GBM-PNET

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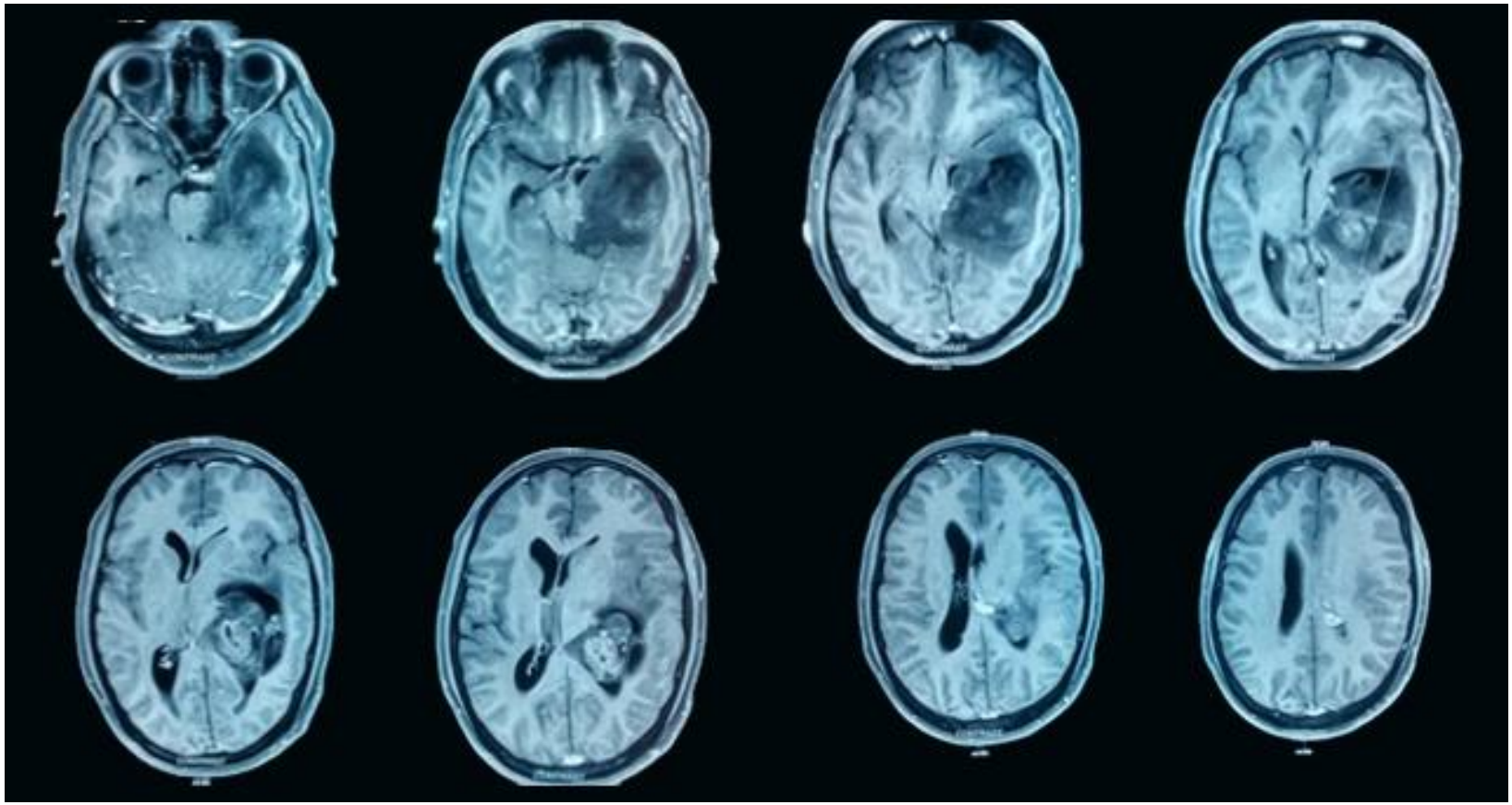
Clinical Features

- 42 yr./M
- Chief complaints
  - Headache x 6 months
  - Blurred vision x 6 months
  - Hearing difficulty x 6 months
  - Episodes of Generalised seizures x 15days
- Known hypertensive previously on medication
- No significant family history
- No h/o any addictions

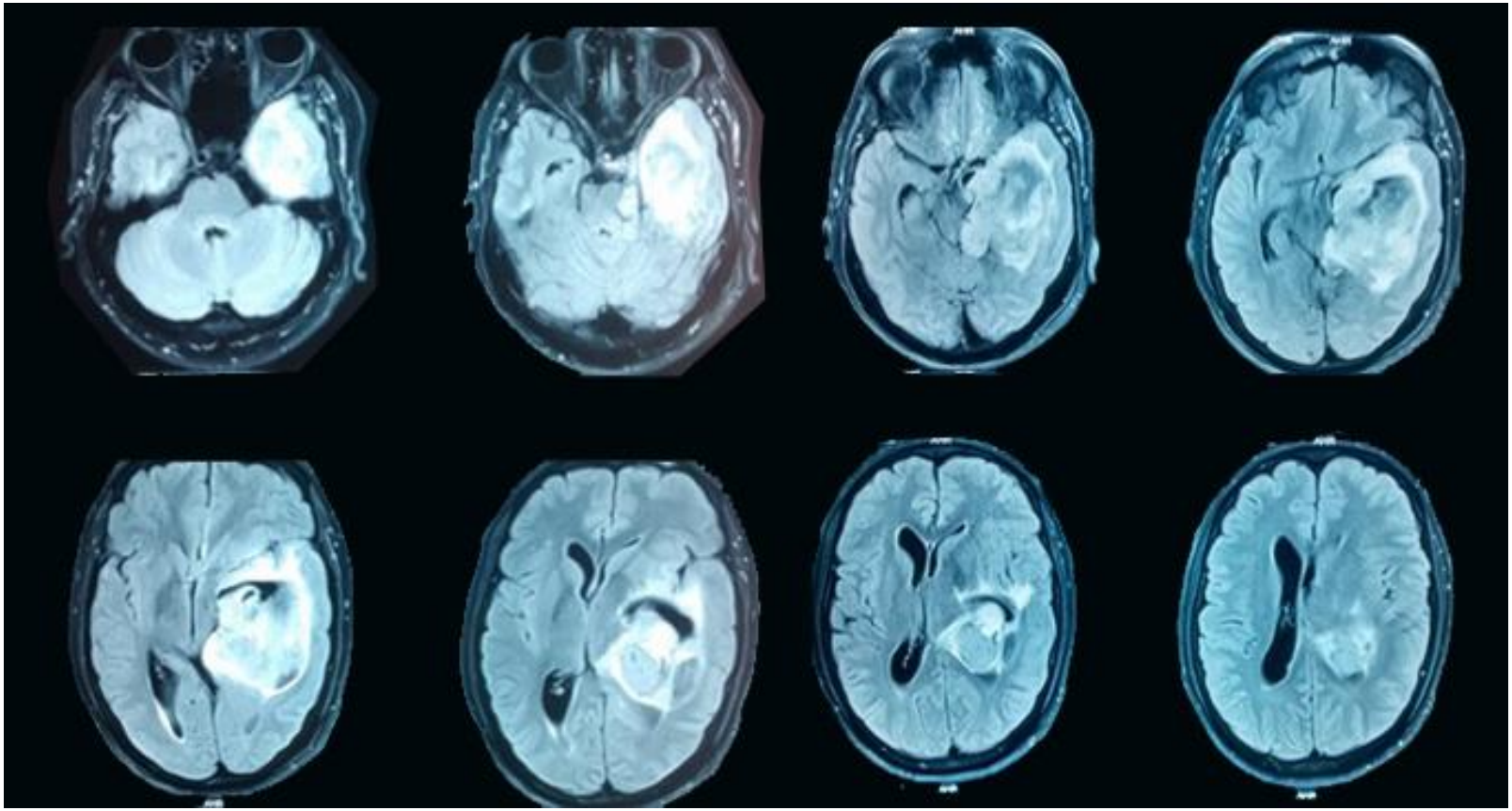
Clinical Features

- KPS -80; GCS- E4V5M6
- Cranial nerves – No deficit
- Motor
  - Tone – Normal
  - Power – 5/5 in all four limbs
  - DTR – Normal
  - Plantar response – Flexor
- Sensory – Normal
- Cerebellar signs – Absent

Imaging – T1W Post contrast



Imaging – FLAIR



Surgery

- Provisional Diagnosis – Left Temporal Glioma
- Gross Total Resection of tumour under Neurosurgery
- Intra op
  - Greyish solid cystic moderately vascular tumour with poorly defined plane with normal brain.
  - Tumour arising from temporal horn and involving atrium and occipital horn.

Histopathology

- Biphasic tumour composed of
  - Astrocytic component with increased cellularity, pleomorphism, mitoses and endothelial proliferation
  - Undifferentiated round cell component
- Immuno-histochemistry
  - Astrocytic component
    - Positive : GFAP and p53
    - Negative : IDH-1 and ATRX
  - Small cell component
    - Positive : Chromogranin, synaptophysin, NeuN, and p53
    - Negative : NF, IDH-1, GFAP and ATRX
- MIB-1 Labelling Index – 30%

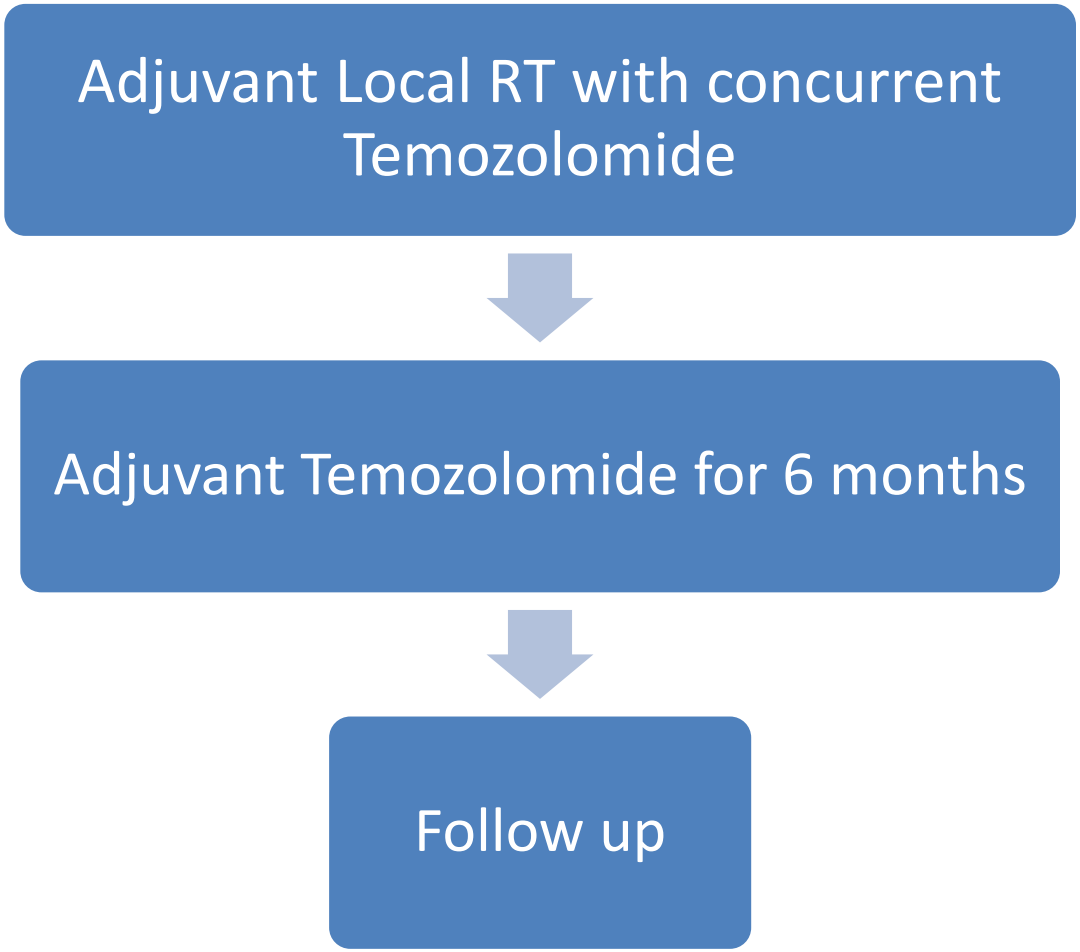
Final Diagnosis

- Glioblastoma multiforme with Primitive Neuroectodermal Tumour component (GBM-PNET)

Work up

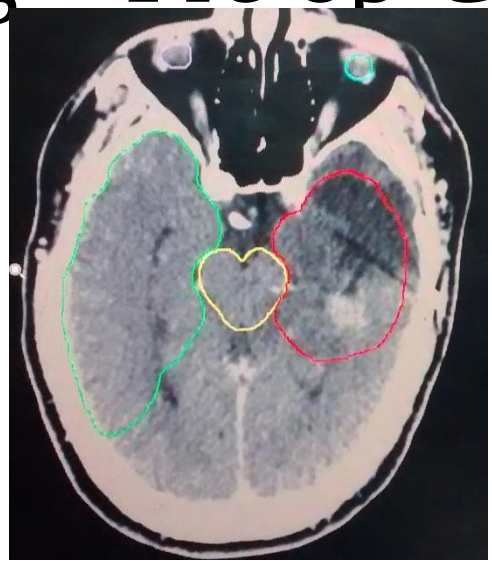
- Post op Contrast enhanced MRI Brain
  - Post operative cavity in left temporal lobe with residual disease in left hippocampal and para hippocampal region and along margin of cavity.
- MRI spine screening in view of PNET component
  - No spinal subarachnoid seeding
- Cerebrospinal fluid cytology
  - Negative
- Complete blood count/Liver function test/Kidney function test
  - Within normal limits

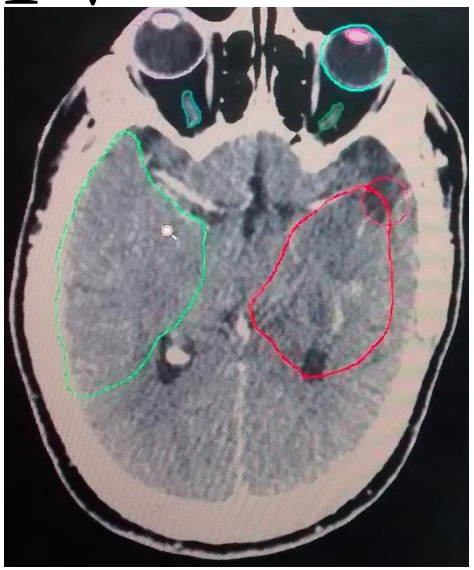
Plan


Adjuvant Local RT with concurrent Temozolomide
Adjuvant Temozolomide for 6 months
Follow up

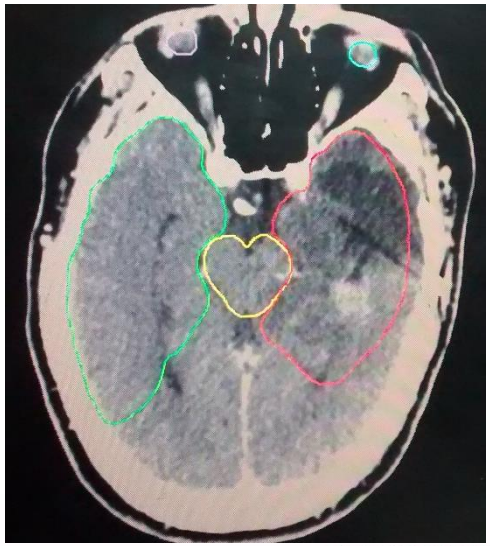
Contouring – Pre op GTV

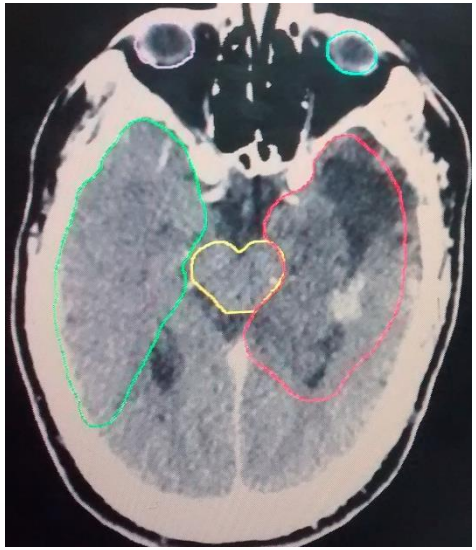
Pre -op Post contrast GTV

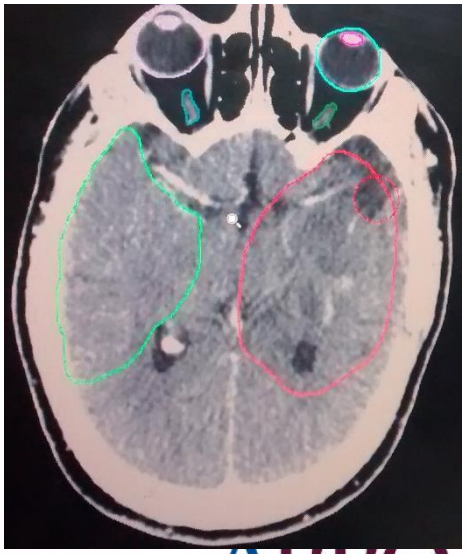




Pre-op FLAIR GTV

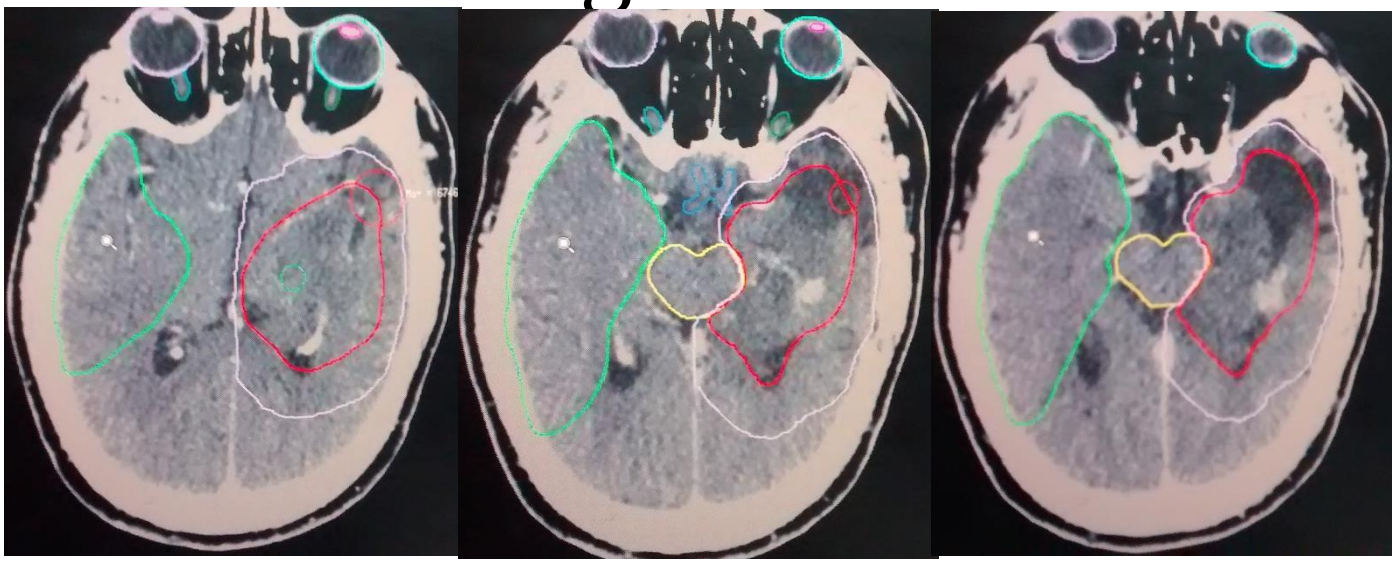




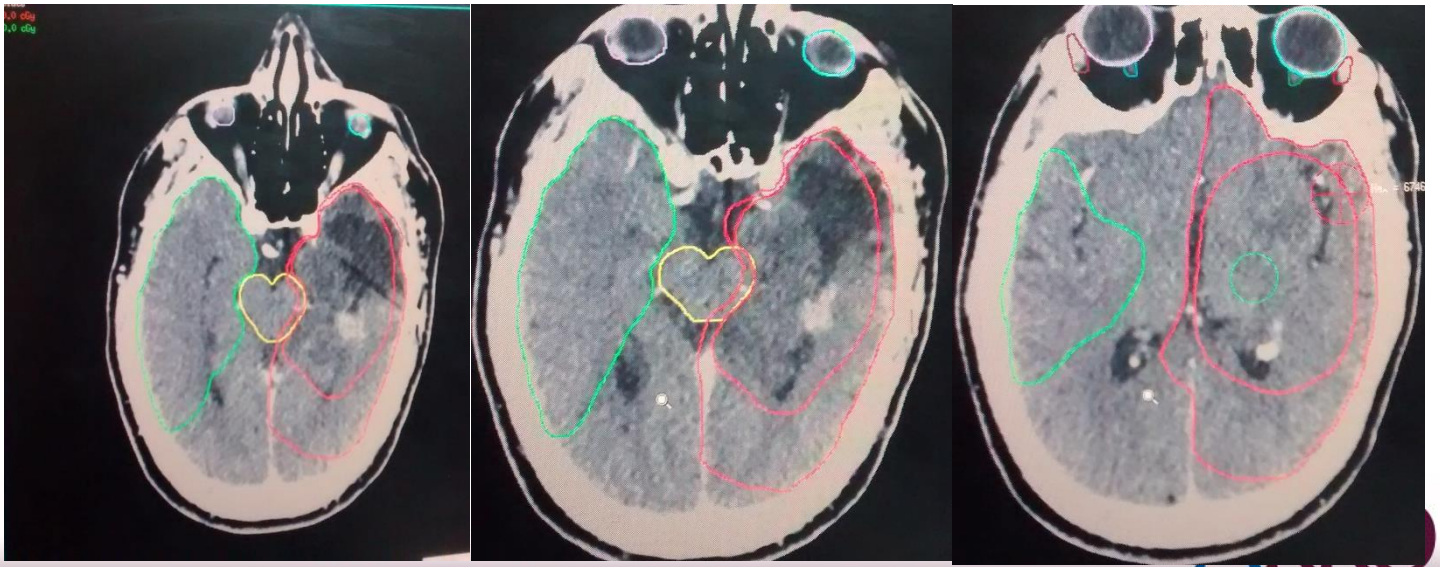


Contouring - CTV

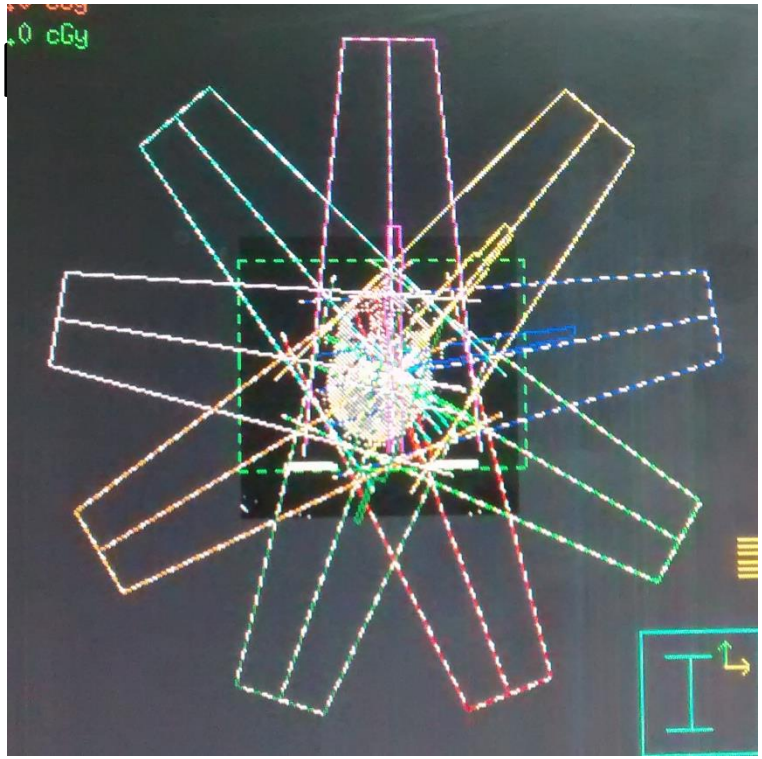
CTV
60Gy



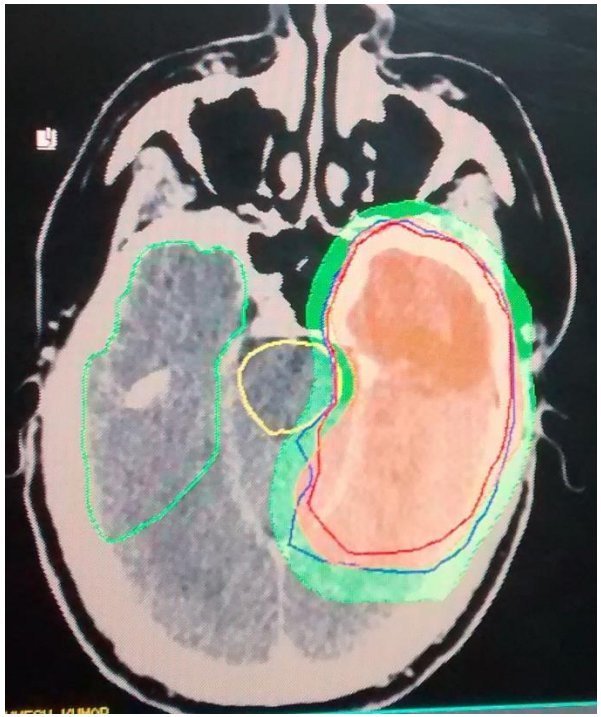
CTV
50Gy

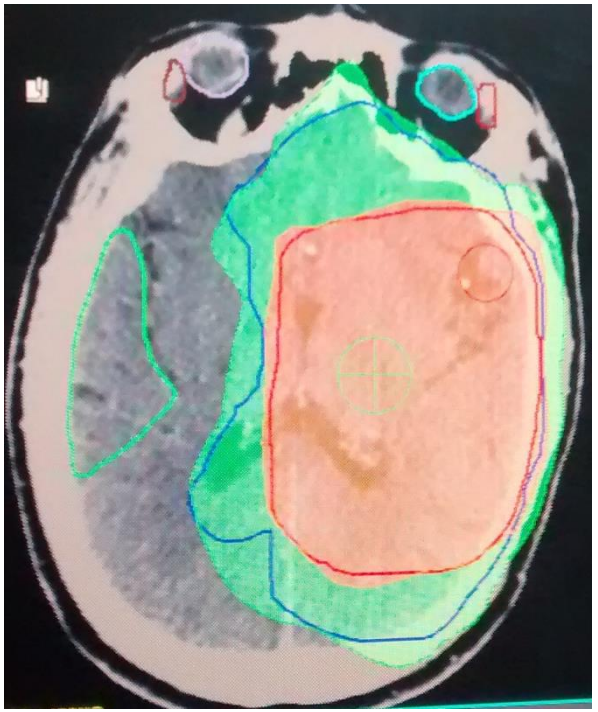


IMRT-SIB plan

- 

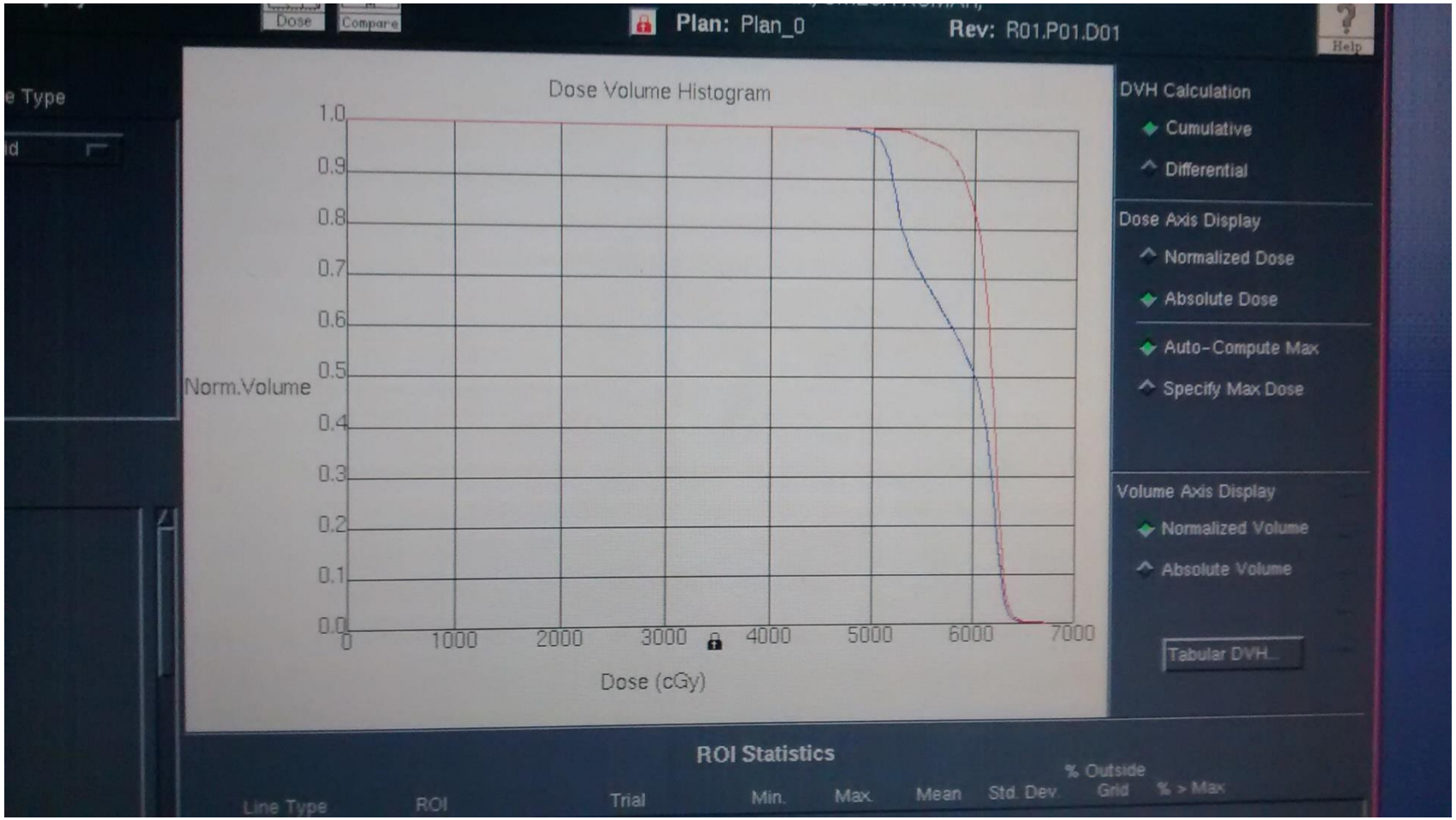
Dose :60Gy/20#/4wks (PTV 60)
50Gy/20#/4wks (PTV 50)





Orange – 57 Gy Isodose
Green – 47.5 Gy Isodose

DVH


Dose
Compare
Plan: Plan_0
Rev: R01.P01.D01
Help
Dose Volume Histogram
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
Dose (cGy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
ROI Statistics
Line Type
ROI
Trial
Min.
Max.
Mean
Std. Dev.
% Outside Grid
% > Max

DVH parameter - Target

- D95
  - PTV 60 = 57.5Gy
  - PTV 50 = 51 Gy
- Heterogeneity index – 1.1
- Conformity index – 1.1

DVH parameter - OARs

OAR	Constraint	Achieved
Brain stem Dmax	54 Gy	**57.5 Gy** (>54 Gy = 2cc)
Optic chiasm Dmax	50 Gy	**53.5 Gy** (>50 Gy = 0.4cc)
Right Optic Nerve Dmax	50 Gy	36 Gy
Left Optic Nerve Dmax	50 Gy	47.5 Gy
Right Eye Dmax	45 Gy	27 Gy
Left Eye Dmax	45 Gy	37.8 Gy
Right Temporal lobe Dmax	60 Gy	43.6 Gy
Spinal Cord	45 Gy	4.1 Gy

DVH parameter – OARs

OAR	Dose received	Tolerance dose
Right Cochlea Dmean	15.4 Gy	45 Gy
Left Cochlea Dmean	25 Gy	45 Gy
Right Lacrimal Gland Dmean	22.3 Gy	25 Gy
Left Lacrimal gland Dmean	23.2 Gy	25 Gy
Right Lens Dmax	9.9 Gy	10 Gy
Left Lens Dmax	**10.4 Gy**	10 Gy

Review of Literature

Glioblastoma Multiforme

- Most common malignant brain tumour
  - 75% of all high grade gliomas.*
- Median survival – 14 to 24 months
- Standard of care
  - Surgery
  - Adjuvant radiotherapy with conc. Chemo and Tumour treating fields
  - Adjuvant chemotherapy

Perez & Brady's Principle and Practice of Radiation Oncology 6th ed.

GBM Variants

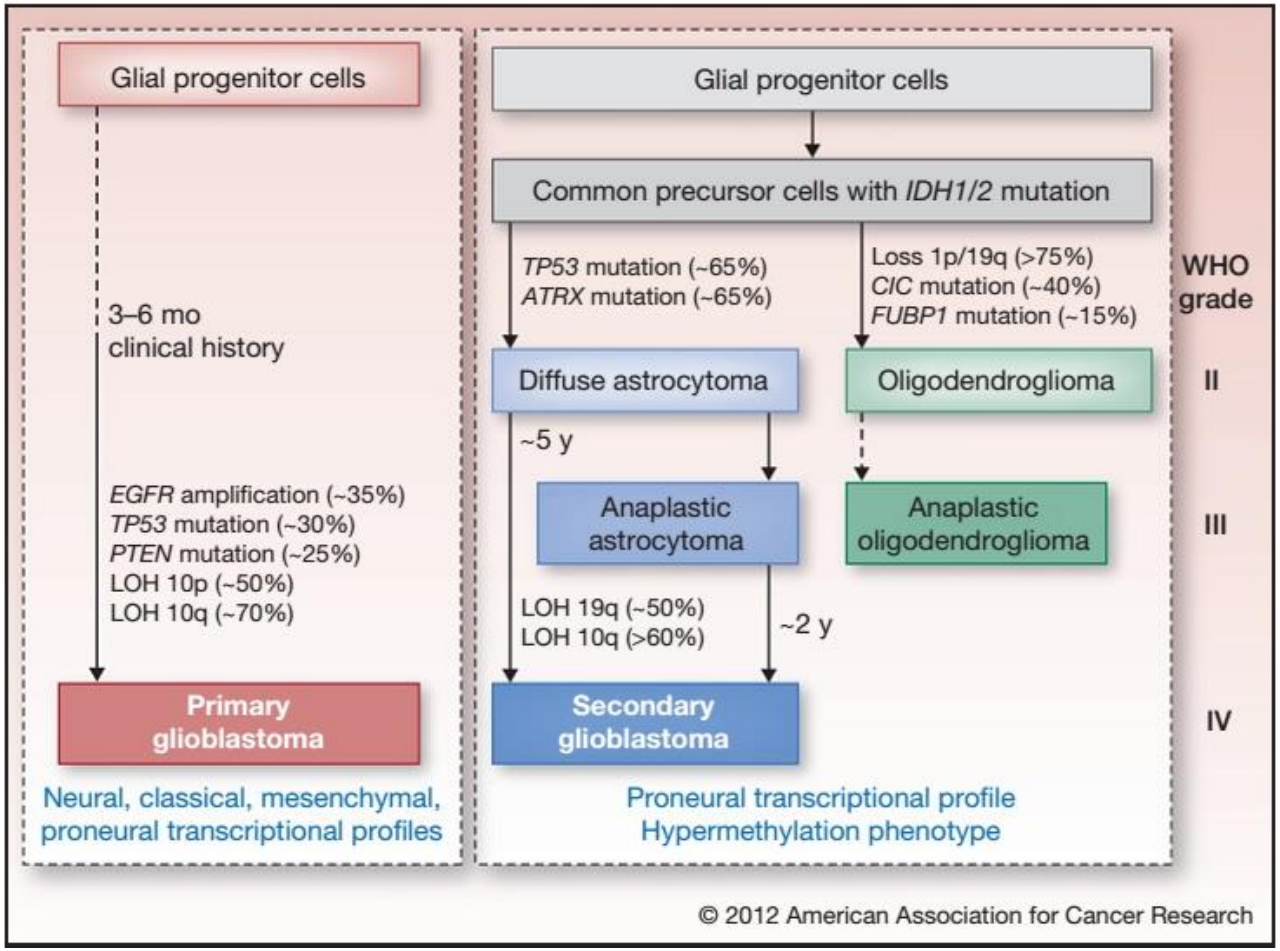
- WHO defined variants
  - Classical GBM – primary vs secondary
  - Gliosarcoma
  - Giant cell GBM
- Emerging variants*
  - Fibrillary/epithelial GBM
  - GBM with oligodendroglioma component
  - GBM with primitive neuroectodermal tumor (GBM-PNET)
  - Small cell GBM
  - Gemistocytic astrocytoma
  - Granular cell astrocytoma

**Karsy et al. Established and emerging variants of glioblastoma multiforme. Folia Neuropathol 2012*

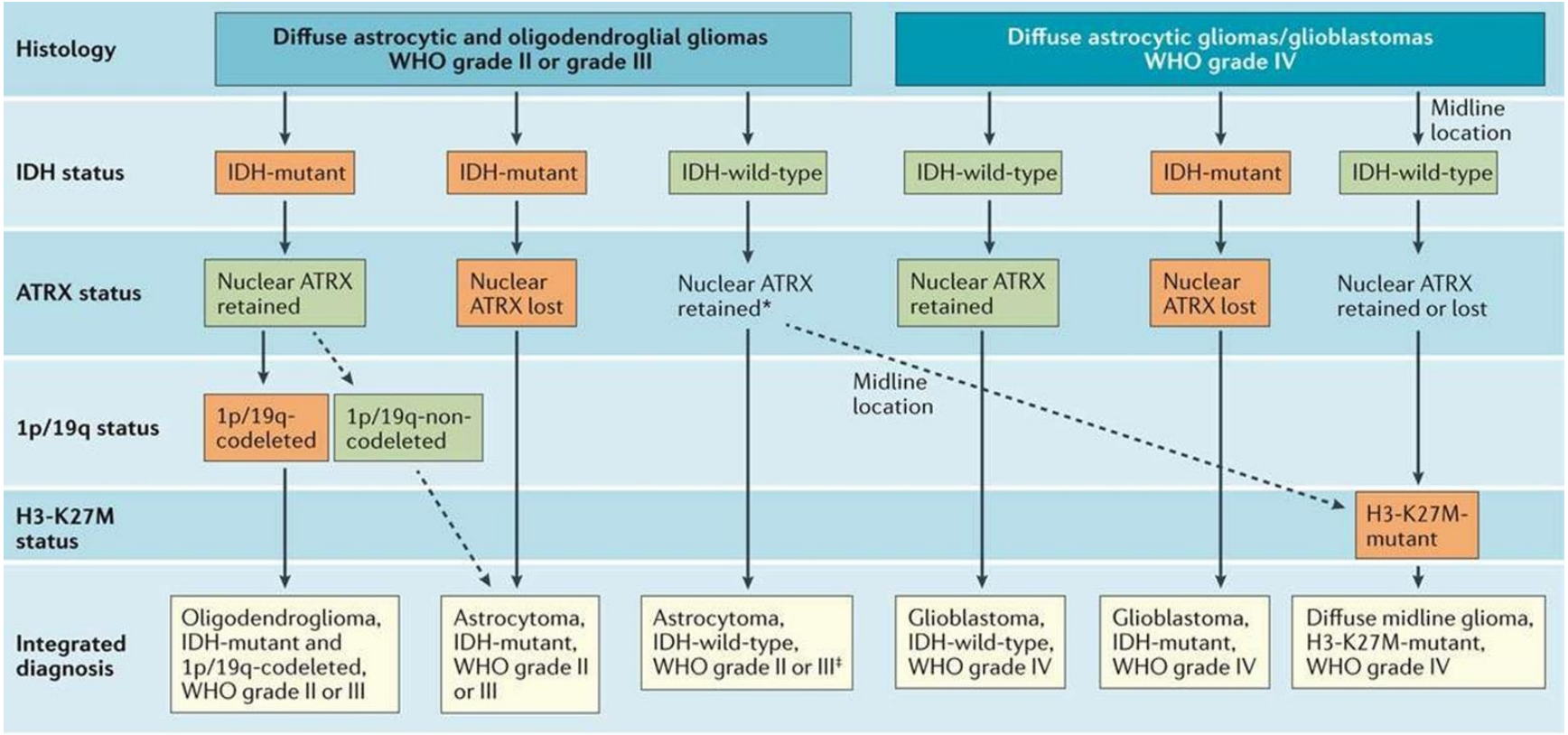
GBM-PNET

- Approx. 0.5% of GBM cases
- Median age – 51 to 54 yrs.
- Male preponderance
  - M:F = 1.3
- Location
  - Most common – Temporal lobe (~50%)
  - Infratentorial – rare
- Increased risk of CSF dissemination (?)
- Median survival – 9.1 months

Primary vs Secondary GBM

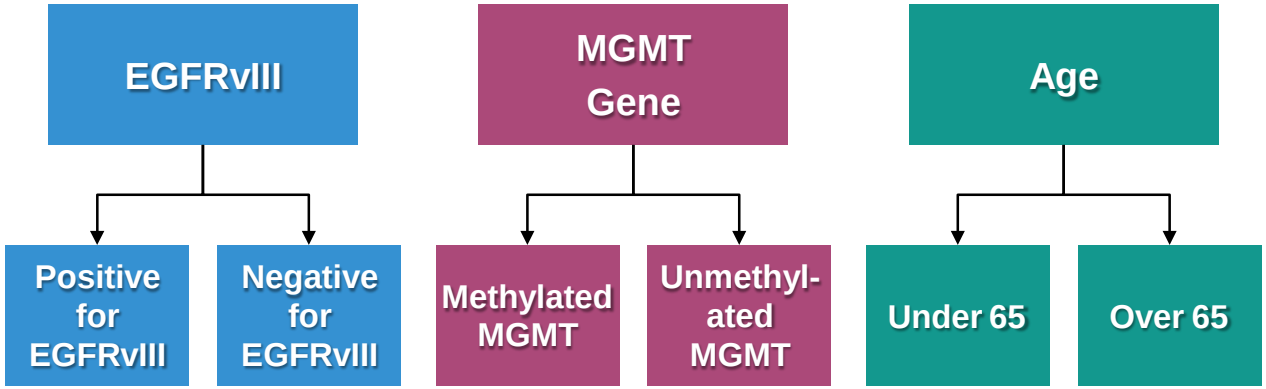


Algorithm for molecular classification diffuse glioma



Louis et al 2016 Acta Neuropath

Survival outcomes

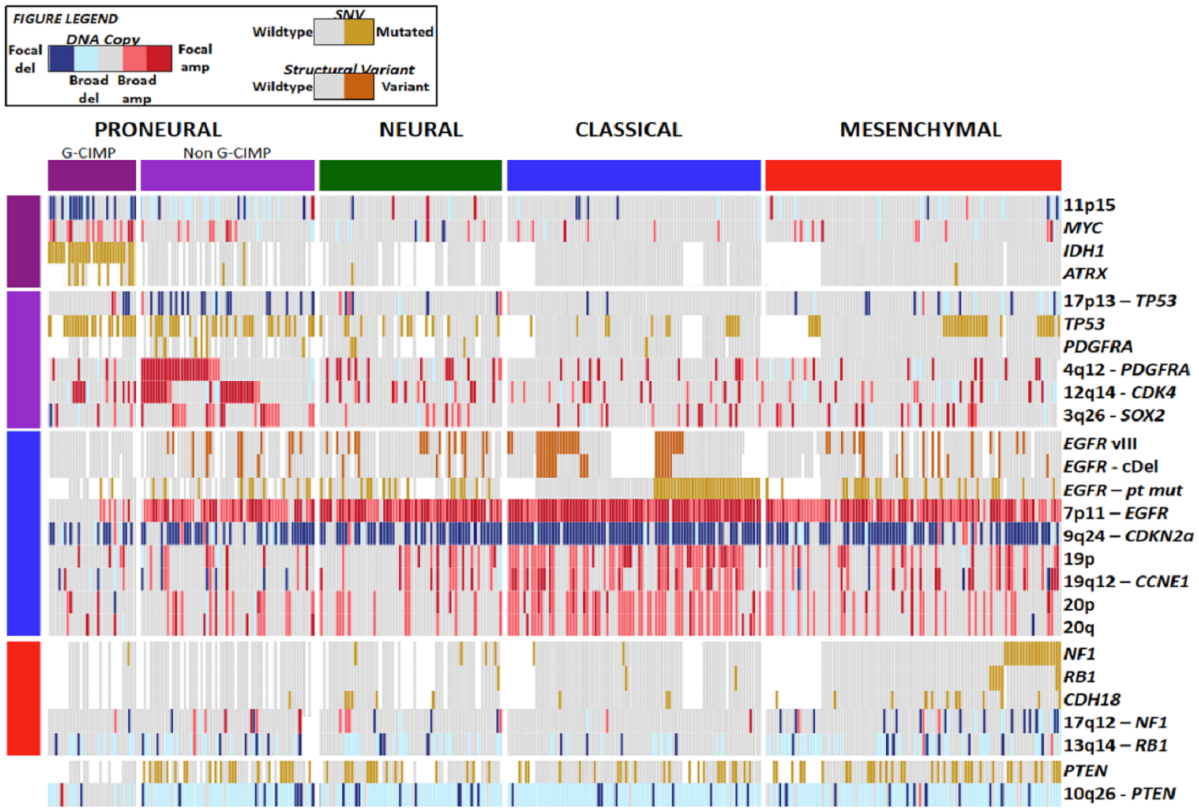


Frequency	25%	75%	45%	55%	50%	50%
Overall Survival	23 months[1]	15 months	22 months[2]	13 months[2]	15 months[2]	9 months[2]

[1] Data based on general patient populations treated with rindopepimut immunotherapy and temozolomide and lacking a placebo control.
[2] Data based on patient populations receiving radiotherapy and temozolomide.
Source: Babu, R., Core Evidence, 2012; Hegi, M., NEJM, 2005; Oszvald, A., Journal of Neurosurgery, 2012.

Somatic Genomic landscape of GBM

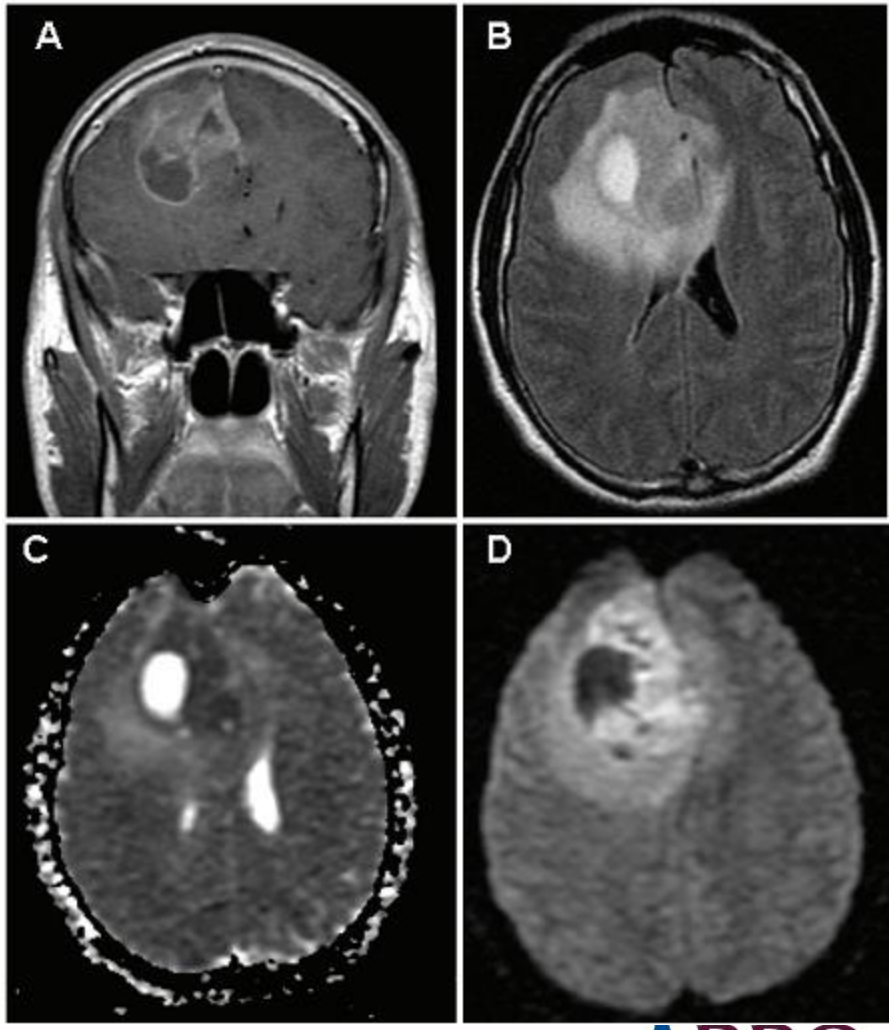
A



Cell 2013

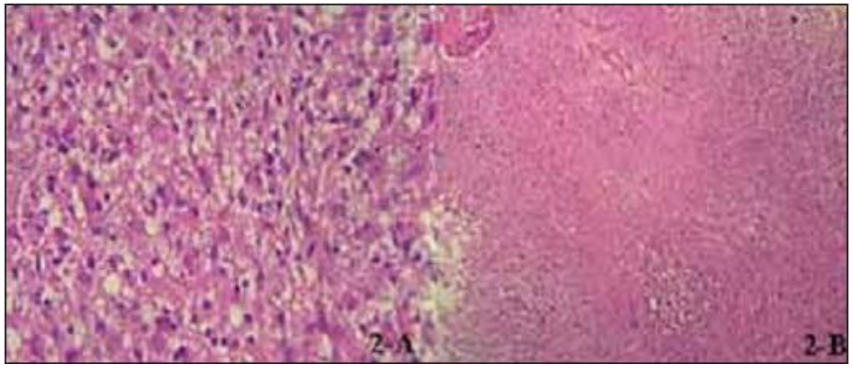
Imaging

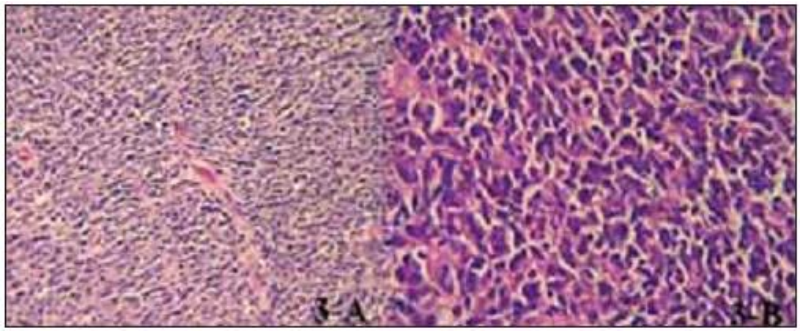
- Heterogeneously enhancement ;solid cystic lesion
- Mass effect
- Peritumoral edema
- Diffusion restriction in DWI
  - High cellularity of PNET component



Histopathology

- Two distinct architecture
- GBM
  - Neoplastic astrocytes
  - Necrosis
  - Nuclear atypia
- PNET foci
  - High nuclear to cyctoplasmic ratio
  - Mitotic activity
  - Homer-Wright rosettes





Immuno-histochemistry

- Glial component
  - GFAP +
- PNET component
  - S100
  - Synaptophysin
  - NeuN
  - NFP

Neuronal Markers

- Proliferative index (MIB-LI or Ki-67)
  - Glial- 10 to 40%
  - PNET- 40 to >90%
- p53 nuclear staining
  - Both Glial and neuronal component
  - ~ 83%
- N-myc amplification in PNET component

Origin

- Monoclonal origin with different differentiation pattern
  - Neuronal and glial cells of CNS originate from same stem cell
  - Neural stem cell markers CD113 and nestin found in stem cells isolated from gliomas*
- Secondary GBM
  - Younger age of onset as compared to primary GBM (62 yrs)
  - Frequent history of prior low grade gliomas
  - Strong and diffuse immunoreactivity for p53
  - Frequent IDH1 mutation
  - Rarity of EGFR amplification

**Singh et al. Identification of a cancer stem cell in human brain tumors. Cancer Res 2015*

Differentiation from other GBM Variants

	Classical GBM	GBM PNET	Small cell GBM	Gliosarcoma
Histo-pathology	Infiltrating pleomorphic cells, mitoses, endothelial proliferation and necrosis	GBM with PNET areas showing hypercellularity, Homer-Wright rosettes, small hyperchromatic nuclei	Monomorphic cells with small round nuclei	GBM along with heterogeneous sarcomatous differentiation
IHC/FISH	GFAP	GFAP Synaptophysin Chromogranin NeuN	EGFR amplification	Reticulin Vimentin Laminin Collagen IV α1-antitrypsin
Median Survival	14-24 months	9 months	6-14 mo	4-11 mo

Case series/report	n	Adjuvant RT	Adjuvant Chemo	Outcome
Perry et al 2009	53	Local RT (17) CSI (1) Concurrent chemo (1)	Temozolomide/ BCNU (16)* Platinum based (3)	Median Survival – 9.1 mo Local progression – all CSF dissemination – 21%
Song et al 2011	10	Local RT (9)	Temozolomide (10)	Median Survival – 10 mo CSF dissemination – 20%
Lee et al 2012	3	Local RT 60 Gy with Temozolomide and Carboplatin	Ifos+Carbo+Eto → Temozolomide	1 local progression at 32 mo 2 disease free at 36 and 56 mo
Kaplan et al 2007	1	Local RT	NA	Local progression – 10 mo
Kandemir et al 2009	1	Local RT	NA	No recurrence at 9 mo
Chu et al 2015	1	Local RT 59.4 Gy → 17Gy SRS boost	Temozolomide	Local progression – 1 mo Survival – 28 mo

Adjuvant Treatment

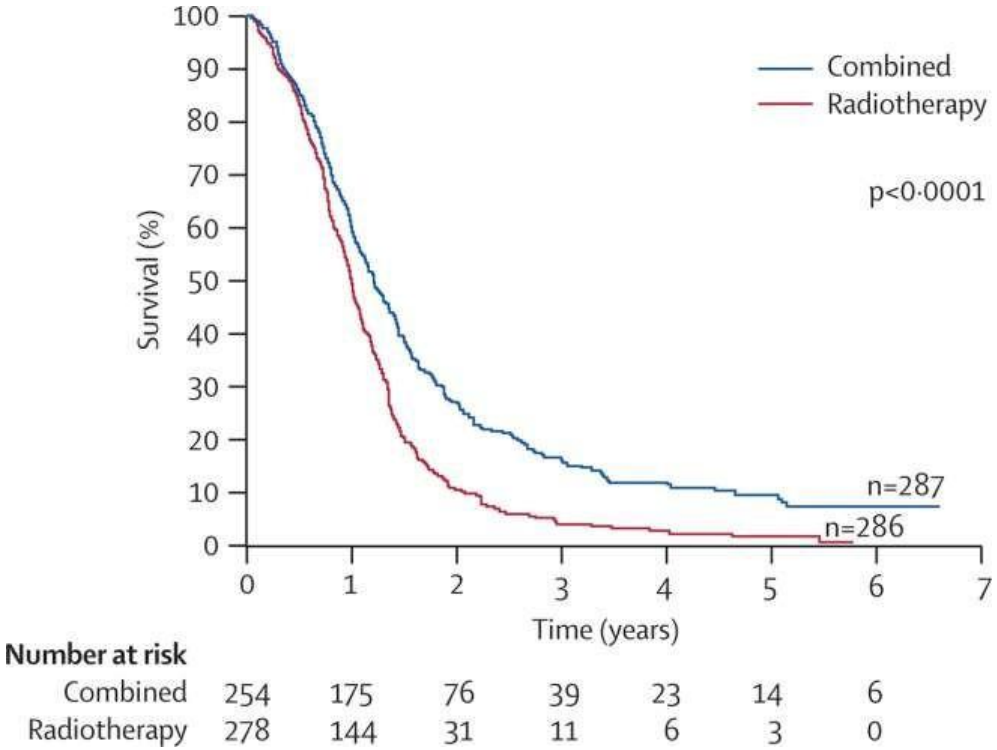
- Local Radiotherapy
  - Similar to GBM
  - Dose 60 Gy
- CSI
  - Controversial
  - Rarely used in retrospective series
  - Local failure most common
- Chemotherapy
  - Temozolomide
  - Platinum based chemotherapy who fail on temozolomide and RT.

Conclusion

- Rare entity
- Monoclonal origin from secondary GBM
- Biphasic tumour in histopathology, IHC to differentiate from GBM
- Prognosis similar to GBM
- Adjuvant treatment in line of GBM

Literature on GBM

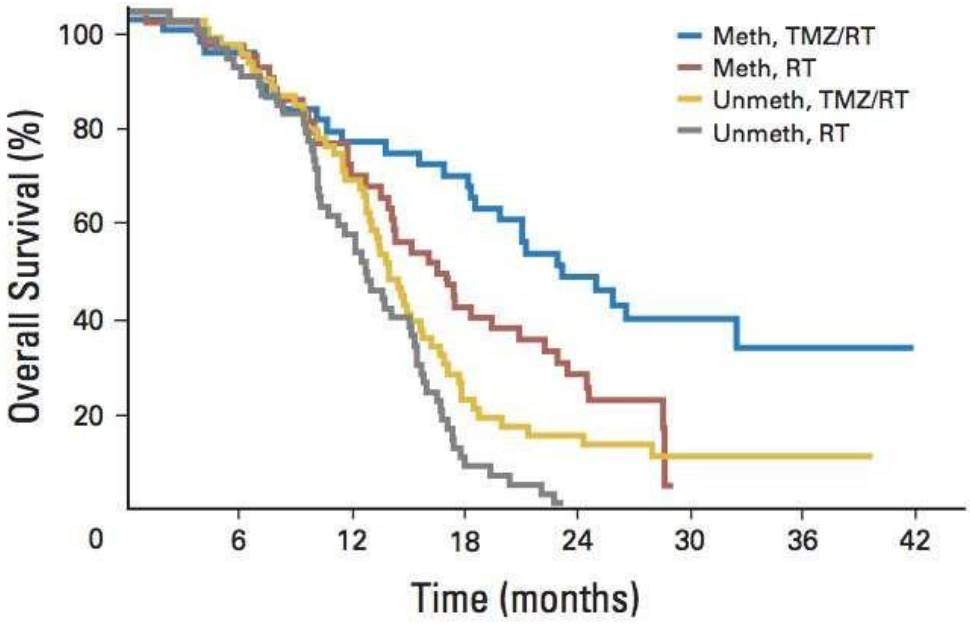
GBM Standard: EORTC/NCIC Trial



- Age <= 70
- 574 pts randomized 1:1
  - 60 Gy
  - 60 Gy/TMZ → TMZ
- Improved median survival
  - 12.1 → 14.6 months
  - P<0.001

Stupp R, et al. N Engl J Med 2005
Stupp R, et al. Lancet 2009

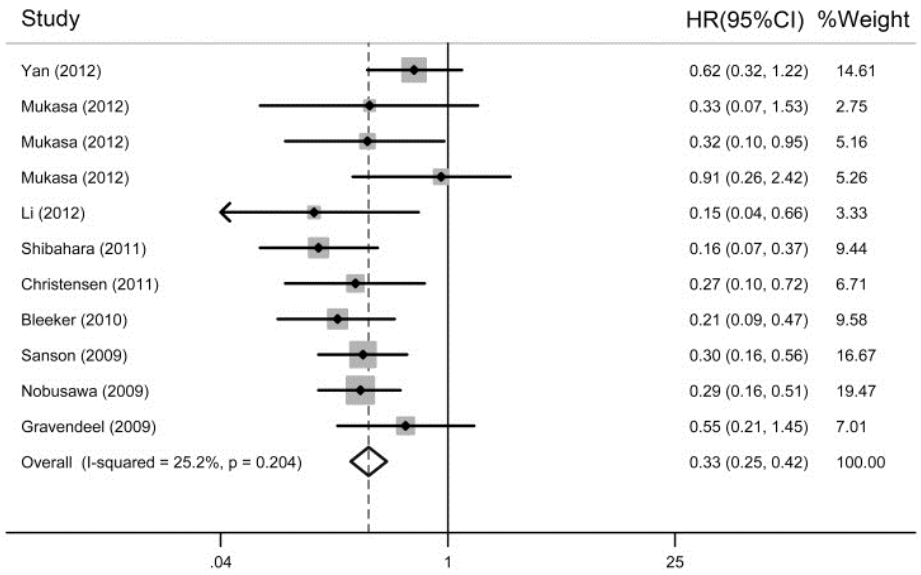
MGMT methylated confers better outcomes



- DNA repair by O6 - methylguanine methyltransferase
- Resistance to alkylating agents
- Prognostic and predictive significance

Hegi M, et al. JCO 2008

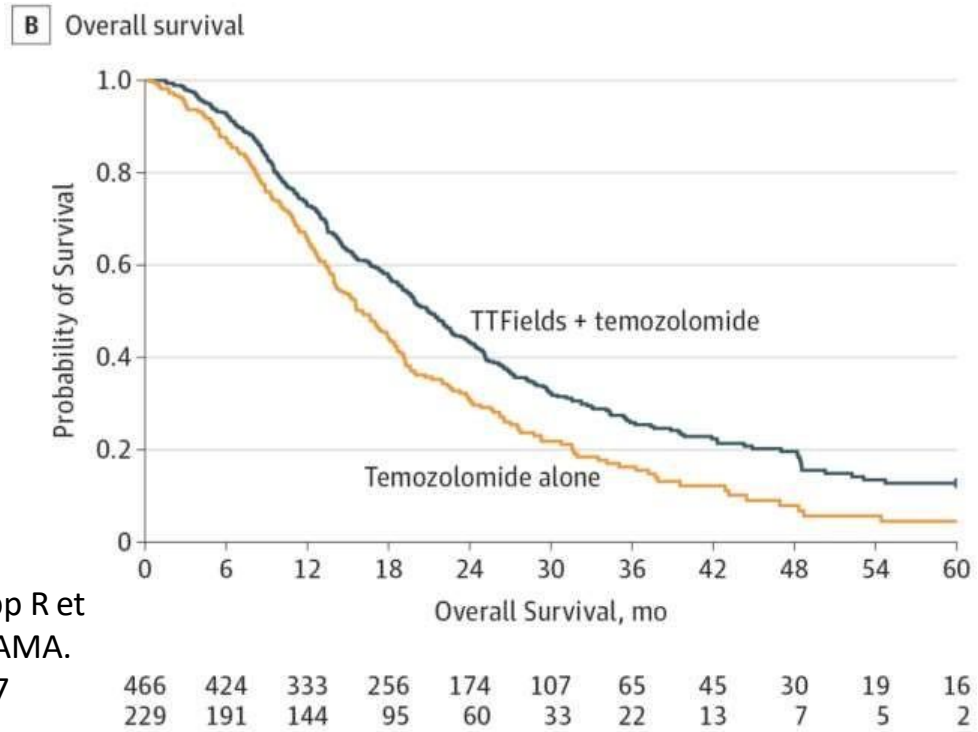
IDH mutated GBM does better



Zou P et al. PLOS One 2013
Ohgaki and Kleihues. Clin Cancer Research 2013
Sanson M et al. JCO 2009

- IDH mutations are earliest detectable genetic alterations in precursor LGG
- Primary GBM = IDH wt
  - Secondary GBM = IDH mut
- Prognostic but not necessarily predictive

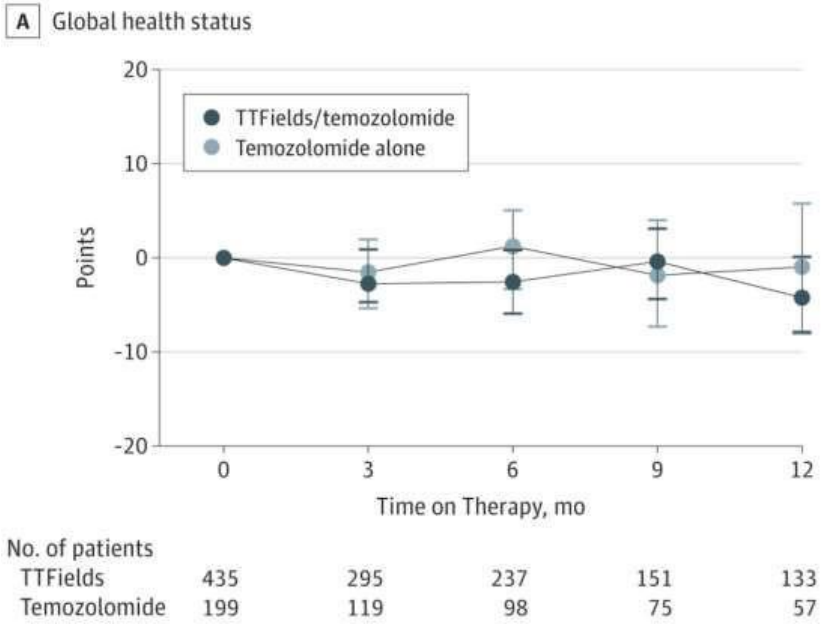
Tumor-Treating Fields



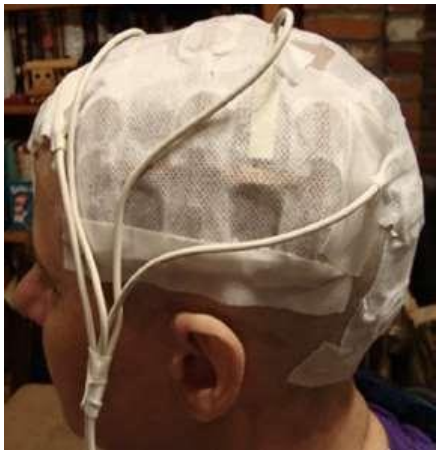
Stupp R et al. JAMA. 2017

- KPS ≥ 70; median age 56
- 695 pts randomized 2:1 after 60 Gy/TMZ
  - Adjuvant TMZ + TTFields
  - Adjuvant TMZ
- Improved median survival (from time of randomization)
  - 16.0 → 20.9 months
  - P<0.001
- Toxicity
  - Skin toxicity in 52%

Tumor-Treating Fields



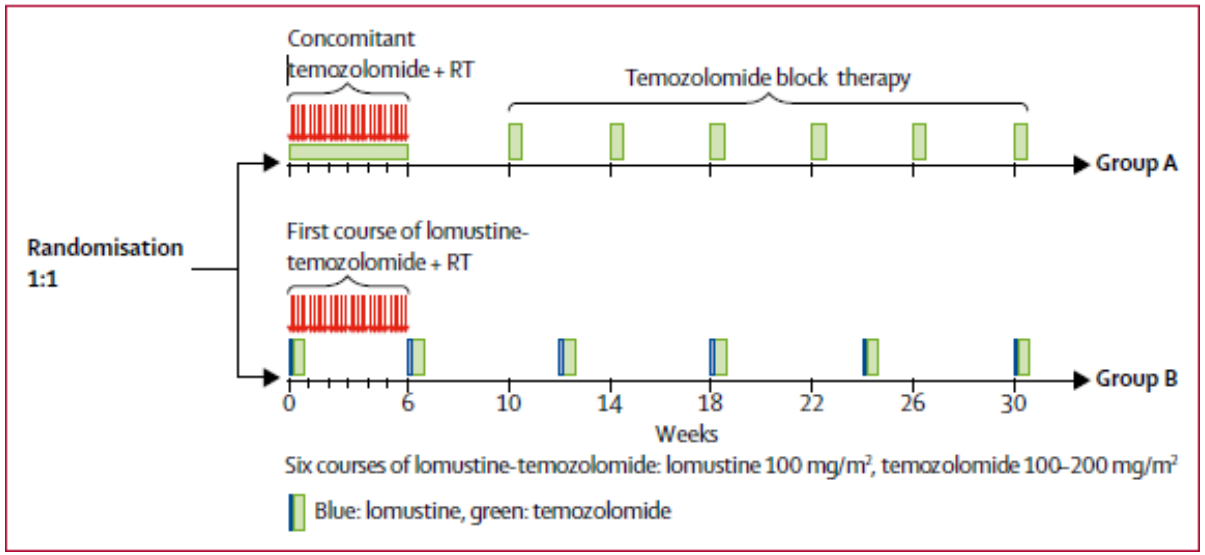
- HRQOL data
- Same global health status



Taphoorn MJ et al. *JAMA Oncol.* 2018;4(4):495-504.

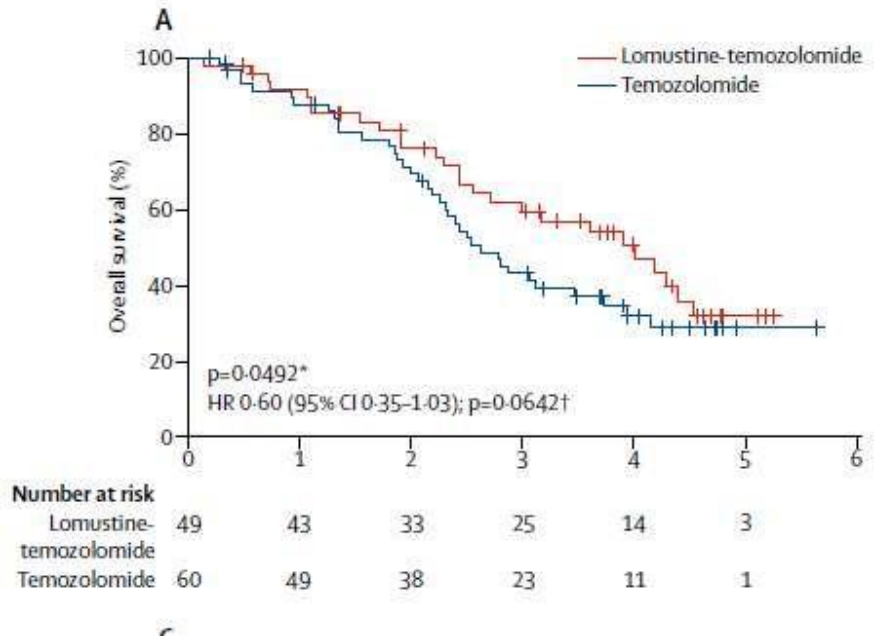
Methylated GBM: CeTeG/NOA-09 Trial

- 129 patients with MGMT methylation and age ≤ 70
- Randomized 1:1



Herrlinger U, Tzaridis T, et al. Lancet 2019; 393: 678-88.

Methylated GBM: CeTeG/NOA-09 Trial



- Age ≤ 70 (median age 58, 61% GTR)
- 129 pts randomized 1:1
  - 60 Gy/TMZ → 6 cycles TMZ
  - 60 Gy/6 cycles TMZ & CCNU
- Improved median survival
  - 31.4 → 48.1 months
  - P=0.0492
  - Based on stratified log rank test, not significant on Cox regression analysis
  - No effect on PFS (?pseudoprogression)

Herrlinger U, Tzaridis T, et al. Lancet 2019; 393: 678-88.

Methylated GBM: CeTeG/NOA-09 Trial

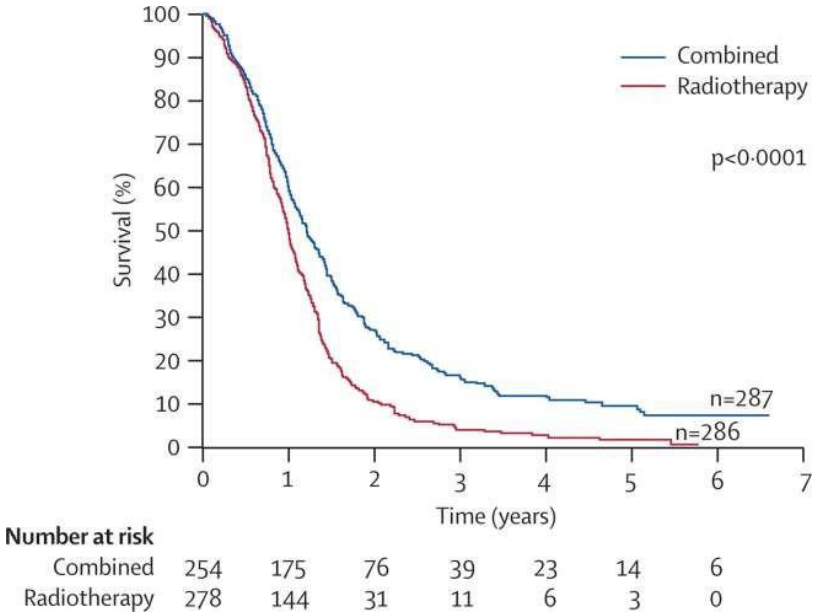
Table 2: Grade 3 events 51% → 59%

	Temozolomide (n=63)		Lomustine-temozolomide (n=66)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Haematological events				
Leukopenia	10 (16%)	8 (13%)	24 (36%)	10 (15%)
Neutropenia	7 (11%)	4 (6%)	12 (18%)	8 (12%)
Thrombocytopenia	19 (30%)	15 (24%)	40 (61%)	19 (29%)
Lymphopenia	4 (6%)	4 (6%)	6 (9%)	3 (5%)
Anaemia	3 (5%)	3 (5%)	5 (8%)	1 (2%)

Herrlinger U, Tzaridis T, et al. Lancet 2019; 393: 678-88.

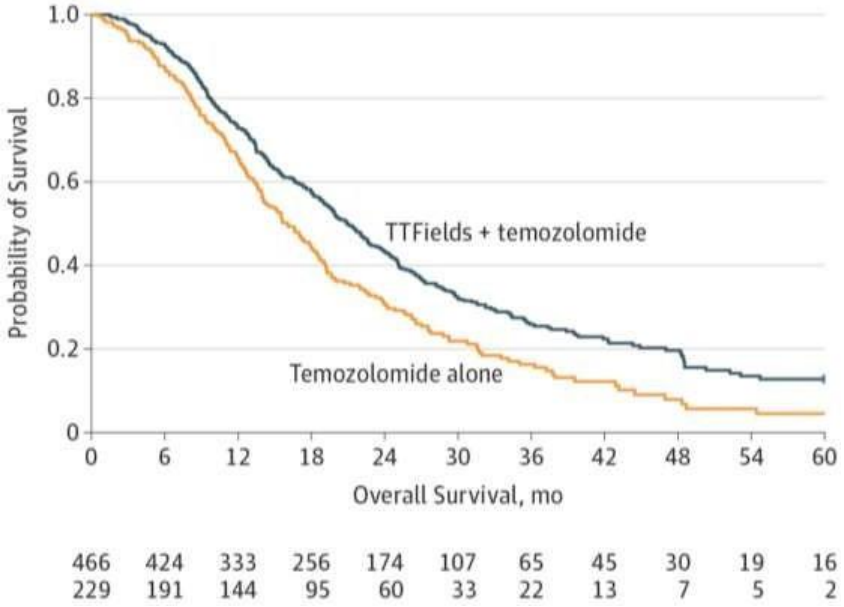
GBM Standard

2005: Temozolomide



Stupp R et al. Lancet 2009.

2015: Tumor treating fields



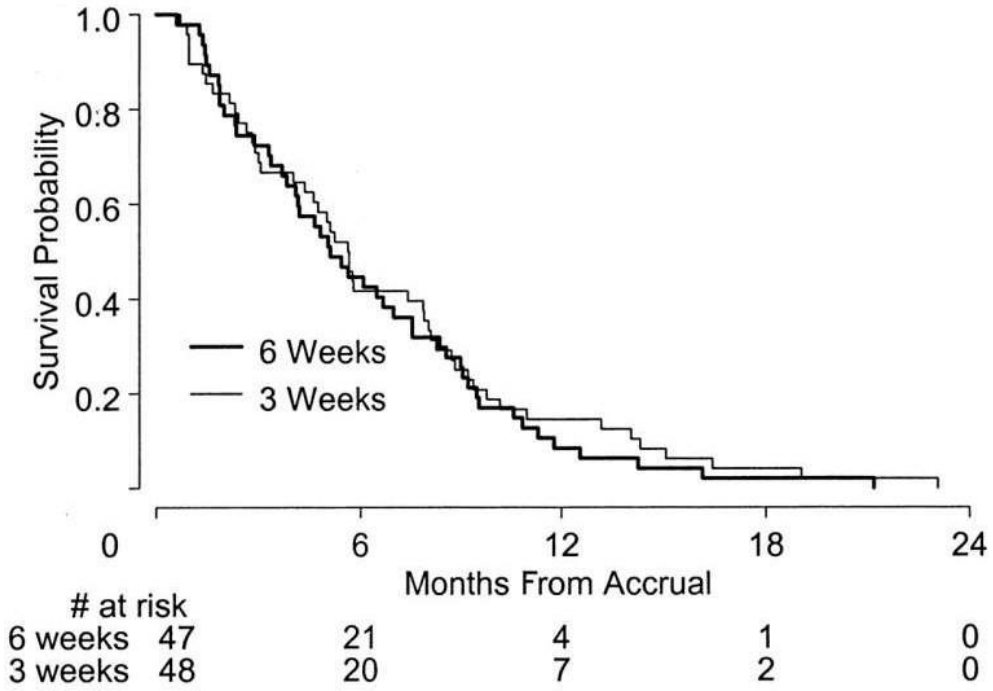
Stupp R et al. JAMA 2017

GBM ongoing trials for upfront treatment

Randomized

- Nivolumab vs TMZ for unmethylated: CheckMate 498
- Placebo/TMZ vs nivolumab/TMZ: CheckMate 548
- Antibody drug conjugate to EGFR(depatuxizumab mafodotin: ABT-414) vs placebo: M13-813/RTOG 3508
- Dose escalation to TMZ/75 Gy/30 fx vs TMZ/60 Gy: NRG BN001

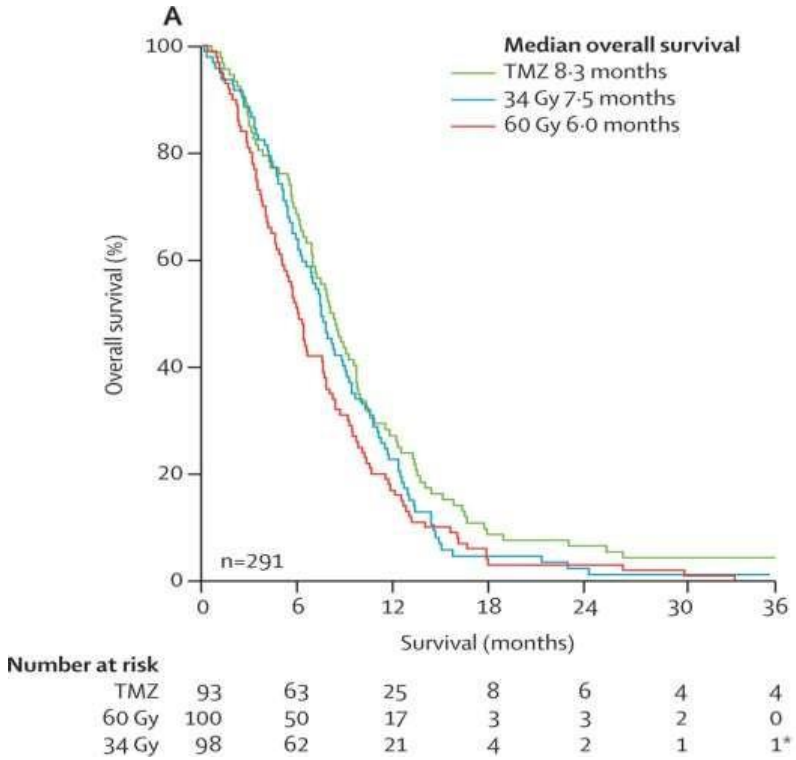
Elderly GBM: Canadian Study "Roa"



- Age > 60
- 40 Gy in 15 = 60 Gy in 30
  - 5.6 vs 5.1 months median survival
  - P=0.57
- No temozolomide

Roa et al. J *of Clin Oncol* 2004

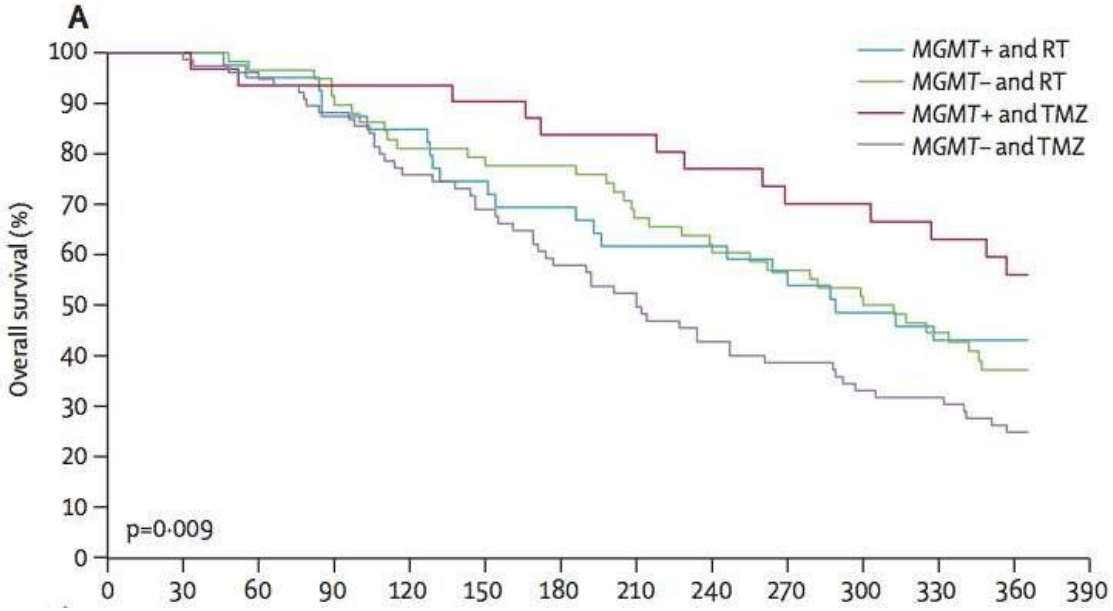
Elderly GBM: Nordic Trial



- Age > 60
- 60 Gy worse than 34 Gy/10 or TMZ alone
- Methylated MGMT associated with better survival for TMZ
  - Did not matter for RT

Malmstrom A et al. Lancet Oncology. 2012

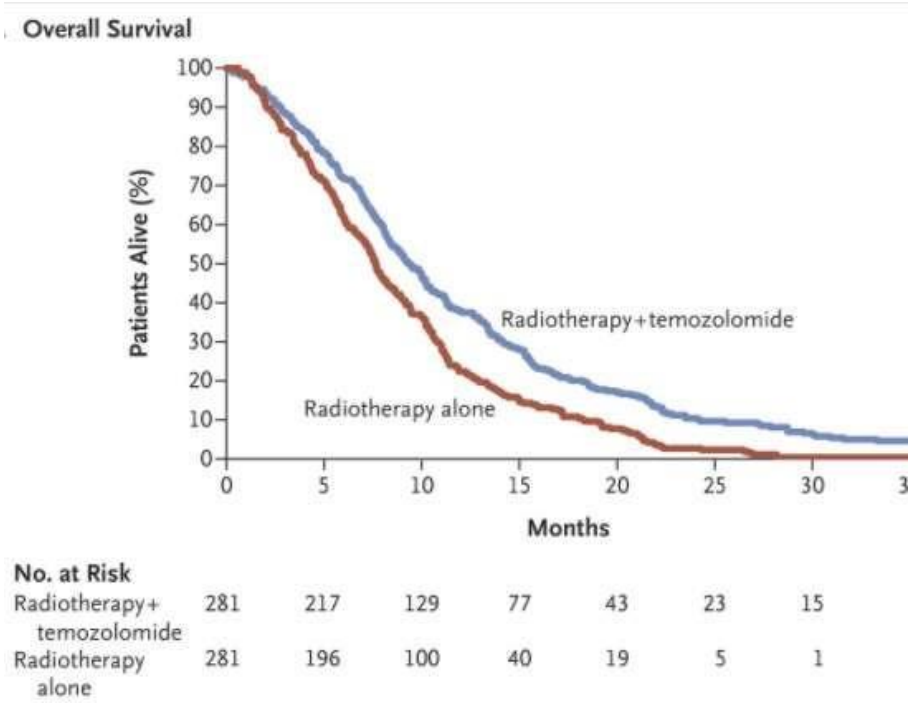
Elderly GBM: NOA-08



- Age > 65, KPS > 60
- TMZ = 60 Gy RT
  - 8.6 vs 9.6 mo median survival
- MGMT- benefited from RT not TMZ
- More toxicity with TMZ

Wick W, et al. Lancet Oncology. 2012

Elderly GBM: CCTG/EORTC/TROG



Perry J, et al. N Engl J Med 2017; 376:1027-1037

- Age ≥ 65, ECOG PS 0-2
- 40 Gy/TMZ →better
  - 9.3 vs 7.6 mo median survival
  - p<0.001
- Benefit mostly for MGMT+ but also in MGMT-
  - ?whether methylation is most accurate test of MGMT

GBM standard: Contouring guidelines

RTOG	EORTC
46 Gy in 23 fractions	**60 Gy in 30 fractions**
GTV1= surgical cavity + residual enhancing tumor + *surrounding edema*	GTV = surgical resection cavity + residual enhancing tumor
CTV1=GTV1 + 2 cm	CTV = GTV + 2 cm
14 Gy in 7 fractions	
GTV2= surgical cavity + residual enhancing tumor	
CTV2=GTV2 + 2 cm	

**In RTOG 0525 and CENTRIC trials, no difference in OS between EORTC and RTOG sites*

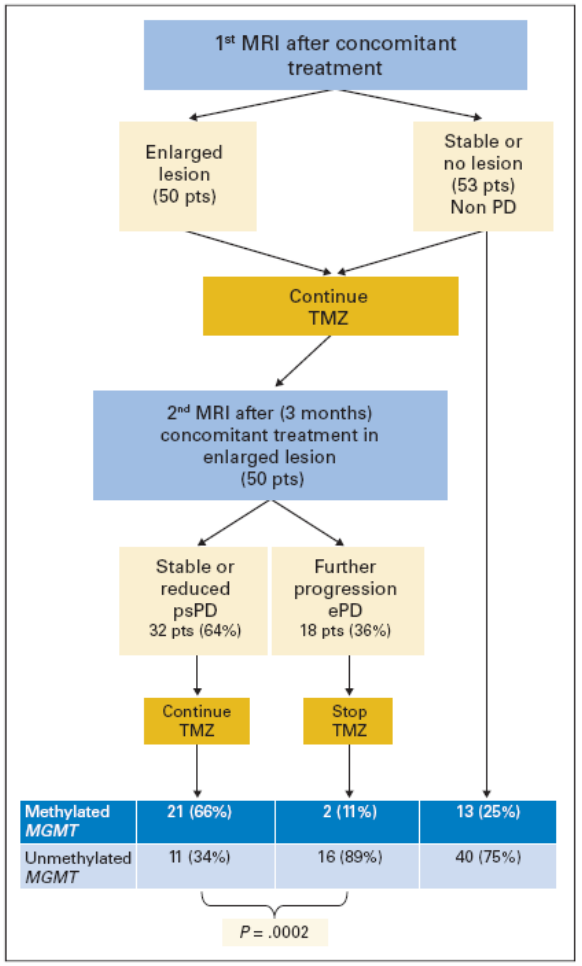
Gilbert JCO 31, 2013 and Stupp Lancet Onc 15, 2014

GBM: Smaller margins?

Center	n	Initial	Boost	Infield recurrences	OS (months)
Emory McDonald MW et al. Int J Radiat Oncol Biol Phys 2011	62	CTV=T2 + 0.7cm	PTV=T1 gad/cavity + 0.5 cm	93%	
Alabama Gebhardt BJ et al Radiat Oncol 2014	95	PTV=T2+ 1 cm	PTV=T1 gad/cavity + 0.5 cm	81%	
Wake Forest Paulsson AK et al Am J Clin Oncol 2014	29 78 38	0.5 cm 1 cm 1-2 cm			No difference
Iowa Guram K et al IJROBP 2018	191	PTV=T2+ 0.4-1 cm	PTV=T1 gad/cavity + 0.4-1.0 cm		16.1

Pseudoprogression

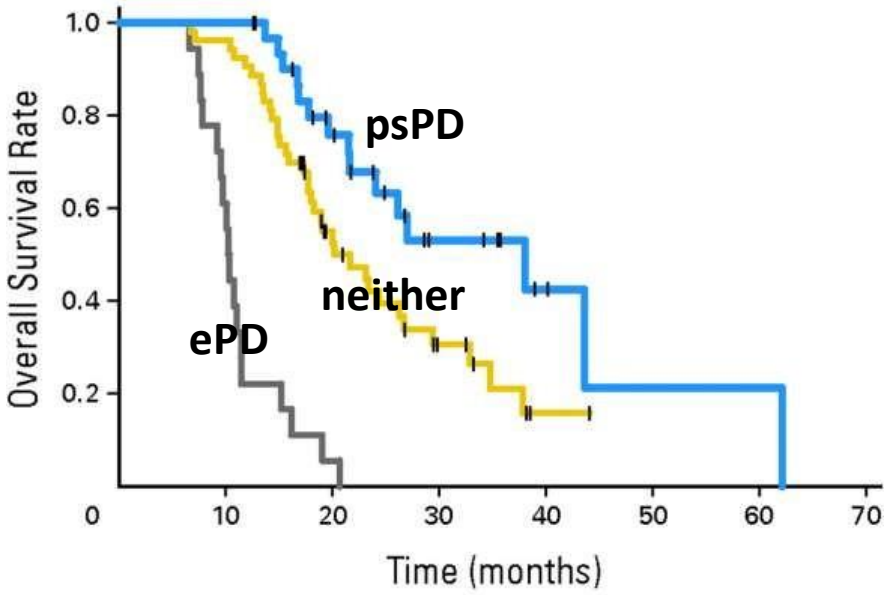
- One month post-chemoradiation
  - Half are bigger
  - 2/3 turn out to be pseudoprogression
  - If pseudoprogression, 2/3 have methylated MGMT
  - If early progression, 90% have unmethylated MGMT



Brandes et al. JCO 2008

Pseudoprogression

- pSPD associated with better survival (p=0.045)
- Unclear if psPD is a marker for better prognosis (mostly methylated patients) or leads to better prognosis



Brandes et al. JCO 2008

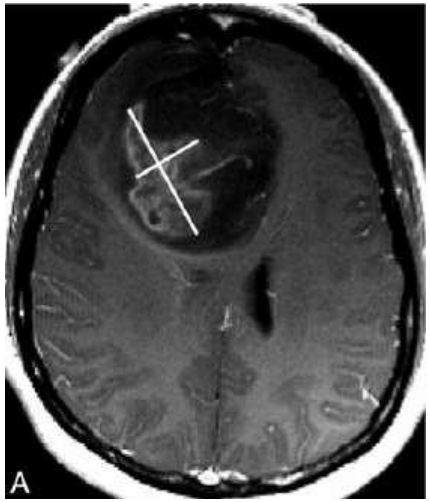
RANO: Response Assessment in Neuro-Oncology Criteria

- Call progression within 3 months of radiation therapy ONLY if:
  - New enhancement is beyond 80% isodose line
  - Unequivocal pathologic evidence of viable tumor

Wen PY et al. JCO 2010

RANO after 3 months

RANO Criteria	CR	PR	SD	PD
T1 enhancing disease	None	≥ 50%	< 50% if ↓ but < 25% if ↑	≥ 25% ↑
T2/FLAIR	Stable / improved	Stable / improved	Stable / improved	Stable / improved
New lesion	None	None	None	Present
Corticosteroid use	None	Stable or ↓	Stable or ↓	NA
Clinical status	Stable / improved	Stable / improved	Stable / improved	Declined



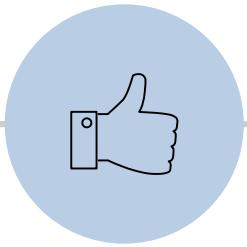
Yang D, et al. Neuro-Oncology Practice 2015

Summary: GBM

- <70 yo, good KPS
  - 60 Gy/TMZ → TMZ (*Stupp 2005)*
  - Consider TTFields *(Stupp 2017)*
  - Consider CCNU/TMZ for *select patients* with methylated MGMT (Herrlinger 2019)
  - Consider clinical trials
- ≥70 yo, good KPS
  - 40 Gy/TMZ → TMZ *(Perry 2017)*
- Poor KPS
  - Consider RT alone, TMZ alone, or best supportive care (*Wick 2012, Malstrom 2012, Roa 2004 and 2015)*
- Unknowns
  - Target volumes
  - Ongoing experimental agents

Resources

- ASTRO refresher course
- Previous ARRO cases



Thanks!