XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

QUANDO L'INDICE TERAPEUTICO E' AL LIMITE: TUMORI SNC

Isacco Desideri

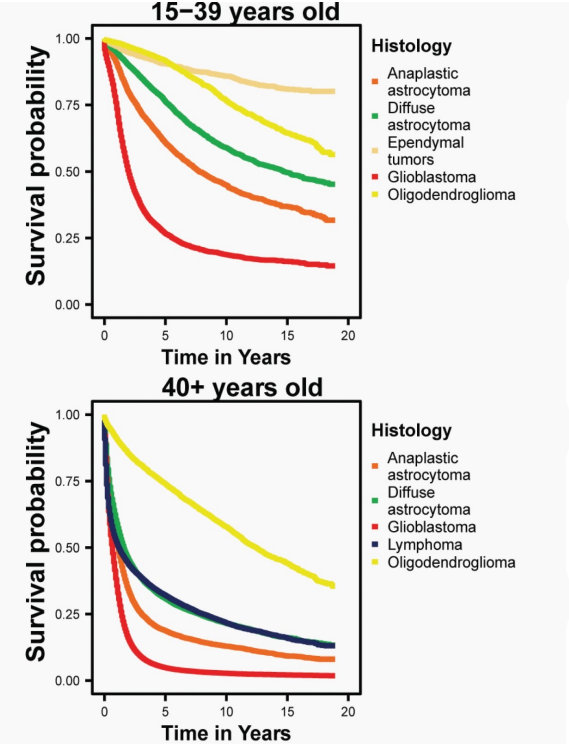
Università di Firenze

Associazione Italiana
Radioterapia e Oncologia clinica

Overview

- Setting the context: the trajectory of relapsed GBM patients
- Striking the ideal balance: the case of re-irradiation in recurring GBM patients
- Final considerations and conclusion

Glioblastoma overview



Most common malignant primary brain tumour in adults with an incidence of 3–4/100,000

Accounting for approx. 50% of all malignant primary brain tumours

Median PFS: 7 months

Median OS: 15 months

CBTRUS 2023

Our common clinical scenario: recurrent Glioblastoma (GBMr)

No standard treatment validated

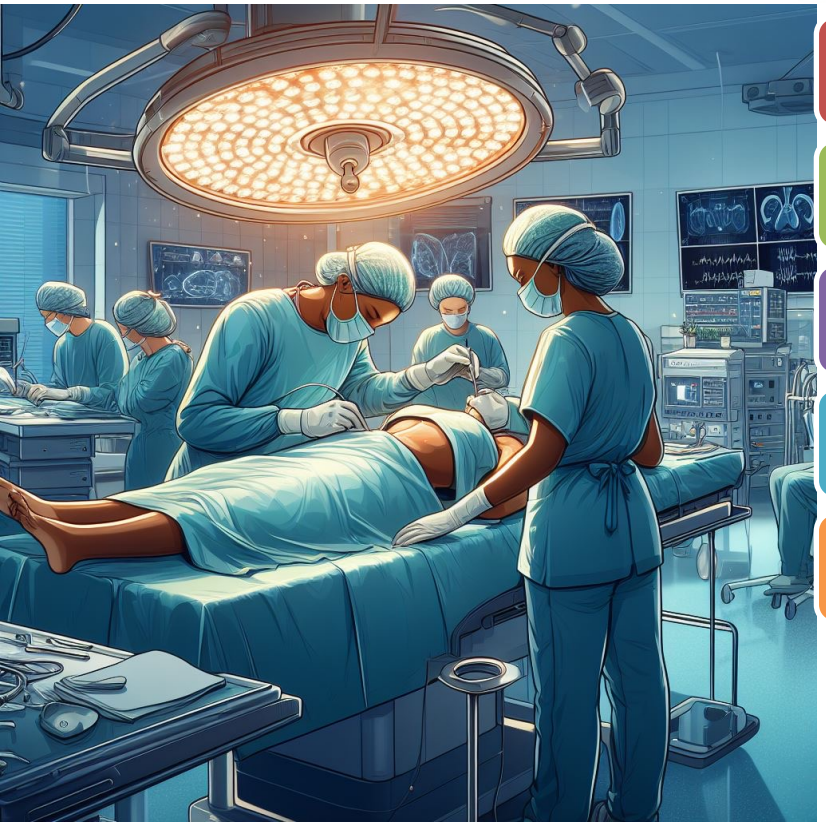
Median OS: < 1 year (4-8 months)

Key issue: harnessing the potential toxicity of any active intervention in a such a dismal prognosis

Re-surgery

Re-irradiation

Systemic Therapy



Viable option in 20-30% of patients

Mean OS after re-surgery: **9 mos**

Mortality: up to 11%

Morbidity: 13-69%

Main prognostic factors:

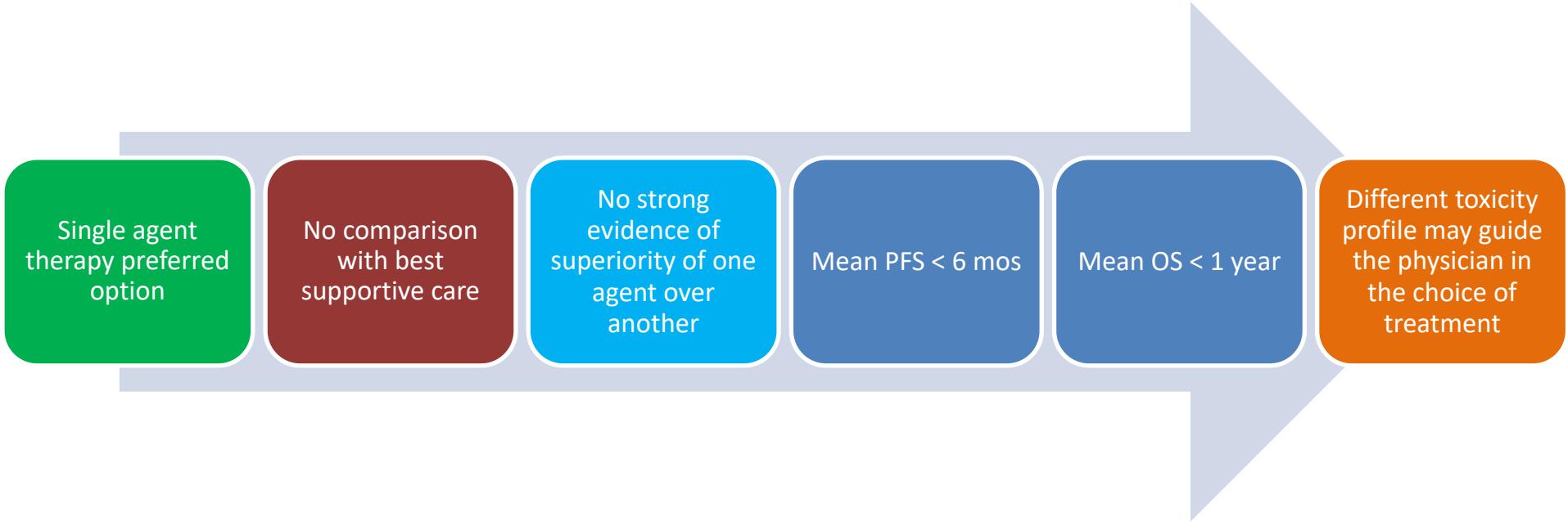
- KPS
- Age
- Extent of Surgery

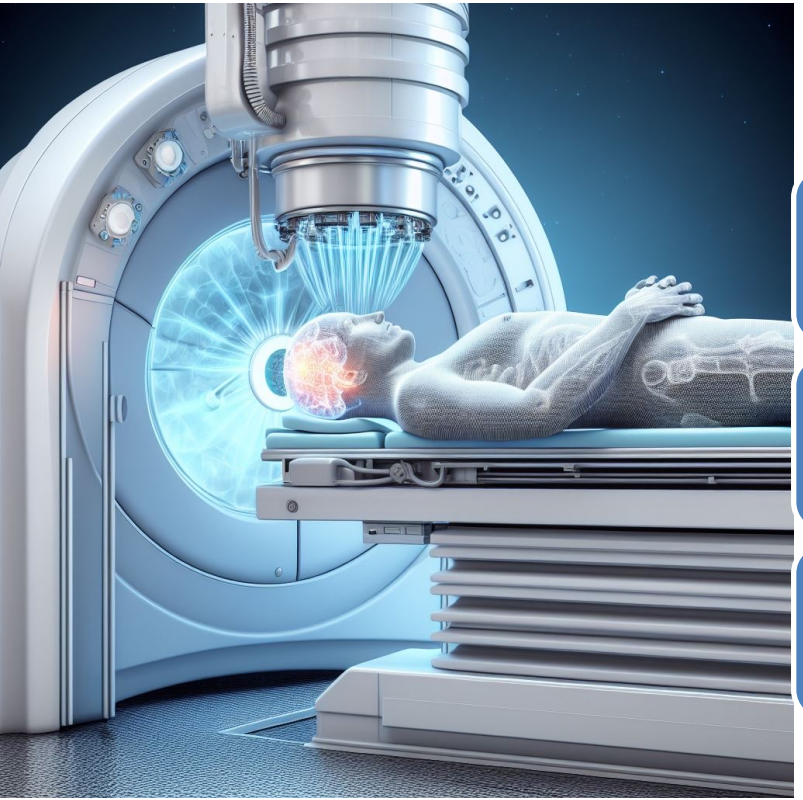
Robin AM et al. 2017

Systemic Treatments for GBMr

- Nitrosureas
- Bevacizumab
- TKIs
- Immunotherapy
- TTF

Systemic Treatments for GBMr: short summary





Re-irradiation

Increasingly adopted option

Easier thanks to technical advances of radiation oncology

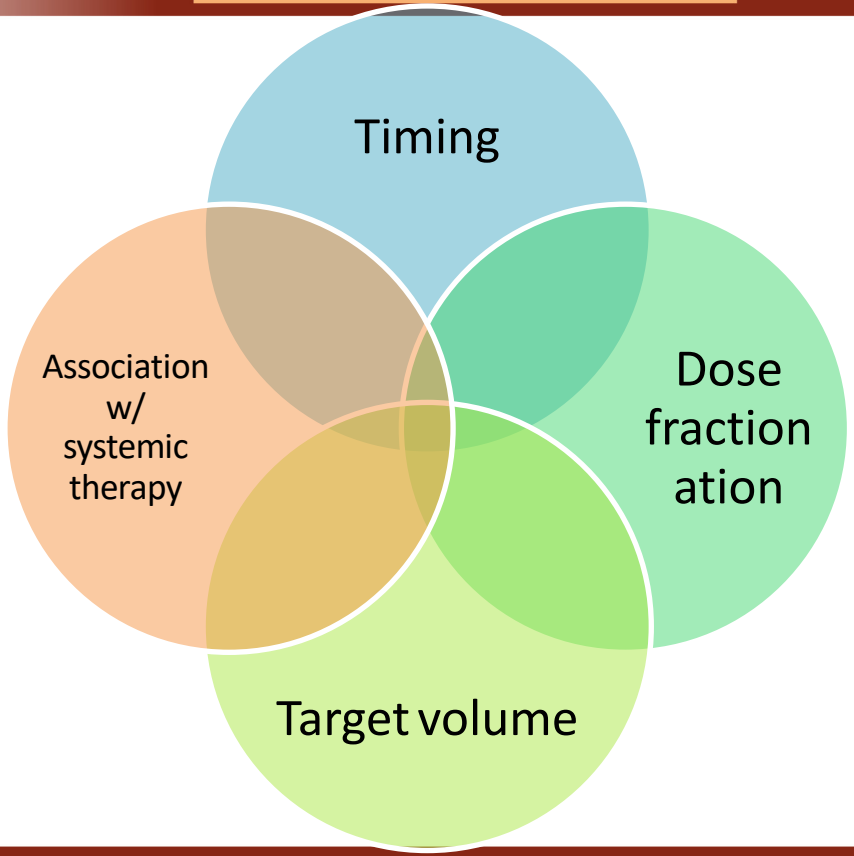
Suffer from same biases as re-surgery and/or systemic therapy:

- Lack of prospective data
- No comparison w/ BSC

90% of GBMr relapse within the previous high-dose (60Gy) irradiated area

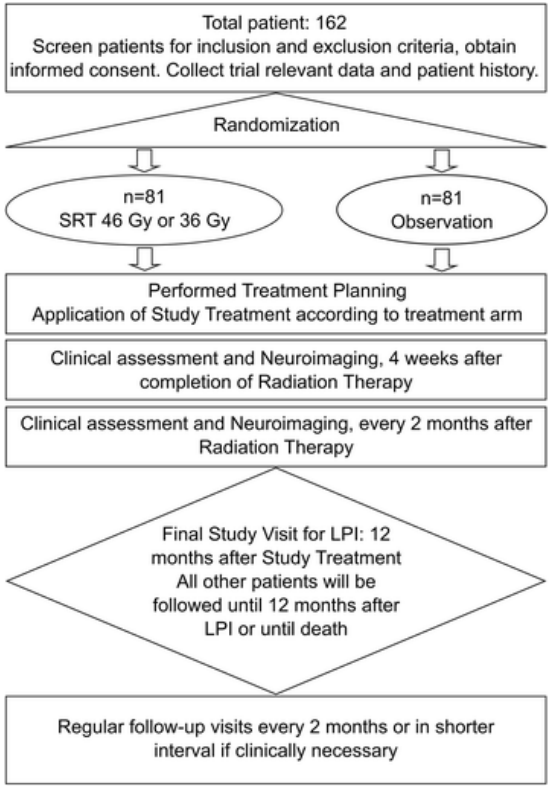
Neurotoxicity of re-irradiation (radionecrosis!) is a real concern in these scenario

Other issues exist besides technical aspects



Timing: The GLIOCAVE Study

- Phase III trial (ongoing)
- 162 patients to accrue
- Will answer the question if patients resected for GBMr benefit from adjuvant reRT or not



Author	No pts	RT Type	Median Dose (Gy/fr)	Median PFS (months)	Median OS (months)	Radionecrosis (%)
Combs et al., 2005	59	FSRT	36/18	5	8, 23% at 12 months	0
Grosu et al., 2005	34	HSRT	30/6	NR	8 (both), 11 (RT + TMZ), 6 (RT alone)	20.5
Kong et al., 2008	65	SRS	16/1	4.6	23	37.5
Cuneo et al., 2009	49	SRS	15/1	5.2 (+ BEV), 2.1 (-BEV)	11.9 (+ BEV), 3(-BEV)	10
Minniti et al., 2011	36	HSRT	37.5/15	5; 42% at 6 months	9.7; 33% at 12 months	22.2
Minniti et al., 2013	38	HSRT	30/5	6 24% at 12 months	12.4; 53% at 12 months	
Martinez-Carrillo et al., 2014	46	SRS	18/1	NR	7.5	10
Wick et al., 2014	91	FSRT	36/18	2.5 (RT), 4.5 (RT + APG101)	11.5 (both groups)	1.3
Kim H.R. et al., 2015	57	SRS	15/1	3.6 (2.3 + TMZ)	9.2 (15.5 + TMZ)	NR
Minniti et al., 2015	42	HSRT	25/5	50% (BEV), 18% (BEV + FTM) at 6 months	30% (BEV), 8.3% (BEV + FTM) at 12 months	16.6
Pinzi et al., 2015	88	SRS	16–22/1	NR	11.5 48% at 12 months	6
Imber et al., 2017	174	SRS	16/1	NR	10.6	13
Kim et al., 2017	57	SRS	15/1	3.6, 6 (+ TMZ)	9.2, 15.5 (+ TMZ)	24.4
Sharma et al., 2017	53	SRS	18/1	4.4	11	4
Palmer et al., 2018	87	SRT	35/10	NR	13.9	NR
Fleischmann et al., 2019	124	FSRT	36/18	5	9	6.9
Kaul et al., 2020	133	HSRT	41.8–49.4/12–15	NR	6	5.6
Saeed et al., 2020	45	PBRT	42.6/20	13.9	14.2	8.8
Attia et al., 2022	57	FSRT	36/18	8	11	3.5
Tsien et al., 2023	170	HSRT	35/10	54% vs. 29% at 6 months	10.1 BEV + RT, 9.7 BEV alone	0

Re-irradiation recommendations for dose & planning (1)

Dose

- <12.5 cc: SRS @ 12–15 Gy
- 12.5–35 cc: HFRT (25 Gy /5fx
- 35–50 cc: CFRT (36Gy (20/fx)

Target definition

- Enhancing lesion on T1 seq.
- GTV=CTV in RS and HFRT
- PTV ≤ 5mm (daily IGRT)

Risk of Severe Toxicity ≤ 3.5%

Scoccianti et al. 2018

Re-irradiation recommendations for dose & planning (2)

Dose

- 4-10cc: SRS @ 15–18 Gy
- 8.5–34cc: HFRT (35 Gy /10fx)
- 35–100cc: HFRT (25Gy /5fx)
- >100cc: CFRT (35Gy /10fx)

Target definition

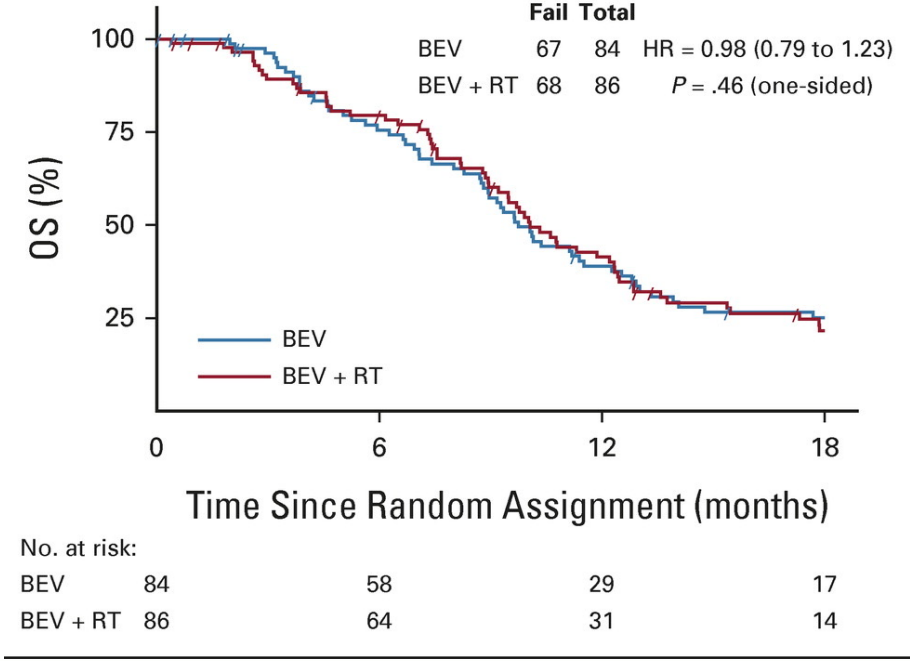
- Enhancing lesion on T1 seq.
- GTV=CTV for SRS
- CTV 5mm for HFRT
- CTV 1cm for CFRT
- PTV ≤ 5mm (daily IGRT)

Risk of Severe Toxicity ≤ 10%

Minniti et al. 2021

Association with Systemic Therapy

- 170 patients
- Beva vs Re-RT + Beva
- Median PFS for BEV + RT was 7.1 versus 3.8 months for BEV
- Median OS 10.1 versus 9.7 months for BEV + RT vs BEV alone
- **NO improvement in OS**
- G3+ AE: 5%



Tsien et al. JCO 2022

Factor	In Support of Reirradiation	Against Reirradiation
Age	Younger (eg, < 70 years, but no absolute cutoff)	Elderly (eg, > 70 years, but no absolute cutoff)
KPS	Higher (eg, > 60 years, but no absolute cutoff)	Lower (eg, < 60 years)
Mental status/neurocognitive status	Good	Severely impaired
Other available reasonable therapeutic options	No	Yes
PFS from initial radiation to first recurrence	> 12 months (the longer the better)	< 12 months (the shorter the worse)
Site of recurrence relative to initial tumor	Distant, outside the prior radiation field	Within the prior radiation field
Neuroanatomic site of recurrence	Less radiation-sensitive areas of brain (unilateral cerebral cortex)	Eloquent and radiation sensitive areas of brain (eg, brainstem, visual apparatus, medial temporal lobes, and bilateral frontal lobes)
Radiographic pattern of recurrence	Localized, small (contrast enhancement and FLAIR)	Diffuse contrast and flare abnormality, large multifocality, and diffuse leptomeningeal involvement
Rapidity of radiographic and/or clinical progression	Relatively slowly	Rapid
Glucocorticoid requirement for control of symptomatic cerebral edema	Low (eg,< 4 mg/day once daily dexamethasone)	High (eg, > 8 mg/day once daily dexamethasone)

Knisely JCO 2022

Unmet Need: evaluation of **QoL** in the re-RT of GBMr

Data regarding the QoL trajectory in patients undergoing re-RT are scarce

Given the mean OS of GBMr, these data would be of valuable importance for any future clinical trial

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Original Article

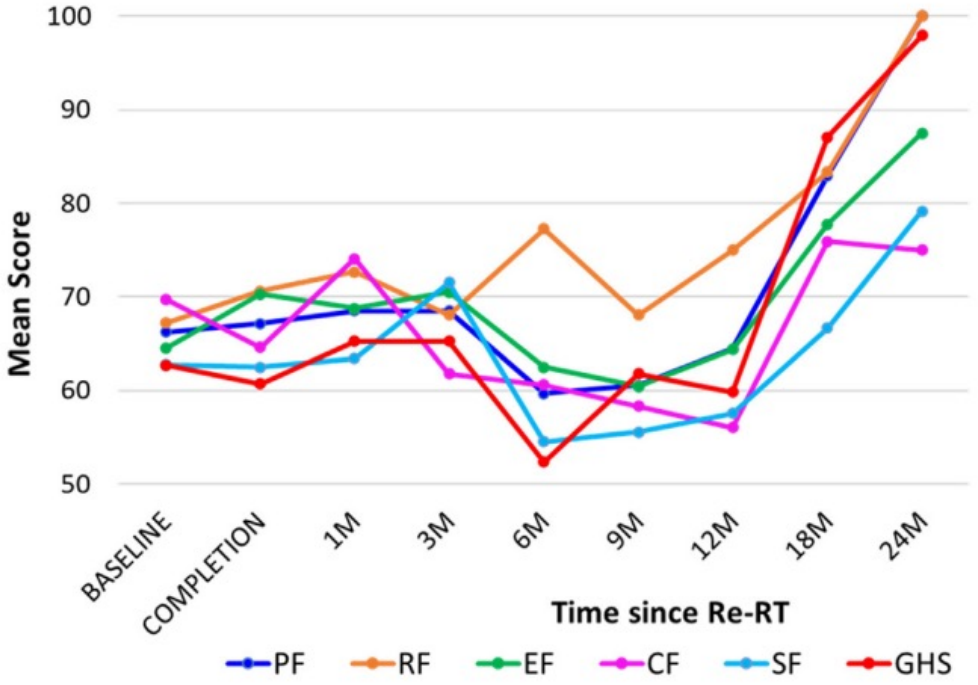
Prospective Longitudinal Assessment of Quality of Life and Activities of Daily Living as Patient-Reported Outcome Measures in Recurrent/ Progressive Glioma Treated with High-dose Salvage Re-irradiation

P. Maitre *, T. Gupta *, M. Maitre *, J. Goda *, R. Krishnatry *, A. Chatterjee *, E. Sridhar †, A. Sahay †, S. Mokal ‡, A. Moiyadi §, P. Shetty §, V. Patil ¶, R. Jalali *

60 patients undergoing re-RT for recurrent gliomas

- Qol: EORTC QLQ-C30 + BN-20
- ADL: modified Barthel's Index
- 16 patients (26.7%) w/ GBM

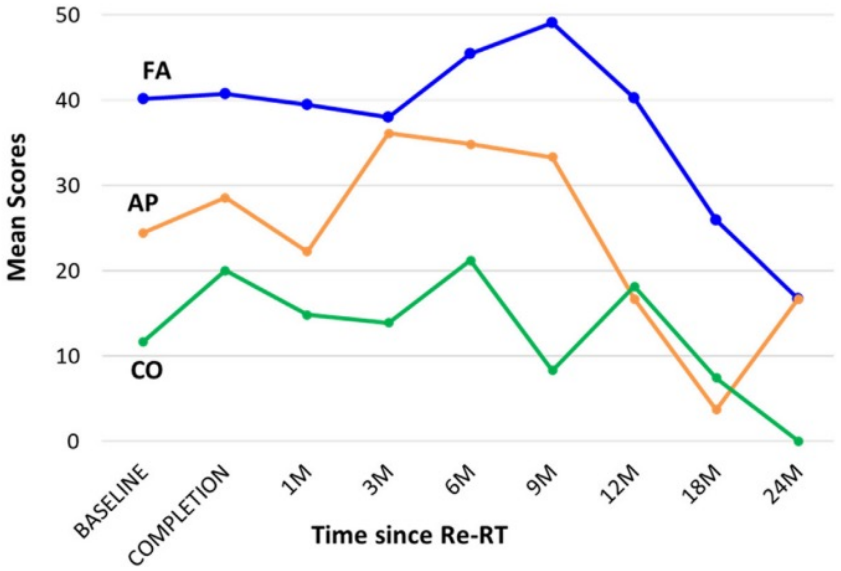
Maitre et al. 2021



Significant improvement in physical (PF), emotional (EF), cognitive (CF) and social functioning (SF) over time

Role functioning (RF) and global health status (GHS) remained stable

Maitre et al. 2021

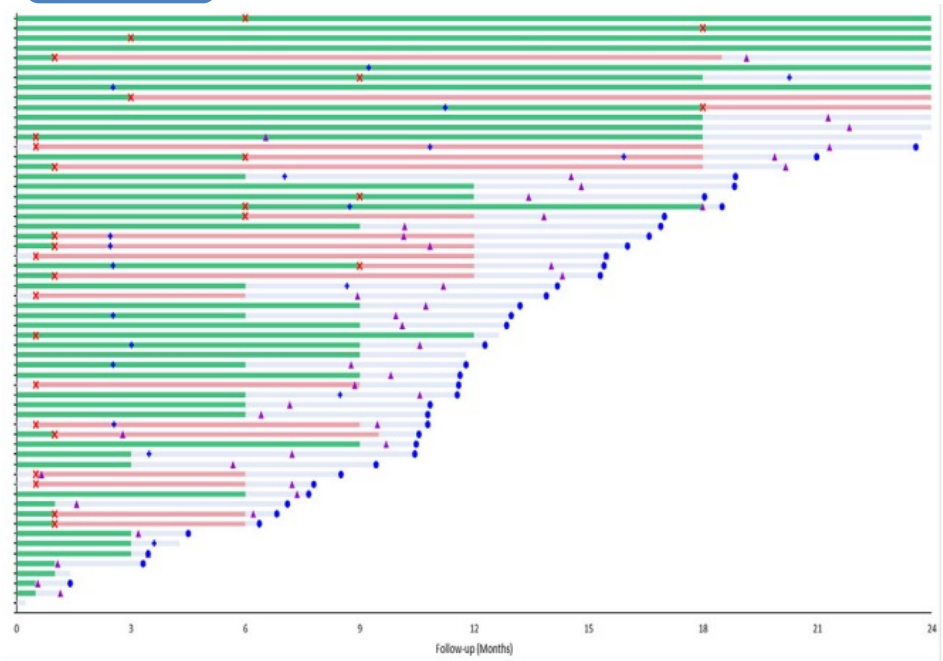


Mean symptom scores of a quality of life questionnaire (QLQ-C30) assessed at baseline (prior to re-irradiation) and subsequently longitudinally at pre-specified time points.

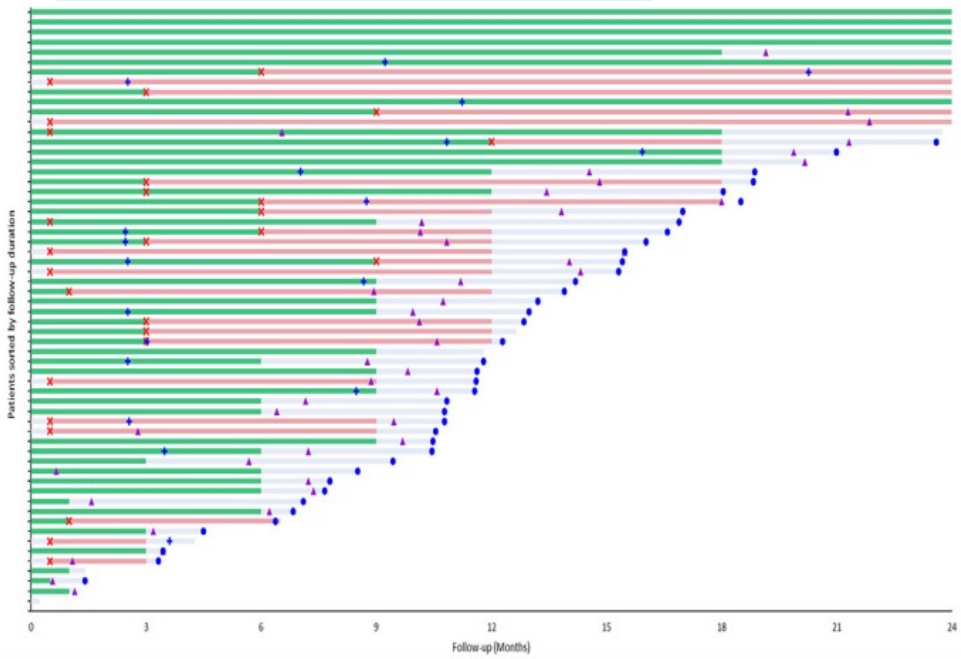
Significant improvement in fatigue (FA), loss of appetite (AP) and constipation (CO) over time,

Maitre et al. 2021

GHS



Physical Functioning



Maitre et al. 2021

The "Time Toxicity" of Cancer Treatment

Time Toxicity — Time spent coordinating treatments and in-visits to a health care facility (including travel and waiting), seeking urgent/emergent care for side effects, hospitalizations, and follow-up tests and rehabilitation.

Proposed Metric of Time Toxicity — Days with Physical Health Care System Contact

(a 1-hour lab visit = a 6-hour infusion = a 12-hour urgent care visit = an overnight hospitalization; all these are "all-day affairs")

Overall survival = **Days With Physical Health Care System Contact** + **Home Days**

Hypothetical Treatment	Clinical Trajectory	Overall Survival (in days)	Home Days
Option A (Chemotherapy)	Frequent clinic visits; Chemotherapy toxicity, hospitalization, and rehabilitation	150	90
Option B (No cancer-directed treatment)	Short hospitalization for symptom control	120	115

Day 0 — Day 30 — Day 90 — Day 180

With information on **"Time Toxicity"** and **"Home Days"**, a clinician can better guide a patient regarding a treatment strategy that best aligns with the patient's goals.

Concept with growing interest in the oncological community

Particularly relevant in this clinical scenario

Gupta JCO 2022

Conclusions

Re-irradiation of GBMr is technically feasible in a large percentage of GBMr patients

BUT not appropriate in a non-negligible portion of these patients

An honest and clear discussion among physician, patient and care-givers is of paramount importance in this context

Prospective data on these particulary complex population of patients regarding QoI is an unmet need that should be resolved by the neuroncology community

Grazie per l’attenzione