Journey of Glioma

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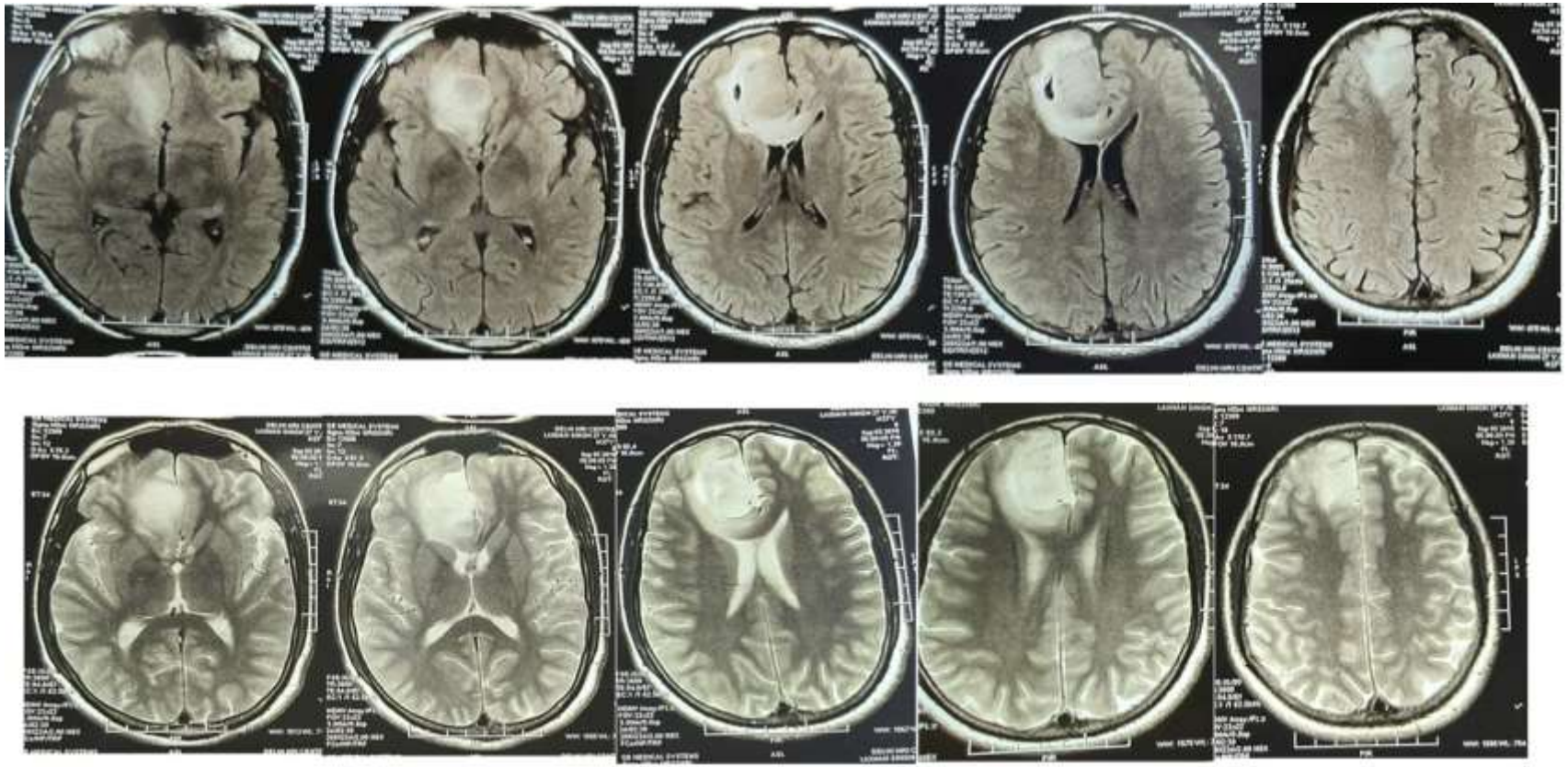
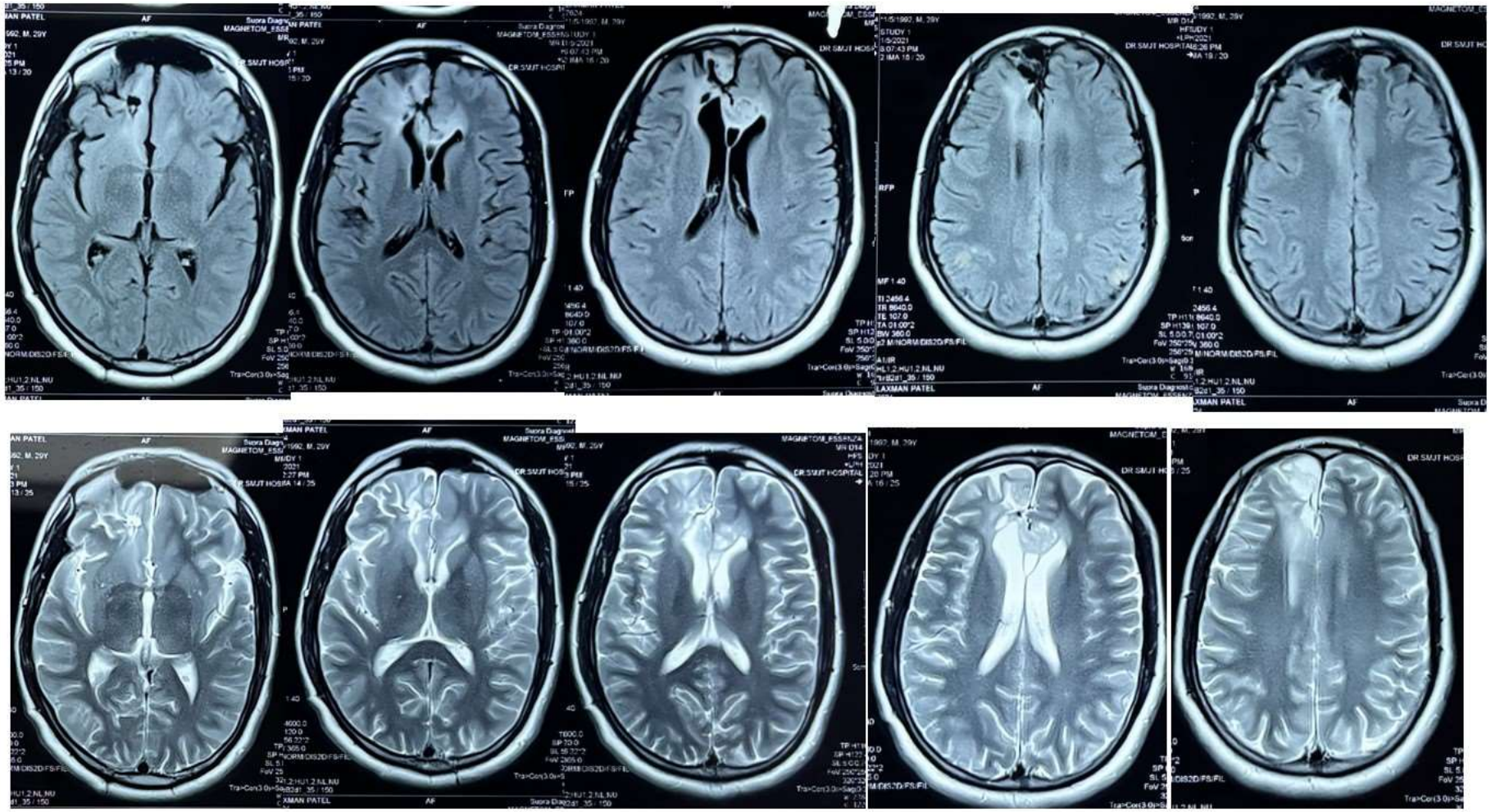
Case 1

32/M/Laborer / h/o headache followed by RTA



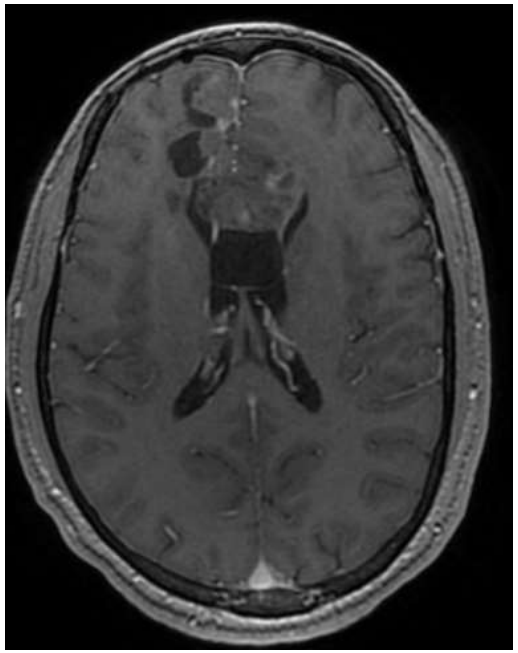
2018

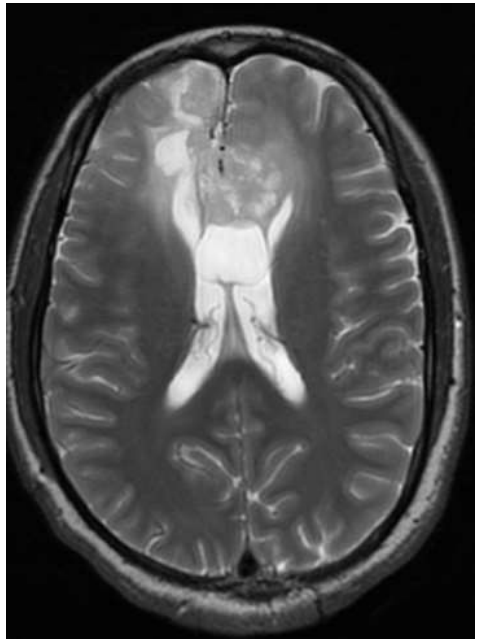
Post op-Astrocytoma Gd 1- kept on AEDs

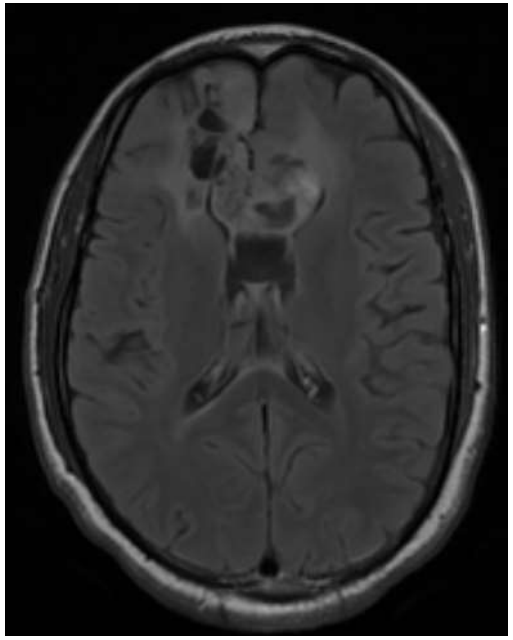


- Wait?
- Treat ?

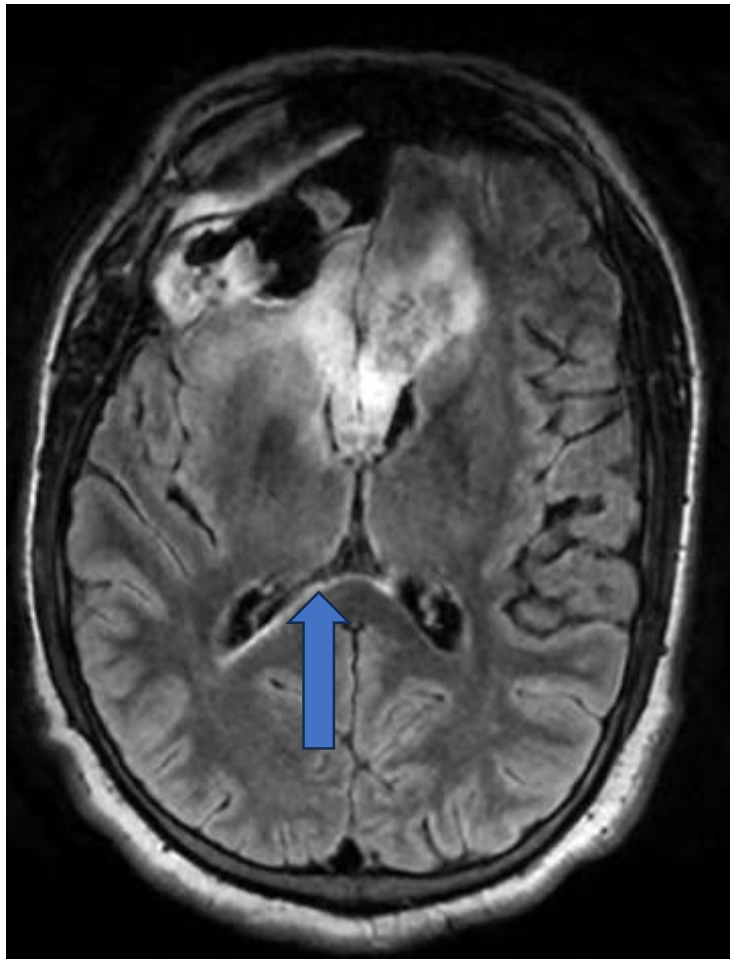
Headache/heaviness in eyes /RTA

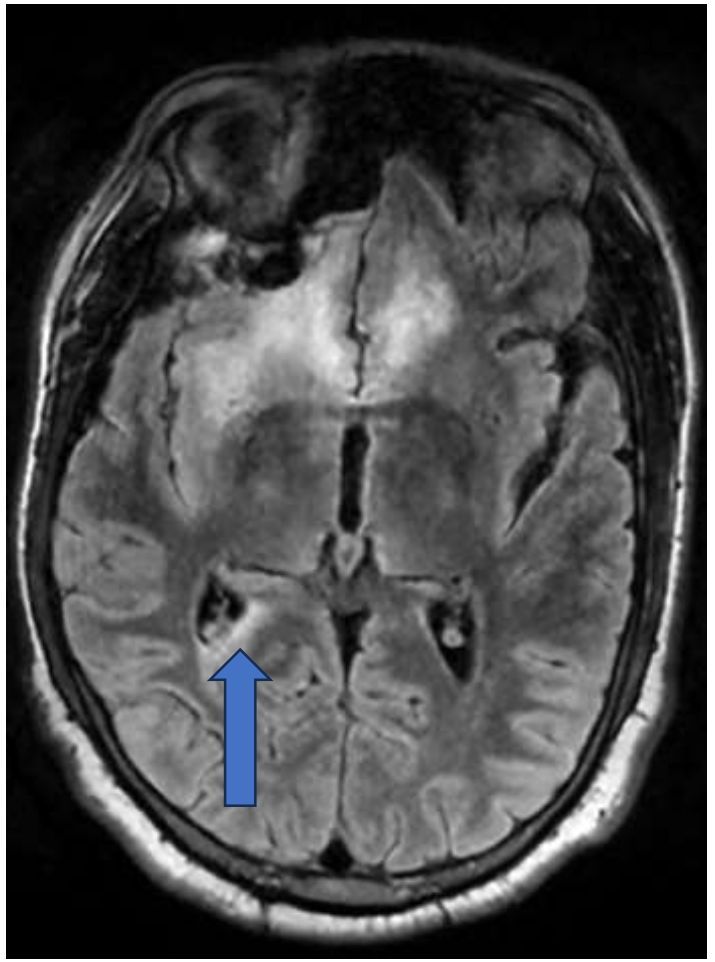






Post op-A-ODG





NCCTG/RTOG/ECOG

- Randomized LGG patients (95% grade 2) after surgery to 50.4 Gy in 28 fx vs. 64.8 Gy in 36 fx
  - **No difference in 5-yr OS with higher rate of radiation necrosis in high dose arm (5% vs. 2%)**

EORTC 22844 "Believers Trial"

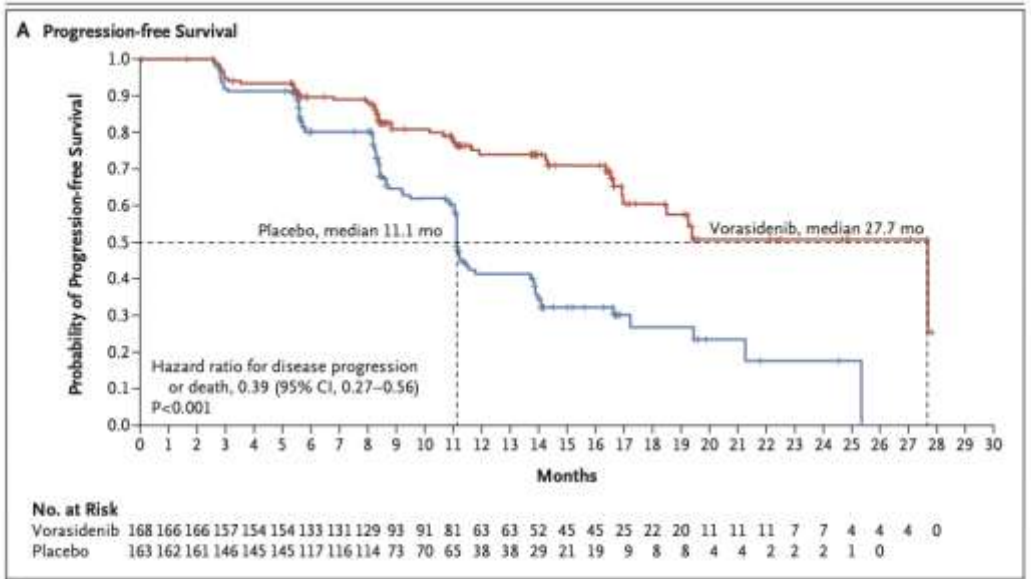
- Randomized LGG patients after surgery to 45 Gy in 25 fx vs. 59.4 Gy in 33 fx
  - **No difference in 5-yr OS or PFS with dose escalation**

Shaw et al. JCO 2002
Karim et al. Int J Radiat Oncol Biol Phys 1996

EORTC 22845 "Non-Believers Trial"

- Randomized patients with LGG after surgery to early RT vs observation with RT at progression
  - **Early (vs delayed) RT improved PFS and decreased seizure rate (25% vs. 41% at 1 year), but did not improve OS**
    - 65% patients in *observed* arm eventually received RT
    - Malignant transformation equal between arms 70%
    - QOL not studied (?relationship between time to progression and neurocognitive deterioration)

BACKGROUND: Radiation Therapy Oncology Group 9802 was a phase III trial for patients with centrally confirmed LGG (WHO grade II). Participants ³ 40 years or those with neurosurgeon defined less than gross total resection (GTR) were randomized to radiotherapy (RT) +/- PCV. In a separate cohort, adults age < 40 years with neuro surgeon defined GTR were observed by MRI every 6 months without adjuvant therapy. At last report, outcome for the observation cohort was immature with median follow-up of only 4.4 years. Here, we present mature outcomes for the observation arm. METHODS: Eligible adults (as above) were observed by MRI every 6 months. OS and PFS were estimated by Kaplan-Meier method and estimated hazard ratios to characterize the prognostic variables. RESULTS: There were 111 eligible patients (median age 30; median KPS = 100). Median follow-up was 16.1 years with 71 (64%) alive at the last follow-up. 79 patients (71%) had progressed with median PFS of 6.9 years. 5, 10 and 15 year-PFS and OS rates were 54%, 39%, 28% and 94%, 77% and 65%. 1p19q status was codeleted in 32%, IDH1/2 mutant in 78% and MGMT promoter methylated in 39% of tested cases. Multivariate Cox analyses showed that preoperative tumor size ³ 4 cm (HR = 2.43 for PFS, p = 0.001; HR = 2.58 for death, p = 0.016) and residual disease on imaging ³ 1 cm (HR = 2.97 for PFS, P < 0.001; HR = 2.02 for death, p = 0.05) were associated with worse outcomes. Analyses based on molecular results will be presented. CONCLUSION: A subset of low-grade gliomas can be observed after the initial resection based on younger age, smaller tumor size, and no residual disease on neuroimaging. This can likely be further refined by prognostic molecular markers. Patients with the most favorable prognostic factors can avoid or delay the acute and long-term side effects of RT and chemotherapy for several years.



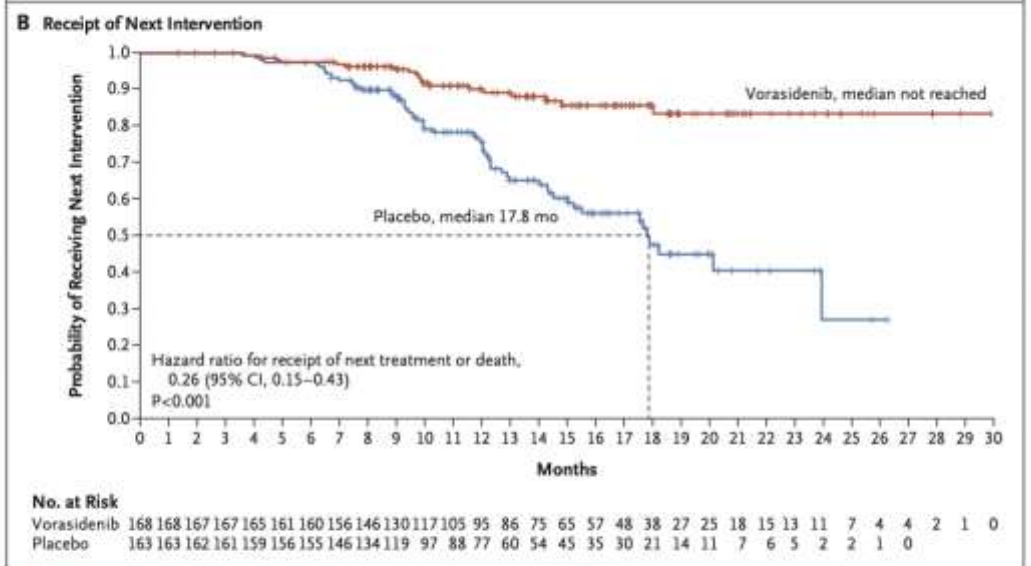


Figure 2. Progression-free Survival and Time to Next Intervention (Full Analysis Set).

Panel A shows the Kaplan–Meier plot of the probability of imaging-based progression-free survival as assessed by blinded independent review among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group (full analysis set). The median time to disease progression or death is shown. Panel B shows the Kaplan–Meier plot of the probability of receipt of a next anticancer treatment or death among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group. The median time to the receipt of the next anticancer treatment is shown. In both panels, tick marks indicate censored data.

IDH inhibition

RESULTS

A total of 331 patients were assigned to receive vorasidenib (168 patients) or placebo (163 patients). At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or placebo. Progression-free survival was significantly improved in the vorasidenib group as compared with the placebo group (median progression-free survival, 27.7 months vs. 11.1 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.27 to 0.56; P<0.001). The time to the next intervention was significantly improved in the vorasidenib group as compared with the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; P<0.001). Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

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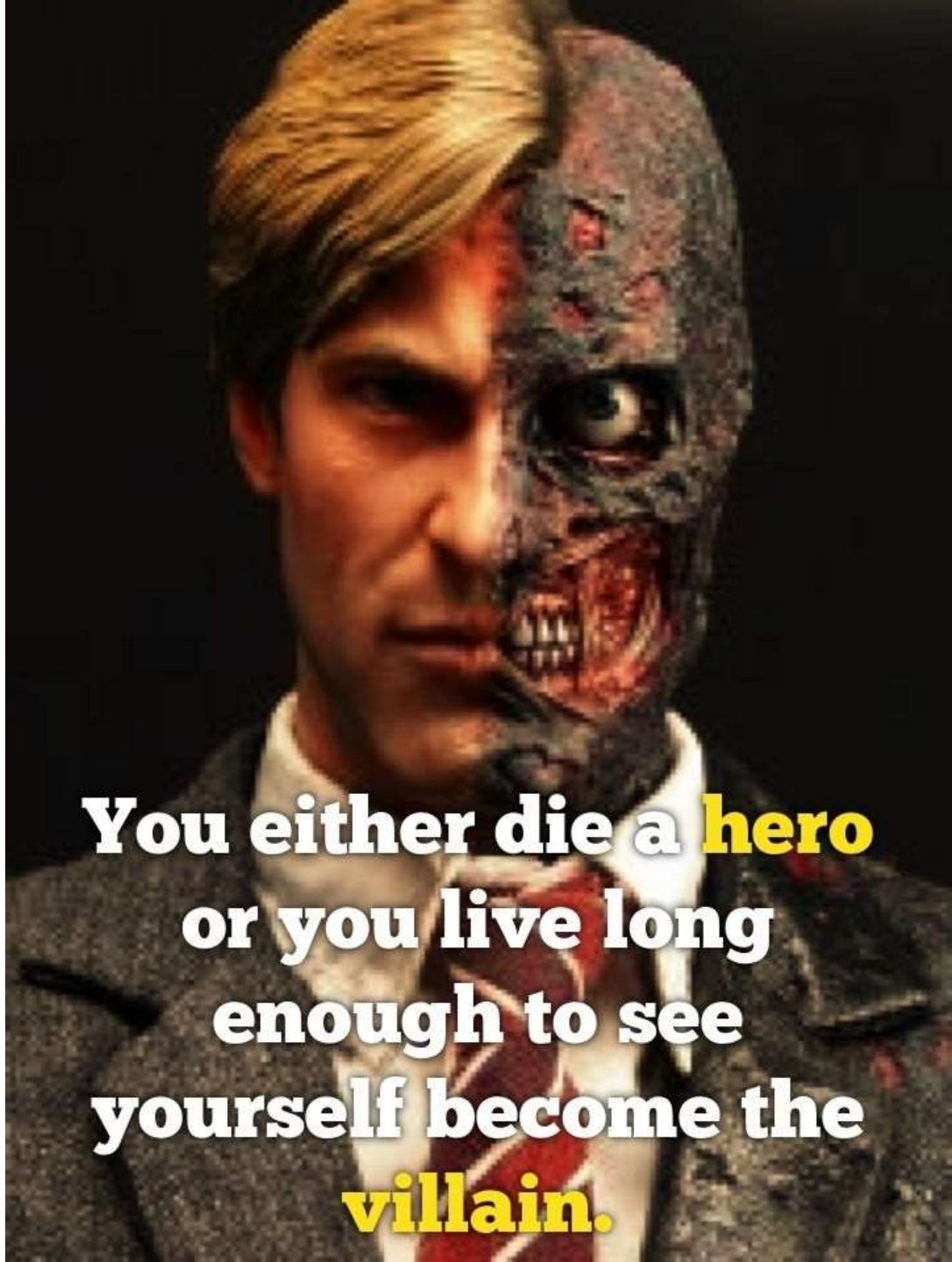
(Un)Comfort zone

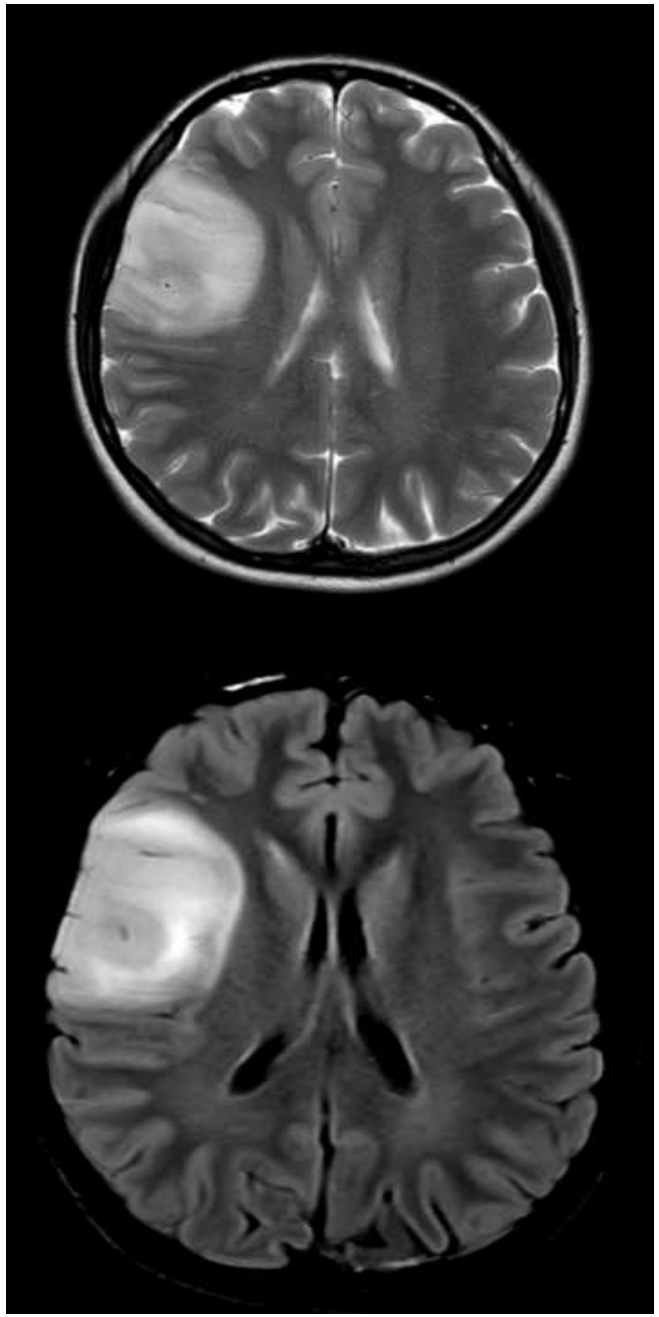
- Gd 2 ODG
- Compliant
- GTR
- 6 monthly image-based follow up

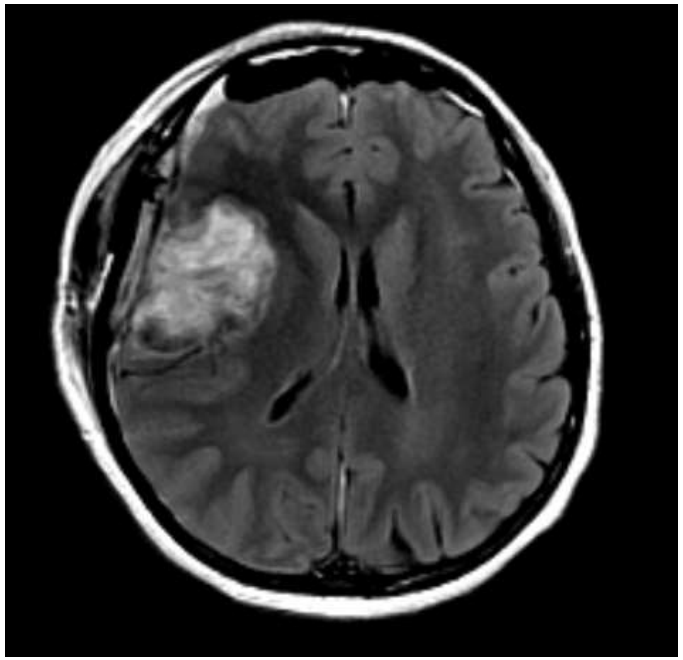


Case 2

- 32/F/4 e/o focal seizures with secondary generalization

- IDH mt Gd 2-3
- GTR



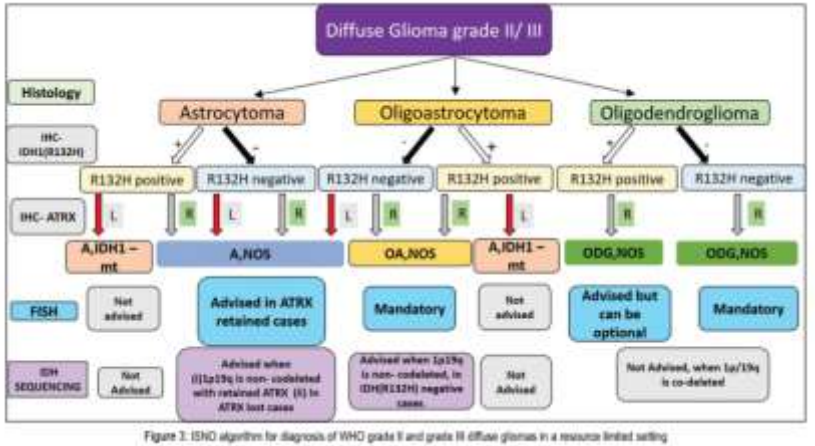


Questions

- Importance of extent of resection?
- Choice of observation?
- Choice of adjuvant ?
- Avoid RT ?
- Emerging therapies ?

Diffuse gliomas

- IDH pathway mutations
- Transformation to HGG (IDH mt disease)
- Upfront adverse behaviour in IDH wt disease (GBM like in the presence of EGFRamp,+7/10-phenotype, TERT Promoter mutation, Homozygous deletion of CDKN2A/B)
- Maximal safe resection – initial cornerstone of management



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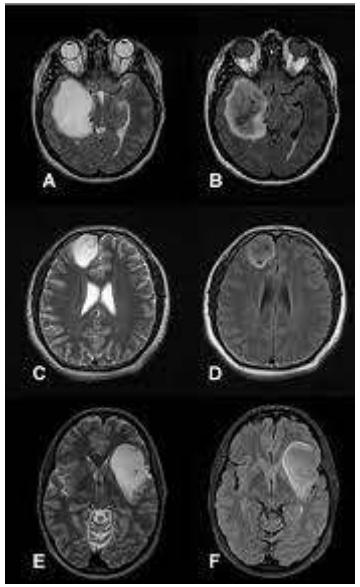
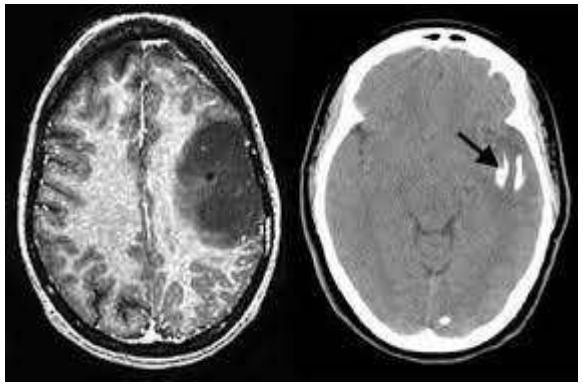
Entities
-Low risk Low grade – rare
- HR –LGG
- Gd III
- **Gd IV IDH mutant astrocytoma**

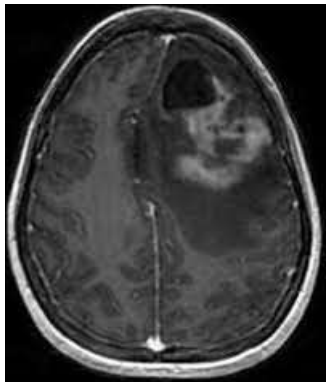
RT Doses – 54-59.4Gy/30-33#



AA
IDH +/ATRX-loss



ODG
IDH+/ATRX-retained
1p19q codel



IDH mt Gd 4

Conclusion: Necrosis and *CDKN2A* HD are adverse prognostic factors of WHO grade 3 oligodendrogliomas, IDH mutant and 1p/19q co-deleted. Besides, in group 1 patients, lack of contrast enhancement is a factor of better prognosis.

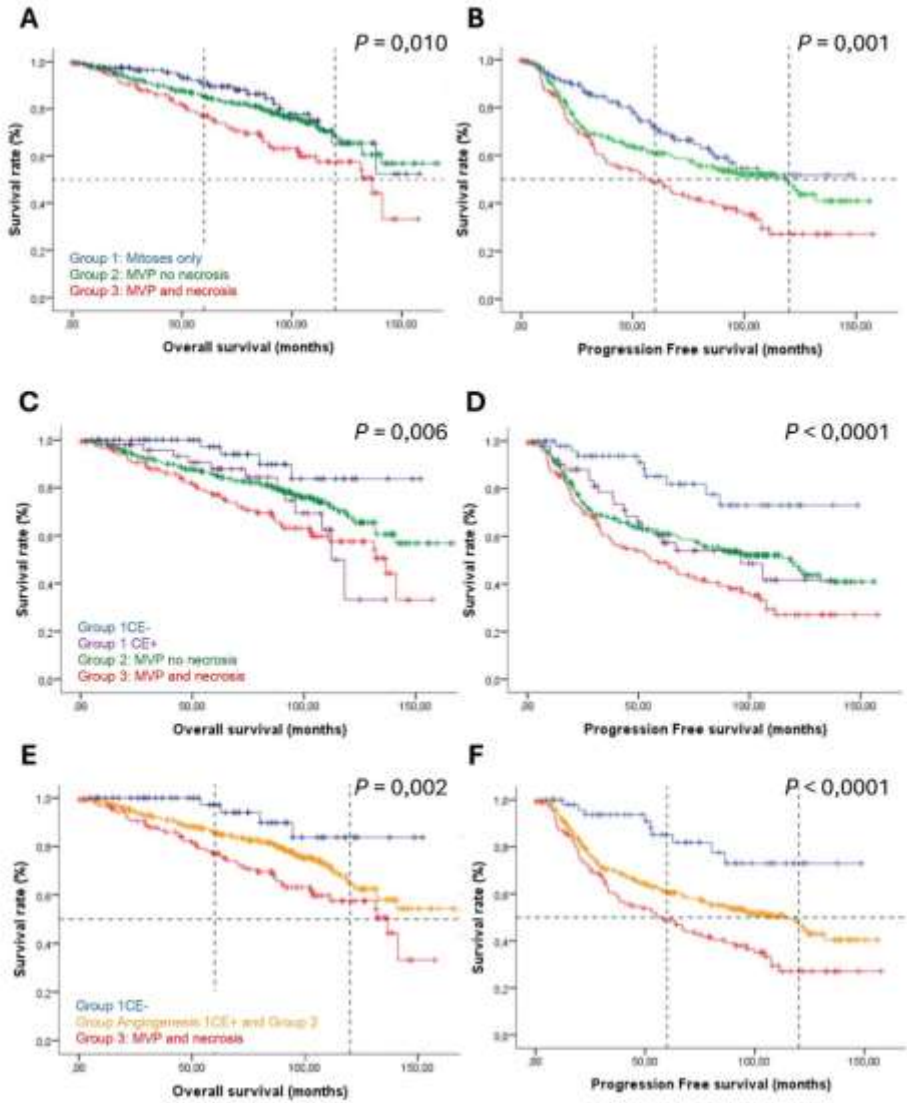


Figure 2

https://doi.org/10.1093/neuonc/noae221

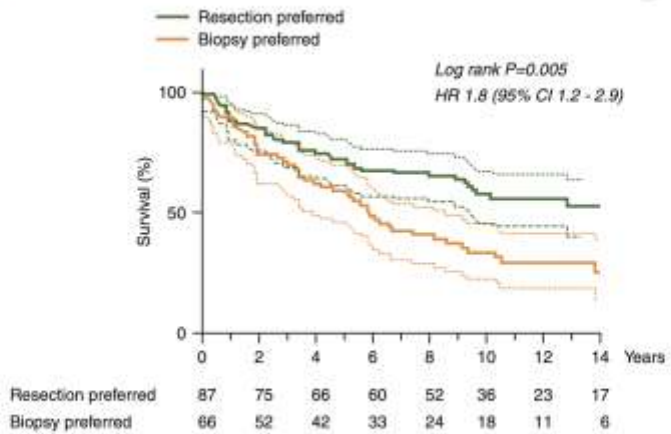


Figure 2. Survival analysis comparing cohorts, where *region A* preferred biopsy while *region B* preferred early resection. In *region A* the median survival was 5.8 years (95% CI 4.5–7.2) compared with 14.4 years (95% CI 10.4–18.5) in *region B*.

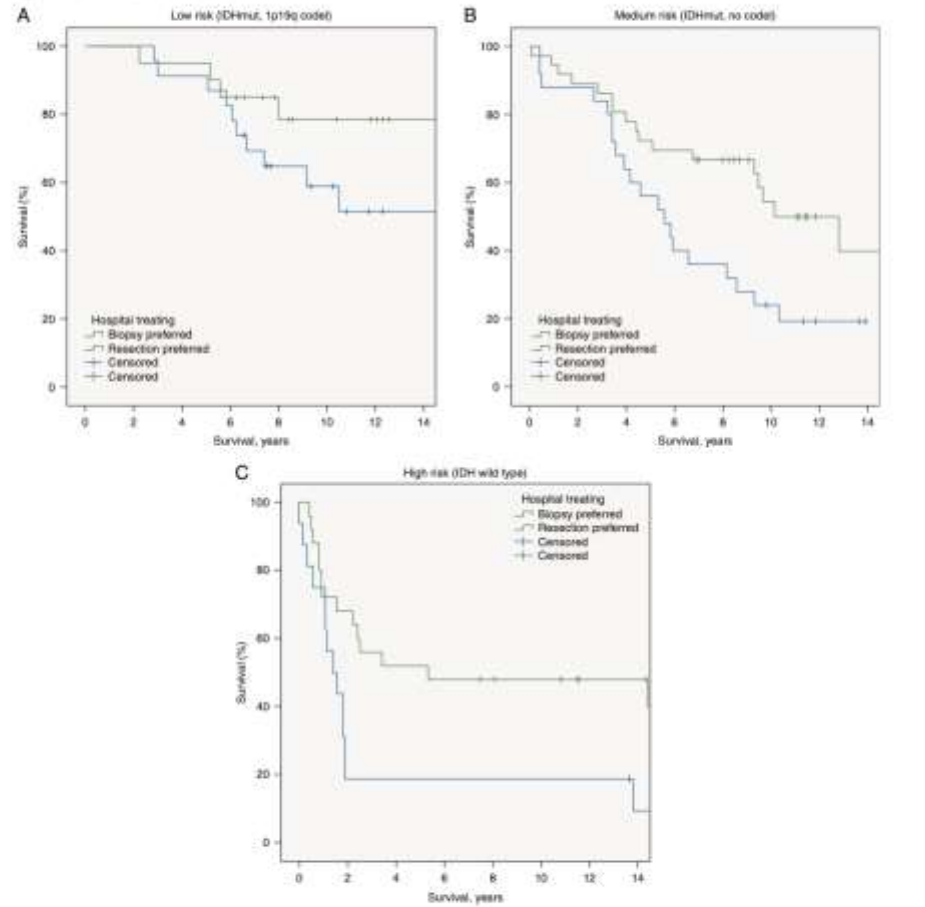


Figure 3. Survival in cohorts (A–C) with adjustment for molecular risk-group (log-rank test, $P = 0.001$). Results are presented stratified according to risk groups (A) low-risk (B) medium-risk and (C) high-risk group. (A) *IDH mutated*, 1p19 codeleted LGGs ($n = 43$). Median survival was not reached. (B) *IDH mutated*, non-codeleted LGGs ($n = 61$). Median survival in *region A* was 5.6 years (95% CI 3.5–7.6) compared with 10.2 year (95% CI 6.9–13.4) in *region B*. (C) *IDH wild-type* LGGs ($n = 41$). Median survival in *region A* was 1.4 year (95% CI 0.6–2.2) compared with 5.3 year (95% CI 0.0–20.0) in *region B*.

doi:10.1093/annonc/mdx230

AVOID RT

- Not shown to improve OS
- Cognitive concerns
- Oligosymptomatic disease – IWOT/IMPROV-CODEL

Table 3 Indication and timing for RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
Oligodendroglioma, IDH-mutant, and 1p/19q codeleted		
1. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, <4-6 cm tumor, with gross total resection (defined as <1 cm residual tumor on MRI) and age <40 y, close surveillance alone is recommended.	Strong	Low 18,19
2. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, with high-risk features, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 y, tumor size ≥4-6 cm, tumor crosses midline, refractory seizures, or presurgical neurologic symptoms from tumor.	Conditional	Low 19-24
3. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, with any extent of surgery, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is recommended.	Strong	Moderate 25-29
Astrocytoma, IDH-mutant		
1. For patients with astrocytoma, IDH-mutant, WHO grade 2, <4-6 cm tumor, with gross total resection (defined as <1 cm residual tumor on MRI), and age <40 y, close surveillance alone is conditionally recommended.	Conditional	Low 18,19
2. For patients with astrocytoma, IDH-mutant, WHO grade 2, with high-risk features, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 y, tumor size ≥4-6 cm, tumor crosses midline, refractory seizures, or presurgical neurologic symptoms from tumor.	Conditional	Low 19-24,30
3. For patients with astrocytoma, IDH-mutant, WHO grade 3, with any extent of surgery, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is recommended.	Strong	Low 27,28,31

Abbreviations: IDH = isocitrate dehydrogenase; KQ = key question; MRI = magnetic resonance imaging; RT = radiation therapy; WHO = World Health Organization.

pro

Clinical Practice Guideline

Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline

Lia M. Halasz, MD,[a,*] Albert Attia, MD,[b] Lisa Bradfield, BA,[c] Daniel J. Brat, MD, PhD,[d] John P. Kirkpatrick, MD, PhD,[e] Nadia N. Laack, MD,[f] Nafisha Lalani, MD, MPH,[g] Emily S. Lebow, MD,[h] Arthur K. Liu, MD, PhD,[i] Heather M. Niemeier, PhD,[j] Joshua D. Palmer, MD,[k] Katherine B. Peters, MD, PhD,[l] Jason Sheehan, MD, PhD,[m] Reena P. Thomas, MD, PhD,[n] Sujay A. Vora, MD,[o] Daniel R. Wahl, MD, PhD,[p] Stephanie E. Weiss, MD,[q] D. Nana Yeboa, MD,[r] Jim Zhong, MD,[s] and Helen A. Shih, MD, MS, MPH[t]

TMZ Alone

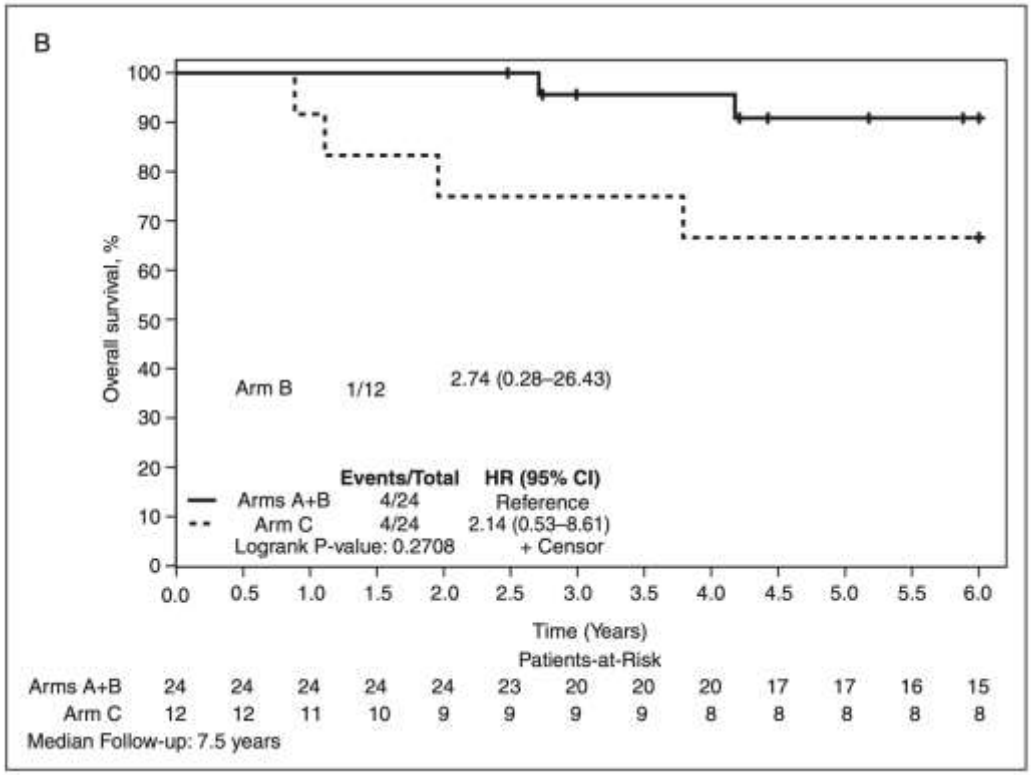


Table 2. Cognitive progression at 3 months

	Arm A: RT Alone ($N = 9$)	Arm B: RT + Concomitant TMZ ($N = 11$)	Arm C: TMZ Alone ($N = 9$)	Total ($N = 29$)	*P*-value
Median Days to Testing (range)	87 (84–105)	85 (73–130)	82 (59–97)	86 (59–130)	0.13[e]
Frequency of Deterioration[a]					
HVLT-R Immediate Recall, *n* (%)	1 (11.1)	1 (9.1)	1 (11.1)	3 (10.3)	0.93[d]
COWAT, *n* (%)	0 (0.0)	1 (9.1)	1 (11.1)	2 (6.9)	0.20[d]
Trail Making A, *n* (%)	1 (12.5)	0 (0.0)	3 (37.5)	4 (15.4)	0.18[d]
Trail Making B, *n* (%)	5 (71.4)	3 (33.3)	3 (42.9)	11 (47.8)	0.29[d]
HVLT-R Delayed Recall, *n* (%)	3 (33.3)	1 (9.1)	0 (0.0)	4 (14.3)	0.18[d]
HVLT-R Delayed Recognition, *n* (%)	2 (22.2)	2 (18.2)	1 (12.5)	5 (17.9)	0.24[d]
Progression Determination					
Neurocognitive Progression[b], *n* (%)	7 (77.8)	8 (72.7)	6 (66.7)	21 (72.4)	0.87[d]
Clinical Progression[c], *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA

RCI, reliable change index; HVLT-R, Hopkins Verbal Learning Test–Revised; COWAT, Controlled Oral Word Association Test.
[a]>RCI90 value decrease from baseline.
[b]Number deteriorating on any one subtest >RCI90 value decrease from baseline.
[c]Defined by clinical exam and/or radiographic progression at 3 months after registration.
[d]Chi-square.
[e]Kruskal–Wallis.

Neuro-Oncology
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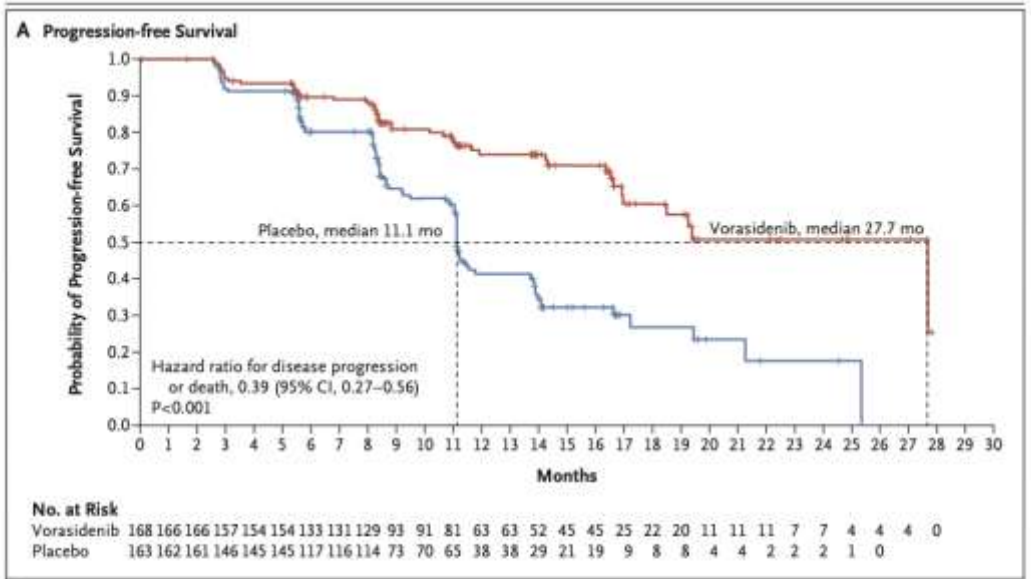
CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design



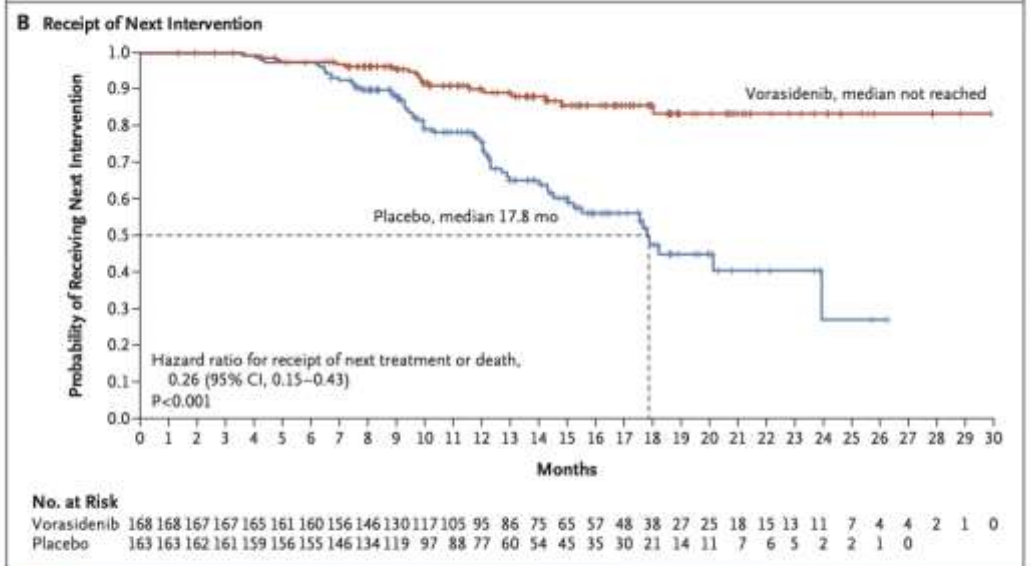


Figure 2. Progression-free Survival and Time to Next Intervention (Full Analysis Set).

Panel A shows the Kaplan–Meier plot of the probability of imaging-based progression-free survival as assessed by blinded independent review among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group (full analysis set). The median time to disease progression or death is shown. Panel B shows the Kaplan–Meier plot of the probability of receipt of a next anticancer treatment or death among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group. The median time to the receipt of the next anticancer treatment is shown. In both panels, tick marks indicate censored data.

IDH inhibition

RESULTS

A total of 331 patients were assigned to receive vorasidenib (168 patients) or placebo (163 patients). At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or placebo. Progression-free survival was significantly improved in the vorasidenib group as compared with the placebo group (median progression-free survival, 27.7 months vs. 11.1 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.27 to 0.56; P<0.001). The time to the next intervention was significantly improved in the vorasidenib group as compared with the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; P<0.001). Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo.

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HR -LGG

	Pignatti	RTOG 9802	RTOG 0424 (≥3 Risk factors)
Age (Years)	≥40	≤40 with STR ≥40	≥40
Size(cm)	≥6cm		≥6cm
Histology	Astrocytoma		Astrocytoma
Extent	Tumor crossing midline		Bihemispheric
PS	Presence of neurological deficit		>1 preop
	≤2 – Low risk >2 –High Risk		
Differential survival	7.8 vs 3.7 yrs (HR =1.83,95% CI-1.48-2.26)		

	RTOG 9802(PCV)	RTOG 0424 (TMZ)
Initial result	OS – NS PFS – 17 % Difference favoring PCV	3 yr OS – 73.1% PFS – 59.2% Better than historical ctrl.
Updated result	Median OS – Significant benefit (**13.3 vs 7.8** yrs) 10 YR OS – 60% vs 40% PFS – 51% vs 21%	5 yr OS –60.9% PFS –46.8% 10 yr OS – 34.6% PFS – 25.5%
Molecular Era Data (106/251)	Benefit restricted to IDH mutant ds.	MGMT carries prognostic significance even in the setting of IDH mutation

When we give RT-HR LGG

Table 3. Comparison of Survival Outcomes Across Studies Using Combined Modality Treatment (Radiotherapy Plus Systemic Chemotherapy) in High-Risk Low-Grade Glioma

Stratification Type	Survival Outcomes	RTOG 9802 (RT + PCV) *N* = 125 (51)*	RTOG 0424 (RT + TMZ) *N* = 129 (80)*	Present Study (RT + TMZ) *N* = 64 (37)*
Survival overall outcomes of the study				
High-risk low-grade glioma	5-year PFS 5-year OS	61% 72%	46.8% 60.9%	74.6% 84.3%
Survival outcomes based on histomorphologic classification				
Oligodendroglioma	5-year PFS 5-year OS	79% 88%	58.7%† 74.9%†	81.5% 87.5%
Mixed oligoastrocytoma	5-year PFS 5-year OS	52% 66%		78.0% 90.4%
Astrocytoma	5-year PFS 5-year OS	45% 57%	39.5%† 47.4%†	65.2% 71.9%
Survival outcomes based on molecular classification*				
Oligodendroglioma	5-year PFS 5-year OS	88% 91%	73% 85%	80.7% 85.8%
IDH-mutant astrocytoma	5-year PFS 5-year OS	60% 76%	53% 75%	65.6% 90%
IDH wild-type astrocytoma	5-year PFS 5-year OS	17% 27%	10% 20%	33.3% 66.7%

RTOG, Radiation Therapy Oncology Group; RT, radiotherapy; PCV, procarbazine–CCNU–vincristine; TMZ, temozolomide; PFS, progression-free survival; OS, overall survival; IDH, isocitrate dehydrogenase.

*Outcome analysis based on molecular classification is limited to subset of patients with available data on molecular markers in RTOG 9802 ($n = 51$), RTOG 0424 ($n = 80$), and present study ($n = 37$), respectively.

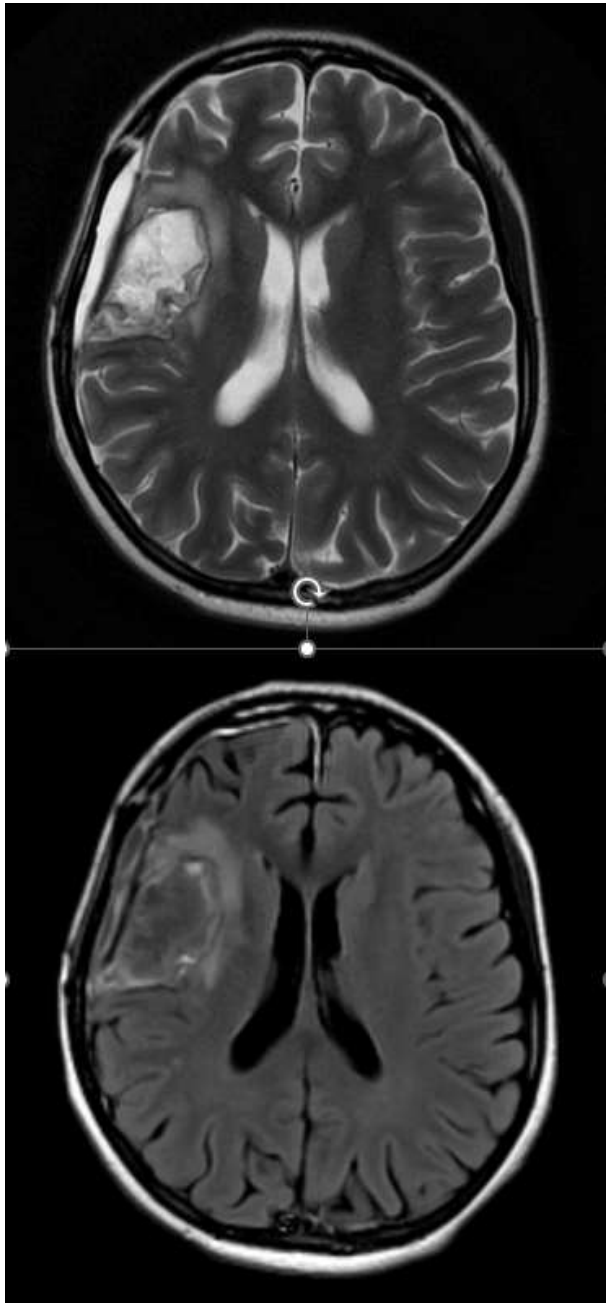
†Five-year outcomes are estimated from reported hazard ratio (HR) including 95% confidence interval (CI) and events of interest (progression and/or death). The HRs for PFS and OS of oligodendroglioma/oligoastrocytoma versus astrocytoma were 0.572 (95% CI 0.341–0.950; $P = 0.0339$) and 0.385 (95% CI 0.207–0.718; $P = 0.0027$), respectively.

Upfront Therapy of Aggressive/High-Risk Low-Grade Glioma: Single-Institution Outcome Analysis of Temozolomide-Based Radio-Chemotherapy and Adjuvant Chemotherapy

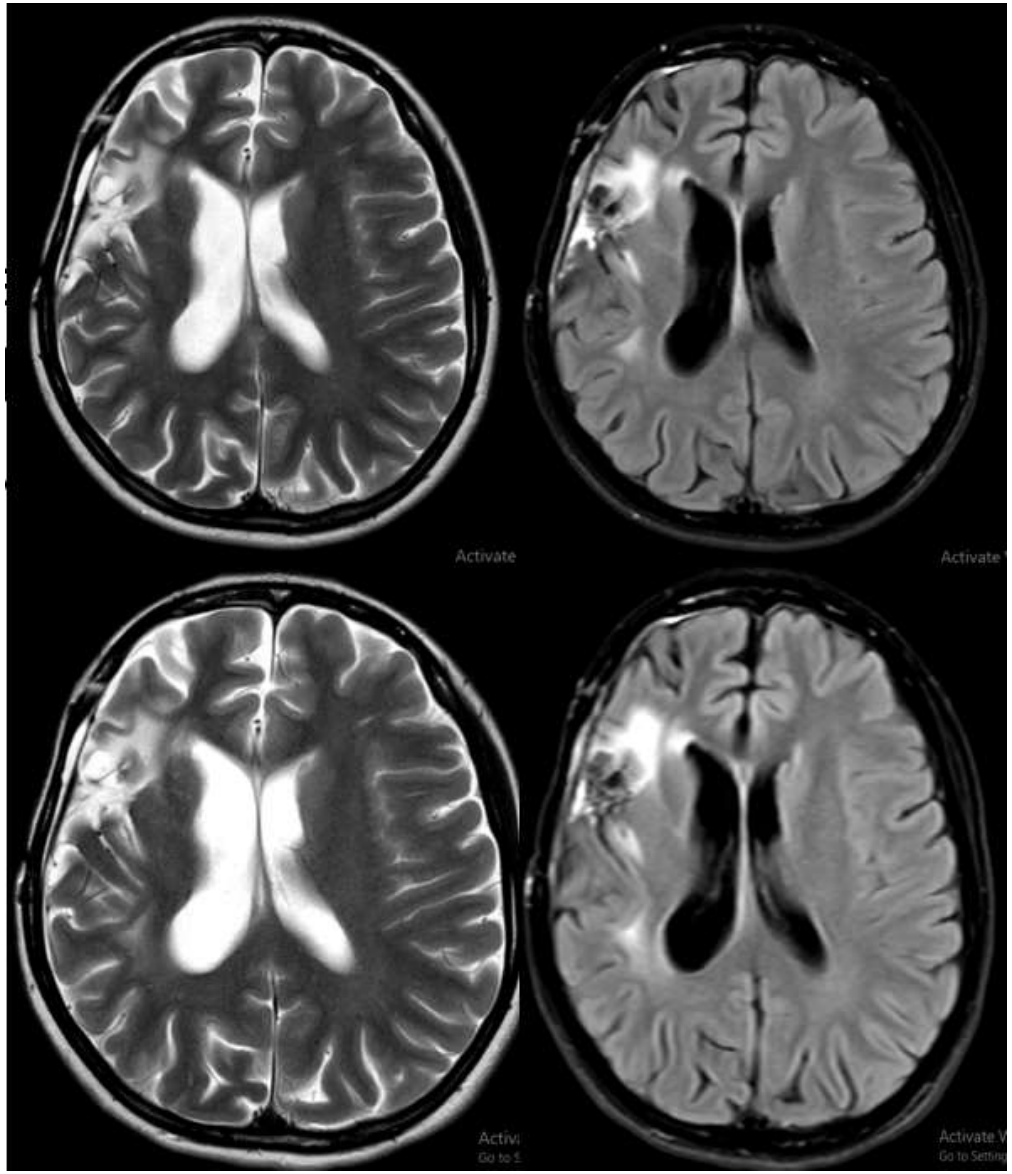
Sachith Anand[1], Abhishek Chatterjee[1], Tejpal Gupta[1], Pankaj Panda[2], Aliasgar Moiyadi[3], Sridhar Epari[4], Vijay Patil[5], Rahul Krishnatry[1], Jayant Sastri Goda[1], Rakesh Jalali[1]

Course

- RT-59.4Gy/33# +conc. TMZ
- Adj. TMZ X 12 cycles



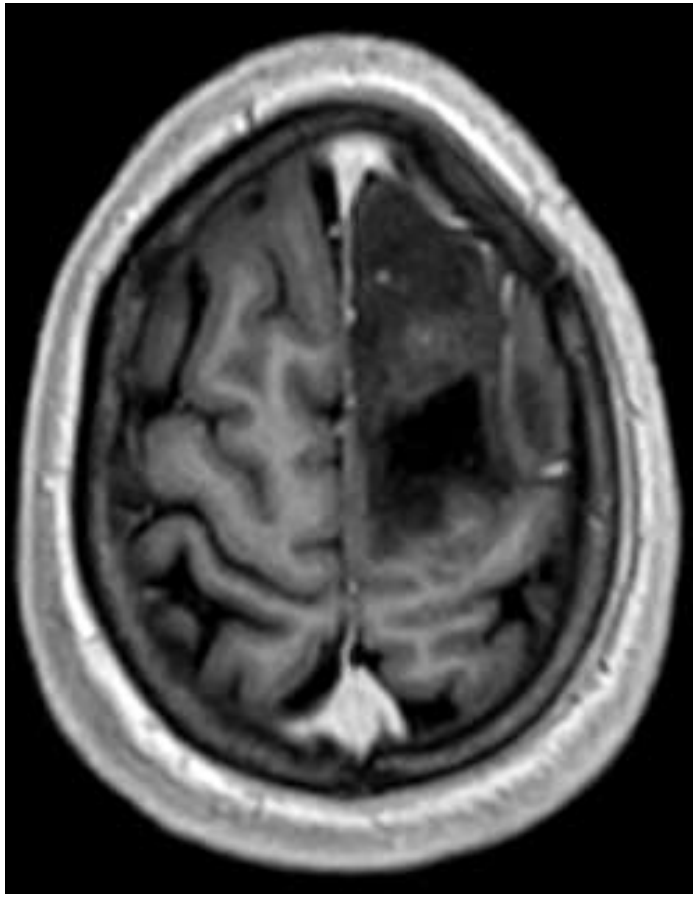
Post RT

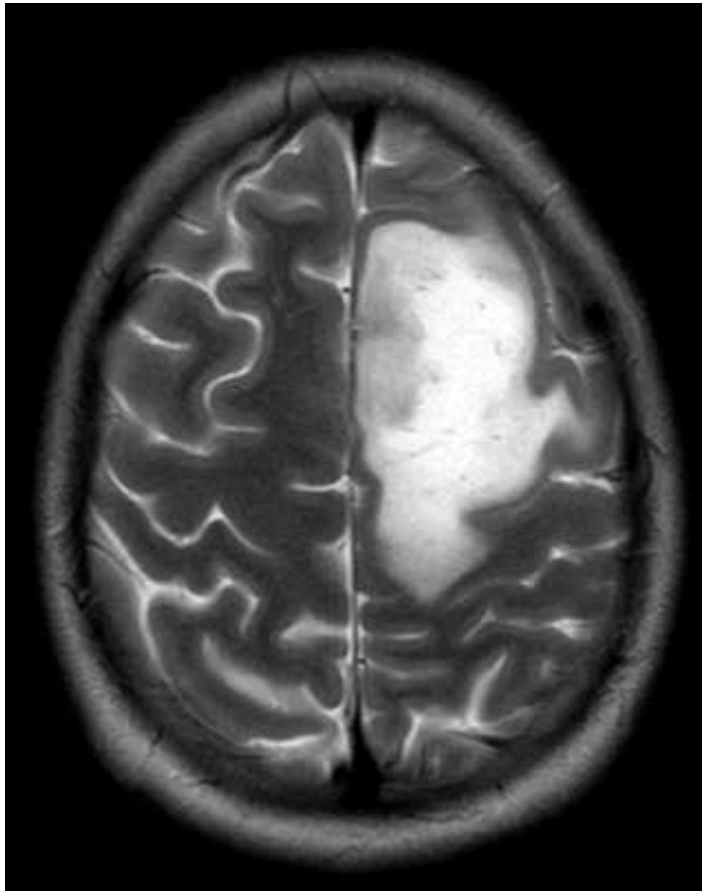


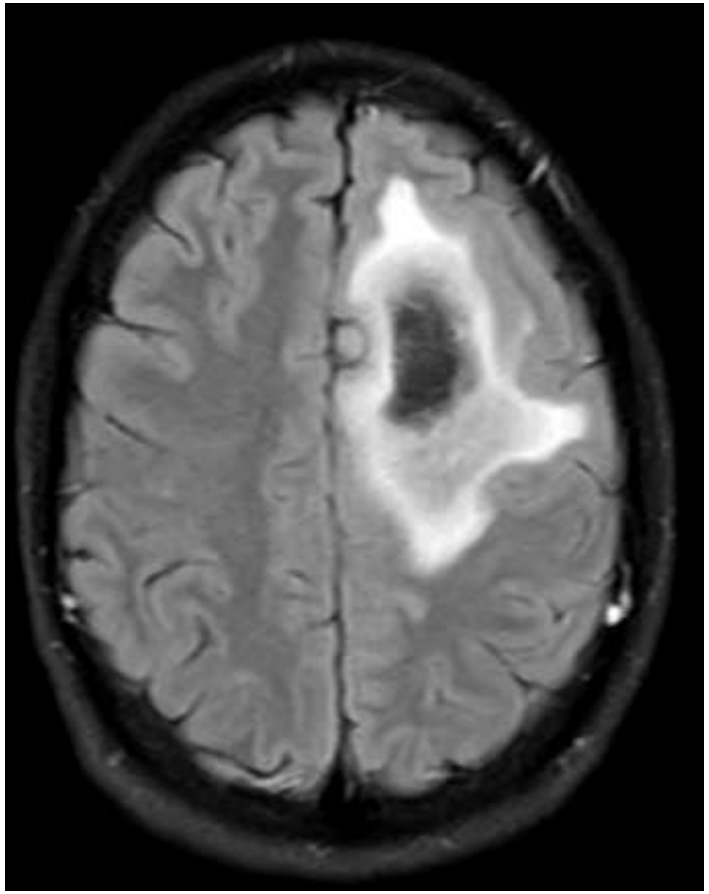
Post chemo on follow up

Case 3

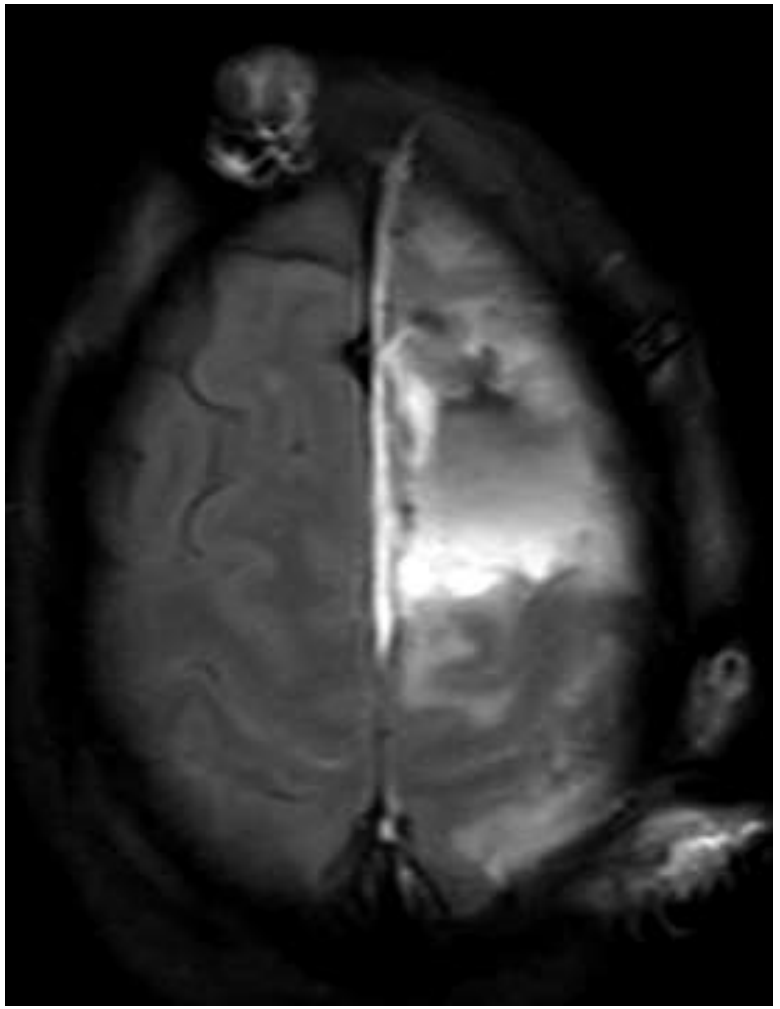
21/M/Single episode of GTCS







IDH mt AA



Questions

- Importance of extent of resection?
- Choice of observation?
- Choice of adjuvant ?
- Avoid RT ?
- Delineation principles ?

Grade III Glioma

AA

CATNON	
Initial Data (2017)	5 yr OS- 55.9% (RT f/b adj.TMZ) vs. 44.1%(without adjuvant TMZ)
Second analysis(2022)	Overall cohort – no benefit of concurrent TMZ Adjuvant MTZ – **mOS-82.3 vs 46.9 months** IDH mt – OS benefit for adjuvant Trend towards OS benefit for concurrent
Third analysis(*post hoc* - 2022)	IDH wt mol GBM No benefit for TMZ MGMT prognostic not predictive

A-ODG

- RTOG 9402/EORTC – 25951- extrapolated data – significant non- codel included in original dataset
- RT followed by adjuvant PCV associated with survival benefit (OS and PFS)
- **Doubling of Median OS in co-deleted tumors - 14.7 vs 7.3 years in RTOG 9402)**
- **20 year update –sustained benefit overall(7-13%) and in 1p19q codel(20%- 20 year actuarial-37%)**
- **IWOT- unanswered**
- **TMZ vs PCV**
  - **POLA suggests benefit for PCV for ODG**
  - **TOP/CODEL – overall IDH**

POLA

RESULTS 305 newly diagnosed patients with O3$^{IDHmt/Codel}$ treated with RT and chemotherapy between 2008 and 2022 were included, of which 67.9% of patients (n = 207) were treated with PCV/RT and 32.1% with TMZ/RT (n = 98). The median follow-up was 78.4 months (IQR, 44.3-102.7). The median OS was not reached (95% CI, Not reached [NR] to NR) in the PCV/RT group and was 140 months (95% CI, 110 to NR) in the TMZ/RT group (log-rank $P = .0033$). On univariable analysis, there was a significant difference in favor of PCV/RT in both 5-year (PCV/RT: 89%, 95% CI, 85 to 94; TMZ/RT: 75%, 95% CI, 66 to 84) and 10-year OS (PCV/RT: 72%, 95% CI, 61 to 85; TMZ/RT: 60%, 95% CI, 49 to 73), which was confirmed using the multivariable Cox model adjusted for age, type of surgery, gender, Eastern Cooperative Oncology Group performance status, and *CDKN2A* homozygous deletion (hazard ratio, 0.53 for PCV/RT, 95% CI, 0.30 to 0.92, $P = .025$).

First-Line Chemotherapy in Anaplastic Oligodendroglioma

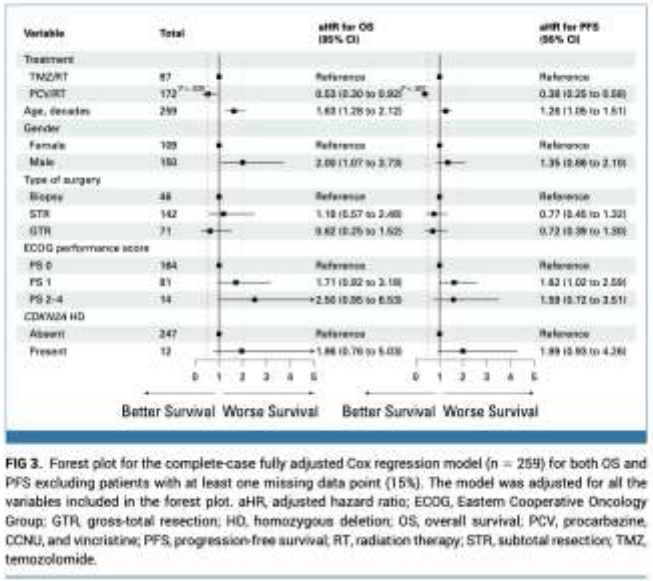


FIG 3. Forest plot for the complete-case fully adjusted Cox regression model (n = 259) for both OS and PFS excluding patients with at least one missing data point (15%). The model was adjusted for all the variables included in the forest plot. aHR, adjusted hazard ratio; ECOG, Eastern Cooperative Oncology Group; GTR, gross-total resection; HD, homozygous deletion; OS, overall survival; PCV, procarbazine, CCNU, and vincristine; PFS, progression-free survival; RT, radiation therapy; STR, subtotal resection; TMZ, temozolomide.

View Online Article

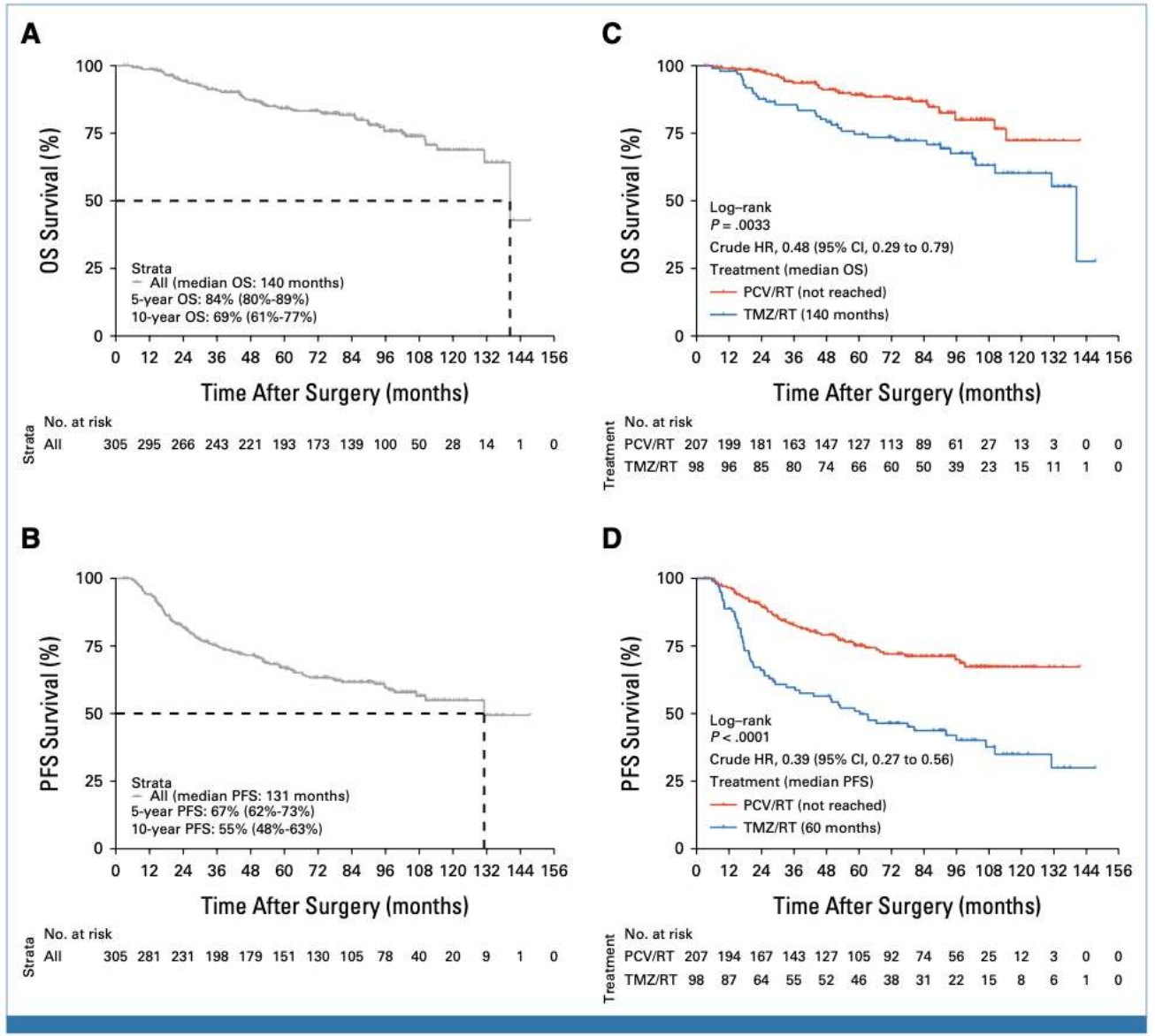
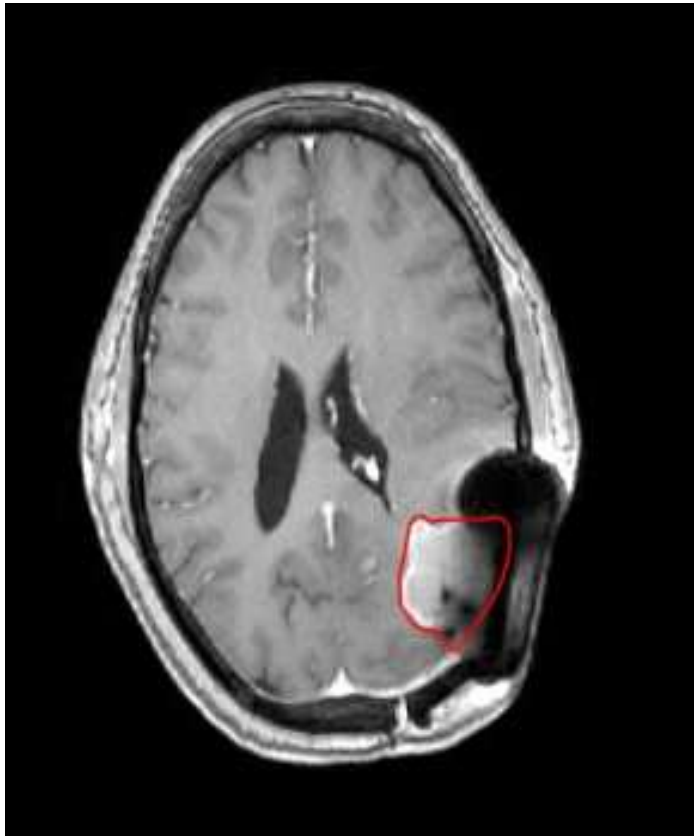


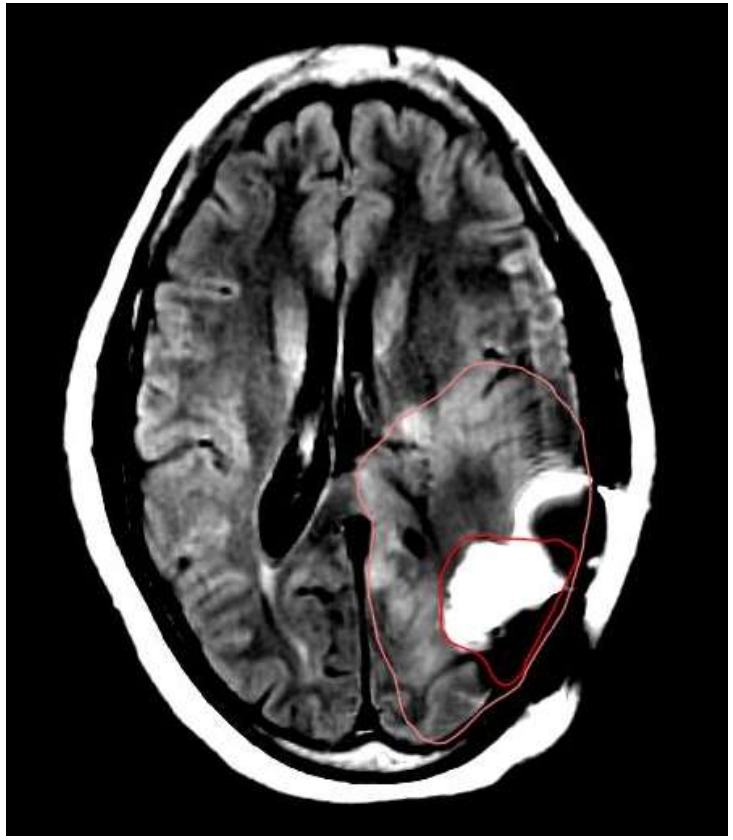
FIG 2. Kaplan-Meier estimates of OS and PFS for chemoradiotherapy-treated patients with *O3IDHmt/Codel* who received either PCV or TMZ for the entire cohort (A, B) and for treatment groups (C, D). OS, overall survival; PCV, procarbazine, CCNU, and vincristine; PFS, progression-free survival; TMZ, temozolomide.

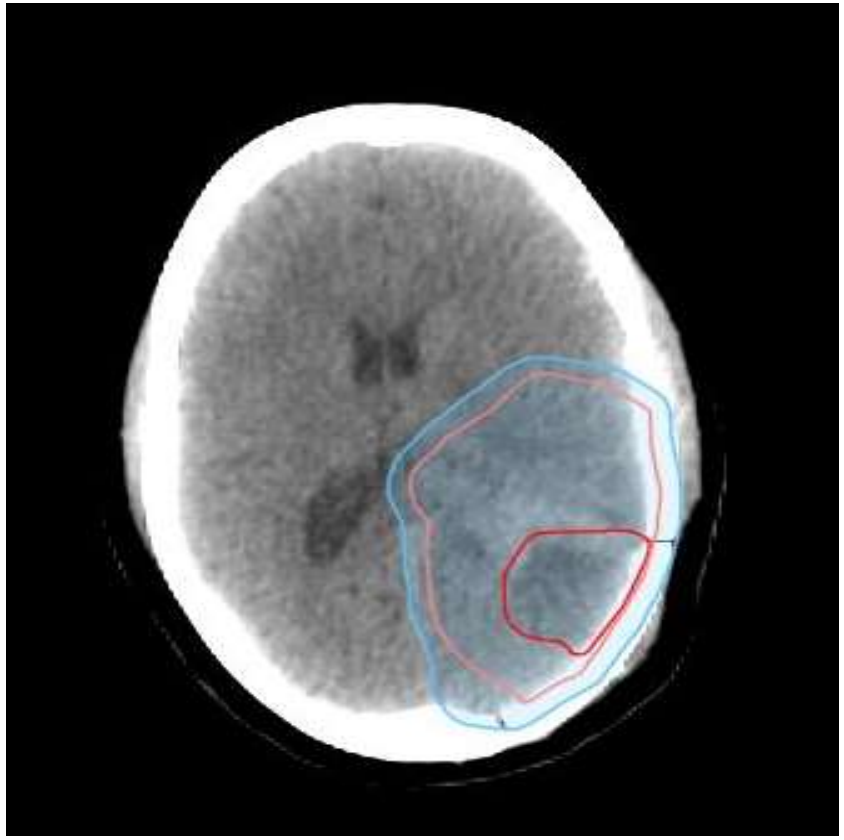
Summary

- RT f/b PCV – proven benefit in HR –LGG and A-ODG- Difficult to administer toxic regimen
- RT f/b TMZ – proven OS benefit in AA – equivalence with PCV unknown
- RT +TMZ f/b Adj. **TMZ-Benefit of concurrent likely to be restricted to IDH mutant**

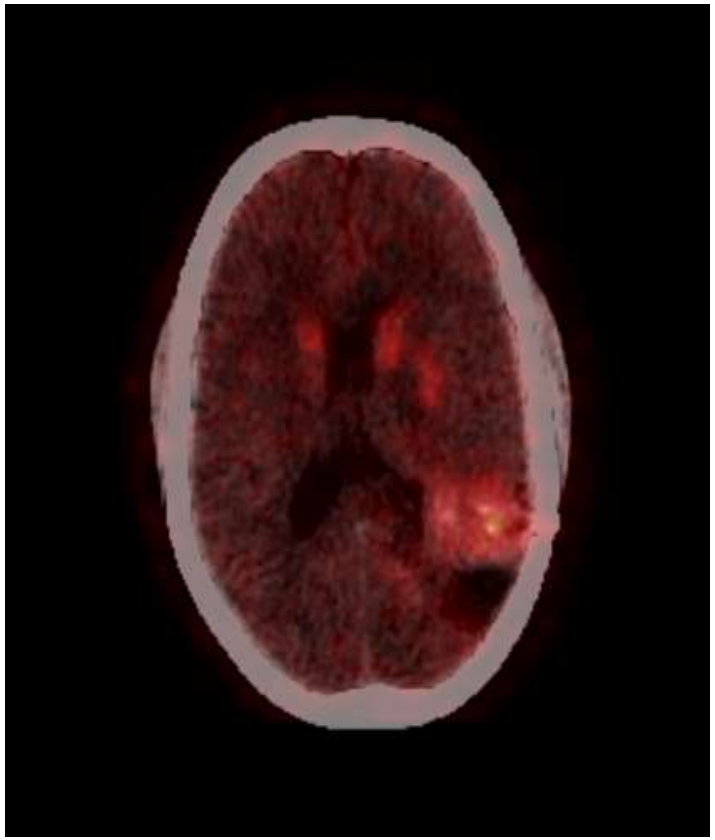
Delineation-MRI

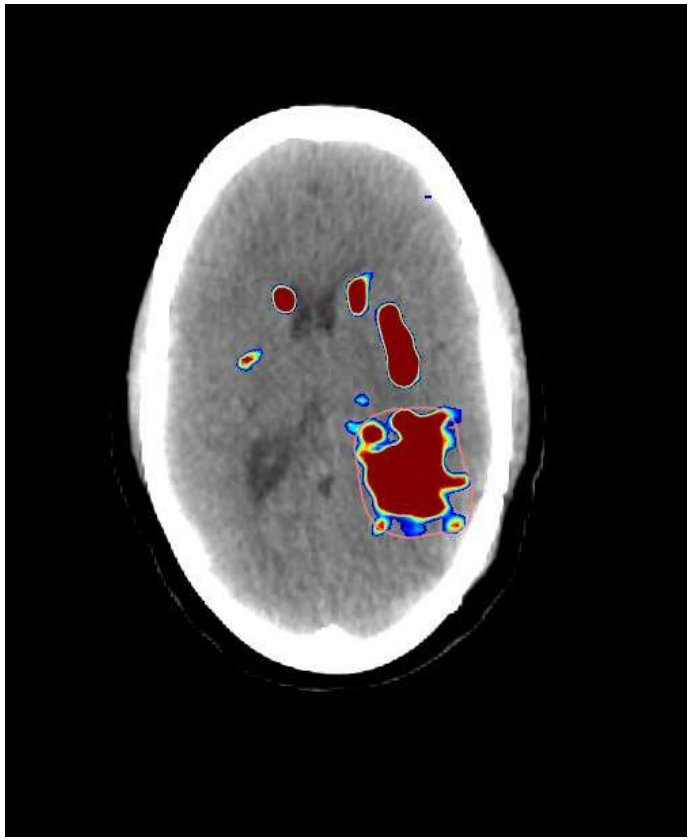


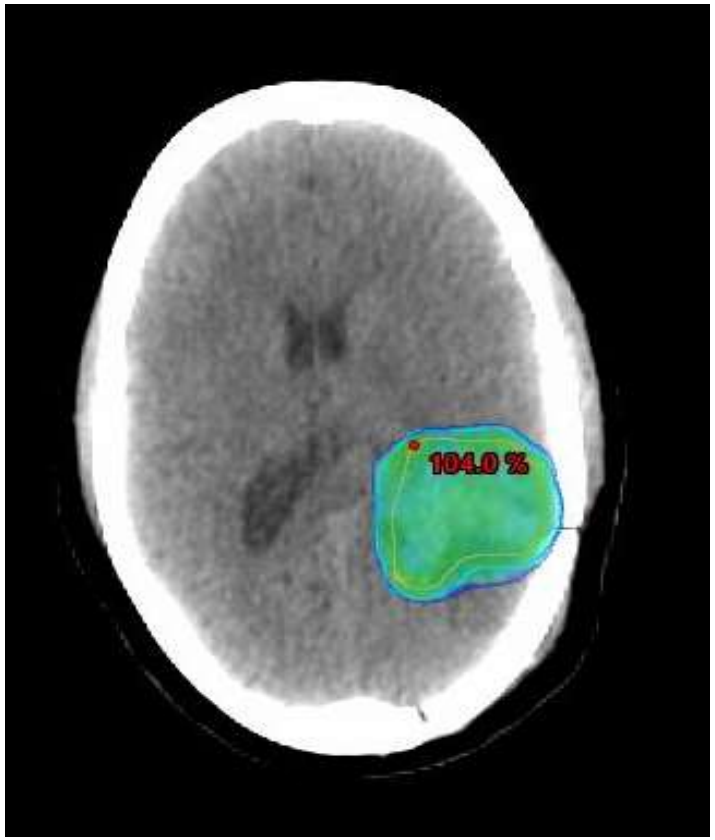




Delineation -PET







ESTRO EANO 2023 Gd 4

Topic	Guideline 2016	Current guideline
GTV	Cavity + contrast-enhanced T1	Cavity + T1 contrast enhancement, optionally PET-based BTV, or FLAIR alteration clearly visualized as tumour
Role of FLAIR	Optional inclusion of oedema	Exclude vasogenic oedema, if FLAIR indicates presence of non contrast-enhancing tumour, include with variable/no margin
Role of PET	Lack of definite evidence	Amino acid PET is a valuable tool for target delineation
CTV margin	20 mm	15 mm
PTV margin	3-5 mm, audit own IGRT capabilities	3 mm advised
Anatomical adaptations	falx/tentorium 5 mm	falx/tentorium 0 mm
Histology	Classical glioblastoma	Novel WHO 2021 classification, molecular types considered as well

OAR	Objective(s)
BRAINSTEM	D ≤ 54 Gy [72] $D_{0.03cc}$ ≤ 56 Gy** 1-10cc*** < 59 Gy (periphery) [72] Surface $D_{0.03cc}$ ≤ 60 Gy [73]** Interior $D_{0.03cc}$ ≤ 54 Gy [73]
CHIASM	D_{max} < 55 Gy [72] $D_{0.03cc}$ ≤ 55 Gy [73]**
COCHLEA	Ideally one side mean <45 Gy [74] ALARA
EYES	Macula <45 Gy [75] Eye balls D_{max} ≤ 40 Gy** (low priority)
LACRIMAL GLANDS	D_{max} < 40 Gy [76] Mean ≤ 25Gy [73] ALARA
LENS	Ideally <6 Gy Max 10 Gy [76]
OPTIC NERVES	D_{max} ≤ 54 Gy [77] D_{max} < 55 Gy [72] $D_{0.03cc}$ ≤ 56 Gy**
PITUITARY	D_{max} < 50 Gy [78] ALARA

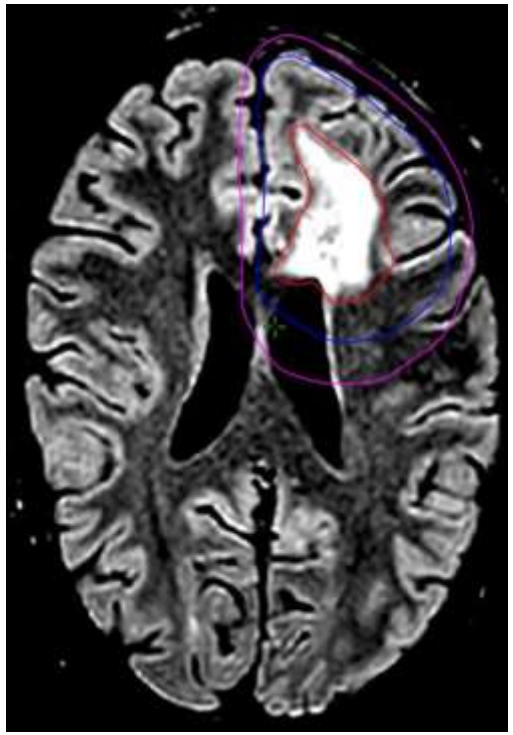
https://doi.org/10.1016/j.radonc.2023.109663

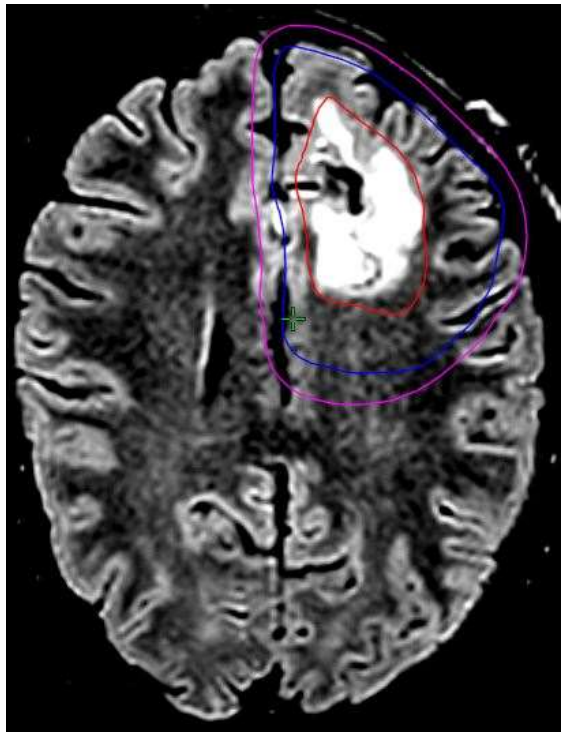
ESTRO EANO 2024-Gd 2-3

Question	Topic	Answer	Level of agreement (%)
Imaging	MRI	3 Tesla MRI is desired clinical standard	92.9
	Pseudo-progression	clinically stable patients should receive follow-up with the lowest frequency acknowledged acceptable	84.6
RT volumes	GTV - general	GTV should include resection cavity and any residual tumour volume after surgery.	100
		Amino-acid PET and perfusion/diffusion advanced MRI can be good tools to improve the differentiation between oedema and tumour	92.9
	GTV – grade 2	T2/FLAIR abnormalities that are thought to represent tumour should be included in the GTV	100
	GTV – grade 3	T2/FLAIR abnormalities could either be tumour or oedema, but areas which are thought to represent oedema do not need to be included in the GTV	85.7
	CTV – grade 2	CTV should be created with an expansion of the GTV with a margin of 10 mm	90.9
	CTV – grade 3	CTV should be created with an expansion of the GTV 15 mm	91.7
	CTV - general	CTV margin should be edited to respect anatomical boundaries unless tumour invasion is explicitly suspected	100
	Hippocampal sparing	If uni- or bilateral hippocampal sparing is used, the original constraint (D40% of bilateral hippocampus <7.3Gy) is recommended	91.7
RT techniques	Planning	IMRT and VMAT are preferred approach due to the improved target conformity with associated better sparing of OARs	100
	Set-up control	Daily image guidance, including MV and KV cone beam CT and orthogonal X-ray imaging systems, is recommended	100
	Brachytherapy	application of interstitial brachytherapy adds to the treatment portfolio if used in experienced hands and selected cases	50
Dose, fractionation		50.4 Gy in 28 fractions is recommended	100
		54 Gy in 30 fractions as also used in several trials including the RTOG 9802, is also acceptable	83.3
		A lower dose level such as 45 Gy in 25 fractions, is advised against	100
		60 Gy in 30 fractions should not be exceeded in WHO grade 3 tumours	100

https://doi.org/10.1016/j.radonc.2024.110594

Evolve(d) Principles





Photon planning

- Check contour and adequacy of simulation
- Dose (55.8-59.4Gy/31-33#)/Volume/Fields(Arcs)
- Coverage – 100/95/50/30/Slice by slice coverage
- Hotspots /Cold spots
- DVH – PTV coverage
- OAR – clinical goals

OAR	Objective(s)
BRAINSTEM	$D \leq 54$ Gy [72] $D_{0.03cc} \leq 56$ Gy** 1–10 cc*** < 59 Gy (periphery) [72] Surface $D_{0.03cc} \leq 60$ Gy [73]** Interior $D_{0.03cc} \leq 54$ Gy [73]
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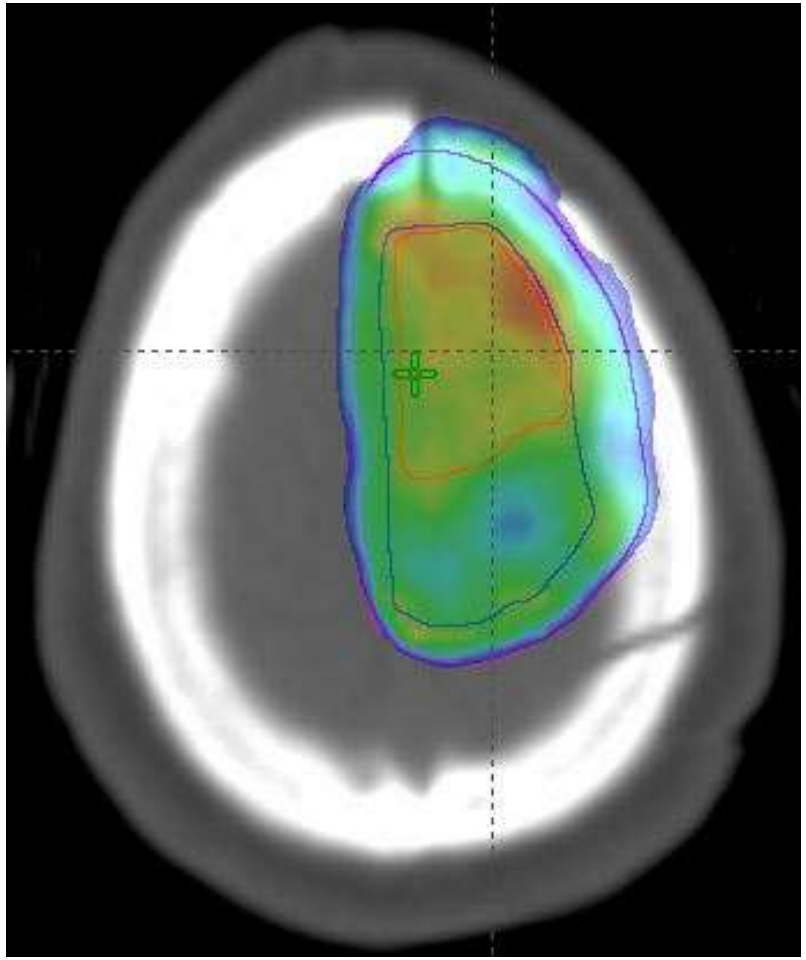
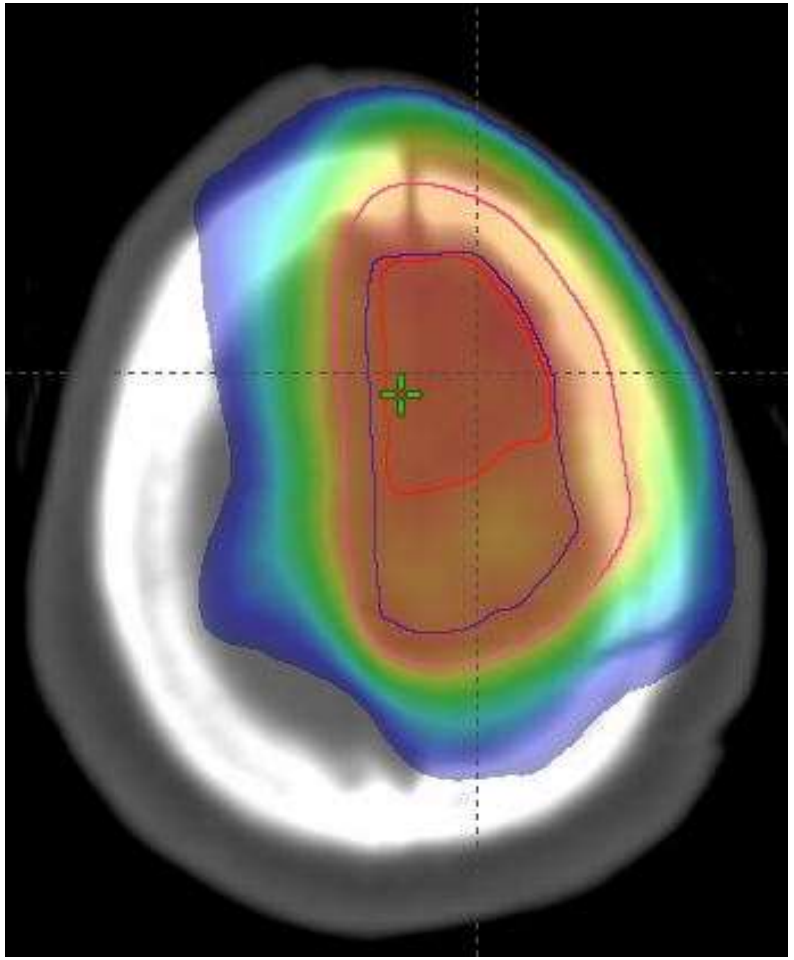
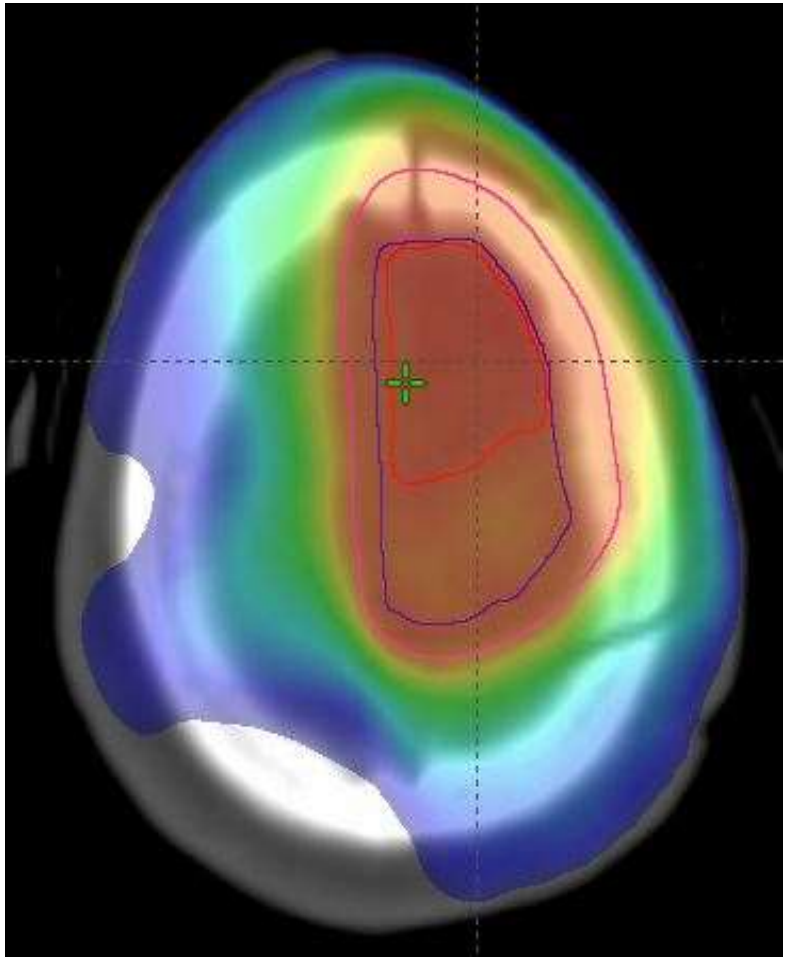
Eyeballing Color Washes







Case 4

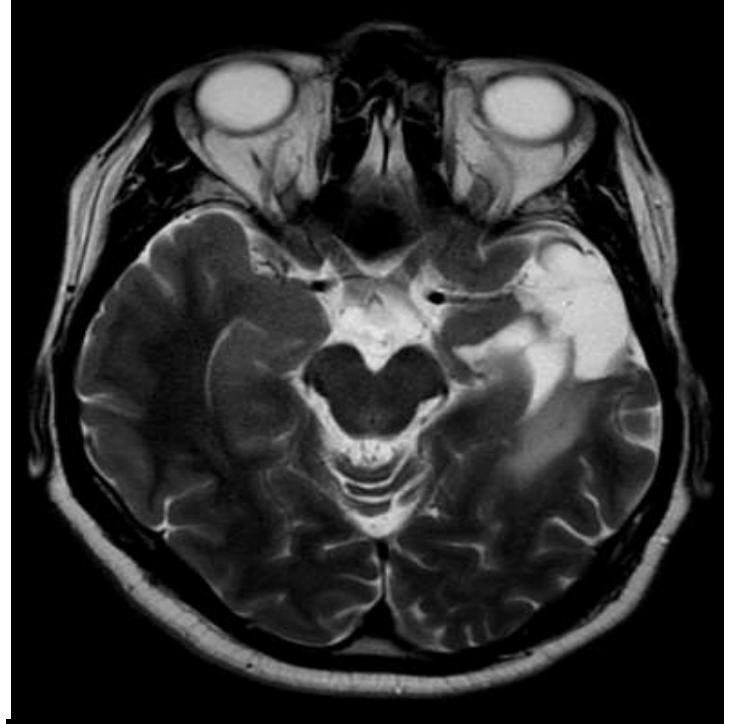
Re-irradiation-Adult Diffuse Gliomas

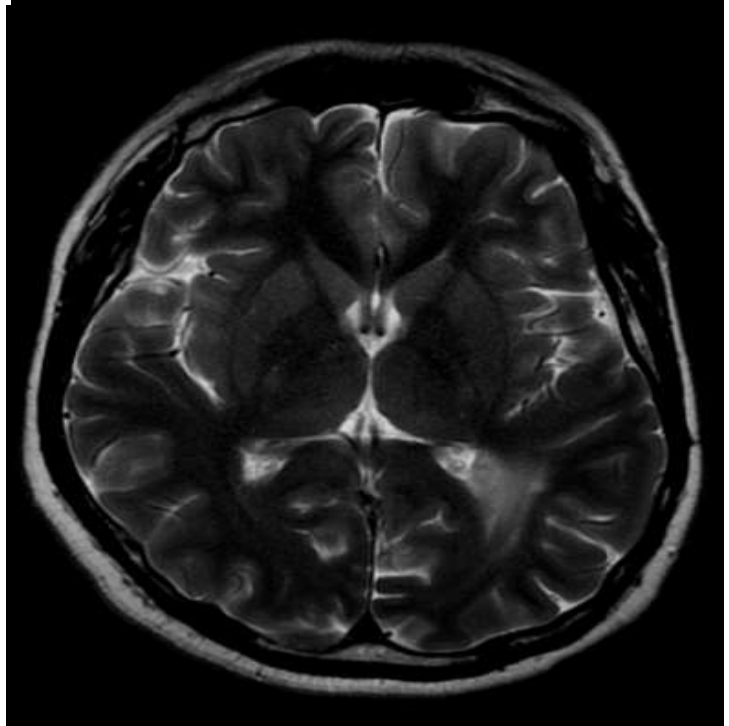
Questions

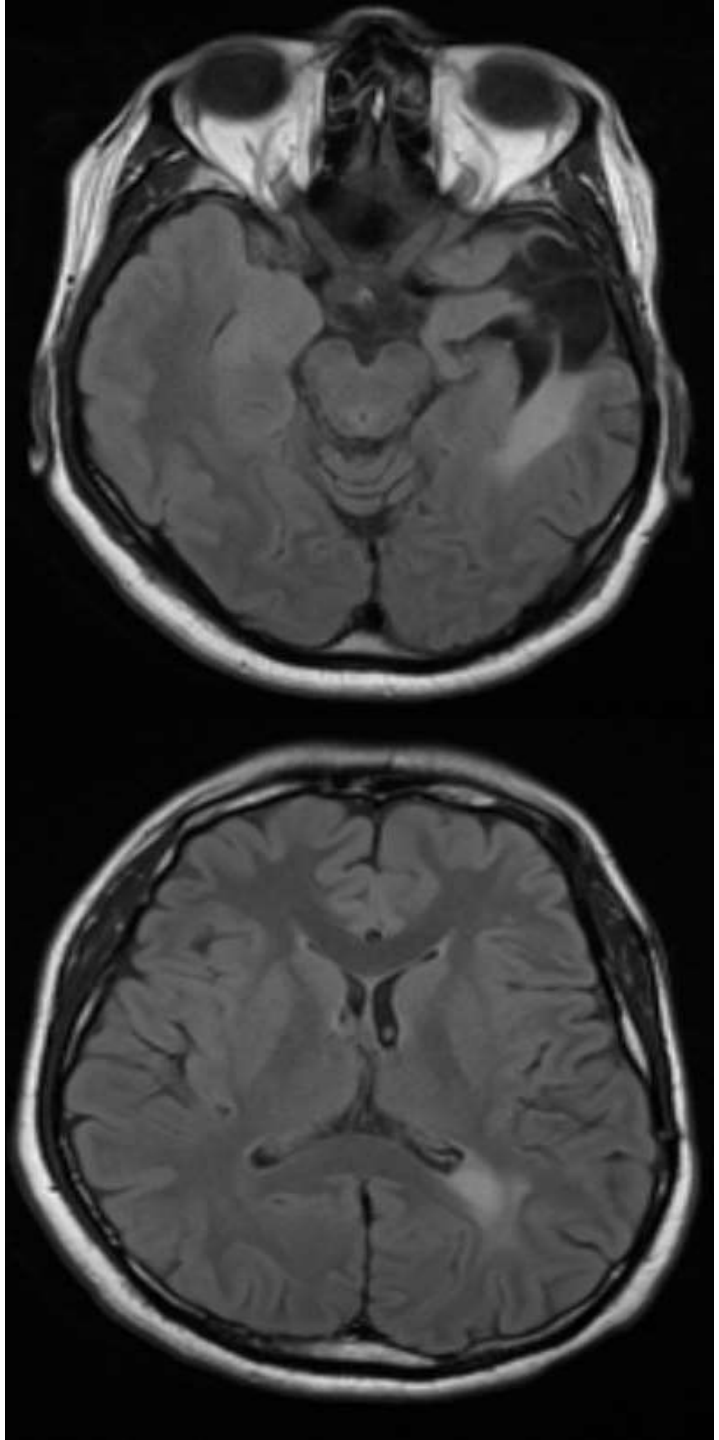
- Who constitutes an ideal candidate?
- Doses and volumes ?
- Concurrent therapies ?
- Toxicities ?

- 30/M/Cabin crew/Single episode GTCS
- A-ODG – 1p19q non-codel
- Received **adjuvant EBRT** to postop bed + residual disease **60 Gy/30 fractions** @ 2 Gy/# from 07.02.2013 to 11.04.2013 along with **concurrent Temozolomide** (75 mg/m^2).
- On follow up with ambiguous imaging findings

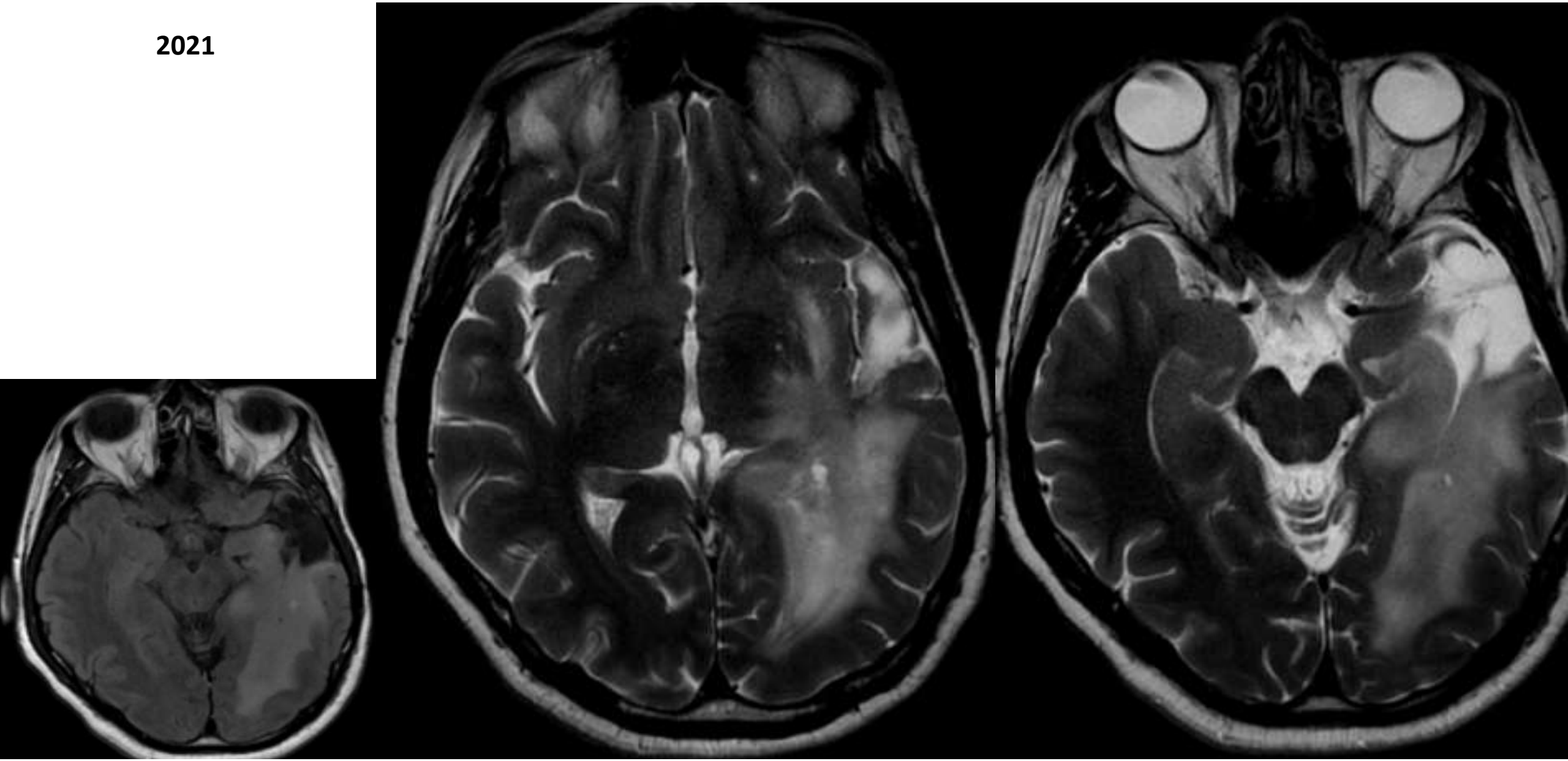
2019



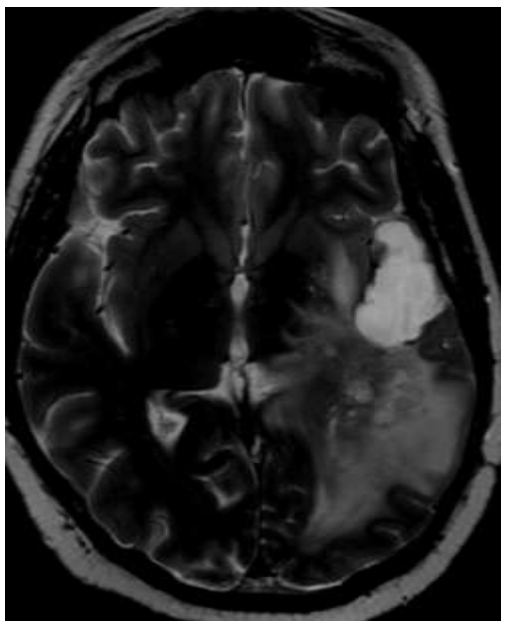
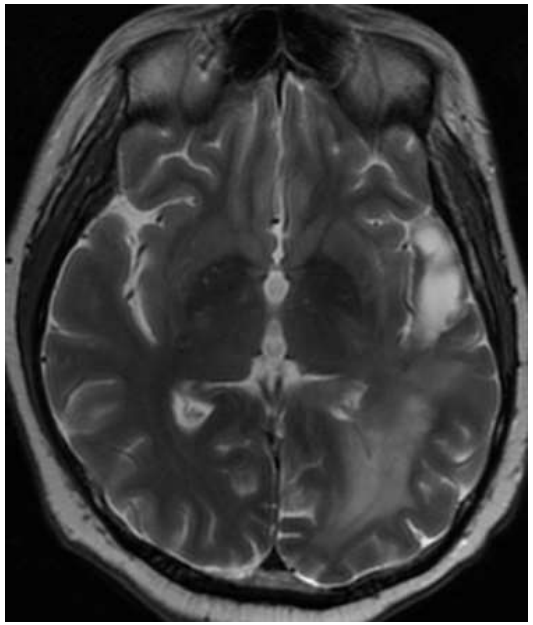




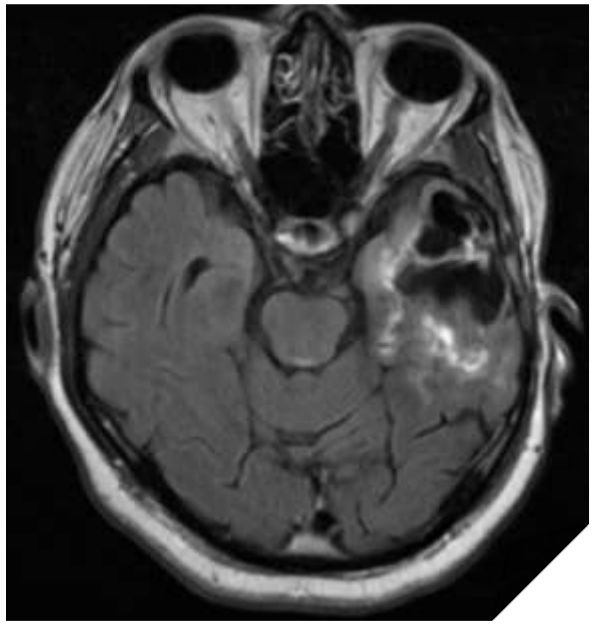
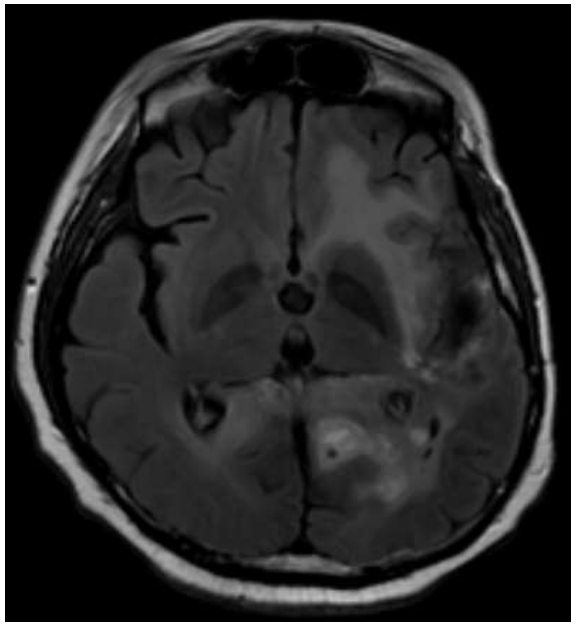
2021



- Received **ReRT to residual disease 50.4 Gy/ 28 fractions** @ 1.8 Gy/# from 27.09.2021 to 09.11.2021 along with **concurrent Temozolomide (75 mg/m^2).**
- **3 courses and 2 challenges with bevacizumab**
- **Now progressing – started on CCNU**

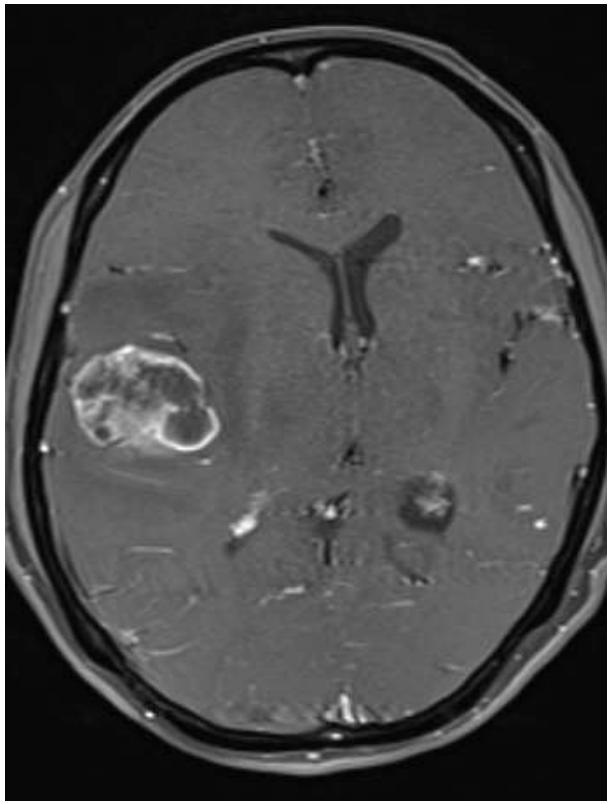
2022

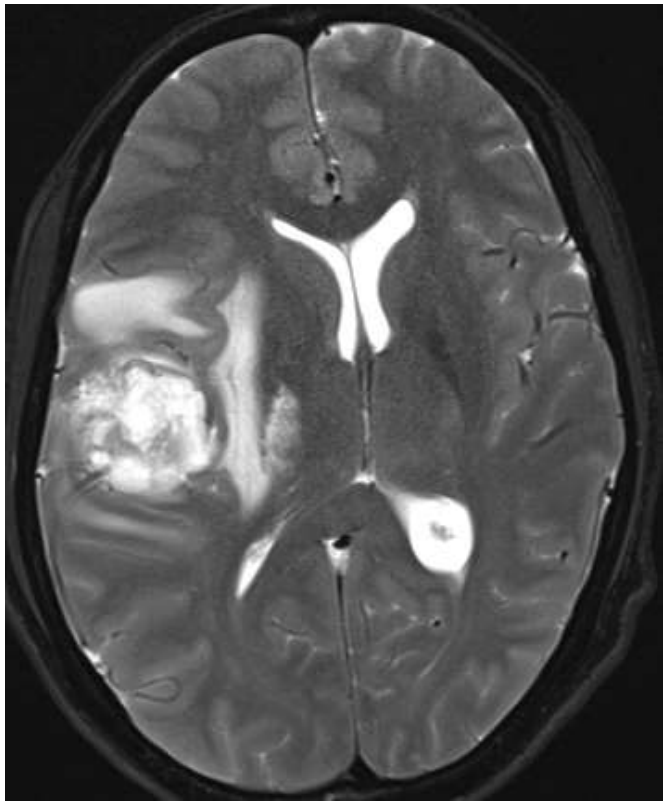



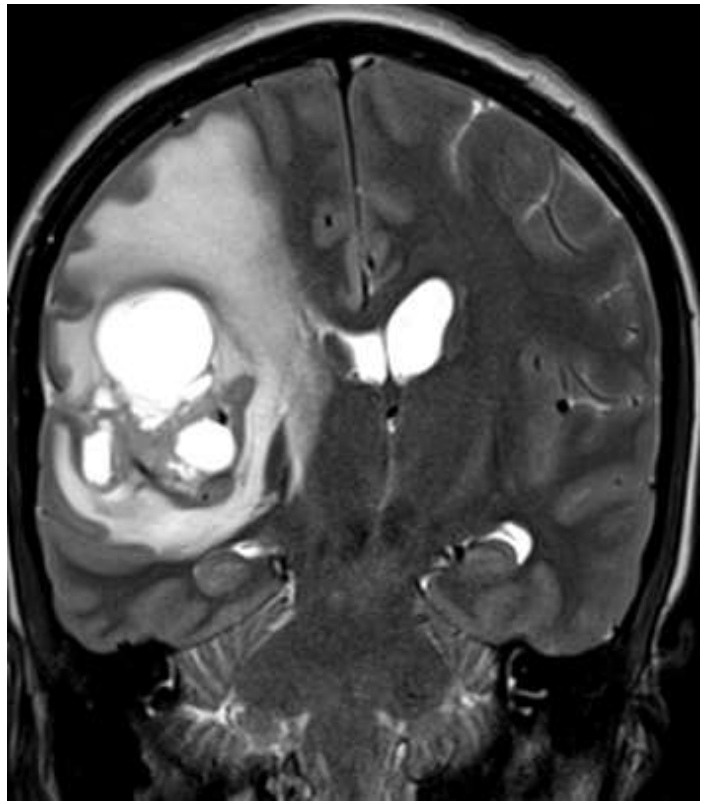
2024

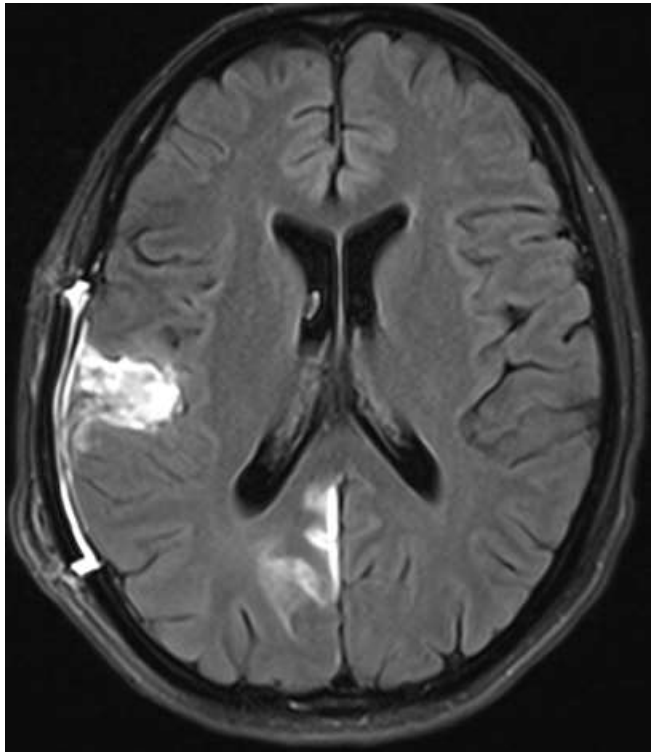
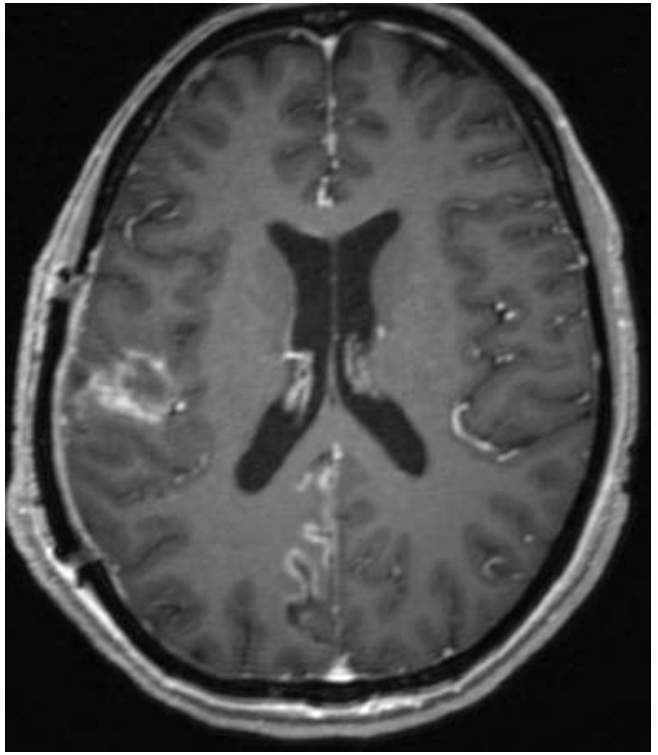
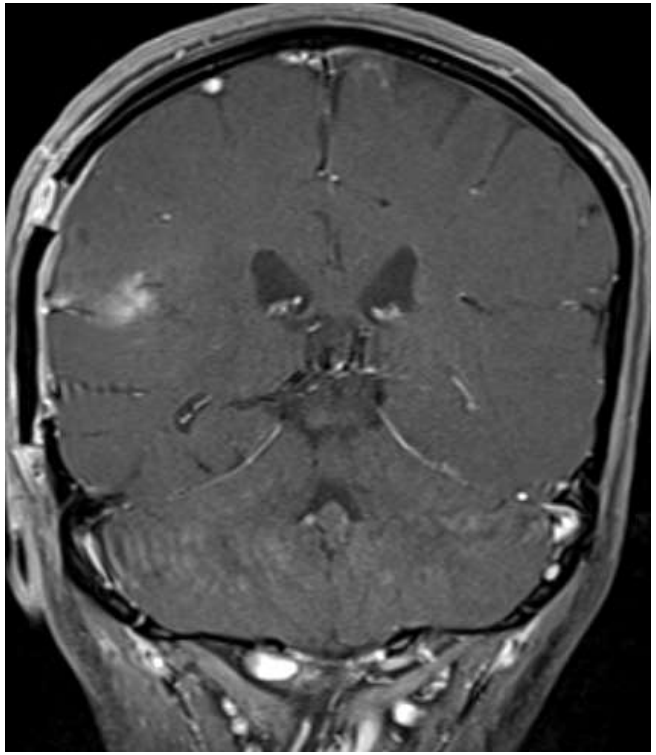
Case 5

32/F/Presenting – GTCS /Headache /Vomiting-Dec 2018



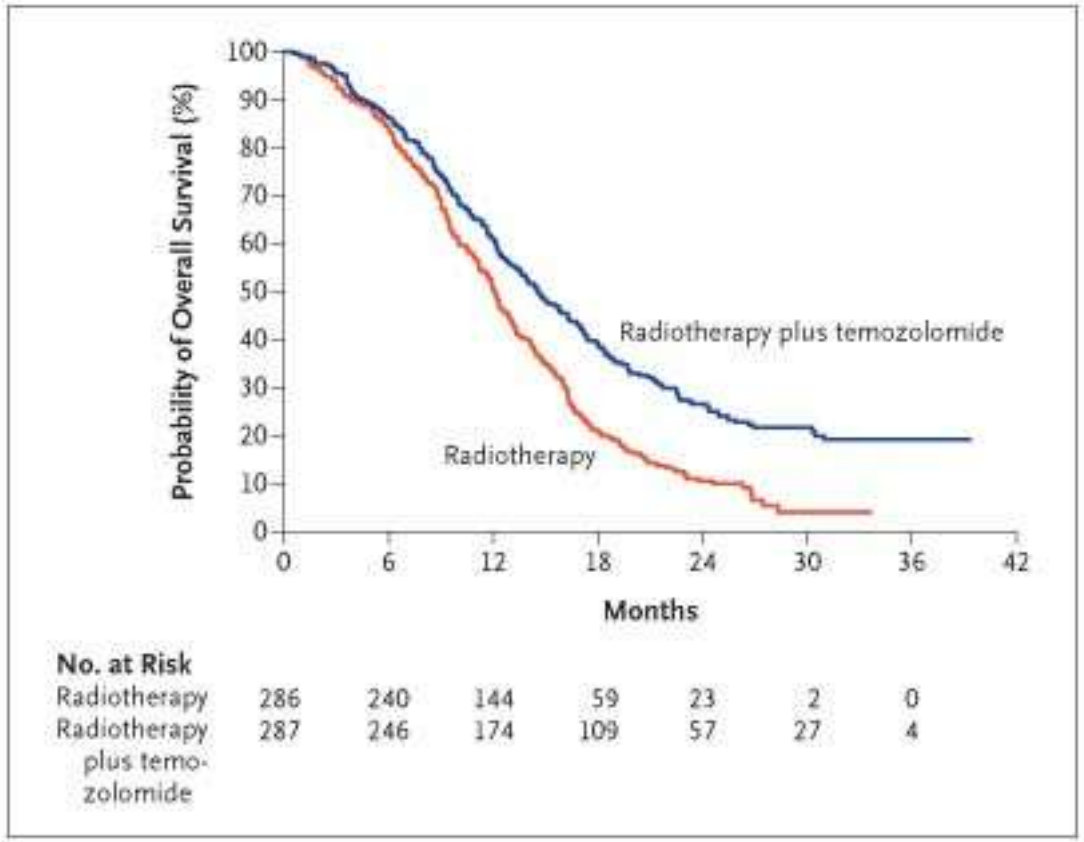




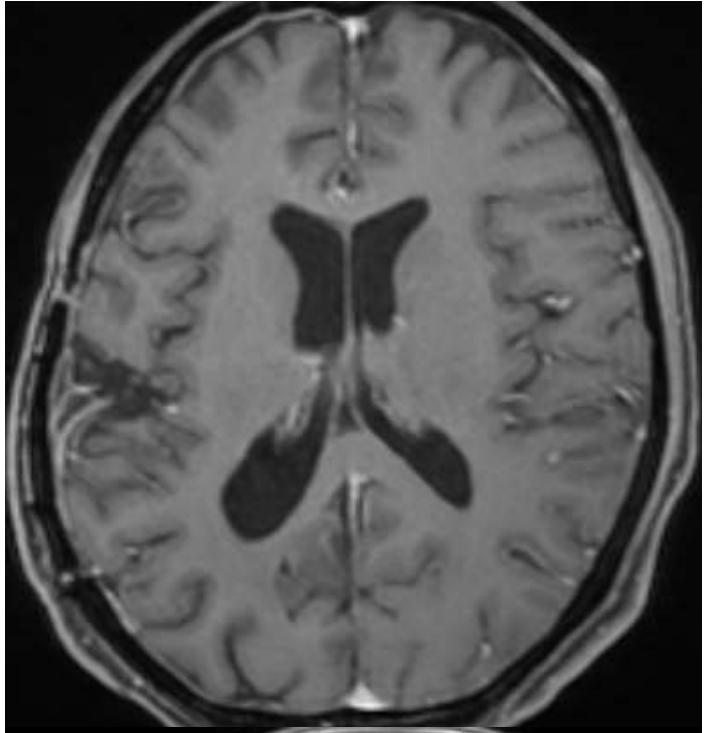




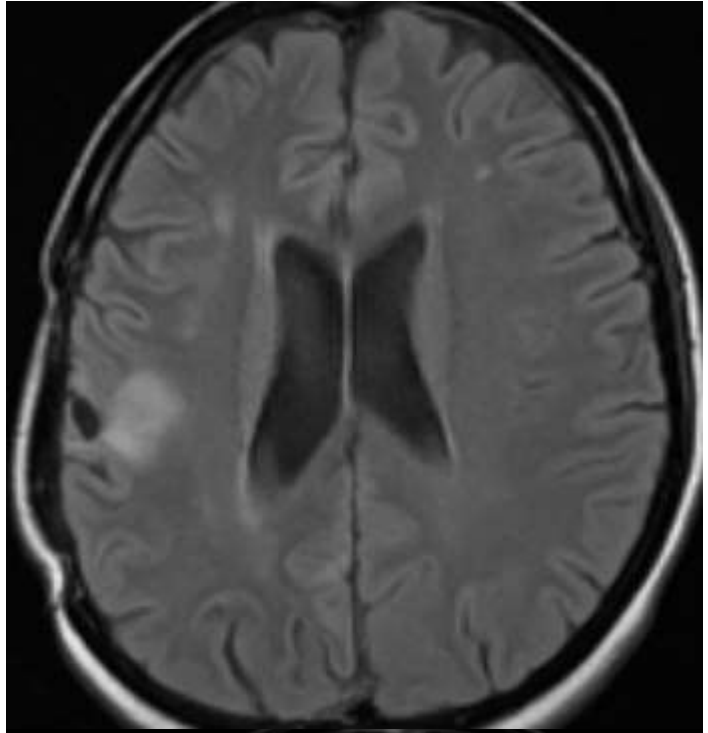
- **HPR review in TMH:** Glioblastoma, Grade 4
  IHC: IDH wild type, ATRX retained, CD34, p53 (+);
  MIB1: 6-8%
  MGMT unmethylation
- **Postop MRI brain (11.01.2019):** Postop changes & no residual disease

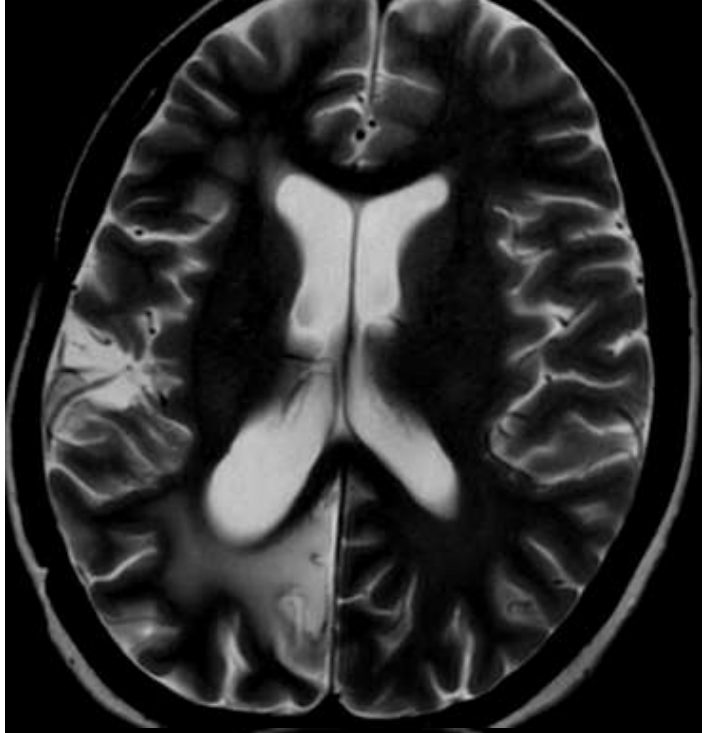
RT -59.4Gy/33# f/b 6 # TMZ (Sept 2019)



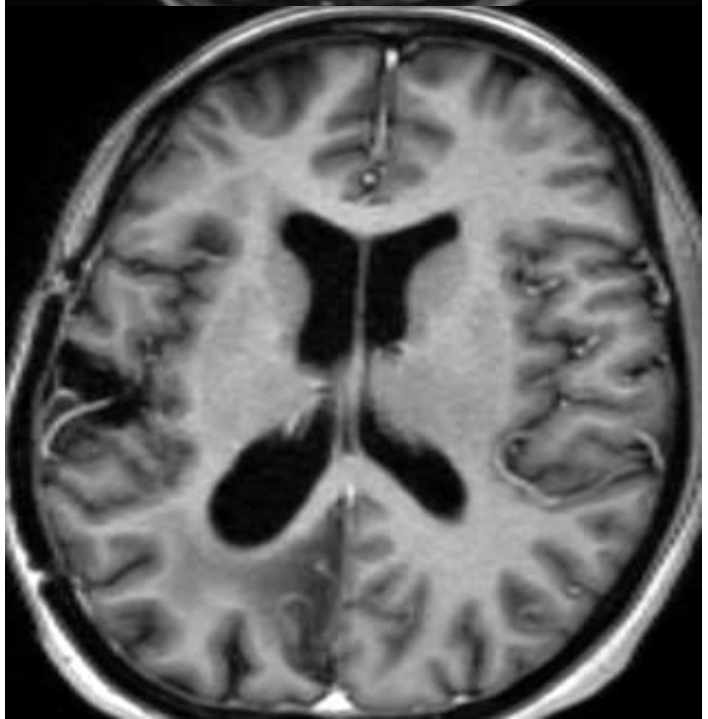
October
2019

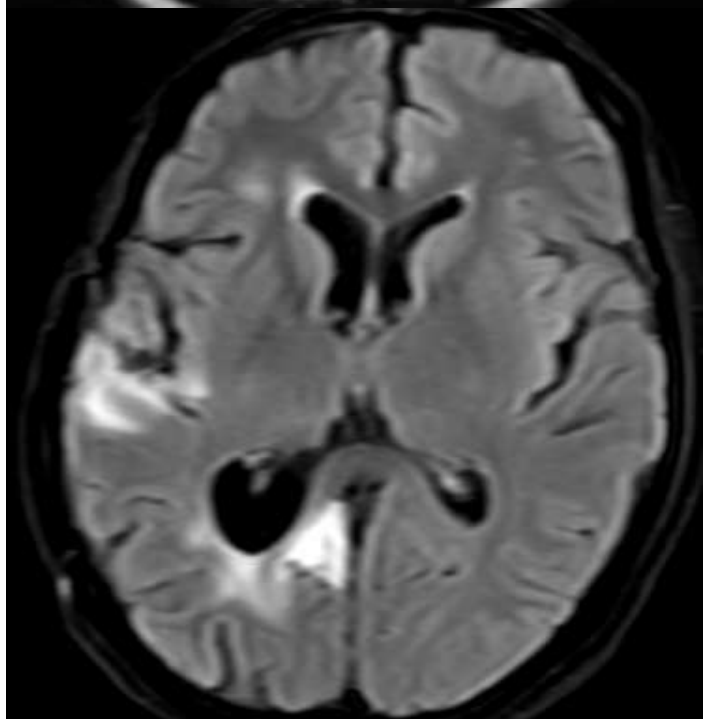


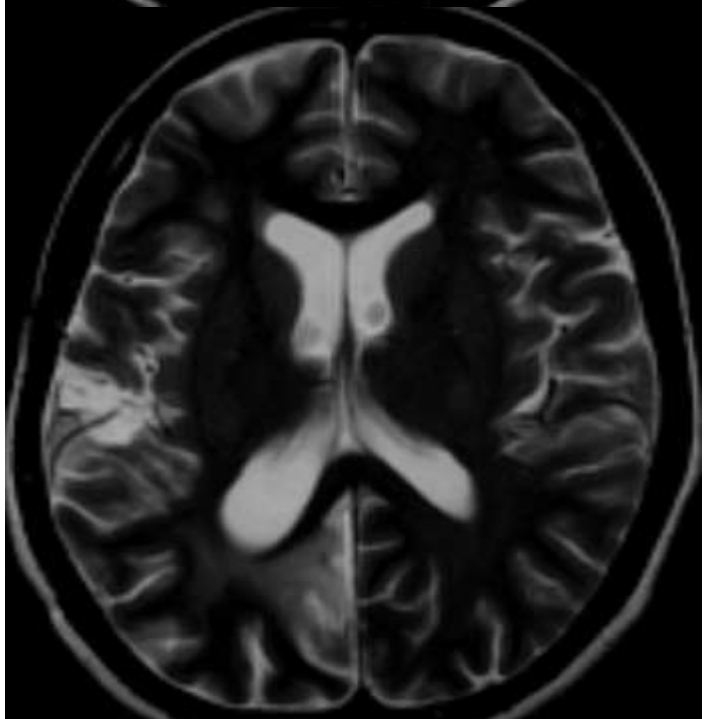


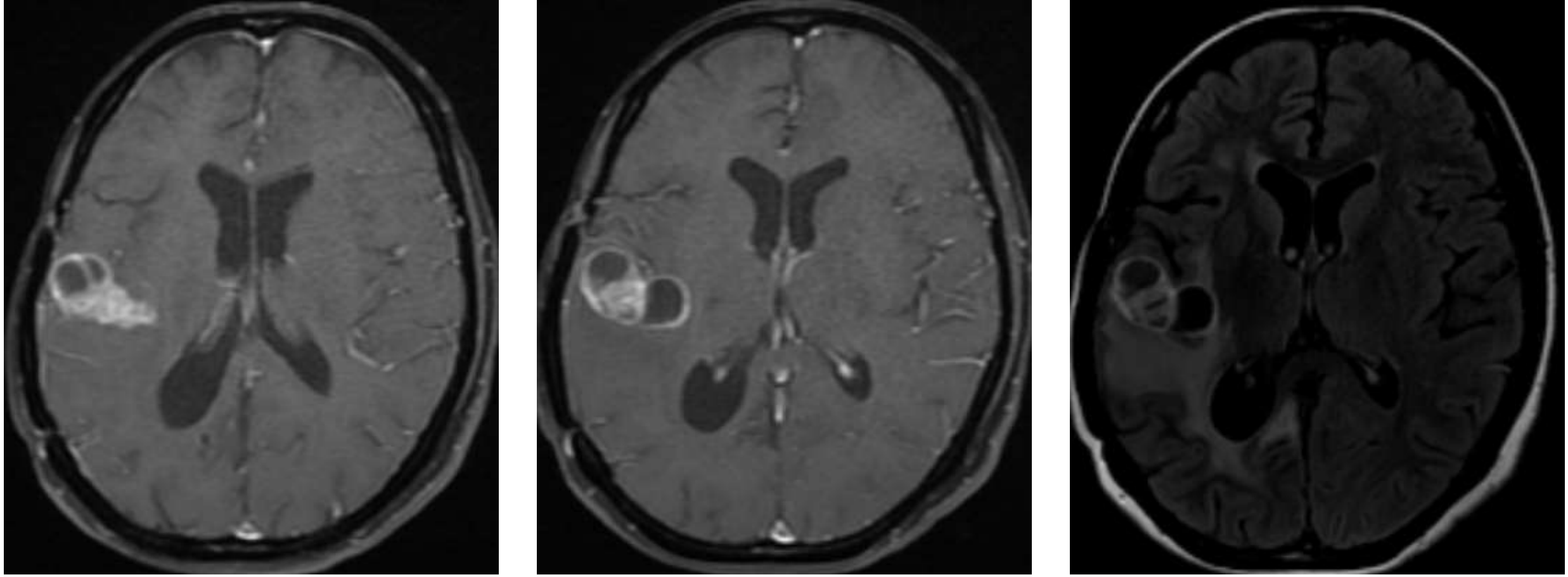


October
2020

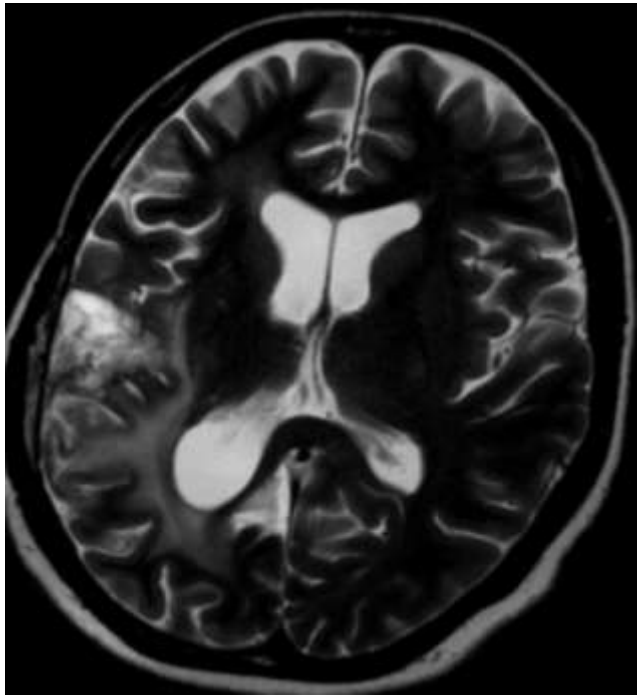




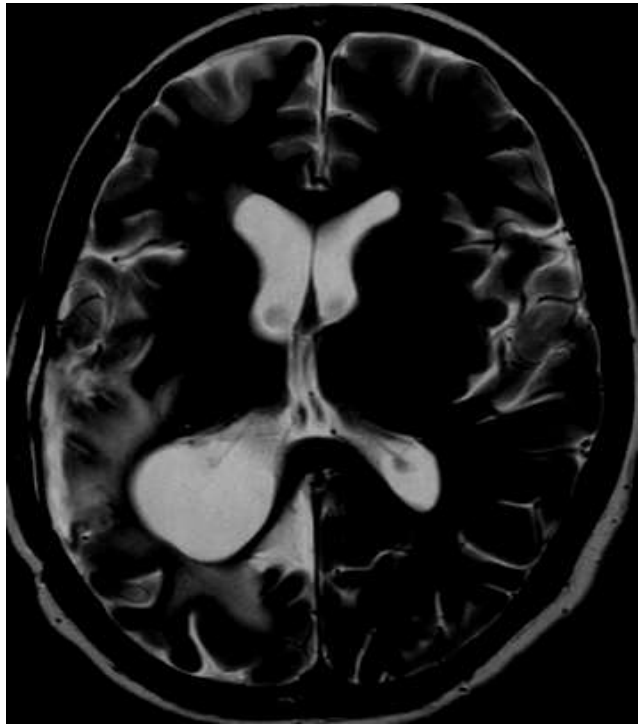




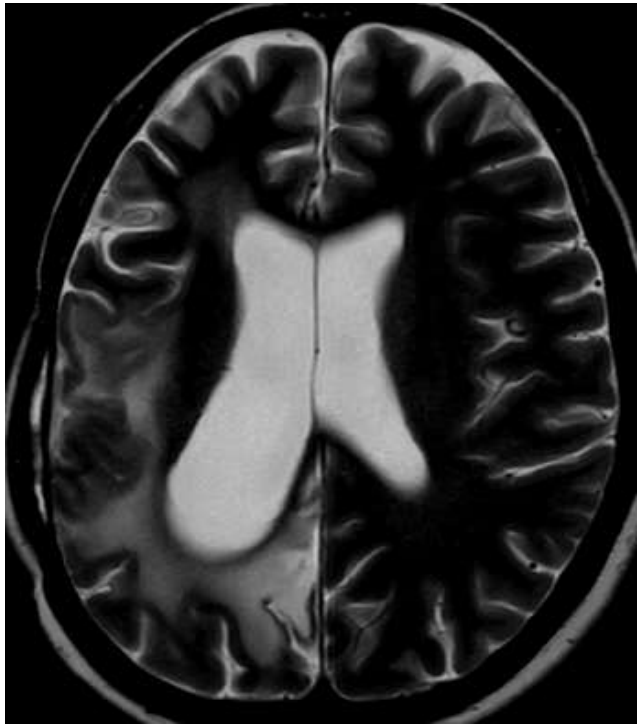
MRI brain (02.02.2022):progression



Re -surgery

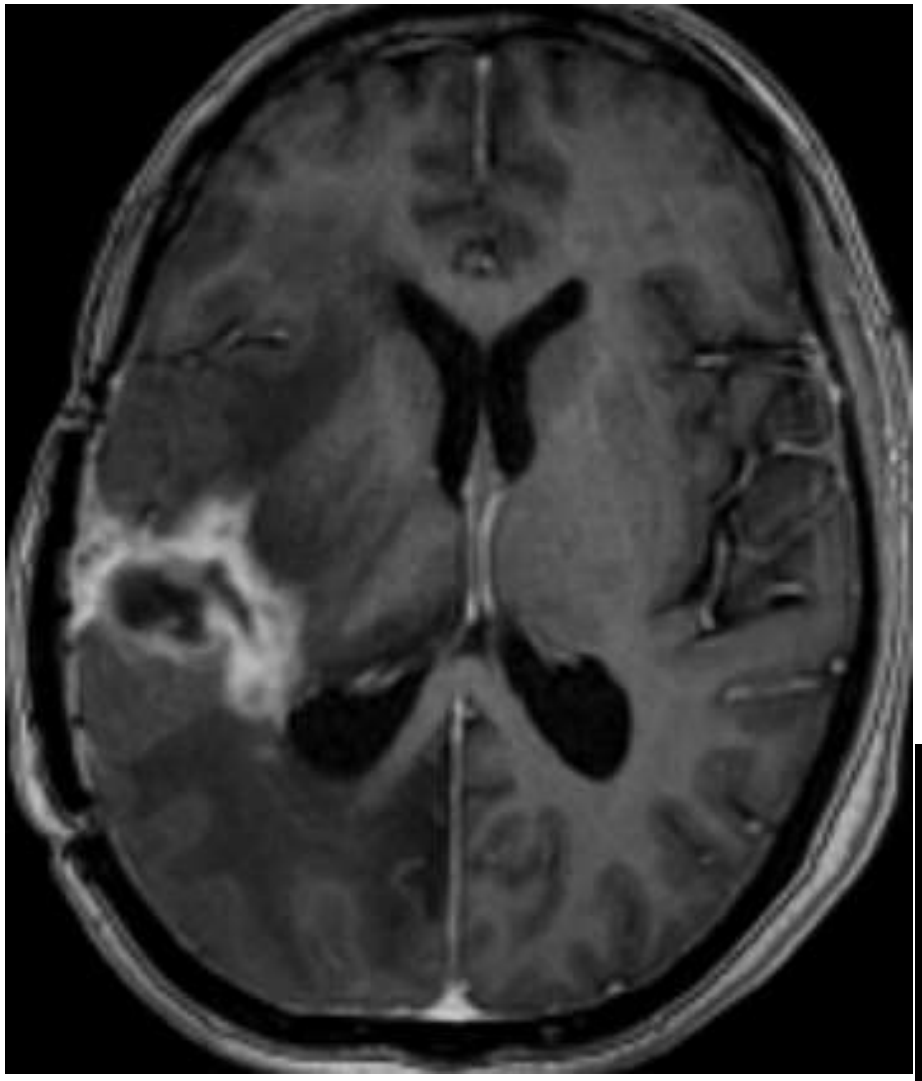


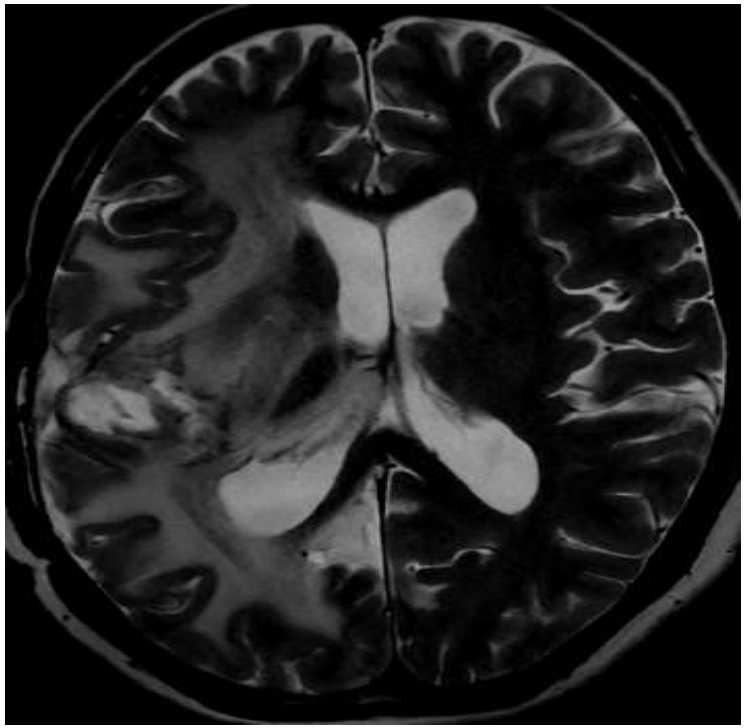
Re-RT-54Gy/30#

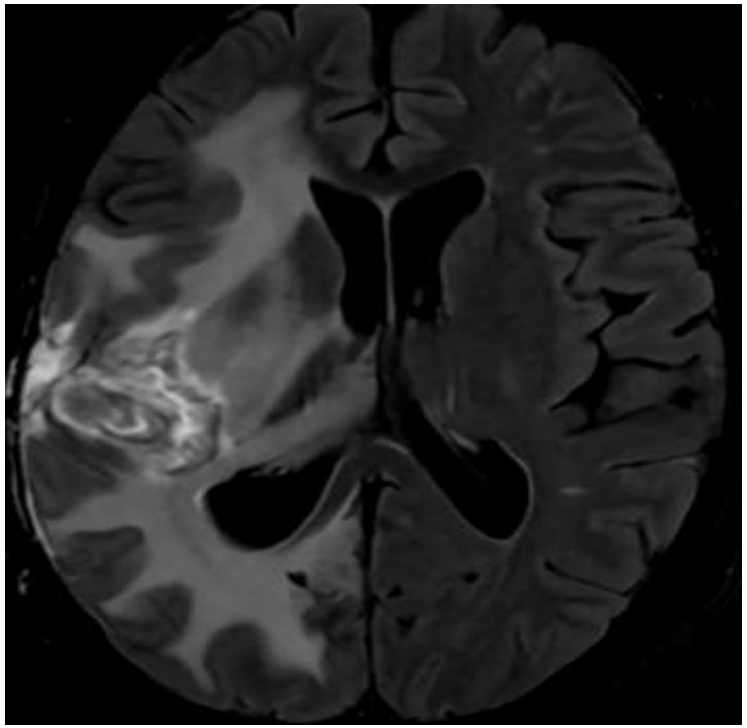


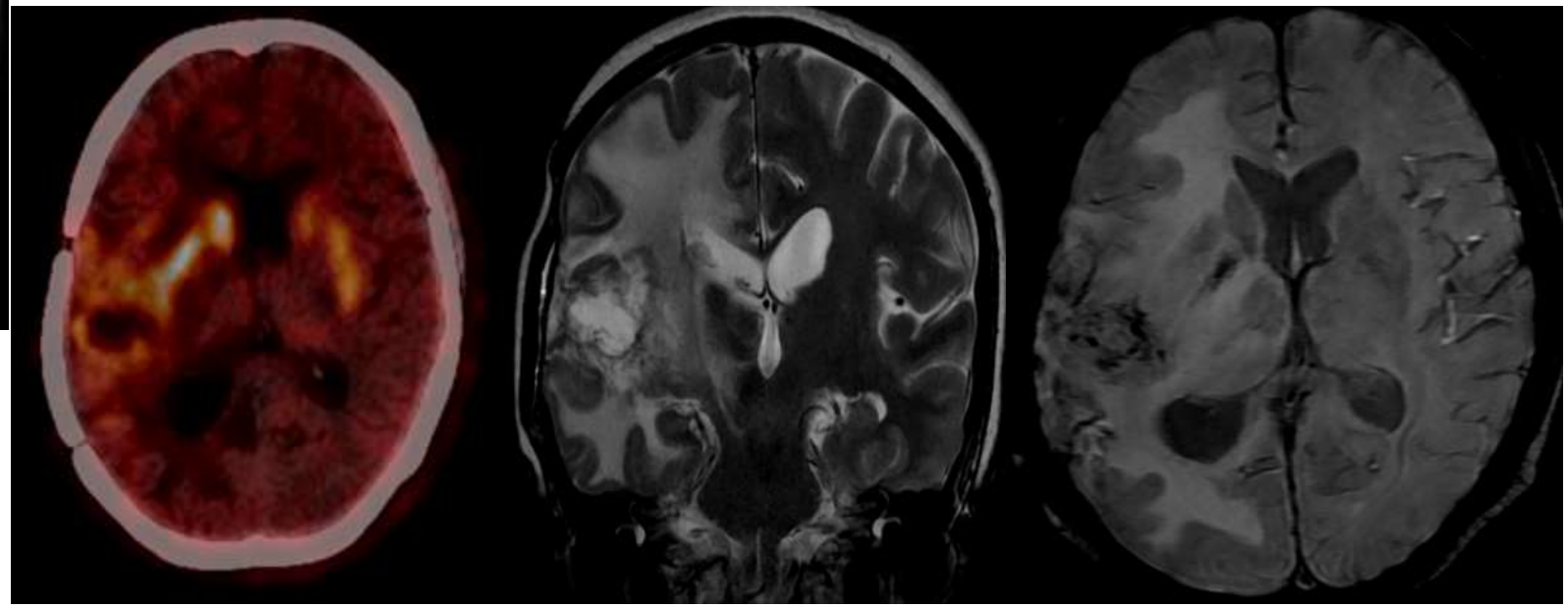
TMZ rechallenge – 6#

Oct 2023 – treatment complete







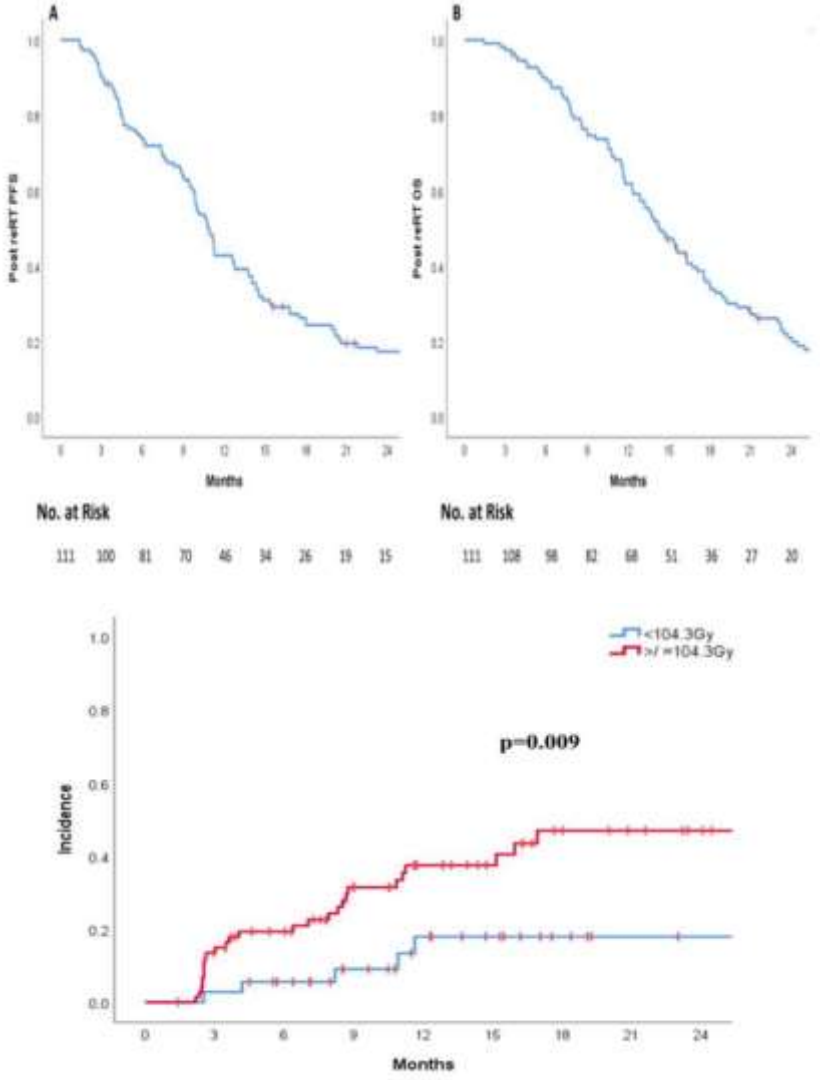


Necrosis +

Death- sepsis , PE – 01.01.2024

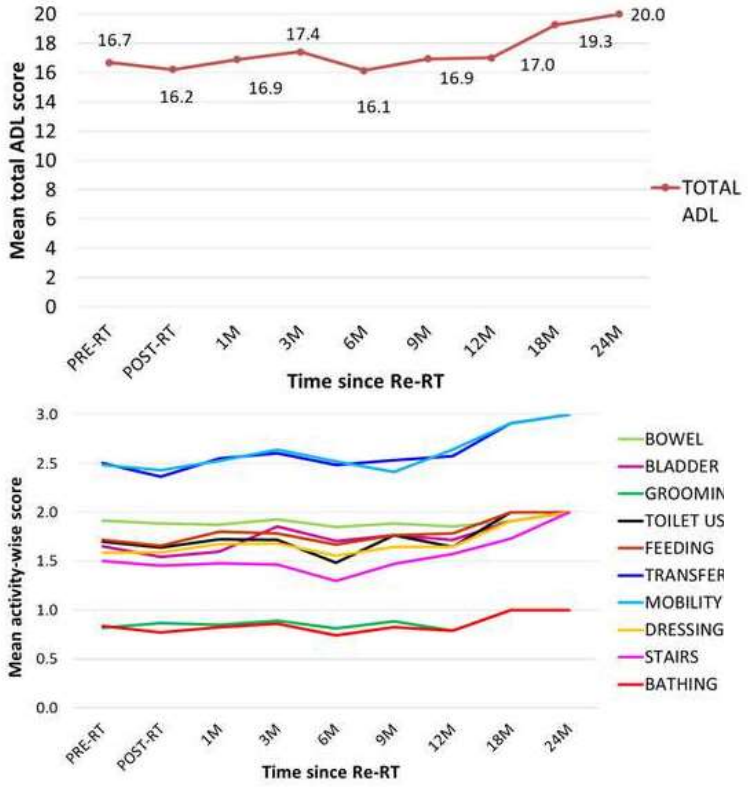
TMH experience-Outcomes

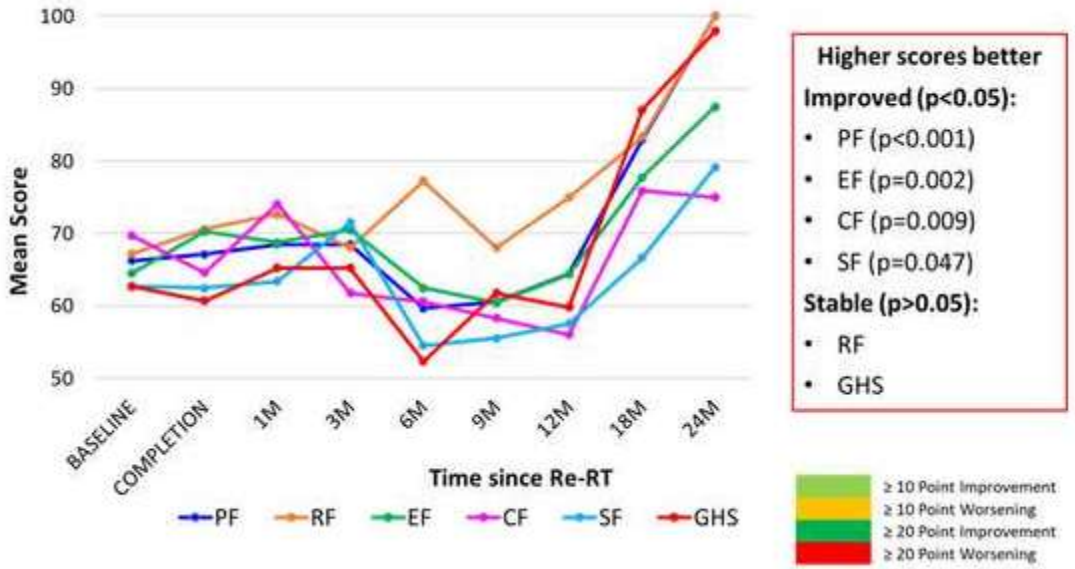
- N=111(Gd III- 37, Gd IV – 74)
- IDH mt – 49(44%),MGMT meth- 30(27%)
- Median time to Recurrence – 4.3 yrs
- Median time to Re RT – 4.8 yrs
- Median Re RT dose - 54Gy (IQR=50.4-55.8Gy)
- Cumulative median EQD2 – 104.3Gy(IQR = 102.6-109.4 Gy)
- **Median volume -325 cc**
- **1 yr Re RT –PFS – 42.8% (median- 10.9 months)**
- **1 yr Re RT OS – 61.8% (median – 14.4 months) ,2 yr OS - 20%**
- **MVA for OS – PS**
- **MVA for PFS – DFI, Time to Re RT , IDH,KPS**
- **Post treatment changes – 30% - higher risk of pseudo-progression with EQD2>104.3Gy**

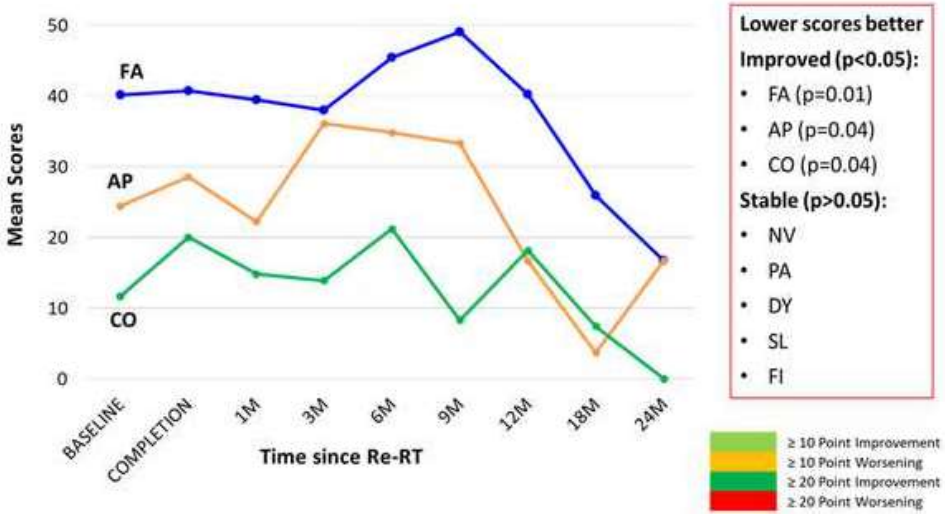


Clin Transl Oncol. 2021 Jul;23(7):1358-1367. doi: 10.1007/s12094-020-02526-0. Epub 2021 Feb 2. PMID: 33528810.

Quality of Life







Clin Oncol (R Coll Radiol). 2021 Mar;33(3):e155-e165. doi: 10.1016/j.clon.2020.08.011. Epub 2020 Sep 8. PMID: 32917486.

Benchmark Outcomes with Re-RT in recurrent/progressive HGG

144

Neuro-Oncology Practice

6(2), 144–155, 2019 | doi:10.1093/nop/npy019 | Advance Access date 14 June 2018

Re-irradiation for recurrent high-grade gliomas: a systematic review and analysis of treatment technique with respect to survival and risk of radionecrosis

Mihir Shanker, Benjamin Chua, Catherine Bettington, Matthew C. Foote, and Mark B. Pinkham

Table 3 Unadjusted Outcome Variable Characteristics by Treatment Technique

Variable (n = number of patients)	Type	Median (Mean)	Min	Max	Standard Deviation	IQR	Overall *P* value	Pairwise *P* value
Median Overall Survival (months) (n = 3190)	Conventional	10.4 (10)	5.3	16	2.6	3.6	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	11.5 (12.1)	6.5	30	4.3	3.0		<.01 vs FSRT
	FSRT	10.8 (10.6)	6.7	18	2.14	1.4		-
Radionecrosis (%) (n = 2860)	Conventional	0 (0.9)	0	10.3	2.1	1.0	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	8.0 (10.6)	0	31.3	9.1	17.7		<.01 vs FSRT
	FSRT	0 (3.3)	0	28.0	5.5	5.0		-

Abbreviations: IQR, interquartile range; SRS, stereotactic radiosurgery; FSRT, Fractionated stereotactic radiotherapy.

Courtesy :Prof. Tejpal Gupta

Caveats of selection bias

Table 1
Radiosurgery as salvage treatment in recurrent glioblastoma.

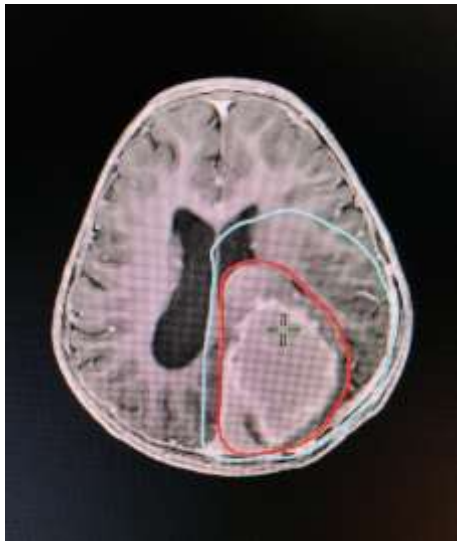
Author	Number of patients	Histotype	Median tumor volume	Median marginal dose	mOS and actuarial OS from the time of reirradiation		mPFS and actuarial PFS from the time of reirradiation		Severe toxicity	EQD 2 for second course RT (alpha/beta ratio = 2 Gy)
					Whole series	GBM only	Whole series	GBM only		
Hall et al. (1995)	35	26 GBM, 9 WHO III gliomas	28 ml	20 Gy	8 m	n.a.	n.a	n.a.	5.7% histologically confirmed radionecrosis	110 Gy
Shrieve et al. (1995)	86	All GBM	10 ml	13 Gy	-	10.2 m; 45% at 12 m	-	n.a.	3.5% severe toxicity other than necrosis	48.75 Gy
Kondziolka et al. (1997)	19	All GBM	6,5 ml	15 Gy	-	16 m	-	n.a.	0%	63.75 Gy
Cho et al.(1999)	46	27 GBM, 19 WHO III gliomas	10 ml	17 Gy	11 m; 42% at 12 m	n.a.	n.a	n.a.	4.3% histologically confirmed radionecrosis	80.75 Gy
Combs et al. (2005a)	32	All GBM	10 ml	15 Gy	-	10 m; 38% at 12 m	-	7 m; 33% at 6 m	0%	63.75 Gy
Hsieh et al. (2005)	26	All GBM	21,6 ml	12 Gy	-	10 m	-	n.a	31.3% radiological radionecrosis	42 Gy
Kong et al. (2008)	114	65 GBM, 49 WHO III gliomas	10,6 ml	16 Gy	n.a.	13 m; 58.4% at 12 m	n.a.	4,6 m; 20.5% at 12 m	24.4% radiological radionecrosis	72 Gy
Patel et al. (2009)	26	All GBM	10,4 ml	18 Gy	-	8,5 m	-	n.a	7.6% histologically confirmed radionecrosis	90 Gy
Skeie et al. (2012)	51	All GBM	12,4 ml	12,2 Gy	-	9 m	-	n.a.	0%	43.3 Gy
Martinez-carrillo et al. (2014)	87	46 GBM, 41 WHO III gliomas	4 ml	18 Gy	10 m; 37.9% at 12 m	7.5 m; 0.4% at 12 m	n.a	n.a.	0%	90 Gy

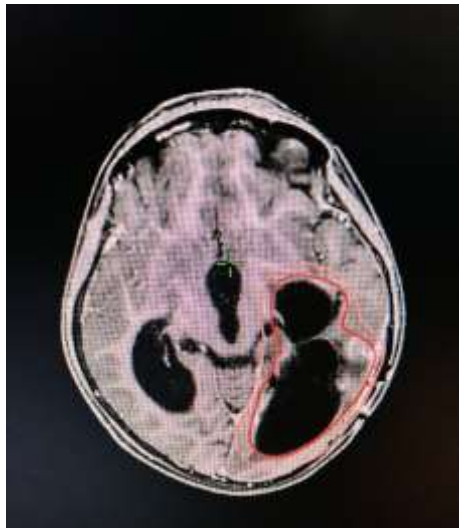
HGG: high grade gliomas; GBM: glioblastoma; OS: overall survival; PFS: progression free survival; m:months.

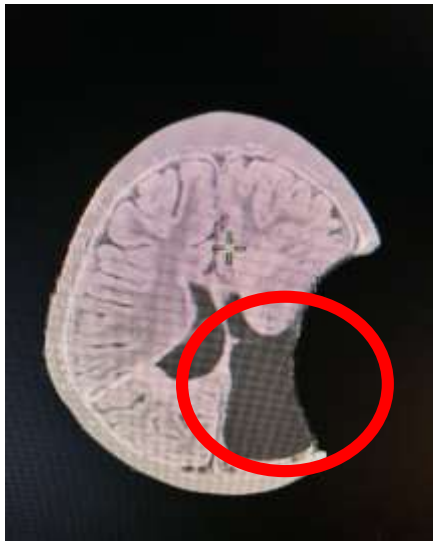
Critical Reviews in Oncology / Hematology 126 (2018) 80–91

Times,Doses and Volumes

- DFI – 1.5-2 years
- GTV using multiparametric MRI
- Careful co-registration
- Fusion with previous contours and plans(Isodoses –30/ 50/95)
- CTV – 5-7mm- individualise
- PTV – 3 mm with daily IGRT
- Doses – 50-54Gy @ 1.8Gy/#







Concurrent therapies

Before, After, or Concurrently?

ChemoRx-naïve patient (transformed from an erstwhile LGG)

- Give 6-12 cycles of monthly temozolomide as salvage to defer ReRT
- Follow-up with concurrent temozolomide during ReRT
- In patients with known 1p/19q deletion, PCV may be offered instead of TMZ

Patient progressed after prior chemoRx (either PCV/TMZ)

- <6 months from last exposure to chemoRx: Not much rationale of chemoRx
- 6-12 months from last exposure to chemoRx: Value judgement
- >12 months from last exposure to chemoRx: Rechallenge with chemoRx

Bevacizumab-naïve patient (but received multiple chemoRx)

- Consider ReRT with concurrent bevacizumab followed by maintenance Rx

Patient progressed after prior chemoRx + Bevacizumab

- Enter patient into a clinical trial (either IND or combining IND + ReRT)

Courtesy :Prof. Tejpal Gupta

Reducing RN- Bev +RT

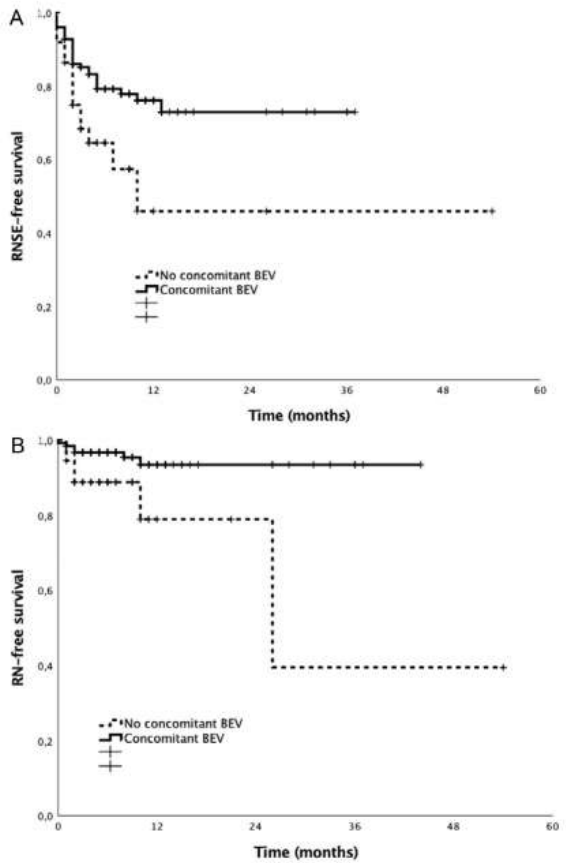


Fig. 2. RN/SE-free survival (A) and RN-free survival (B) stratified for concomitant BEV treatment to reRT.

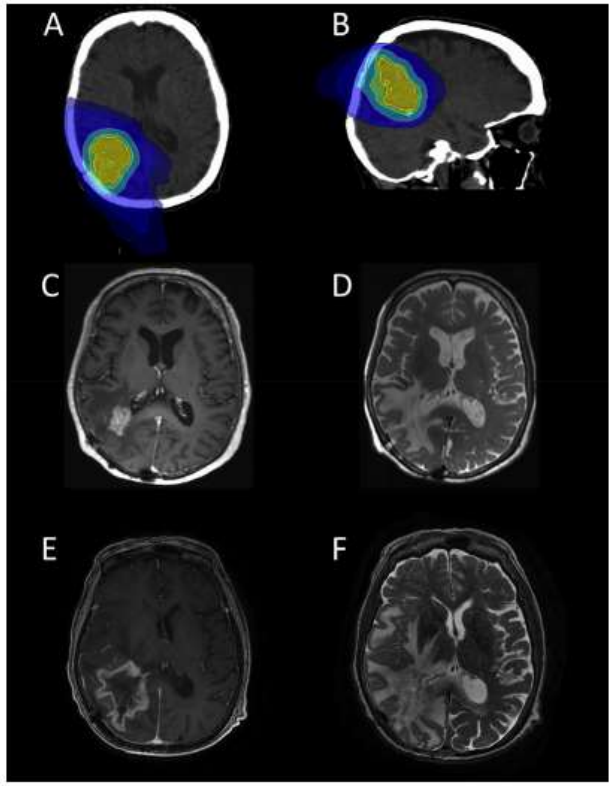


Fig. 1. 75 year old, female patient with recurrent glioblastoma treated with reRT without bevacizumab. Representative axial (A) and sagittal (B) plane of a VMAT plan of reRT [PTVboost (red), 43.2 Gy isodose line (yellow), 41.04 Gy isodose line (green), PTV (red), 34.2 Gy isodose line (light blue), 20 Gy isodose line (blue), 15 Gy isodose line (dark blue)]. Representative axial planes in CE-T_1 and T_2 MRI sequences before reRT (C and D) and four months after reRT (E and F) with symptomatic radionecrosis resulting in left-sided hemiparesis despite high-dose dexamethasone therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Recent Data

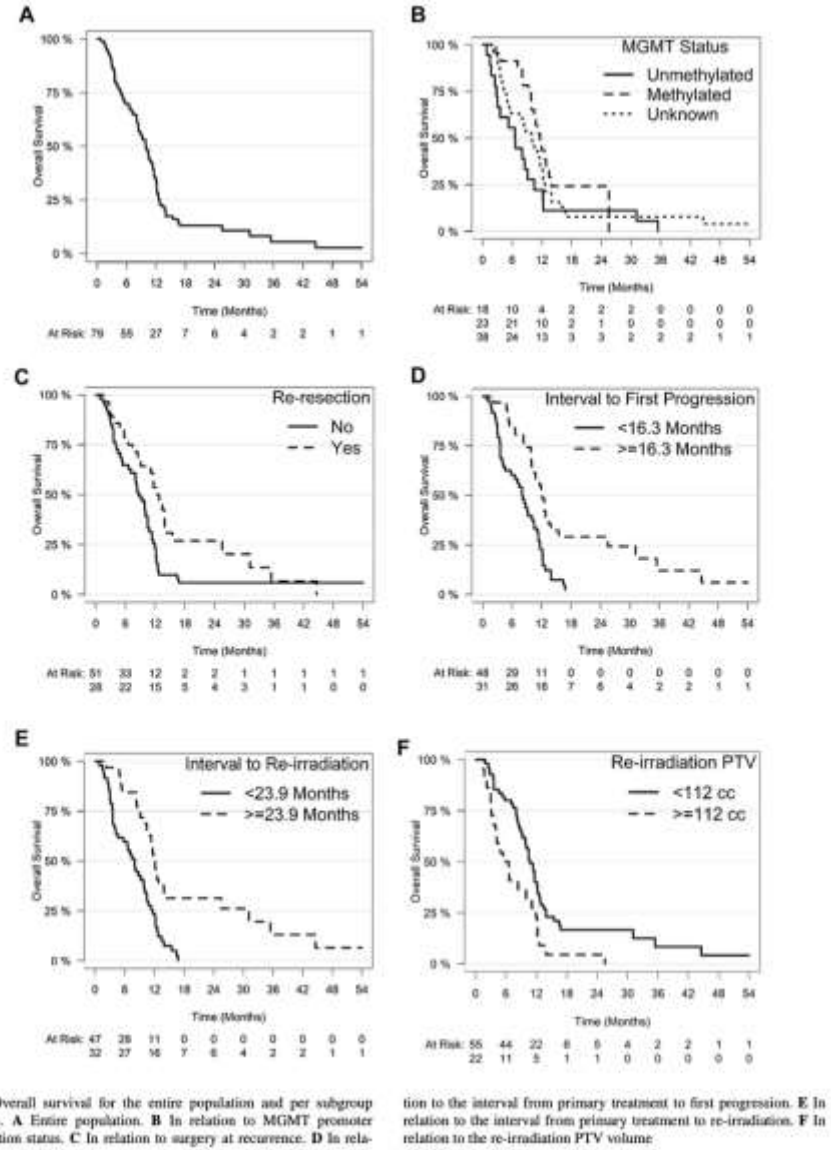
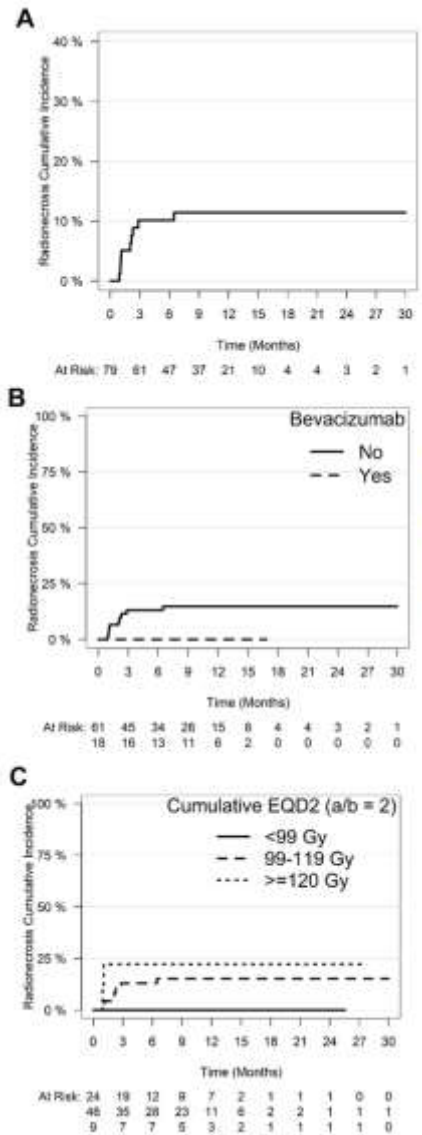


Fig. 1 Overall survival for the entire population and per subgroup analyses. **A** Entire population. **B** In relation to MGMT promoter methylation status. **C** In relation to surgery at recurrence. **D** In relation to the interval from primary treatment to first progression. **E** In relation to the interval from primary treatment to re-irradiation. **F** In relation to the re-irradiation PTV volume



Results For the 79 patients identified, the median OS after re-RT was 9.9 months (95% CI 8.3–11.6). On multivariate analyses, re-resection at progression (HR 0.56, p = 0.027), interval from primary treatment to first progression ≥ 16.3 months (HR 0.61, p = 0.034), interval from primary treatment to re-RT ≥ 23.9 months (HR 0.35, p < 0.001), and re-RT PTV volume < 112 cc (HR 0.27, p < 0.001) were prognostic for improved OS. Patients who had unmethylated-MGMT tumours (OR 12.4, p = 0.034), ≥ 3 prior systemic treatment lines (OR 29.1, p = 0.022), interval to re-RT < 23.9 months (OR 9.0, p = 0.039), and re-RT PTV volume ≥ 112 cc (OR 17.8, p = 0.003) were more likely to die within 6 months of re-RT. The cumulative incidence of RN was 11.4% (95% CI 4.3–18.5) at 12 months. Concurrent bevacizumab use (HR < 0.001, p < 0.001) and cumulative equivalent dose in 2 Gy fractions (EQD2, $\alpha/\beta = 2$) < 99 Gy_2 (HR < 0.001, p < 0.001) were independent protective factors against RN. Re-RT allowed for less corticosteroid dependency. Sixty-six percent of failures after re-RT were in-field.

Conclusion We observe favorable OS rates following re-RT and identified prognostic factors, including methylation status, that can assist in patient selection and clinical trial design. Concurrent use of bevacizumab mitigated the risk of RN.

https://doi.org/10.1007/s11060-023-04340-4

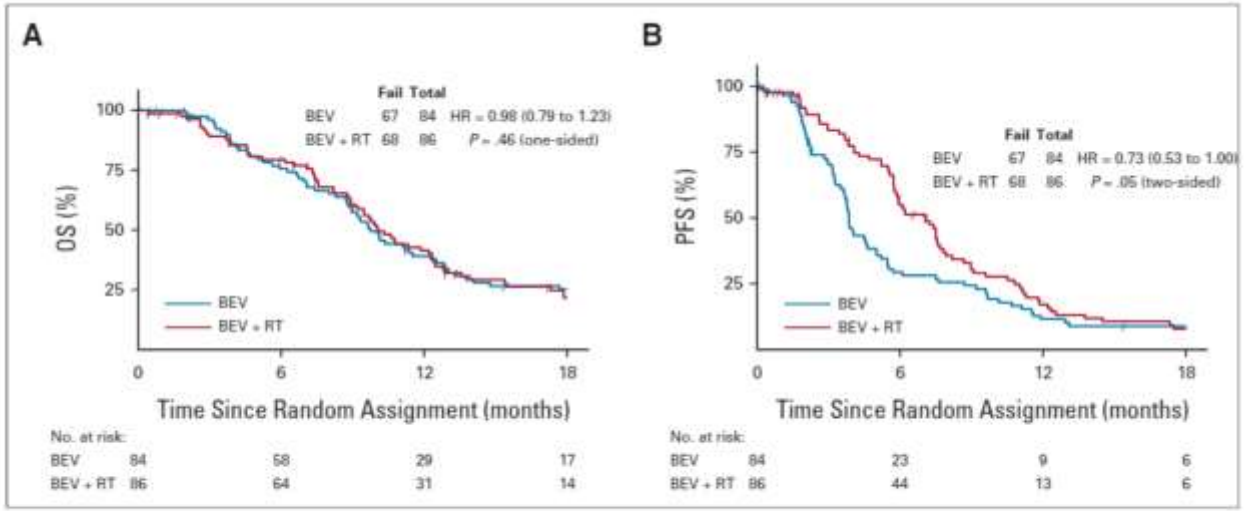


FIG 2. (A) OS and (B) PFS by treatment arm. CIs for OS are 80% and 95% for PFS. BEV, bevacizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiation therapy.

RESULTS From December 2012 to April 2016, 182 patients were randomly assigned, of whom 170 were eligible. Patient characteristics were well balanced between arms. The median follow-up for censored patients was 12.8 months. There was no improvement in OS for BEV + RT, hazard ratio, 0.98; 80% CI, 0.79 to 1.23; $P = .46$; the median survival time was 10.1 versus 9.7 months for BEV + RT versus BEV alone. The median PFS for BEV + RT was 7.1 versus 3.8 months for BEV, hazard ratio, 0.73; 95% CI, 0.53 to 1.0; $P = .05$. The 6-month PFS rate improved from 29.1% (95% CI, 19.1 to 39.1) for BEV to 54.3% (95% CI, 43.5 to 65.1) for BEV + RT, $P = .001$. Treatment was well tolerated. There were a 5% rate of acute grade 3+ treatment-related AEs and no delayed high-grade AEs. Most patients died of recurrent GBM.

CONCLUSION To our knowledge, NRG Oncology/RTOG1205 is the first prospective, randomized multi-institutional study to evaluate the safety and efficacy of re-RT in recurrent GBM using modern RT techniques. Overall, re-RT was shown to be safe and well tolerated. BEV + RT demonstrated a clinically meaningful improvement in PFS, specifically the 6-month PFS rate but no difference in OS.

Reducing RN – Precise delineation

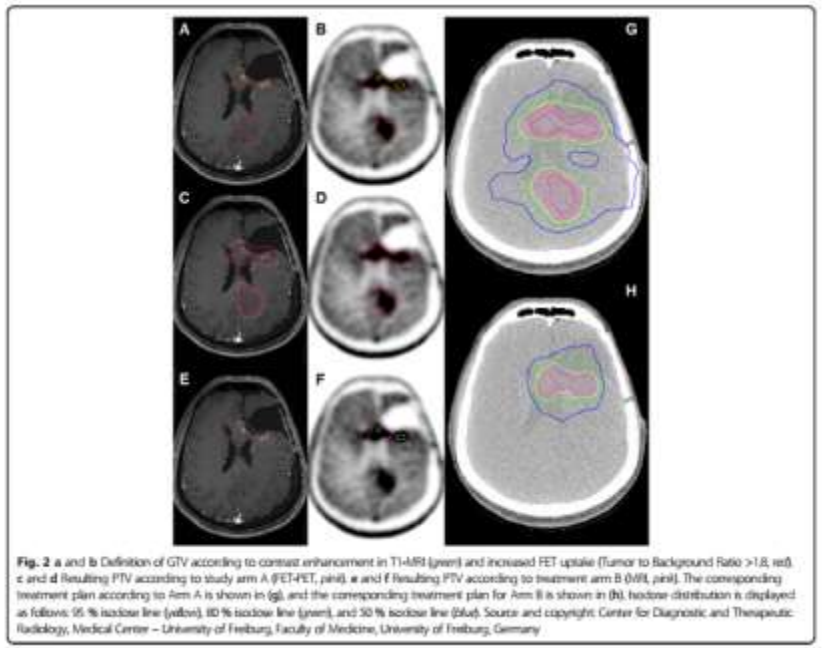


Fig. 2 **a** and **b** Definition of GTV according to contrast enhancement in T1-MRI (*green*) and increased FET uptake (Tumor to Background Ratio >1.8; *red*). **c** and **d** Resulting PTV according to study arm A (FET-PET, *pink*). **e** and **f** Resulting PTV according to treatment arm B (MRI, *pink*). The corresponding treatment plan according to Arm A is shown in (**g**), and the corresponding treatment plan for Arm B is shown in (**h**). Isodose distribution is displayed as follows: 95 % isodose line (*yellow*), 80 % isodose line (*green*), and 50 % isodose line (*blue*). Source and copyright: Center for Diagnostic and Therapeutic Radiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

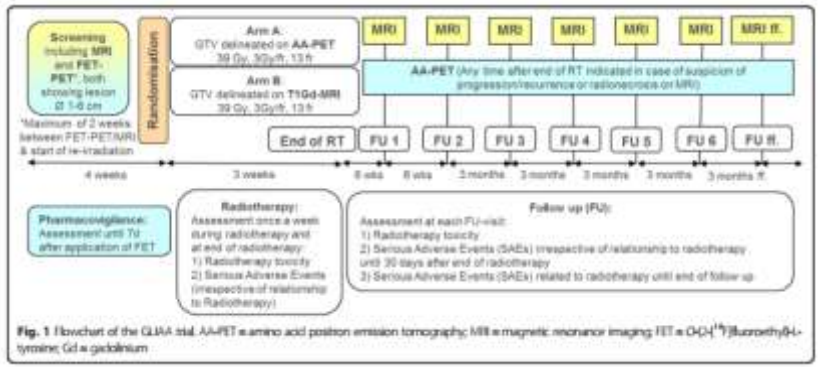


Fig. 1 Flowchart of the GLIAA trial. AA-PET = amino acid positron emission tomography; MRI = magnetic resonance imaging; FET = O-(2-[^{18}F]fluoroethyl)-L-tyrosine; Gd = gadolinium

Oehlke *et al. BMC Cancer* (2016) 16:769
DOI 10.1186/s12885-016-2806-z

Article

Imaging-Based Patterns of Failure following Re-Irradiation for Recurrent/Progressive High-Grade Glioma †

Debanjali Datta [1,2], Archya Dasgupta [1,2], Abhishek Chatterjee [1,2], Arpita Sahu [2,3], Kajari Bhattacharya [2,3], Lilawati Meena [2,4], Kishore Joshi [2,4], Ameya Puranik [2,5], Indraja Dev [2,5], Aliasgar Moiyadi [2,6], Prakash Shetty [2,6], Vikas Singh [2,6], Vijay Patil [2,7], Nandini Menon [2,7], Sridhar Epari [2,8], Ayushi Sahay [2,8] and Tejpal Gupta [1,2,*]

Abstract: Background: Re-irradiation (ReRT) is an effective treatment modality in appropriately selected patients with recurrent/progressive high-grade glioma (HGG). The literature is limited regarding recurrence patterns following ReRT, which was investigated in the current study. Methods: Patients with available radiation (RT) contours, dosimetry, and imaging-based evidence of recurrence were included in the retrospective study. All patients were treated with fractionated focal conformal RT. Recurrence was detected on imaging with magnetic resonance imaging (MRI) and/ or amino-acid positron emission tomography (PET), which was co-registered with the RT planning dataset. Failure patterns were classified as central, marginal, and distant if >80%, 20–80%, or <20% of the recurrence volumes were within 95% isodose lines, respectively. Results: Thirty-seven patients were included in the current analysis. A total of 92% of patients had undergone surgery before ReRT, and 84% received chemotherapy. The median time to recurrence was 9 months. Central, marginal, and distant failures were seen in 27 (73%), 4 (11%), and 6 (16%) patients, respectively. None of the patient-, disease-, or treatment-related factors were significantly different across different recurrence patterns. Conclusion: Failures are seen predominantly within the high-dose region following ReRT in recurrent/ progressive HGG.

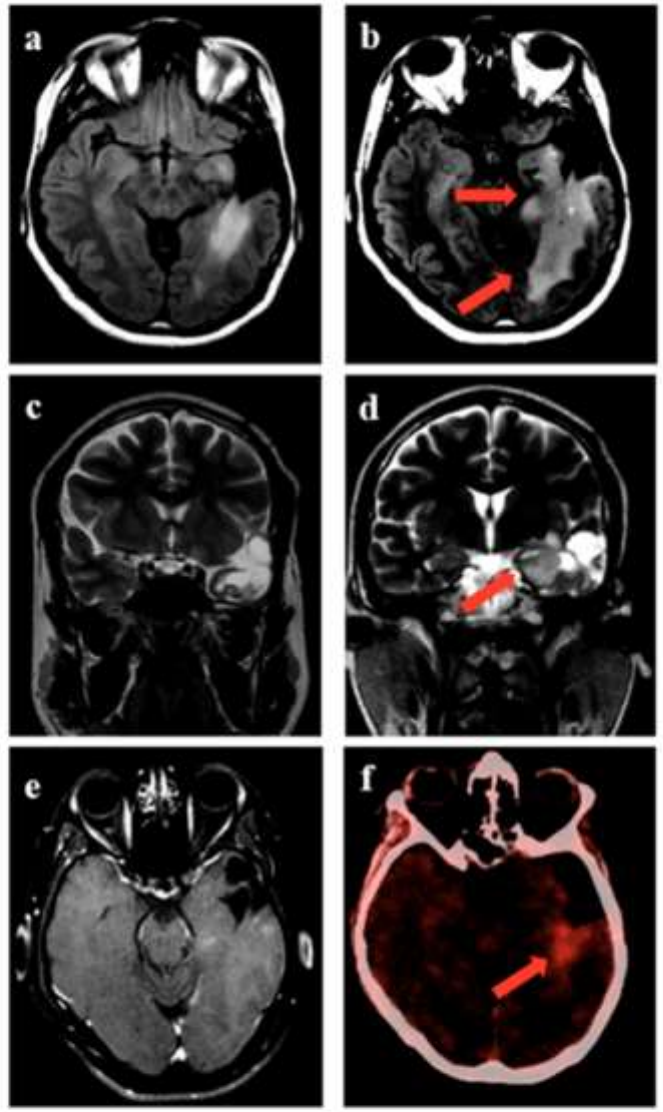


Figure 2. Progression in a 32-year male with IDH-mutant astrocytoma. (**a**) shows residual disease following treatment completion, with (**b**) showing an increase in disease extent (arrow) after 7 years, as appreciated on axial T2-FLAIR sequences when reirradiation was considered. Representative images showing an increase in disease extent over medial extent of the cavity on coronal T2w sequence (**c**,**d**). (**e**) shows T1w-post gadolinium images showing no uptake of contrast in the area of new disease, suggesting absence of transformation to grade 4. (**f**) shows PET avidity over the area of active disease.

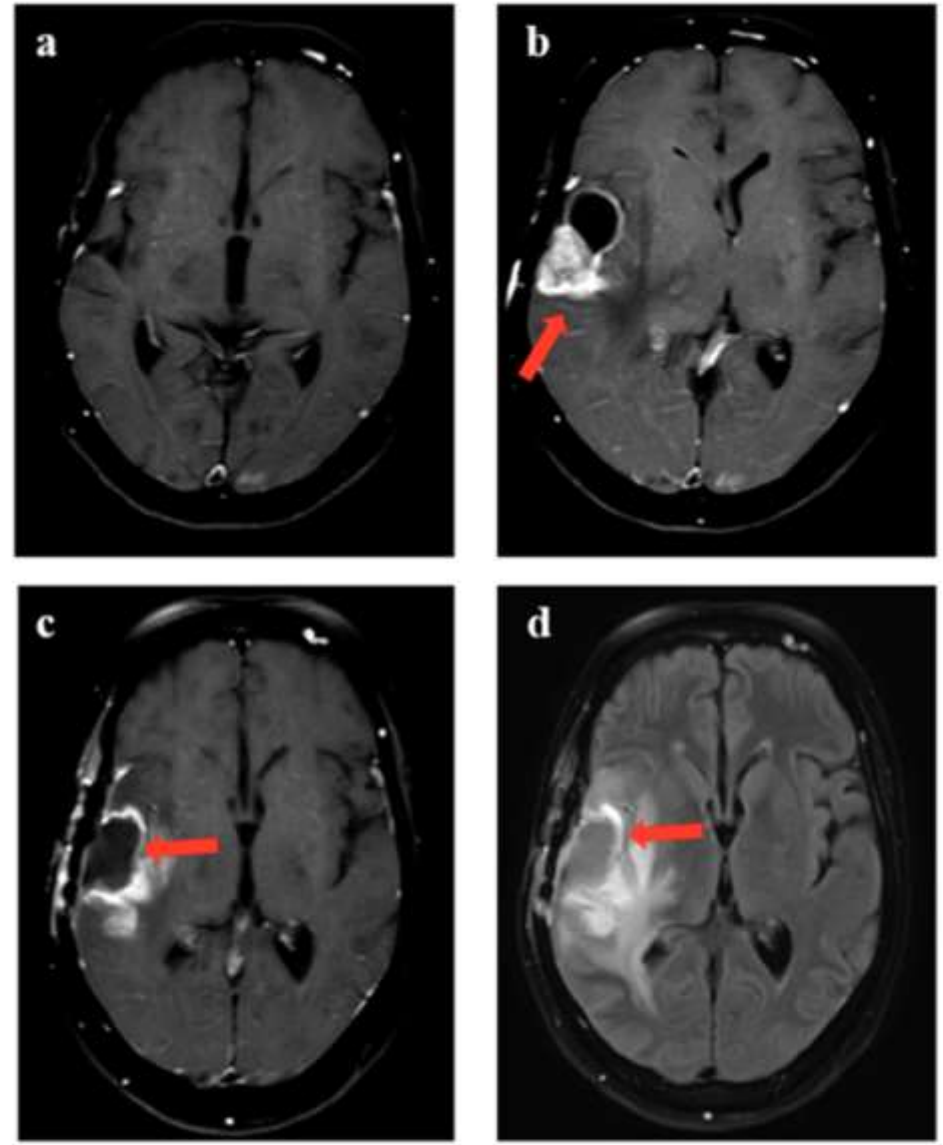


Figure 3. Progression in a 47-year female with glioblastoma with MGMT gene promoter methylation. (**a**) shows T1w axial view following completion of adjuvant chemotherapy (after surgery and radiation), with (**b**) showing local recurrence after 2.5 years with enhancing component and cystic component (arrow). (**c**,**d**) represented the surgical cavity on T1w contrast and T2w FLAIR axial view when the patient was considered for reirradiation.

Don't wanna hear about it
Every single one's got a story to tell
Everyone knows about it
From the Queen of England to the hounds of hell

Journeys don’t have happy endings …..

- 1-High ranked corporate-lost job , divorced , developed OCD
- 2- Father had GBM- expired , now one son has HGG
- 3- Cabin crew – restaurant manager – waiter- unemployed ,marriage proposal cancelled , elderly parents – divesting assets, house sold , father expired now mother is the only caregiver , persistent feelings of worthlessness and suicidal thought

- **All KPS 80-90**
- **All NPS 0-1**
- **All GCS E4V5M6**

Conclusions

- Evolving paradigms
- Cognizance of molecular biology essential
- Multidisciplinary decision making
- Focus on QOL and survivorship

I think it's very healthy to spend time alone.
You need to know how to be alone
and not be defined by another person.

Oscar Wilde

THANK YOU

Dr.Asesh
Dr.Madhan
Dr.Sagar