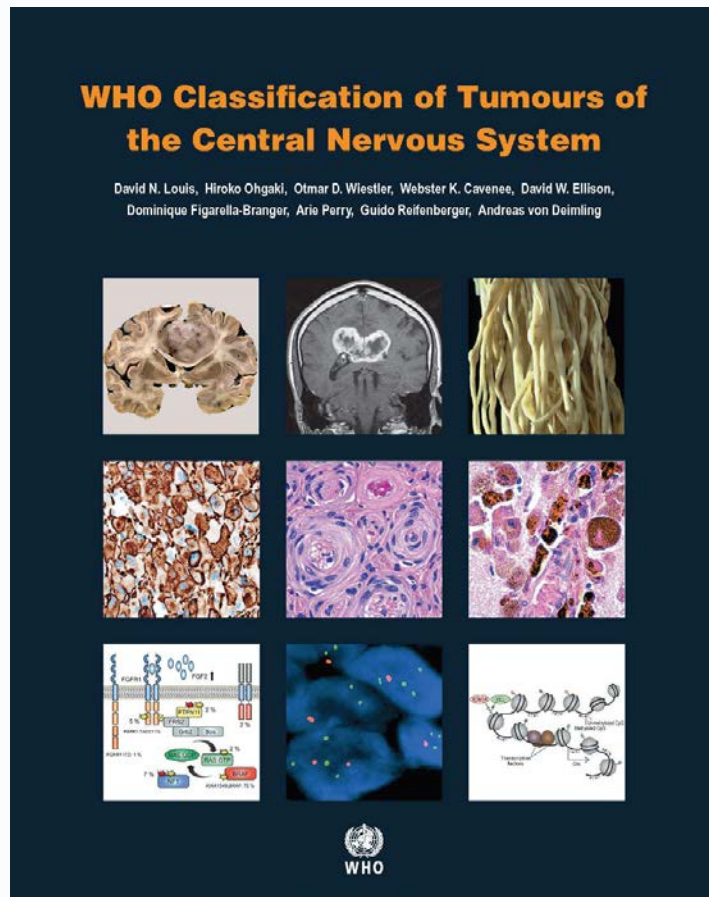
Endothelial proliferation

Necrosis

WHO

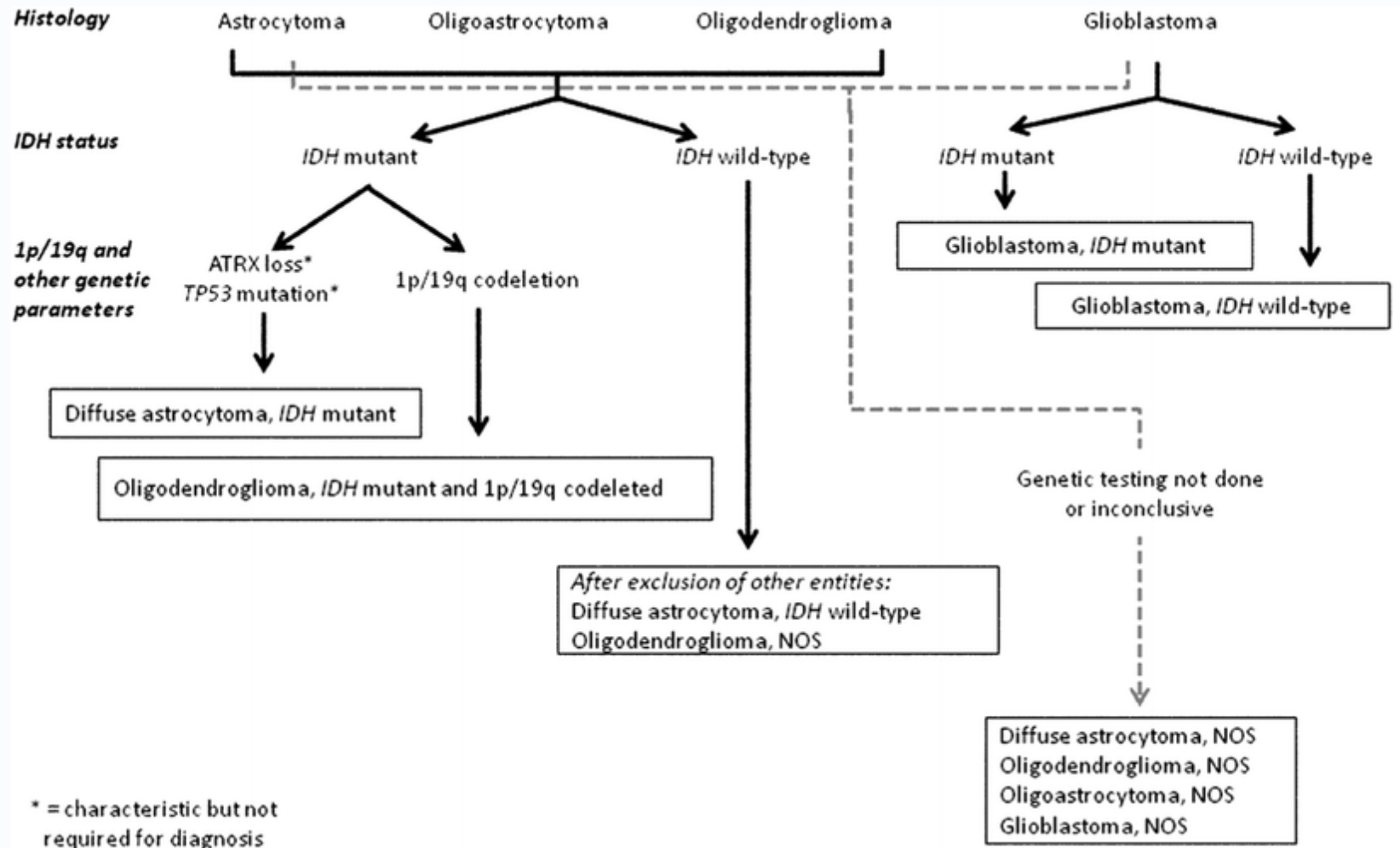
II - 1; III - 2; IV - 3 or 4

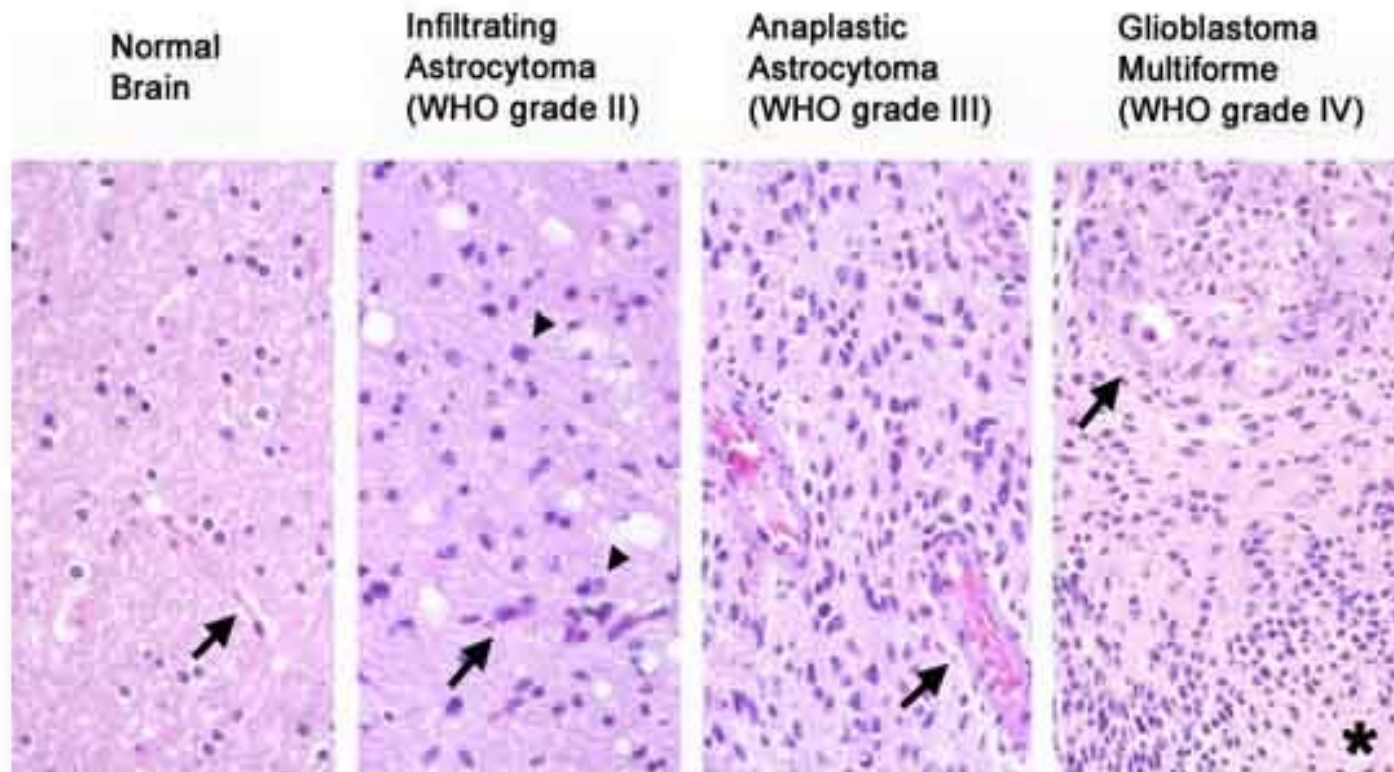
WHO classification of Tumors of the Central Nervous System 2016



- Seminal shift from the concept of classification of tumors according to their microscopic similarities and level of differentiation, to the current classification based on the genetic basis of tumorigenesis
- Formulates the concept of how CNS tumor diagnoses should be structured in the molecular era
- Restructures how clinical research is stratified going forward

Major Changes in 2016 CNS WHO: Diffuse Gliomas





Biology:

Infiltration

Proliferation/
Expansion

Hypoxia/
Necrosis

Genetic events:

p53 loss

p16, p14^{ARF} loss

EGFR amplification

PDGFR amplification

Chrom. 10 losses (PTEN)

Angiogenic events:

bFGF, VEGF ↑

PDGFR ↑

VEGF ↑↑

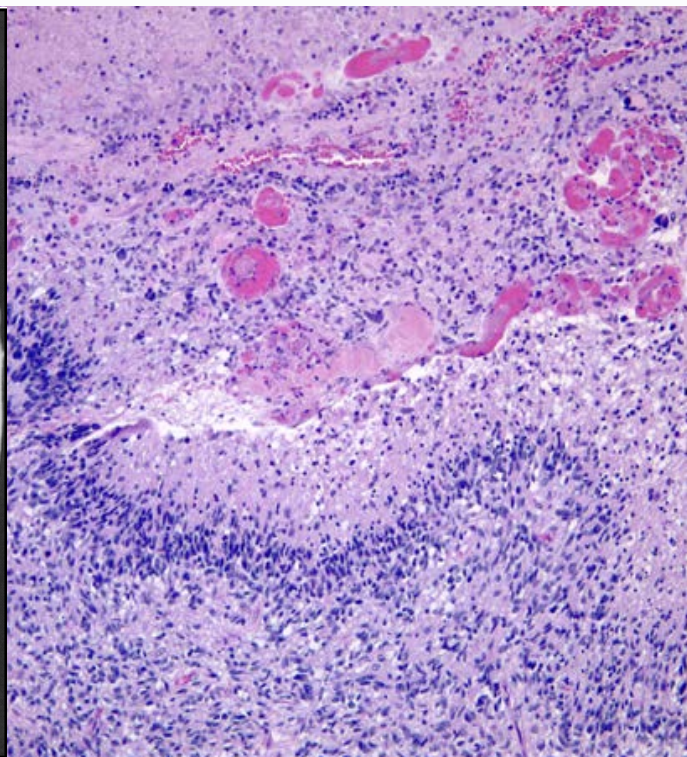
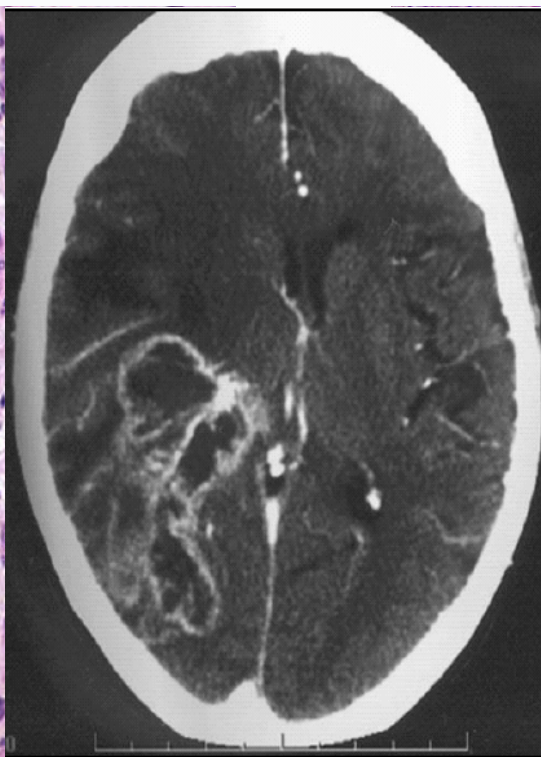
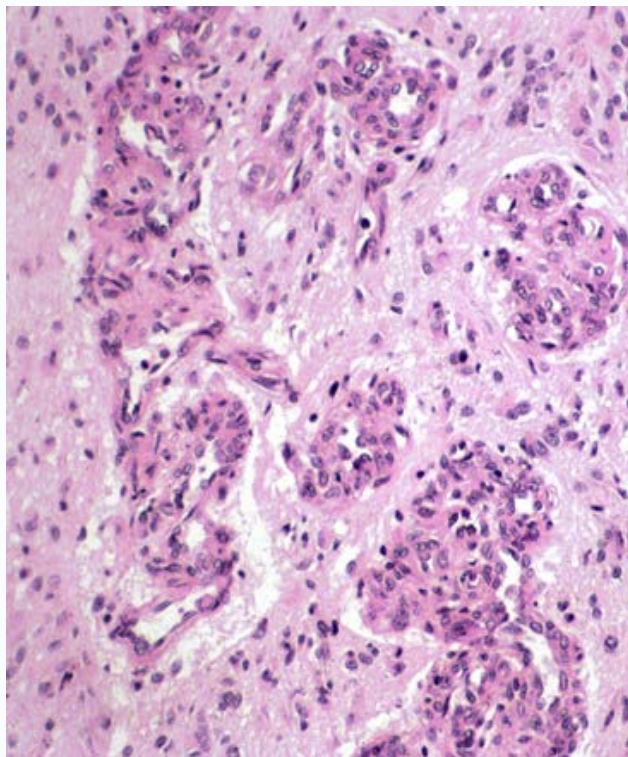
GD-AIF ↓

BAI1 ↓

TSP-1 ↓

Angiogenesis

Microvascular hyperplasia



Glioblastoma

- Grossly, spherical to irregular or ‘butterfly’ shaped in larger centrally located tumors. More superficial tumors penetrate cortex and invade adjacent leptomeninges to attach to dura. Mottled appearance with frequent hemorrhage and necrosis. Multiplicity in 10% of cases
- Microscopically, features of anaplastic astrocytoma with key presence of *endothelial proliferation and necrosis*

Glioblastoma - Survival

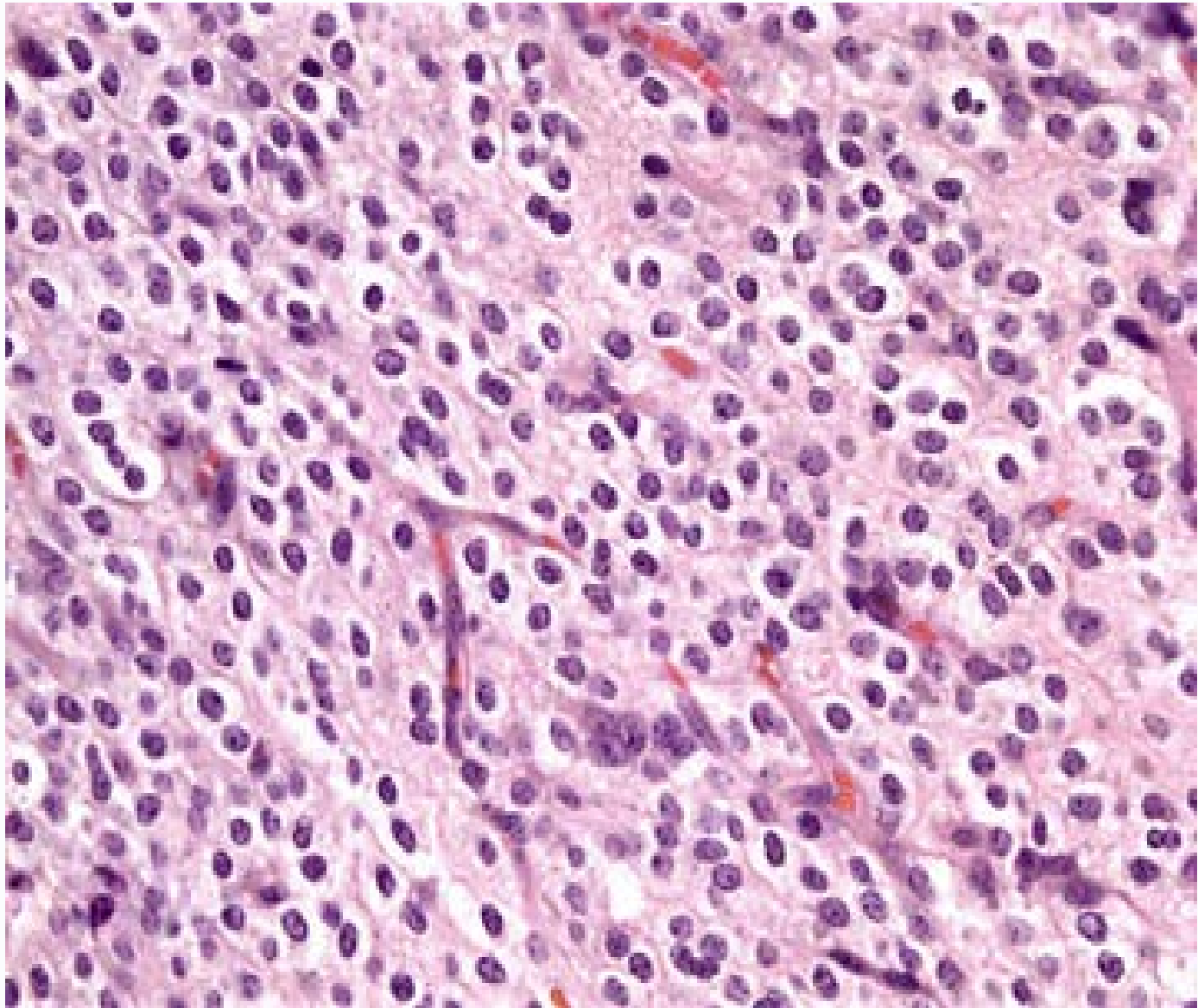
Surgery : 20 weeks

Surgery + RT : 36 weeks

Surgery + RT + pre-Temodar chemotherapy :
40-50 weeks

Surgery + RT + Temodar x 6 months: 14.6
months

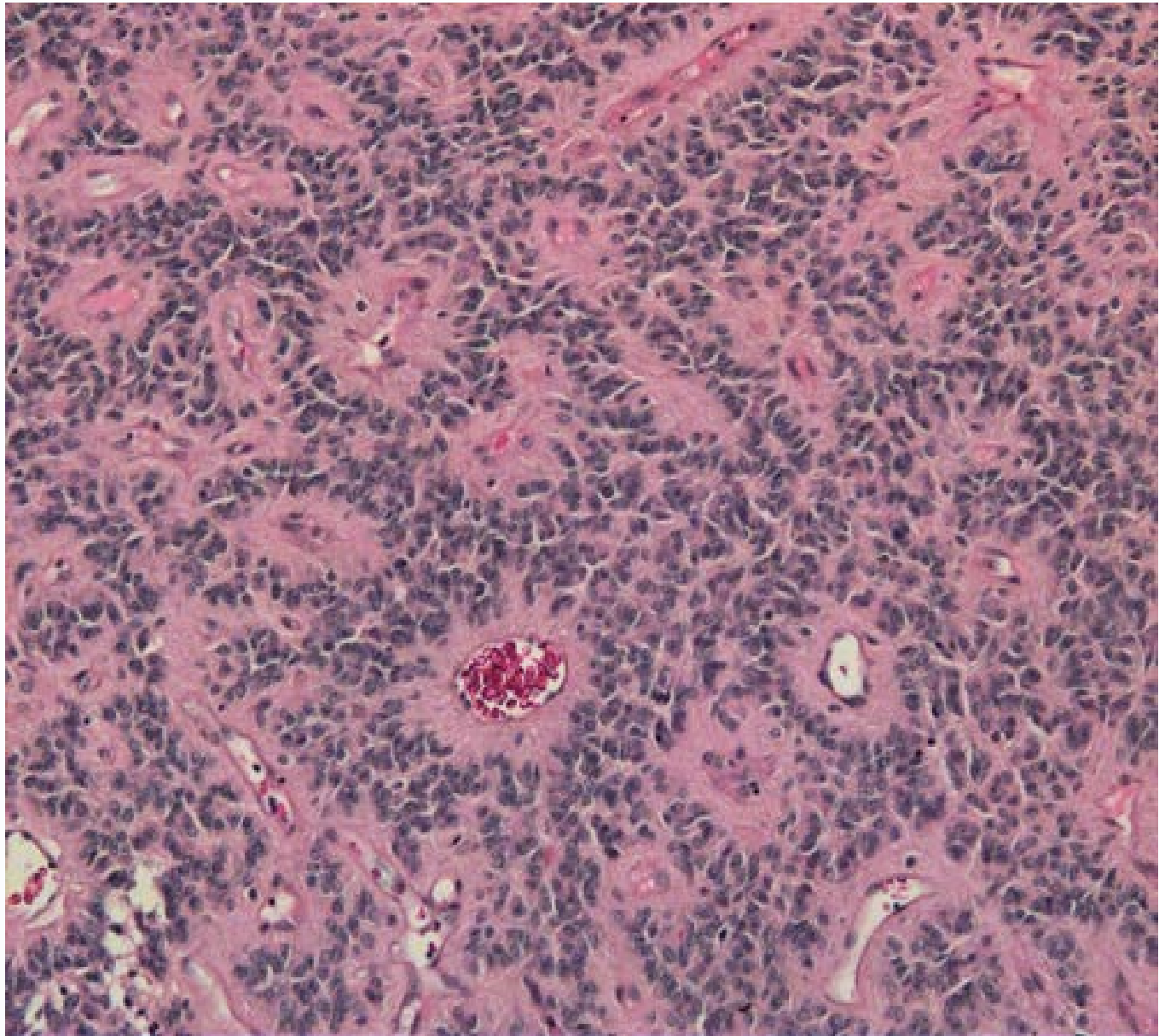
Surgery + RT + Temodar x 6 months + TTF: 24
months



Oligodendroglioma – 1p/19q

Specific genetic predictor of chemotherapeutic response and survival in patients with anaplastic oligodendroglioma - 1p/19q status

- Combined loss (co-deletion) of 1p/19q predicts increased recurrence free survival, better chemosensitivity (to alkylating agents), prolonged progression free survival following radiotherapy either with or without chemotherapy, and prolonged overall survival in anaplastic oligodendroglioma
- Techniques for assessing 1p/19q deletion status: LOH (loss of heterozygosity), QuMA (quantitative microsatellite analysis), FISH (fluorescent in situ hybridization)

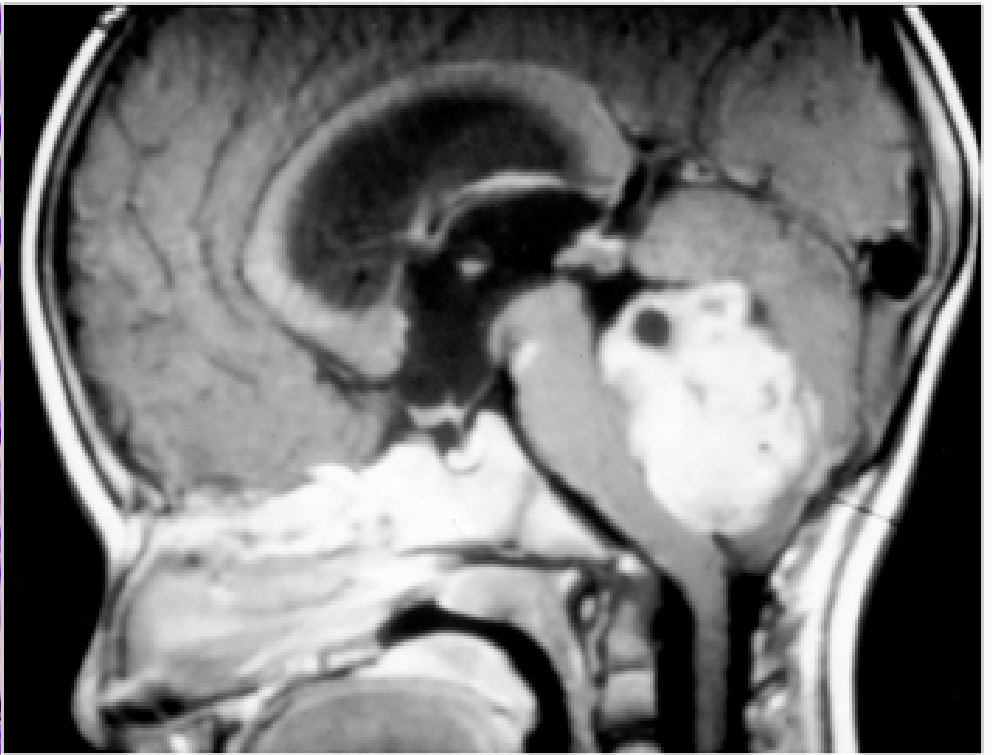
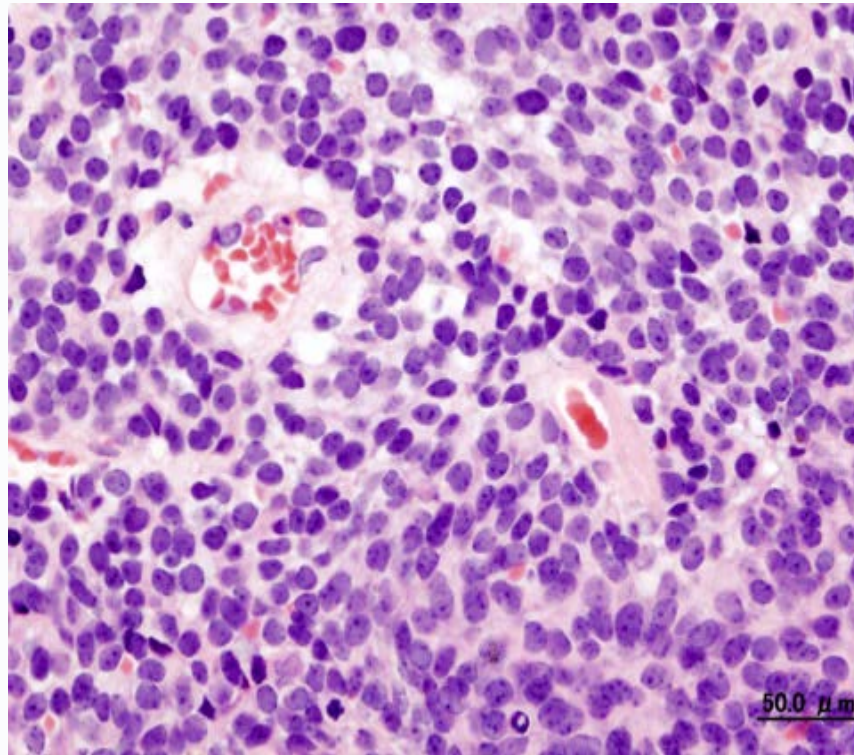


Major Changes in 2016 CNS WHO: Ependymomas

Anatomical location	Group	Genetic characteristic	Dominant pathology	Age at presentation	Outcome
Supratentorial	ST-EPN- <i>RELA</i>	<i>RELA</i> fusion gene	Classic/anaplastic	Infancy to adulthood	Poor
	ST-EPN- <i>YAP1</i>	<i>YAP1</i> fusion gene	Classic/anaplastic	Infancy to childhood	Good
	ST-SE	Balanced genome	Subependymoma	Adulthood	Good
Posterior fossa	PF-EPN-A	Balanced genome	Classic/anaplastic	Infancy	Poor
	PF-EPN-B	Genome-wide polyploidy	Classic/anaplastic	Childhood to adulthood	Good
	PF-SE	Balanced genome	Subependymoma	Adulthood	Good
Spinal	SP-EPN	<i>NF2</i> mutation	Classic/anaplastic	Childhood to adulthood	Good
	SP-MPE	Genome-wide polyploidy	Myxopapillary	Adulthood	Good
	SP-SE	6q deletion	Subependymoma	Adulthood	Good

Ependymoma - Categorization

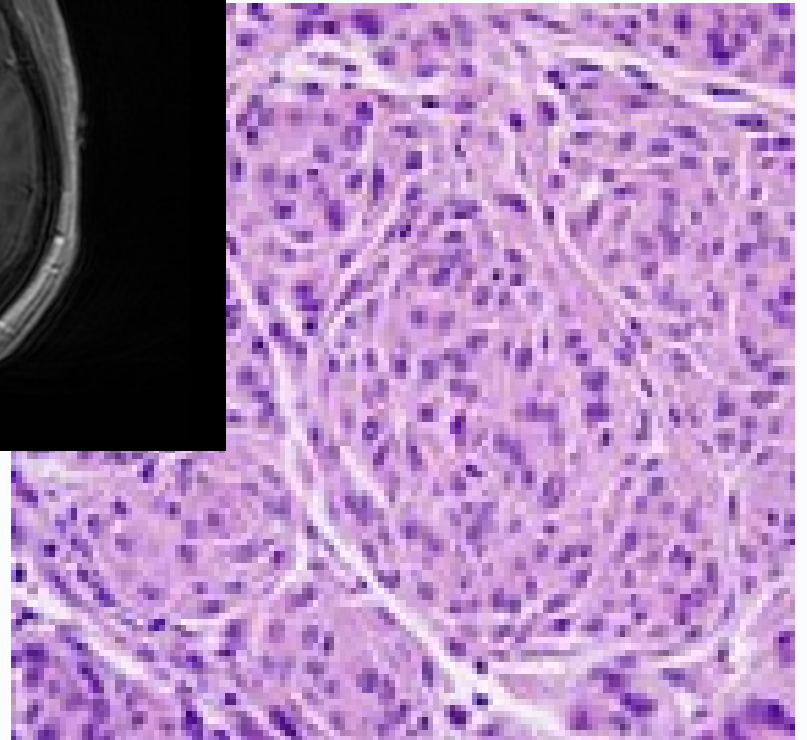
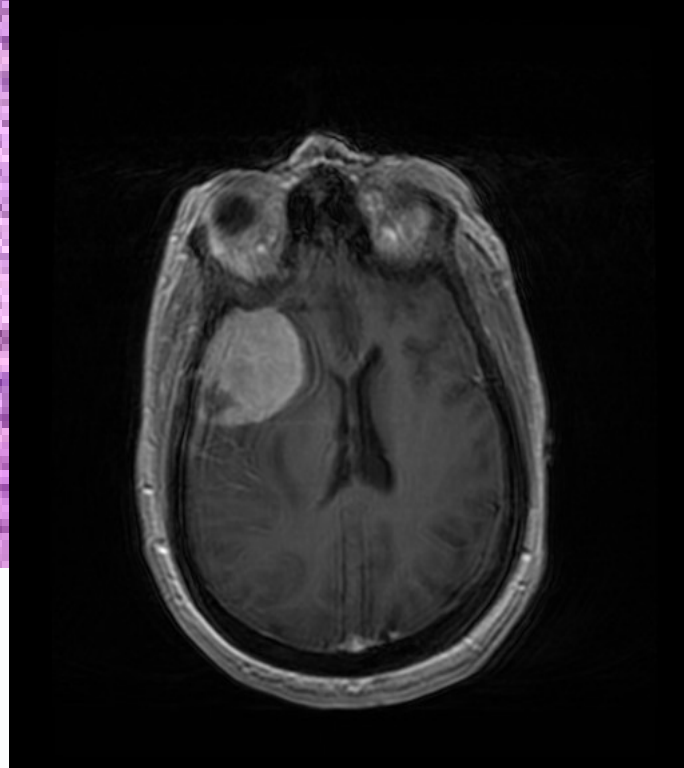
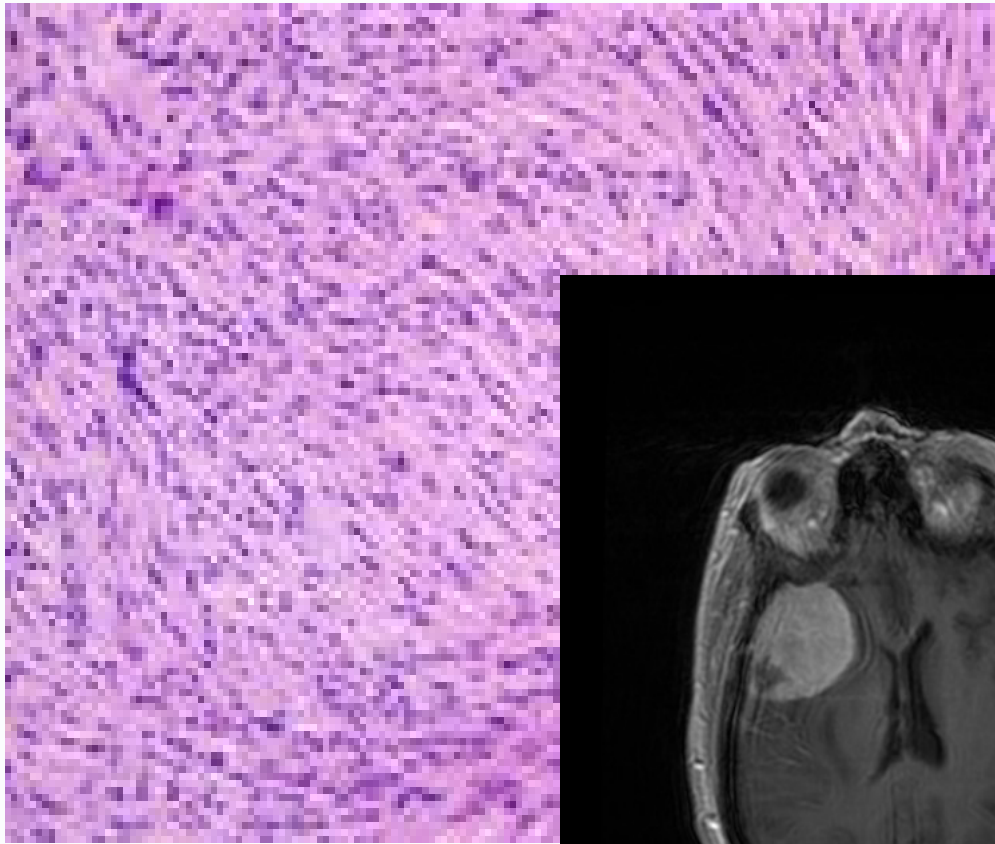
- Supratentorial ependymomas with C11orf95-RELA fusion or YAP1 fusion, infratentorial ependymomas with or without a hypermethylated phenotype (CIMP), and spinal cord ependymomas.
- Myxopapillary ependymomas and subependymomas have different biology than ependymomas with typical WHO grade II or III histology.



1

2

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, <i>TP53</i> -mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
Medulloblastoma, SHH-activated, <i>TP53</i> -wildtype	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
Medulloblastoma, non-WNT/non-SHH, group 3	Extensive nodularity	Low-risk tumour of infancy
	Classic	Standard-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Large cell / anaplastic	High-risk tumour
	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance



Meningioma

Table 1. World Health Organization (WHO) grading system

WHO grade	Frequency	Pathologic features	Histologies	Recurrence rates
Grade I	80%–90%	Pleomorphic; occasional mitotic figures; lacks criteria of anaplastic or atypical meningiomas	Meningothelial, psammomatous, secretory, fibroblastic, angiomatous, lymphoplasmacyte rich, transitional, microcytic, metaplastic	7%–20%
Grade II	5%–15%	≥4 mitotic figures per 10 high-power fields; three of the following: (a) increased cellularity, (b) small cells with high N:C ratio, (c) prominent nucleoli, (d) sheet-like growth, (e) necrosis; or brain invasion	Clear cell, chordoid, atypical	30%–40%
Grade III	1%–3%	≥20 mitotic figures per 10 high-power fields or frank anaplastic features	Papillary, rhabdoid, anaplastic	50%–80%

Table 2. Simpson grade

Simpson grade	Definition	10-yr recurrence rate
1	Macroscopic GTR with excision of dura, sinus, and bone	9%
2	Macroscopic GTR with coagulation of dural attachment	19%
3	Macroscopic resection without resection or coagulation of dural attachment	29%
4	Subtotal resection	40%
5	Biopsy	NA

Abbreviations: GTR, gross-total resection; NA, not available.

Meningioma

- 13-19% of all primary brain tumors. 12% of meningiomas found in spinal cord area
- Occur in 5th decade with a predominance in women
- Proposed etiologic factors include genetic, head injury, irritation from a chronic SDH, long standing infection, ionizing radiation

Meningioma

- In cerebral convexities, about 50% of meningiomas are found along the sagittal sinus (middle 1/3 > frontal > occipital).
- In spinal cord, thoracic > other regions
- Grossly hemispheric, globular growths that are firmly attached to the dura. Thin investing capsule from the soft meninges. Hyperostosis in about 5% of cases

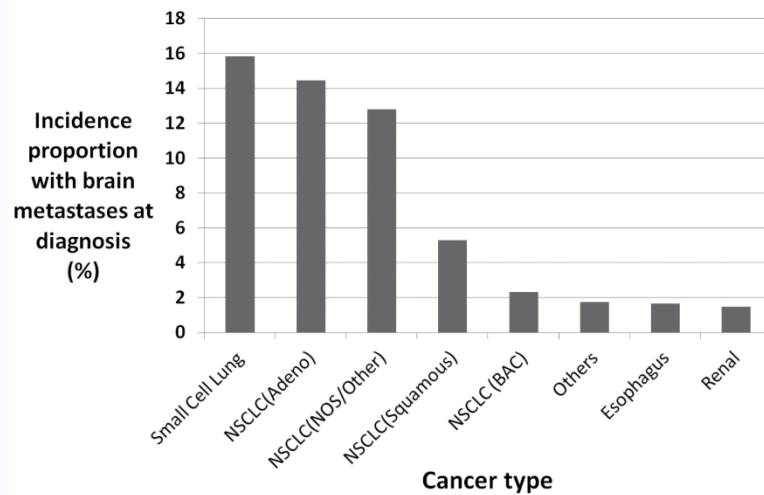
Brain Metastases - Epidemiology

- The incidence of metastatic brain tumors exceeds that of primary brain tumors, accounting for 50-70% of total brain tumors and for as many as 30% of tumors seen on imaging studies alone.
- **An estimated 100,000 new cases (8-11/100,000 general incidence) are diagnosed per year in the United States;** about 60% of patients are aged 50-70 years.

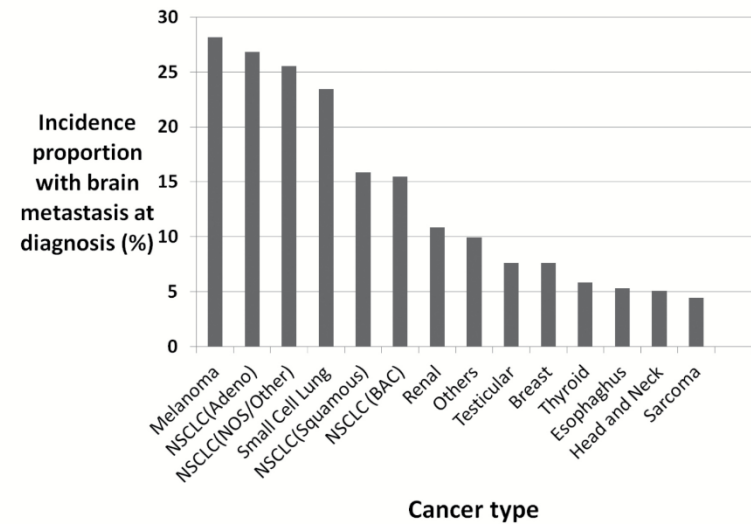
Brain Metastases - Epidemiology

- About 15% of patients with cancer present with neurologic symptoms before their systemic cancer is diagnosed.
- Brain metastases affect 8%–10% of all cancer patients and 40% of patients with metastatic cancer. The majority of BrMet originate from lung cancer (40%–50%), breast cancer (15%–25%), and melanoma (5%–20%).
- In 9%, the CNS is the only site of spread.
- About 10% of patients with proven metastatic disease have no identifiable primary source.

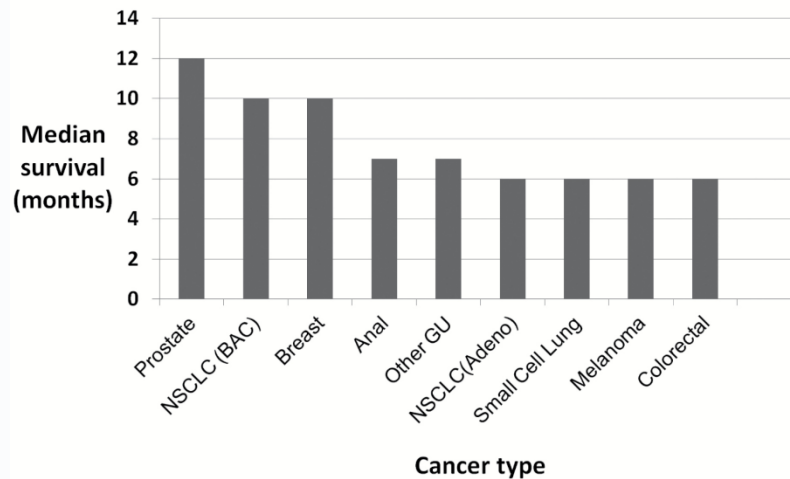
A.



B.



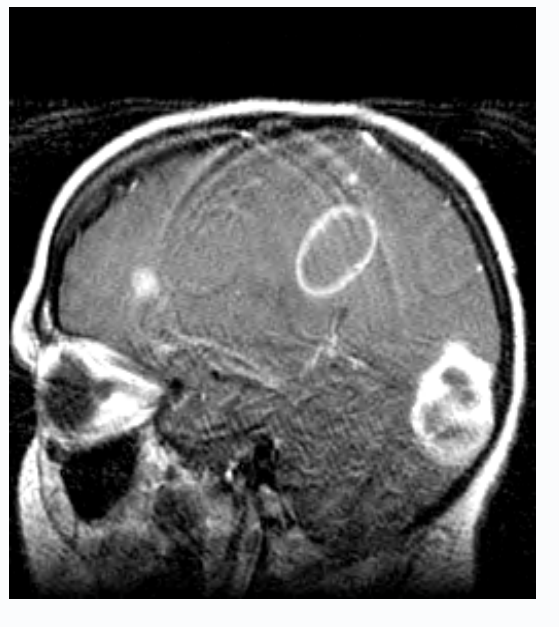
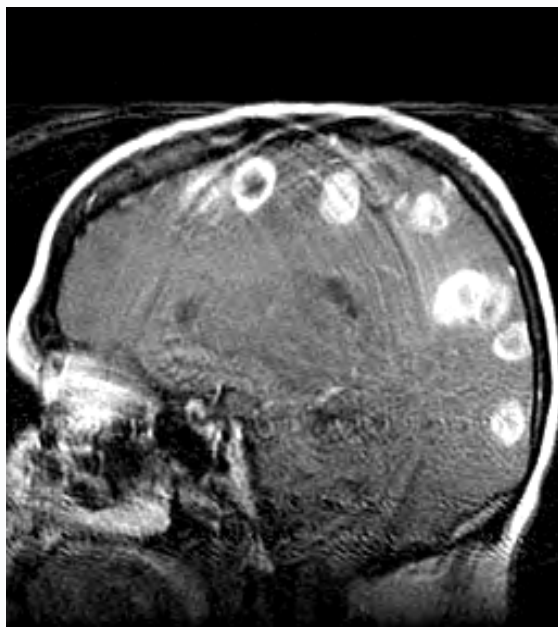
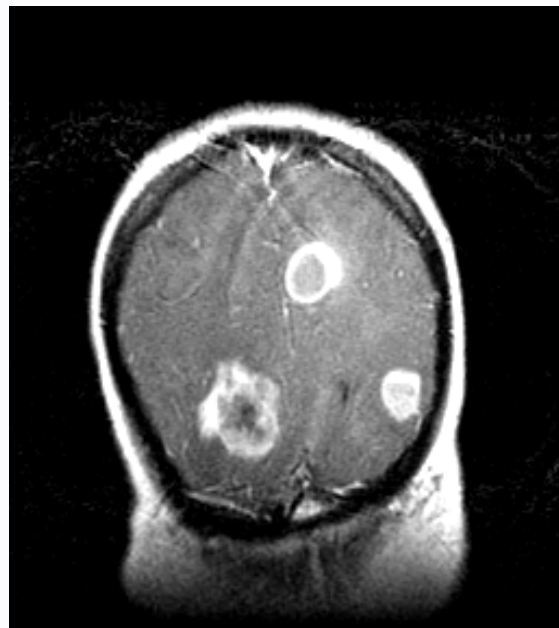
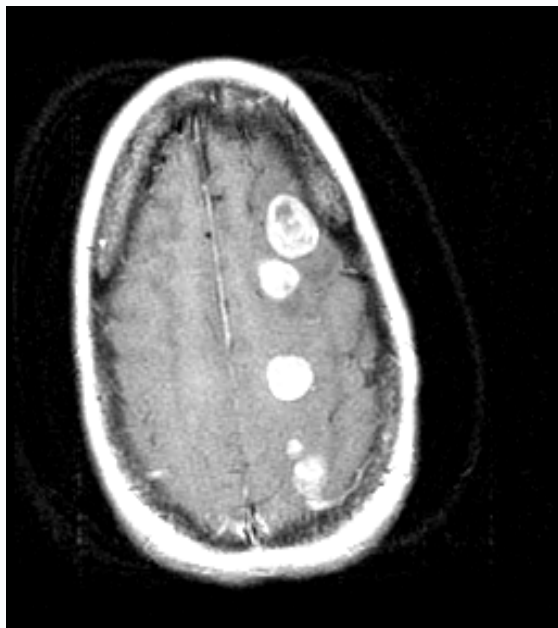
C.

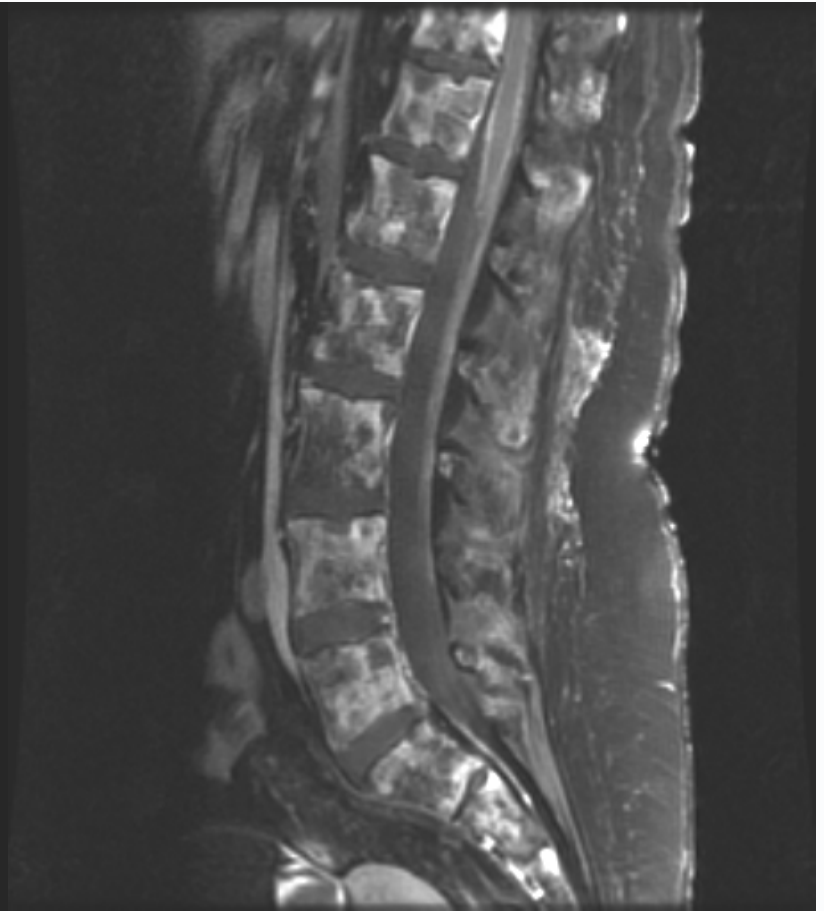
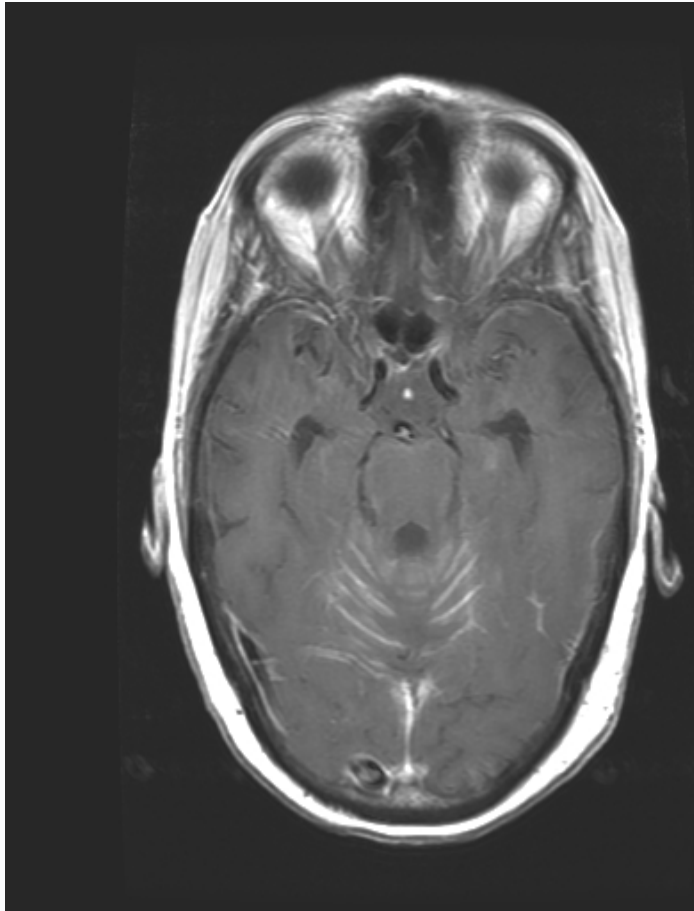


From: Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study

Neuro Oncol. 2017;19(11):1511-1521. doi:10.1093/neuonc/nox077

Neuro Oncol | © The Author(s) 2017. Published by Oxford University Press on behalf of the Society for Neuro-Oncology. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com





Common LMD etiologies

Primary-Specific Characteristics of LMD

Primary Cancer	Prevalence of LMD	Prognosis	Additional Treatment Modalities
Melanoma	30-75%	Median: 6.9 months	BRAF inhibitors (Vemurafenib and Dabrafenib) and Checkpoint inhibitors (Ipilimumab and Nivolumab) improved survival (16.9 weeks vs. 2.9 weeks) in prospective studies
NHL	5-30%	Median: 2.6 months	IT Rituxumab in Phase 1 studies. Prophylaxis with IT chemotherapy.
NSCLC	9-25%	Median: 3.5 months	EGFR TKI improved survival if EGFR+ in multiple case reports
Breast Cancer	5%	Median: 4.2 months (longer if hormone receptor positive)	High-Dose MTX trial IT Trastuzumab if HER2+.

Selected IT chemotherapies

- DepoCyt
- Cytarabine
- Thiotepa
- Methotrexate
- Hydrocortisone
- RTX
- Trastuzumab

Systemic chemotherapies for LMD

- HD MTX
- Gefitinib
- Pemetrexed
- Capecitabine

Neurologic Complications of Cancer

- Neurologic complications are seen in about 30-40% of cancer patients
 - Metabolic encephalopathy
 - Metastatic disease
 - Paraneoplastic syndromes
- Lambert-Eaton, dermatomyositis, carcinomatous neuromyopathy, polyradiculopathy, retinal degeneration, opsoclonus-myoclonus, myelitis
 - Complications related to cancer therapy
- Radiation encephalopathy, radiation necrosis, neuropathy, psychosis, cerebellar dysfunction, leukoencephalopathy

End Part I – Brain and Spine Tumor Overview



SKIP TO THE END.