Primary Brain Tumours in Adults: Overview of Epidemiology, Classification, Clinical Presentation, Treatment, Outcome and Goals of Rehabilitation

Warren P. Mason, MD, FRCPC, FAAN, FANA

Staff Physician, Department of Medicine, Princess Margaret Cancer Centre

Medical Director, Gerry and Nancy Pencer Brain Tumour Centre, Princess Margaret Cancer Centre

Kirchmann Family Chair in Neuro-Oncology Research

Professor of Medicine, University of Toronto

Disclosures

- **Relevant relationships with commercial entities:**
  - Have served as a consultant to Novocure, Cureteq, Century Therapeutics and Viatris in the past year
  - Involved in clinical trials sponsored by Roche, Agios, Lilly, AstraZeneca, Orbus Therapeutics, Karyopharm and Novocure
- **Potential for conflicts within this presentation:**
  - None
- **Steps taken to review and mitigate potential bias:**
  - During my lecture I will identify all agents that are not approved for CNS tumours but are currently in development for and under investigation in brain cancers, and will be adhering to national/international guidelines for all agents currently approved.

Learning Objectives

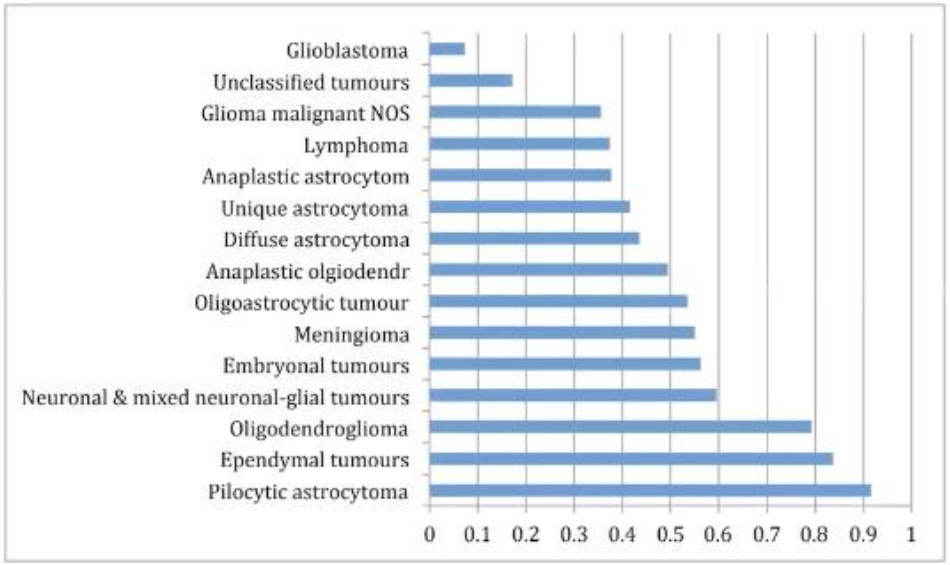
1. Understand how the revised WHO Classification of primary brain tumours in adults can be used to guide therapy and inform prognosis.
2. Be familiar with the current therapeutic approaches to patients with primary brain tumours.
3. Understand how goals of rehabilitation are influenced by tumour diagnosis, prognosis and performance status of patients with primary brain tumours.

Brain Tumors in Canada

- 27 new primary brain tumor cases per day
- Glioblastoma (GBM) is the most common primary brain tumor 4.1/100,000 per year
- Overall survival for GBM remain poor (<10% over 5 years), better prognosis in other types of gliomas

Brain Tumour Registry of Canada (BTRC):
Survival Report 2010 - 2015

Figure 5: 5-year survival for adults (20+) with malignant brain and CNS tumors by histology.



Epidemiology: Common gliomas in adults

- Grade 4
  - GBM
- Grade 3
  - Anaplastic astrocytoma
  - Anaplastic oligodendroglioma
- Grade 2
  - Low grade astrocytoma
  - Low grade oligodendroglioma
- Grade 1
  - Pilocytic astrocytoma

CNS Tumor Classification

2007

WHO CNS 3rd edition

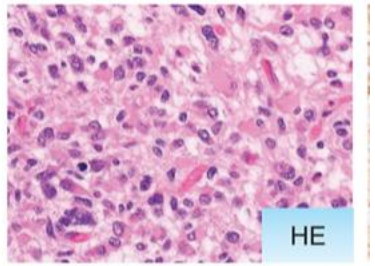
Astrocytoma/Oligodendroglioma

Grade 2
- Increase cellularity
- Nuclear atypia

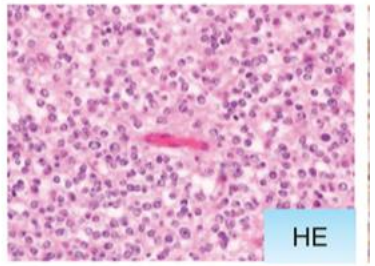
Grade 3 (Anaplastic)
- Nuclear pleomorphism
- Mitotic activity
- Microvascular proliferation

Grade 4 (Glioblastoma)
- Highly pleomorphic
- Microvascular proliferation
- Pseudopallisading necrosis

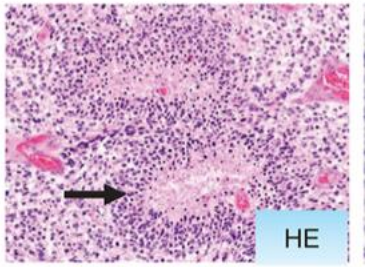
Anaplastic astrocytoma



Anaplastic oligodendroglioma



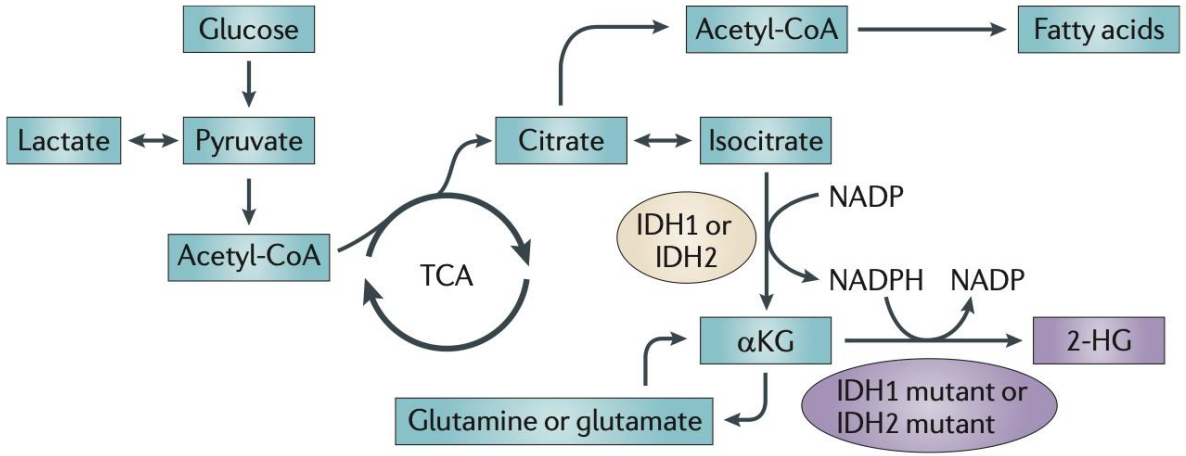
Glioblastoma IDH-wildtype



CNS Tumor Classification

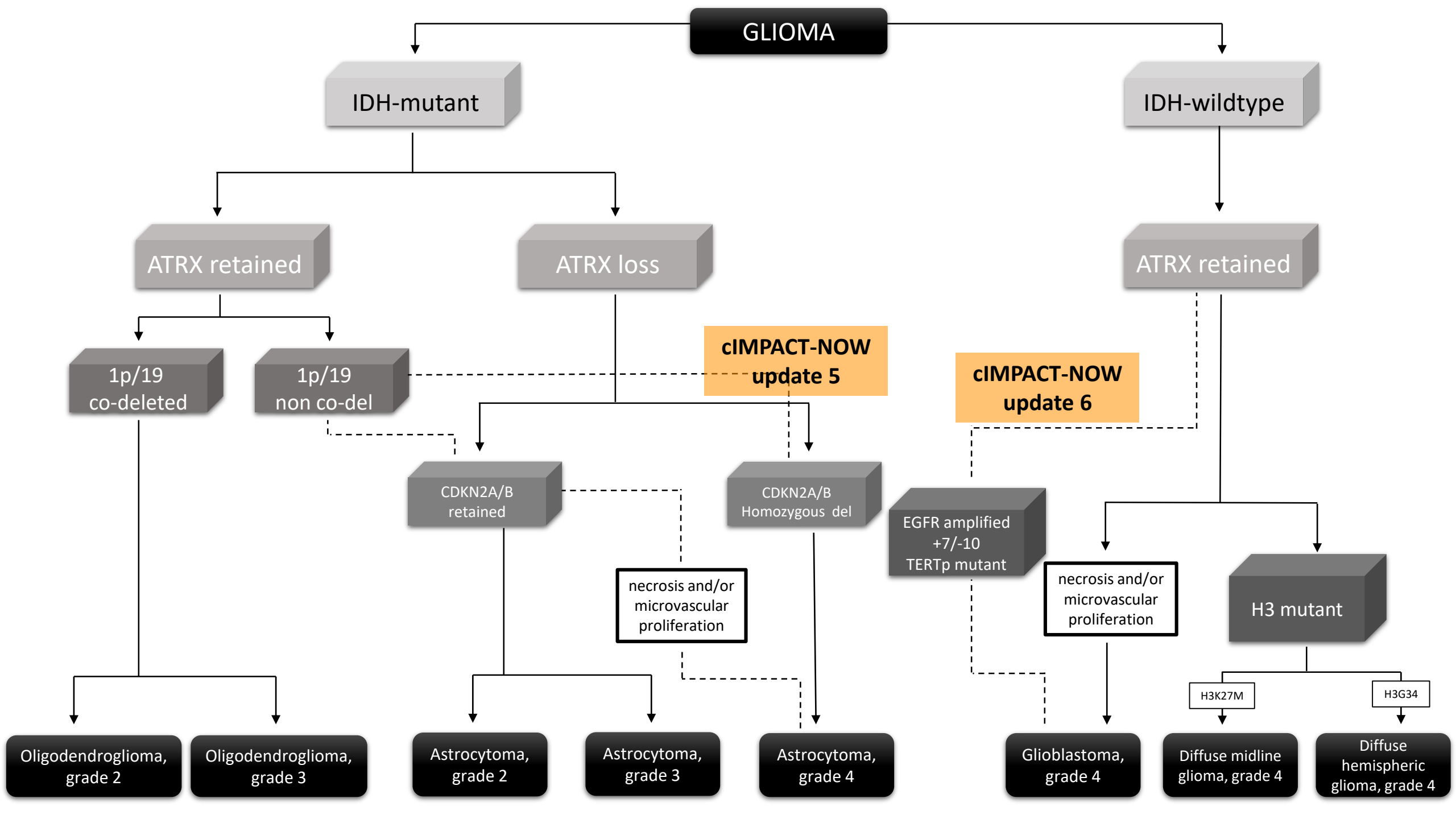
2009

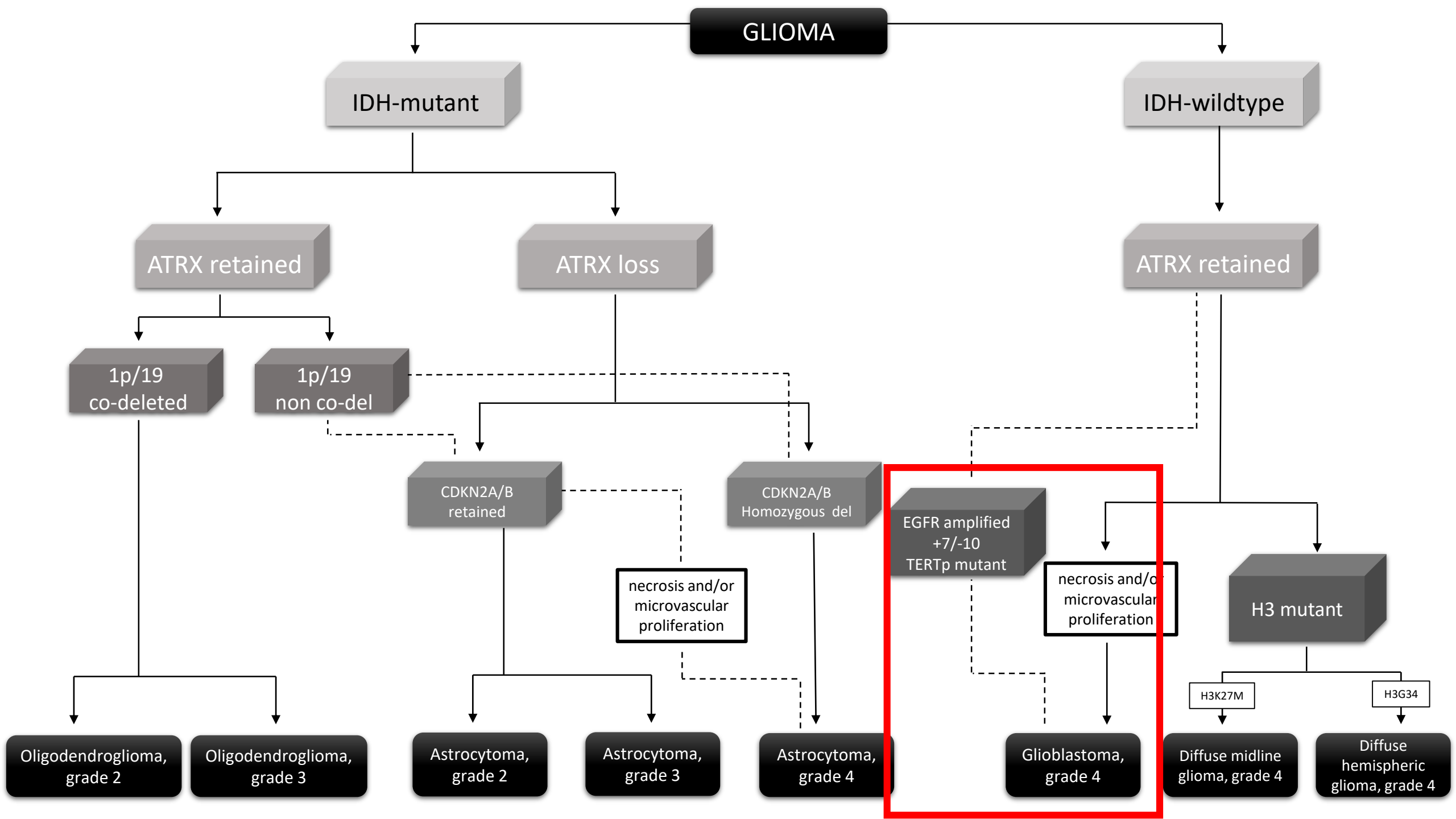
IDH MUTATION



Cairns et al. Nature Reviews. 2011

- observed in **70-80% of WHO Grade II and III glioma**, 5-10% WHO Grade IV glioma
- **IDH1 R132H mutation** (>80%) by IHC
- Non canonical mutations in IDH1 or IDH2 identified by sequencing
- prognostic biomarker
- predictive of chemotherapy sensitivity in gliomas


GLIOMA
IDH-mutant
IDH-wildtype
ATRX retained
ATRX loss
ATRX retained
1p/19 co-deleted
1p/19 non co-del
cIMPACT-NOW update 5
cIMPACT-NOW update 6
CDKN2A/B retained
CDKN2A/B Homozygous del
EGFR amplified +7/-10 TERTp mutant
necrosis and/or microvascular proliferation
necrosis and/or microvascular proliferation
H3 mutant
H3K27M
H3G34
Oligodendroglioma, grade 2
Oligodendroglioma, grade 3
Astrocytoma, grade 2
Astrocytoma, grade 3
Astrocytoma, grade 4
Glioblastoma, grade 4
Diffuse midline glioma, grade 4
Diffuse hemispheric glioma, grade 4


GLIOMA
IDH-mutant
IDH-wildtype
ATRX retained
ATRX loss
ATRX retained
1p/19 co-deleted
1p/19 non co-del
CDKN2A/B retained
CDKN2A/B Homozygous del
EGFR amplified +7/-10 TERTp mutant
necrosis and/or microvascular proliferation
necrosis and/or microvascular proliferation
H3 mutant
H3K27M
H3G34
Oligodendroglioma, grade 2
Oligodendroglioma, grade 3
Astrocytoma, grade 2
Astrocytoma, grade 3
Astrocytoma, grade 4
Glioblastoma, grade 4
Diffuse midline glioma, grade 4
Diffuse hemispheric glioma, grade 4

GBM: Incidence

- 3.7/100, 000 per year
- Incidence appears to be increasing
- Peak incidence in 7^{th} decade
- Sexes equally affected with slight male preponderance

GBM: Symptoms

- Symptoms and neurologic findings are determined by location and size of tumour
  - Increased intracranial pressure can cause headaches, nausea and vomiting, diminished sensorium
  - Seizures occur In approximately 25%
  - Focal weakness, aphasia, memory and concentration problems, impaired sensation and vision are common

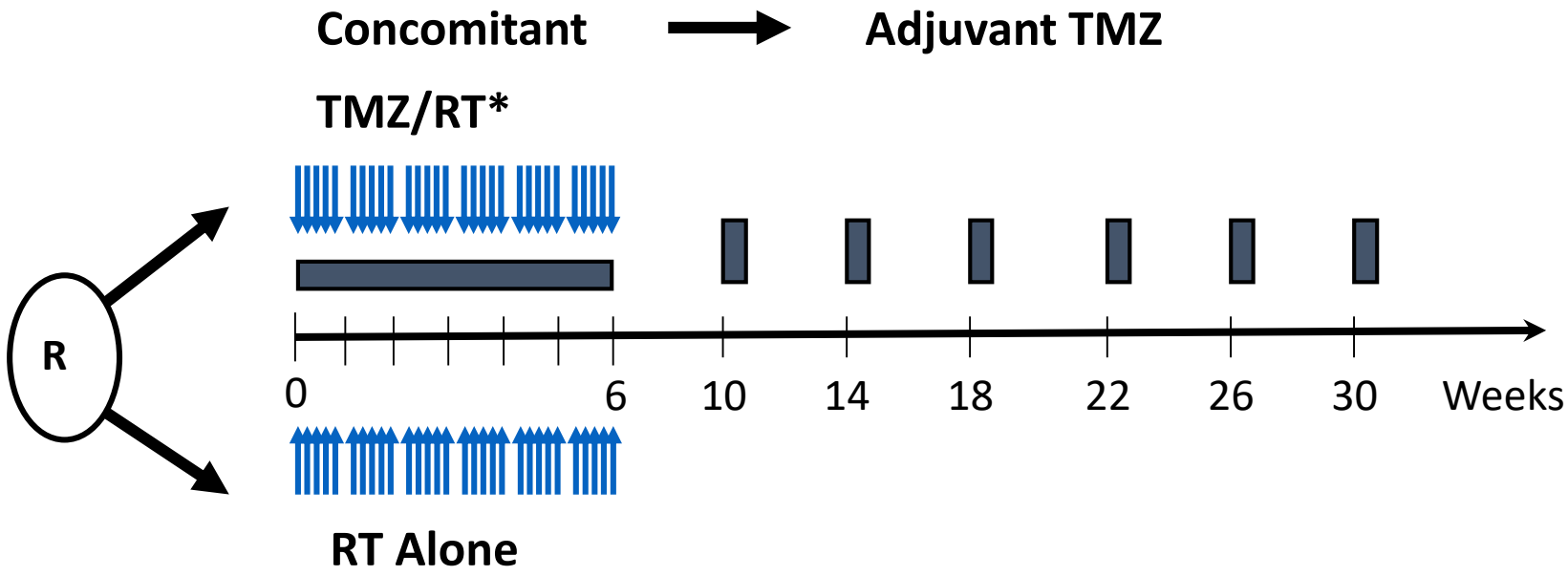
GBM: Initial Management

- Maximal safe surgical resection
  - Establishes pathologic diagnosis
  - Can relieve symptoms and neurologic deficits
  - Prolongs life
- Further treatment with radiotherapy and temozolomide chemotherapy is influenced by patient age and performance status
- Approximately 20% receive only palliative care due to very poor performance status at diagnosis

Temozolomide for Glioma

- Developed for CNS tumors
- Oral alkylating chemotherapy
- Excellent CNS/CSF penetration
- Rapid and complete absorption after oral administration
- Rapid renal elimination
- No cumulative toxicity
- Approved for recurrent glioblastoma and anaplastic astrocytoma in 1998

Treatment Schema



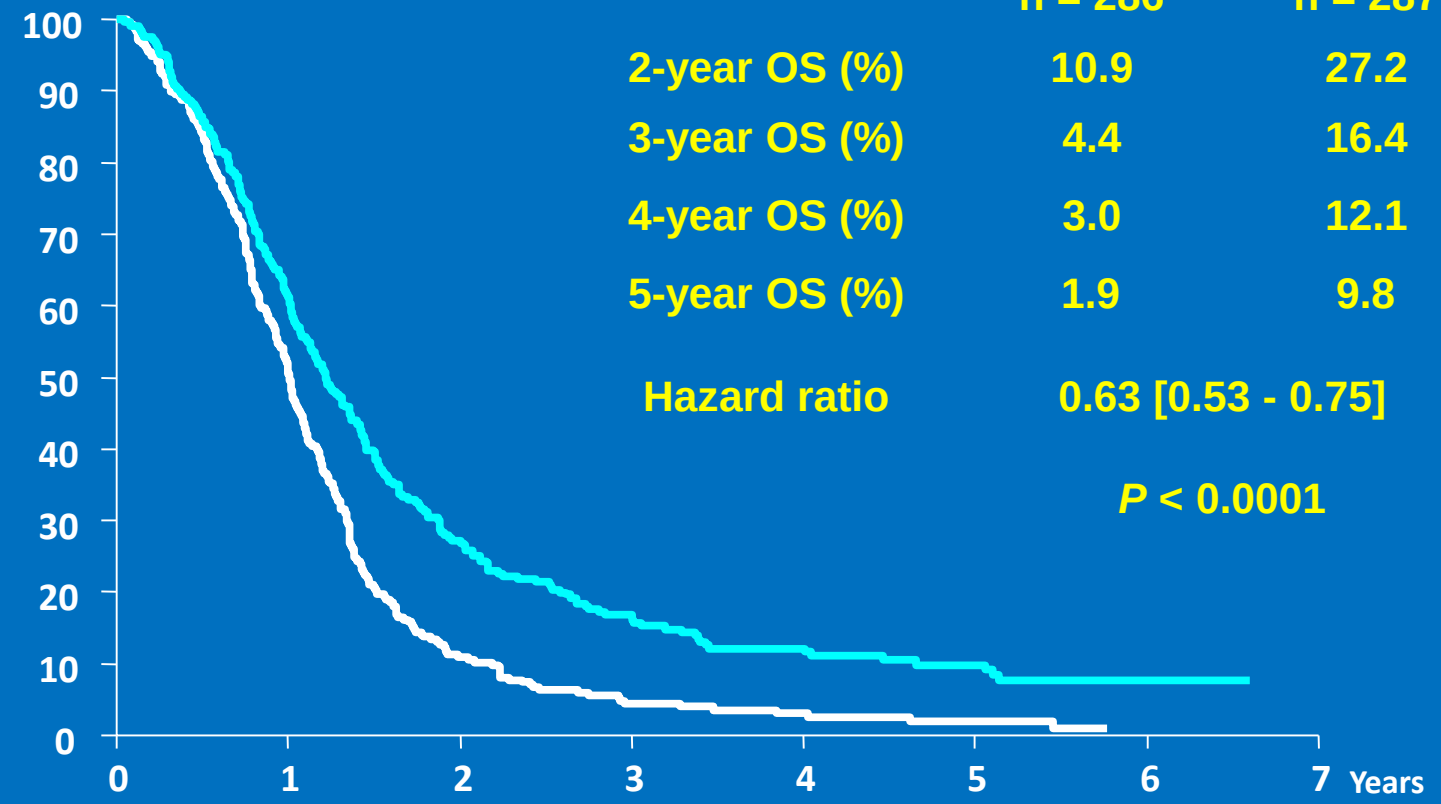
Temozolomide 75 mg/m^2 po qd for 6 weeks,
then 150–200 mg/m^2 po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

Results: Overall Survival

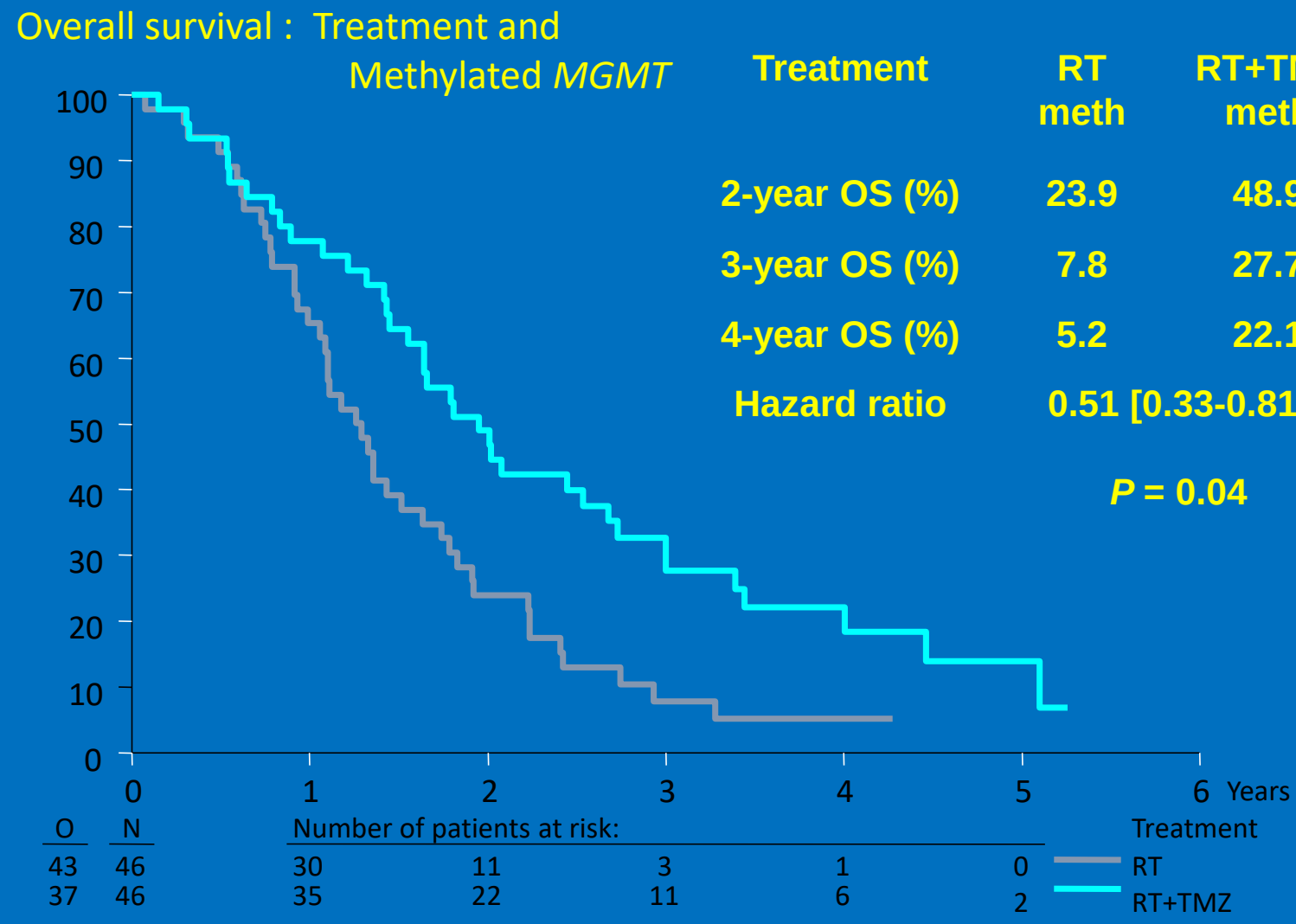
Treatment	RT n = 286	RT+TMZ n = 287
2-year OS (%)	10.9	27.2
3-year OS (%)	4.4	16.4
4-year OS (%)	3.0	12.1
5-year OS (%)	1.9	9.8
Hazard ratio	0.63 [0.53 - 0.75]	
	P < 0.0001	



O	N	Number of patients at risk:					
278	286	144	31	11	6	3	0
254	287	175	76	39	23	14	6

Treatment
RT
RT+TMZ

Overall Survival Methylated *MGMT* Promoter

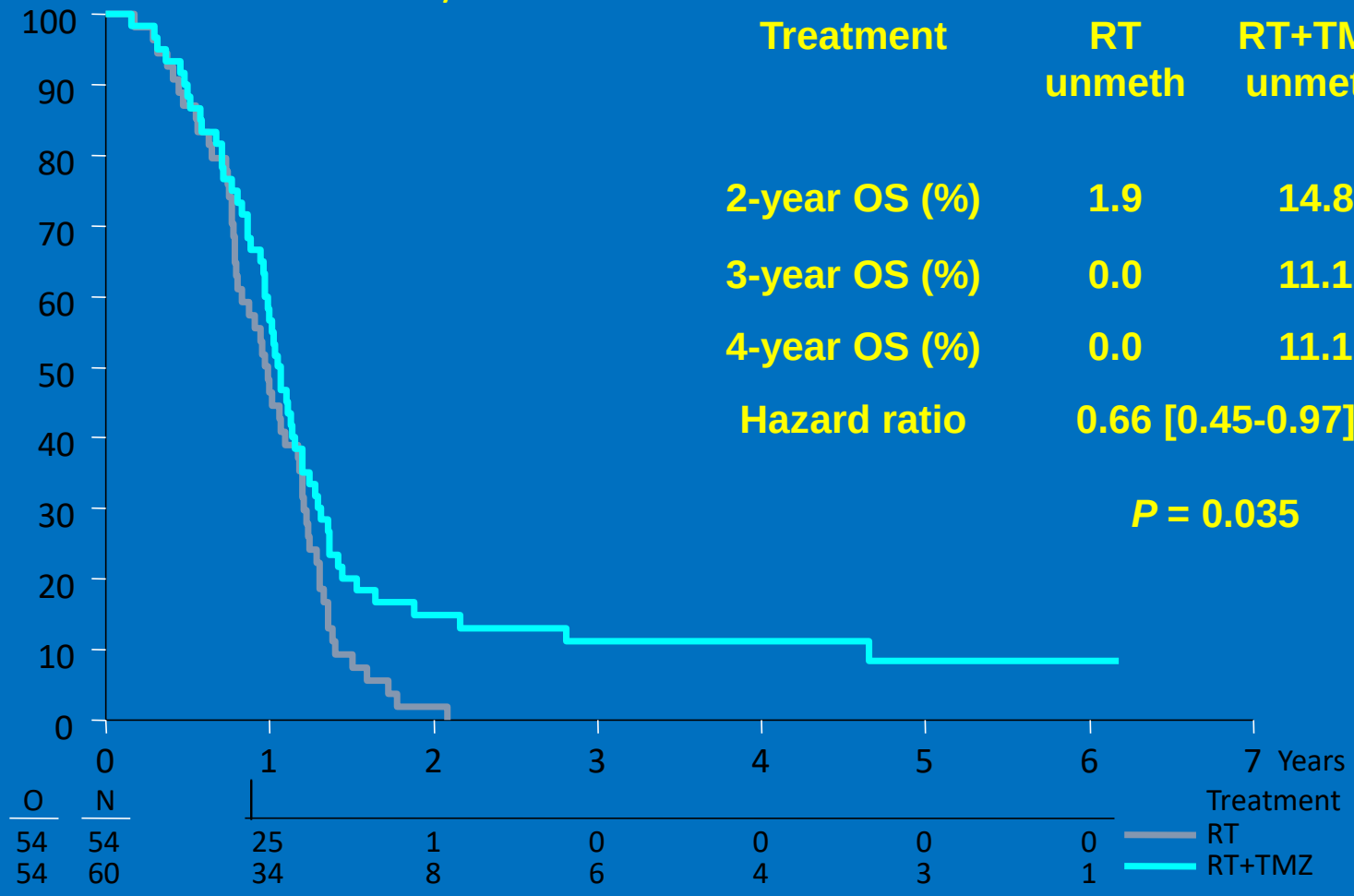


Treatment	RT meth	RT+TMZ meth
2-year OS (%)	23.9	48.9
3-year OS (%)	7.8	27.7
4-year OS (%)	5.2	22.1
Hazard ratio	0.51 [0.33-0.81]	

P = 0.04

Overall Survival
Unmethylated *MGMT* Promoter

Overall Survival: Treatment and Unmethylated *MGMT*



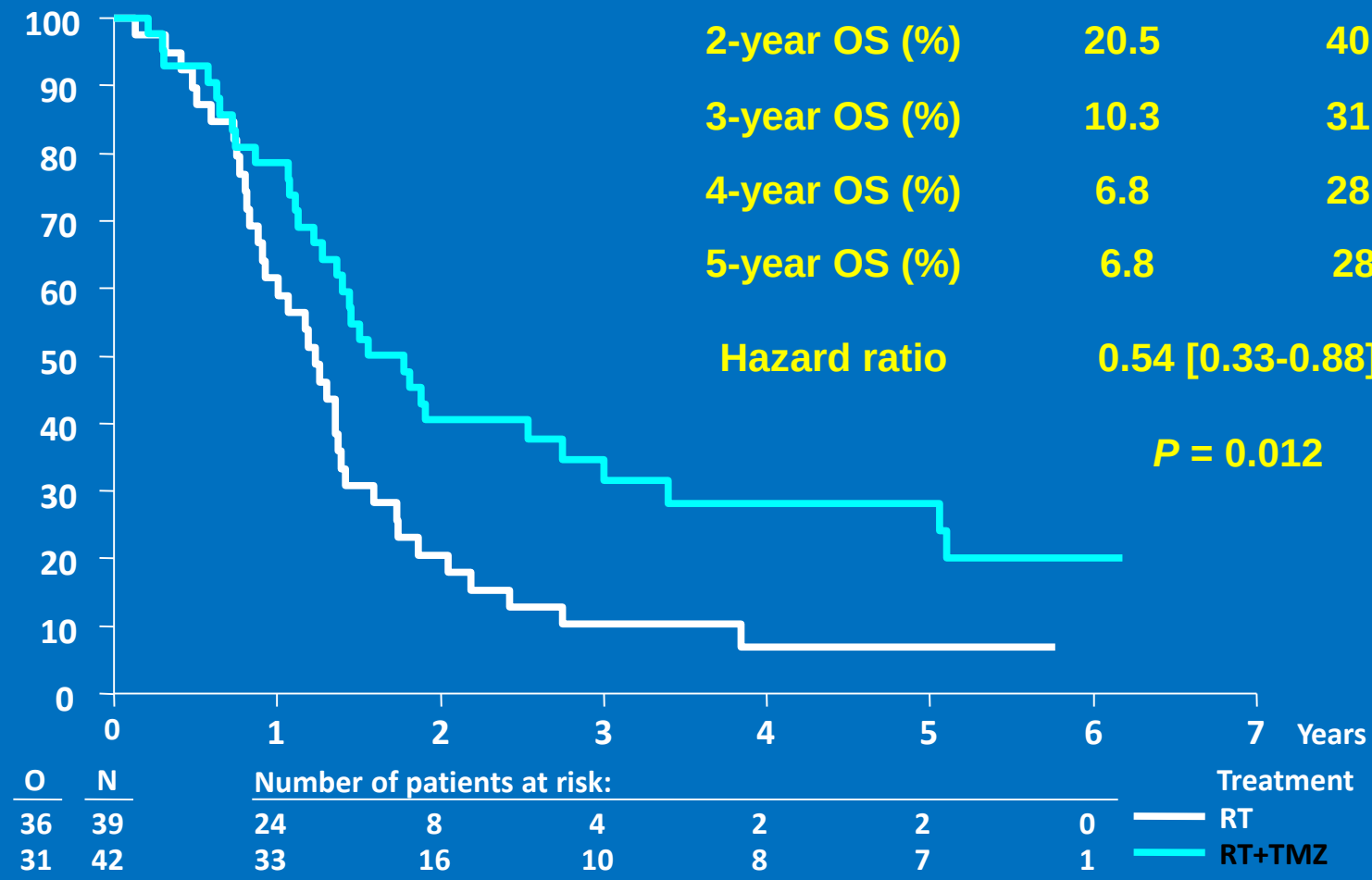
Treatment	RT unmeth	RT+TMZ unmeth
2-year OS (%)	1.9	14.8
3-year OS (%)	0.0	11.1
4-year OS (%)	0.0	11.1
Hazard ratio	0.66 [0.45-0.97]	
	P = 0.035	

EORTC RPA System

Class	
III	Age < 50, WHO PS 0 – 1
IV	Age < 50, WHO PS 2 or
	Age ≥ 50, MMSE ≥ 27 and resection
V	Age ≥ 50, MMSE < 27, and biopsy only

Results:
Overall Survival RPA III

Overall survival: Treatment in RPA class 3



Treatment	RT n = 286	RT+TMZ n = 287
2-year OS (%)	20.5	40.5
3-year OS (%)	10.3	31.5
4-year OS (%)	6.8	28.4
5-year OS (%)	6.8	28.0
Hazard ratio	0.54 [0.33-0.88]	

P = 0.012

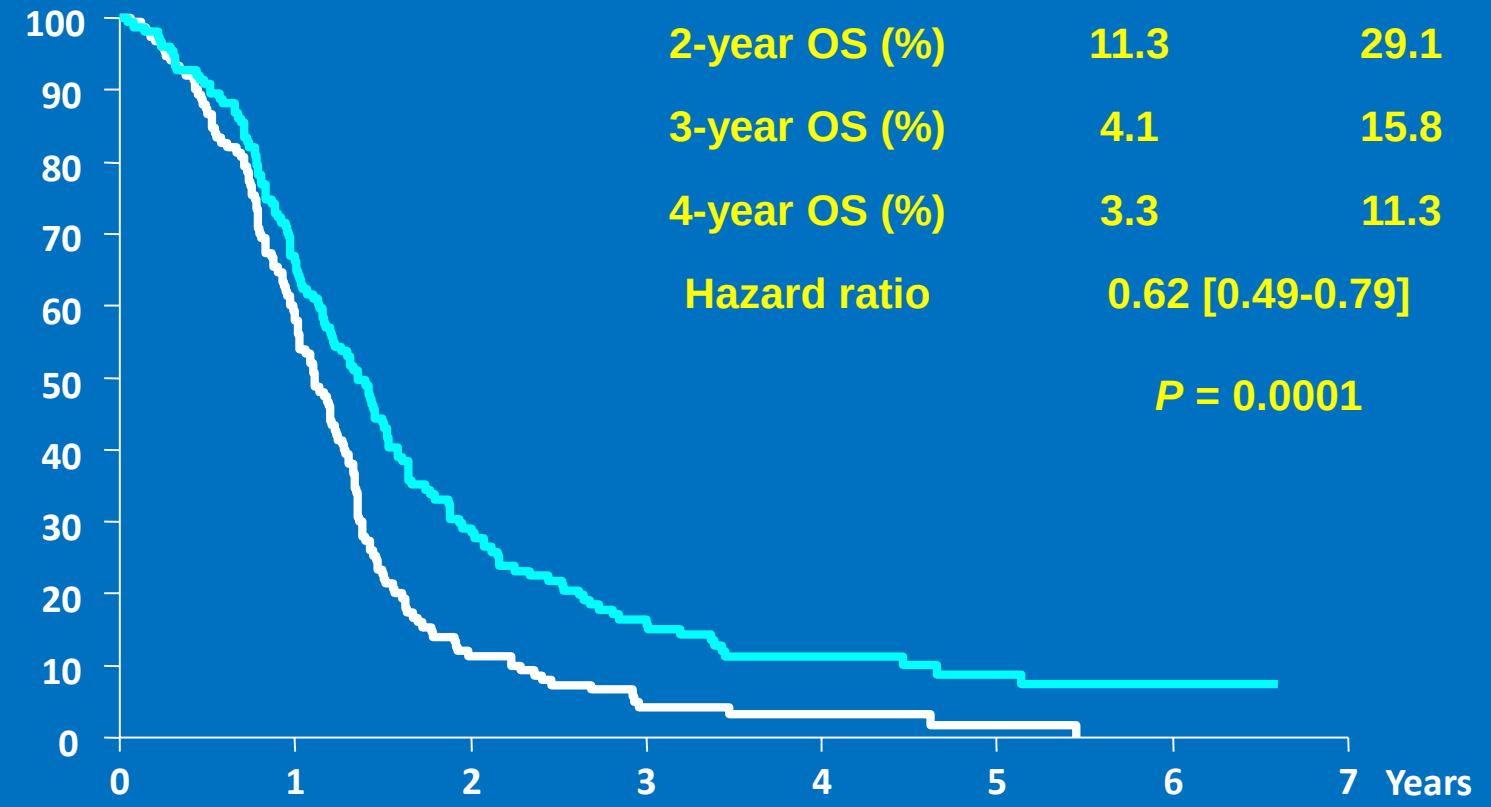
What are RPA Classes: The EORTC System

Class	
III	**Age < 50, WHO PS 0 – 1**
IV	**Age < 50, WHO PS 2 or**
	Age ≥ 50, MMSE ≥ 27 and resection
V	**Age ≥ 50, MMSE < 27, and biopsy only**

Results:
Overall Survival RPA IV

Treatment	RT n = 286	RT+TMZ n = 287
2-year OS (%)	11.3	29.1
3-year OS (%)	4.1	15.8
4-year OS (%)	3.3	11.3
Hazard ratio	0.62 [0.49-0.79]	

P = 0.0001

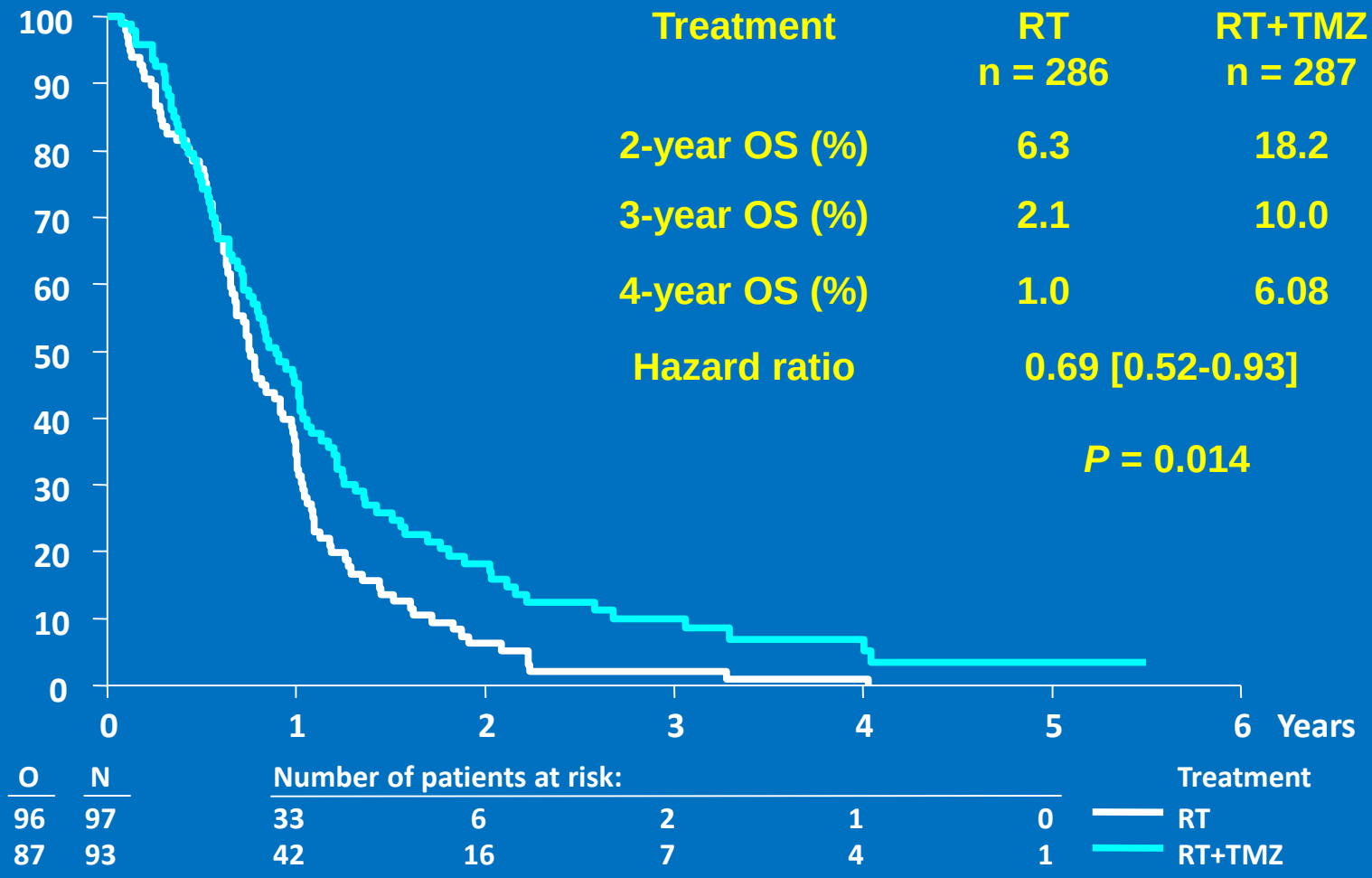


What are RPA Classes: The EORTC System

Class	
III	**Age < 50, WHO PS 0 – 1**
IV	**Age < 50, WHO PS 2 or**
	Age ≥ 50, MMSE ≥ 27 and resection
V	**Age ≥ 50, MMSE < 27, and biopsy only**

Results:
Overall Survival RPA V

Overall survival : Treatment in RPA class 5



Treatment	RT n = 286	RT+TMZ n = 287
2-year OS (%)	6.3	18.2
3-year OS (%)	2.1	10.0
4-year OS (%)	1.0	6.08
Hazard ratio	0.69 [0.52-0.93]	

P = 0.014

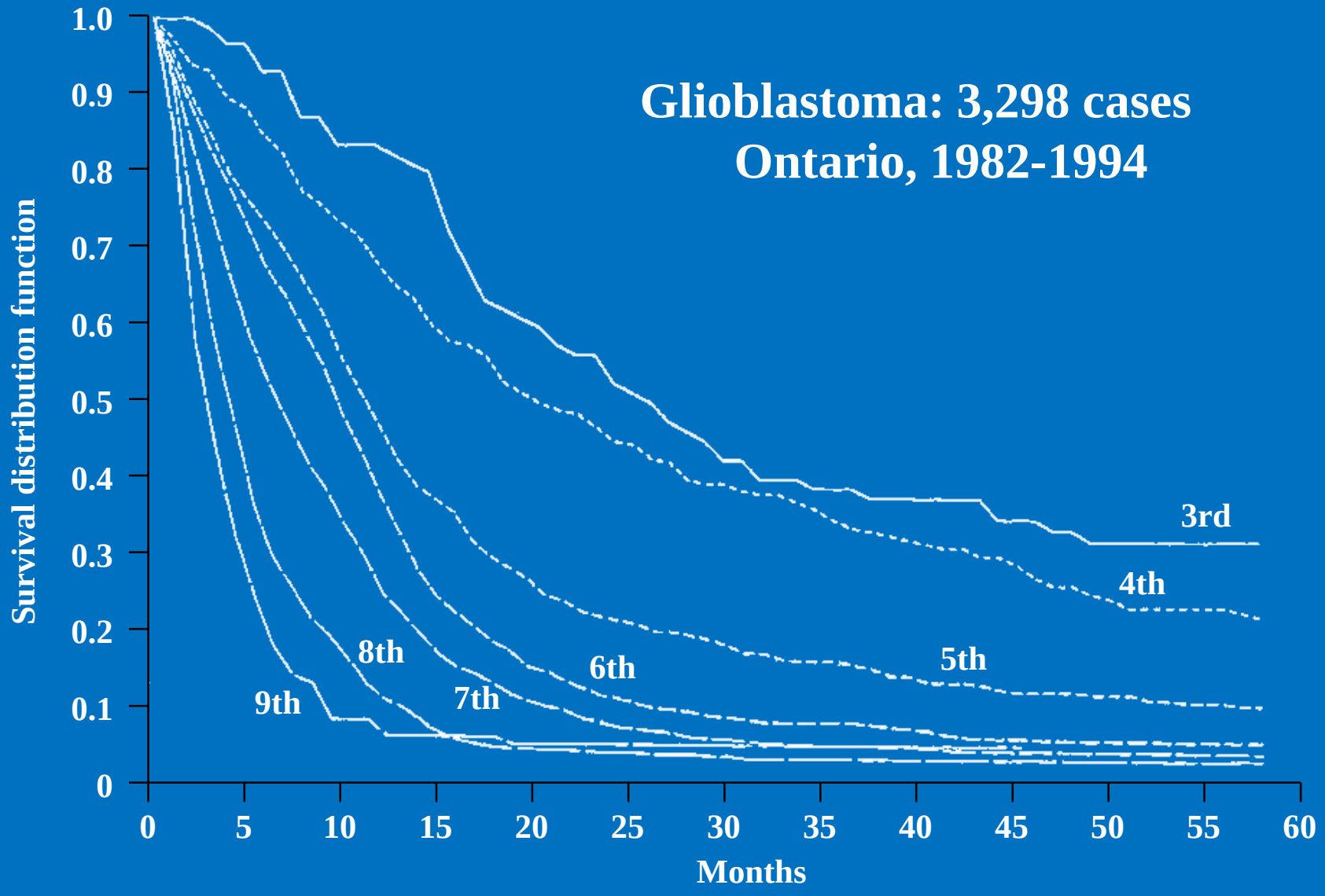
Conclusions

- The survival advantage conferred by the addition of temozolomide to RT in glioblastoma remains significant and clinically relevant with longer follow up
- Observed a modest but significant proportion of patients surviving at least 4 years with the RT + TMZ regimen
- Patients in RPA III benefit most from the RT + TMZ regimen

GBM in the Elderly

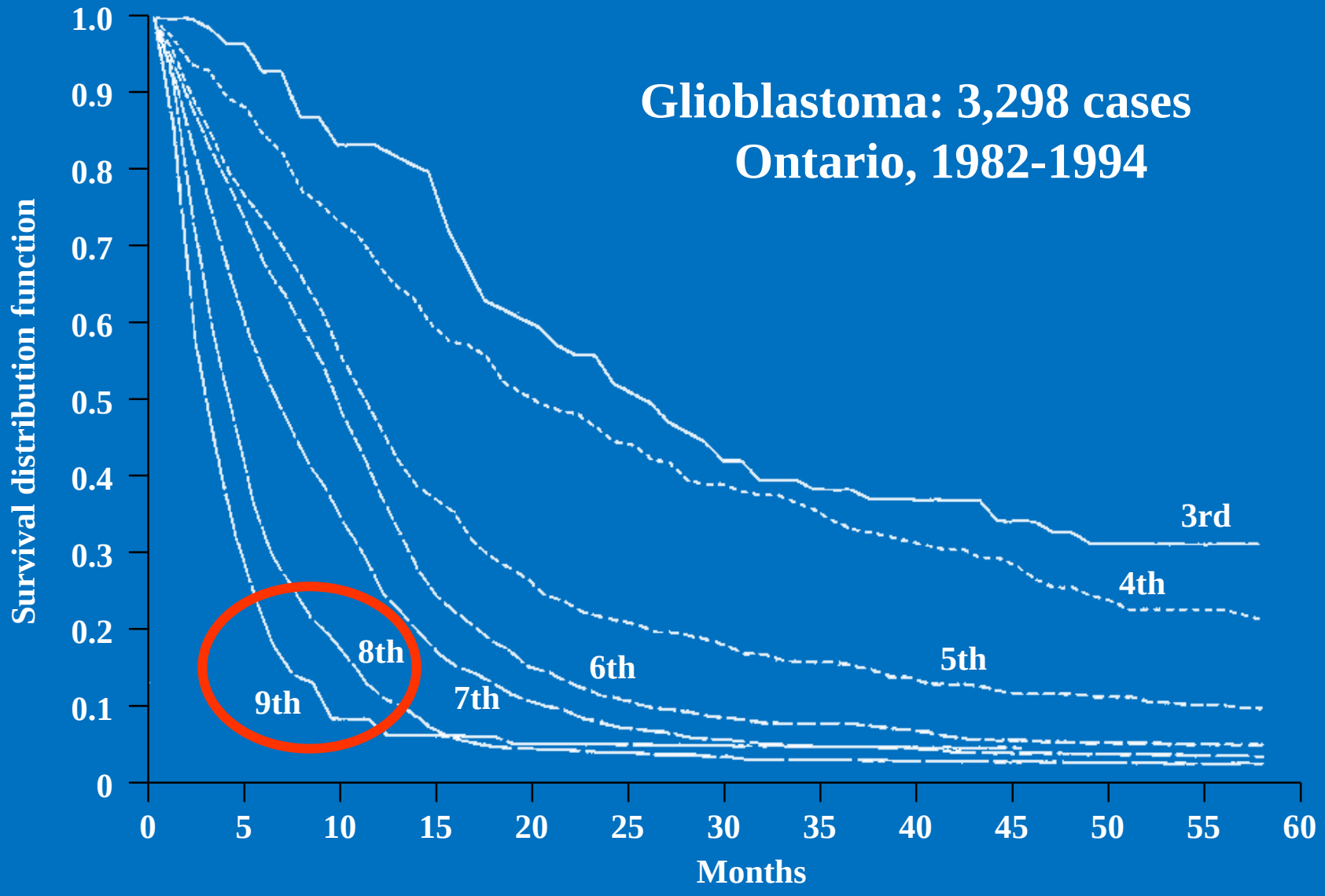
- The incidence of GBM is increasing modestly, and this increase is most apparent in the elderly
- Approximately 22% of all GBM cases arise in patients age $\geq$ 70
- Elderly cases of GBM will become increasingly common as the population ages

Effect of Age on Survival in GBM



Paszat L, et al. *Int J Radiat Oncol Biol Phys*. 51:100-107, 2001

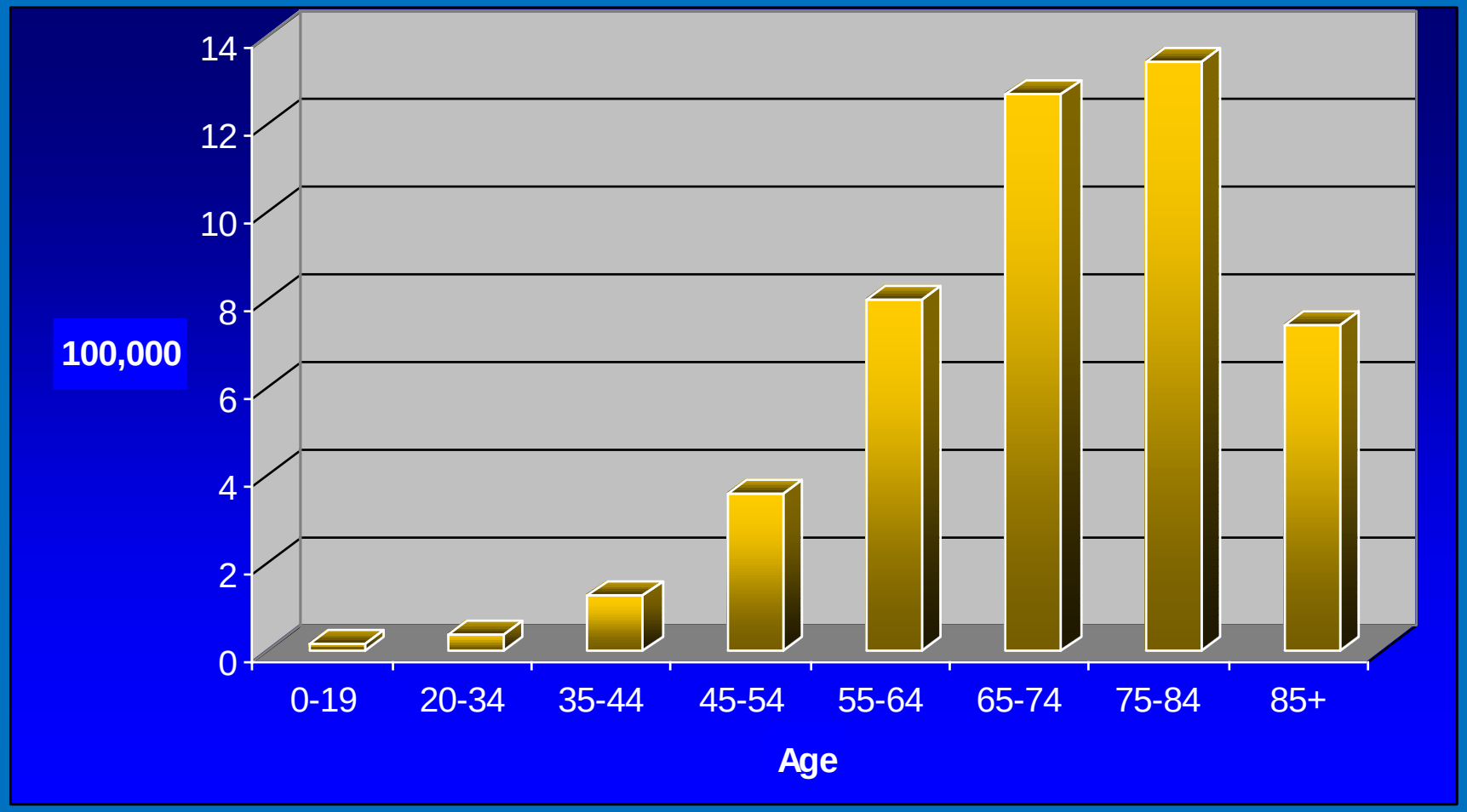
Effect of Age on Survival in GBM



Paszat L, et al. *Int J Radiat Oncol Biol Phys*. 51:100-107, 2001

Incidence

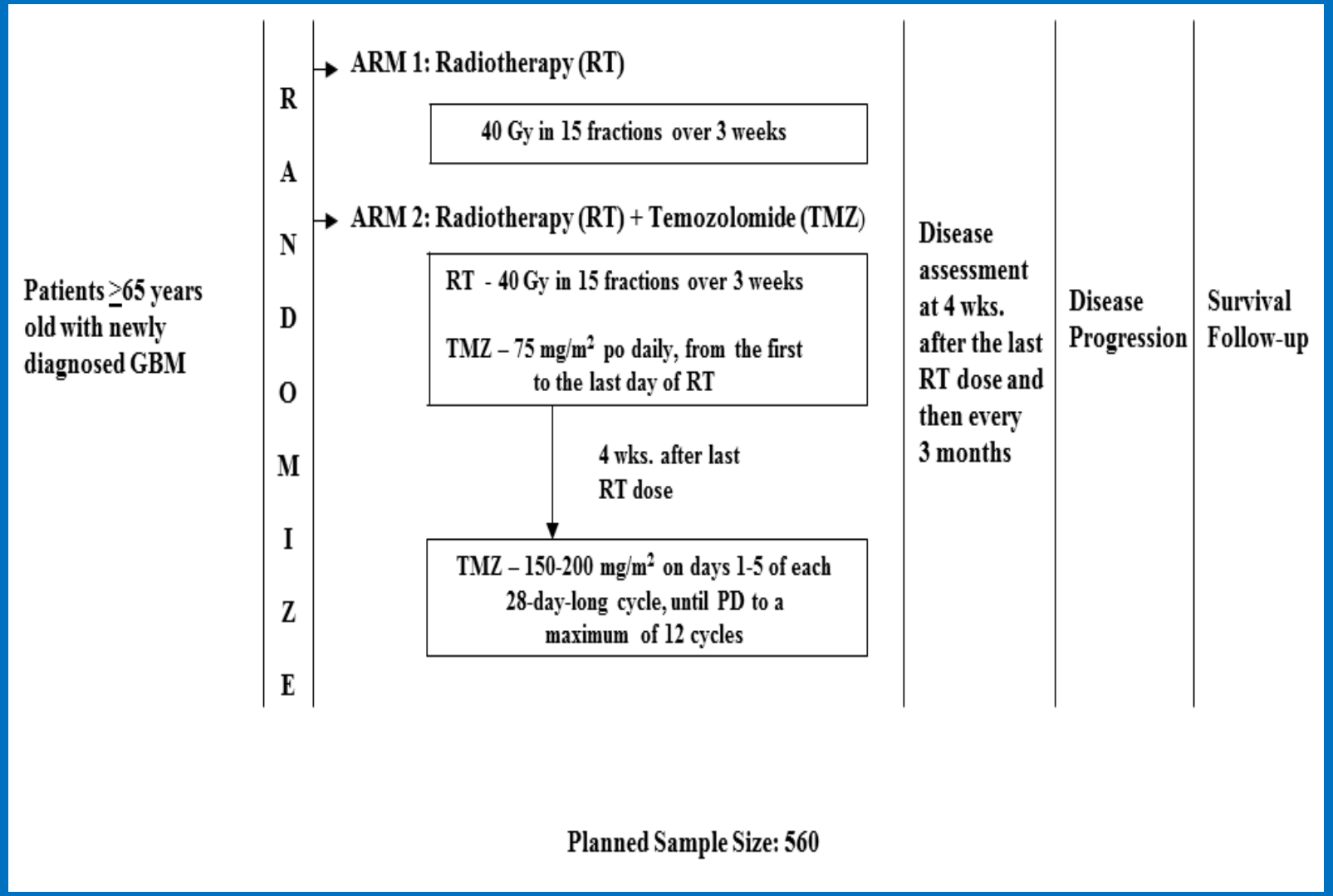
data from CBTRUS 1998-2002 (2005)



Older patients with glioblastoma challenges CNS oncology teams

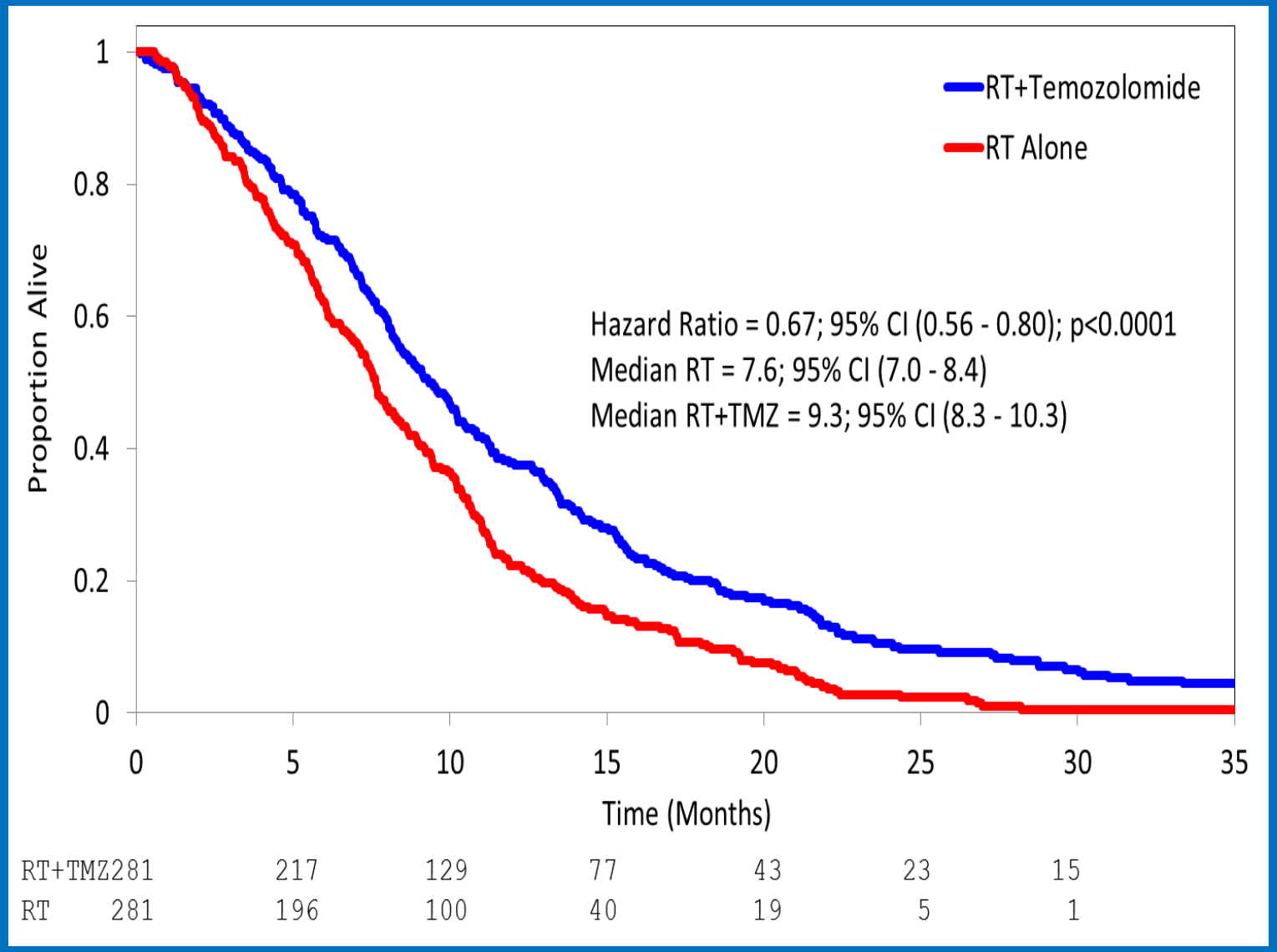
- Biology more aggressive, survival expectations limited
- Frailty, including the aging brain
- Comorbidities
- Access to care and to caregivers
- Population based practice patterns show:
  - Less aggressive surgery
  - Less use of RT
  - Less use of chemotherapy, even though up to 40% have MGMT promoter methylation, same as their younger counterparts

CCTG CE.6 - Study Schema



Planned Sample Size: 560

CCTG CE.6 – Overall Survival



CCTG CE.6 - Conclusions

- The addition of TMZ chemotherapy to standard short course RT significantly improves both PFS and OS in newly diagnosed elderly patients with glioblastoma

- Benefit is particularly evident in patients with *MGMT* promoter methylation where median survival is nearly doubled

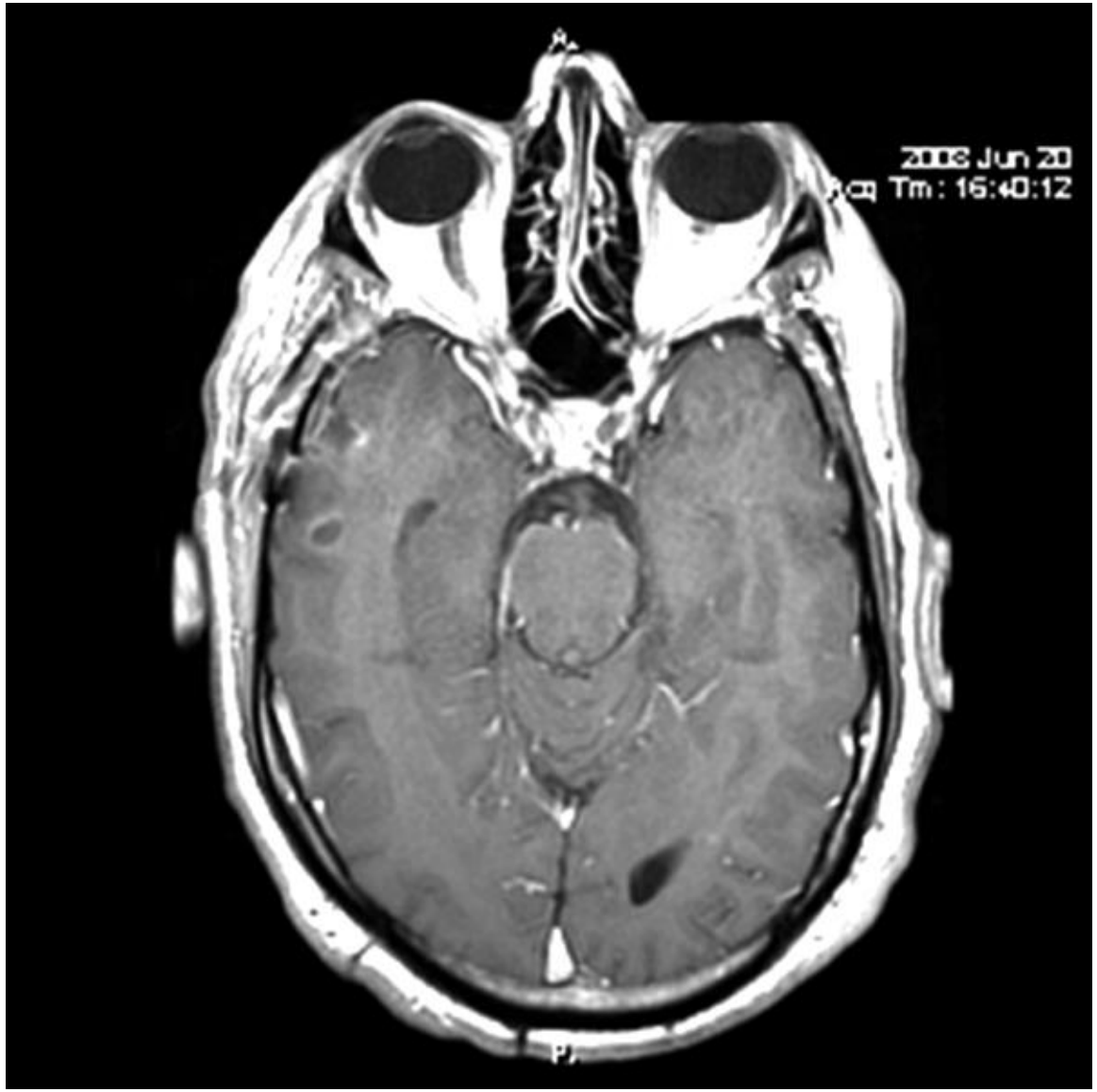
- Remarkably, clinical benefit was also observed in pts with unmethylated tumours and these provide the strongest data to date for the use of TMZ in all elderly GB patients

GBM: Management of Progression after Temozolomide

- Surgery
- RT
- Chemotherapy
- Experimental Therapeutics
  - Targeted therapies
- Palliative Care

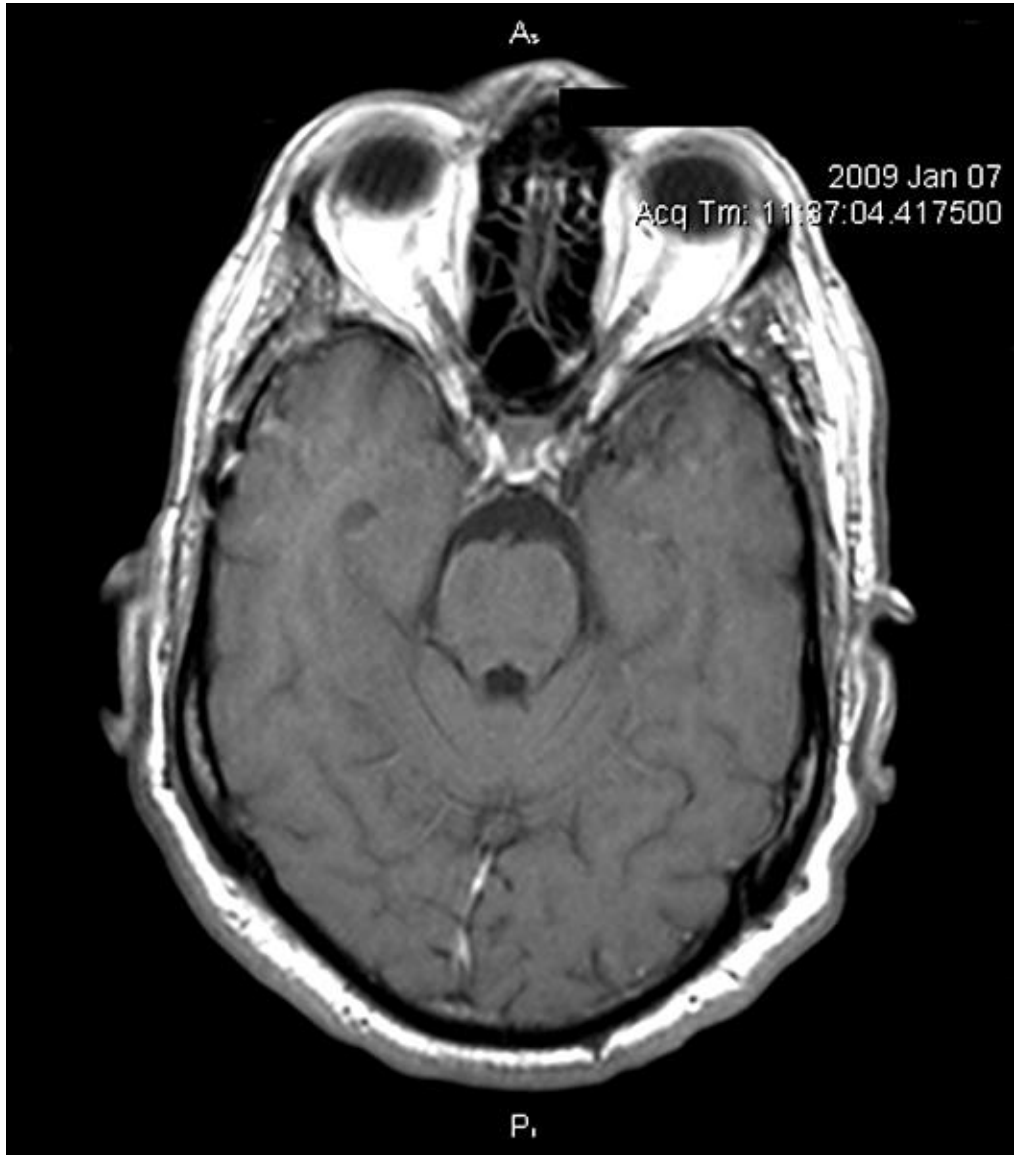
Case Vignette: Newly-diagnosed GBM

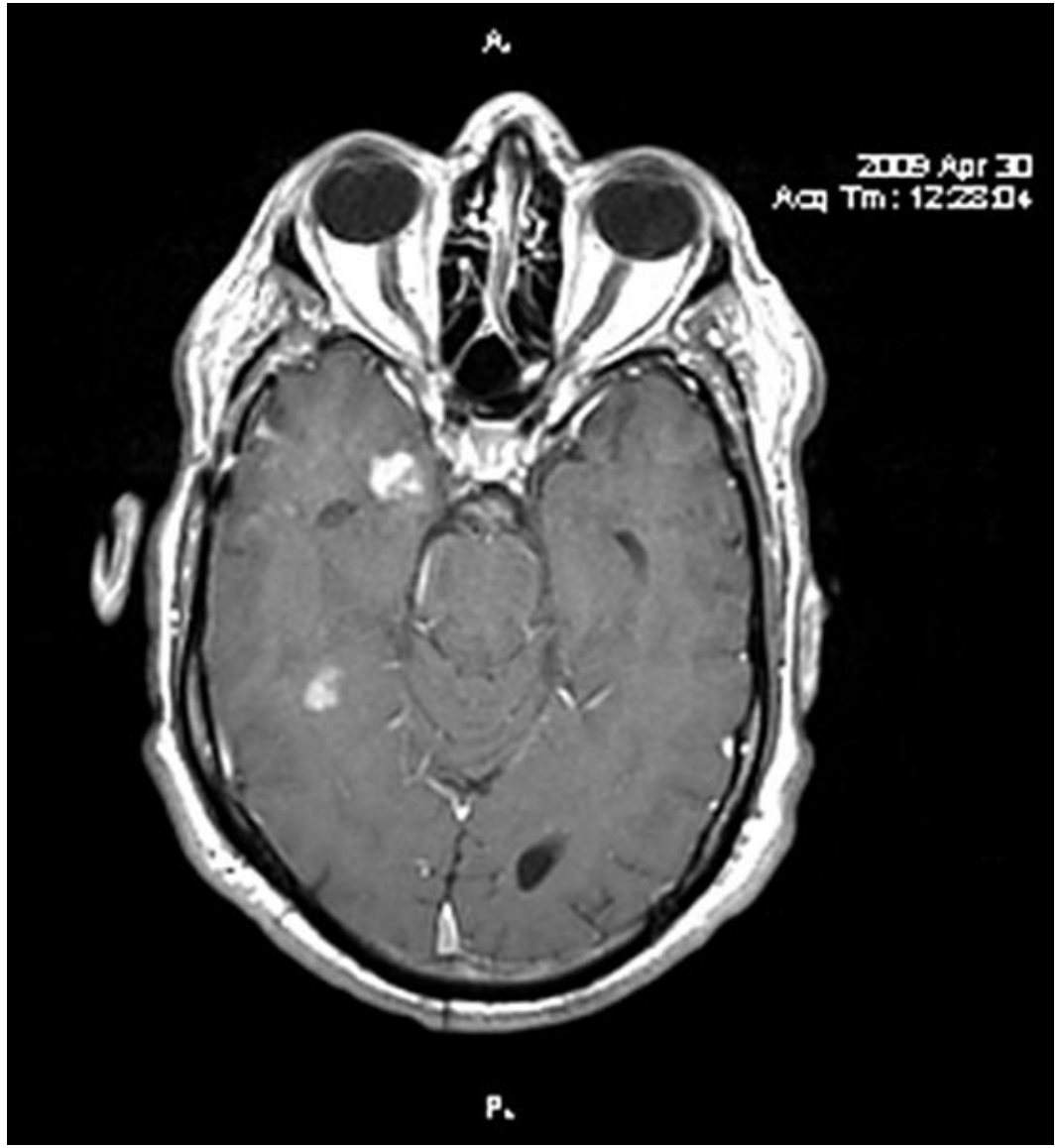
- April-May 2008
  - Receives 60 Gy RT with concurrent temozolomide
  - Post-RT imaging reveals interval improvement
  - Offered clinical trial that involves combining adjuvant temozolomide with mTor inhibitor (everolimus)


2006 Jun 20
Tm: 16:40:12
A
P

Case Vignette: Newly-diagnosed GBM

- Declines trial but receives temozolomide adjuvantly for 10 cycles
- MR scan dated January 2009 shows almost CR
- MR scan dated April 2009 shows progression


A
2009 Jan 07
Acq Tm: 11:37:04.417500
P

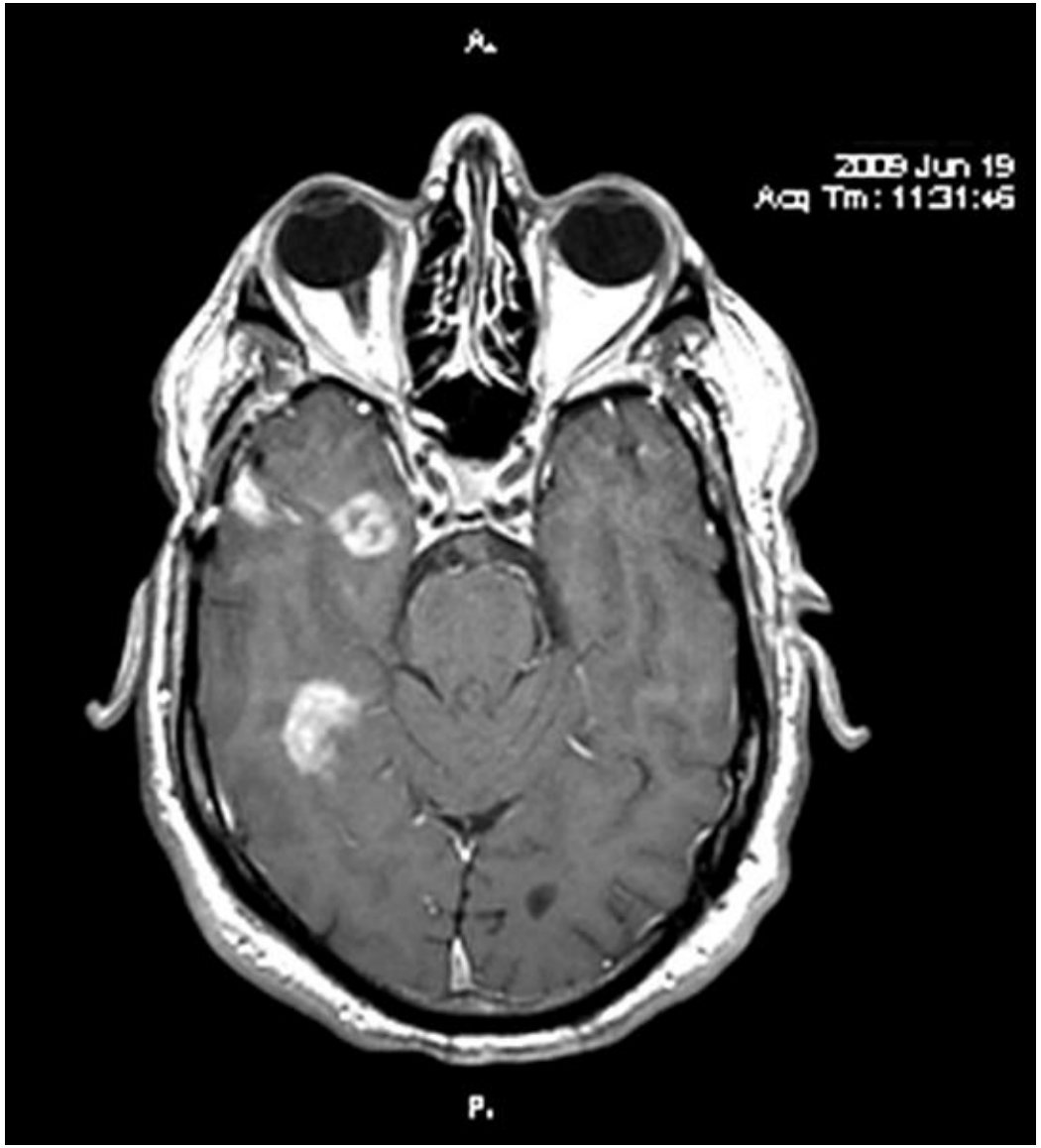

A
2008 Apr 30
Acq Tm: 12:23:04
P

Case Vignette: Newly-diagnosed GBM

- Patient offered a variety of options including conventional chemotherapy and clinical trials with investigational agents
- He chooses a novel targeted therapy, TLN-4601, that inhibits ras/raf-mediated signaling.

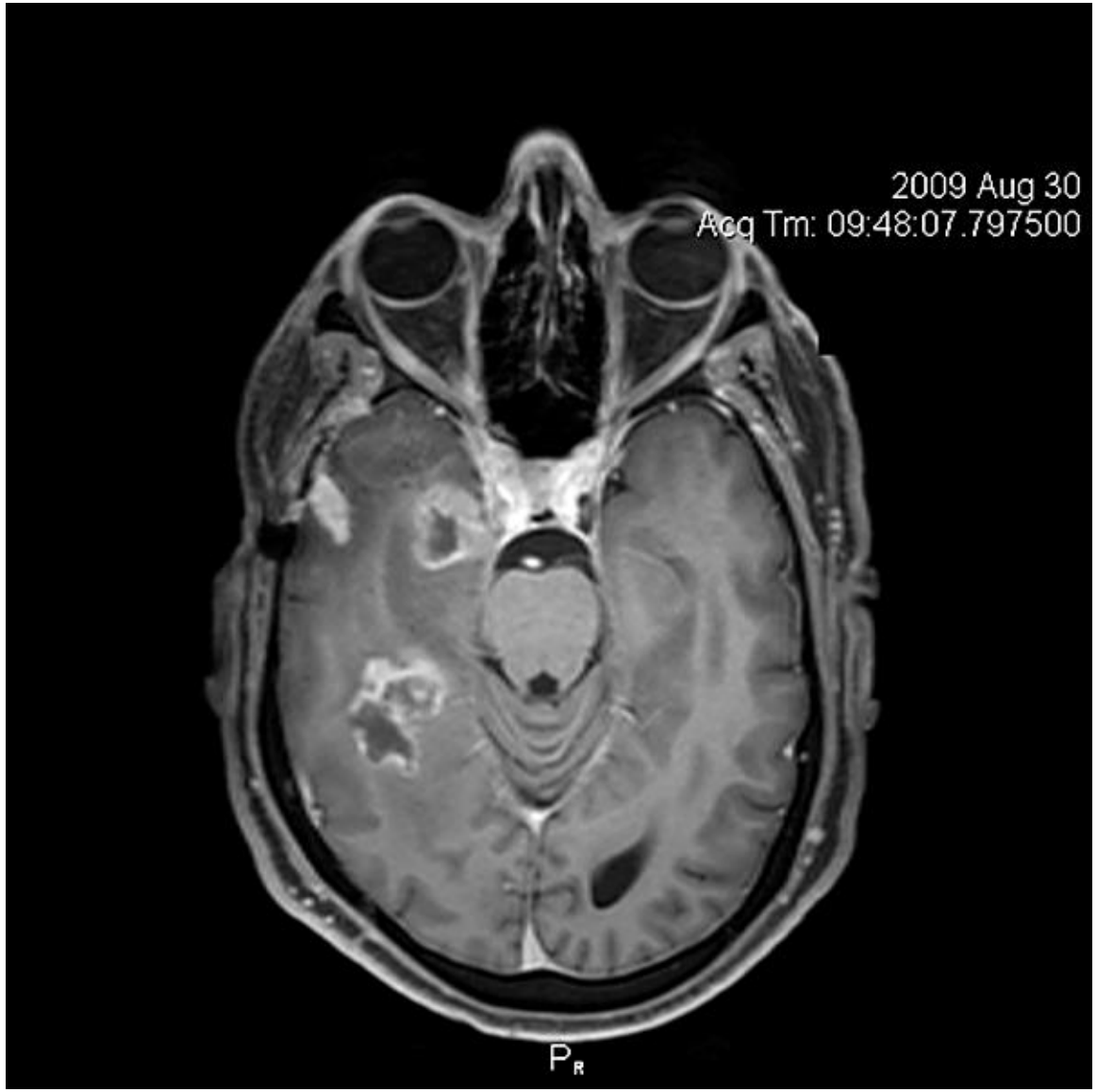
Case Vignette: Newly-diagnosed GBM

- After 2 cycles of TLN-4601, MR scan shows further progression
- Patient offered conventional chemotherapy


A.
2008 Jun 19
Acq Tm: 11:31:45
P.

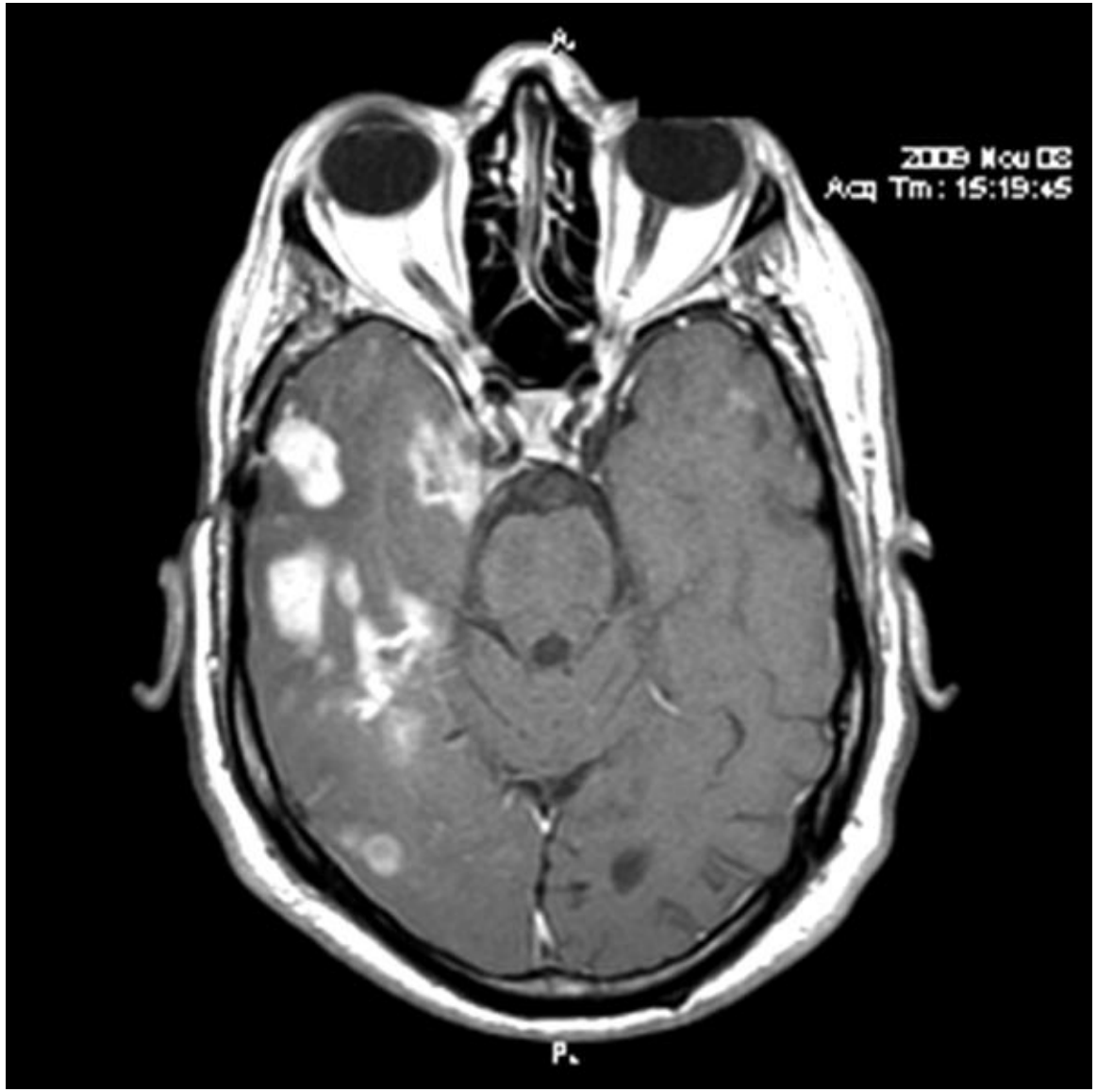
Case Vignette: Newly-diagnosed GBM

- After 2 cycles of lomustine, MR shows further tumour growth
- Alternative chemotherapy administered


2009 Aug 30
Acq Tm: 09:48:07.797500
P R

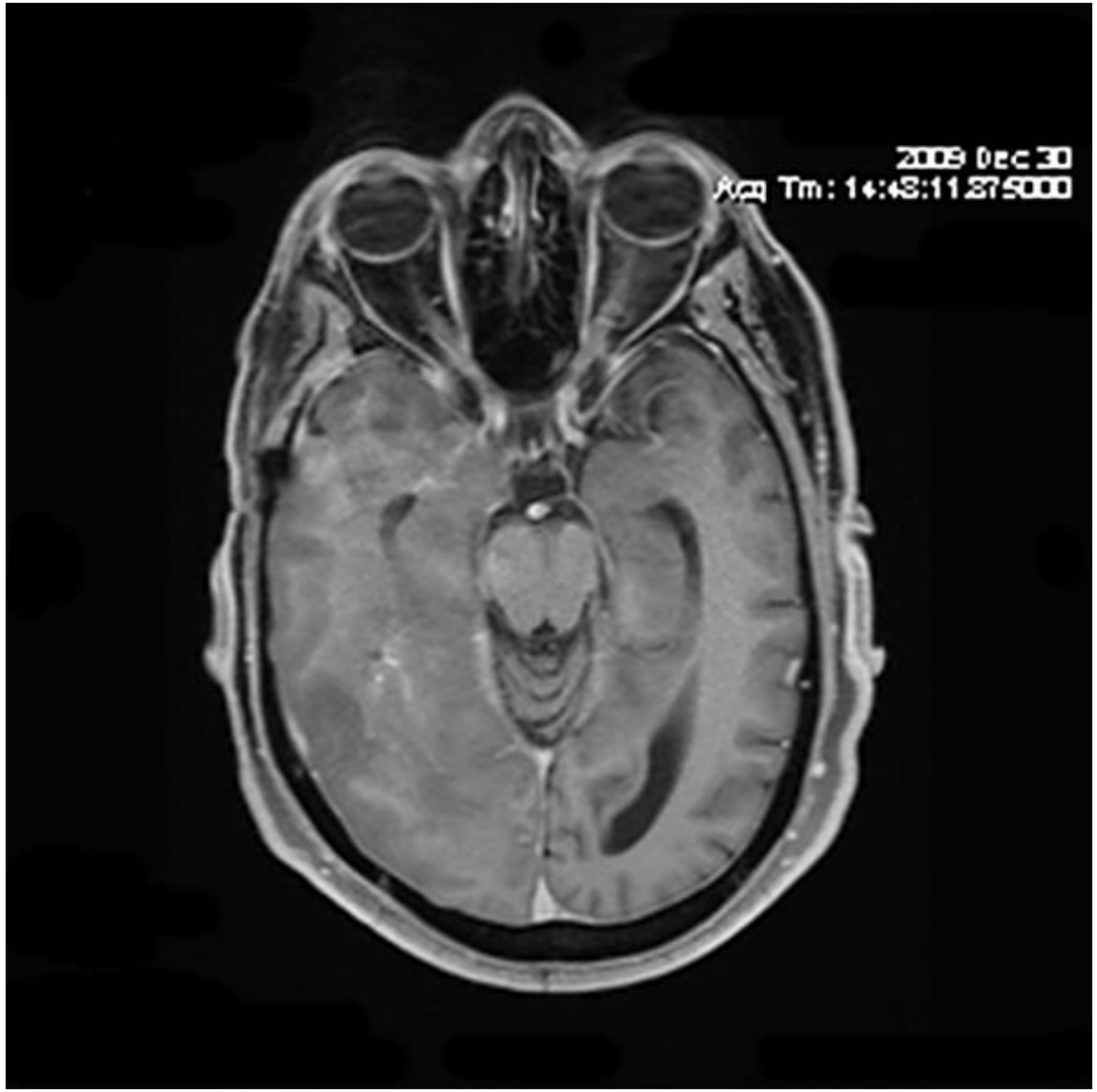
Case Vignette: Newly-diagnosed GBM

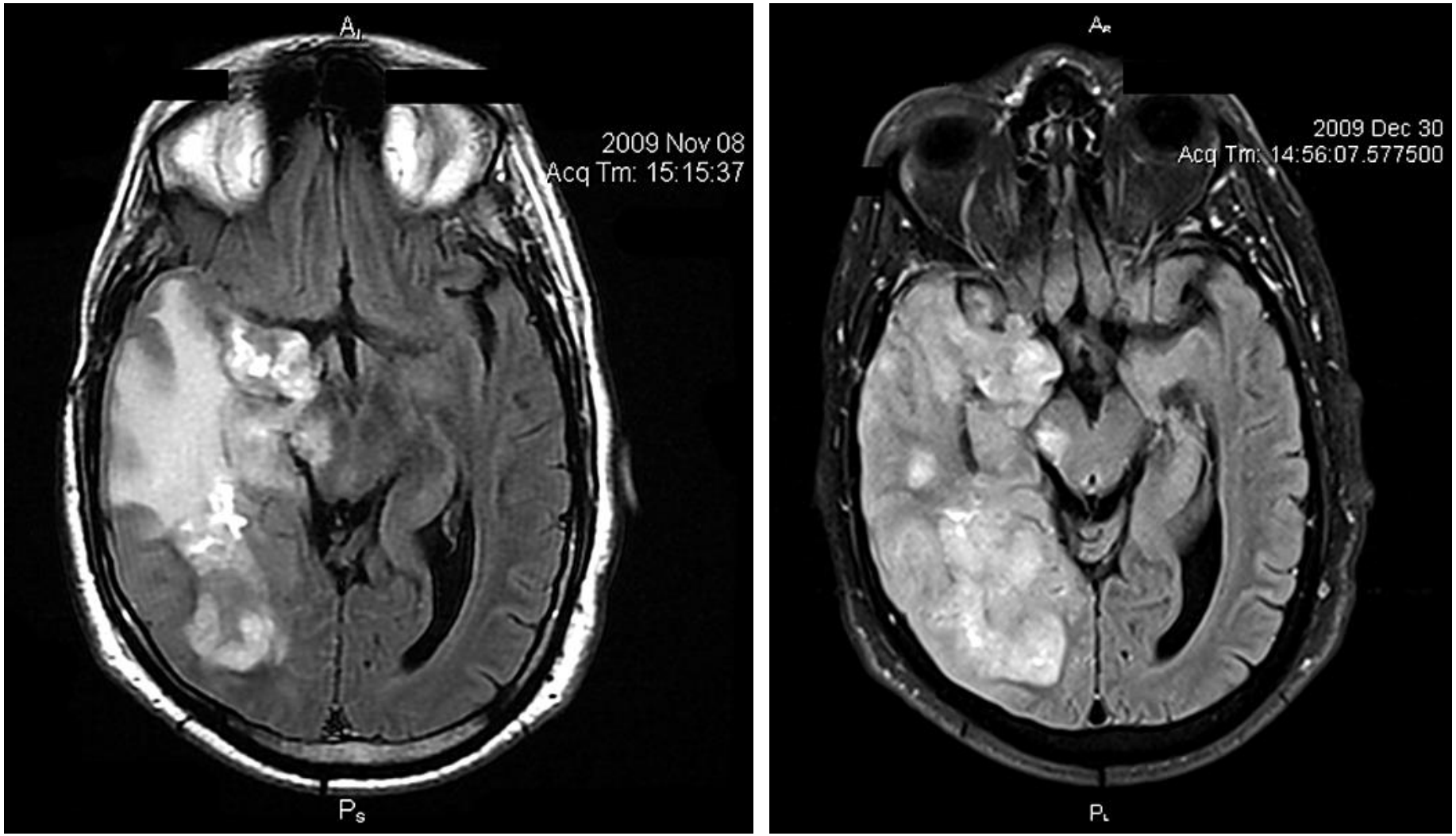
- After 2 cycles of palliative oral etoposide, MR scan shows disease progression
- Patient begins bevacizumab monotherapy


A
P
Acq Tm: 15:19:45

Case Vignette: Newly-diagnosed GBM

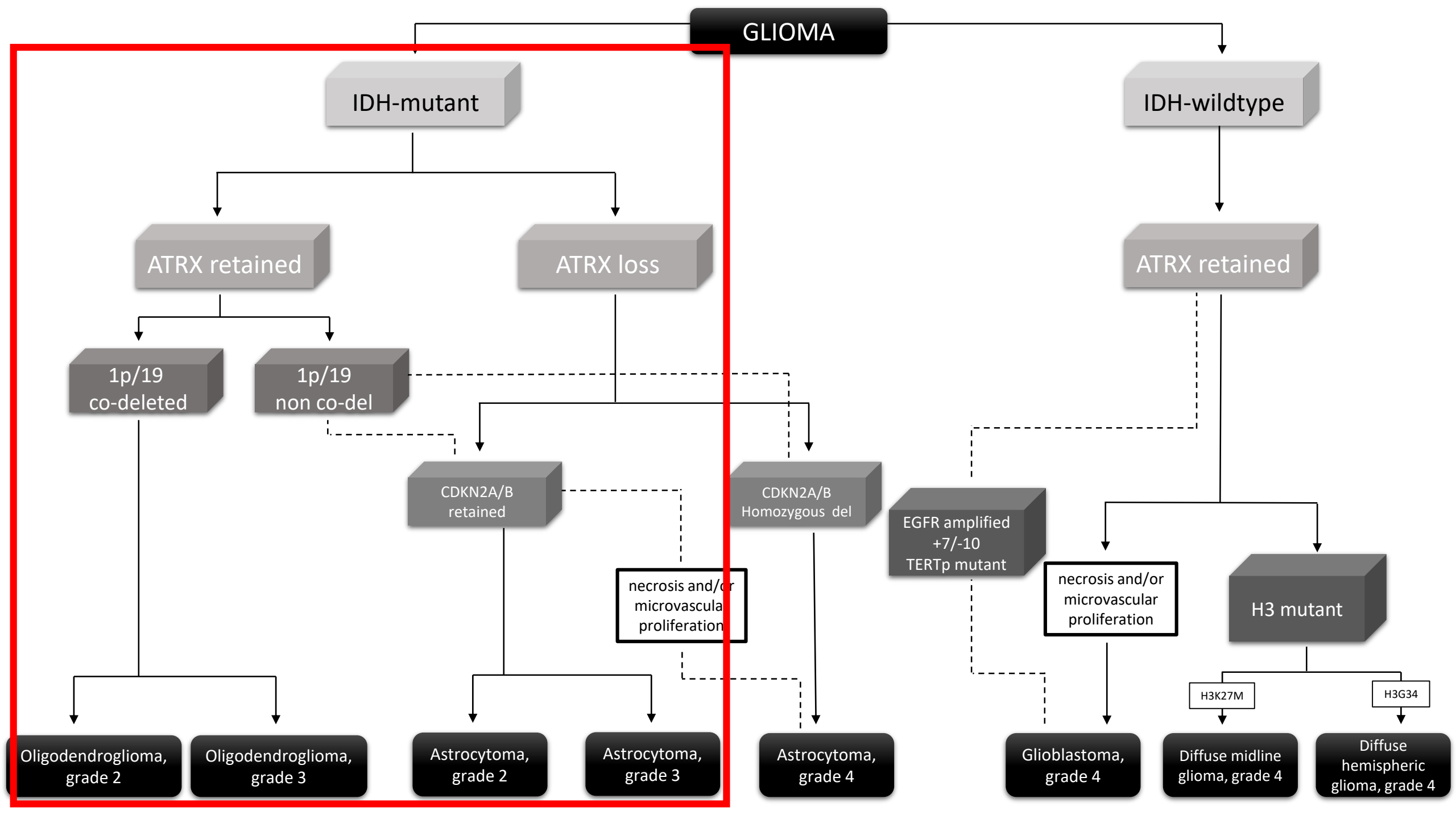
- Patient has dramatic clinical improvement after 1 cycle of bevacizumab
- MR scan shows dramatic improvement in extent of contrast enhancement
- FLAIR sequences reveal concurrent and paradoxical progression of what appears to be nonenhancing tumour


2008 Dec 30
Acq Tm: 14:43:11.875000


A
2009 Nov 08
Acq Tm: 15:15:37
P
A
2009 Dec 30
Acq Tm: 14:56:07.577500
P

Case Vignette: Newly-diagnosed GBM

- While initially improving symptomatically on bevacizumab, patient soon experiences clinical deterioration
- Bevacizumab discontinued and patient dies in March 2010


GLIOMA
IDH-mutant
IDH-wildtype
ATRX retained
ATRX loss
ATRX retained
1p/19 co-deleted
1p/19 non co-del
CDKN2A/B retained
CDKN2A/B Homozygous del
EGFR amplified +7/-10 TERTp mutant
necrosis and/or microvascular proliferation
necrosis and/or microvascular proliferation
H3 mutant
H3K27M
H3G34
Oligodendroglioma, grade 2
Oligodendroglioma, grade 3
Astrocytoma, grade 2
Astrocytoma, grade 3
Astrocytoma, grade 4
Glioblastoma, grade 4
Diffuse midline glioma, grade 4
Diffuse hemispheric glioma, grade 4

IDH mutant gliomas

- Predominant in young adults
- Indolent behavior
- Gross total resection and radiation therapy (+/- chemotherapy) showed prolong survival
- Practice can be heterogeneous in choosing chemotherapy (PCV vc TMZ)

Anaplastic Astrocytoma and Anaplastic Oligodendroglioma: Background

- Males and females equally affected
- Tumors of young and middle-aged adults
- Arise from subcortical white matter and overlying cortex
- No distinctive radiographic features
- Distinctive histologic appearance
- Following resection and pathologic diagnosis, treatment usually consists of radiotherapy with concurrent and adjuvant temozolomide
- Survival for AA in the range of 5-10 years; for AO, 10-20 years

Low grade gliomas: Management

- Remains one of the most controversial areas in neuro-oncology despite significant advances
- Diagnosis can be suspected by MRI, first therapeutic intervention is surgery but timing is controversial
- Surgery required for accurate diagnosis, can alleviate symptoms
- Maximal feasible resection is goal, may have significant impact on survival
- Survival for patients with low grade gliomas can be prolonged, typically in the 10-20 year range

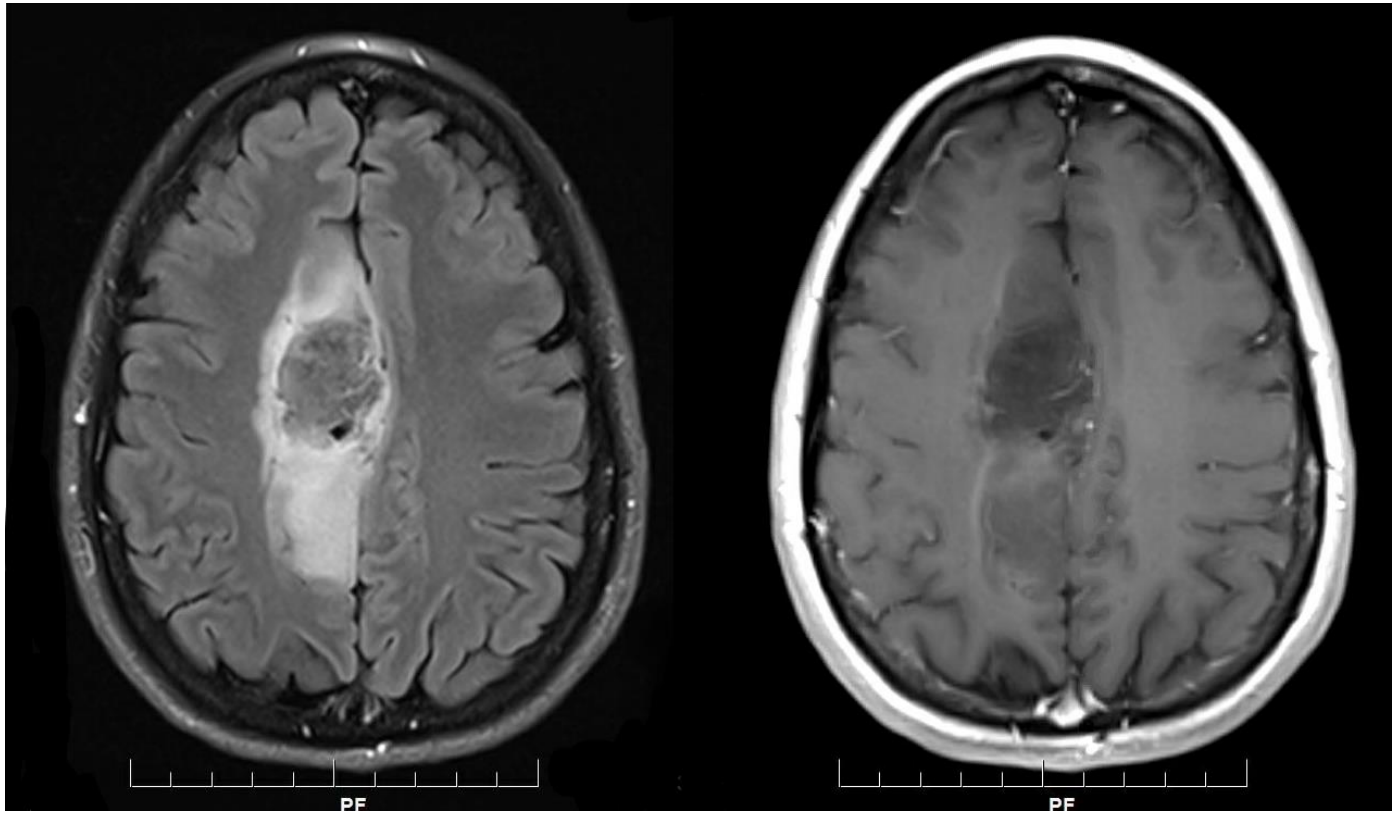
Low grade gliomas: Roles of Radiotherapy and Chemotherapy

- Radiotherapy prolongs survival but is associated with the potential of serious late side effects
- Low grade gliomas (particularly with 1p19q co-deletion) are chemosensitive
- Timing and sequence of radiotherapy and chemotherapy are controversial and have been the focus of recent landmark phase III trials

CASE Vignette

- 39-year-old female with left sided numbness

- MRI demonstrated a nonenhancing mass on the right paramedian frontoparietal region

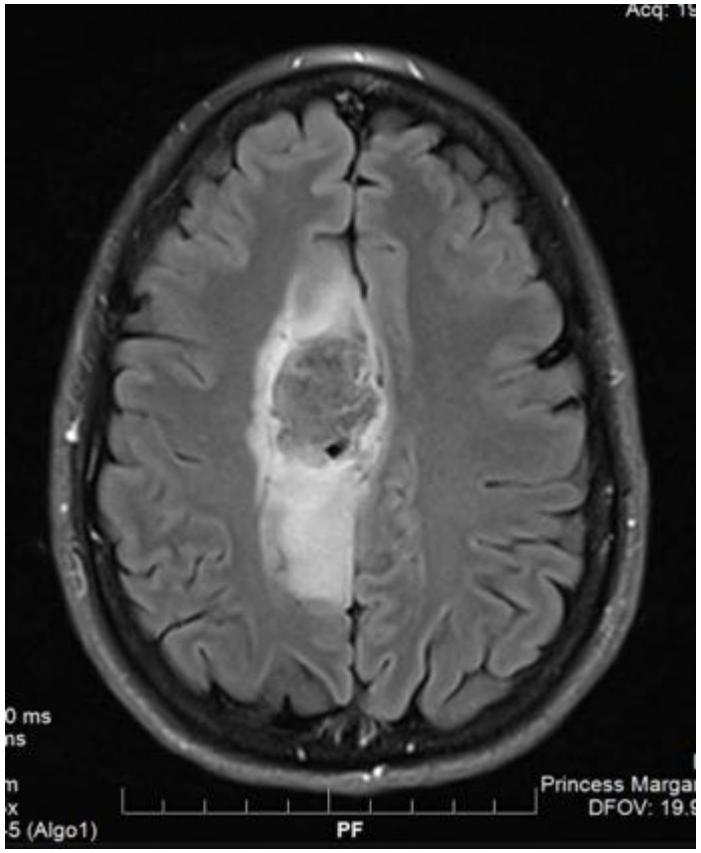


T2 flair – Pre surgery

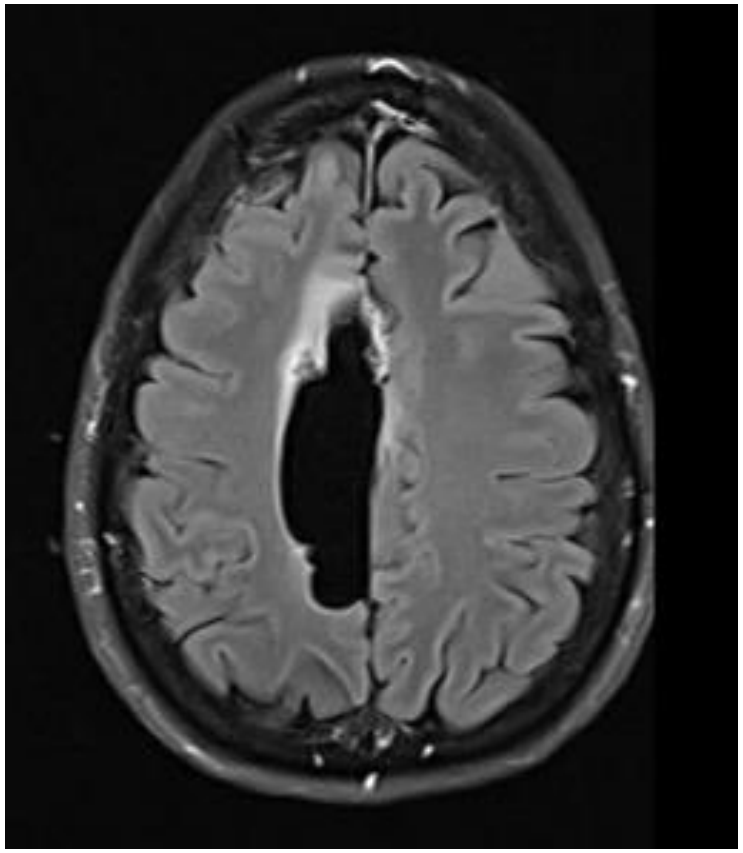
T1 post gadolinium – Pre surgery

Case Vignette

- .She underwent resection with pathology of **oligodendroglioma, IDH mutated, 1p19q codeleted, CNS WHO grade II.**



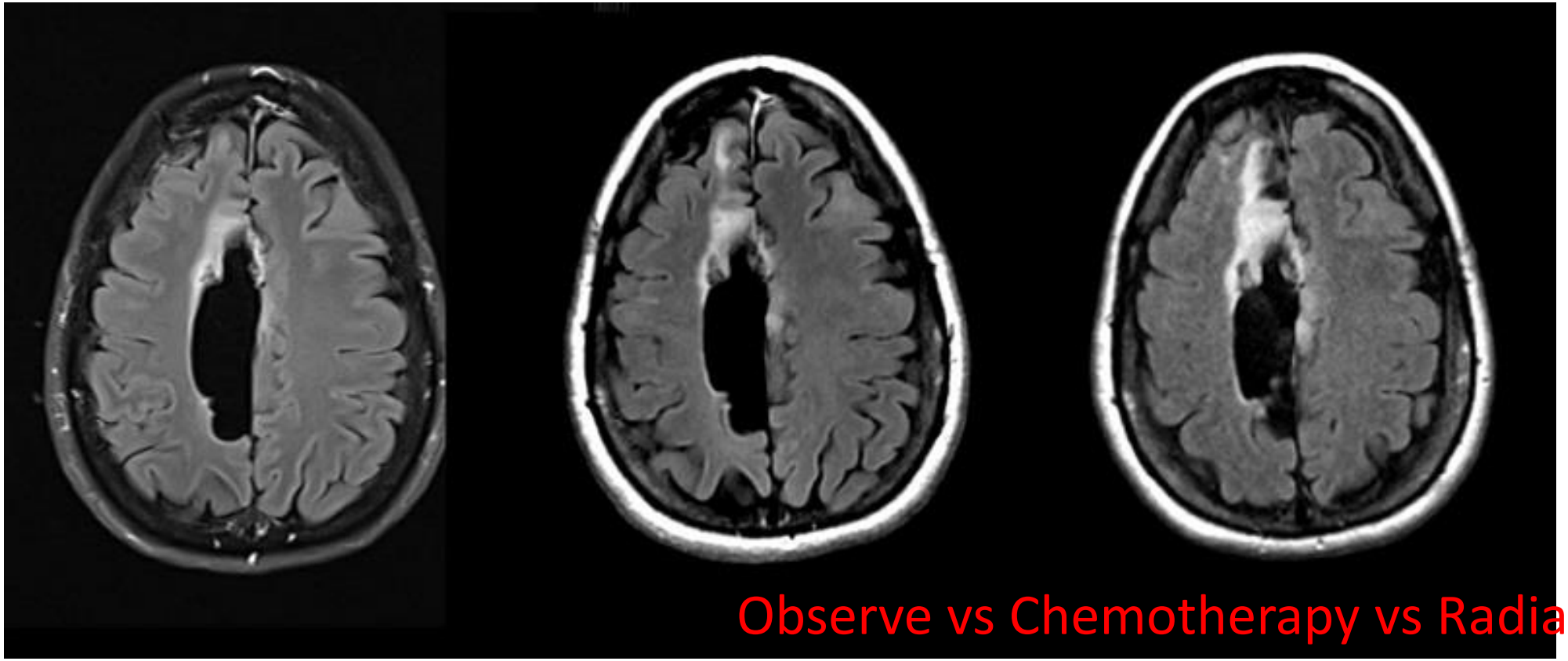
T2 flair – Pre surgery



T2 flair – 6 months Post surgery

Case Vignette

- 39 year old female with oligodendroglioma, IDH mutated, 1p19q codeleted, CNS WHO grade II.

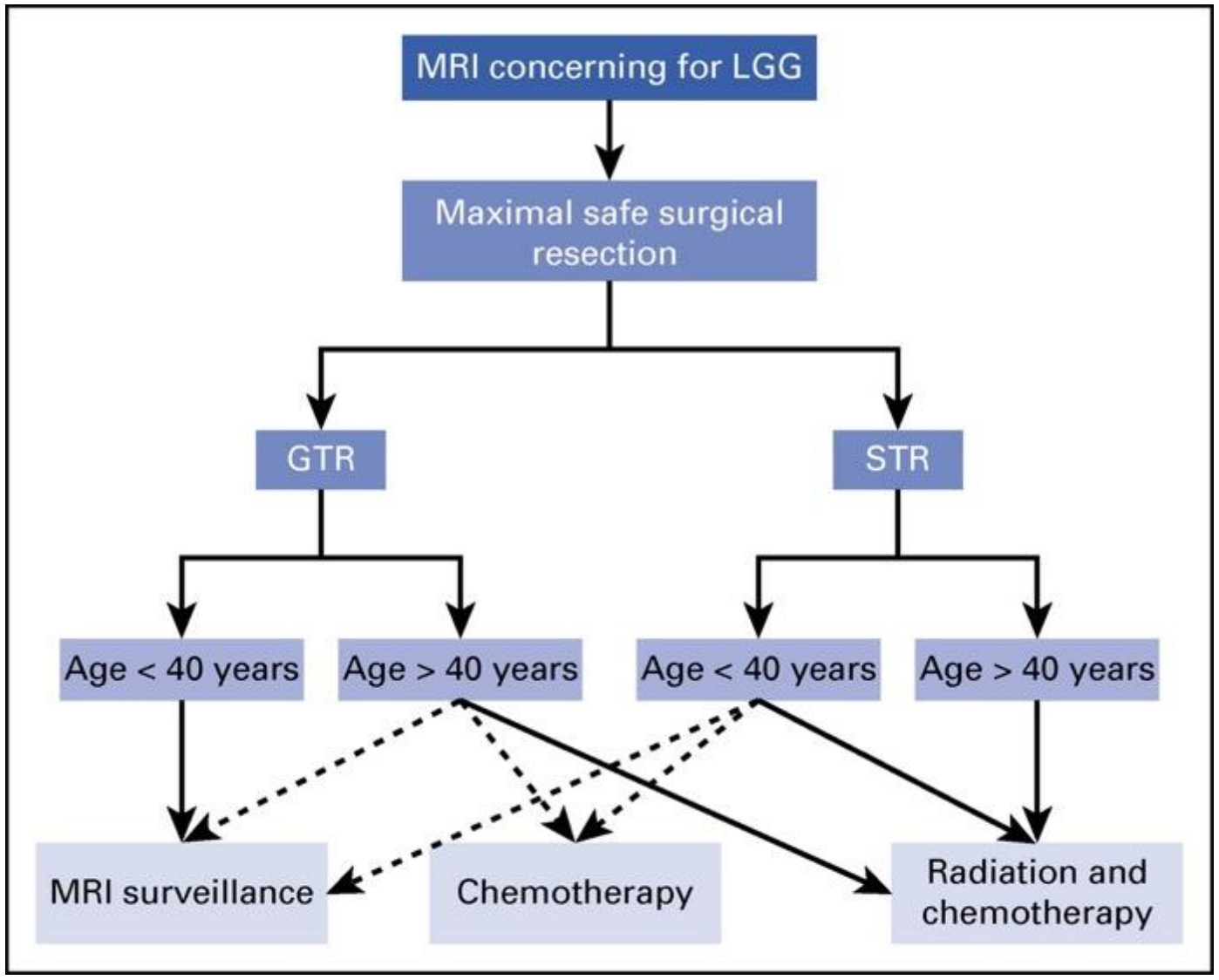


Axial T2 flair
6 months post surgery

Axial T2 flair
2 years post surgery

Axial T2 flair
3 years post surgery

Strategy for treatment decisions for low-grade



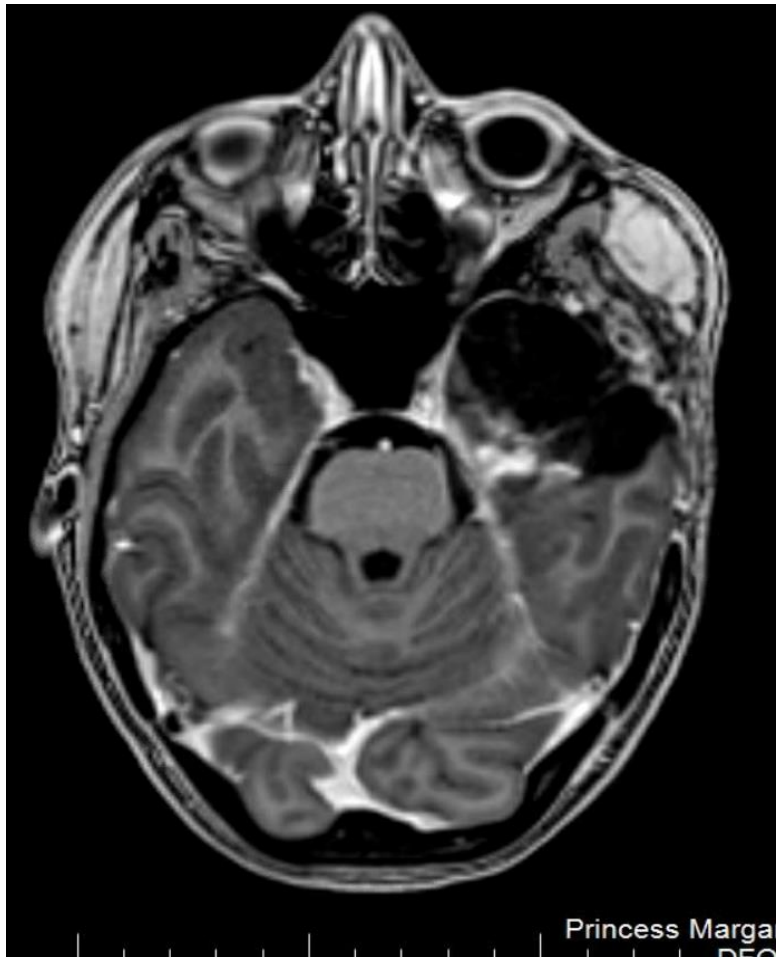
Bush NA, Chang S. Treatment Strategies for Low-Grade Glioma in Adults. American Society of Clinical Oncology Vol 12 Issue 12 Dec 2016

Young Adults with Pediatric-type Gliomas

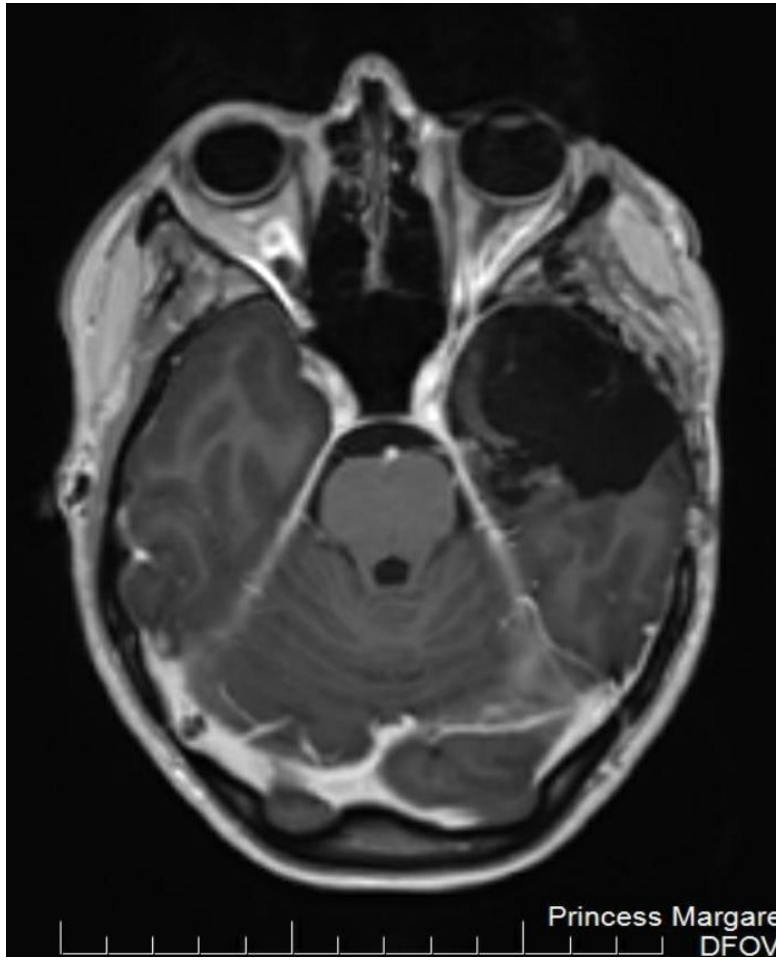
- Molecular characterization of CNS tumors has significantly improved classification and prognosis and identified a subset of young adults with tumours that have molecular features of pediatric gliomas
- Most of these tumours are rare low grade glial neoplasms with survival rates in the multiple decades
- Distinct molecular derangements provide opportunities of treatment with novel targeted therapies
- Preliminary results of therapeutic trials are encouraging

CASE Vignette

- 25-year-old female with recurrent left temporal **pleomorphic xanthoastrocytoma, BRAF V600 mutation**. She had multiple resection in the past. She has never had radiotherapy.



Postcontrast T1 weighted
Pre treatment



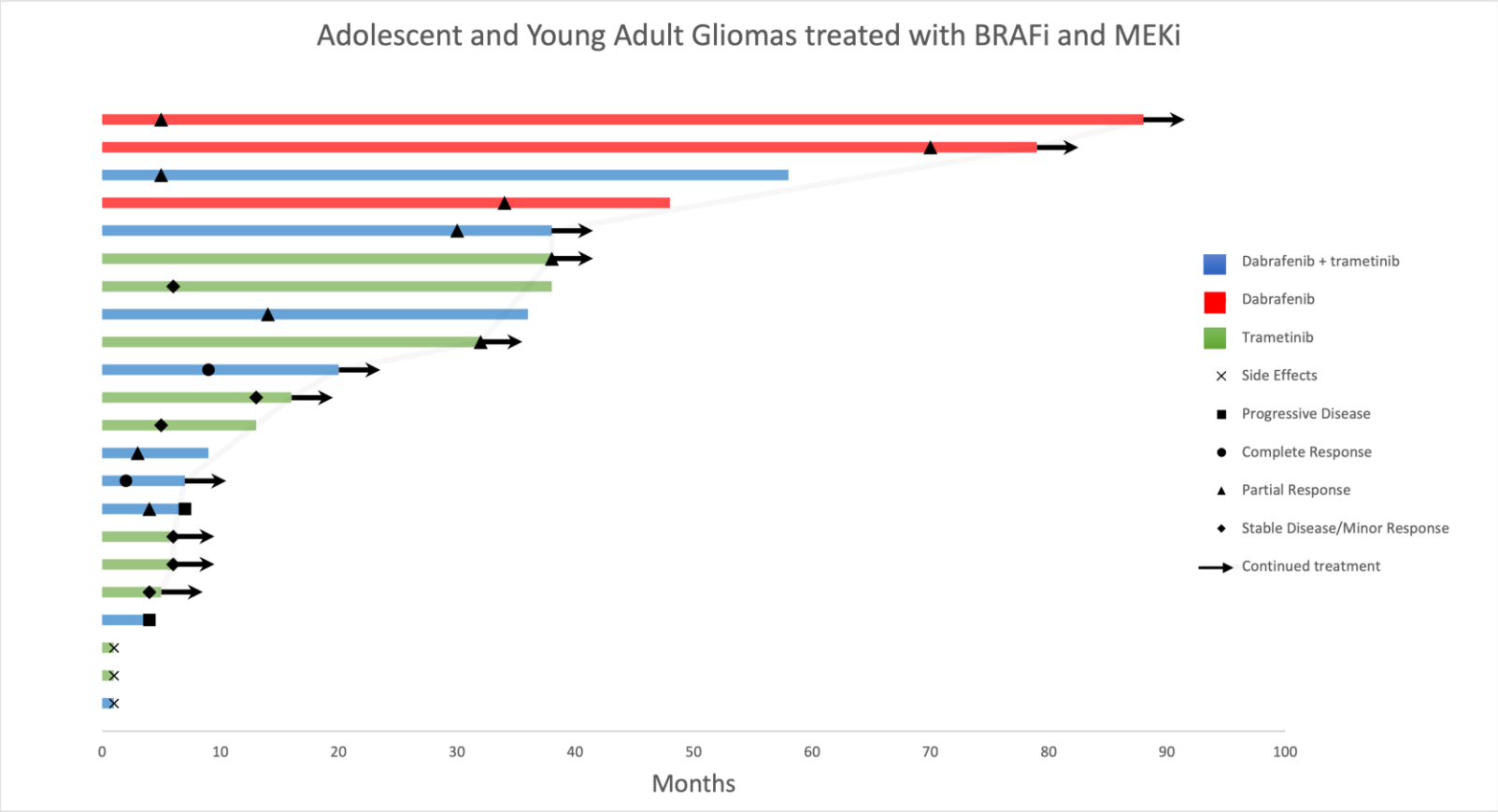
Postcontrast T1 weighted
4 months after initiation of treatment

Common BRAF mutations in Glioma

- BRAF KIAA 1549 fusion
  - Most common mechanisms of BRAF activation in glioma
  - Genetic fusion results in loss of regulatory domain of BRAF
  - 60-70% of pilocytic astrocytoma
- BRAF V600E mutation
  - Disrupts auto-inhibitory mechanism and converts BRAF into active form thus activating MAPK pathway
  - ~10-15% of pilocytic astrocytoma
  - ~ 60% of pleomorphic xanthoastrocytoma
  - ~15-20 of ganglioglioma
  - High-grade gliomas (ei. epitheliod glioblastoma)

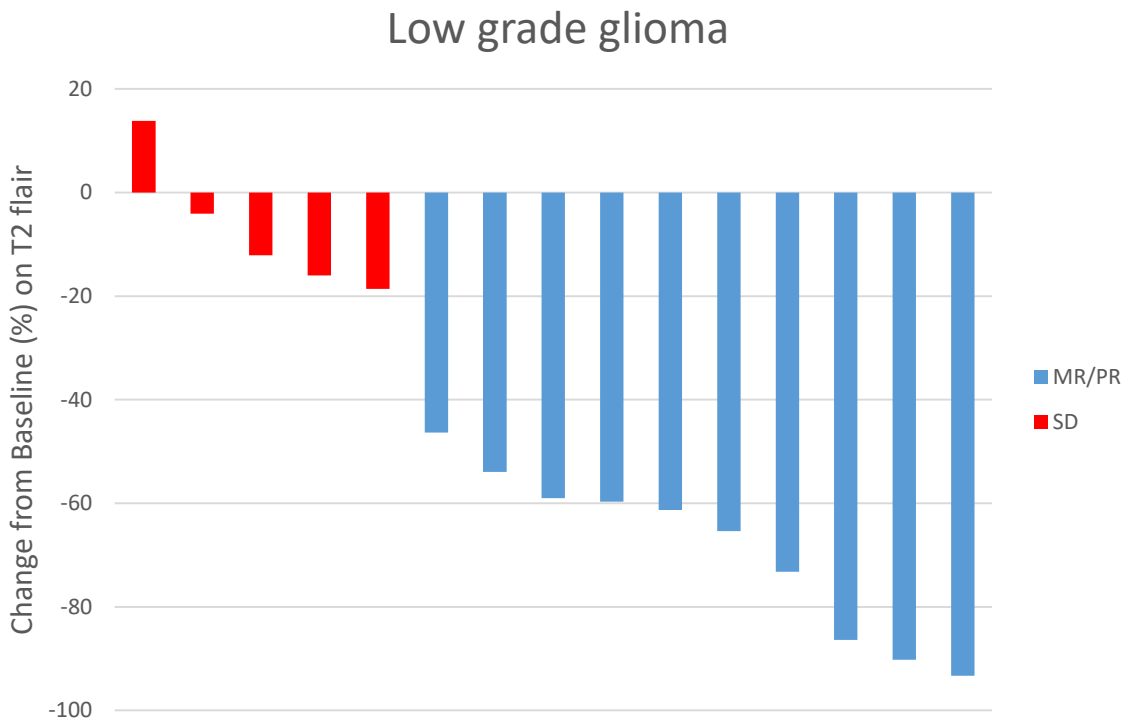
MEK and BRAF inhibition in AYA

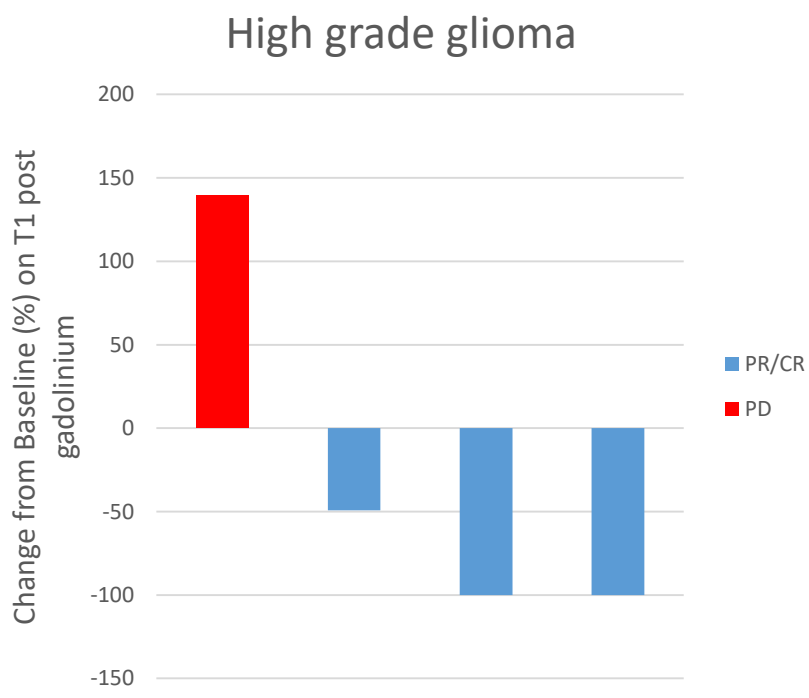
Characteristic	(n = 22)
Sex, No. (%)	
Male	10 (45.45%)
Female	12 (54.55%)
Age at the time of diagnosis, y	18 (14-41)
Pathology	
Glioblastoma wildtype	4 (18.18%)
Pilocytic astrocytoma	7 (31.82%)
Pleomorphic xanthoastrocytoma	2 (9%)
Ganglioglioma	4 (18.18)
Diffuse astrocytoma, grade 2	2 (9%)
Presumed low grade glioma	2 (9%)
Glioneuronal tumor	1 (4.55%)
Mutation	
BRAF V600E	12 (54.55%)
BRAF-KIAA1549 fusion	5 (22.73%)
Non canonical BRAF mutation	1 (4.55%)
FGFR1-K656E	1 (4.55%)
FGFR1-TKD	1 (4.55%)
NF germline mutation	2 (9%)
Previous treatment	
Surgery alone	2 (9%)
Radiation alone	1 (4.55%)
One line of chemotherapy	6 (27.7%)
One line of chemotherapy and RT	6 (27.7%)
Two lines of chemotherapy	1 (4.55%)
Two lines of chemotherapy and RT	1 (4.55%)
Three or more lines of chemotherapy	3 (13.64%)
Three or more lines of chemotherapy and RT	2 (9%)



Ramos. 2021

MEK and BRAF inhibition in AYA





Objective response rate 66.67%

Ramos. 2021

Role of Rehabilitation Therapy in Adult Patients with Gliomas

- Minority of patients with gliomas receive rehabilitation, although this is increasing
- Few studies have examined benefits of motor and cognitive rehabilitation in this population, results are confounding
  - Studies include patients with various tumour grades
  - Functional improvement observed in motor and cognitive domains in patients with all tumour grades
  - Quality of life and tumour prognosis improved in patients who achieve functional gains from rehabilitation
  - Inpatient stay is longer in patients with higher grade tumours

Role of Rehabilitation Therapy in Adult Patients with Gliomas Goals

- Motor rehabilitation to improve function and mobility and enable ADLs
- Cognitive rehabilitation to enable communication and enhance memory
- Sphincter rehabilitation

Role of Rehabilitation Therapy in Adult Patients with Gliomas
Factors influencing Patient Selection

- Tumour grade and prognosis
- Planned therapy
- Age
- Extent of motor and cognitive deficits
- Need for hospitalization
- Potential for repatriation to home

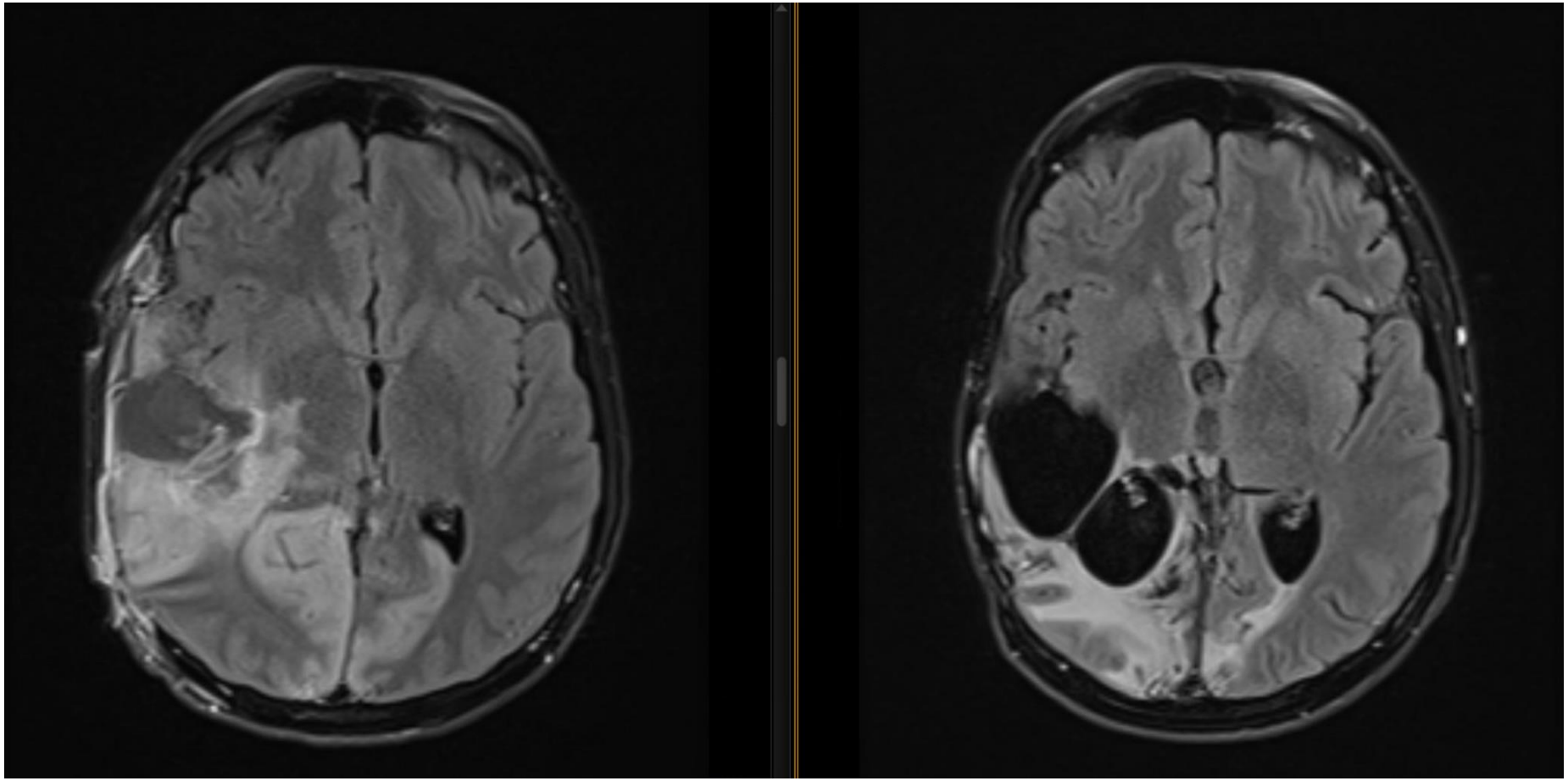
Role of Rehabilitation Therapy in Adult Patients with Gliomas Timing

- Largely determined by tumour grade
  - GBM
    - Urgent need for antitumour therapy often precludes concurrent rehabilitation
    - Patients with unmethylated GBM may benefit more from rehabilitation than temozolomide chemotherapy
  - Anaplastic and low grade gliomas
    - Radiation therapy and chemotherapy can often be deferred until rehabilitation is completed
    - Rehabilitation may enable greater access to antitumour therapy

Case Vignette

- 30 year old man diagnosed with IDHmt Grade 4 glioma involving right temporal lobe in February 2021
- Suffered massive post-operative stroke involving right middle cerebral and bilateral posterior cerebral arteries following uncal herniation. Required craniectomy. Deficits due to stroke included bilateral cortical blindness, impaired auditory processing, left-sided cortical sensory dysfunction.
- Admitted to TRI for intensive inpatient rehabilitation. Radiotherapy with concurrent temozolomide initiated at this time. Adjuvant temozolomide completed in April 2022.
- Has made a remarkable functional recovery without any tumour progression to date.

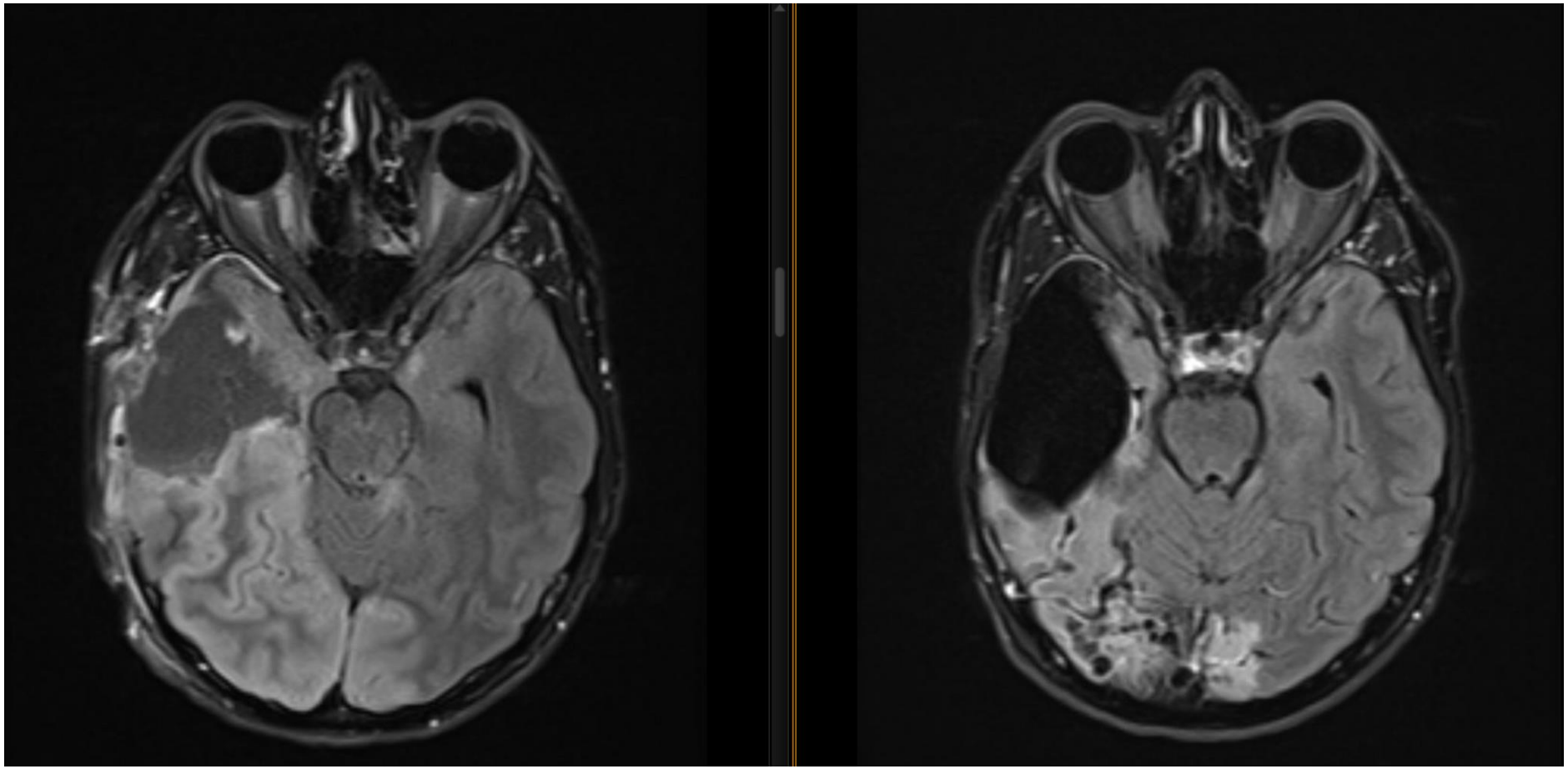
Case Vignette



March 2021

October 2022

Case Vignette



March 2021

October 2022

Conclusions

- Molecular profiling of adult gliomas has significantly improved classification and has enabled precision medicine
- Prognosis for adult patients with gliomas has improved remarkably with therapeutic advances
- More adult patients with gliomas of all grades should receive rehabilitation services as an integral component of their treatment