Stereotactic Radiosurgery and Stereotactic Radiotherapy for Gliomas

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Frontiers of Radiosurgery
Centro Diagnostico Italiano - the Radiosurgery Society
Milan, Italy October 2019

Disclosures

- Stanford University: Employer
- Inovio Pharmaceuticals, Inc.: Consultant
- IJROBP: Senior Editor - CNS

Objectives

- Review the data that support stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (fSRT) for primary and recurrent gliomas

Outline – SRS/fSRT for Gliomas

Stereotactic radiosurgery and stereotactic radiotherapy for:

- Recurrent Gliomas
- Primary Gliomas
  - Newly diagnosed lower grade gliomas
  - Newly diagnosed glioblastoma

Objectives:

- Given the lack of high level evidence for guidance, I will share example cases of how I manage repeat irradiation for recurrent gliomas…

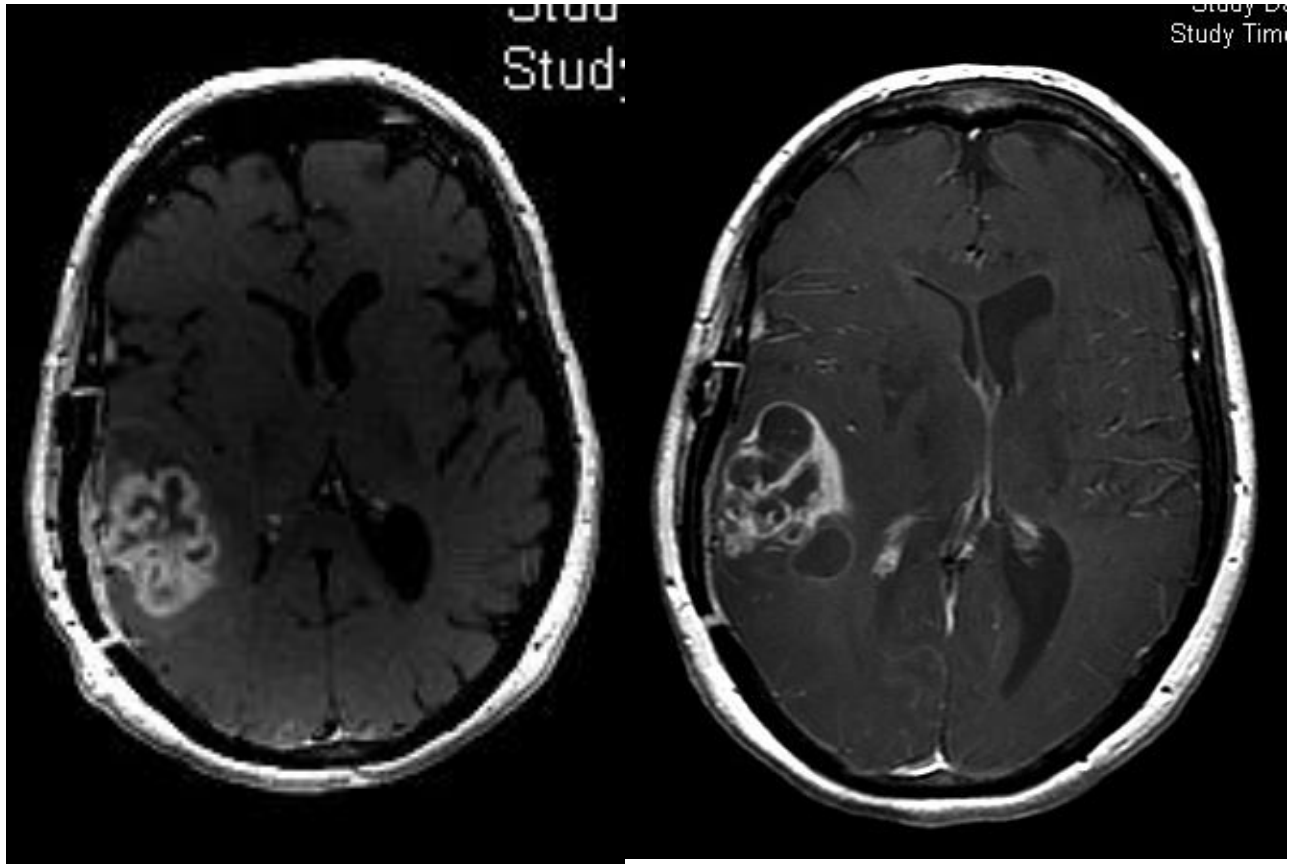
Recurrent GBM: No Standard of Care…

- Clinical Trial
- Repeat surgery
- Chemotherapy
- Bevacizumab
- Tumor Treating Fields (TTF)
- Repeat Irradiation:
  - Conventionally fractionated
  - Hypofractionated
  - Stereotactic radiosurgery
- Supportive Care

Outline: Repeat Radiotherapy for Recurrent Glioma

- Background:
  - Recurrence, Patterns of Progression
- Repeat Radiotherapy
  - Conventionally fractionated radiotherapy
  - Hypofractionated radiotherapy
  - Stereotactic Radiosurgery (SRS)

Recurrence?



Prior to RT/TMZ **1 month**

Post-ChemoRT Pseudoprogression (psPD)

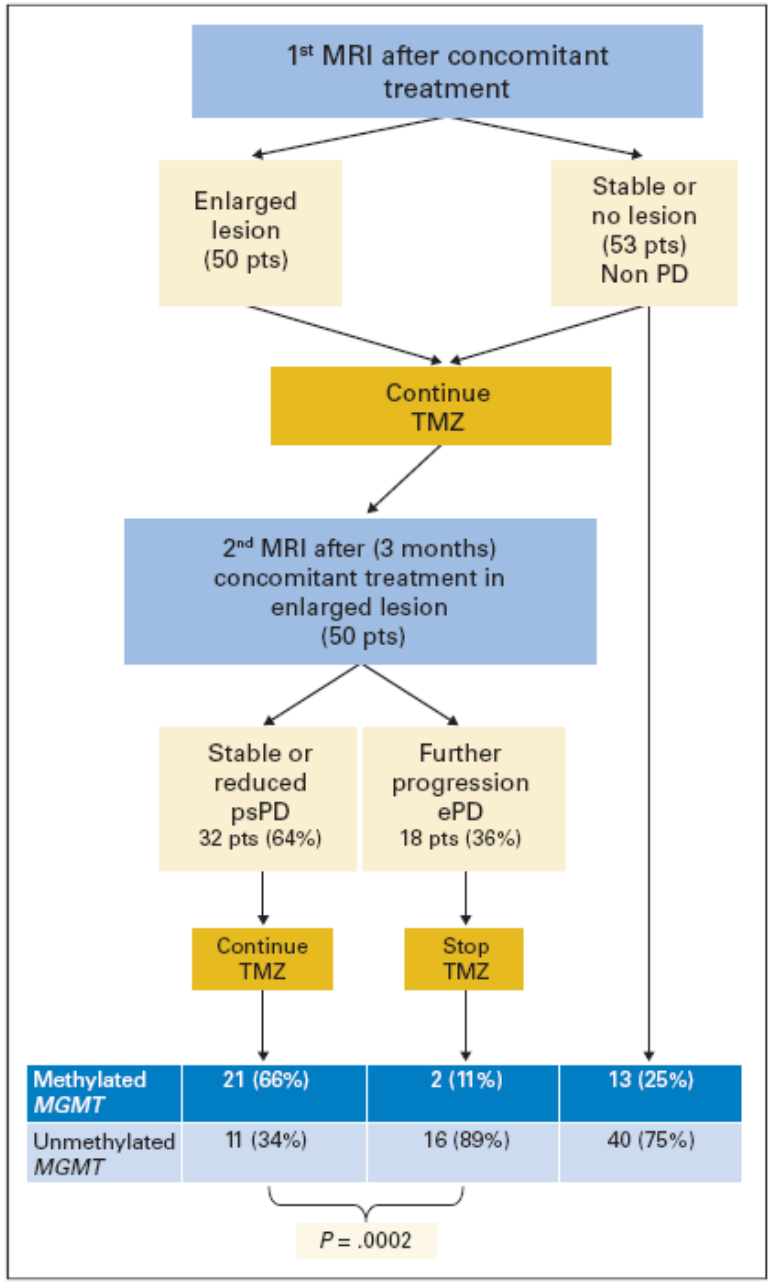


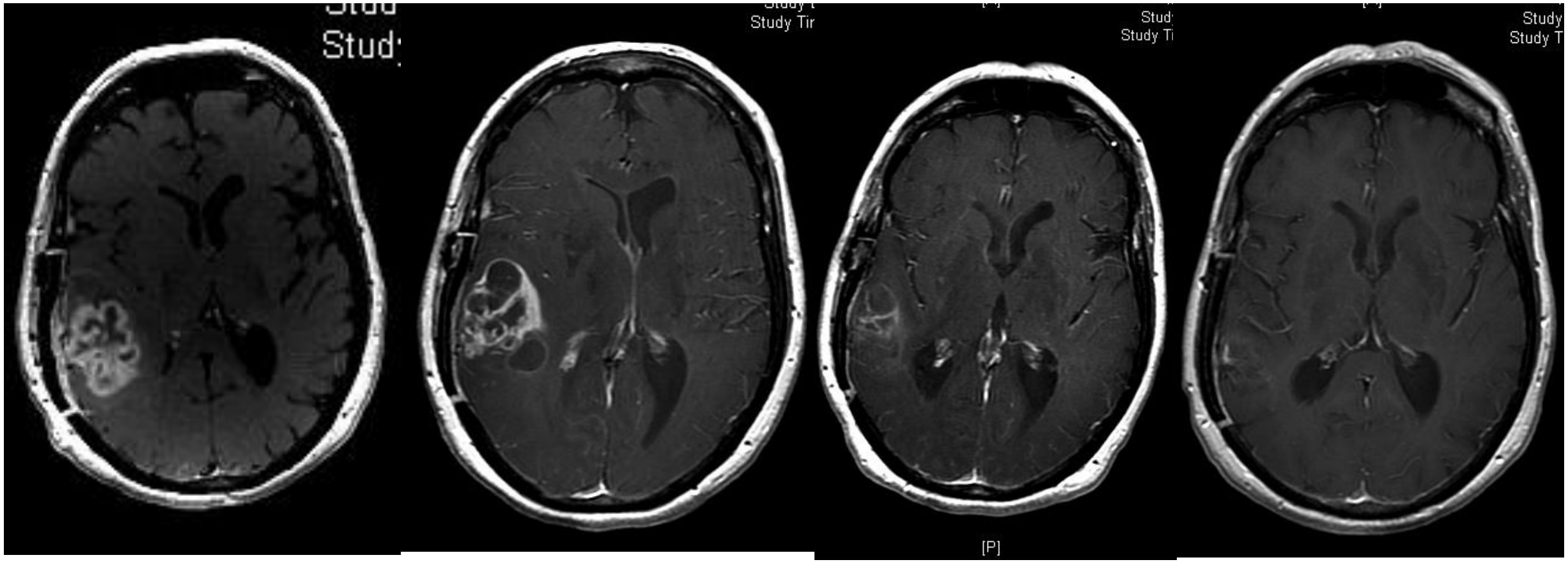
Fig 1. MRI findings, outcomes and MGMT status of patients. MRI, magnetic resonance imaging; PD, disease progression; TMZ, temozolomide; psPD, pseudoprogression; ePD, early disease progression; *MGMT*, O^6-methylguanine–DNA methyltransferase.

At the MRI at 1 month after chemoRT:

- If tumor was larger: 64% were psPD
- If psPD: 66% had methylated MGMT
- If early progression: 90% unmethylated MGMT

Brandes JCO 26, 2008

Pseudoprogression



Prior to RT/TMZ **1 month** **3 months** **5 months**

Response Assessment in Neuro-Oncology (RANO)

- Can call progression <3 months after chemoradiotherapy ONLY if:
  - New enhancement beyond 80% isodose line
  - Unequivocal pathologic evidence of viable tumor

Table 2. Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

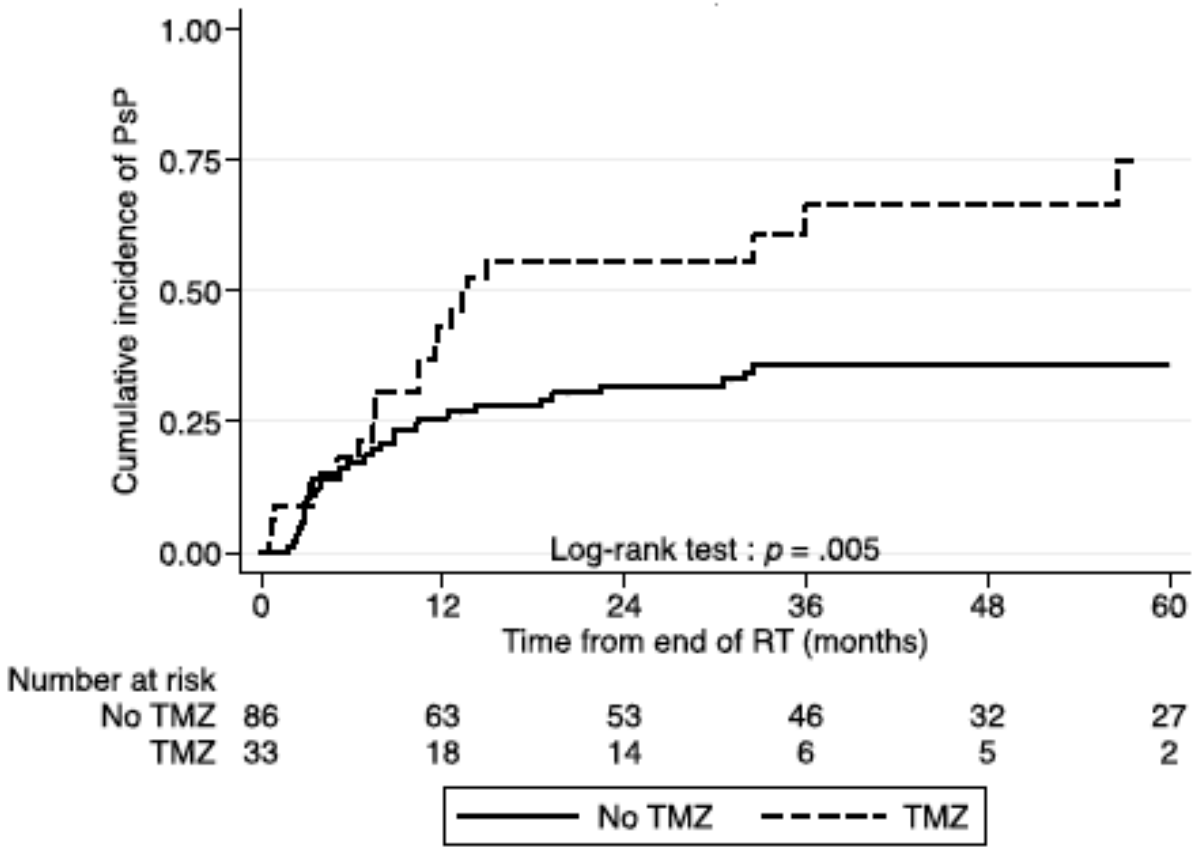
Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Wen JCO 28, 2010

Pseudoprogression in Lower Grade Glioma

- n=199
- IDH mt or grade 2

- Pseudoprogression in 44%
- Higher risk with RT + TMZ than RT alone (HR 2.2)
- Better OS in those with pseudoprogression



Dworkin, Shih JNeuroOnc 142, 2019

Outline: Repeat Radiotherapy for Recurrent Glioma

- Background:
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- Repeat Radiotherapy
  - Conventionally fractionated radiotherapy
  - Hypofractionated radiotherapy
  - Stereotactic Radiosurgery (SRS)

Repeat RT Example: 60 Gy in 30 fractions

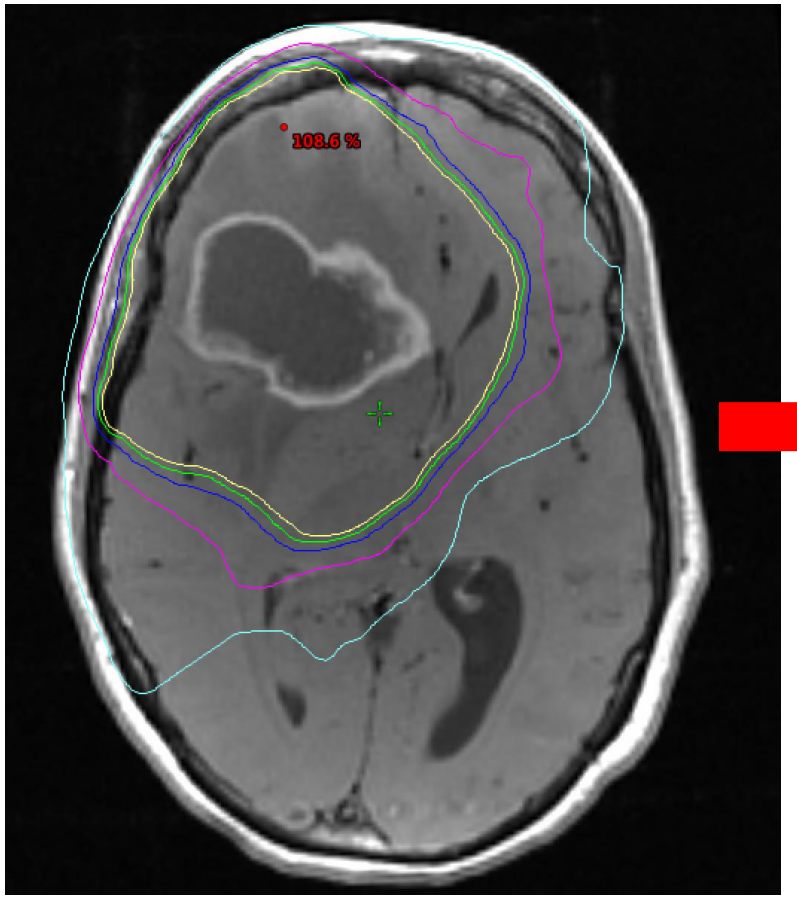
51 yo woman with GBM:
60 Gy in 30 + TMZ

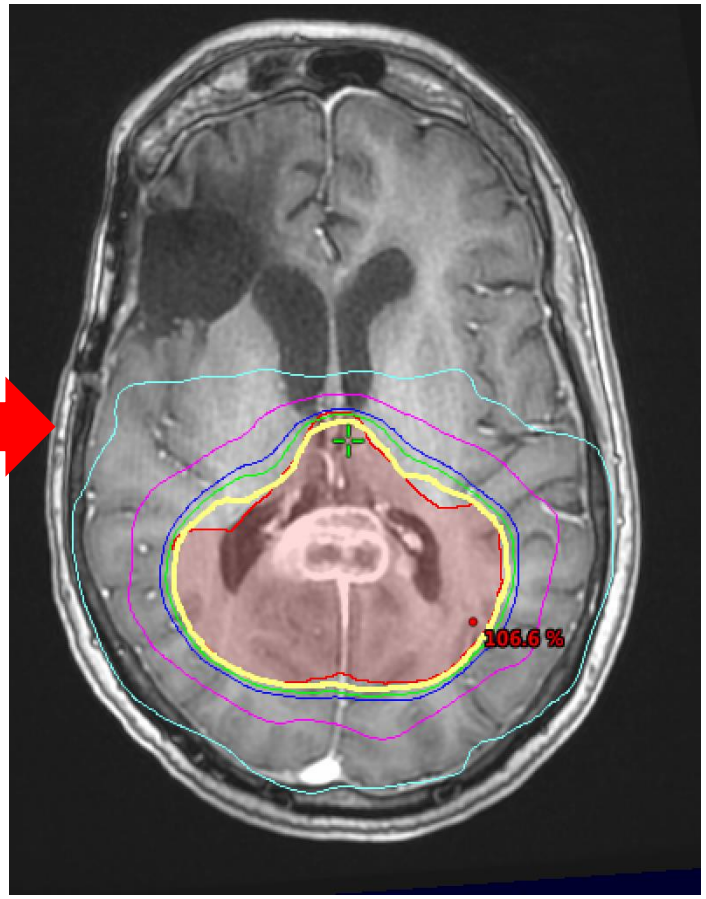
↓

Recurred 8 years later
(MGMT hypermethylated)
Mainly out of prior RT field

↓

Repeat 60 Gy in 30 + TMZ





Initial Diagnosis:
60 Gy in 30
(note: pre-resection MRI shown)

8 years later:
60 Gy in 30

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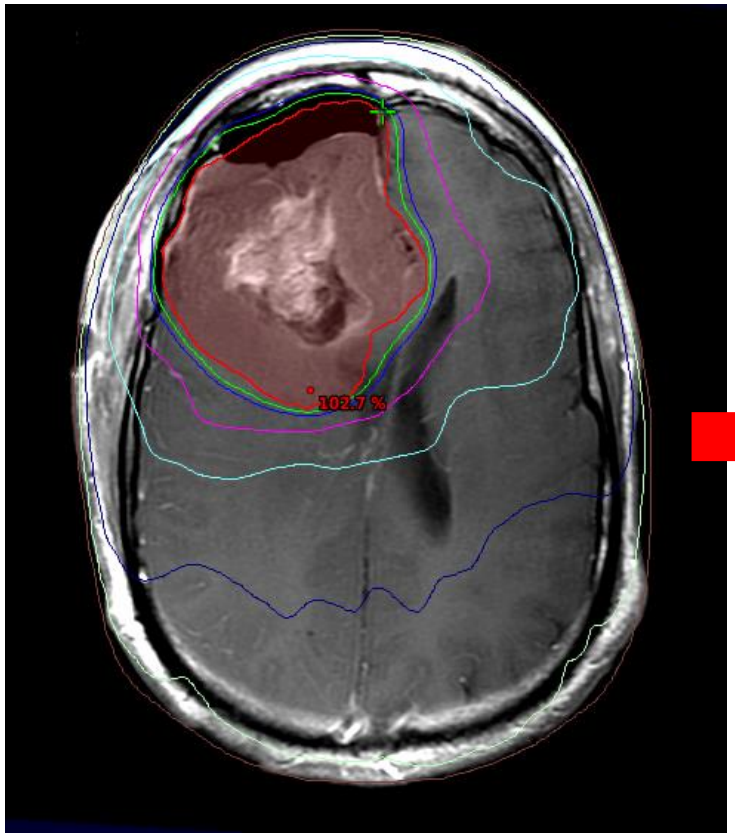
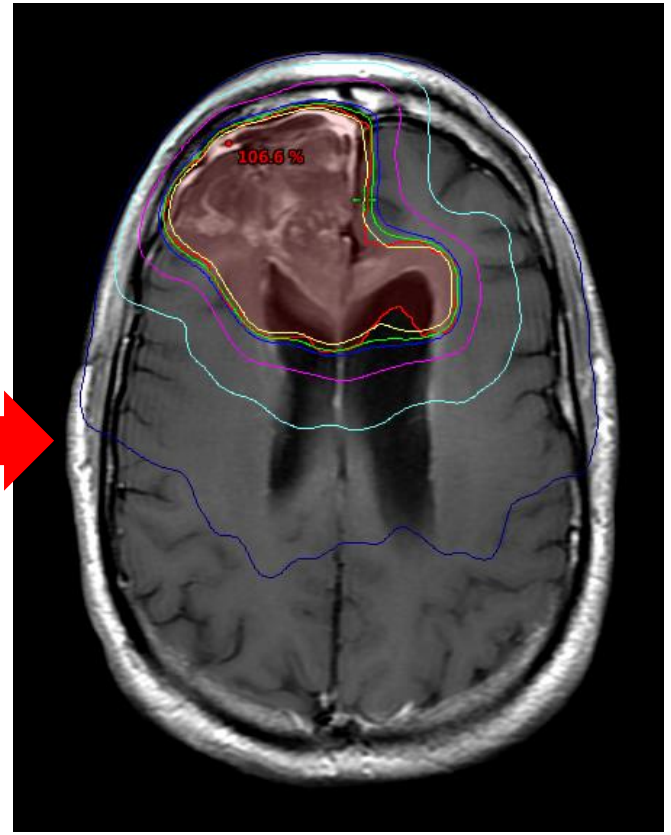
Repeat RT Example: 35 Gy in 10 fractions

50 yo man with GBM:
60 Gy in 30 + TMZ
↓
Recurred in 5 months
(MGMT not hypermethylated)
↓
Resection #2
↓
Clinical Trial
↓
Still localized, so repeated RT



Initial Diagnosis:
60 Gy in 30



1 year later:
35 Gy in 10

GBM Re-Irradiation: Hypofractionated RT

- n=147
- Median 35 Gy in 10 fractions to T1 post-contrast GTV
- Median OS – 11 m

No RT Necrosis

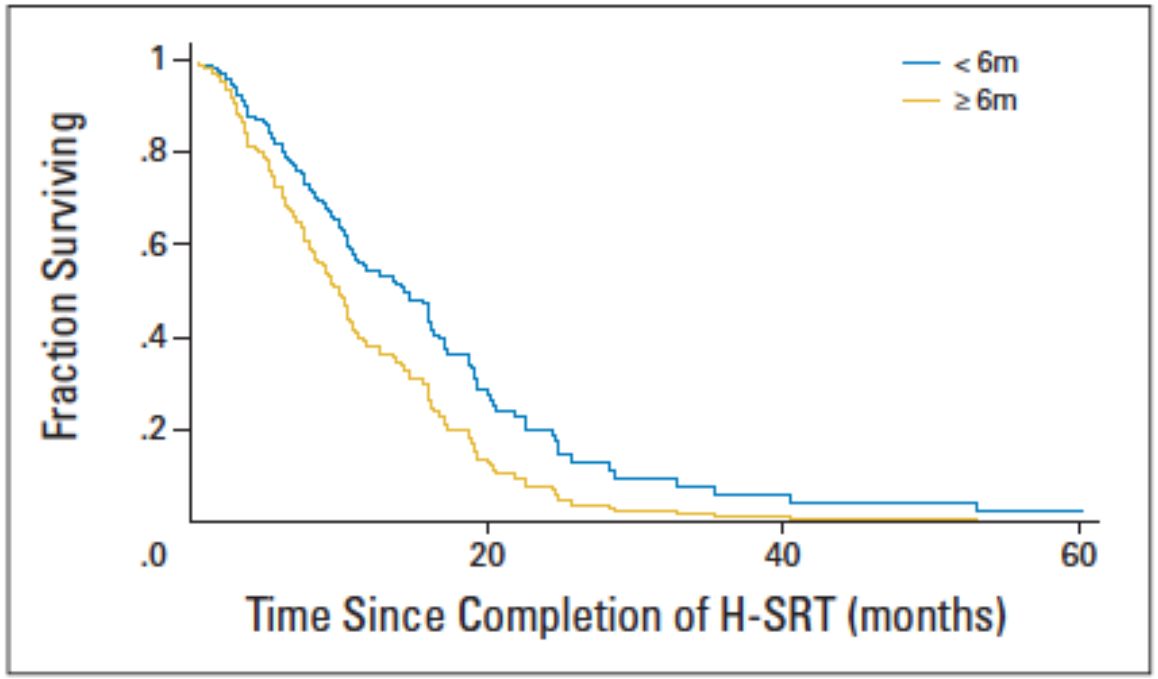


Fig 1. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who experienced recurrence less than 6 months *v* ≥ 6 months from initial treatment.

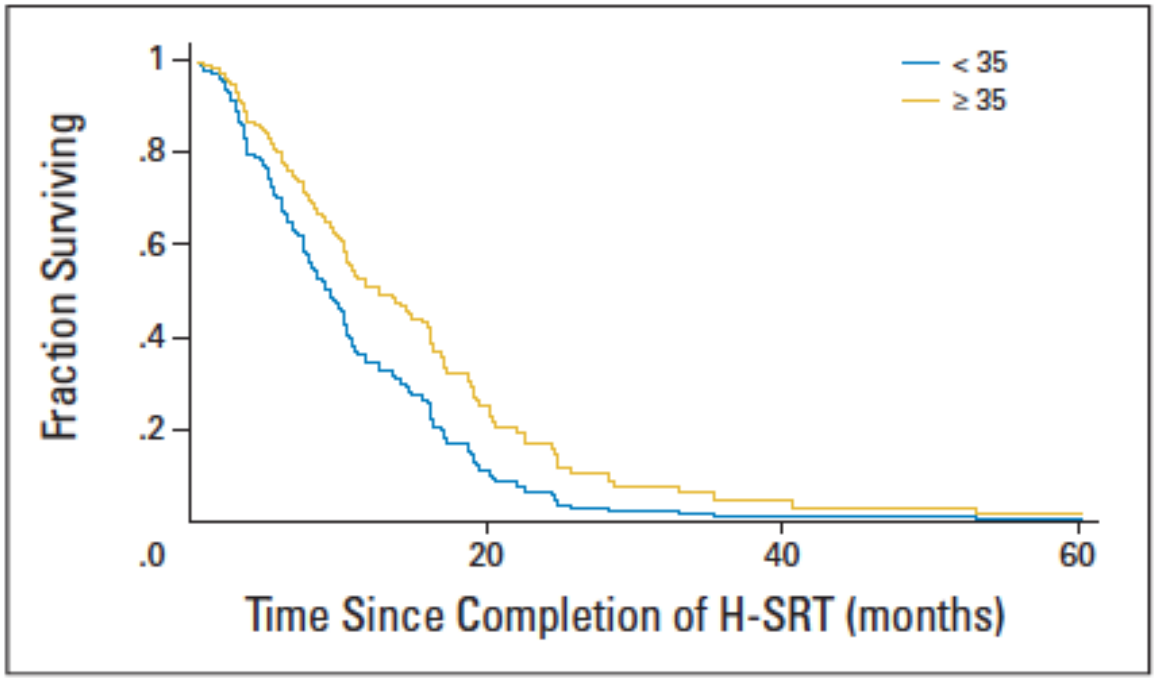


Fig 2. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who received ≥ 35 Gy *v* < 35 Gy.

Fogh JCO 28, 2010

RTOG 1205: BEV +/- 35 Gy in 10 for Recurrent GBM

- n=182 with recurrent GBM

	Median OS
• Bevacizumab alone	9.7 months
• Bevacizumab + 35 Gy in 10	10.1 months
	p=0.5

Conclusion:

- In all patients enrolled, no benefit to re-irradiation
- Await patterns of progression data

PI: Christina Tsien – ASTRO 2019

Outline: Repeat Radiotherapy for Recurrent Glioma

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  - Hypofractionated radiotherapy
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Repeat RT Example: SRS

44 yo man grade III astro

59.4 Gy + TMZ

↓

3 years later:

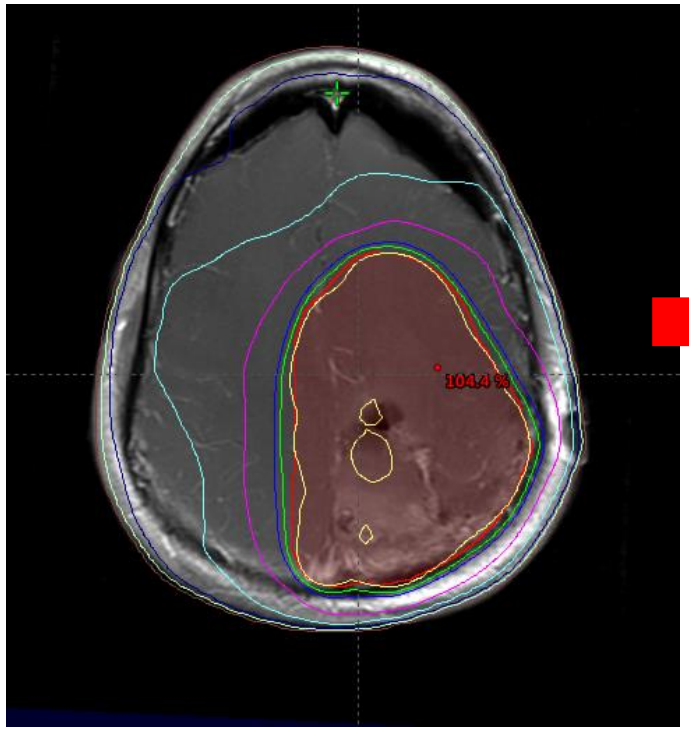
1 cm recurrence

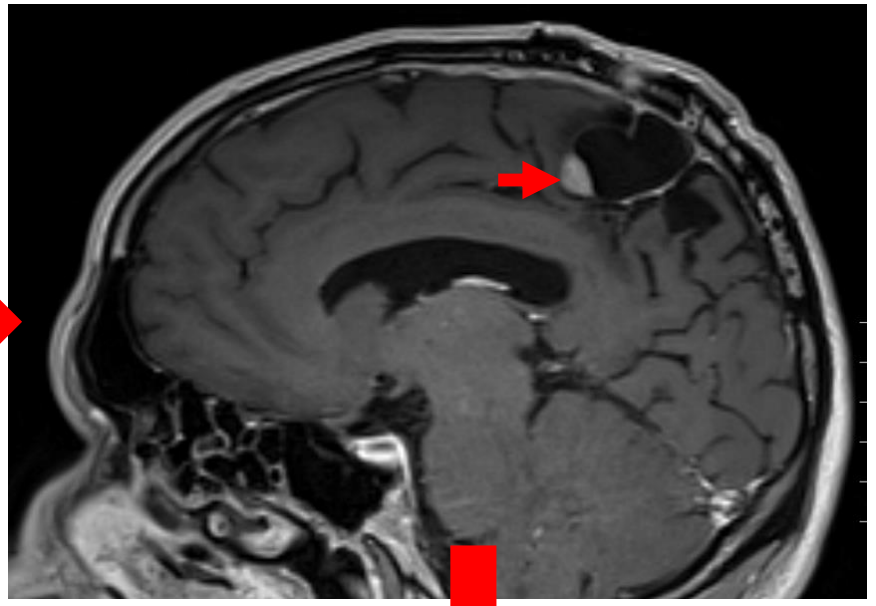
↓

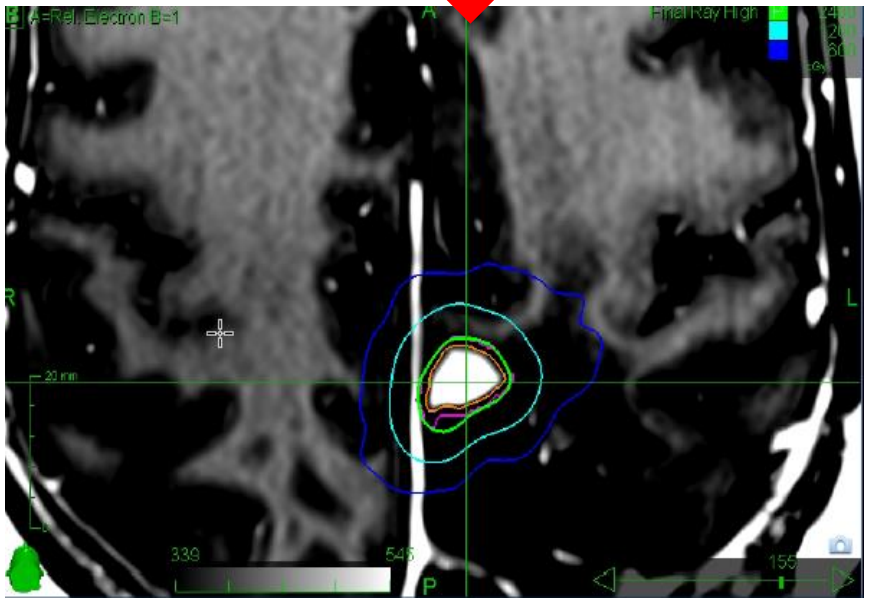
Offered Surgery vs. SRS*

↓

Stable 1.4 years later







*Generally, I only offer SRS as an option if surgery is an option. Otherwise I do hypofractionation over 1-2 weeks.

SRS for Recurrent GBM

- No randomized data (phase III or phase II)
- Most all data are retrospective case series
  - Many reviews exist…

SRS/HFRT for Recurrent GBM

Author	Year	Type of Study	Number of patients	HFRT or SRS	Re-RT Dose	Median OS from SRS (months)	Adverse Radiation Effect (ARE)
Laing [42]	1993	phase 1/2	22	HFRT	5 Gy x 4-10	9.8	23%
Shepherd [41]	1997	retrospective	33	HFRT	5 Gy x 4-10	10.7	36%
Hudes [45]	1999	phase 1	20	HFRT	3 – 3.5 x 7-10	10.5	0%
Schwer [54]	2008	phase 1	15	HFRT	6-12 Gy x 3	10	13%
Park [17]	2012	case-control	11	SRS	16 Gy x 1	18	9% with BEV vs 43%
Cuneo [43]	2012	retrospective	63	SRS	15 Gy x 1 25 Gy in 5	11.2 with BEV, 3.9 no BEV	19% no BEV, 5% with BEV
Koga [18]	2012	retrospective	18	SRS	20 Gy x 1	9-10.5	22% for C-SRS, 44% for EF-SRS

Shah, Soltys NSurg 2017
Redmond, Cureus Dec 2015

Brainstem Toxicity: Repeat Irradiation with SRS

- n=38 Pediatric recurrent Ependymoma
- Median time between RT courses: 16 months
  - n=32 Conventionally fractionated re-irradiation:
    - Median combined dose 111.6 Gy (typically 55.8Gy + 55.8Gy again)
  - n=6 had SRS → <u>'significant brainstem toxicity and one death'</u>

Merchant IJROBP 71, 2008
Updated: Tseng IJROBP 100, 2018

Without randomized data to guide us, multiple reasonable re-irradiation strategies exist...

Re-irradiation for GBM: Systematic Review

- n=29 re-irradiation studies
- Re-irradiation Proposal:

Table 6

Strategy proposed in the present analysis (to be confirmed in prospective further studies): patients should be stratified according to different disease volume and then, treated with differentiated total dose and fractionation. RS: radiosurgery; HFSRT: hypofractionated stereotactic radiotherapy; CFRT: conventionally fractionated radiotherapy.

Tumor Volume	Technique	EQD2	Example of total dose and number of fractions
≤ 12.5 ml	RS	< 65 Gy	12-15 Gy in a single fraction
> 12.5 ml and < 35 ml	HFSRT	< 50 Gy	25 Gy in 5 fractions
> 35 ml up to 50 ml	CFRT	36 Gy	36 Gy in 20 fractions

Scoccianti Crit Review Onc 126, 2018

Re-irradiation for GBM: Critical Review

- Re-irradiation Proposal:

Table II. *Examples of re-irradiation techniques and regimens for patients with recurrent supratentorial gliomas.*

Low-volume recurrence*	Consider SRS, brachytherapy or FSRT, *e.g.* 35 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, *e.g.* by reducing fraction size (35 Gy in 10 fractions)
Intermediate volume recurrence**	Consider FSRT, *e.g.* 30 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, *e.g.* by reducing fraction size (30 Gy in 10 fractions)
Large-volume recurrence	Consider FSRT, *e.g.* 25 Gy in 5 fractions	Proximity to critical structures might require reduced EQD2, *e.g.* by reducing fraction size (36 Gy in 18 fractions)

Nieder Anticancer Research 36, 2016

Conclusion: My Approach to Repeat RT for Glioma

- No high level data to guide dose/fractionation
- Conventional Fractionation: 54-60 Gy in 30
  - Lower Grade Glioma with long time to progression
  - GBM if out of prior RT field (and therefore long time to progression)
- Hypofractionation: 25-30 Gy in 5, 35 Gy in 10
  - Lower Grade Glioma if early recurrence or transformation to GBM
  - GBM if within prior RT field
- SRS: 16-22 Gy x 1
  - As a replacement for surgical resection

Conclusion: Prospective Data are Needed..

Ongoing clinical trials:

- NCT02709226: NCI – Dose escalation: 3.5 Gy x 10, x12, x 14
- NCT01925573: U Maryland – BEV + 35 Gy in 10 or 30 in 5 + TTF
- NCT01252459: U Freiburg – 39 Gy in 13 + PET
- NCT01464177: Brazil – 25 Gy in 5 vs. 35 Gy in 5
- NCT01666600: NOA-12 – 36 Gy in 18 + BIBF 1120
- NCT02149459: Sheba – 30-35 Gy in 10 + SMC 0712-13

Outline – SRS/fSRT for Gliomas

Stereotactic radiosurgery and stereotactic radiotherapy for:

- Recurrent Gliomas
- Primary Gliomas
  - Newly diagnosed lower grade gliomas
  - Newly diagnosed glioblastoma

SRS for Pilocytic Astrocytomas

- SRS (maybe) makes sense:
  - Grade I
  - Usually well demarcated
- But, concerns with toxicity → IMRT is standard
- Overall, little data:

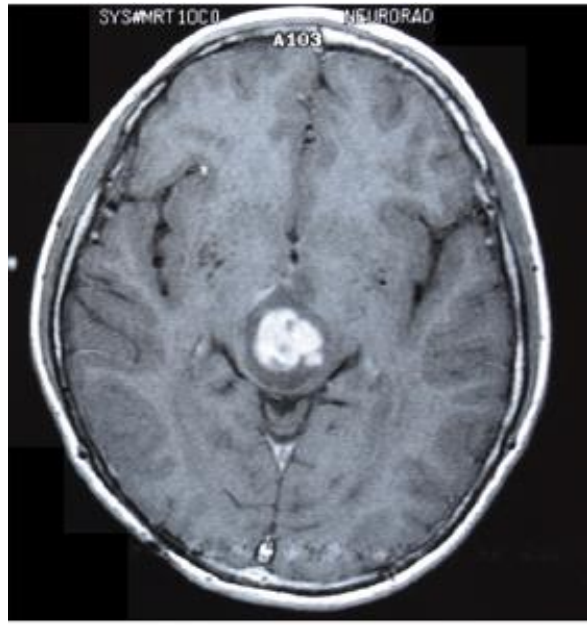


Table 1 Articles reporting results following GKS of JPA

Author	*N*	Dose	Mean follow-up	Tumor control (%)	Cyst progression (%)	Complications (%)
Boethius (1)	17	10–20 Gy	6 years	100	12	30
Hafez (6)	1	12 Gy	3 years	100	0	0
Kano (7)	50	11–22 Gy	4.5 years	96	20	10
Kida (10)	12	Mean 12 Gy	2 years	92	8	17
Trifiletti (23)	28	Median 16 Gy	Median 5.2 years	93	7	0

Liu Child's Nervous System 35, 2019

SRS for Newly Diagnosed GBM

- If ~80% of GBMs recur within the 60 Gy radiotherapy field, why not give more dose with SRS?

RTOG 9305: ChemoRT +/- SRS Boost

- n=203 GBM (<40cc)

- 60 Gy + BCNU
- Upfront SRS → 60 Gy + BCNU
  - SRS dosing per RTOG 9005
    - 0-2cm 24Gy, 2-3cm 18Gy, 3-4cm 15Gy

Souhami IJROBP 60, 2004

RTOG 9305: CRT +/- SRS Boost

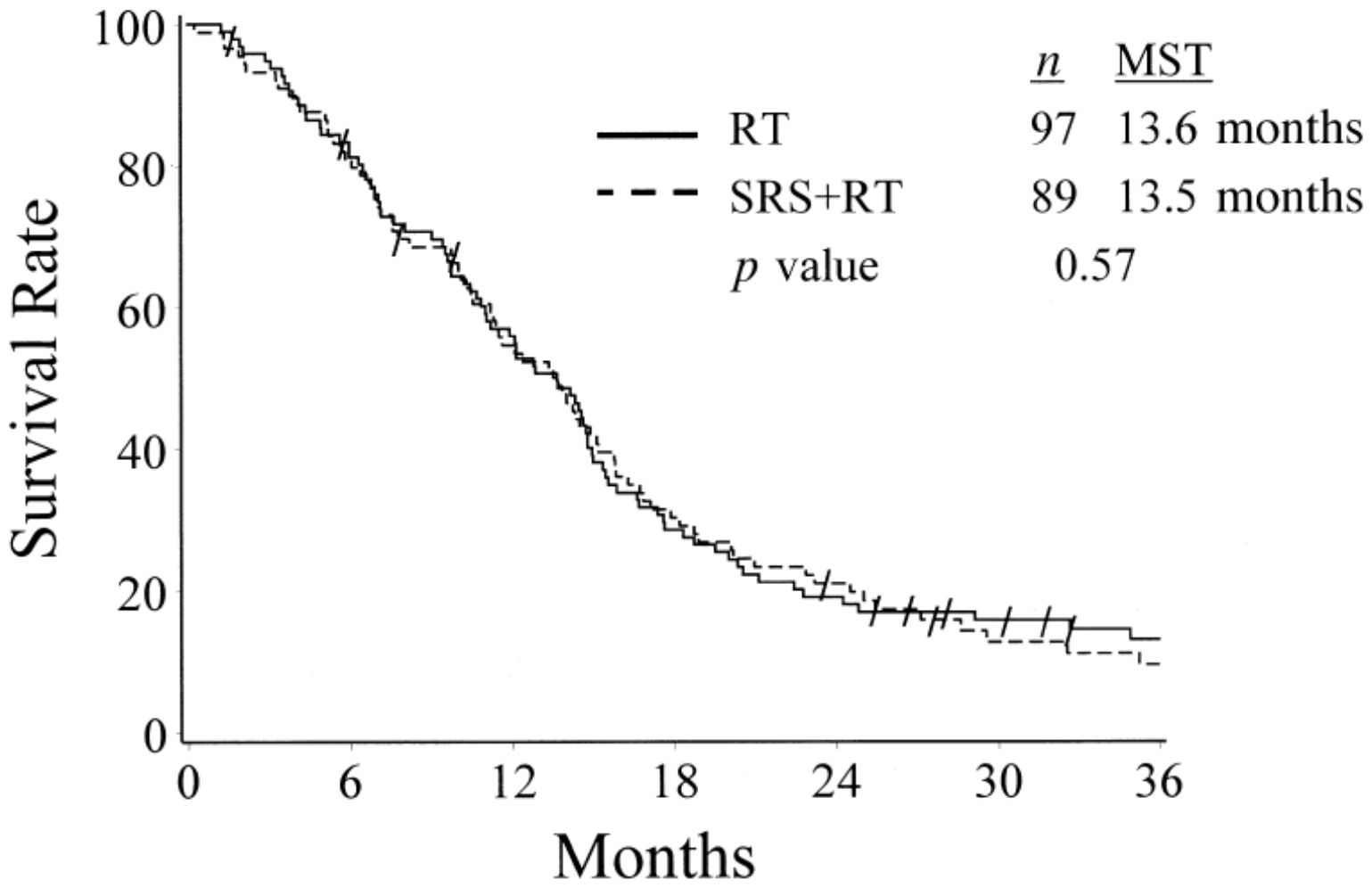


Fig. 1. Survival by treatment arm. RT = radiation therapy; SRS = stereotactic radiosurgery; MST = median survival time.

Results:

- No difference in OS
- No difference in patterns of progression

Conclusion:

No role of SRS boost in newly diagnosed GBM

Souhami IJROBP 60, 2004

Dose escalation with SRS boost added to 6 weeks of radiotherapy was a negative trial

What about other trials of dose escalation through hypofractionation in 1 to 2 weeks?

GBM Hypofractionation + TMZ: Phase I

- n=16 Phase I Tumor <6cm
- With TMZ
- Dose escalation trial of:
  - 60 Gy in 20 fractions
  - 60 Gy in 15 fractions
  - 60 Gy in 12 fractions
  - 60 Gy in 10 fractions

Table 2. Hypofractionated intensity-modulated radiotherapy regimens

		PTV1		PTV2	
Level	Fractions (*n*)	Total dose (Gy)	Fraction size (Gy)	Total dose (Gy)	Fraction size (Gy)
1	20	60	3	45	2.25
2	15	60	4	40.5	2.7
3	12	60	5	36	3
4	10	60	6	30	3

Abbreviation: PTV = planning target volume.

- No Dose limiting toxicity → 60 Gy in 10 is safe
  - Confirmed in another phase II trial of 24 patients

Chen IJROBP 81, 2011
Reddy, Chen IJROBP 84, 2012

Phase II: 60 Gy in 10 + TMZ + BEV

- n=30 phase II
- 60 Gy in 10 fractions with TMZ + Bevacizumab
- Median OS: 16.3 months
- 50% with symptomatic radiation necrosis → Trial stopped

- Conclusion: Large tumor volumes (rather than BEV) likely led to necrosis at doses of 60 Gy in 2 weeks
  - Abandoned further trials at this high dose

Ney, Chen JNOnc 2015

SRS for Newly Diagnosed GBM

- Problems with 60 Gy in 2 weeks:
  - Perhaps dose too high for volumes of that size (up to 6 cm)
  - 2 weeks of treatment is still too long for some patients

- What about 1 week (5 days) of SRS for GBM → Stanford Trial

Shortened Treatment for Glioblastoma

- Rationale for Hypofractionated RT (shorter than 6 weeks):
  - 6 weeks of radiotherapy may be 5-10% of remaining life
  - Shorter course → better access to specialized care
  - Less cost than 6 weeks
  - Possibly a different radiobiology (combine with immunotherapy)

Stanford 5-Fraction Trial Design

- Standard 3 + 3 Dose Escalation Schema
- 2 Arms Based on PTV Size
- PTV = GTV + 5 mm margin (Stupp was 20 mm margin)
- Standard Concurrent TMZ (8 days) → Adjuvant TMZ

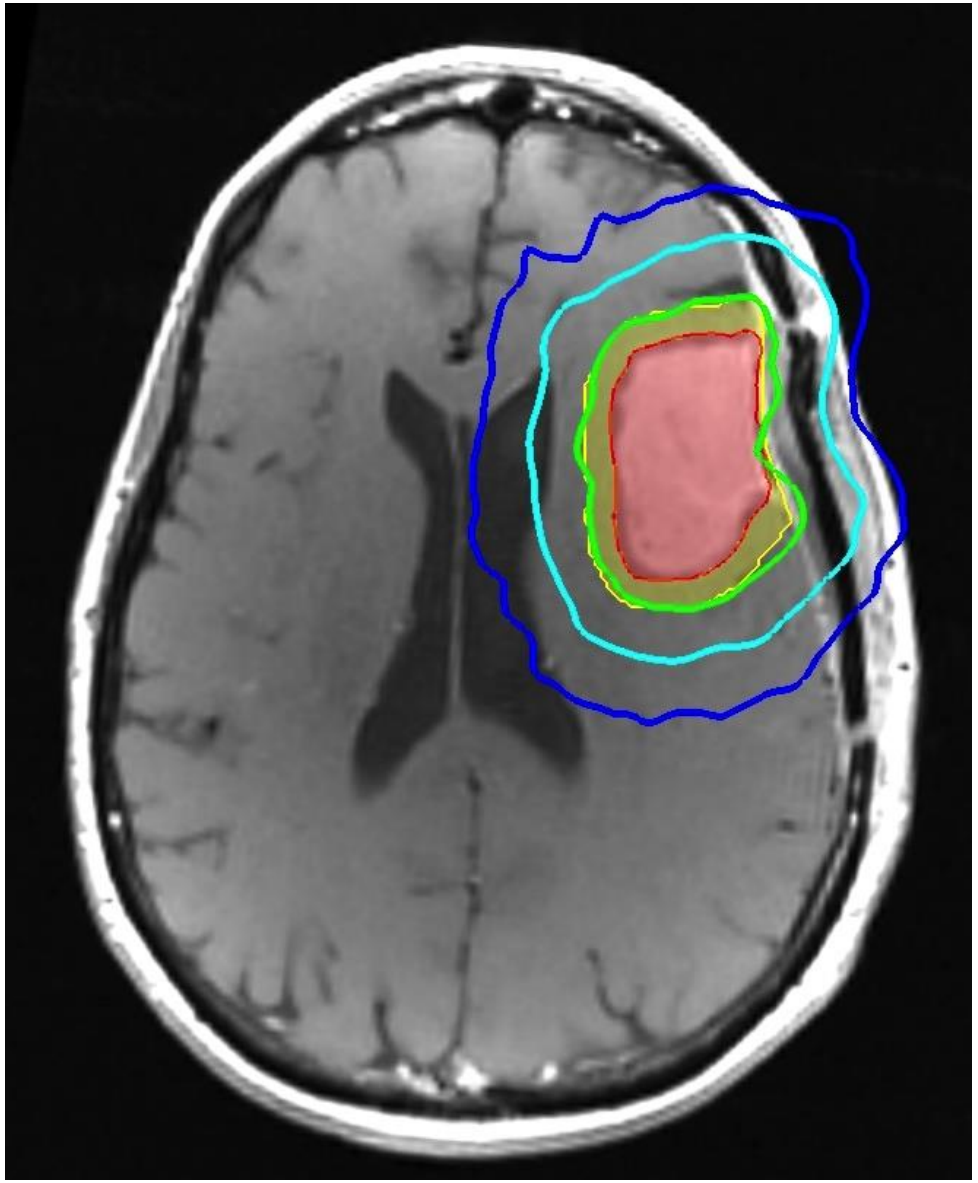
	PTV Size	Diameter	Dose Levels
Arm 1:	<60 cm^3	~5 cm	25 → 30 → 35 → 40 Gy
Arm 2:	60-150 cm^3	~6.6 cm	25 → 30 → 35 → 40 Gy

Azoulay, Soltys – under review Oct 2019

SRS Treatment

- GTV = Cavity/Residual Tumor
- CTV = 5 mm margin
  - shaved at anatomic boundaries
- PTV = 0 mm

- Non-enhancing tumor included, but no intent to cover edema



Results: Acute and Late SRS-Related Toxicity

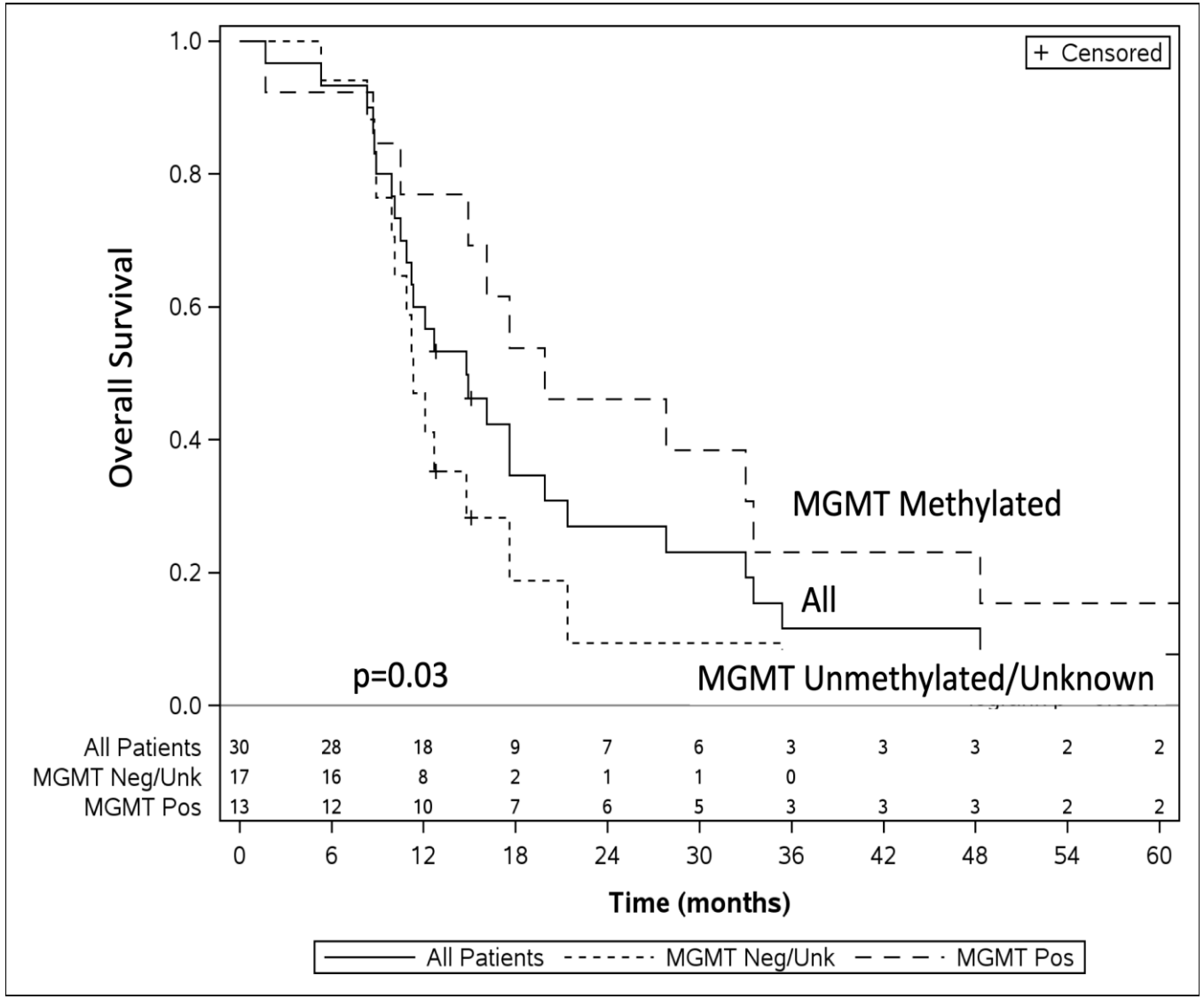
	Toxicity and Grade (number)			
Treatment Arm:	**Dose 25 Gy**	**Dose 30 Gy**	**Dose 35 Gy**	**Dose 40 Gy**
Number per Arm	**n = 6**	**n = 6**	**n = 6**	**n = 12**
Grade 3-5 SRS Related Toxicity	**0%**	**0%**	**0%**	**17%**
Grade 1-5 SRS Related Toxicity	**17%**	**17%**	**67%**	**33%**

Conclusion:

- Per protocol maximum tolerated dose is 40 Gy in 5 fractions

Azoulay, Soltys – under review Oct 2019

Results: Overall Survival

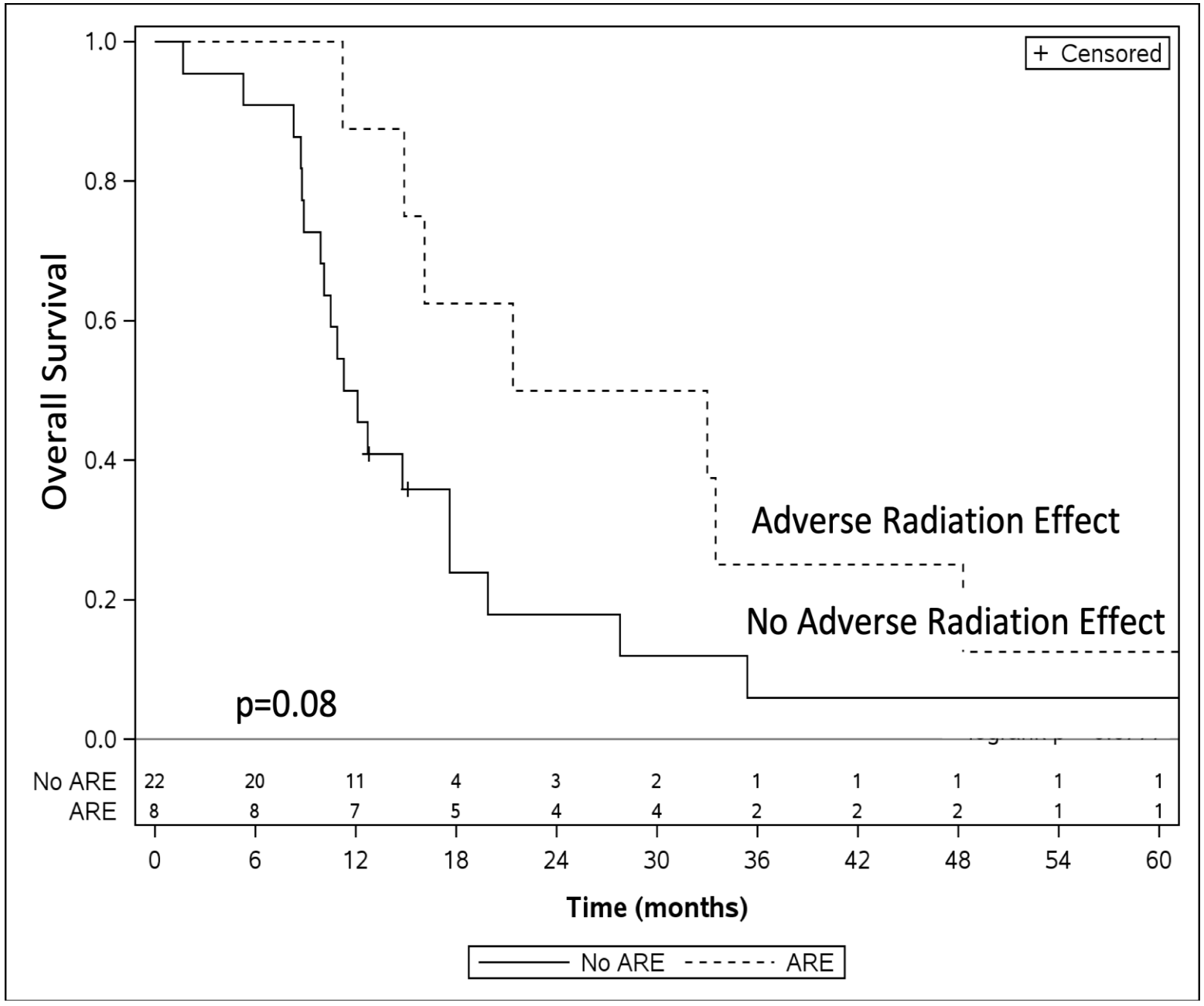


Median OS:

- All 14.8 months
- MGMT:
  - Methylated 19.9 months
  - Unmethylated 11.3 months

p=0.03

Results: Survival Improved in Those with Necrosis



Median OS:

- Necrosis 27.2 months
- None 11.7 months

p=0.08

Time to Necrosis:

Median 8 months (3-12)

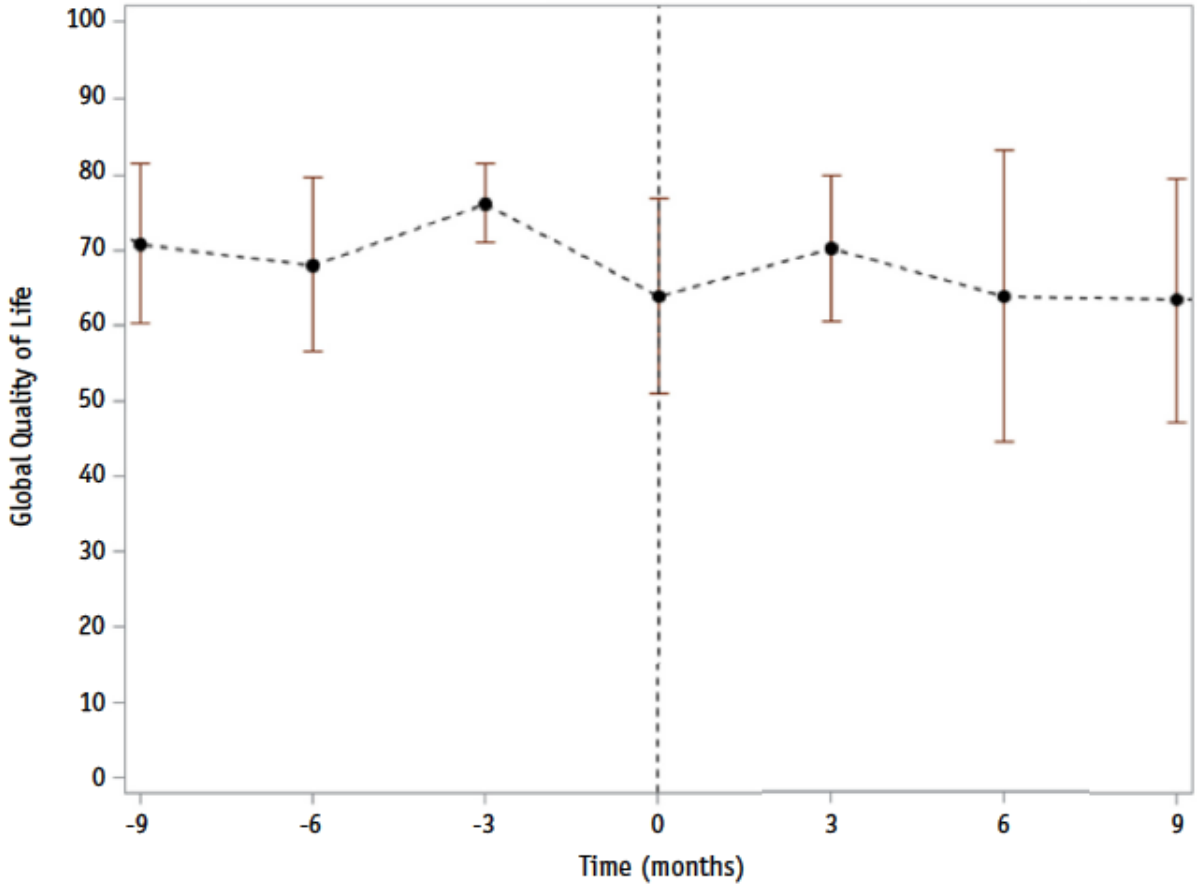
Results: Adverse Radiation Effect Did NOT impact HRQOL

139 total questionnaires: EORTC QLQ-30, BN20, MDASI-BT

Time 0 = date of ARE

Conclusion:

- Tumor progression leads to communication deficit
- Radiation Necrosis did not impact any scale



Pollom IJROBP 98, 2017

Conclusions: 5-Fraction SRS with 5mm Margin with TMZ

- The per-protocol Maximum Tolerated Dose is 40 Gy in 5 fractions
- Although 27% got G1-2 Adverse Radiation Effect
  - ARE did not impact Quality of Life
  - Patients with ARE had improved OS (27 vs. 12 months)
- Asymptomatic ARE, especially in the era of bevacizumab, may be clinically desirable, rather than considered a dose limiting ‘toxicity’

Future Directions in Treatment of GBM: SRS/Hypofractionation and Immunotherapy

Hypofractionation may be:

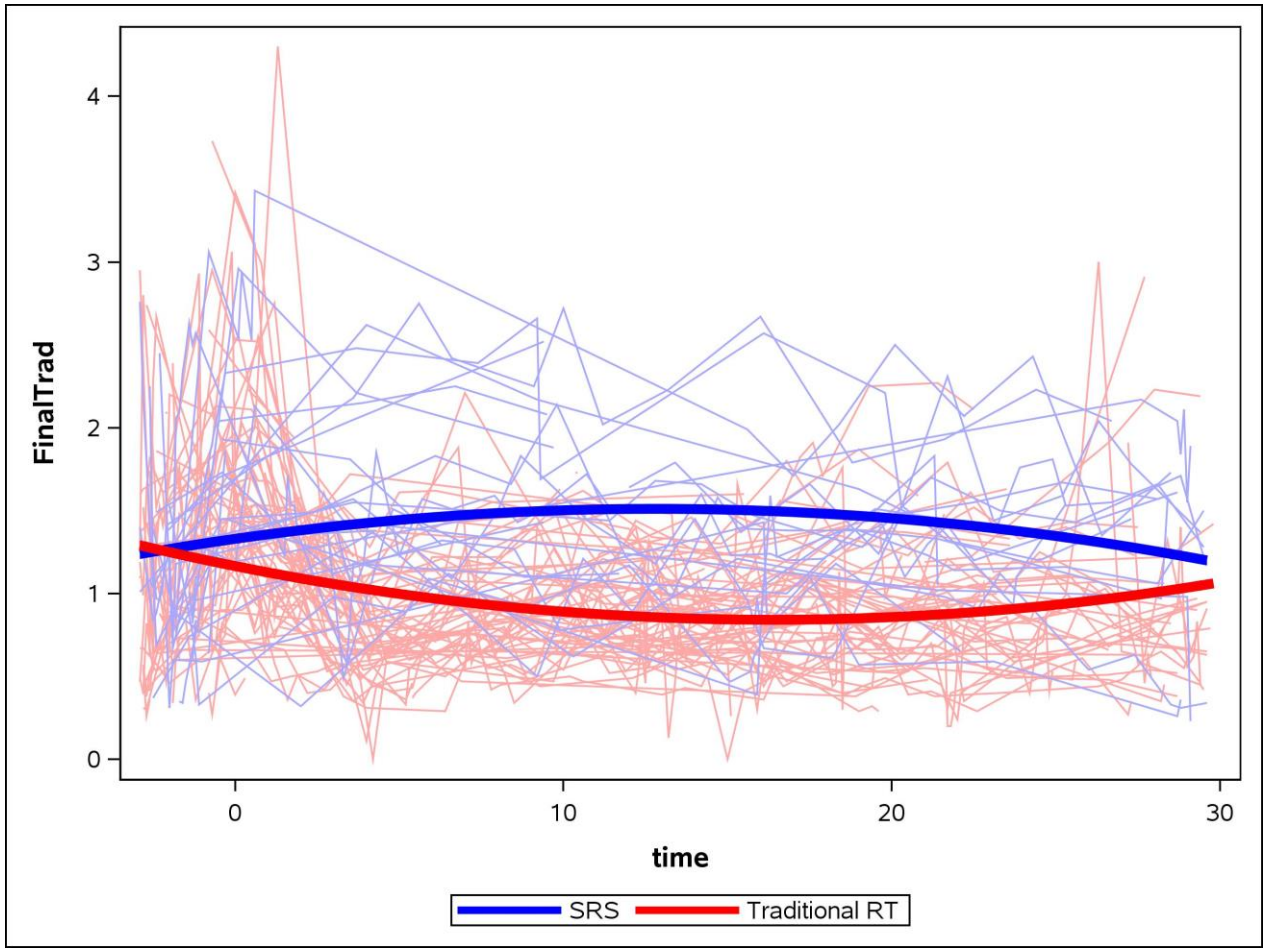
- More immunostimulatory (larger dose per day)
  - Perhaps better to combine with immunotherapy (NCT02383212)

- Less immunosuppressive (less normal brain irradiated)
  - Lymphopenia is independently associated with worse OS[1]
  - 6 weeks of cranial IMRT → irradiates the entire circulating lymphocyte pool, akin to TBI (total body irradiation)[2]

1. Grossman ClinCanRes 17, 2011
2. Yovino Cancer Inv 31, 2013

Lymphopenia: 1 week vs. 6 weeks ChemoRT

- Analyzed 1 week SRS (n=30) vs. 6 weeks IMRT (n=79)
- Treatment-related lymphopenia much higher with 6 weeks of treatment ($p<0.0001$)
- Grade 2-4 lymphopenia:
  - 9% (1 week) vs 56% (6 weeks) at 90 days

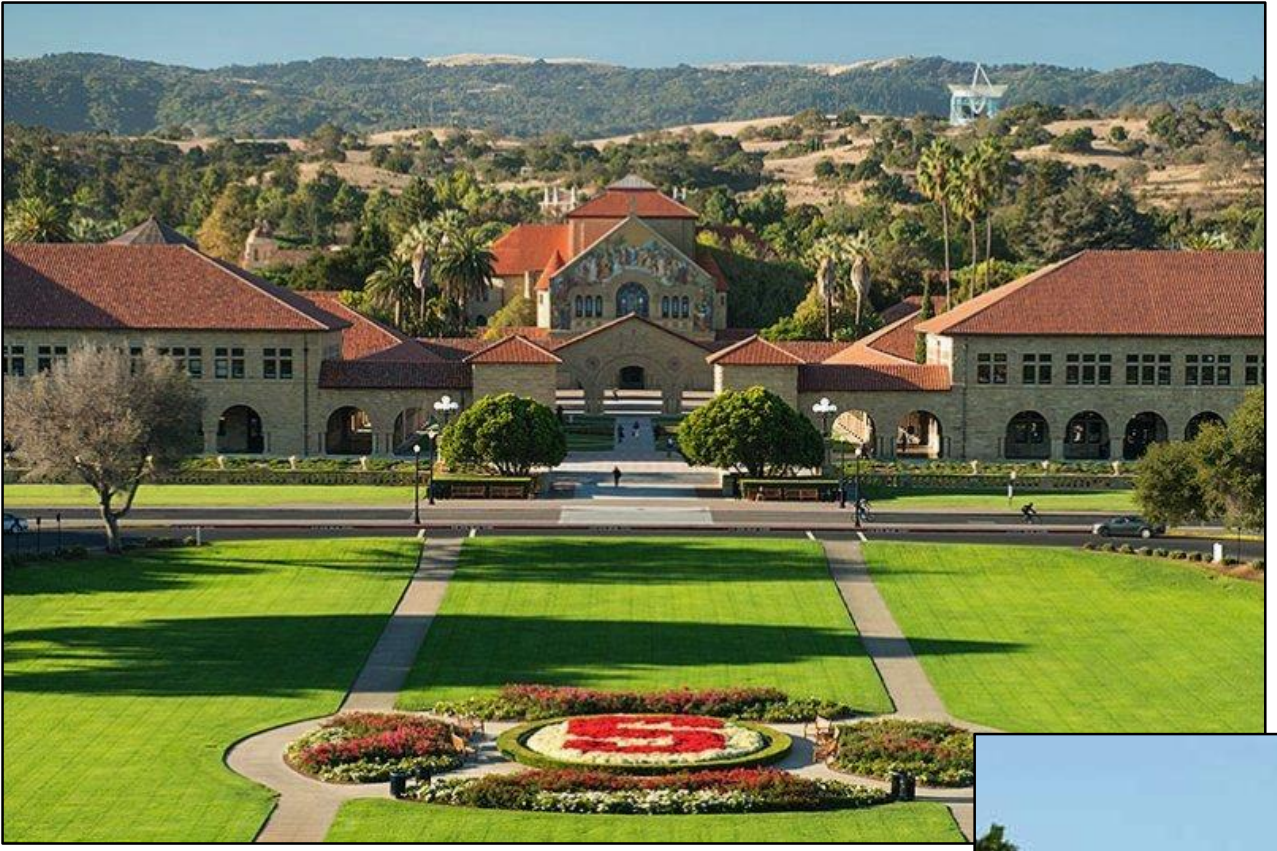


Fujimoto, Soltys ASTRO 2018

Conclusions: SRS for Glioma

- SRS/Hypofractionated RT for recurrent glioma:
  - Lower grade gliomas: reirradiation is an option
    - Fractionation based on histology, time to recurrence, location, size
  - GBM: reirradiation is an option
    - SRS – Data largely limited to retrospective case series
    - Hypofractionated RT: await patterns of progression analysis on RTOG 1205

- SRS for Newly Diagnosed Glioma:
  - Pilocytic gliomas: limited data exist
  - GBM:
    - RTOG 9305 → SRS boost no benefit when added to conventional 60 Gy
    - Single arm prospective data:
      - 10-fraction Colorado studies → high rates of necrosis in later trials
      - 5-fraction Stanford study → SRS perhaps less immunosuppressive



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