Overview of
Brain Tumors

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SRMS IMS, Bareilly

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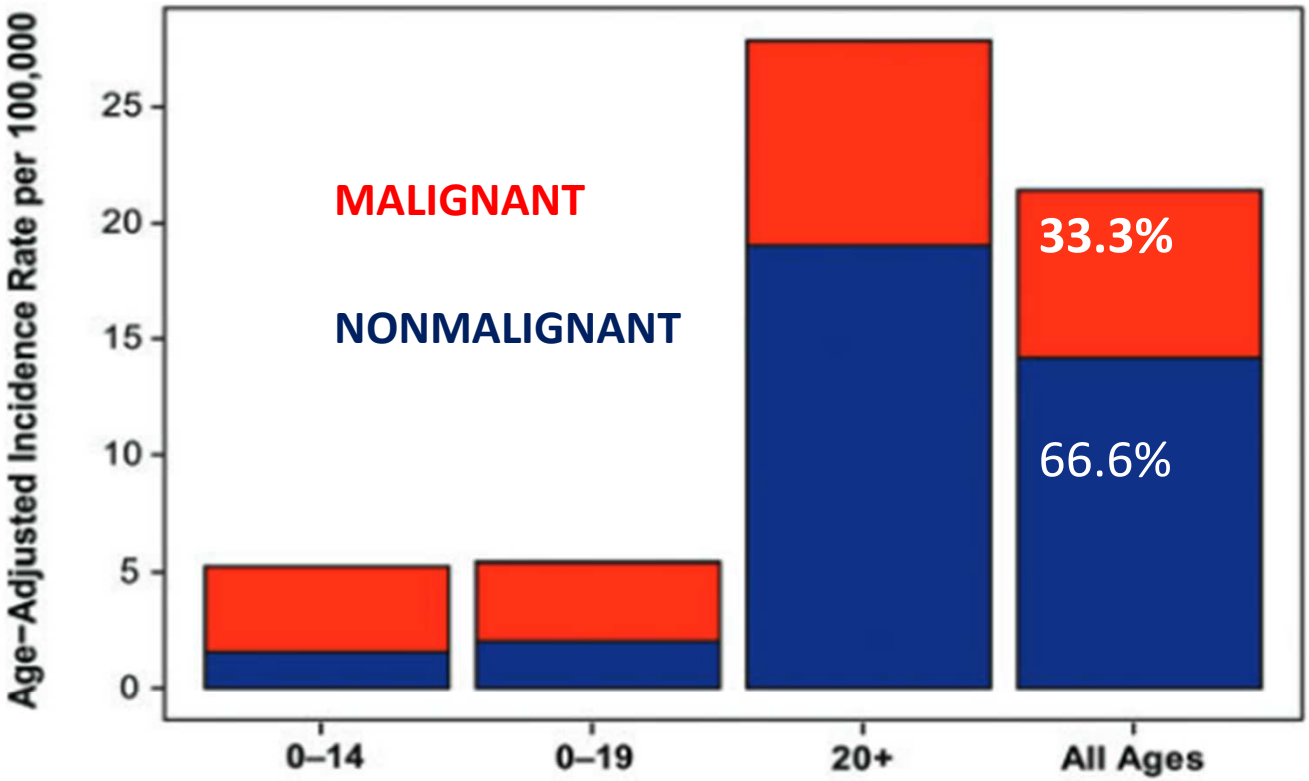
Overview of Brain Tumors

Incidence, prevalence & mortality

- Metastatic vs. Primary CNS tumors =10:1
- World wide incidence of Primary CNS tumors =3.4 (very high human development=5.1, high=4.7, medium=4.0, low=1.3).
- High mortality upto 75%.
- ↑ whites than in blacks.
- Dramatic improvement in children and young adult, mortality ↓ by 50% between 1975 to 2010.
- ↑ males except meningiomas and schwannomas (↑ blacks and low socioeconomic group).

Overview of Brain Tumors

Malignant & Non-malignant



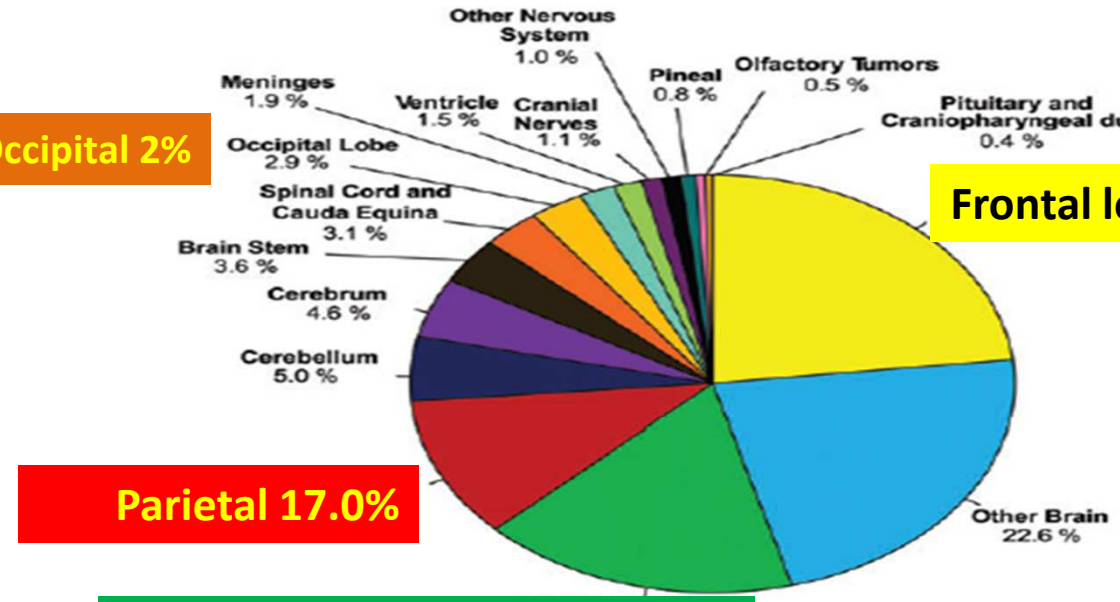
Non-Malignant	1.56	2.03	19.05	14.17
Malignant	3.70	3.39	8.80	7.25
Total	5.26	5.42	27.85	21.42

a. Rates per 100,000 and age-adjusted to the 2000 United States standard population.

Etiologic Factors

- **Environmental factors**
  - Ionizing and non-ionizing radiation
  - Cellular telephones
  - Chemical exposures (formaldehyde, vinyl chloride, acrylonitrile, etc.)
- **Viral Associations**
  - EBV, HCMV, HIV
- **Hereditary Syndromes**
  - Cowden,Turcot, Lynch & Li-Fraumeni (Gliomas)
  - Gorlin(PNET), neurofibromatosis type I&II (meningiomas, optic nerve glioma, shwannoma) ,VHL (haemangioblastoma).

SITE WISE DISTRIBUTION OF MALIGNANT TUMORS CBTRUS 2014

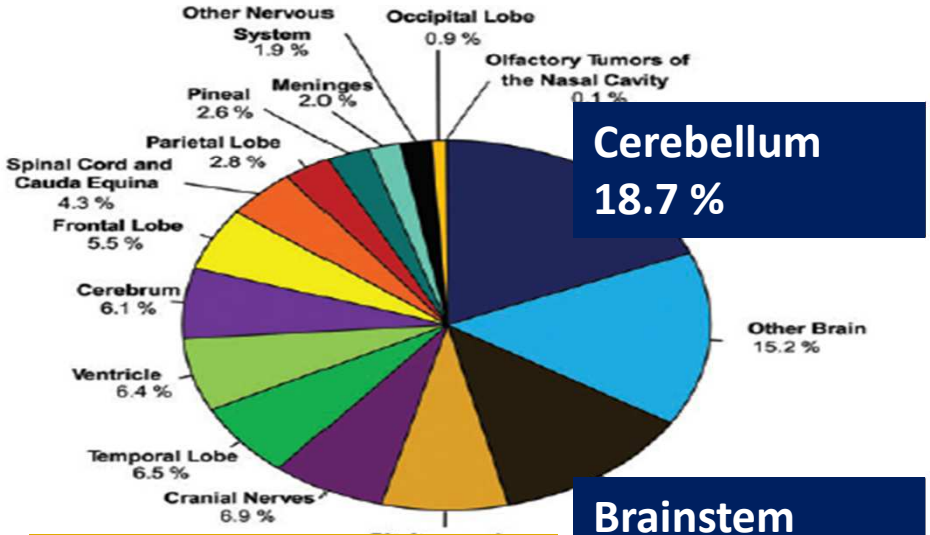


Occipital 2%

Frontal lobe 23.2%

Parietal 17.0%

Temporal 17.0%

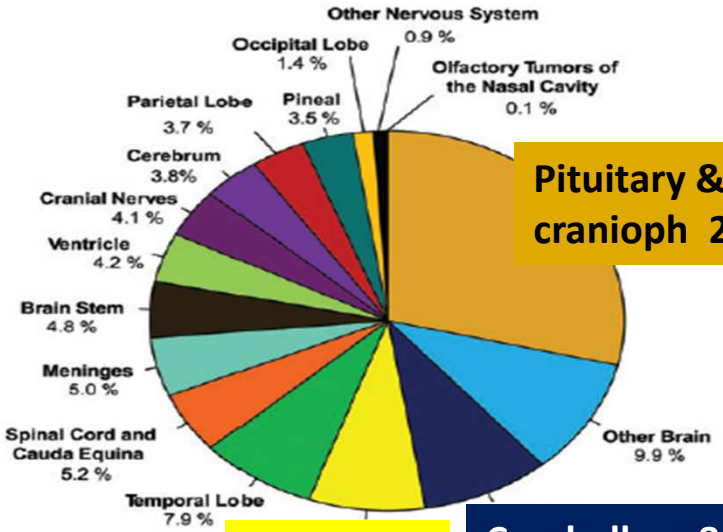


Cerebellum 18.7 %

Brainstem 12.4%

Pituitary & cranioph 7.8%

AGE -- 0 TO 14 YRS



Pituitary & cranioph 28.8%

Frontal

Cerebellum 8.8 %

AGE -- 15 TO 19 YRS

Overview of Brain Tumors

WHO Classification of CNS Tumours, Lyon, 2007.

ASTROCYTIC TUMORS

GRADE I Subependymal giant cell astrocytoma, Pilocytic astrocytoma,
II Pilomyxoid astrocytoma, Diffuse astrocytoma, pleomorphic xanthoastrocytoma
III Anaplastic astrocytoma,
IV Glioblastoma, Giant cell glioblastoma,, gliosarcoma

OLIGODENDROGLIOMA AND OLIGOASRTCYTOMA

GRADE II Oligodendroglioma , Oligoastrocytoma
III Anaplastic Oligodendroglioma, Anaplastic Oligodastrocytoma

EPENDYMAL TUMORS

GRADE I Subependymoma, Myxopapillary ependymoma
II Ependymoma
III Anaplastic ependymoma

CHOROID PLEXUS TUMOR

GRADE I Choroid plexus papilloma
II Atypical choroid papilloma
III Choroid plexus carcinoma

Overview of Brain Tumors

WHO Classification of CNS Tumours, Lyon, 2007.

Pineal tumors

GRADE I		Pineocytoma
	II , III	Pineal parenchymal tumor of intermediate differentiation, Papillary tumor of the pineal region
	IV	Pineoblastoma

Embryonal tumors

Grade IV	Medulloblastoma, PNET
	Atypical teratoid/rhabdoid tumor

Tumors of the cranial and paraspinal nerves

GRADE I	Schwannoma, Neurofibroma
II-IV	Perineurioma
	Malignant peripheral nerve sheath tumor (MPNST)

Overview of Brain Tumors

WHO Classification of CNS Tumours, Lyon, 2007.

Meningeal tumors :

GRADE I Meningioma, Hemangioblastoma

II Atypical meningioma, Hemangiopericytoma

III Anaplastic/malignant meningioma, Anaplastic hemangiopericytoma

Tumors of the sellar region

GRADE I Craniopharyngioma,
Granular cell tumor of the neurohypophysis
Pituicytoma, Spindle cell oncocytoma of the adenohypophysis

Overview of Brain Tumors

Simplified Working Formulation

1) Neuroepithelial Tumors :

Glial cell origin: Asrocytoma, Oligodendroglioma, Ependymoma, choroid plexus

Neuronal and mixed neuro–glial origin: Gangliocytoma, Neurocytoma, Papillary glioneuronal tumor, Rosette-forming glioneural tumor of the fourth ventricle

Embryonal Tumors : Medulloblastoma, PNET

2) Tumors of specialized anatomic structures: Pituitary adenoma, craniopharyngioma, pineocytoma, chordoma, haemangiopericytoma, germ cell tumors, choroid plexus tumors. ,

3)Tumors of meninges (meningoepithilial cells, mesenchymal)

4)Tumors of haematopoitic system : lymphoma, plasmacytoma.

5) metastatic

Overview of Brain Tumors

Classification of Adult Brain Tumors

WHO grade I = low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone.

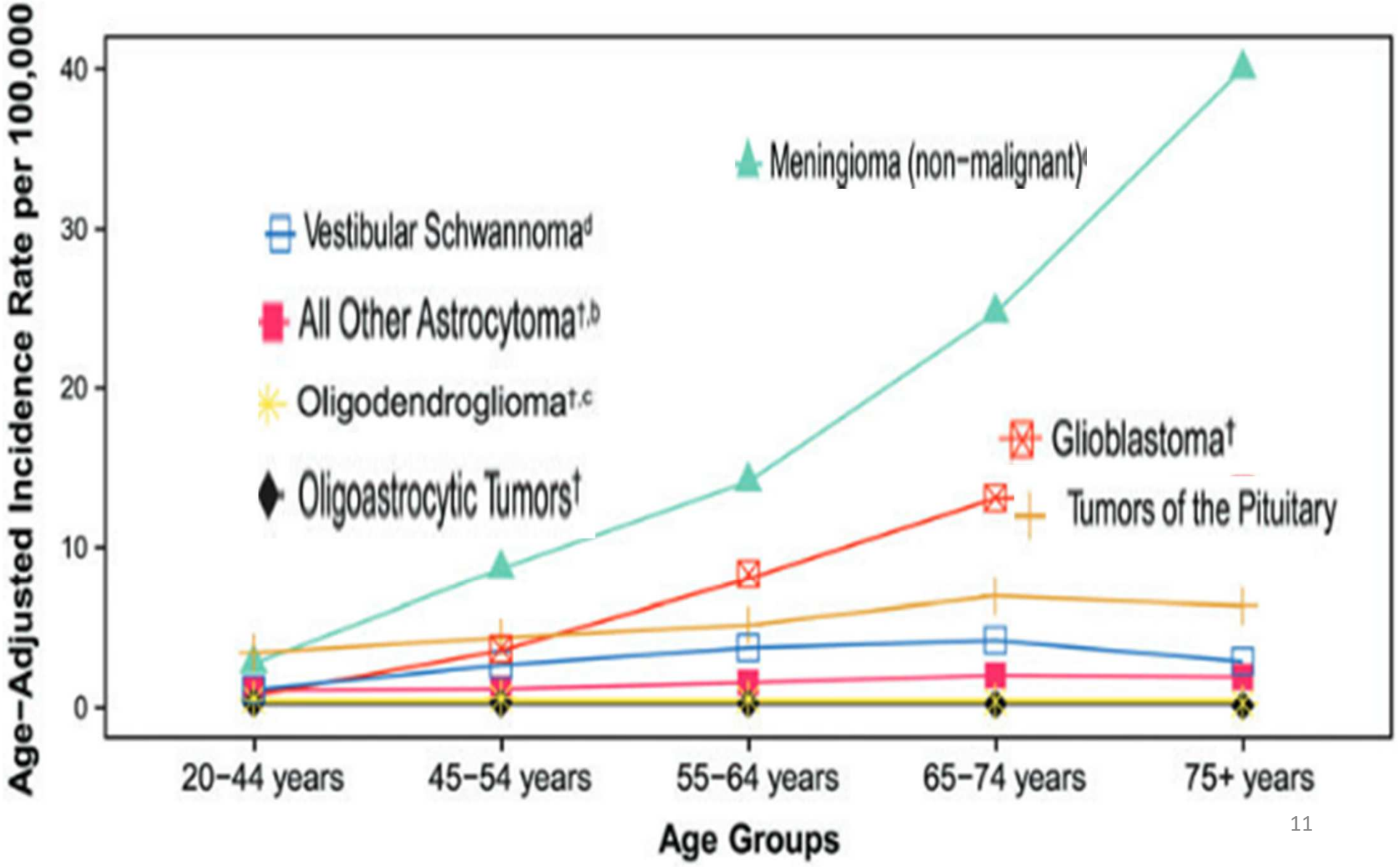
WHO grade II = generally infiltrating and low in mitotic activity but recur more frequently than grade I malignant tumors after local therapy. Some tumor types tend to progress to higher grades of malignancy.

WHO grade III = anaplastic histology & infiltrative, usually treated with aggressive adjuvant therapy.

WHO grade IV = mitotically active, necrosis-prone , micro-vascular proliferation & generally associated with a rapid pre & post-operative progression & fatal outcomes, usually treated with aggressive adjuvant therapy.

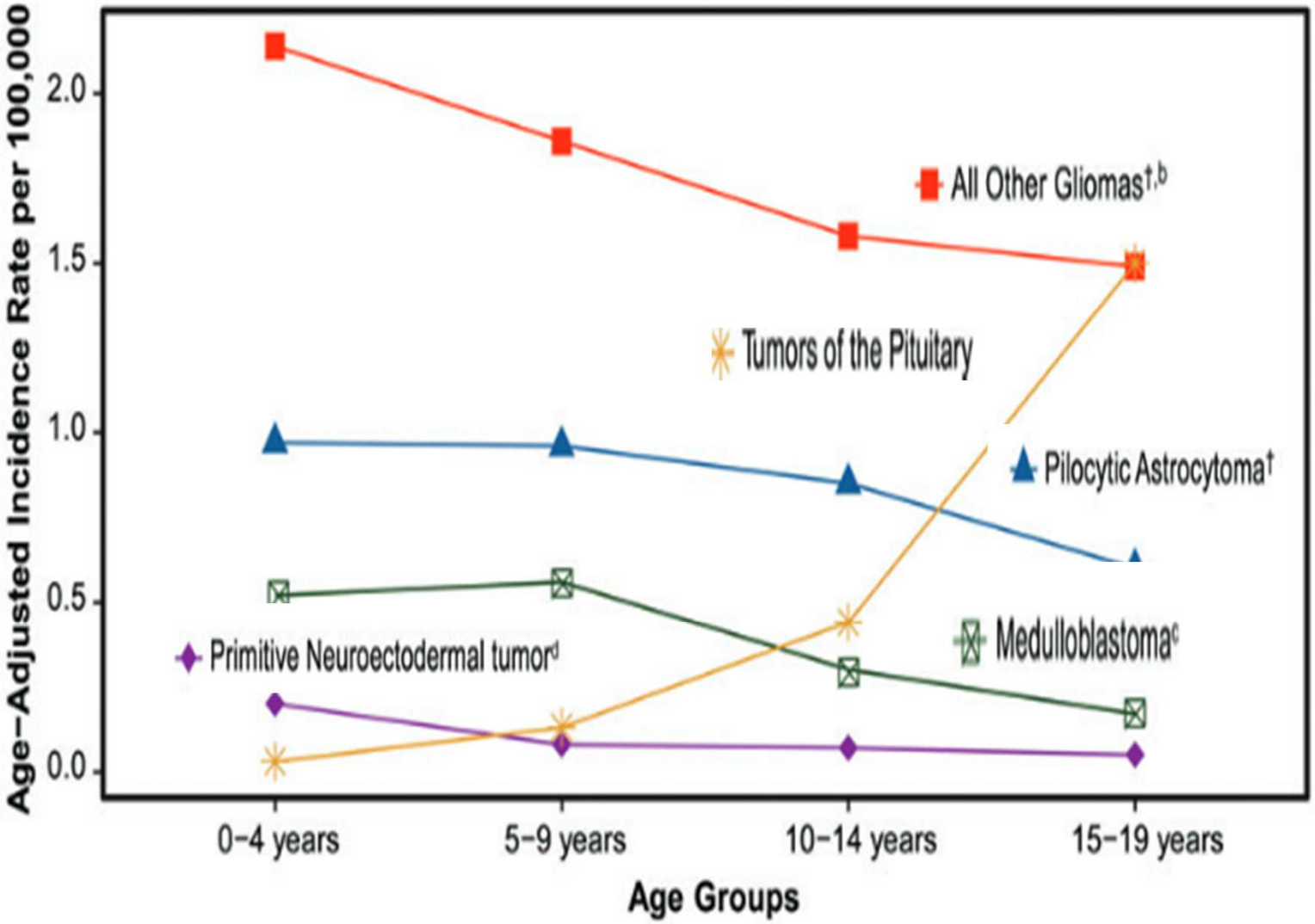
Overview of Brain Tumors

Age vs. Malignant & Non-malignant CBTRUS 2014

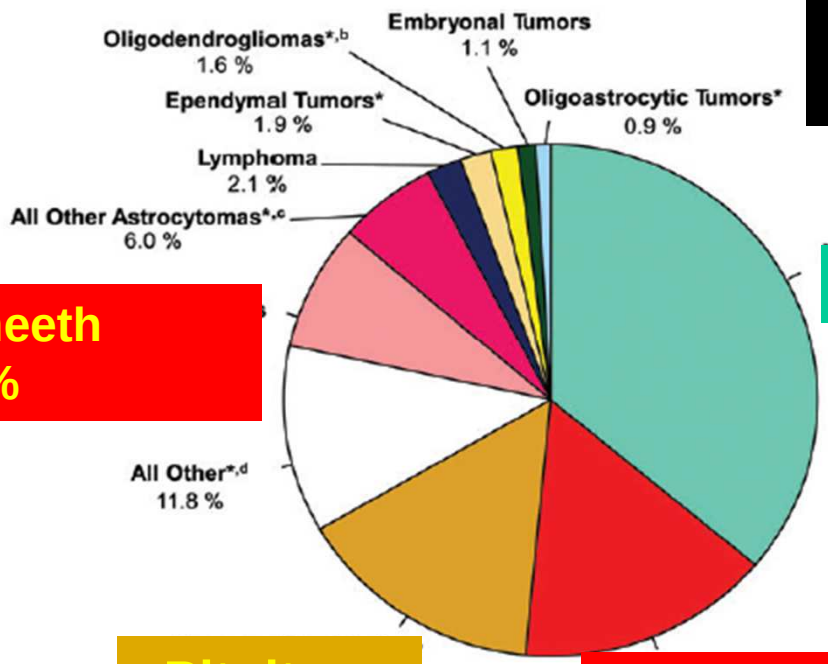


Overview of Brain Tumors

Age vs. Pediatric CNS Tumors CBTRUS 2014



Histology wise distribution CBTRUS 2014



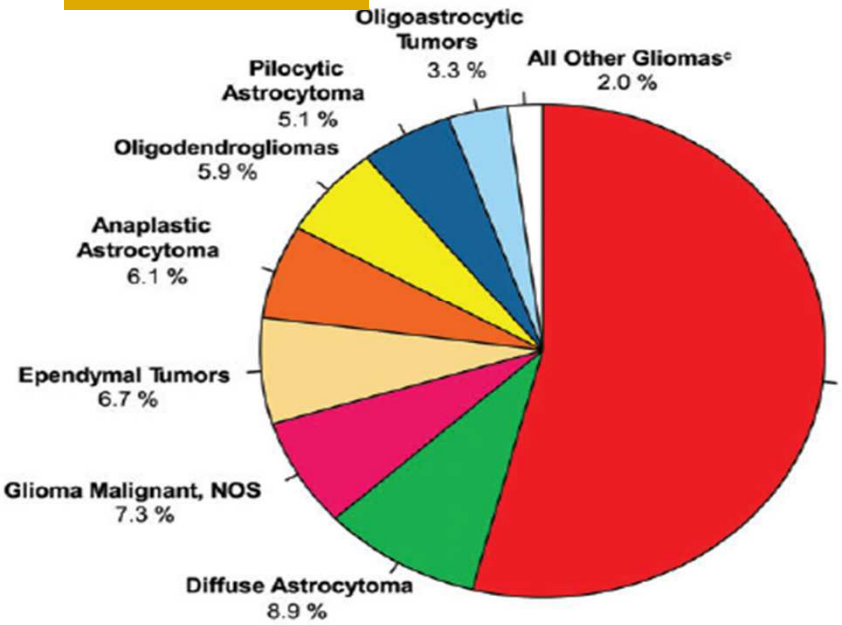
Meningioma 36.1%

Nerve sheeth tumor 8%

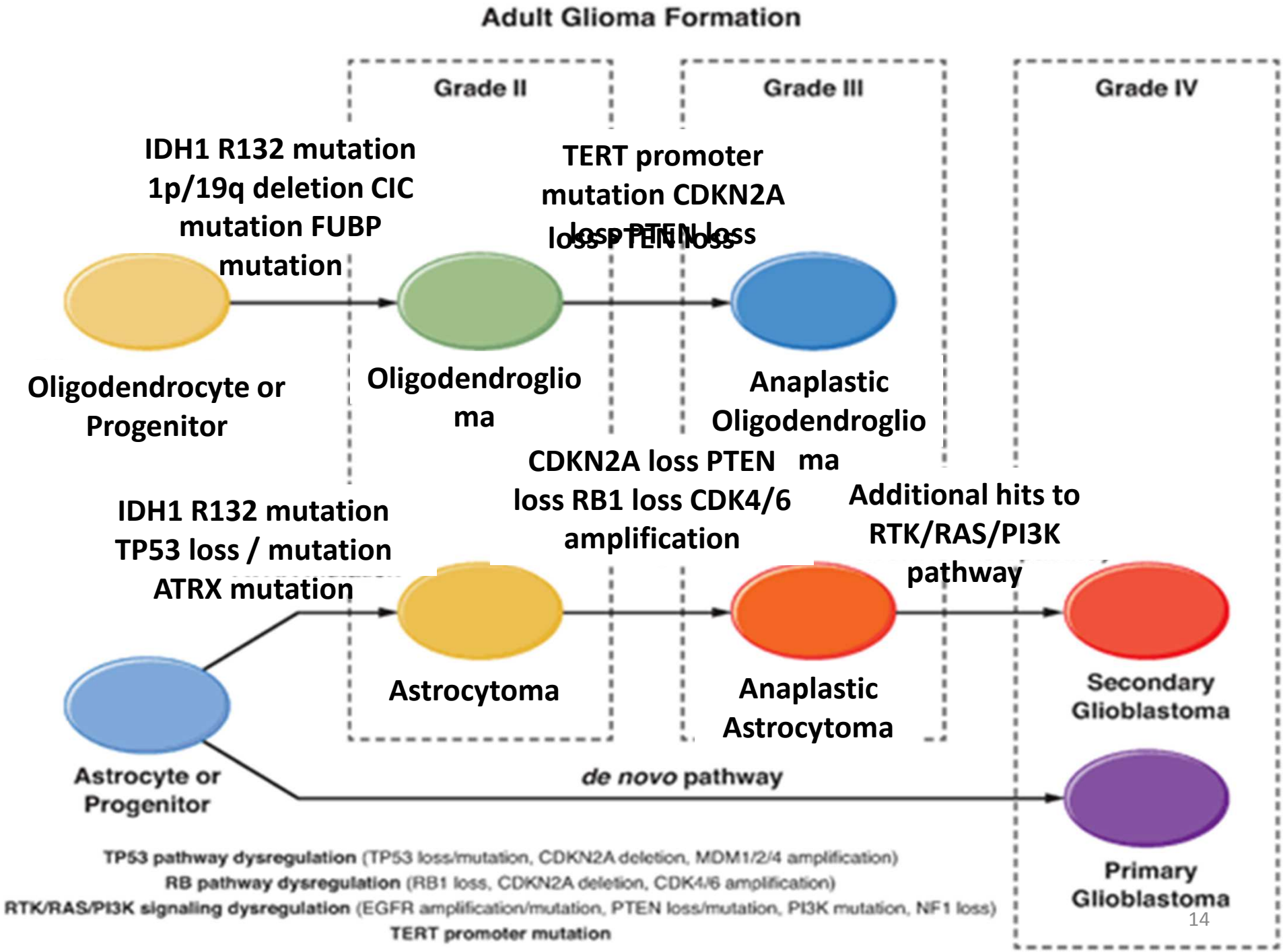
- Meningiomas 36.1%
- Gliomas 28% of all tumors and 80% of malignant tumors

Pituitary 15.1%

Glioblastom 15.4%



Of all gliomas Glioblastom 54.7%


Adult Glioma Formation
Grade II
Grade III
Grade IV
IDH1 R132 mutation
1p/19q deletion CIC
mutation FUBP
mutation
TERT promoter
mutation CDKN2A
loss PTEN loss
Oligodendrocyte or
Progenitor
Oligodendroglio
ma
Anaplastic
Oligodendroglio
ma
CDKN2A loss PTEN
loss RB1 loss CDK4/6
amplification
IDH1 R132 mutation
TP53 loss / mutation
ATRX mutation
Additional hits to
RTK/RAS/PI3K
pathway
Astrocytoma
Anaplastic
Astrocytoma
Secondary
Glioblastoma
Astrocyte or
Progenitor
de novo pathway
Primary
Glioblastoma
TP53 pathway dysregulation (TP53 loss/mutation, CDKN2A deletion, MDM1/2/4 amplification)
RB pathway dysregulation (RB1 loss, CDKN2A deletion, CDK4/6 amplification)
RTK/RAS/PI3K signaling dysregulation (EGFR amplification/mutation, PTEN loss/mutation, PI3K mutation, NF1 loss)
TERT promoter mutation

Overview of Brain Tumors

COMMON CNS TUMORS AND CORRESPONDING GENE ALTERATIONS

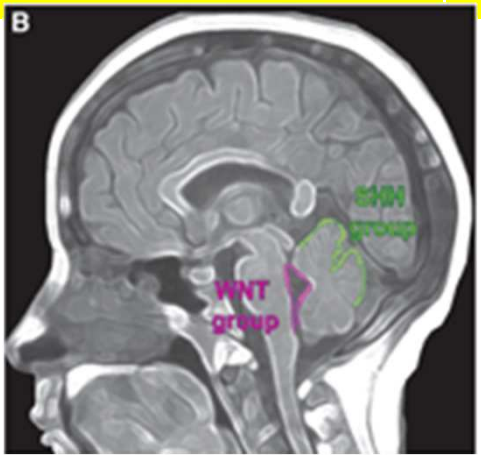
Common Adult Tumors	Frequent Gene and Chromosomal Alterations
Grade II astrocytoma	IDH1 R132, TP53, ATRX
Grade III anaplastic astrocytoma	IDH1, TP53-MDM2/4, CDKN2A, CDK4/6-RB, PTEN
Grade IV glioblastomas	TP53-MDM2/4, CDKN2A, CDK4/6-RB, EGFR, PTEN, NF1, RTK/RAS/PI3K pathway
Grade II oligodendroglioma	IDH1 R132, chromosome 1p-19q translocations, CIC , FUBP1
Grade III oligodendroglioma	IDH1, chromosome 1p-19q translocations, CIC , FUBP1, TERT promoter, CDKN2A,PTEN
Meningioma	NF2 (posterior & lateral), TRAF7 (anterior), AKT1, KLF4 (central) Sonic hedgehog signalling,
Ependymoma	Supratentorial: CDKN2A deletion, amplification of EPHB2 Spinal: NF2/ chromosome 22 loss.

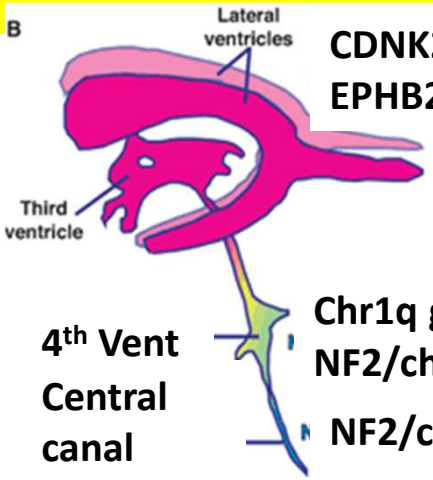
Overview of Brain Tumors

COMMON CNS TUMORS AND CORRESPONDING GENE ALTERATIONS

Common Pediatric Tumors	Frequent Gene and Chromosomal Alterations
Medulloblastoma :	MYCC, MYCN, (Poor Prognosis) chromosome 17p deletions, CTNNB1, DOX3X, SMARCA4, MLL2 (Good prognosis : WNT group), TP53, SUFU, SMO, MLL2, PTCH, KDM6A (Intermediate prognosis : SHH group)
Ependymoma	Lateral infratentorial: NF2/chromosome 22 loss, Medial infratentorial: chromosome 1q gain
Pilocytic astrocytoma	KIAA1549-BRAF fusion rearrangements

<u>Medulloblastoma</u>



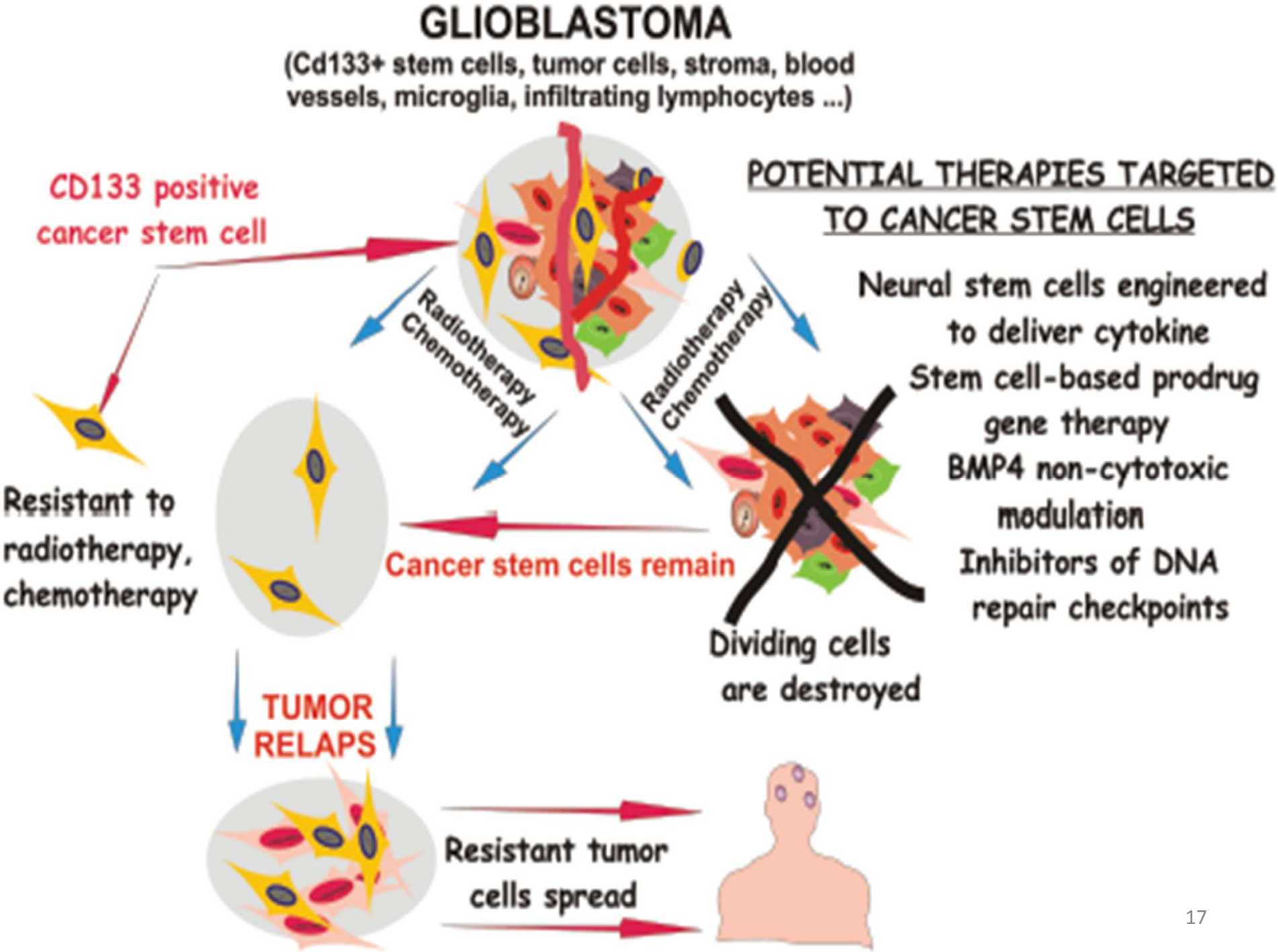


CDNK2A delet
EPHB2 amplification

<u>Ependymoma</u>

Chr1q gain (medial)
NF2/chr22 loss (lateral)

NF2/chr22 loss


GLIOBLASTOMA
(Cd133+ stem cells, tumor cells, stroma, blood vessels, microglia, infiltrating lymphocytes ...)
CD133 positive cancer stem cell
POTENTIAL THERAPIES TARGETED TO CANCER STEM CELLS
Radiotherapy Chemotherapy
Radiotherapy Chemotherapy
Neural stem cells engineered to deliver cytokine
Stem cell-based prodrug gene therapy
BMP4 non-cytotoxic modulation
Inhibitors of DNA repair checkpoints
Resistant to radiotherapy, chemotherapy
Cancer stem cells remain
Dividing cells are destroyed
TUMOR RELAPS
Resistant tumor cells spread

GBM Sub-classification Schemes

Primary (de Novo, ~90%)
- Elderly (>62)
- EGFR amplification
- PTEN inactivation
- CDKN2A deletion
- Shorter survival

Secondary (~10%)
- Younger (<40)
- TP53 alteration
- IDH1 mutation
- Chromosome 19 loss
- Longer survival

Mesenchymal
- 29%
- 57.7 yrs
- NF1 (+)
- IDH1 (-)

Classical
- 27%
- 55.7 yrs
- EGFR (+)
- TP53 (-)

Proneural
- 28%
- 51.8 yrs
- TP53 (+)
- IDH1 (+)

Neural
- 16%
- 62.8 yrs

	IDH 1/2 Mutation	1p/19q Co-deletion	MGMT promoter methylation
Diffuse astro (GRII)	70%-80%	15%	40%-50%
Oligod/astro (GRII)	70%-80%	30%-60%	60%-80%
Astro(GR III)	50%-70%	15%	50%
Oligod/astro (GR III)	50%-80%	50%-80%	70%
GBM (GR IV)	5% - 10%	<5%	35%
Diagnostic role	DD glioma vs.gliosis Typical for transformed LGG	Pathognomonic for oligodendroglioma	None
Prognostic role	Protracted natural history in IDH-mutated tumors	Protracted natural history in 1p/19q codeleted tumours	Prognostic for AG (+/- with IDH mutations) treated with RT / CT
Predictive role	Absence of mutation suggests predictive role for MGMT promoter methylation	Prolongation of survival with early chemotherapy in 1p/19-co-deleted OD	Predictive in GBM for benefit from alkalating CT Elderly GBM: MGMT-methyl = TMZ MGMT – unmethyl=RT

Overview of Brain Tumors

ANATOMIC LOCATION AND CLINICAL CONSIDERATIONS

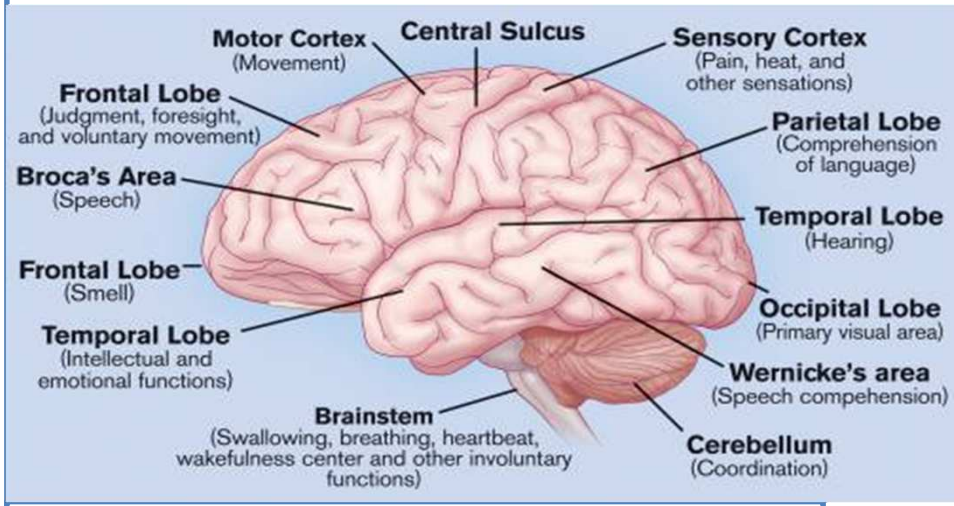
- Increased intracranial pressure
- Seizures
- Physiological deficits specific to location
- Neurocognitive deficits
- Endocrinal dysfunction

Overview of Brain Tumors

Clinical presentation

Frontal Lobe
- Behavioral and emotional changes
- Impaired judgment
- Impaired sense of smell
- Memory loss
- Hemiplegia
- Cognitive dysfunction
- Vision loss
- Papilledema

Seizures :
20% in supratent. tumors , 70% in slow growing, May antidate the clinical diagnosis by months



Brainstem
- Behavioral and emotional changes
- Difficulty speaking and swallowing
- Drowsiness
- Headache
- Hearing loss
- Muscle weakness on one side of the face
- Hemiparesis
- Uncoordinated gait
- Vision loss, ptosis, strabismus
- Vomiting

Parietal Lobe
- Impaired speech
- Inability to write
- Lack of recognition
- Seizures
- Spatial disorders

Occipital Lobe

Temporal Lobe
- Often asymptomatic
- Impaired speech
- Seizures
- Homonymous superior quadrantanopsia
- Auditory hallucinations
- Abnormal behavior

DIAGNOSTIC TESTS

- **Magnetic Resonance Imaging :** Most useful imaging studies are T1-weighted sagittal images, gadolinium (Gd)-enhanced and unenhanced T1 axial images, and T2-weighted axial images
- **CT Scan**
- **Newer Imaging Modalities**
  - Magnetic resonance spectroscopy,
  - Dynamic contrast-enhanced MRI,
  - Diffusion-perfusion MRI, and
  - Functional MRI
  - Quick brain MRI
- **PET**

DIAGNOSTIC TESTS

- **Cerebrospinal Fluid Examination**

  Medulloblastoma, ependymoma, choroid plexus carcinoma, lymphoma, and some embryonal pineal and suprasellar region tumors have high likelihood of spreading to CSF.

- **Biopsy (craniotomy / stereotactic)**
- **IHC**
- **Cytogenetics**

Management of Brain Tumors

- **Surgery**
- **Radiation Therapy**
- **Chemotherapy and targeted agents**

Surgical Procedures

- Biopsy
- Total Resection
- Surgical Debulking
- CSF Diversion
- Re-resection

RADIOTHERAPY:

Radiobiologic and Toxicity Considerations

The process of radiation injury depends on

Technical factors: dose, volume, fraction size, specific target cell population,

- Secondary mechanisms of expression of injury such as vascular leak causing edema, vascular endothelial loss resulting in hypoxic injury,
- Reactive gliosis,
- ? Host factors.

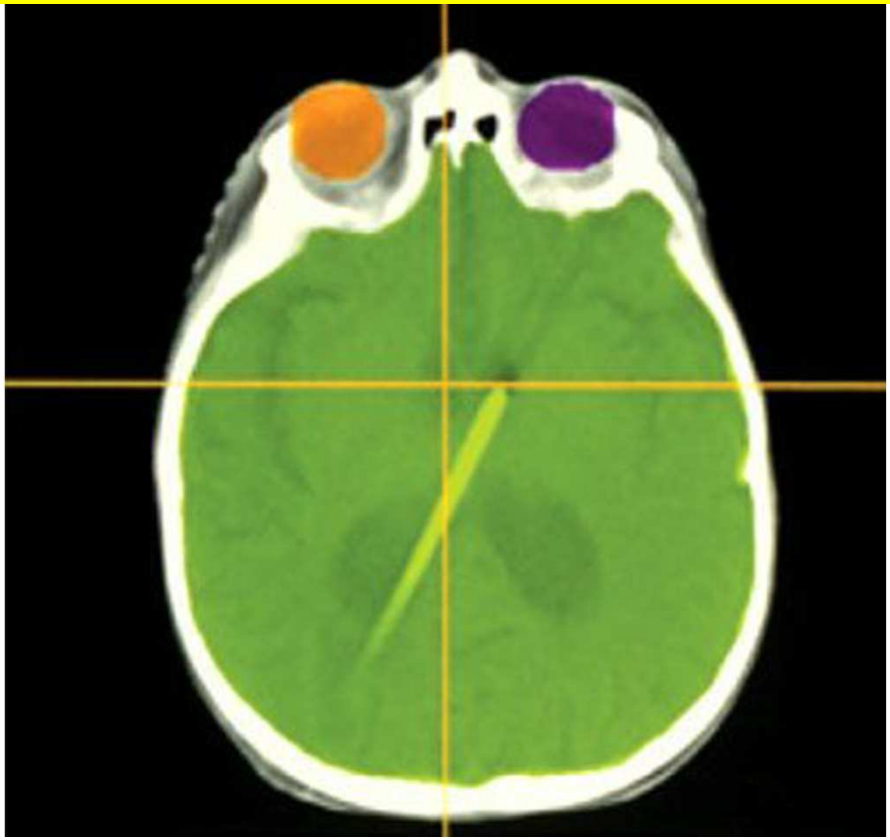
Some structures (e.g., optic chiasm, hypothalamus, lacrimal gland, lenses, etc.) appear to be substantially more sensitive to radiation than others.

Radiotherapy Techniques

- Partial-brain irradiation, 3DCRT, IMRT, IGRT
- Whole-brain radiotherapy (WBRT),
- Cranio-spinal irradiation (CSI),
- Stereotactic radiosurgery (SRS),
- Fractionated stereotactic radiotherapy (FSRT),
- Brachytherapy, (less commonly)
- Proton beam thearpy (3DPT, IMPT).

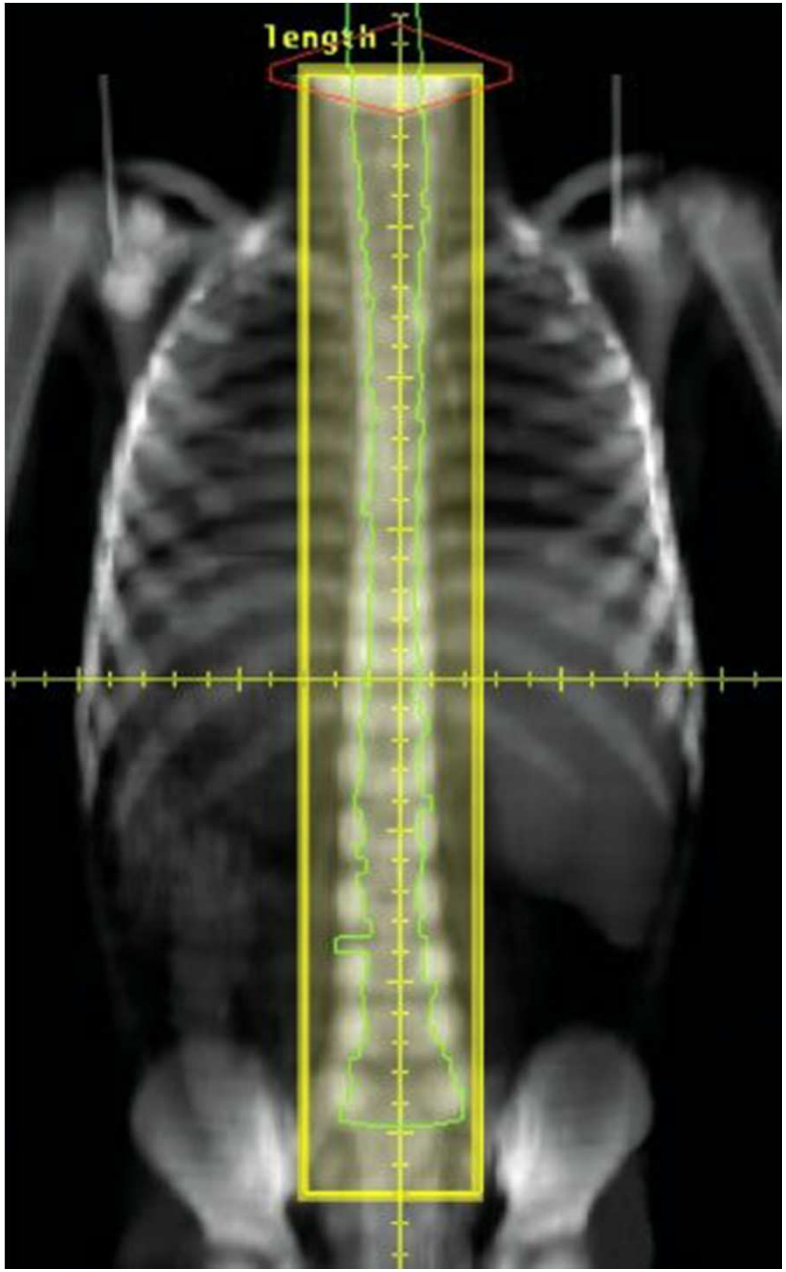
Overview of Brain Tumors

Importance of CT simulation



CT SIMULATION ADVANTAGE : Coverage of meninges in subfrontal region and sparing of lens in CSI.

Overview of Brain Tumors

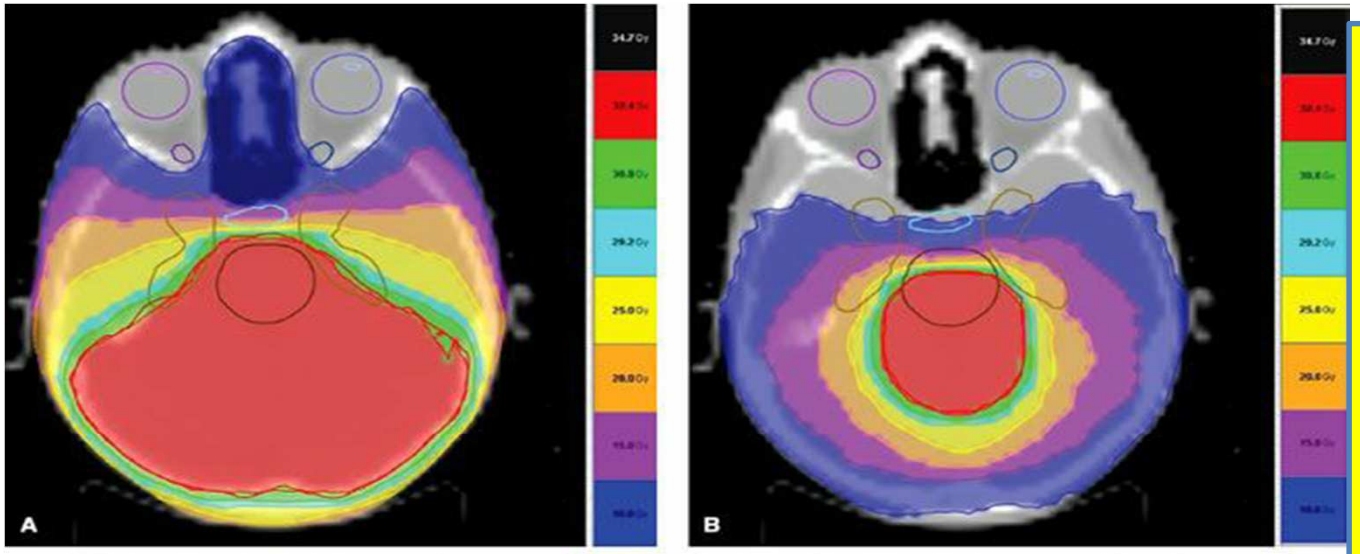


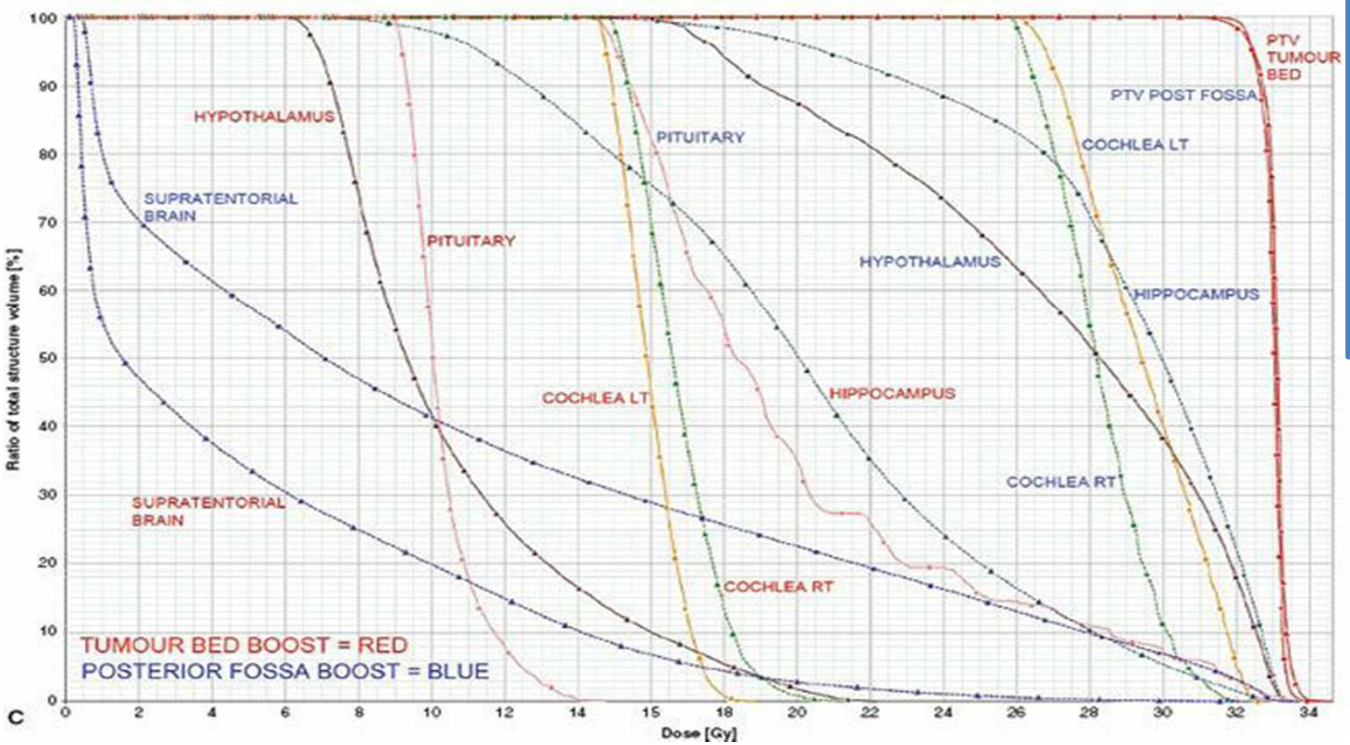
CT SIMULATION

- Contouring of the cord and overlying meninges that extend laterally to the lateral aspect of the spinal ganglia results in a ↓ field width than one based on bony anatomy.

- The addition of shielding further reduces the volume of normal tissues included in the treated volume.

Overview of Brain Tumors



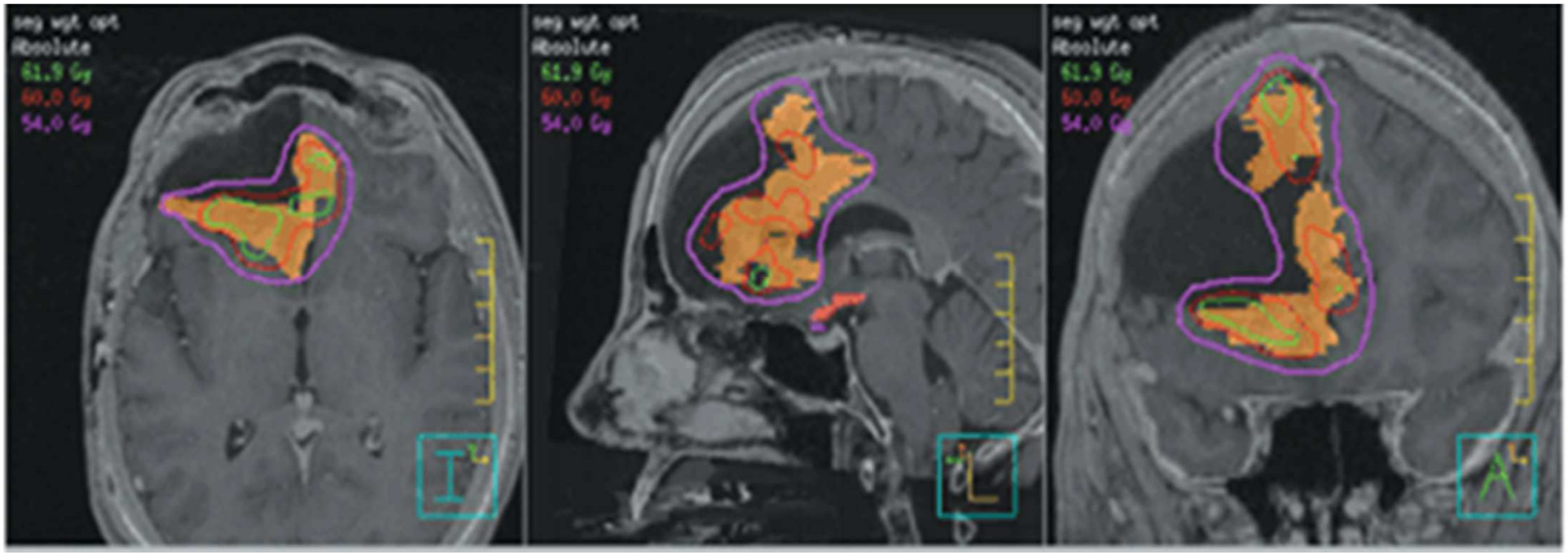


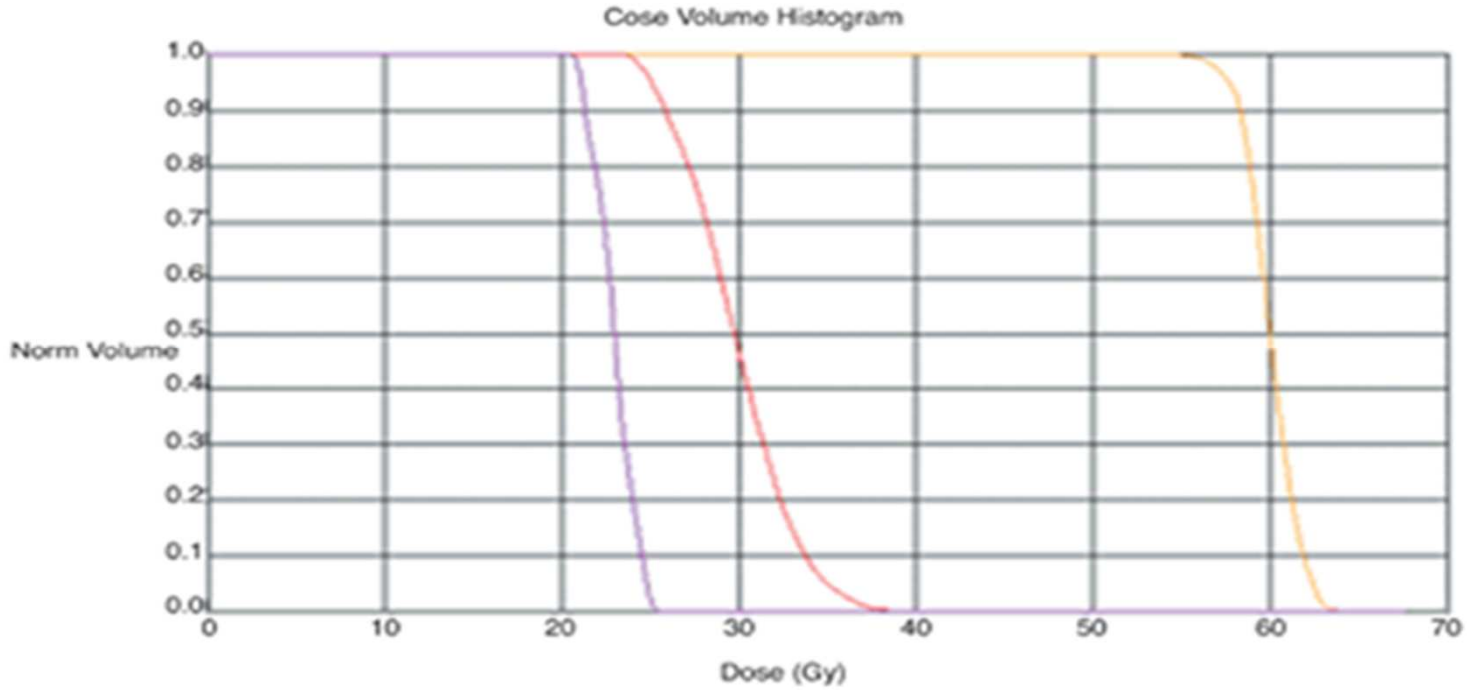
Axial images of an **Image Guided RT** for a whole posterior fossa

(A) and a reduced-volume posterior fossa boost

(B) for a patient with medulloblastoma.

(C) DVH show significant sparing of organs at risk with the reduced-volume boost.

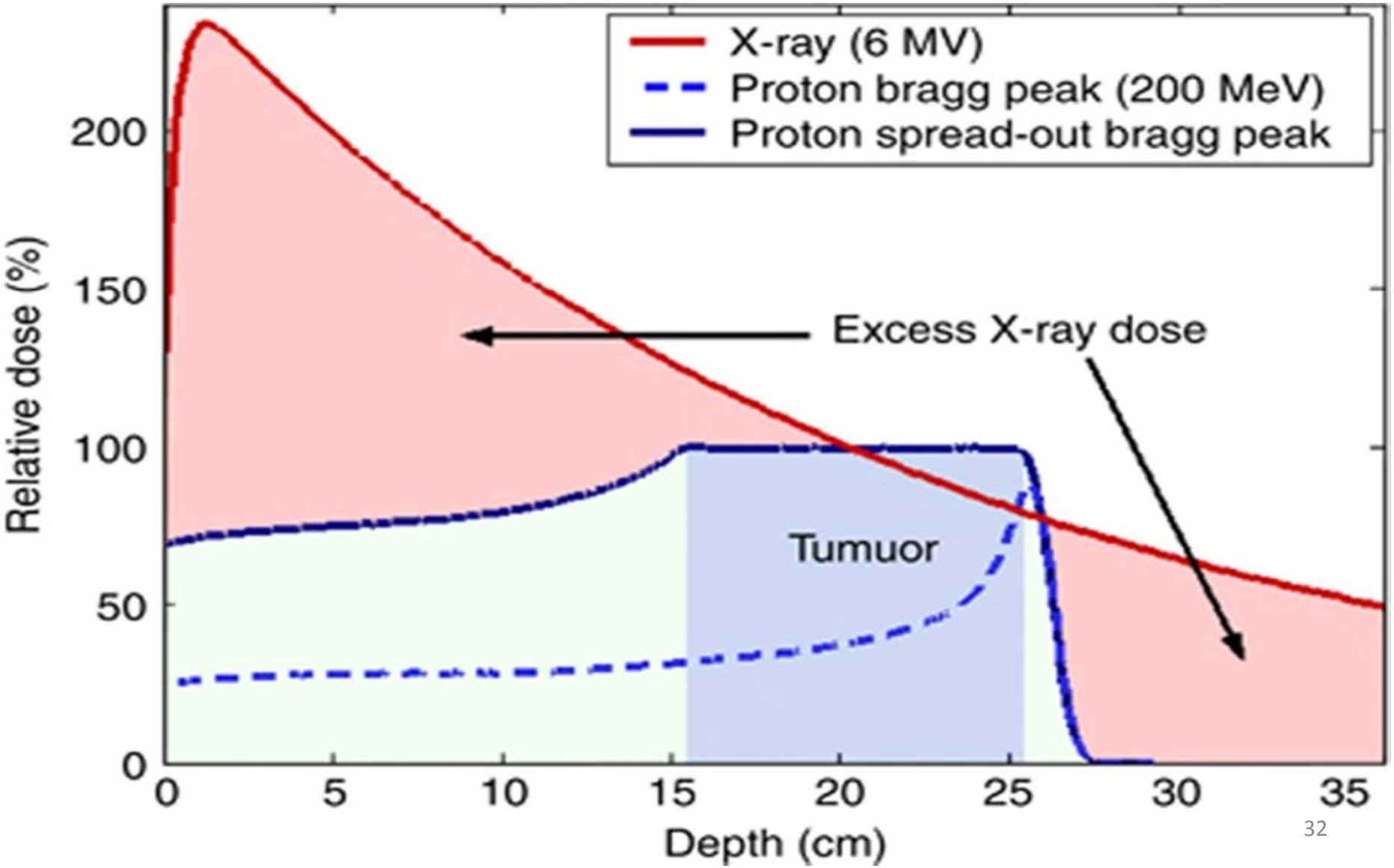


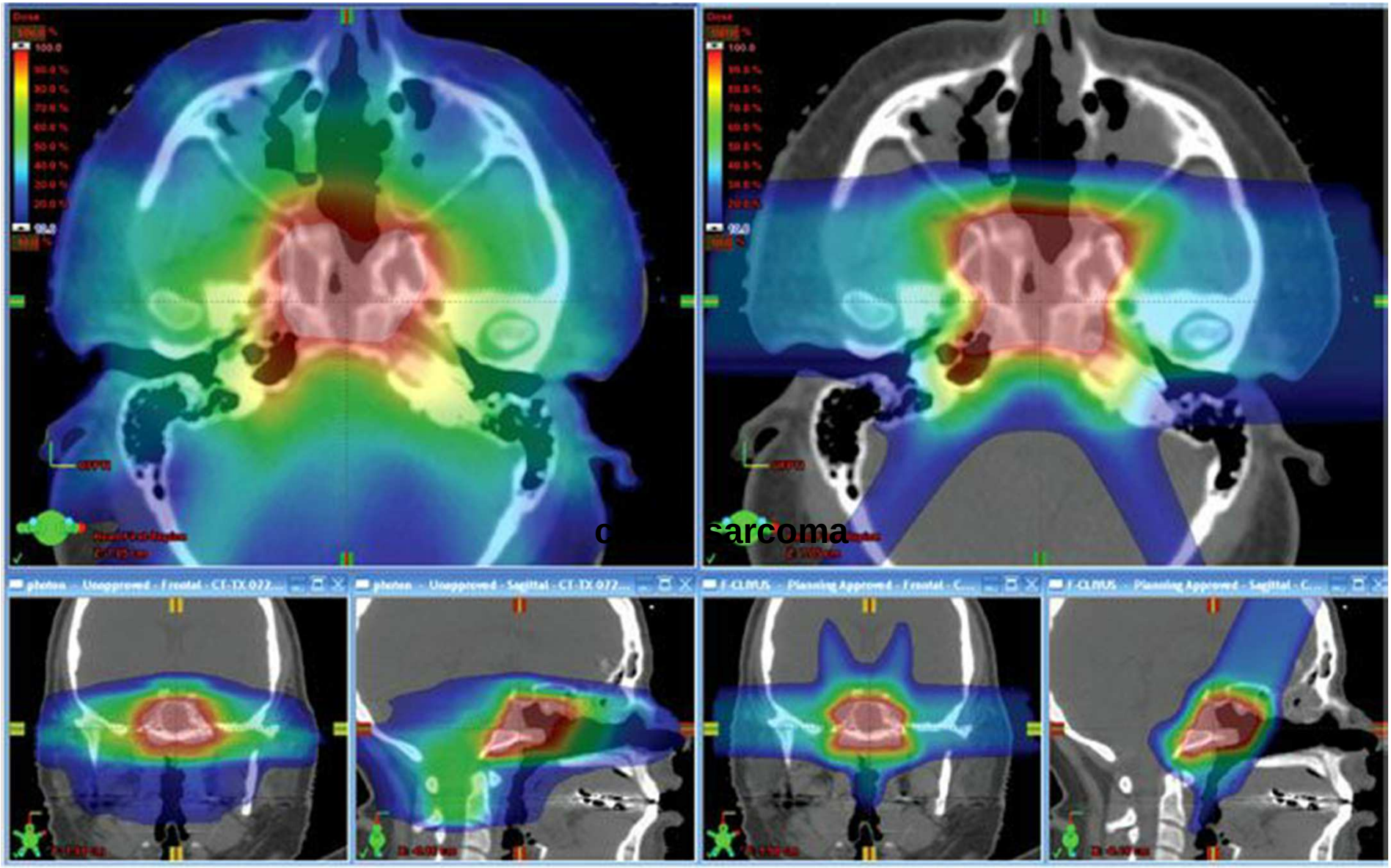


IMRT SPARES CRITICAL ORGANS Example Opticchiasma & pituitary in this case

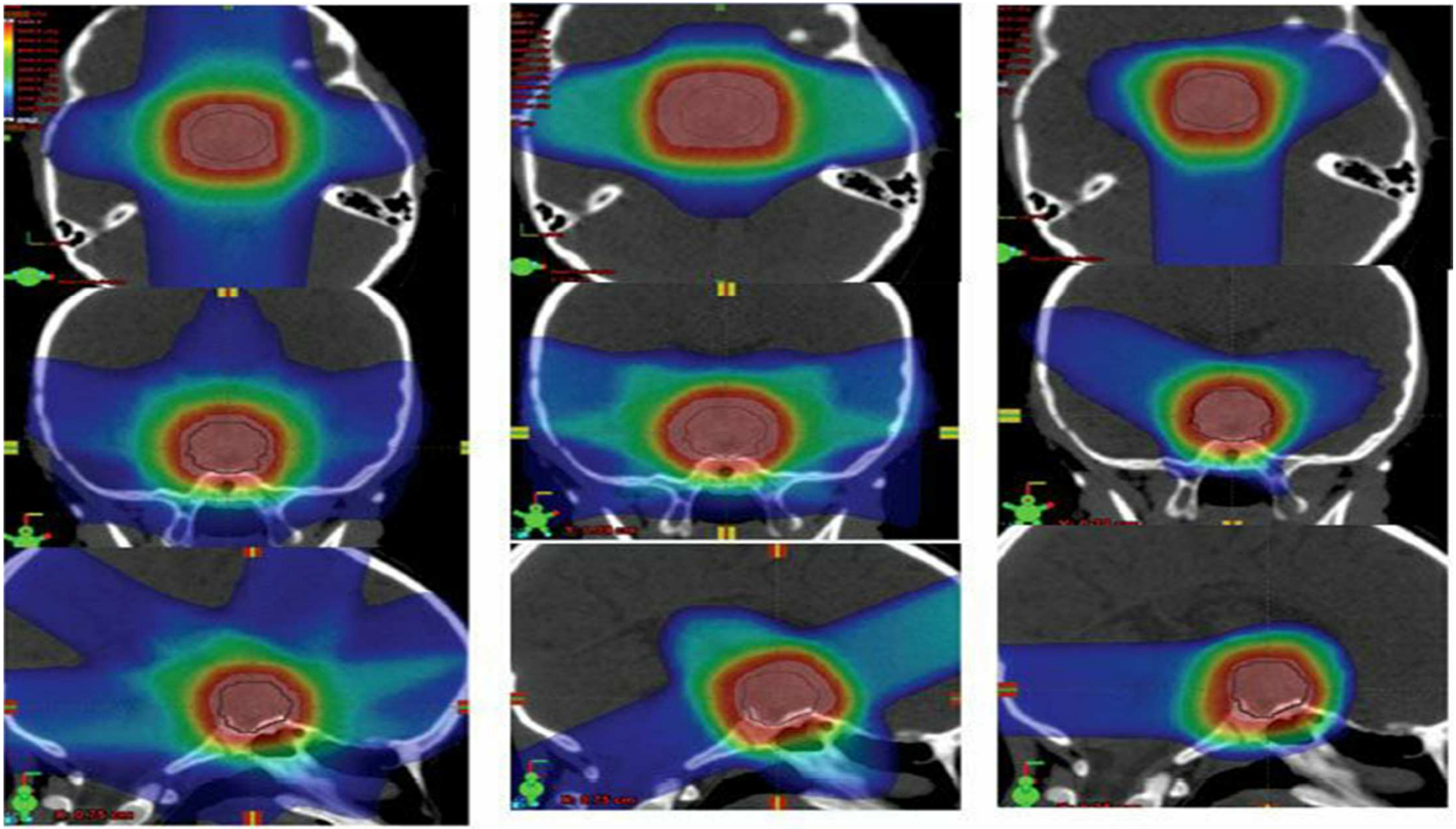
Overview of Brain Tumors

X-Rays vs. Proton

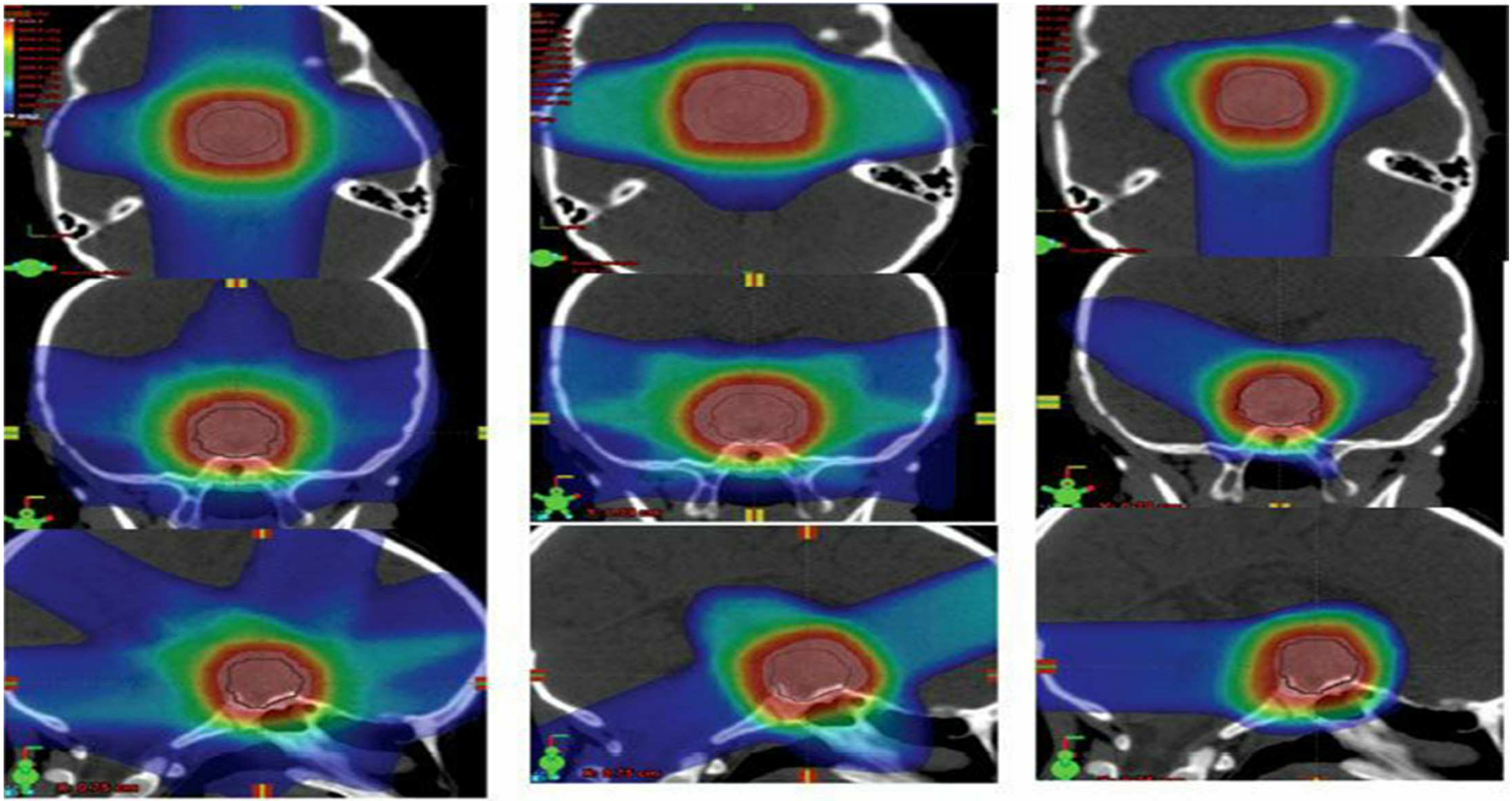




Clivus sarcoma. The maximum and mean relative doses to the brainstem are 71% and 42% with IMRT compared to 59% and 11% with protons, respectively (sharp dose gradient with protons) .



- Mean body and brain doses are 1/3rd with Protons than IMRT or SRT.
- The mean right cochlear dose is 807 cGy with IMRT, 388 cGy with SRT, and 7 cGy (RBE) with protons. The mean left cochlear dose is 792 cGy with IMRT, 887 cGy with SRT, and 5 cGy (RBE) with protons.



The total-body V_{10} and total body integral dose are 37.2% and 0.223 Gy-m^3 with 3DCRT compared with 28.7% and 0.185 Gy-m^3 with proton therapy, respectively.

Overview of Brain Tumors

General principle of treatments in adult Low Grade Gliomas (LGG)

Surgery :

Except deep seated lesions such as pontine glioma
Complete resection not achievable frequently

Radiotherapy :

RT immediately or after progression
EORTC TRIAL 22845 – 7.4 vs .7.2 yrs OS. but PFS 5.3 vs. 3.4
Conclusion in doubt

No difference in survival of dose escalation

Surveillance

Overview of Brain Tumors

Risk factors for survival in Low Grade Gliomas

- **Age (<40 vs, ≥ 40 years old)**
- **Tumor largest diameter (<6 cm vs. ≥ 6 cm)**
- **Tumor crossing midline (yes vs. no)**
- **HPE tumor type (oligodendroglioma or mixed vs. astrocytoma)**
- **Neurologic deficit present preoperatively (absent vs. present)**

Survival

Low risk (0-2)	**7.8 (6.8 - 8.9) yrs.**
High risk (3-5)	**3.7 (2.9 - 4.7) yrs.**

Overview of Brain Tumors

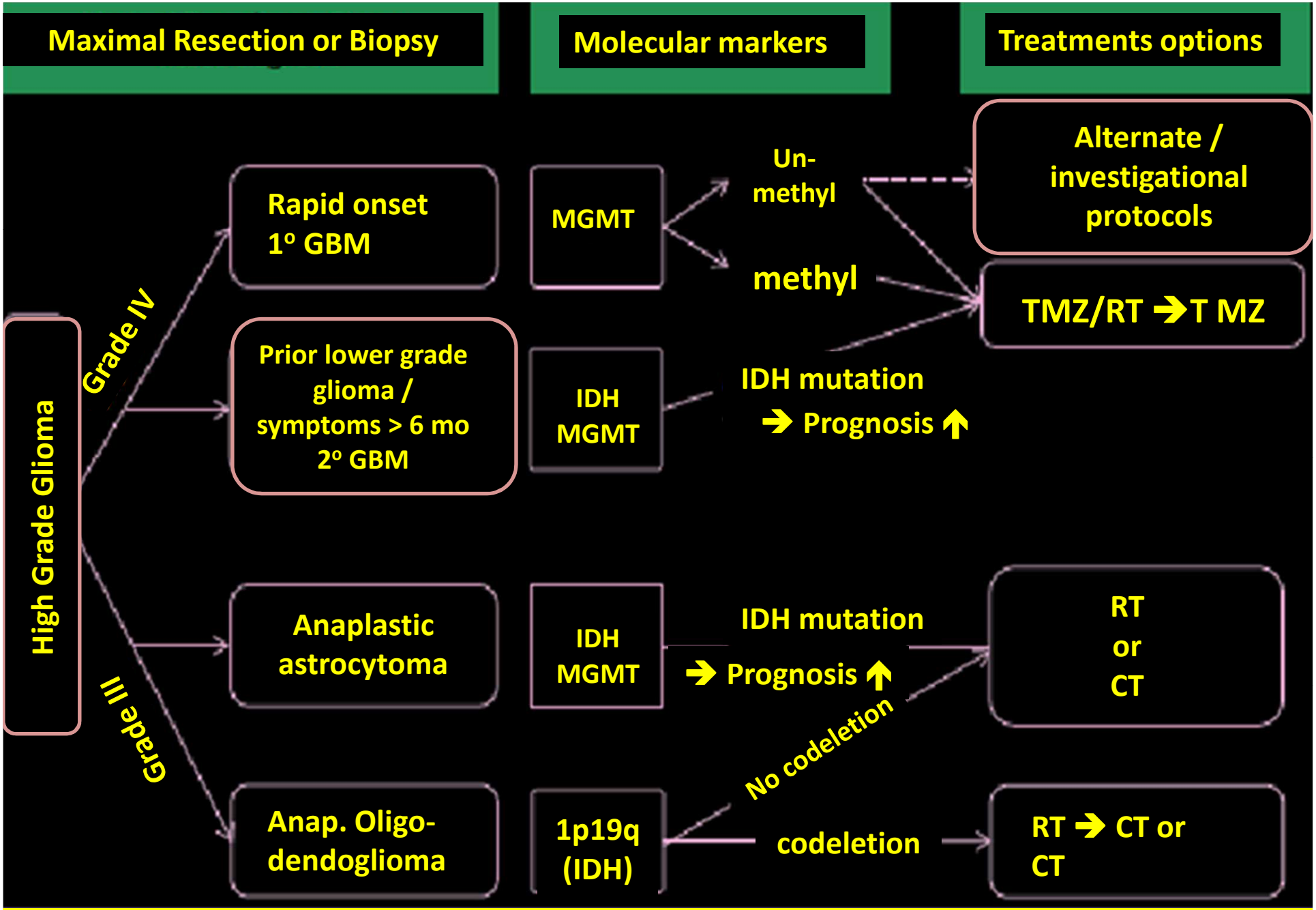
Maximal surgical resection compatible with A good neurological outcome

Follow-up with routine imaging

Second surgical resection (if feasible) at time of progressive disease

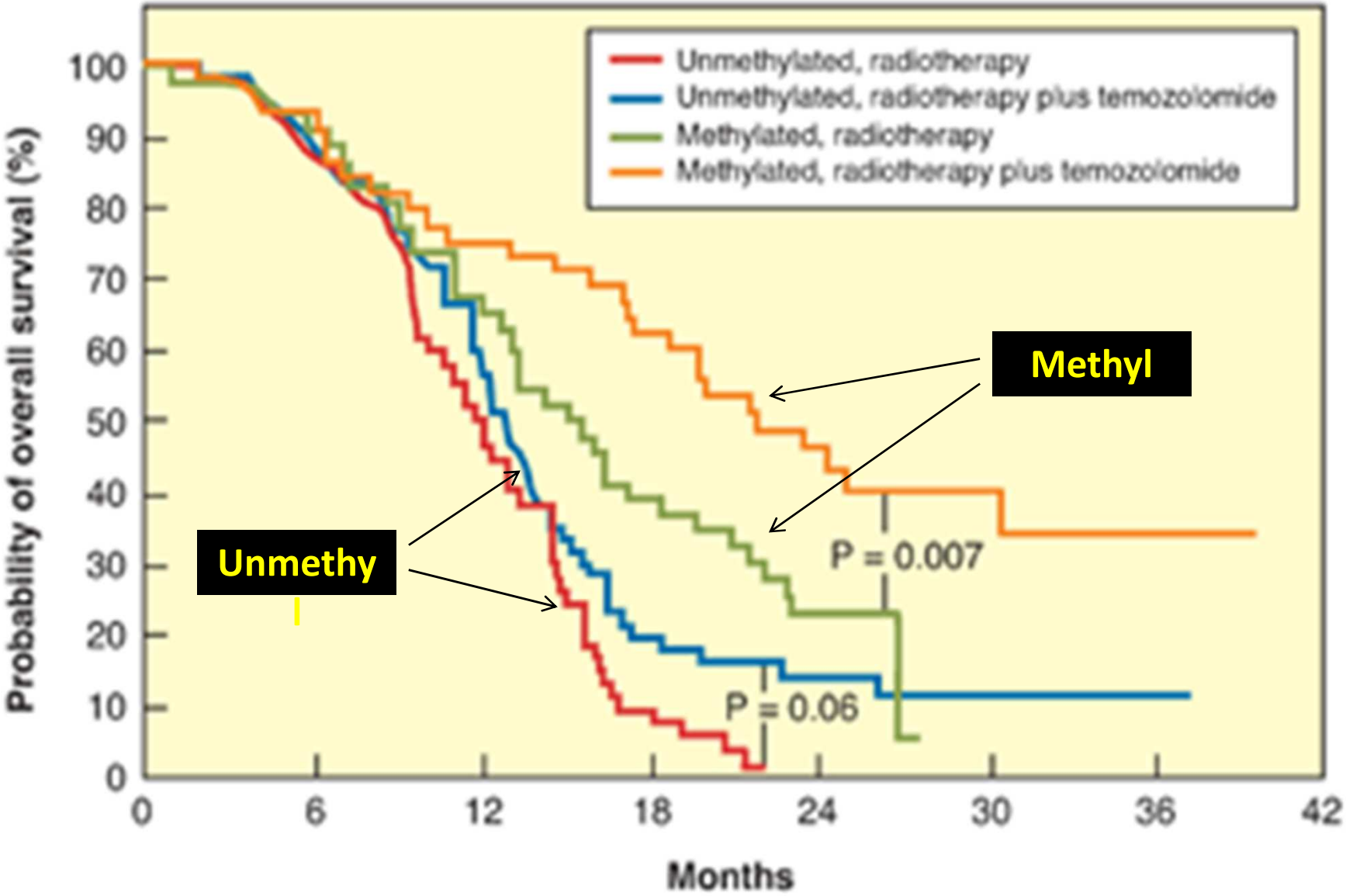
Radiotherapy (or chemotherapy for children ≤ 10 yers and children of all ages with NF-1) at time of progressive disease that is not resectable

An algorithm for the management of patients with low-grade astrocytoma Children & Adults



High Grade Glioma Algorithm (NOA-04, EORTC, RTOG)

Overview of Brain Tumors



Radiotherapy vs. Radio-chemotherapy in GBM - NEJM 2005

Overview of Brain Tumors

Summary of Features of CNS Tumors in Adults

Type :	Location :	Clinical F	Survival	RT	CT
A*	Supratent	slow growing	5 yr MS	Yes	At recc.
AA	Supratent	Rapid growing	2.5 yr MS	Yes	Yes
GBM*	Supratent	↑ Malignant	1 yr MS	Yes	Yes
OG*	Supratent	↑ Seizures	5 yr MS	Yes	Yes
MN	convexity, clival	Women ↑	Long term	Yes	Rare
LYMP	Multifocal, periventricular	↑ CSF/ occular Diss.	3-5 Yr MS	Yes	Yes

A*=Astrocytoma (adult>child), AA=Anaplastic astrocytoma, GBM=Glioblastoma (elderly), OG*=Oligodendroglioma (any age), MN=Meningioma, LYMP= Lymphoma, Diss= Dissamination

Overview of Brain Tumors

Summary of Features of CNS Tumors in Childhood & Young Adults

Type :	Location :	Clinical F:	Survival	RT	CT
BSG*	Pons	Fatal	1 Yr MS	Yes	Seldom
PA*	Cerebellum hypothalamus	Cure with TR	80% 10 yr	in res	Yes
EPDM*	4th ventricle, cauda equina	Cure with TR, can diss. in CSF	70% 5 yr	Yes	Seldom
MDBM	Cerebellum	likely to diss. in CSF	70% - 80%	Yes	Yes
GERM*	Pineal & suprasellar	Sensitive to CT & RT	80% 5Yr	Yes	Yes
NGERM	" "	Marker+	25% 5Yr	Yes	Yes

BSG=brain stem glioma,PA*=Pilocytic astrocytoma (child>adult), EPDM*=Ependymoma (child, adult), MDBM= medulloblastoma (child>adult), GERM = Germinoma, NGERM=Nongerm cell tumor (2nd & 3rd decade)

Ependymal Tumors

- **Grade I and II ependymal tumors**
  - **Standard treatment options:**
    - **Surgery only if totally resectable.**
    - **Surgery → RT if residual**

Anaplastic ependymomas

- **Standard treatment options:**
  - **Surgery plus radiation therapy.**

- **Children younger than 3 yrs Chemotherapy**

Medulloblastomas

- **Standard treatment options:**
  - **Surgery plus craniospinal radiation therapy for good-risk patients.**
- **Treatment options under clinical evaluation:**
  - **Surgery plus craniospinal radiation therapy and various chemotherapy regimens are being evaluated for poor-risk patients.**
- **Medulloblastoma occurs primarily in children, but it also occurs with some frequency in adults**

Meningeal Tumors

- **Standard treatment Options For Grade I :**
  1. **Active surveillance with deferred treatment, especially for incidentally discovered asymptomatic tumors.**
  2. **Surgery.**
  3. **SRS for tumors less than 3 cm.**
  4. **Surgery → RT in residual /recurrence.**
  5. **FRS for patients with unresectable tumors.**

Standard treatment Options For Grade II - III :

1. **Surgery → RT**