Fred Hutch Cancer Center

PRIMARY BRAIN TUMORS

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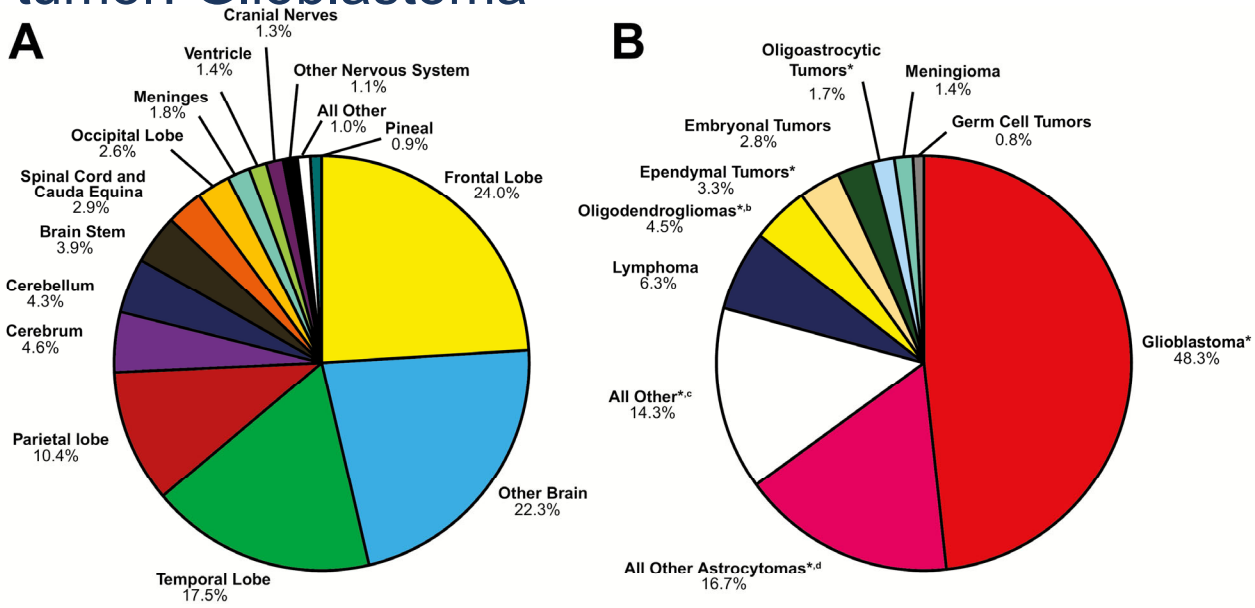
FHCC/UW/Alvord Brain Tumor

Outline

- Epidemiology
- Classification of glioma
- General management of gliomas
- Low grade glioma
- Glioblastoma
- Meningioma
- Things to watch in the future

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

* All or some of this histology is included in the CBTRUS definition of gliomas, including ICD−O−3 histology codes 9380−9384 and, 9391−9460 (Table 2). a. Percentages may not add up to 100% due to rounding. b. Includes oligodendroglioma and anaplastic oligodendroglioma (Table 2). c. 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). d. Includes pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, and unique astrocytoma variants (Table 2).

Classification of Glioma

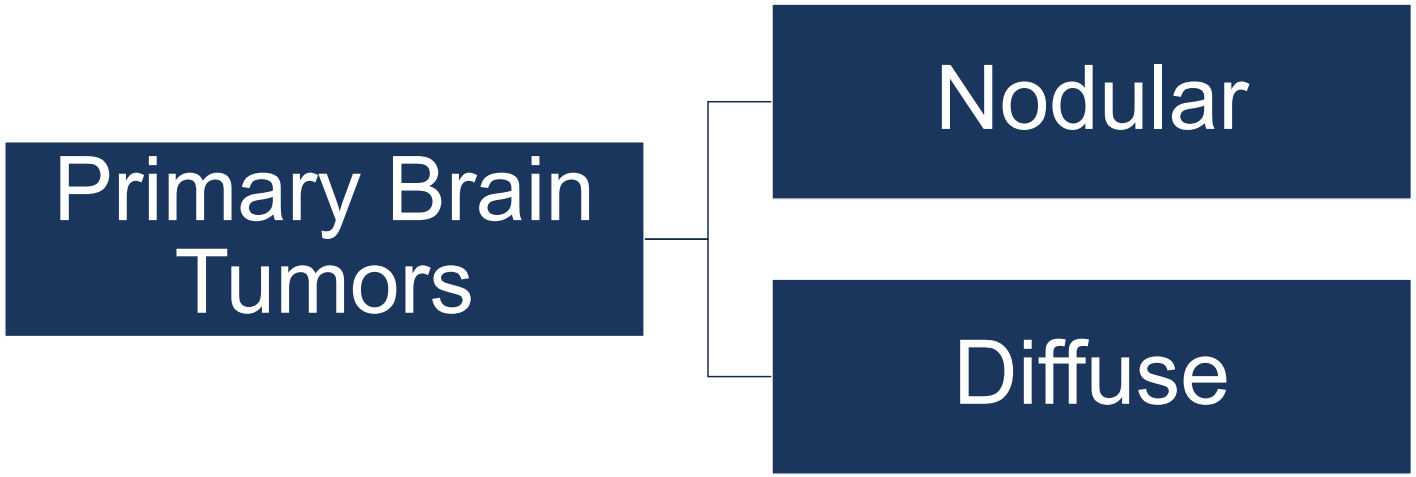
WHO Grade 1: Pilocytic astrocytoma (BRAF/KIAA fusion), common in children, cured by gross total resection.

WHO Grade 2: aka “Low-grade glioma” diffuse astrocytoma, diffuse oligodendroglioma, pilocytic xanthoastrocytoma (PXA) [low/no mitotic activity, no necrosis, no vascular proliferation]

WHO Grade 3: Anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic PXA

[high mitotic activity (>10/hpf), no necrosis, no vascular proliferation]

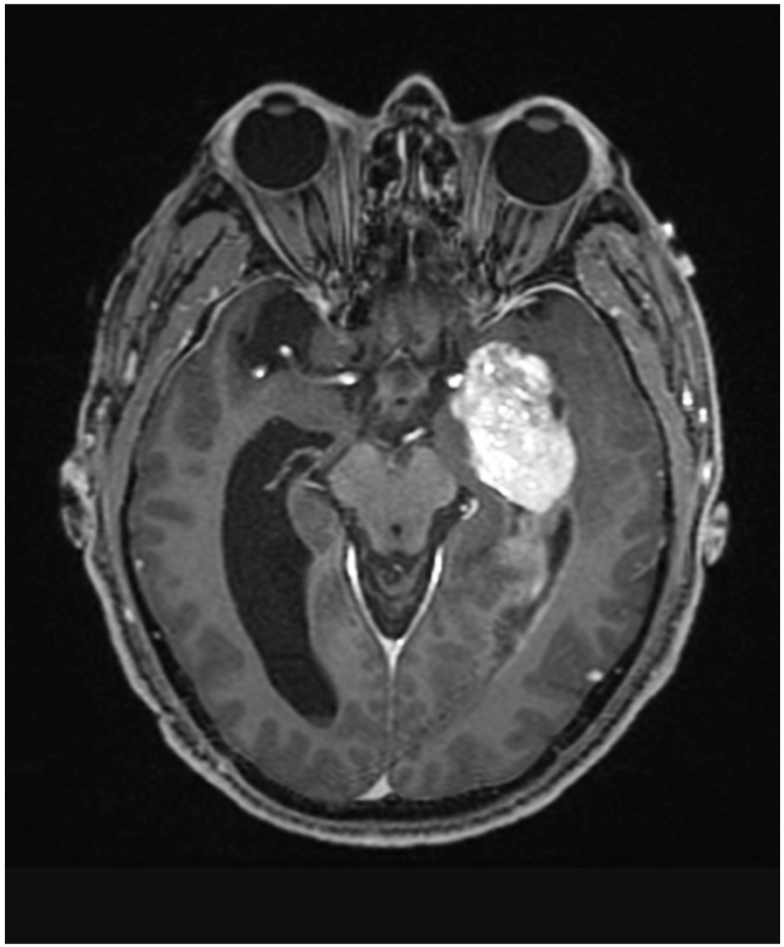
Primary Brain Tumors



Nodular Brain Tumors

Circumscribed astrocytic gliomas

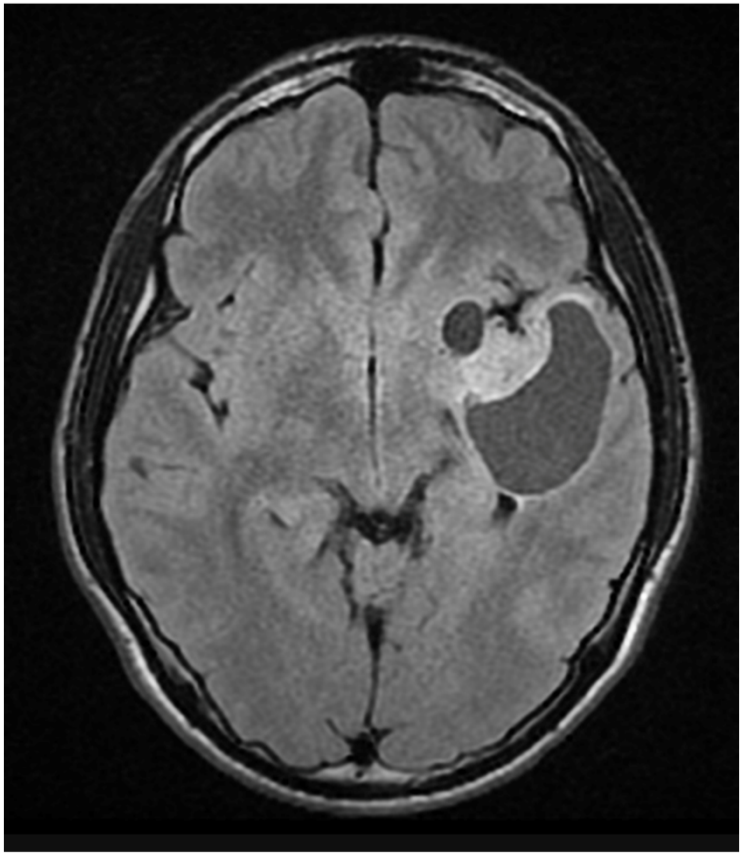
- Pilocytic astrocytoma
- High grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal gait cell astrocytoma
- Chordoid glioma
- Astroblastoma, MN1-altered



Nodular Brain Tumors

Glioneuronal and neuronal tumors

- ganglioglioma
- dysembryoplastic neuroepithelial tumor
- papillary glioneuronal tumor
- rosette-forming glioneuronal tumor
- myxoid glioneuronal tumor
- diffuse leptomeningeal glioneuronal tumor
- gangliocytoma
- multinodular and vacuolating neuronal tumor
- dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- central neurocytoma
- extraventricular neurocytoma



Low Grade Glioma

23-year-old right-handed gentleman, finishing up undergrad with plans to become a physical therapist, was enjoying beer with his friends. His partner noted that he suddenly started shaking and suffered from a generalized seizure. Presented to ER, started on Keppra and underwent MRI brain wwo contrast.

Low Grade Glioma

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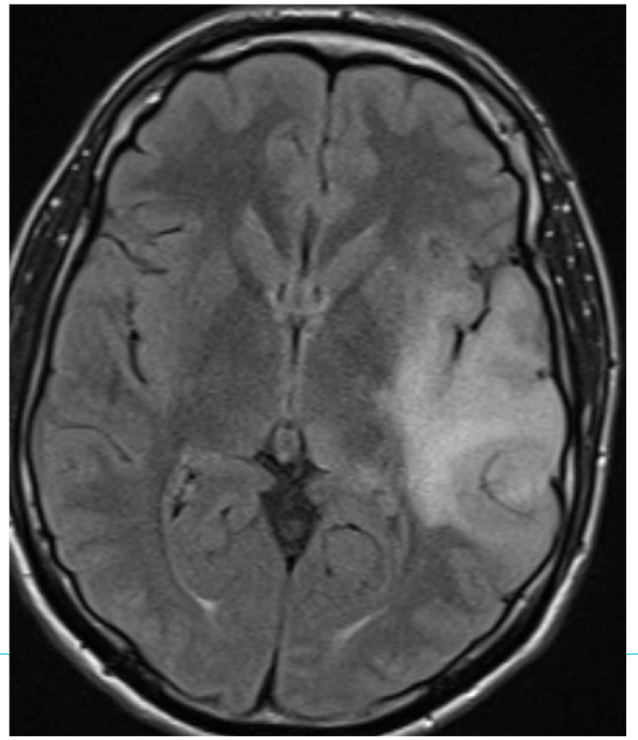
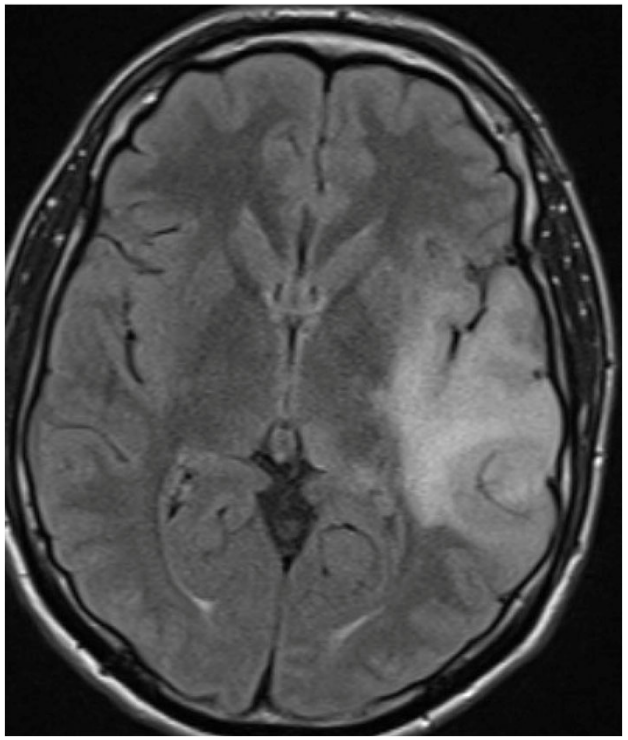
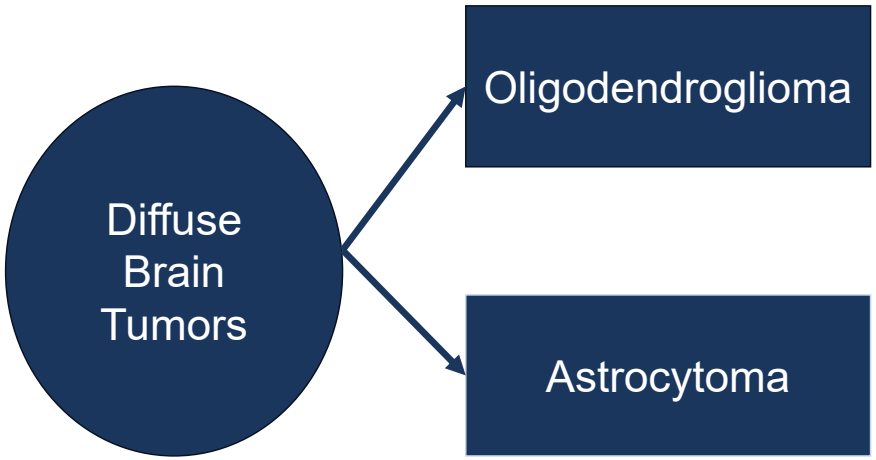
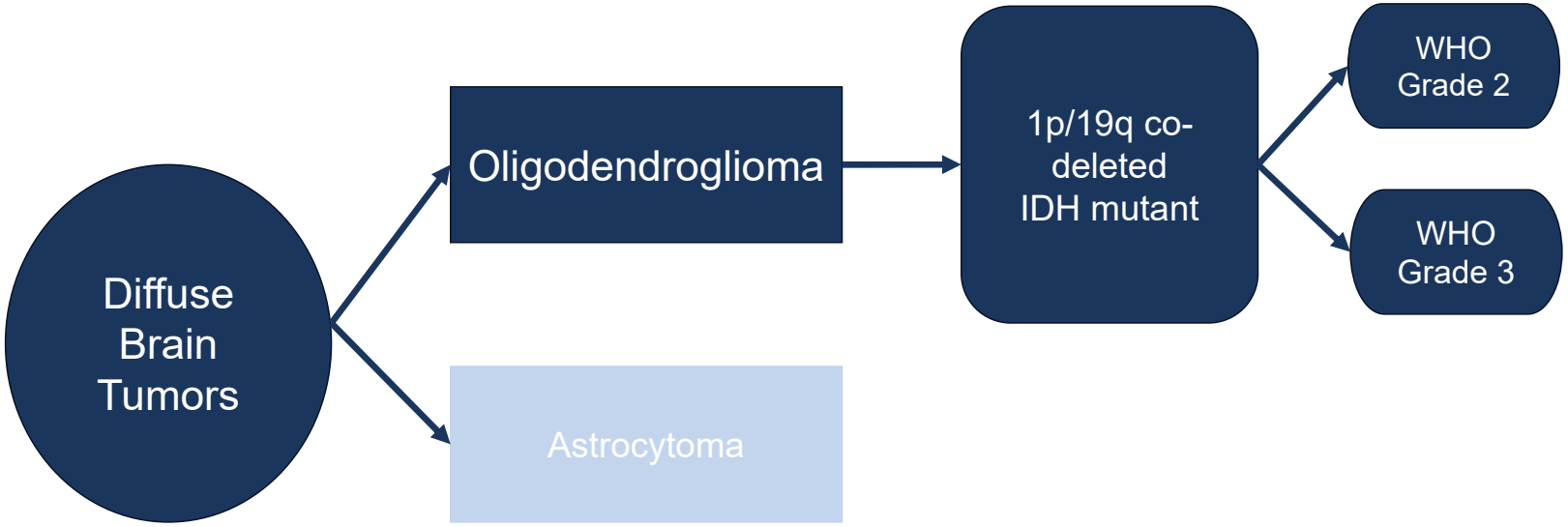


Which of the following genetic alterations provide the best survival advantage?

1. MGMT methylation
2. TERT promoter mutation
3. ATRX alteration
4. 1p/19q co-deletion

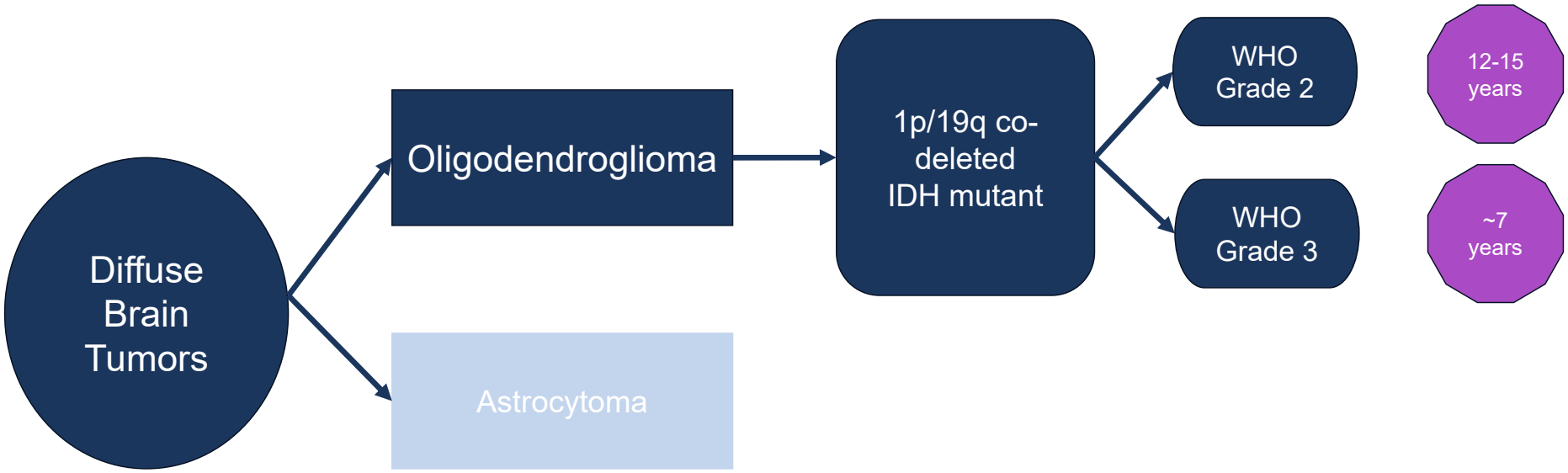



Diffuse
Brain
Tumors
Oligodendroglioma
Astrocytoma


Diffuse Brain Tumors
Oligodendroglioma
Astrocytoma
1p/19q co-deleted IDH mutant
WHO Grade 2
WHO Grade 3

What is the expected survival for patients with oligodendroglioma, WHO Grade 2?

A. 21-24 months
B. 5-7 years
C. 8-10 years
D. 12-15 years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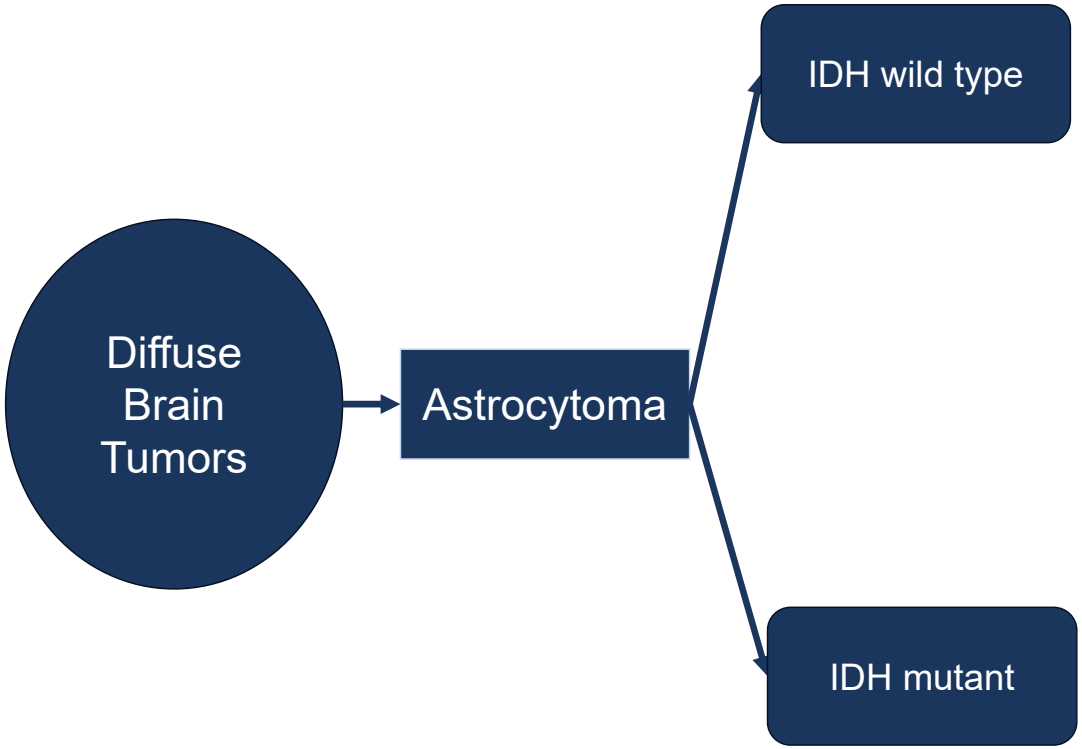
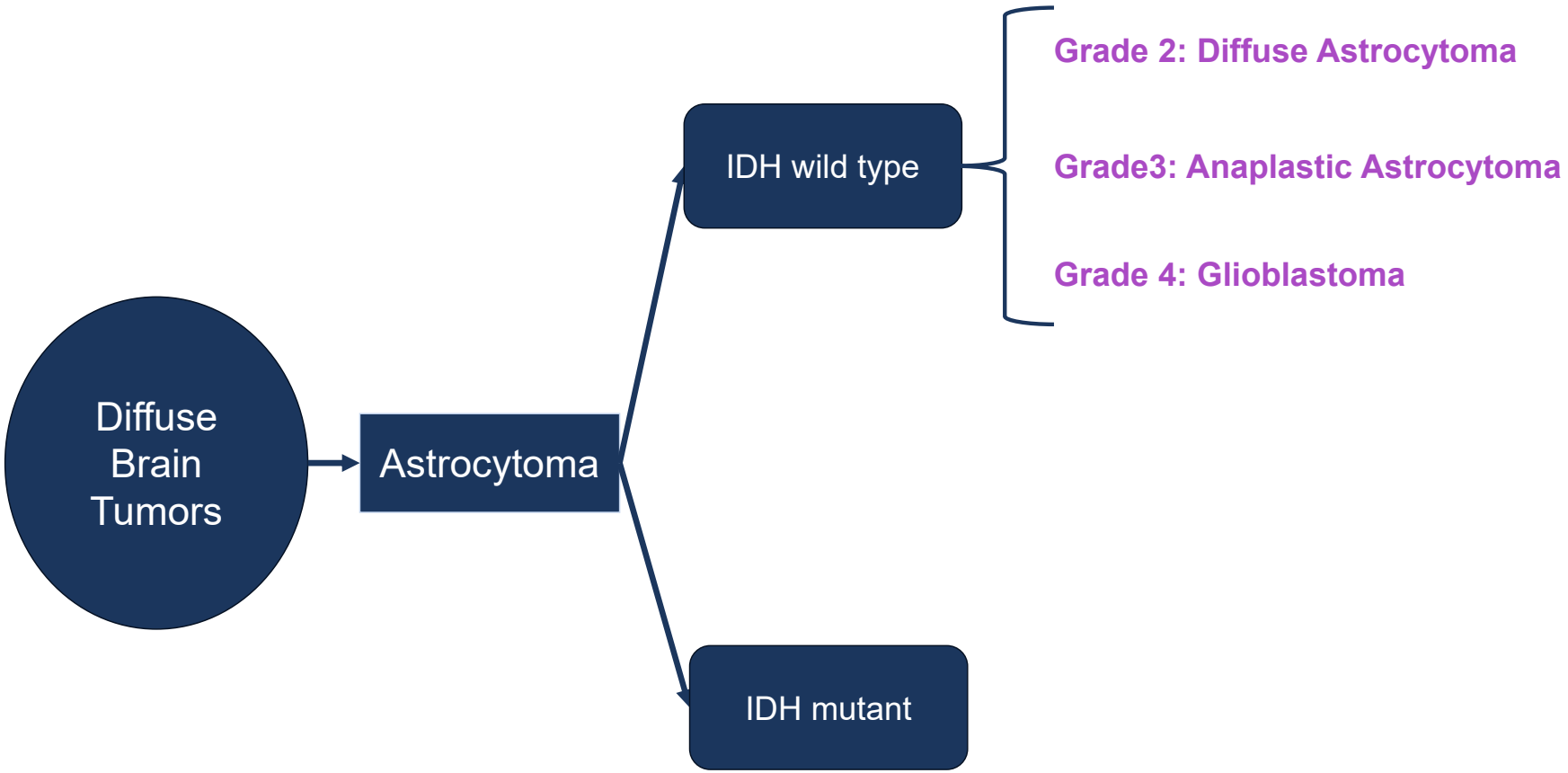
WHO Grade 2
WHO Grade 3
12-15 years
~7 years


Diffuse Brain Tumors
Astrocytoma
IDH wild type
IDH mutant


Diffuse Brain Tumors
Astrocytoma
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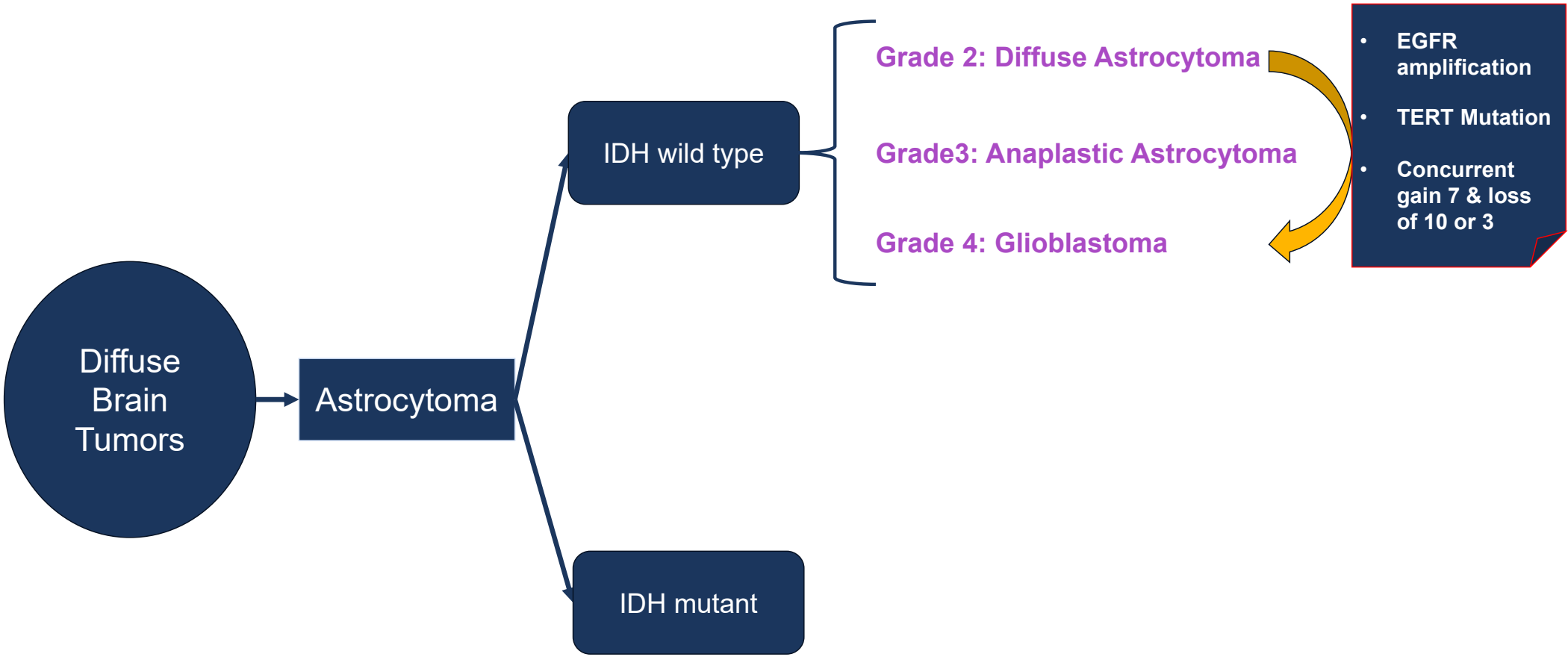
IDH mutant
Grade 2: Diffuse Astrocytoma
Grade3: Anaplastic Astrocytoma
Grade 4: Glioblastoma


Diffuse Brain Tumors
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Grade 2: Diffuse Astrocytoma
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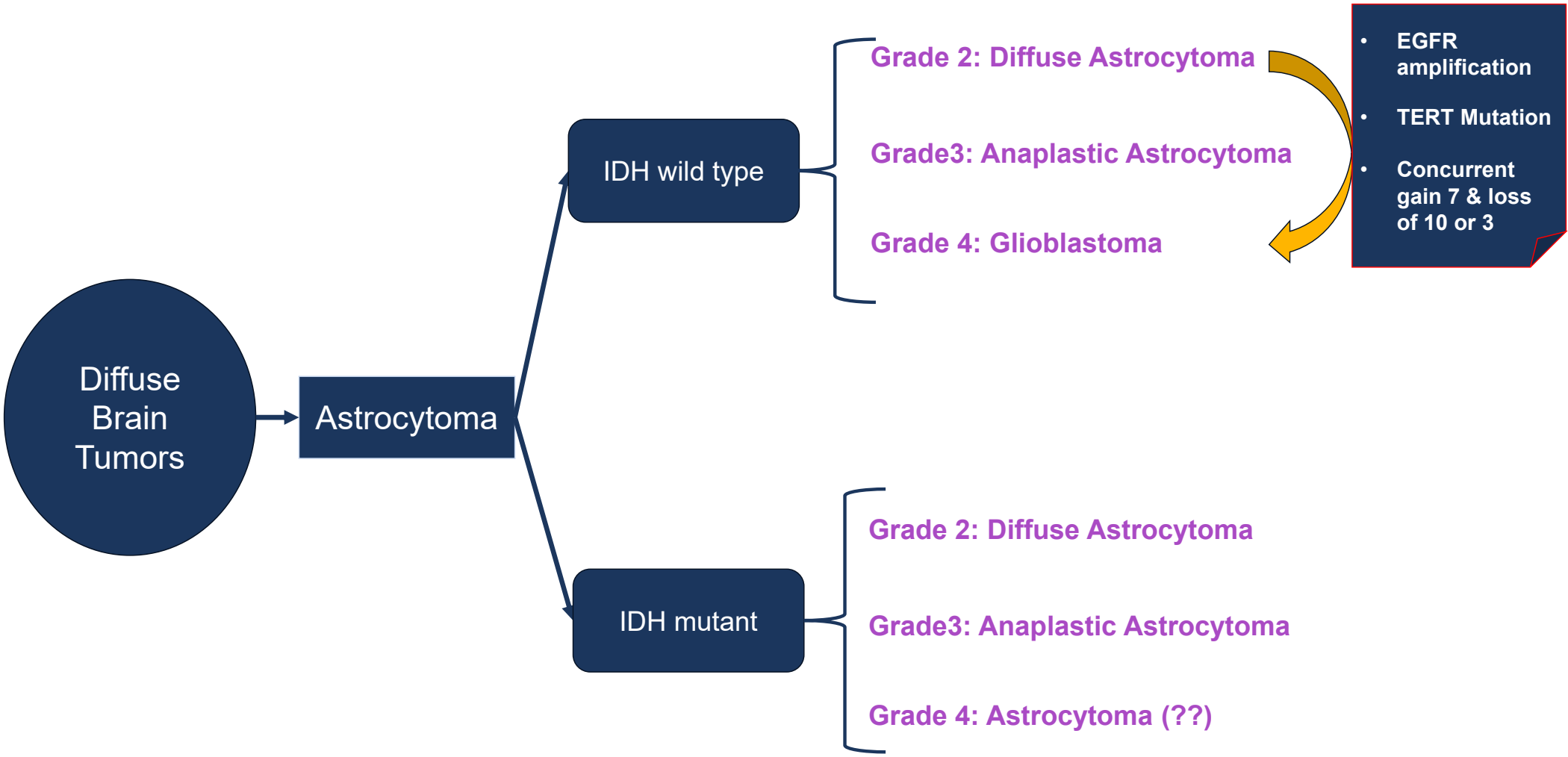
EGFR amplification
TERT Mutation
Concurrent gain 7 & loss of 10 or 3


Diffuse Brain Tumors
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Grade 2: Diffuse Astrocytoma
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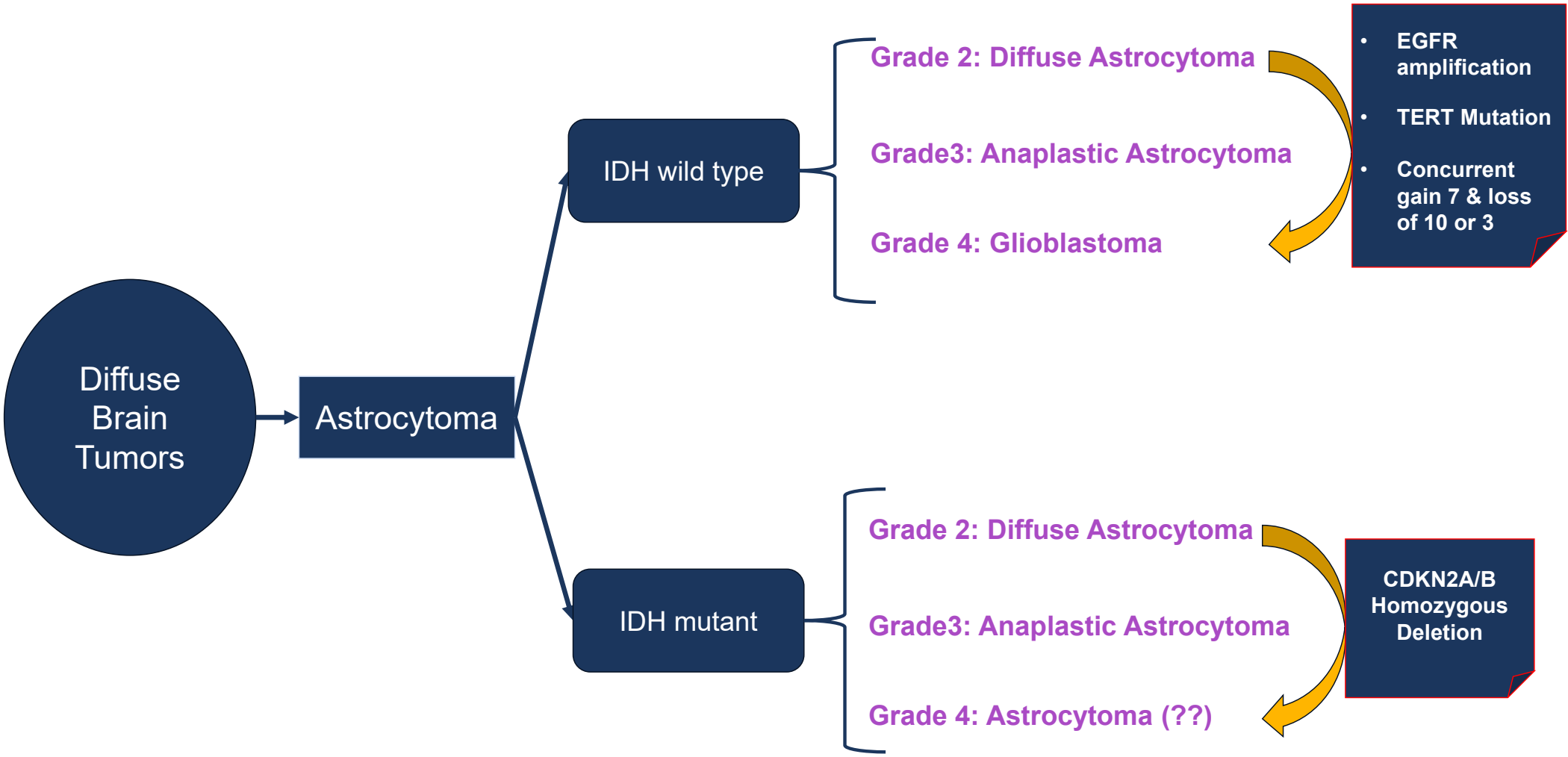
Grade 4: Astrocytoma (??)
• EGFR amplification
• TERT Mutation
• Concurrent gain 7 & loss of 10 or 3


Diffuse Brain Tumors
Astrocytoma
IDH wild type
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Grade 2: Diffuse Astrocytoma
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Concurrent gain 7 & loss of 10 or 3
Grade 2: Diffuse Astrocytoma
Grade3: Anaplastic Astrocytoma
Grade 4: Astrocytoma (??)
CDKN2A/B Homozygous Deletion

Prognosis

Tumor	Median survival
Grade 2, diffuse astrocytoma, IDH mutant	10-12 years
Grade 3, anaplastic astrocytoma, IDH mutant	3-5 years
Grade 3, anaplastic astrocytoma, IDH wild type	1.5-3 years
Grade 4, Glioblastoma (IDH wild type)	1.5-2 years

High grade vs. Low grade glioma

High Grade Glioma:

- Contrast enhancing tumor
- Heterogenous on post contrast imaging
- Significant edema
- Generally includes Grade 4 tumor, some grade 3 tumors.

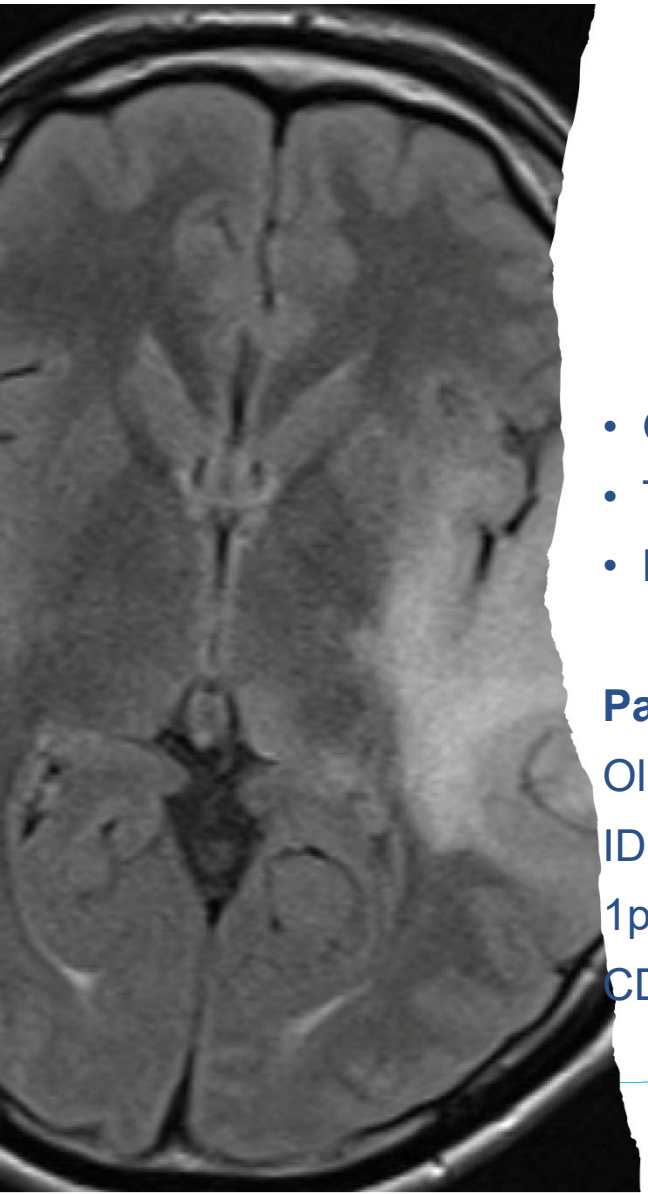
Low Grade Glioma:

- Non-contrast enhancing
- Slow growing
- Not a lot of edema
- Generally includes Grade 2 tumor, some grade 3 tumors

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.



Back to our patient

- Gets subtotal resection of tumor
- Tolerated the surgery well.
- No neurologic deficits

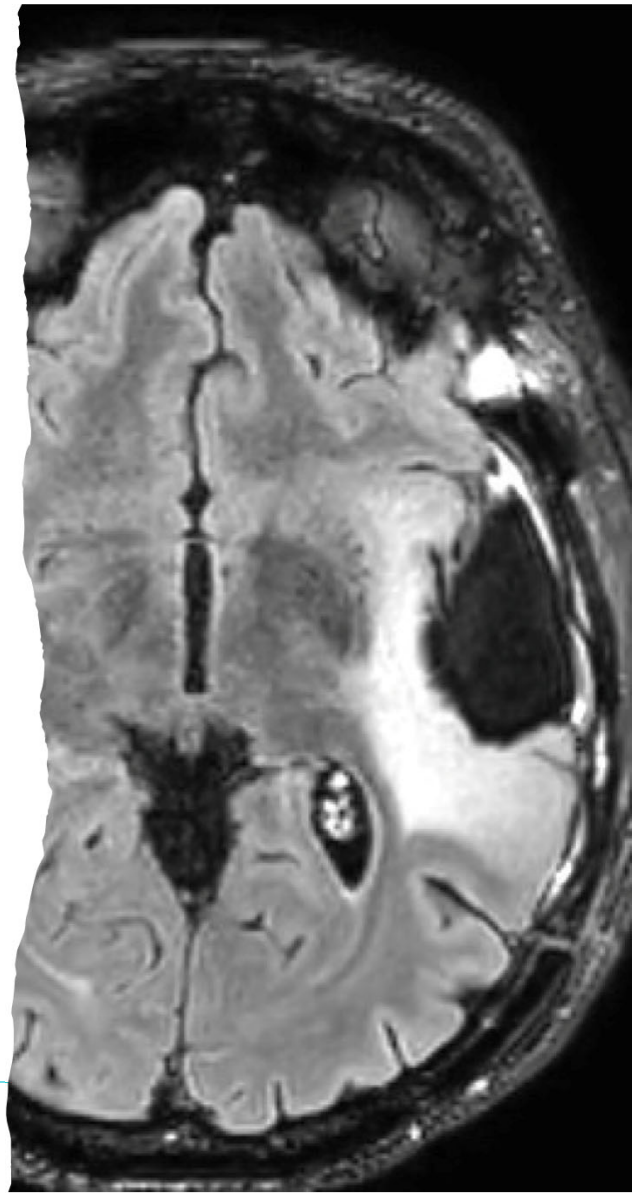
Pathology:

Oligodendroglioma, CNS WHO grade 2

IDH R132H mutant

1p/19q co-deleted

CDKN2A/B intact



What is the next standard treatment option?

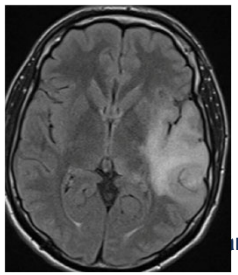
1. Observation
2. Radiation therapy plus PCV
3. Radiation therapy plus TMZ
4. IDH inhibitor

Low grade glioma- Management pathway

Surgery safe?

1st symptom

MRI brain: non enhancing tumor, ?low grade



Low grade glioma- Management pathway

Surgery ?

Observation

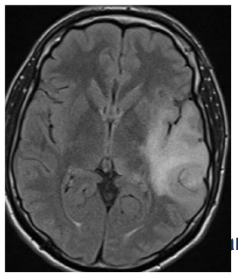
Biopsy

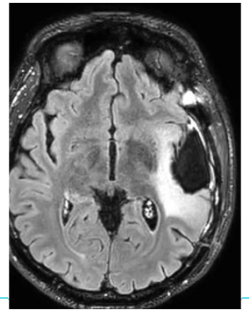
Surgery safe?

Resection

1st symptom

MRI brain: non enhancing tumor, ?low grade





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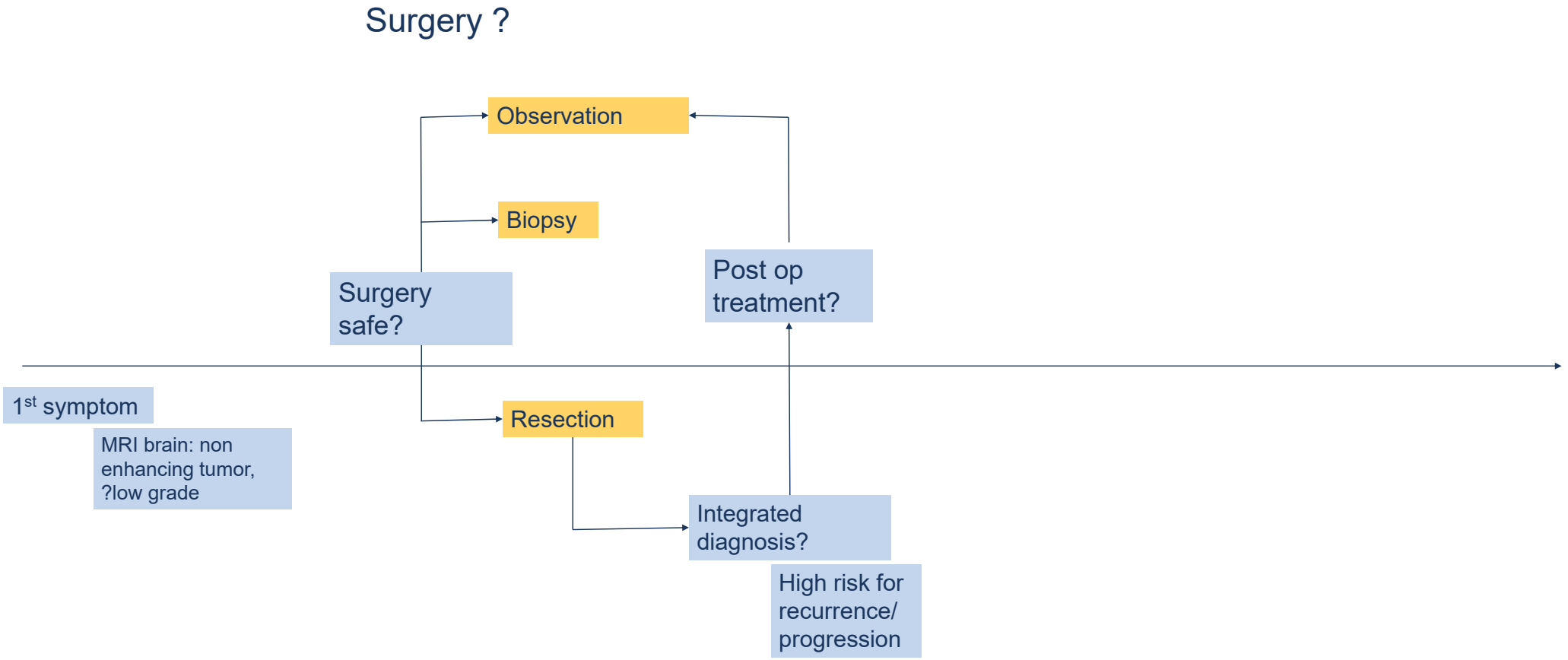
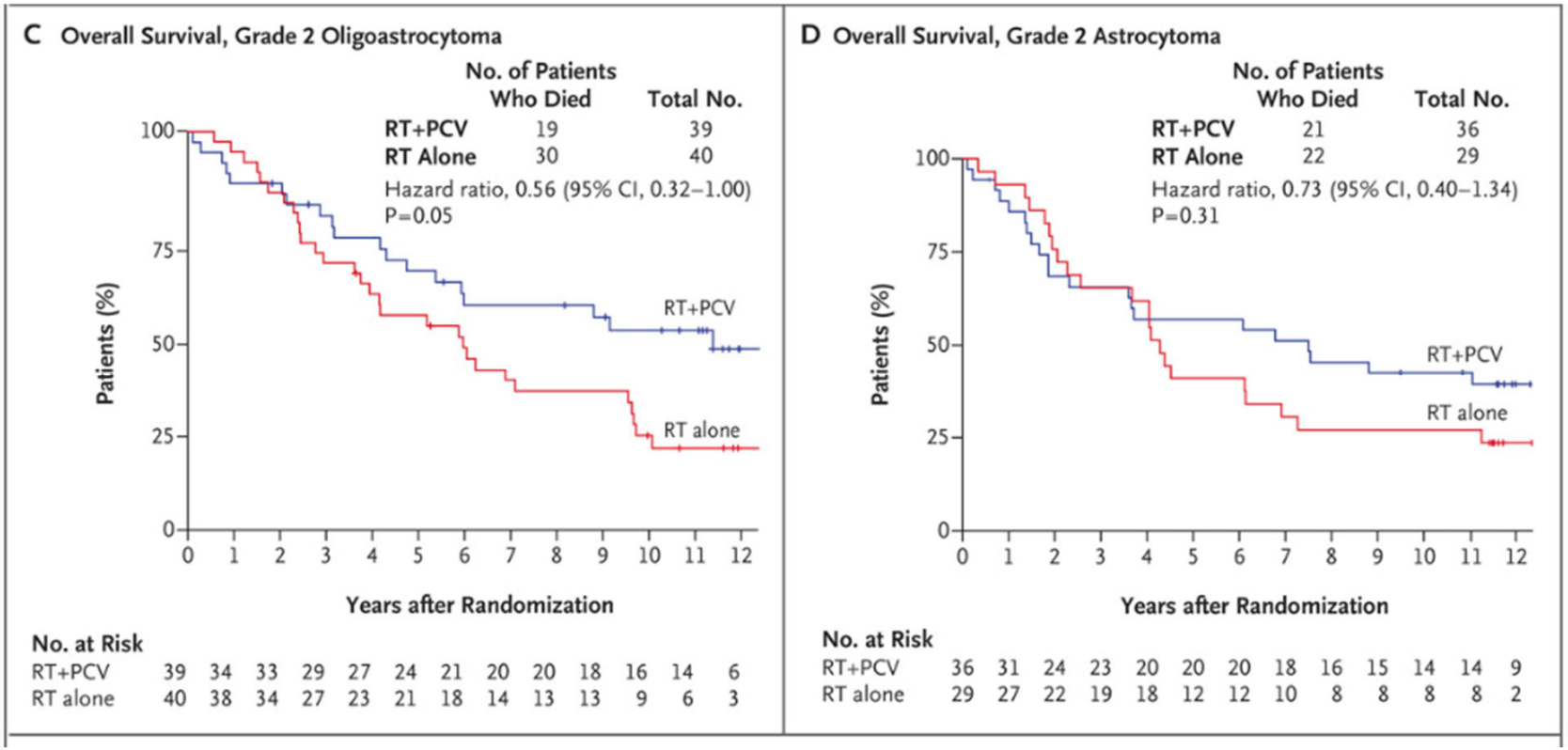
Low grade glioma- Management pathway



High risk LGG: >40 years of age or subtotal resection

N Engl J Med 2016;374:1344-1355

High risk LGG: >40 years of age or subtotal resection



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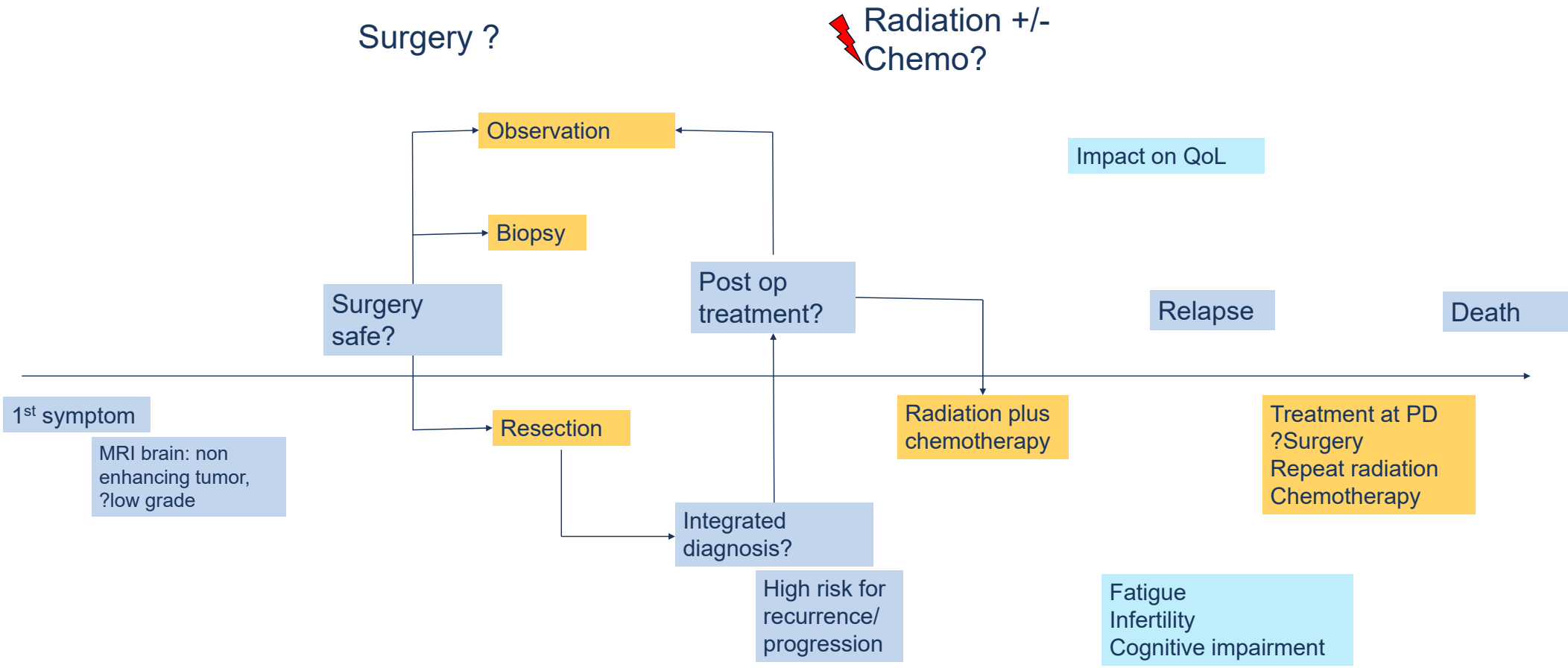
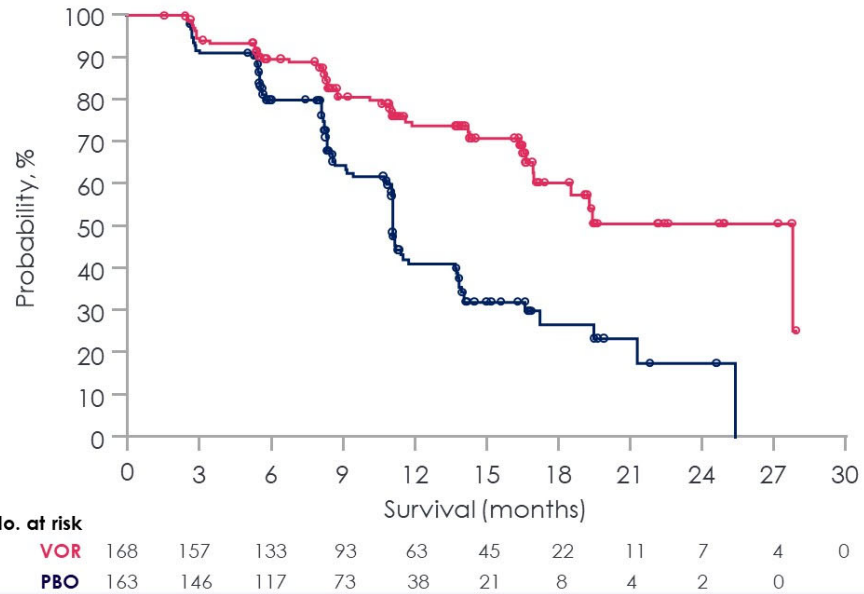
Low grade glioma- Management pathway



Vorasidenib in IDH mutant glioma

Primary endpoint: Treatment with vorasidenib significantly improved PFS per BIRC

Imaging-based PFS was defined as the time from randomization to the first radiographic disease progression as assessed by BIRC or death because of any cause



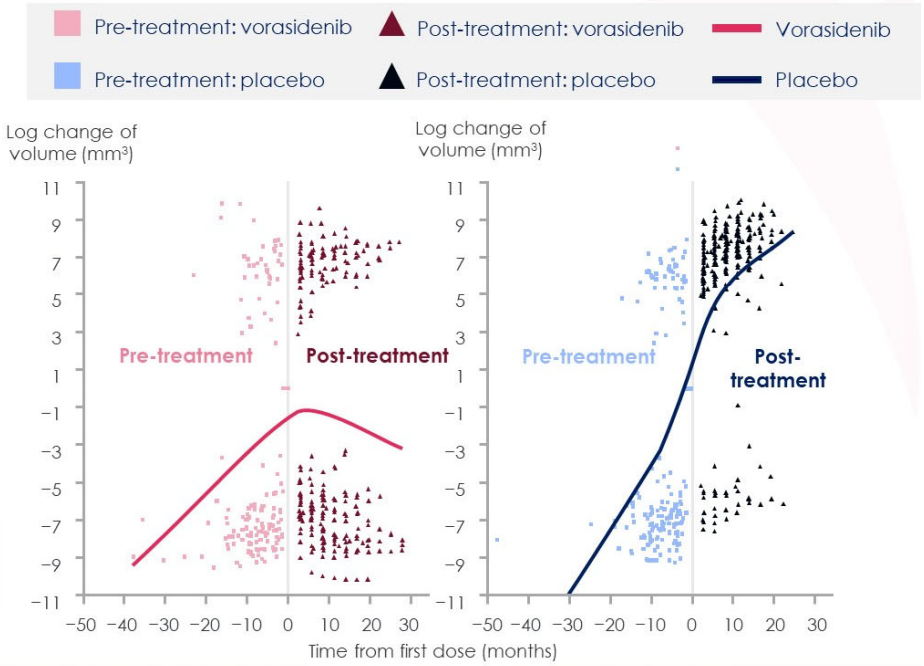
	Vorasidenib (N=168)	Placebo (N=163)
Median PFS, months (95% CI)	27.7 (17.0–NE)	11.1 (11.0–13.7)
HR (95% CI)	0.39 (0.27–0.56)	
One-sided *P* value	0.000000067	

[c]Censored. *P* value is from one-sided stratified log-rank test
NE, not estimable; PBO, placebo; PFS, progression-free survival; VOR, vorasidenib
Figure prepared from data on file at Servier
Mellinghoff IK *et al. N Engl J Med* 2023;389:589–601

Vorasidenib in IDH mutant glioma

Tumor growth continued before treatment and then shrank during treatment with vorasidenib

	n		TGR (95% CI)
Vorasidenib (N=168)	56	**Pre-treatment**	13.2% (10.3, 16.3)
		Post-treatment	−3.3% (−5.2, −1.2)
Placebo (N=163)	67	**Pre-treatment**	18.3% (15.0, 21.7)
		Post-treatment	12.2% (9.5, 14.9)
Difference of slope change (95% CI)			11.0% (4.5, 17.8; *P*<0.001)



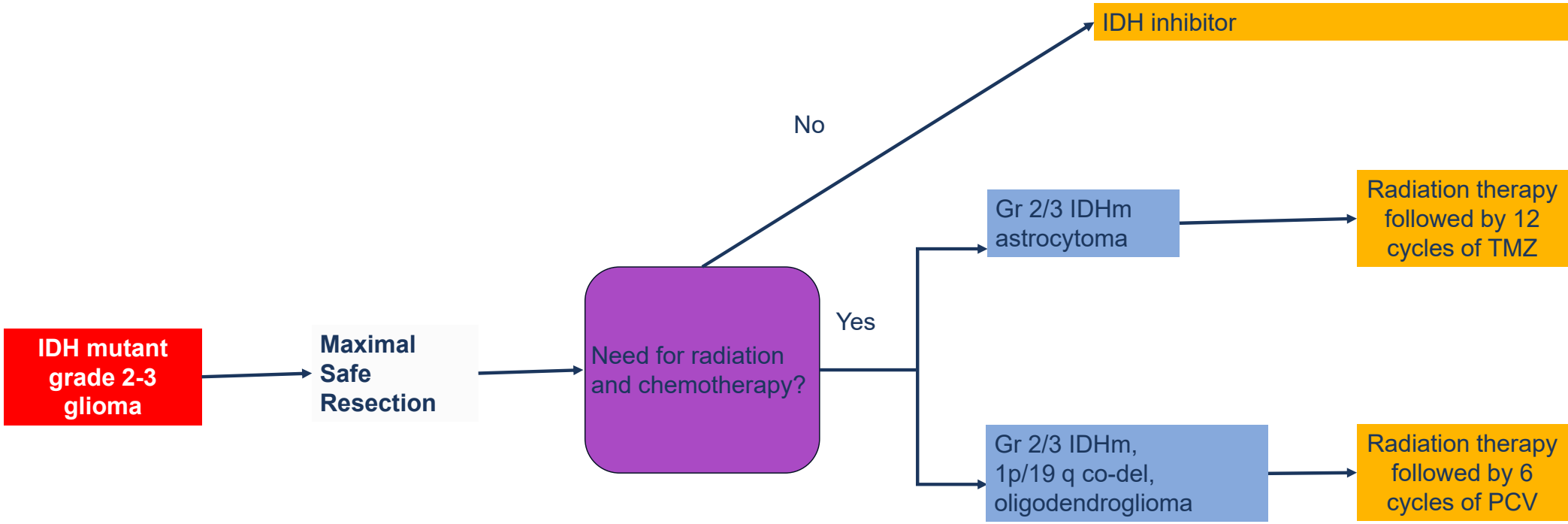
MRI scans were performed at baseline and every 12 weeks on-treatment; up to three pre-treatment scans were requested when available. Tumor volumes were derived per BIRC using a semi-automated approach. TGR was defined as % change in tumor volume every 6 months. n was the number of patients who had at least one volume record during the pre-treatment period and the post-treatment period. The difference in TGR in each arm was assessed by slope of tumor growth over time using a linear mixed model. The *P* value was calculated from a two-sided t-test. The log change of volume was plotted against time from randomization based on non-parametric LOESS regression.

Diagnosed young with a brain tumor, Brian Fauntleroy maximizes quality of life through a clinical trial

Brian and Rachel FauntLeRoy

https://www.fredhutch.org/en/news/blog/2021/08/diagnosed-young-with-a-brain-tumor-brian-fauntleroy-maximizes-quality-of-life.html

Future treatment plan for IDH mutant glioma?



Grade 2 and 3 Glioma (LGG): Management

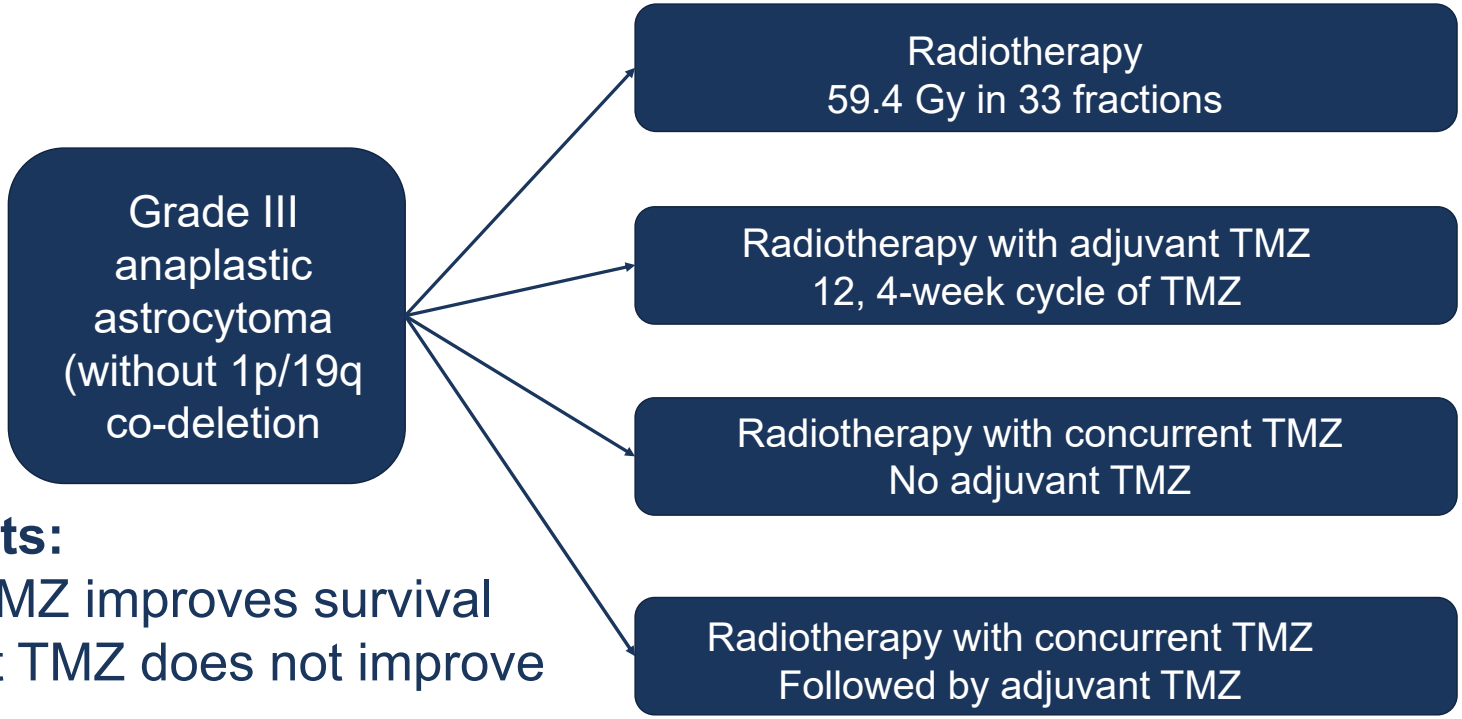
WHO grade 2 glioma: Younger patients 20- 40 year old

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

WHO grade 3 glioma: ?Treated like GBM

Studies to Watch out for

CATNON TRIAL



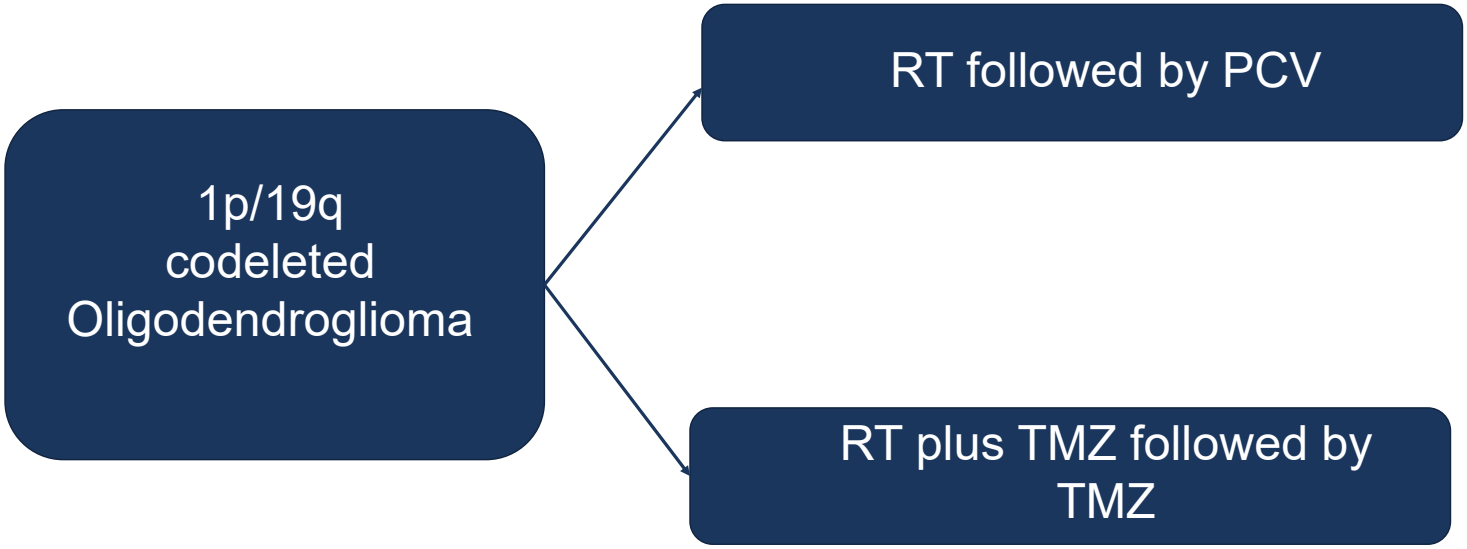
Interim results:

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

Lancet. 2017 Oct 7;390(10103):1645-1653

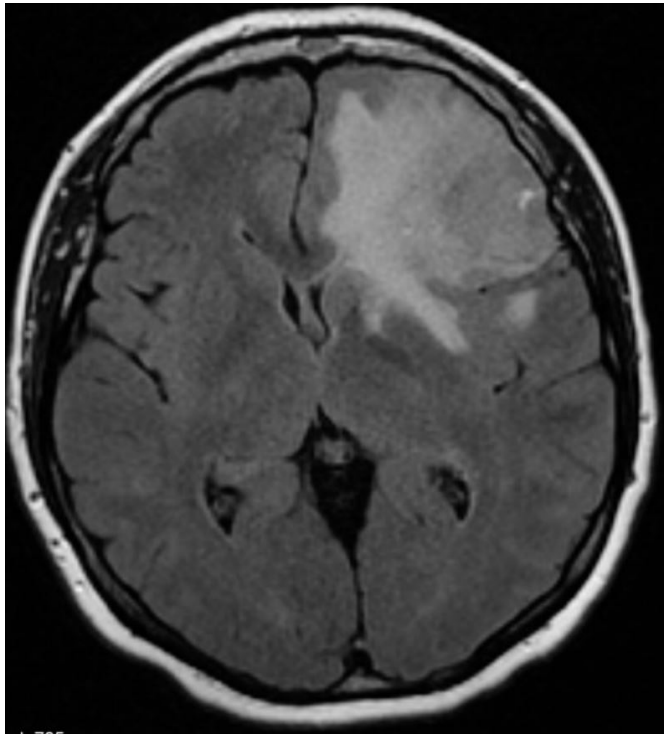
Studies to Watch out for

CODEL trial

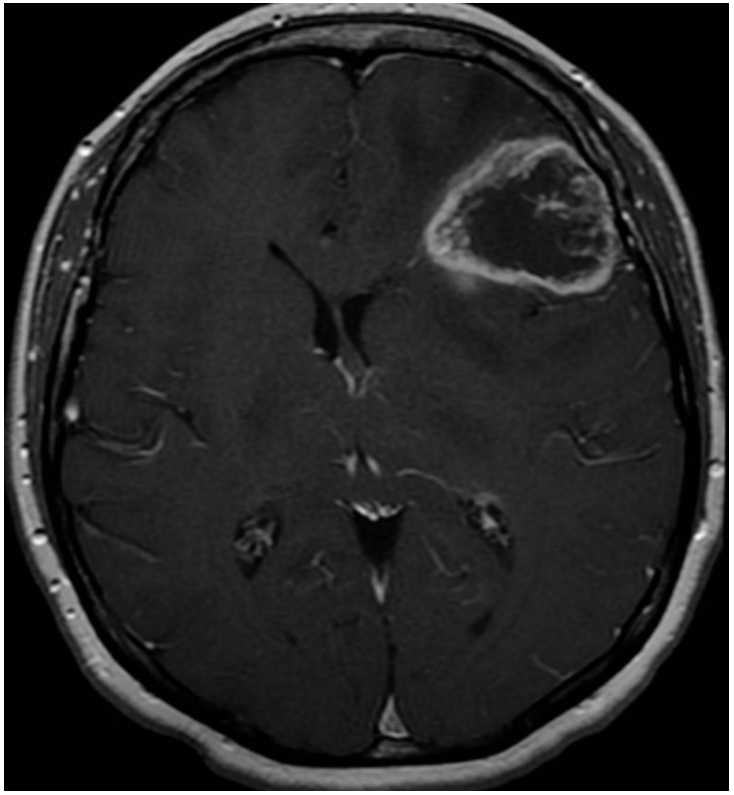


Glioblastoma (GBM)

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

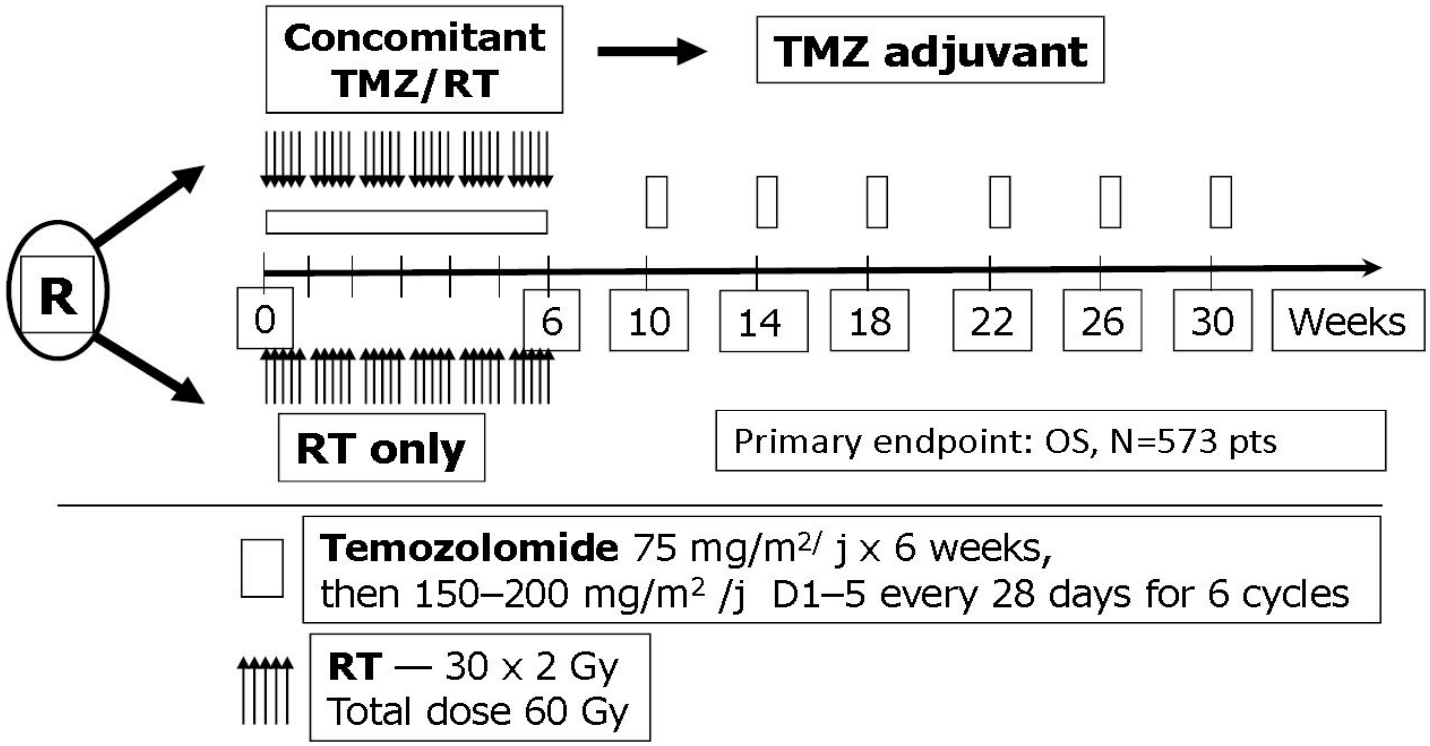


T2-FLAIR



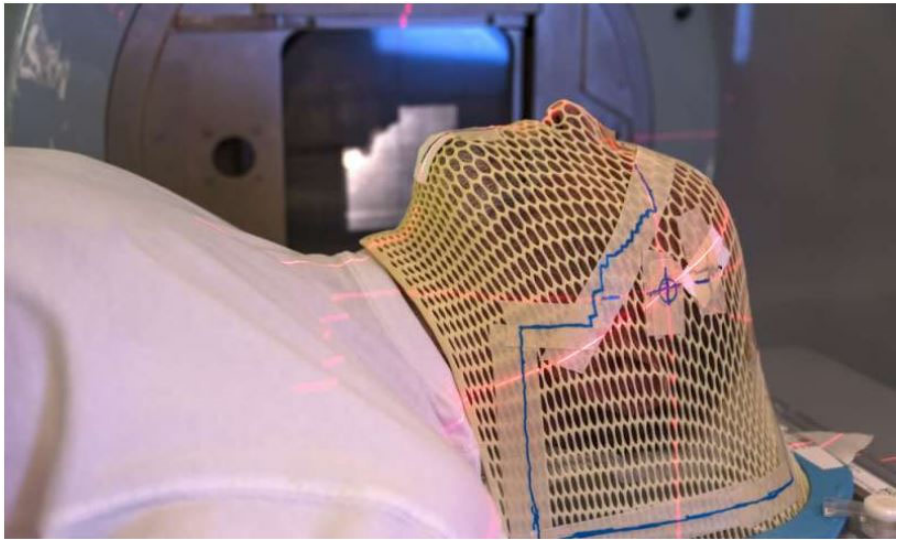
T1 post contrast

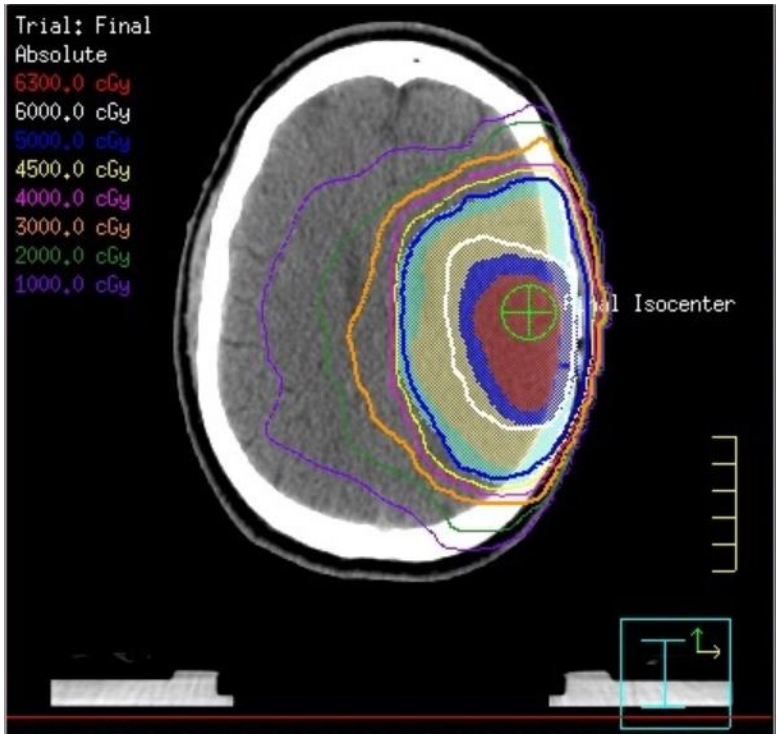
GBM-Treatment



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

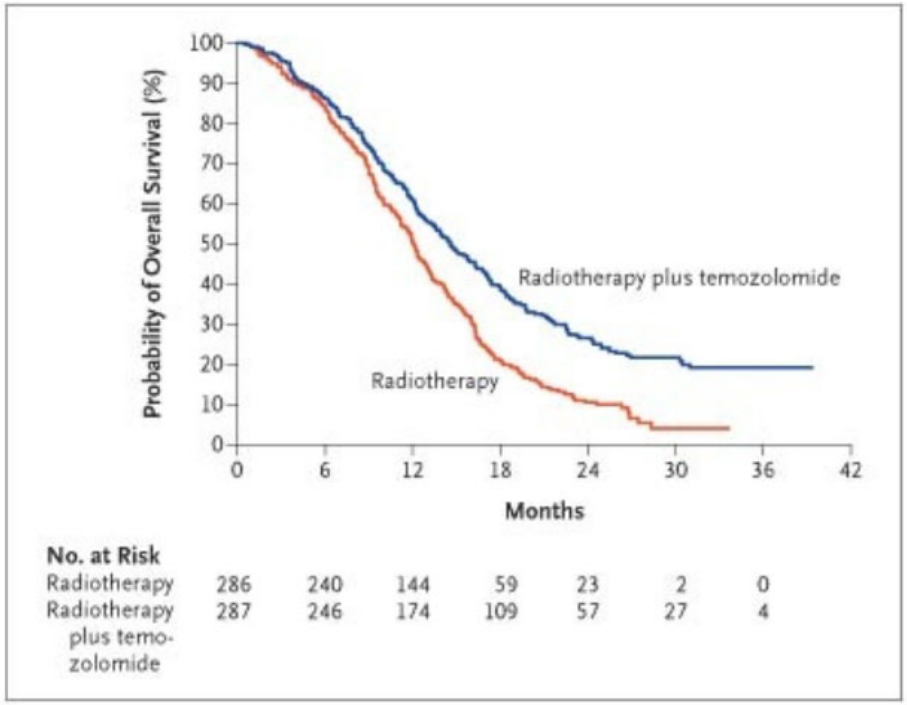


Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
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)

NEJM 2005; 352:987-996

MGMT methylation

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

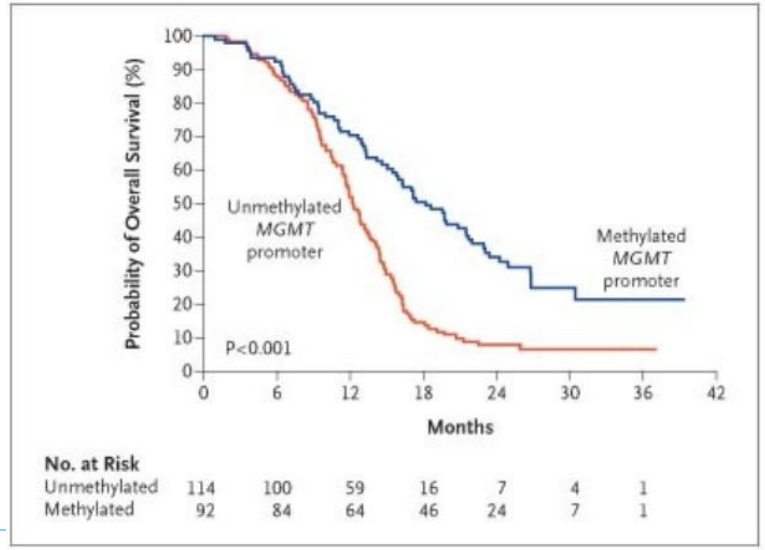


Table 1. Effect of *MGMT* Promoter Methylation Status on Survival, According to Random Treatment Assignment.*

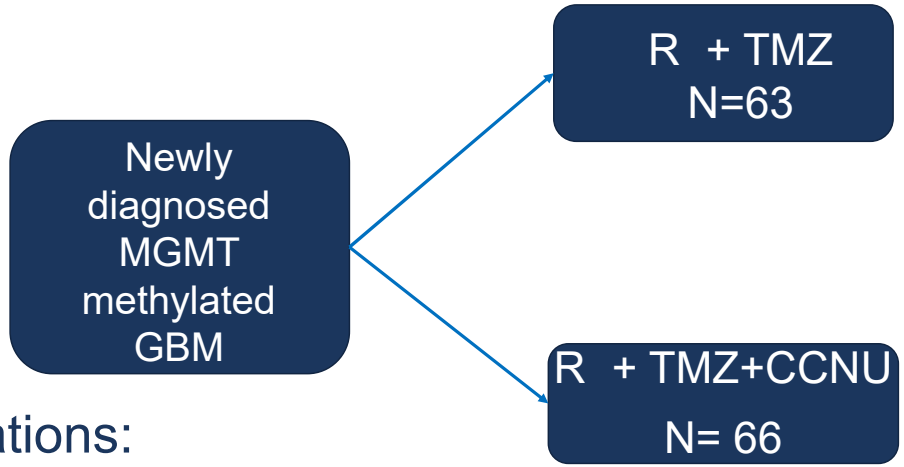
Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
Methylated *MGMT* promoter		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.48 (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)
Unmethylated *MGMT* promoter		
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)

NEJM 2005; 352:997-1003

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 atleast 18 hours/day
- Pros: Survival benefit,
- Cons: Non-blinded study, no placebo, QoL?
- Not yet widely accepted

CeTeG/NOA-09: MGMT Methylated GBM



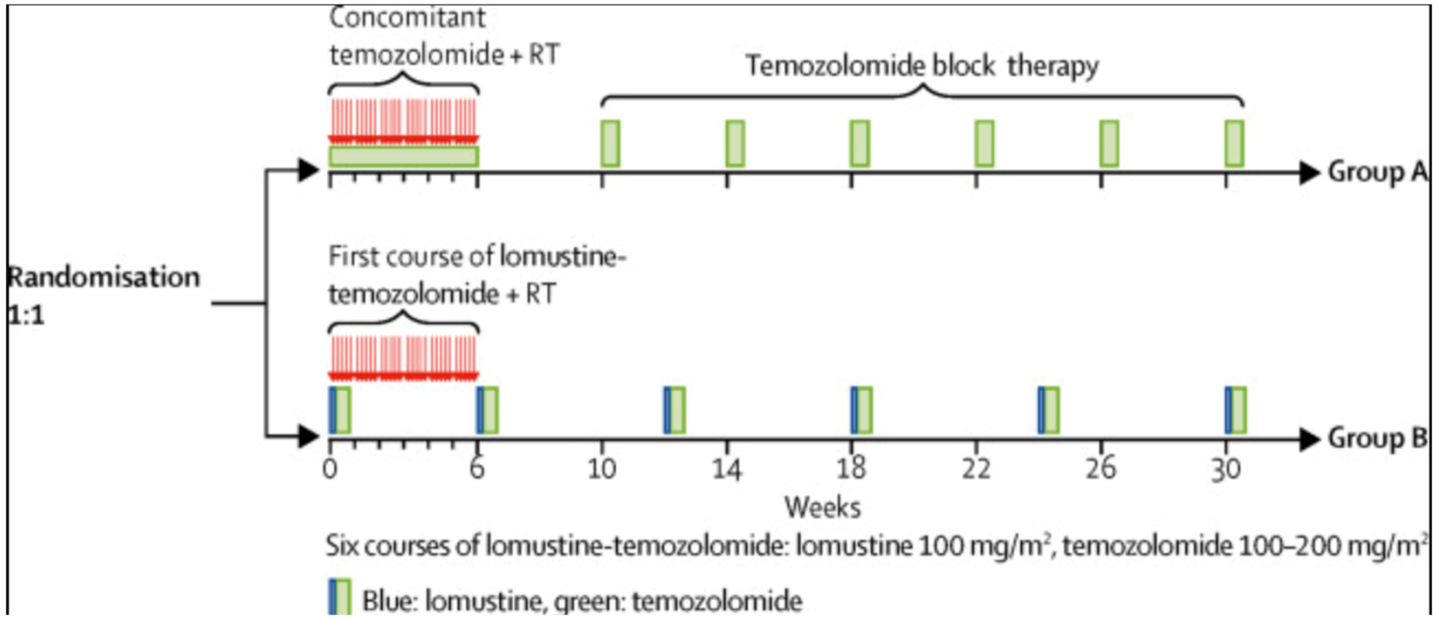
	RT+ TMZ	RT+ TMZ+CCNU
PFS	16.7 months	16.7 months
OS	30.9 months	49.6 months

Limitations:

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

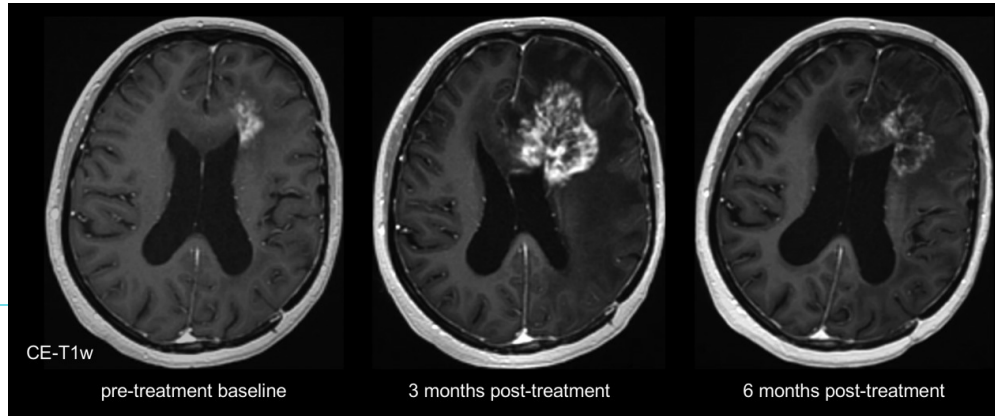
Glioblastoma Treatment: CCNU plus TMZ

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



JMRI, Volume: 48, Issue: 3, Pages: 571-589

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

- VEFG 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

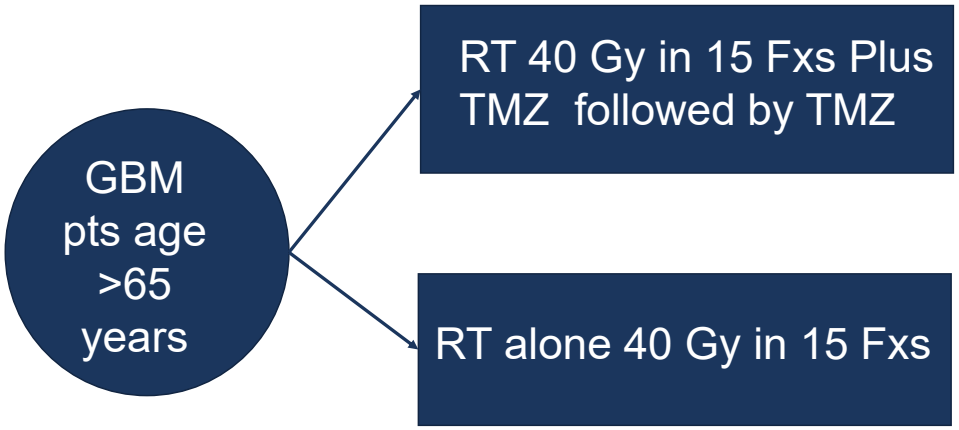
Recurrent GBM					
Trial	**Phase**	**N**	**Intervention**	**Median PFS (95% CI), mo**	**Median OS (95% CI), mo**
Friedman et al,[26] 2009	II	167	Bev	4.2 (2.9–5.8)	9.2 (8.2–10.7)
			Bev + irinotecan	5.6 (4.4–6.2)	8.7 (7.8–10.9)
Taal et al,[27] 2014	II	148	Lomustine	1 (1–3)	8 (6–11)
			Bev	3 (3–4)	8 (6–9)
			Bev + lomustine	4 (3–8)	12 (8–13)
Field et al,[28] 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,[29] 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)
Newly Diagnosed GBM					
Herrlinger,[30] 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,[31] 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,[32] 2014	III	921	TMZ/RT + TMZ	6.2 (NR)	16.7 (NR)
			Bev/TMZ/RT + Bev/TMZ	10.6 (NR)	16.8 (NR)
Unresectable GBM					
Chauffert et al,[33] 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.

The Cancer Journal Issue: Volume 24(4), July/August 2018, p 180-186

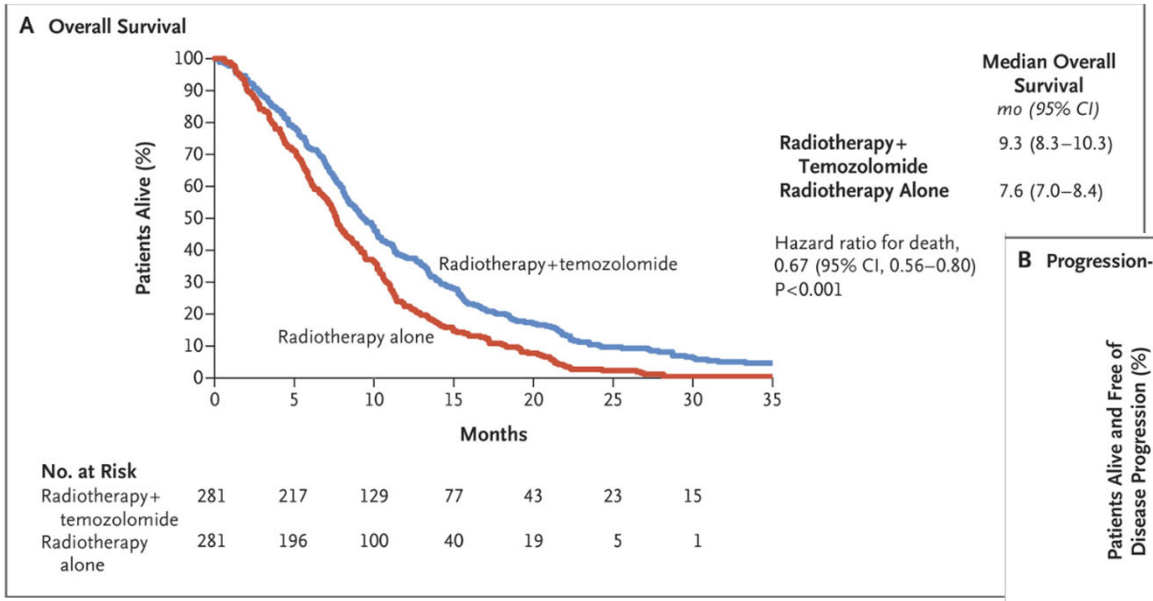
GBM In Elderly

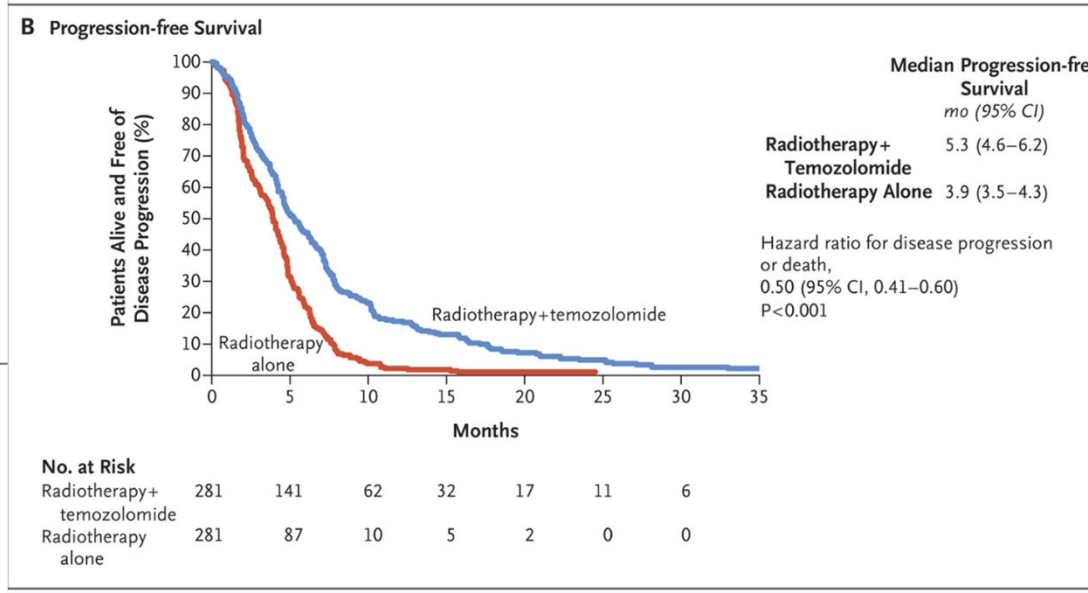
Hypofractionated RT plus TMZ vs. hypofractionated RT alone



N Engl J Med 2017; 376:1027-1037

GBM In Elderly

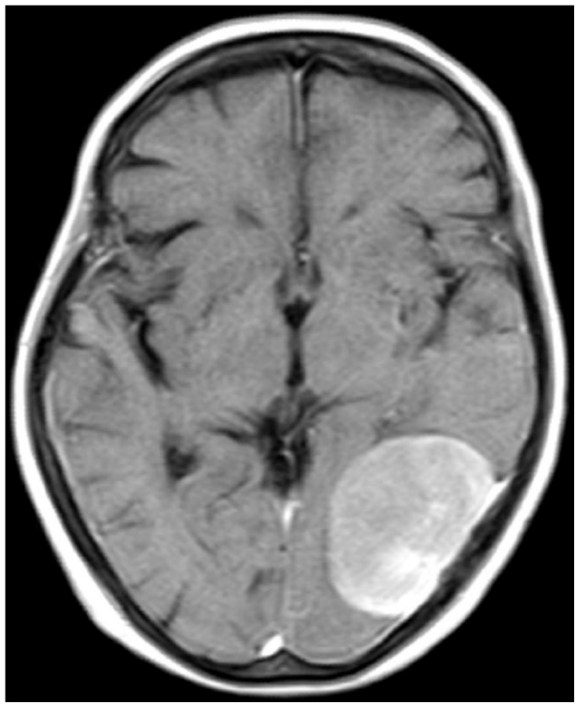




No consensus for treatment in elderly

N Engl J Med 2017; 376:1027-1037

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 1: Surgical resection is curative

WHO grade 2: (high mitotic index): Surgery +/- RT

WHO grade 3: (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/m2 to 8 gm/m2): 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

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.

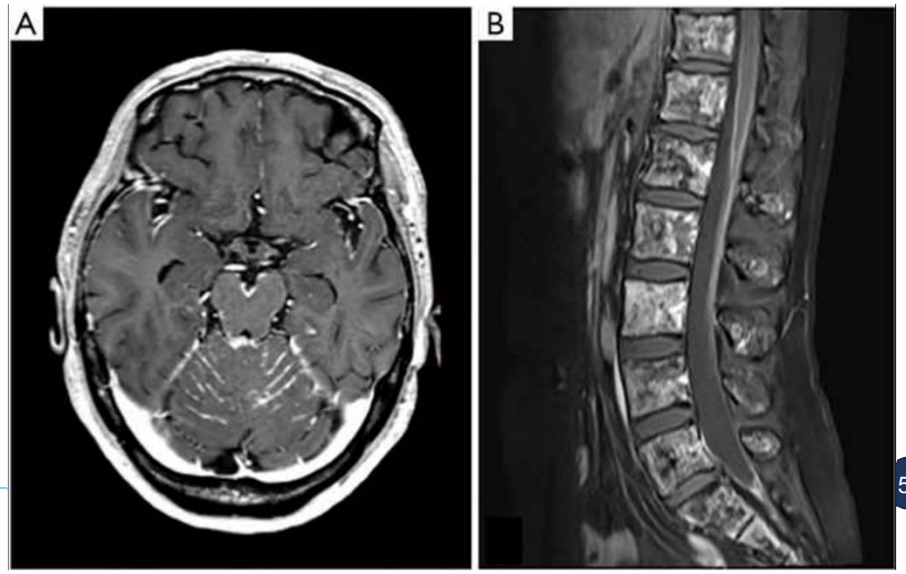
Melanoma: BRAF inhibitors, ipilimumab plus nivolumab, pembrolizumab

Lung: Osimertinib, brigatinib, lorlatinib, pembrolizumab

Breast: Tucatinib, trastuzumab-deruxtecan,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



Fred Hutch Cancer Center

Thank You.