



# CNS CANCERS

**Vyshak Alva Venur, MD**

Assistant Professor of Medicine-Oncology

Neuro-Oncologist, SCCA, UW.

# Disclosures

- Scientific advisor for Seagen
- Editorial board member Practice Update, Elsevier

I **will** be discussion some investigational or off-label use of products during this presentation.

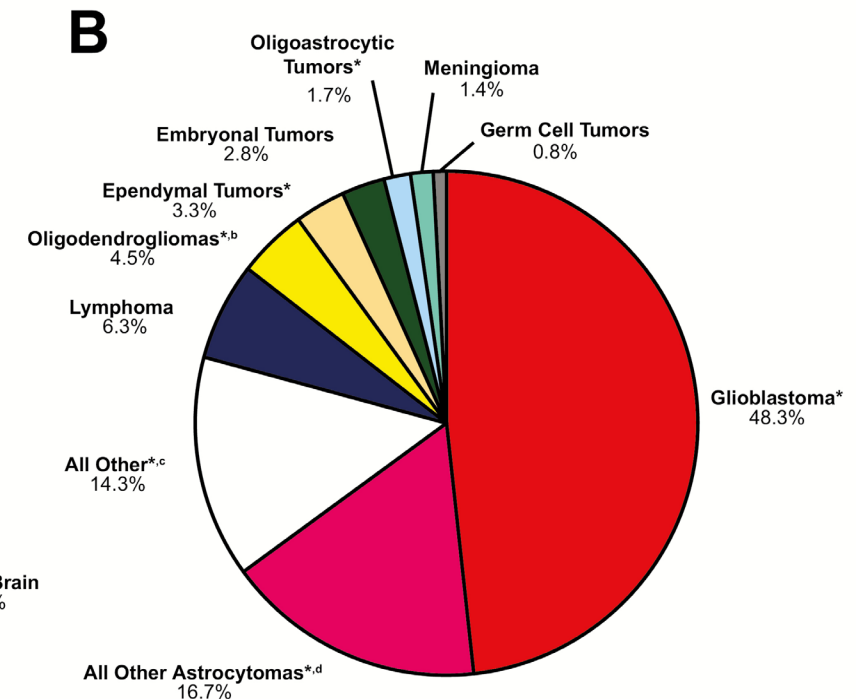
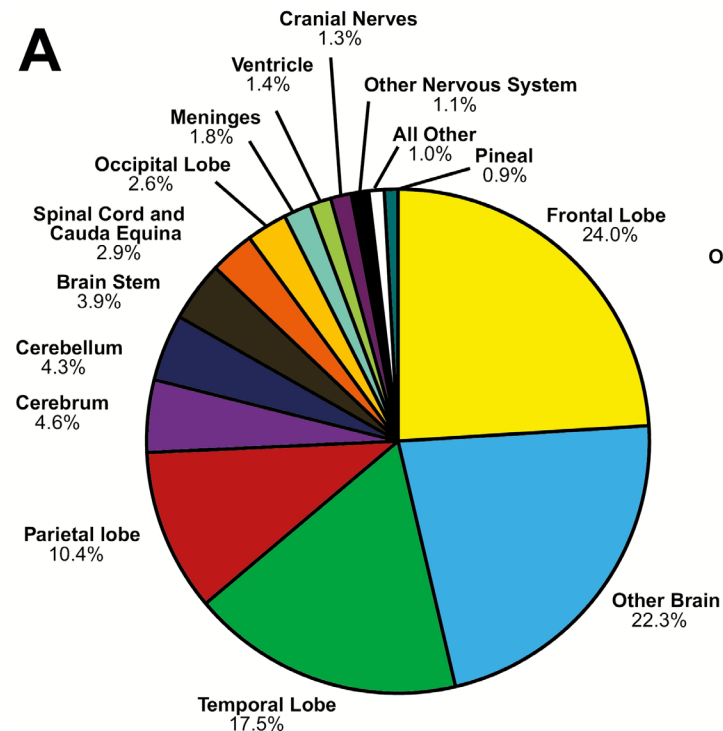
# Outline

- Epidemiology
- Classification of glioma
- General management of gliomas
- Glioblastoma
- Other glioma
- Meningioma
- Primary CNS lymphoma
- Brain metastases
- Leptomeningeal metastases

# Epidemiology of Brain Tumors

- Most common non- malignant CNS tumor: Meningioma (7.33/100,000)
- Most common malignant CNS tumor: Glioblastoma (3.19/100,000)
- Around 13,000 deaths/year
- 1.3% of all adult malignancies

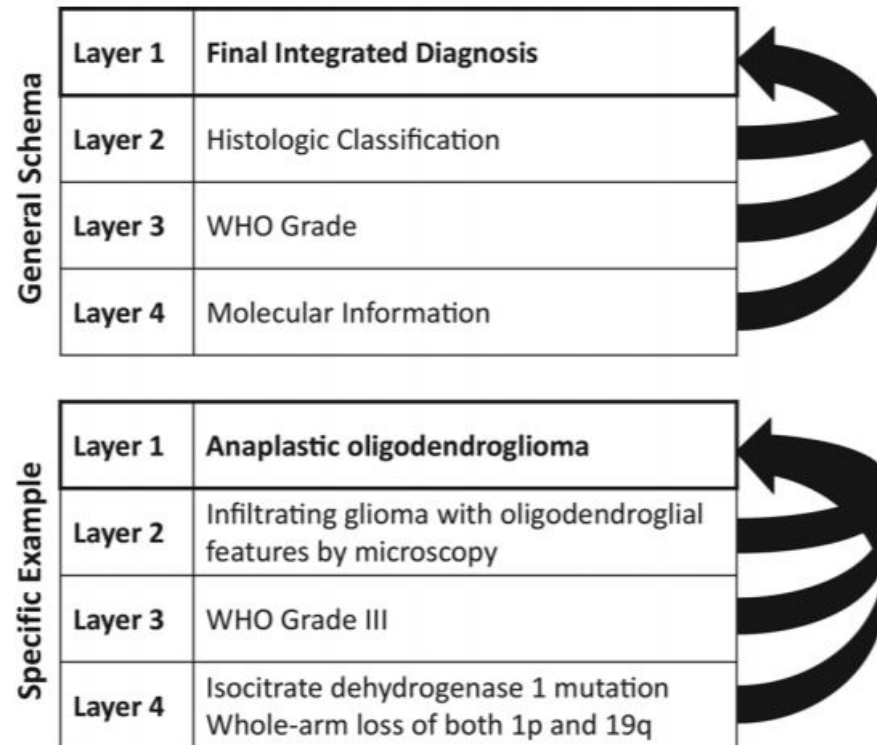
Distribution of malignant brain tumors- CBTRUS 2019



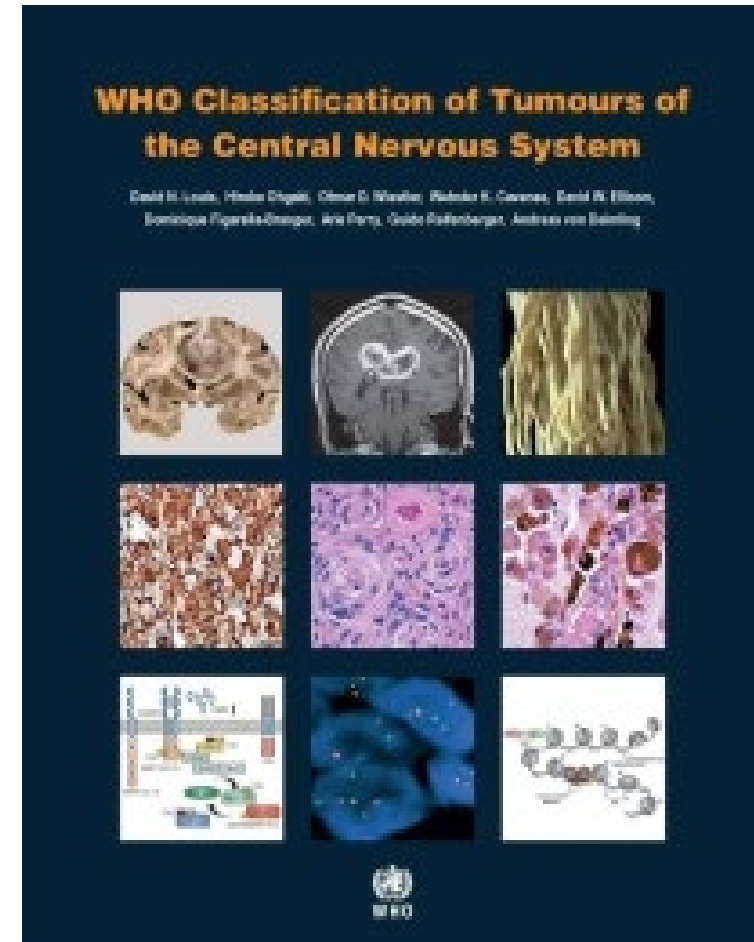
# Epidemiology of Brain Tumors-Risk Factors

- NF1, Li-Fraumeni, Lynch, tuberous sclerosis, prior radiation therapy (TBI/CSI for ALL in childhood lead to multiple meningiomas in adulthood)
- NO DEFINITIVE EVIDENCE WITH CELLPHONES/ BLUETOOTH
- NF1 diagnostic criteria:
  - Family history of NF1
  - Six or more cafe-au-lait skin lesions 5 mm or larger in pre-pubertal individuals, or 15 mm or larger in post-pubertal individuals
  - Presence of two or more neurofibromas of any type, or one or more plexiform neurofibromas
  - Axillary Freckling
  - Two or more Lisch nodules (pigmented lesions in the iris) .
  - Dysplasia of the sphenoid bone or dysplasia of long bones, often in the lower leg
  - Optic glioma

# Classification of Glioma



**Figure 1.** Layered diagnosis of CNS tumors. Integrated diagnosis (layer 1) comes last, only after layers 2–4 are defined. WHO grading criteria (layer 3) and relevant molecular information (layer 4) are separately defined for different histologic tumor types.



# Classification of Glioma

Glioblastoma: WHO Grade IV

Histology: Marked nuclear atypia, high mitotic activity, vascular proliferation, necrosis

Molecular features: TERT promoter mutation, EGFR amplification (EGFRvIII), PTEN alterations, ?BRAF mutations

Molecular features more important than histologic features

**MOLECULAR GBM:** *EGFR* amplification; losses of chromosome 10 (whole chromosome, 10p or 10q); gains of chromosome 7 (whole chromosome, 7p or 7q); *TERT* promoter mutations; homozygous deletion of *CDKN2A/B*

# Classification of Glioma

**WHO Grade I:** Pilocytic astrocytoma (BRAF/KIAA fusion), common in children, cured by gross total resection.

**WHO Grade II:** aka “Low-grade glioma” diffuse astrocytoma, diffuse oligodendroglioma, pilocytic xanthoastrocytoma (PXA) [low/no mitotic activity, no necrosis, no vascular proliferation]

**WHO Grade III:** Anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic PXA  
[high mitotic activity (>10/hpf), no necrosis, no vascular proliferation]



# Classification of Glioma-Molecular Features

## IDH mutation

- Present in >85% of low-grade glioma
- 5% of glioblastoma
- R132H point mutation
- **Favorable prognosis**
- Test by IHC for >55 years of age
- Less than 55 check PCR even if IHC negative

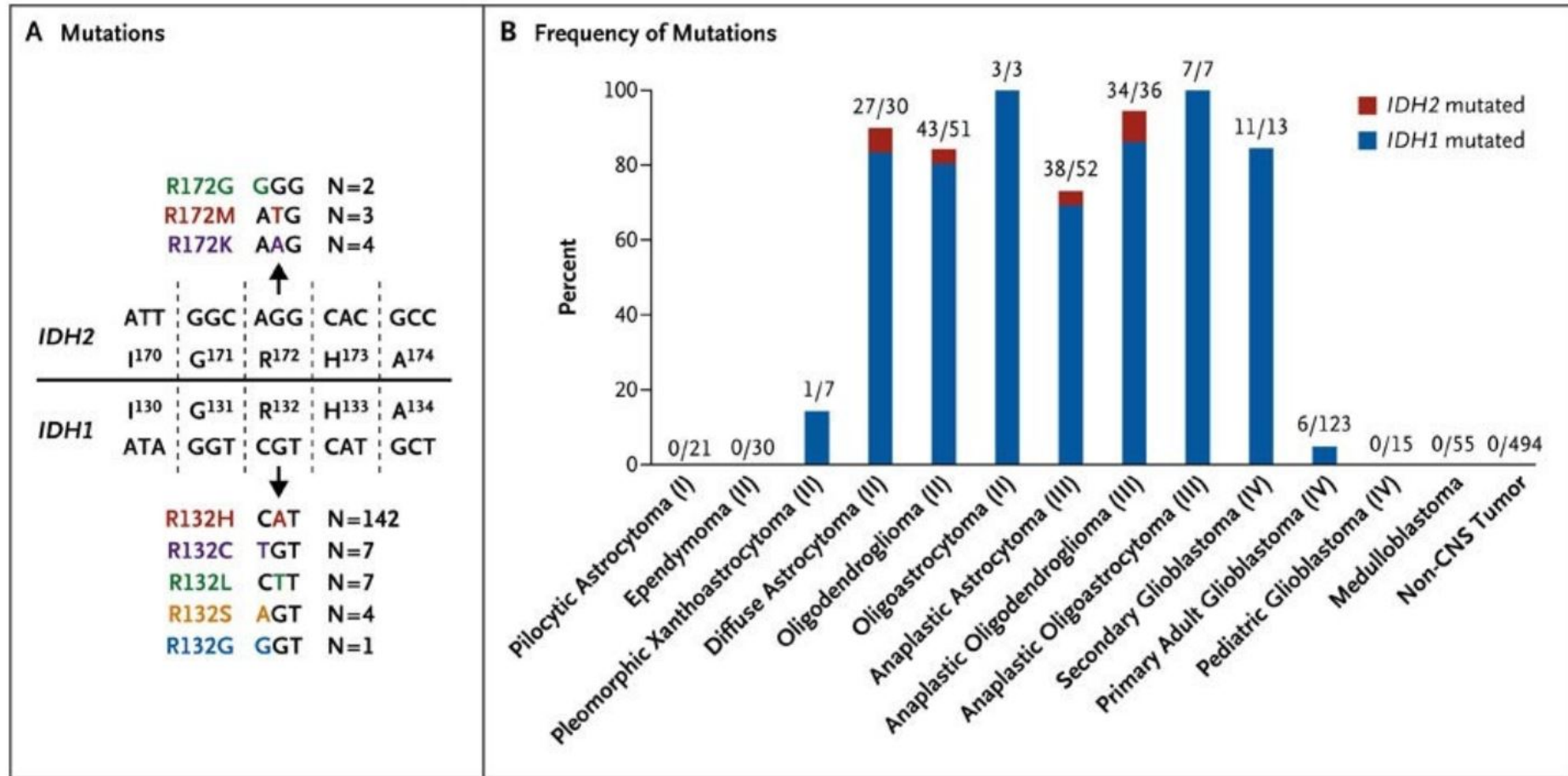
## 1p/19q co-deletion

- Diagnostic feature for oligodendroglioma
- **Favorable prognosis**
- FISH test

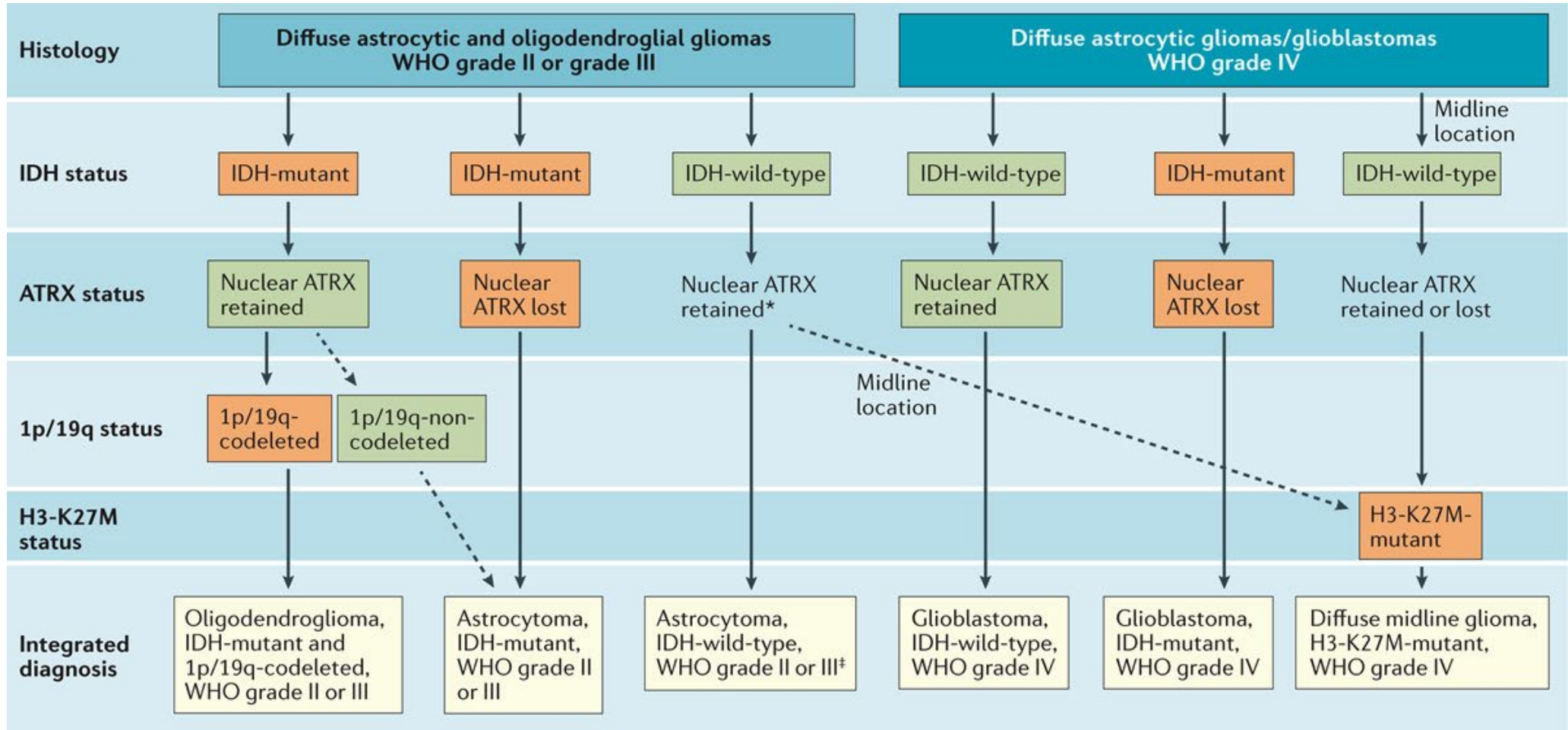
## BRAF mutation (V600E)

- PXA (grade II and III)
- Craniopharyngioma- papillary variant

# IDH Mutation



# Classification of Glioma



# General guidelines- Glioma

- Presentation: Focal neurologic symptoms, seizures, diffuse neuro symptoms
- Imaging of choice: MRI brain w/wo contrast
- No need for systemic imaging
- Surgery: “When tumor is the rumor, tissue is the issue”, debulking, symptom management, gross total resection has better prognosis
- Steroids: Dexamethasone is the steroid of choice. Use the lowest dose.

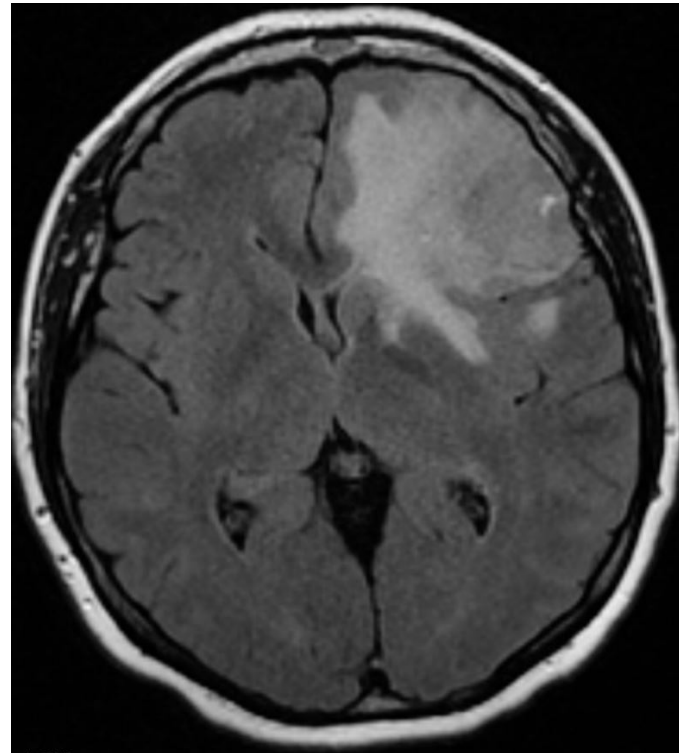
Watch for hyperglycemia, insomnia, mania, PJP prophylaxis with prolong use, negative prognostic factor if prolong use necessary

- Seizure management: Non enzyme inducers like levetiracetam, lacosamide, zonisamide
- DVT/PE: ↑frequency. Anticoagulation not contraindicated. LMWH preferred

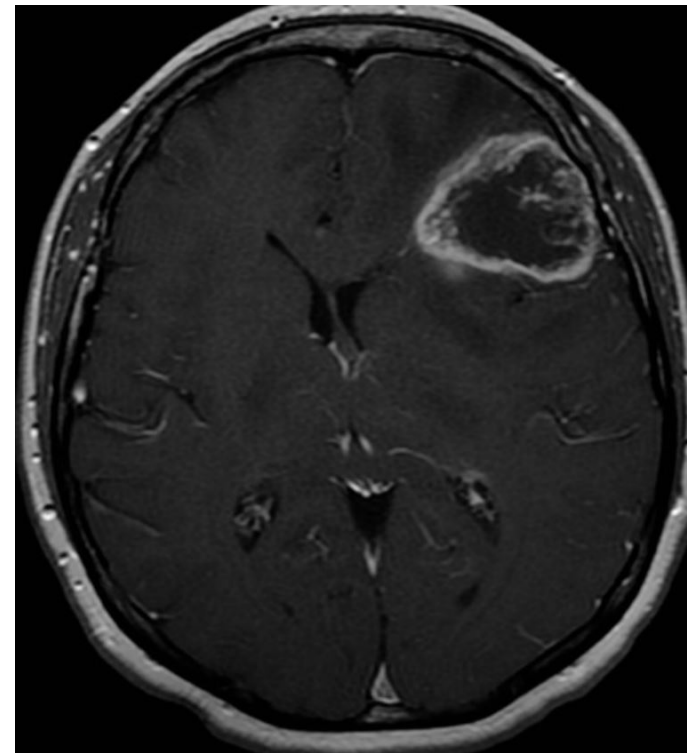
# Glioblastoma (GBM)

Age of onset: 50-60 years, frequent in men

Standard Treatment: Surgery → Concurrent chemoradiation therapy (60 Gy with temozolomide) → Maintenance temozolomide 150-200 mg/m<sup>2</sup> for five consecutive days every 28 days + TTF

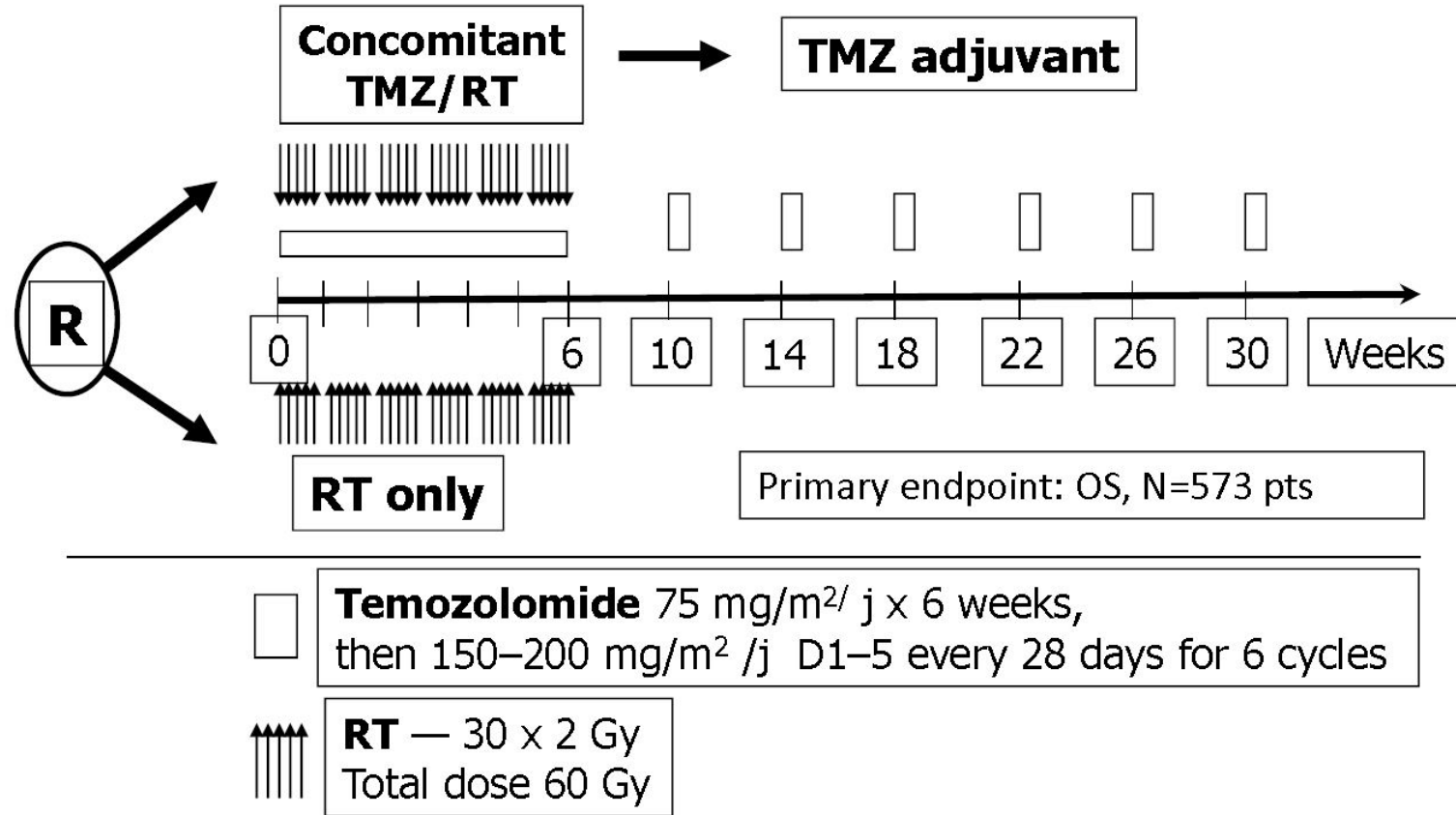


T2-FLAIR



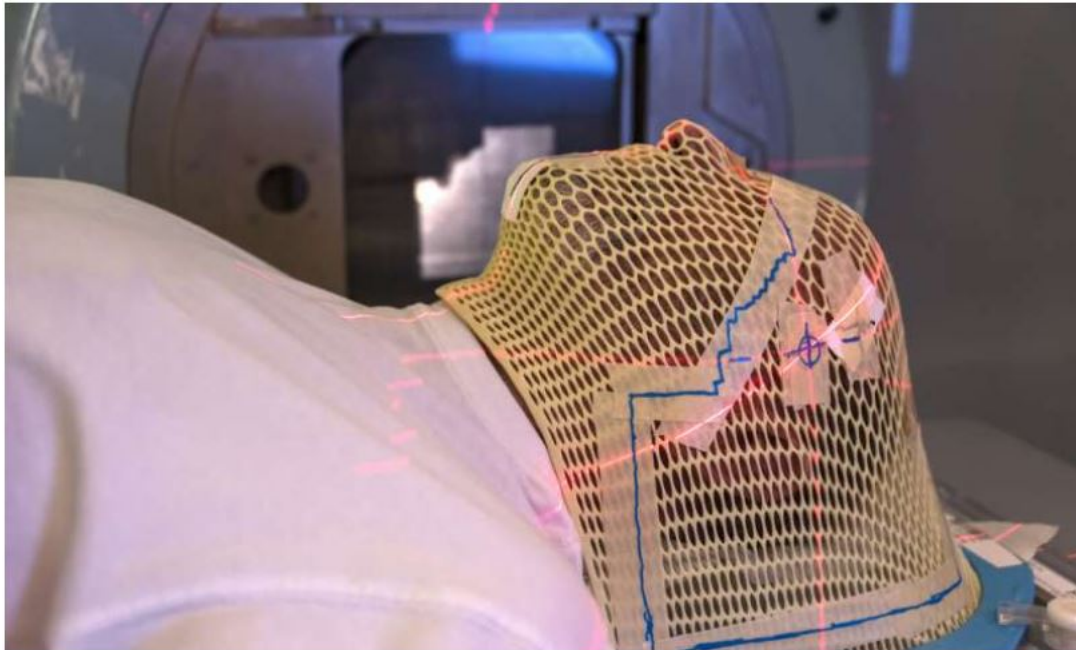
T1 post contrast

# GBM-Treatment

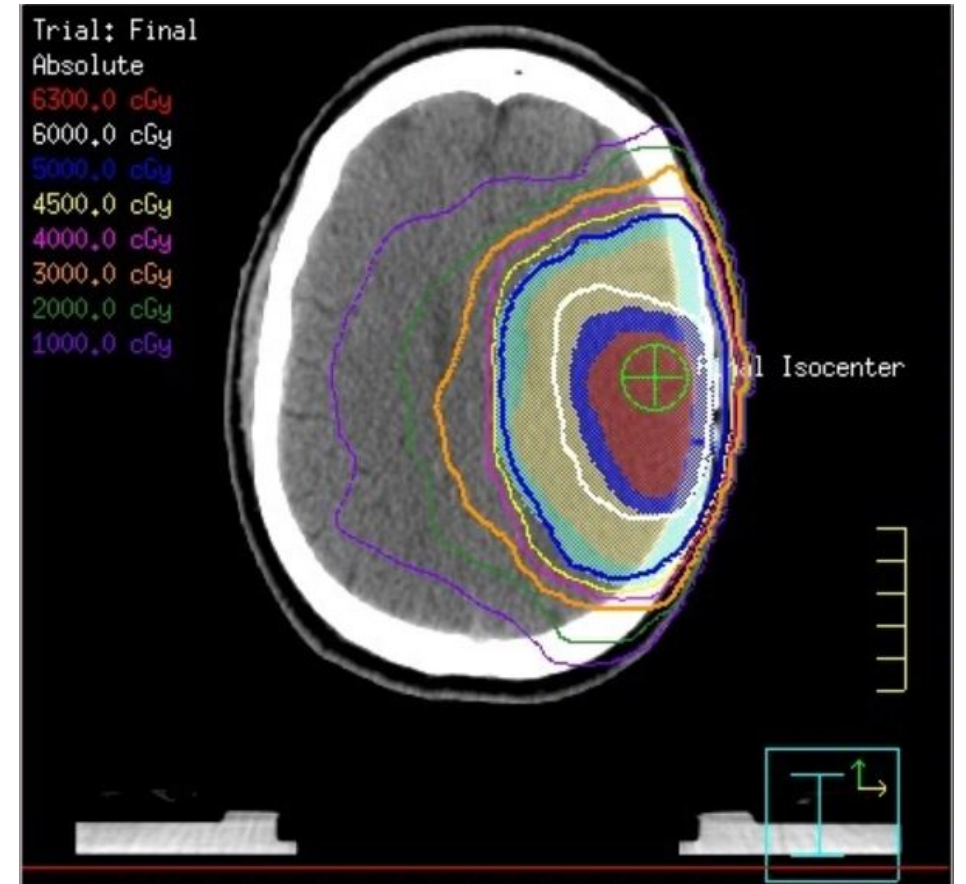


EORTC 22981/ NCIC 26981 (**Stupp**, NEJM 2005)

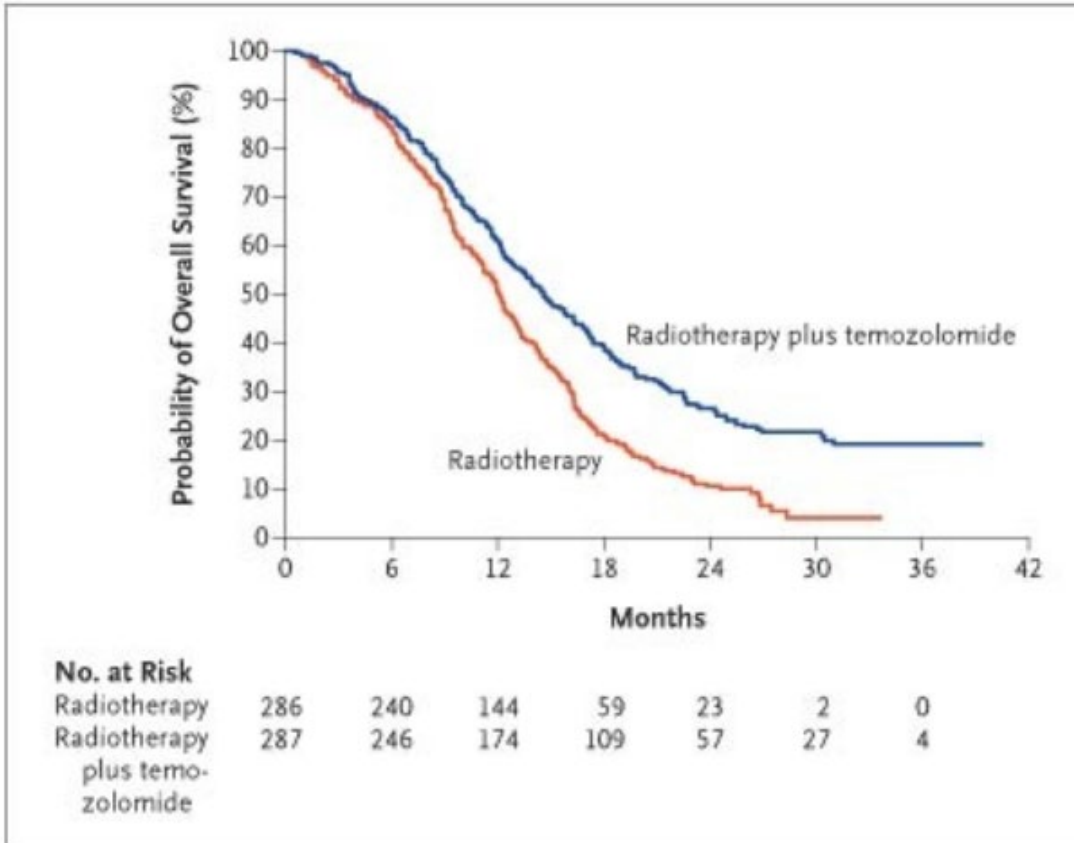
# Radiation Therapy



- Focal radiation therapy for 6 weeks
- 60 Gy in 1.8-2.0 Gy/day
- Concurrently with temozolomide



# GBM- Treatment



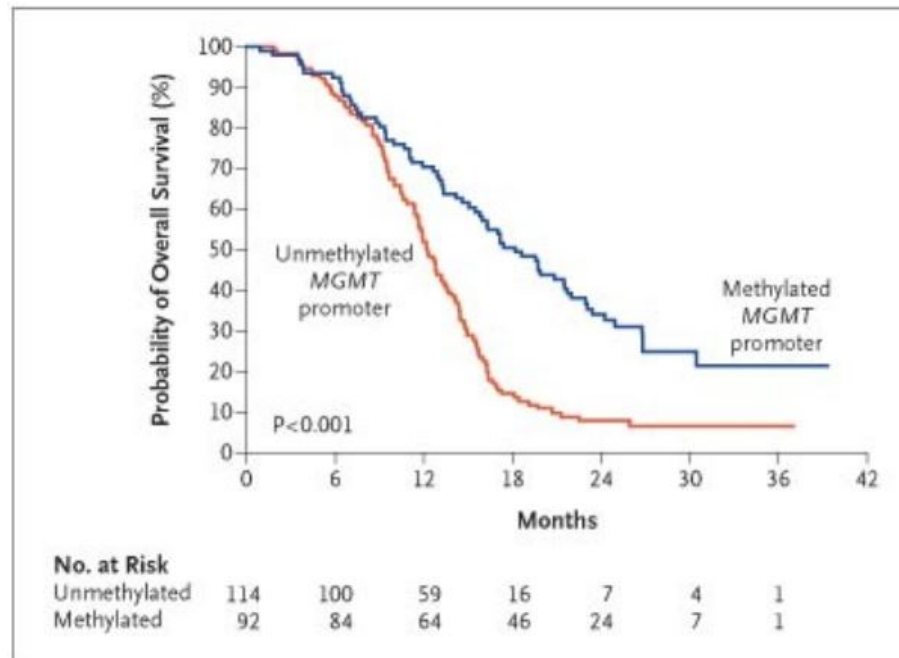
**Table 3. Overall and Progression-free Survival According to Treatment Group.\***

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	<i>value (95% CI)</i>	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)



# MGMT methylation

- O6 methylguanine methyltransferase
- DNA repair enzyme
- Favorable prognosis
- Predicts response to alkylating agent



**Table 1. Effect of MGMT Promoter Methylation Status on Survival, According to Random Treatment Assignment.\***

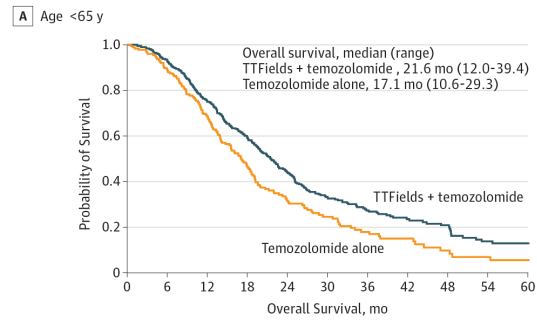
Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
<b>Methylated MGMT promoter</b>		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.48 (0.31–0.75)
Overall survival		
Median duration (mo)	15.3 (13.0–20.9)	21.7 (17.4–30.4)
Rate at 2 yr (%)	22.7 (10.3–35.1)	46.0 (31.2–60.8)
Hazard ratio for death	1.00	0.51 (0.31–0.84)
<b>Unmethylated MGMT promoter</b>		
No. of patients	54	60
Progression-free survival		
Median duration (mo)	4.4 (3.1–6.0)	5.3 (5.0–7.6)
Rate at 6 mo (%)	35.2 (22.5–47.9)	40.0 (27.6–52.4)
Hazard ratio for death	1.00	0.62 (0.42–0.92)
Overall survival		
Median duration (mo)	11.8 (9.7–14.1)	12.7 (11.6–14.4)
Rate at 2 yr (%)	<2†	13.8 (4.8–22.7)
Hazard ratio for death	1.00	0.69 (0.47–1.02)

# Tumor Treating Fields

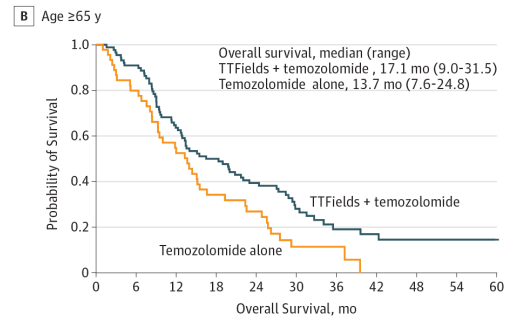
- TTF used after completion of chemoRT
- With adjuvant temozolomide
- N=315 pts
- PFS: 7mo vs. 4mo
- OS: 20 mo vs. 17 mo
- Use at least 18 hours/day
- Pros: Survival benefit,
- Cons: Non-blinded study, no placebo, QoL?
- Not yet widely accepted



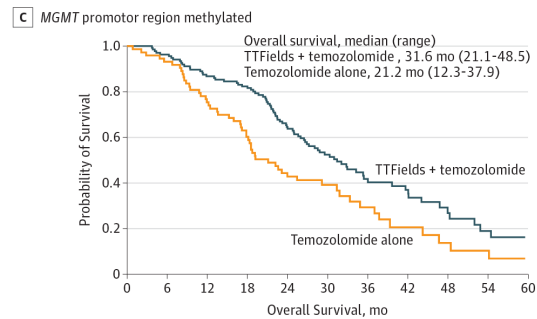
# Tumor Treating Fields



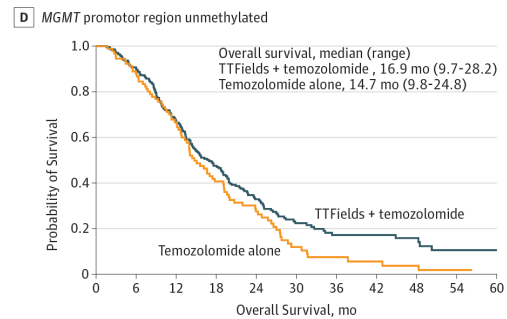
No. at risk	0	6	12	18	24	30	36	42	48	54	60
TTFields	377	277	142	56	28	14					
Temozolomide	184	120	49	20	7	2					



No. at risk	0	6	12	18	24	30	36	42	48	54	60
TTFields	89	56	32	9	2	0					
Temozolomide	45	24	11	2	0	0					



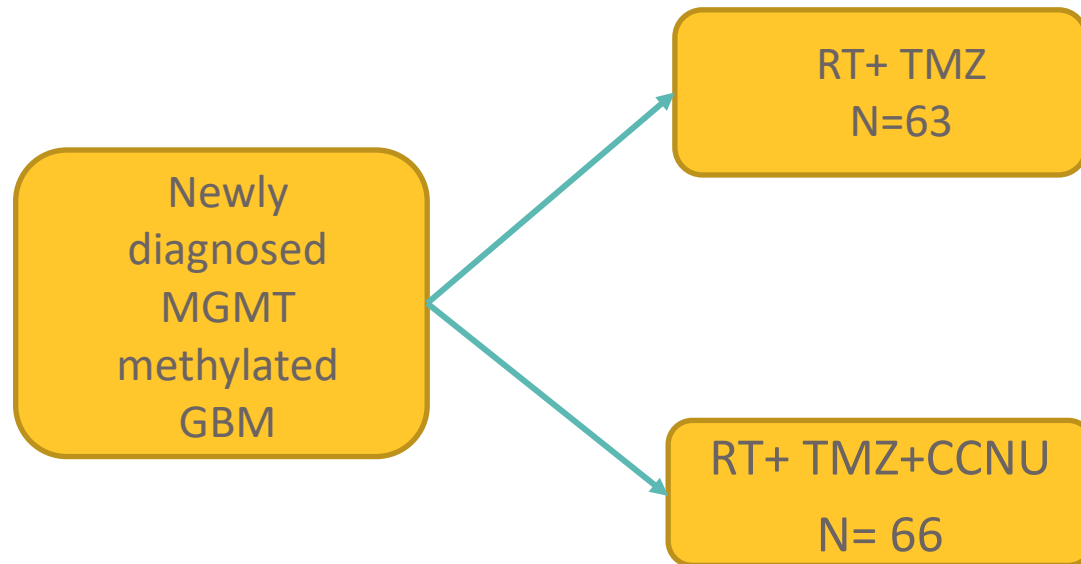
No. at risk	0	6	12	18	24	30	36	42	48	54	60
TTFields	137	118	81	29	12	5					
Temozolomide	77	56	29	12	4	1					



No. at risk	0	6	12	18	24	30	36	42	48	54	60
TTFields	209	137	56	17	10	5					
Temozolomide	95	60	21	4	2	0					



# CeTeG/NOA-09: MGMT Methylated GBM



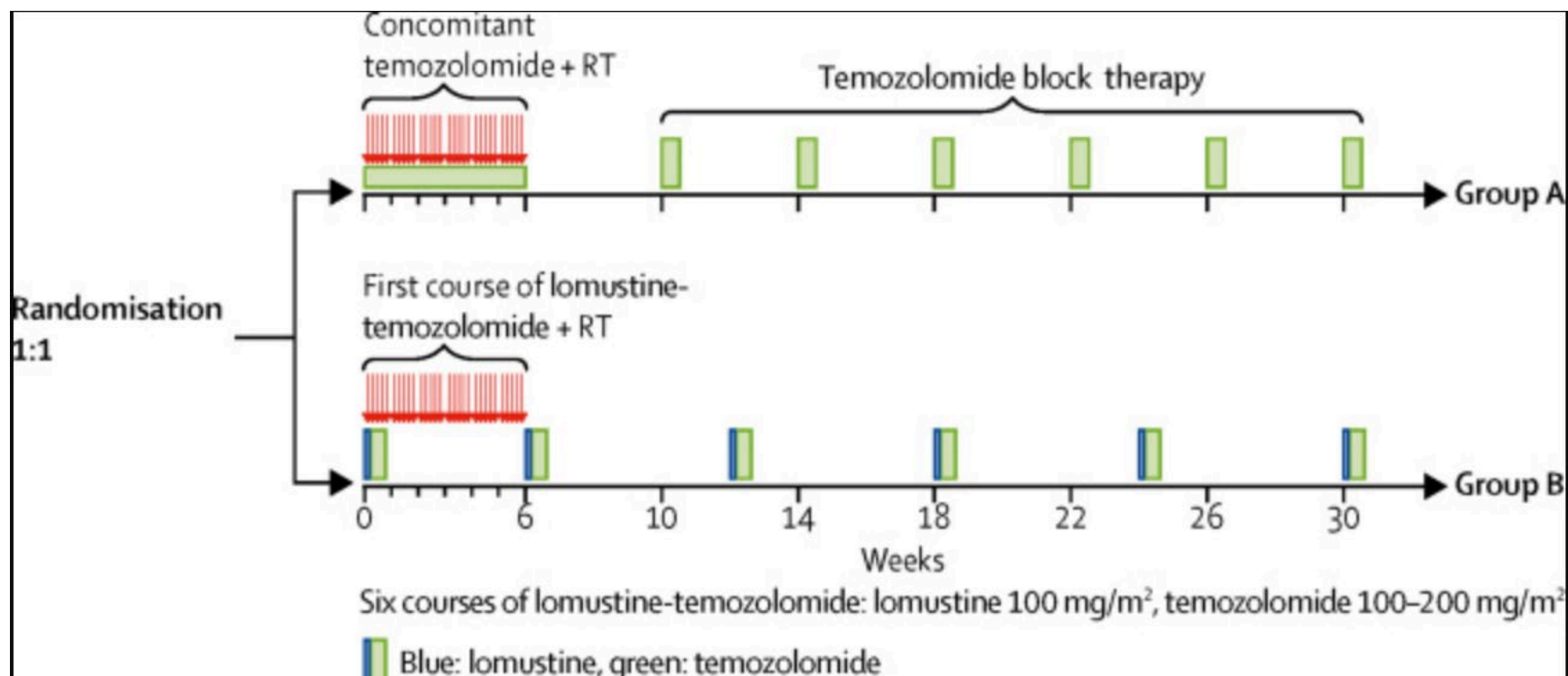
	RT+ TMZ	RT+ TMZ+CCNU
PFS	16.7 months	16.7 months
OS	30.9 months	49.6 months

## Limitations:

1. Small sample size
2. No PFS benefit
3. Significant thrombocytopenia

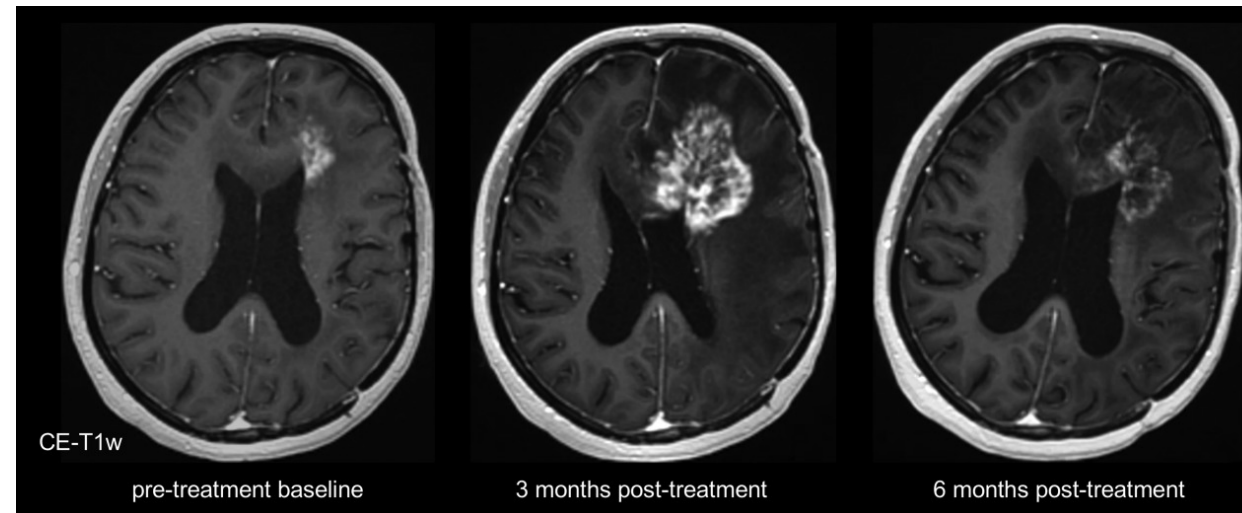
# Glioblastoma Treatment: CCNU plus TMZ

CeTeG/NOA-09- MGMT Methylated newly diagnosed GBM



# Pseudoprogression- Radiation Necrosis

- Upto 40% pts display radiologic worsening of disease after RT, mostly in the RT field
- Common during the first 3-4 months after RT
- Baseline MRI: 4 weeks after RT+ chemo
- Usually asymptomatic, may occasionally be symptomatic
- Avoid making changes to treatment
- Could use steroids or bevacizumab for symptom management
- Consider surgery for confirmation



# Recurrent GBM

- Poor prognosis
- No standard treatment options
- Bevacizumab as a single agent
- Other chemotherapy agents: Lomustine, carboplatin, irinotecan, etoposide
- Tumor treating fields
- The correct answer: **CLINICAL TRIALS**

# Bevacizumab

- VEGF antibody
- Decreases vascular permeability
- Improves edema and MRI
- Improves symptoms
- FDA accelerated approval in 2009 and full approval 2018
- Used for symptomatic patients
- Limited post-bev trials

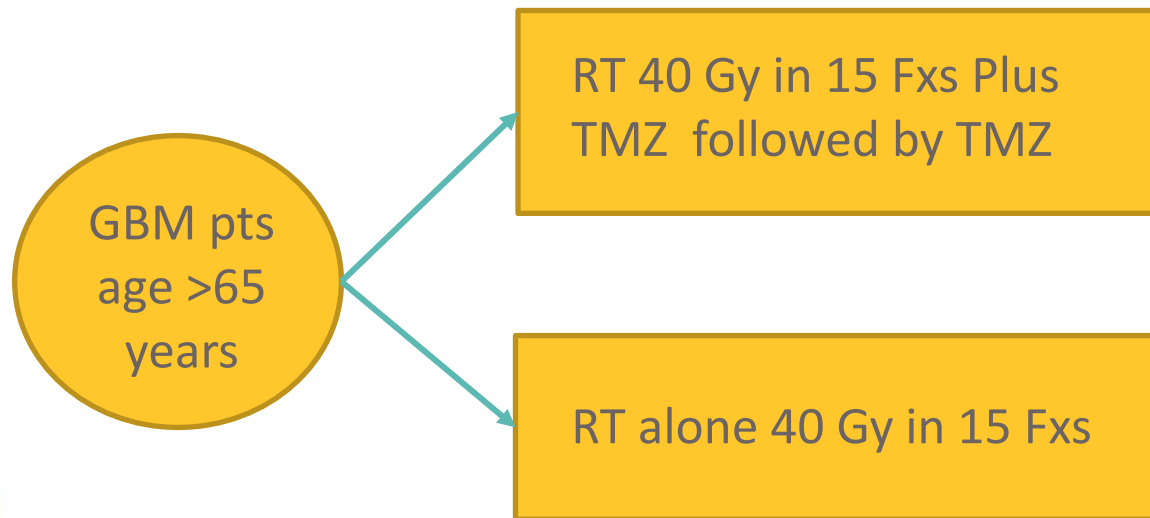
<b>Recurrent GBM</b>					
<b>Trial</b>	<b>Phase</b>	<b>N</b>	<b>Intervention</b>	<b>Median PFS (95% CI), mo</b>	<b>Median OS (95% CI), mo</b>
Friedman et al, <sup>26</sup> 2009	II	167	Bev	4.2 (2.9–5.8)	9.2 (8.2–10.7)
			Bev + irinotecan	5.6 (4.4–6.2)	8.7 (7.8–10.9)
Taal et al, <sup>27</sup> 2014	II	148	Lomustine	1 (1–3)	8 (6–11)
			Bev	3 (3–4)	8 (6–9)
			Bev + lomustine	4 (3–8)	12 (8–13)
Field et al, <sup>28</sup> 2015	II	122	Bev	3.5 (1.9–3.7)	7.5 (NR)
			Bev + carboplatin	3.5 (2.2–3.7)	6.9 (NR)
Wick et al, <sup>29</sup> 2017	III	437	Lomustine	1.5 (1.5–2.5)	8.6 (7.6–10.4)
			Bev + lomustine	4.2 (3.7–4.3)	9.1 (8.1–10.1)
<b>Newly Diagnosed GBM</b>					
Herrlinger, <sup>30</sup> 2016	II	170	TMZ/RT + TMZ	6.0 (2.7–7.3)	17.5 (15.1–20.5)
			Bev/RT + Bev/Iri	9.7 (8.7–10.8)	16.6 (15.4–18.4)
Gilbert et al, <sup>31</sup> 2014	III	621	TMZ/RT + TMZ	7.3 (5.9–7.9)	16.1 (14.8–18.7)
			Bev/TMZ/RT + Bev/TMZ	10.7 (10.0–12.2)	15.7 (14.2–16.8)
Chinot et al, <sup>32</sup> 2014	III	921	TMZ/RT + TMZ	6.2 (NR)	16.7 (NR)
			Bev/TMZ/RT + Bev/TMZ	10.6 (NR)	16.8 (NR)
<b>Unresectable GBM</b>					
Chauffert et al, <sup>33</sup> 2014	II	120	TMZ/RT + TMZ	5.2 (4.3–6.8)	11.1 (9.0–15.0)
			Bev/Iri + Bev/TMZ/RT + Bev/Iri	7.1 (5.5–9.2)	11.1 (9.0–15.0)

Bev indicates bevacizumab; Iri, irinotecan; NR, not reported; TMZ, temozolomide.



# GBM In Elderly

Hypofractionated RT plus TMZ vs. hypofractionated RT alone



	RT alone	RT plus TMZ
PFS	3.9 months	5.3 months
OS	7.6 months	9.3 months

NO consensus for treatment in elderly

# Grade II and III Glioma: Management

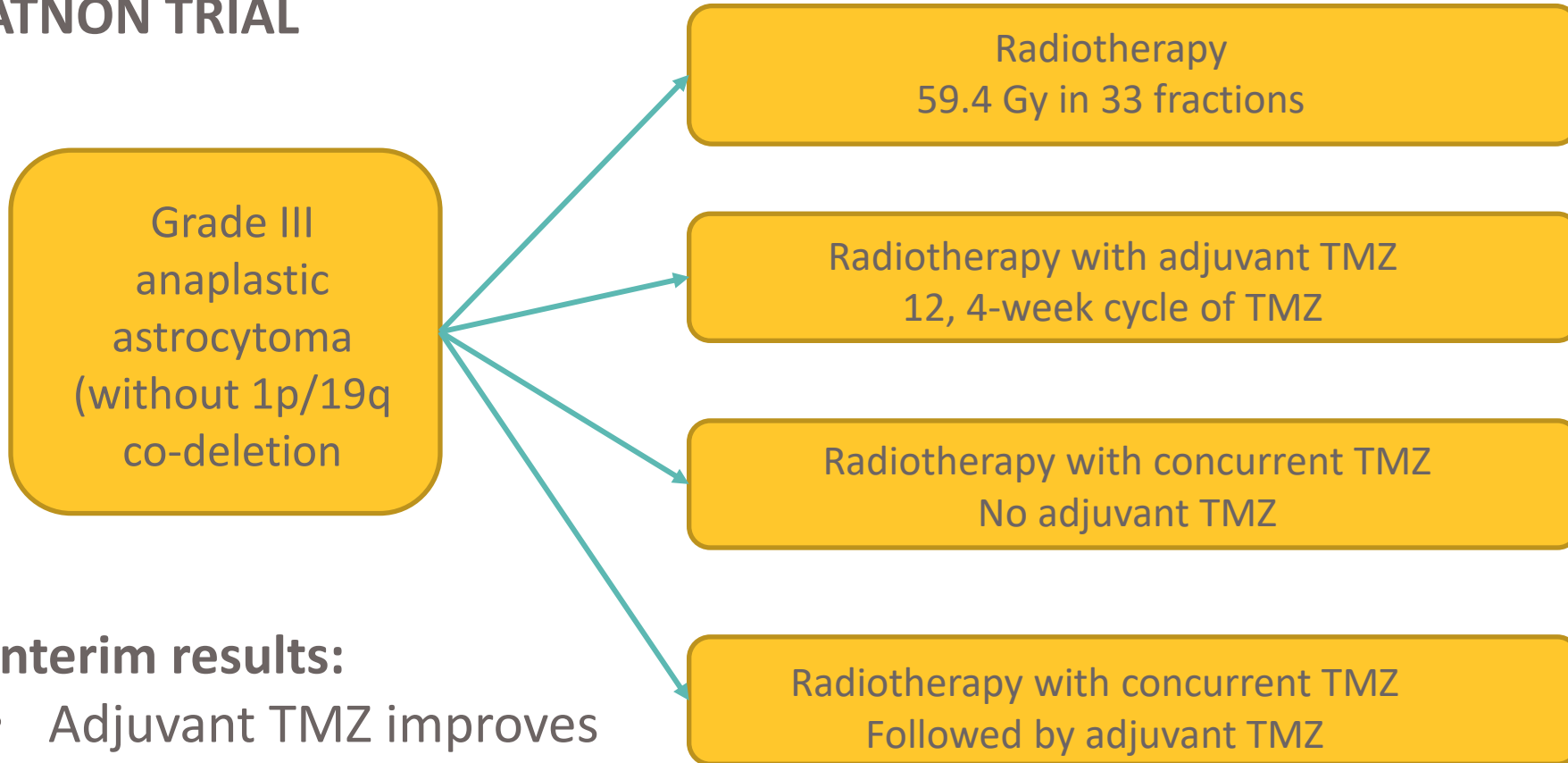
WHO grade II glioma: Younger patients 20-40 year old

- Surgery, if gross total resection, < 40: Observation
- >40 year old or less than gross total resection: Consider chemotherapy
- RT plus PCV has the most evidence
- Could consider RT plus TMZ

WHO grade III glioma: Treated like GBM

# Studies to Watch out for

## CATNON TRIAL

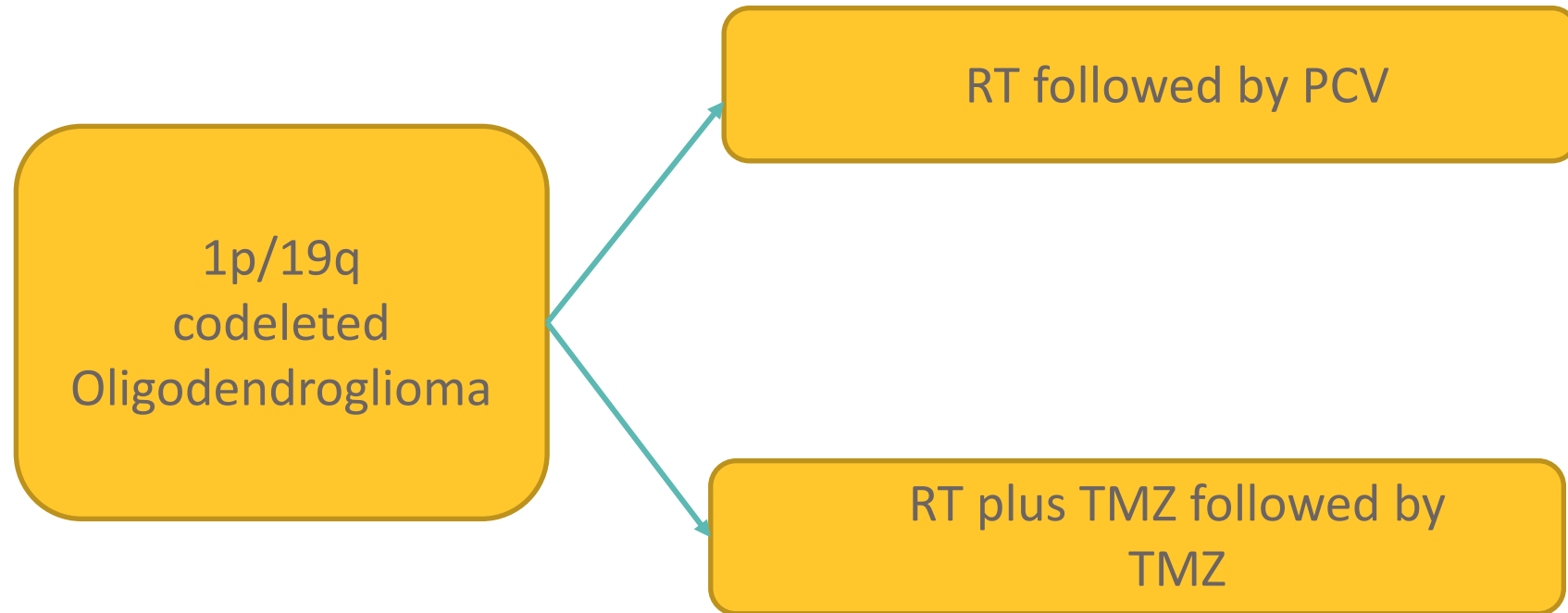


### Interim results:

- Adjuvant TMZ improves survival
- Concurrent TMZ does not improve survival

# Studies to Watch out for

CODEL trial



# Prognosis

Tumor	Median survival
Grade II, diffuse oligodendroglioma	10-15 years
Grade II, diffuse astrocytoma, IDH mutant	10-12 years
Grade II, diffuse astrocytoma, IDH wild type	1.5-3 years
Grade III, anaplastic astrocytoma, IDH mutant	8-10 years
Grade III, anaplastic oligodendroglioma	5-9 years
Grade III, anaplastic astrocytoma, IDH wild type	1.5-3 years
Grade IV, Glioblastoma	1.5-2 years

# Meningioma

Arise from the meninges- most common CNS tumor

Often found in adults

Usually slow growing

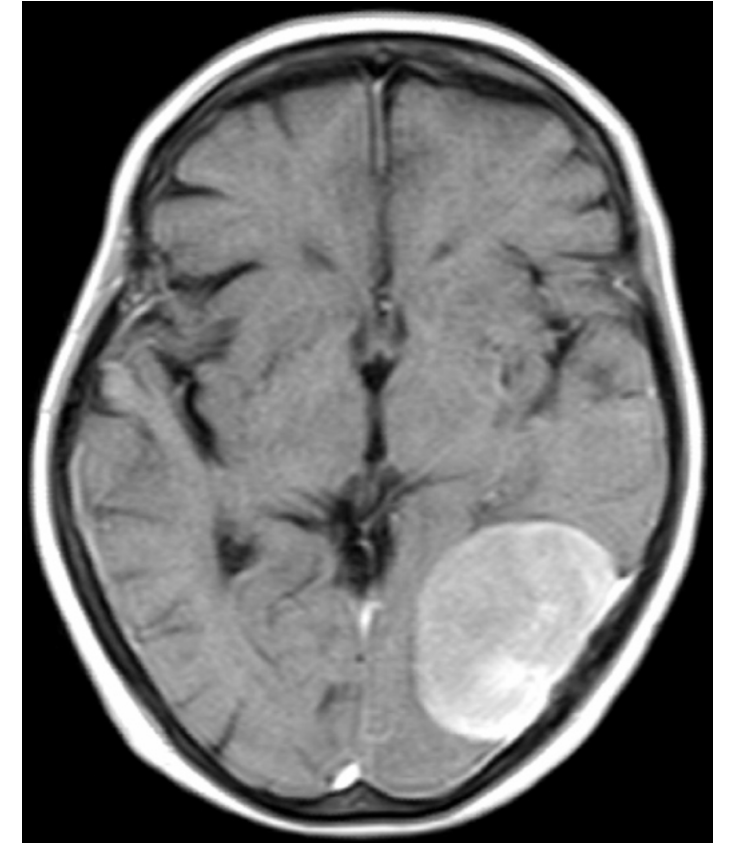
Asymptomatic: followed with periodic CT/MRI

Symptomatic: Surgery

WHO grade I: Surgical resection is curative

WHO grade II (high mitotic index): Surgery +/- RT

WHO grade III (brain invasion, bone invasion): Surgery + RT



# CNS lymphoma

- NHL, aggressive, median age 60 years
- >95% DLBCL, ABC subtype, mostly immunocompetent patients (PTLD could have EBV+)
- Imaging: MRI brain w/wo contrast: periventricular, homogenous contrast enhancing, diffusion restricting
- Extent of disease evaluation: MRI spine, LP, ophthalmology eval, CT CAP, testicular US in males
- Treatment:
  - HD-MTX based regimen (3.5 gm/m<sup>2</sup> to 8 gm/m<sup>2</sup>): MTR, MATRIX
  - Consolidation: consolidation chemotherapy: cytrabine plus etoposide/low dose RT/HDC-ASCT

# Brain Metastases

- Common primaries: Lung, breast, melanoma
- Imaging: MRI brain w/wo contrast
- Factors to consider for treatment selection:
  - Patient factors: Performance status, Symptoms,
  - Local factors: Number/size/location of brain mets,
  - Primary malignancy factors: extracranial disease control, presence of targetable mutation
- Treatment options: observation, surgery, radiation therapy (SRS vs. WBRT), systemic therapy



# Brain Metastases

**Surgery:** Solitary or large or symptomatic

Alleviates mass effect, provides tissue diagnosis, ability to taper steroids fast

Post op RT controversial: could lead to local leptomeningeal disease

**RT: SRS:** 1-3 lesions (? Upto 10 lesions), <3 cm, good focal control

WBRT: Improves CNS control, no OS benefit, consider hippocampal sparing

WBRT and memantine to delay neurocognitive decline

**Systemic therapy:** Consider for targeted therapies with good CNS penetration, small, asymptomatic brain metastases.

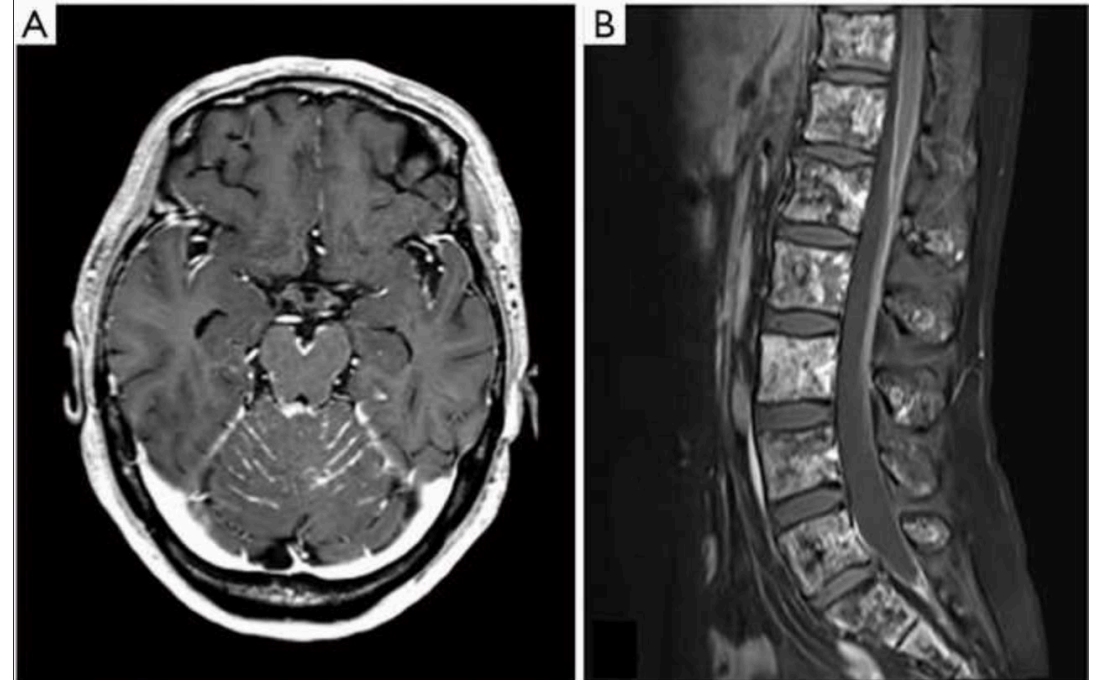
Melanoma: BRAF inhibitors, ipilimumab plus nivolumab, pembrolizumab

Lung: Osimertinib, brigatinib, lorlatinib, pembrolizumab

Breast: Tucatinib, neratinib, lapatinib all with capecitabine

# Leptomeningeal metastases

- Spread to the subarachnoid space
- Imaging: MRI brain plus spine w/wo contrast
- Lumbar puncture: Cell count, glucose, protein, cytology, ?cf-DNA
- Treatment: Focal radiation, WBRT, craniospinal radiation
- IT chemotherapy: MTX, cytarabine, thiotepa, trastuzumab
- Consider shunt for hydrocephalus





# Thank You