Toxicity considerations
and
Re-Irradiation in Brain Tumor

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Topics

- Introduction to Re-Irradiation
- Rationale
- Indication
- Timing
- Dose and Fractionation
- RT Techniques
- Clinical outcomes and evidences
- Toxicity consideration

Introduction

- Delivery of a clinically significant RT dose post initial RT ± Chemotherapy, post proven recurrence.

- Points under consideration
  - What is a clinically significant dose!!
  - How long after initial treatment!!
  - How to define recurrence !!!

Rationale

- Radiobiological consideration- Key to any hypothesis in RT response.

Br. J. Cancer (1986) **53**, Suppl. VII, 207–217

Radiation-induced damage in the central nervous system: An interpretation of target cell responses

A.J. van der Kogel

Preclinical study (monkey and rabbit) and some clinical data

↓

Model of target cell responses in the CNS cells

Radiobiological consideration

- Earliest sign of damage – In the white matter
- Nodal widening and segmental demyelination
- As early as 2 weeks after doses of 60 Gy
- Remyelination - By 2 months
- Latent period of 4-6 months, areas of white matter necrosis - critical depopulation of oligodendrocytes and vascular damage.
- The probability of occurrence of necrosis and the latent period is a function of dose

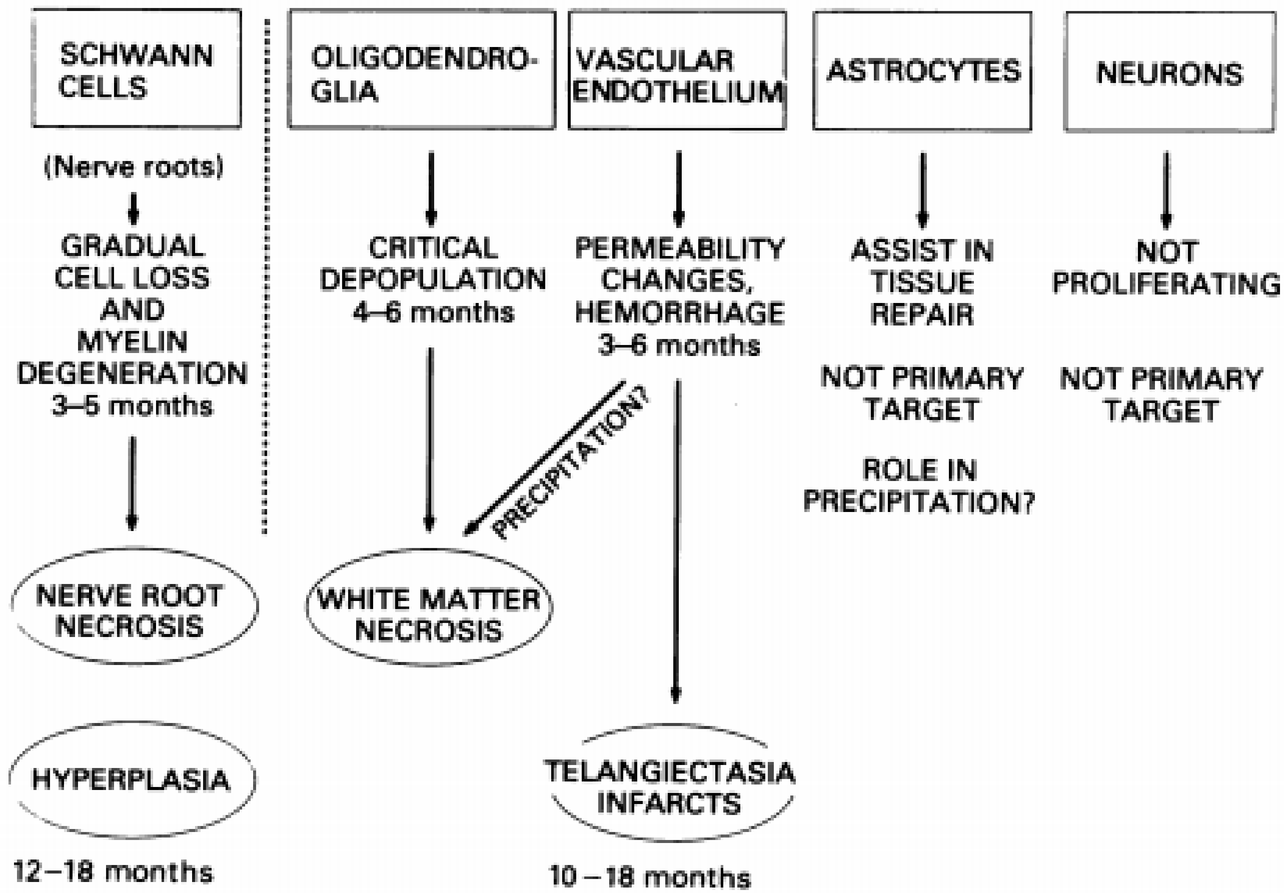


Figure 1 A schematic representation of the major cell types in the CNS, and their assumed participation in the development of different types of radiation-induced lesions. Schwann cells (on the left) are not part of the CNS, but are the primary parenchymal cells in the spinal nerve roots.

Indication

- Glioma: Oligodendroglioma and Astrocytoma
- Brain metastasis : Post WBRT , post SRS/FSR

Defining a Recurrence in Gliomas

- Warning sign
  - ➢ Post treatment after initial improvement developing new neurological deficit
  - ➢ Stable clinical scenario but radiological progression

- Major confounding factor
  - ➢ Recurrence/progression
  - ➢ Pseudo-progression
  - ➢ Radio-necrosis

MRI

- Gadolinium-enhanced T1-weighted MRI – Was Investigation of choice for long time
  - High False positive
  - Only detects the disruption of the blood-brain barrier and not the tumor activity specifically.

- To overcome the limitations multimodal MRI has been proposed, including
  - Magnetic resonance spectroscopy (MRS),
  - Diffusion-weighted imaging (DWI)
  - Perfusion-weighted imaging (PWI)

- High diagnostic accuracy of MRS and PWI but low accuracy of DWI

van et al Diagnostic accuracy of magnetic resonance imaging techniques for treatment response evaluation in patients with high-grade glioma, a systematic review and metaanalysis. Eur Radiol. (2017) 27:4129–44.

PET-CT

- FDG-PET can demonstrate differences in the analysis of areas of radiation injury and residual/recurrent brain tumors.

- Low sensitivity and good specificity.

- High background activity - High glucose use in the brain

- RANO (Response Assessment in Neuro-Oncology) group proposed other PET CT scan
  - 18F-FET PET
  - 11C-MET PET
  - 18F-DOPA PET

MRI vs F-18 FDG PET CT

EUROPEAN JOURNAL OF
RADIOLOGY

FULL LENGTH ARTICLE | VOLUME 81, ISSUE 3, P508-513, MARCH 01, 2012

F-18 FDG PET-CT in patients with recurrent glioma: Comparison with contrast enhanced MRI

Amburanjan Santra [1] • Rakesh Kumar • Punit Sharma • ... Atin Kumar • Pramod Kumar Julka

- Overall sensitivity and specificity of FDG PET-CT were 70% and 97% respectively
- Contrast enhanced MRI was 95% and 23%.
- FDG PET-CT - higher accuracy (80%) compared to MRI (70%).

frontiers in Neurology

SYSTEMATIC REVIEW
published: 20 May 2021
doi: 10.3389/fneur.2021.671867

Check for updates

Diagnostic Accuracy of PET for Differentiating True Glioma Progression From Post Treatment-Related Changes: A Systematic Review and Meta-Analysis

Meng Cui[1,2†], Rocío Isabel Zorrilla-Veloz[3,4†], Jian Hu[3,4], Bing Guan[5] and Xiaodong Ma[1,2*]*

- 33 studies
- 1,734 patients
- 1,811 lesions suspected of glioma recurrence.

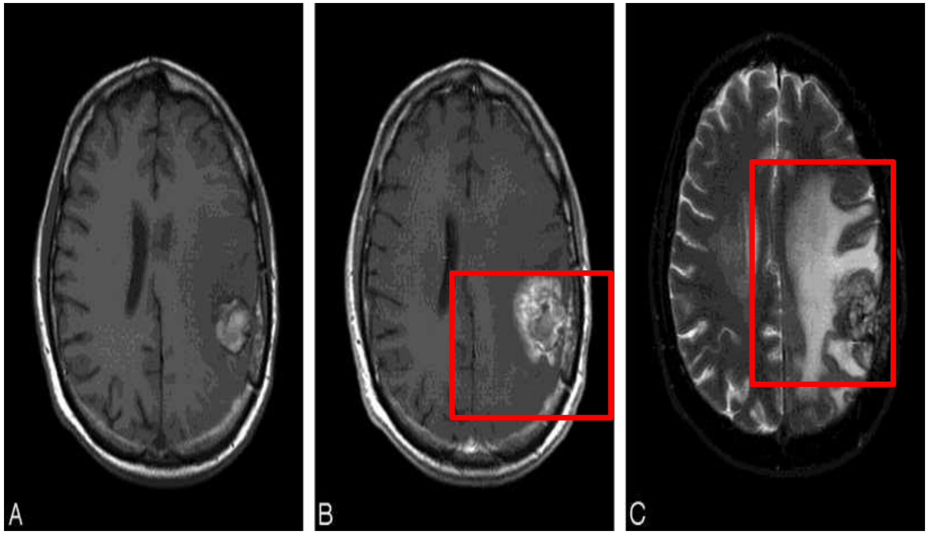
Radiotracer and test technique	Quantitative parameter	Threshold range	ρ and P value	Heterogeneity of pooled Sen (upper) and Spe (lower) (P-value of Q test and I^2)	Pooled Sen and its 95%CI	Pooled Spe and its 95%CI	Pooled DOR and its 95%CI	AUC of HSROC
^{18}F-FET	TBR_{max} (810 tests)	1.95,3.52	0.068 ($P = 0.816$)	**§$P < 0.1$, $I^2 = 85.3\%$** ‖$P = 0.09$, $I^2 = 36.1\%$	0.88 (0.80,0.93)	0.78 (0.69,0.85)	26 (12,57)	0.86 (0.83, 0.89)
	TBR_{mean} (713 tests)	1.52,2.98	**−0.677 ($P = 0.022$)**	NA*	NA*	NA*	NA*	0.90 (0.87, 0.92)
	TTP (317 tests)	20,45	0.714 ($P = 0.111$)	**§$P = 0.03$, $I^2 = 59.1\%$** ¶$P = 0.1$, $I^2 = 45.2\%$	0.80 (0.68,0.88)	0.67 (0.48,0.81)	8 (4,16)	0.81 (0.77, 0.84)
^{18}F-FDG (631 tests)	NA†	NA†	0.432 ($P = 0.161$)	—‖$P = 0.04$, $I^2 = 46.4\%$ ¶$P = 0.5$, $I^2 = 0.0\%$	0.78 (0.71,0.83)	0.87 (0.80,0.92)	23 (14,39)	0.90 (0.87, 0.92)
^{11}C-MET	TBR (409 tests)	1.43,2.51	0.559 ($P = 0.192$)	**§$P < 0.1$, $I^2 = 86.3\%$** ¶$P = 0.35$, $I^2 = 10.8\%$	0.92 (0.83,0.96)	0.78 (0.69,0.86)	39 (15,105)	0.82 (0.78, 0.85)
^{18}F-DOPA	TBR_{max} (175 tests), visual (175 tests)	NA†	−0.638 ($P = 0.173$)	¶$P = 0.30$, $I^2 = 18.2\%$ ¶$P = 0.61$, $I^2 = 0.0\%$	0.85 (0.80,0.89)	0.70 (0.60,0.79)	13 (7,24)	0.85 (0.82, 0.88)
FET-PET and MRI (190 tests)	NA‡	NA‡	0.316 ($P = 0.648$)	**§$P = 0.06$, $I^2 = 60.2\%$** ¶$P = 0.16$, $I^2 = 42.5\%$	0.88 (0.78,0.94)	0.76 (0.57,0.88)	23 (9,59)	0.90 (0.87, 0.92)
FET-PET static/dynamic multi-parameters analysis (354 tests)	NA‡	NA‡	−0.100 ($P = 0.873$)	‖$P = 0.09$, $I^2 = 49.5\%$ ¶$P = 0.30$, $I^2 = 18.4\%$	0.88 (0.81,0.92)	0.79 (0.63,0.89)	26 (9,78)	0.91 (0.88, 0.93)

- High Sensitivity of amino acid PET and high Specificity of FDG-PET
- Combination of commonly used FET-PET and FDG-PET may be more accurate especially for low-grade glioma.

Radio-necrosis

- Typically occurs 18–24 months post-treatment.
- Difficult to distinguish from recurrence
- Gold standard: Biopsy
- Limiting factor for biopsy: Surgical morbidity

Radio-Necrosis



MRI

- **T2/FLAIR:** white matter high signal
  - ➢ Edema and mass effect early
  - ➢ Loss of volume later
- **T1 C+ (Gd)**
  - ➢ White (more common) or grey matter
  - ➢ Single or multiple
  - ➢ Nodular or curvilinear
  - ➢ “Soap-bubble", “cut green pepper” or "Swiss-cheese" enhancement
  - ➢ Occasionally can be ring-enhancing
- **MR spectroscopy:** Low choline, creatine, and NAA
- **MR perfusion:** Areas of enhancement and high T2/FLAIR don't show increased rCBV in radiation necrosis or pseudoprogression and could be helpful in distinguishing them from residual lesion or recurrence
- **FDG-PET**
  - ➢ Radiation necrosis is hypometabolic whereas tumor is hypermetabolic

PSEUDO-PROGRESSION

- Increase of lesion size related to treatment, which simulates progressive disease.
- Especially for high grade gliomas (GBM)
- More common with CTRT (30%) less with RT alone (15%)
- Disruption of BBB, Endothelial damage and consequent tissue hypoxia post CTRT
- ~60%- First 3 months
- May occur from 1st weeks to 6 months post treatment

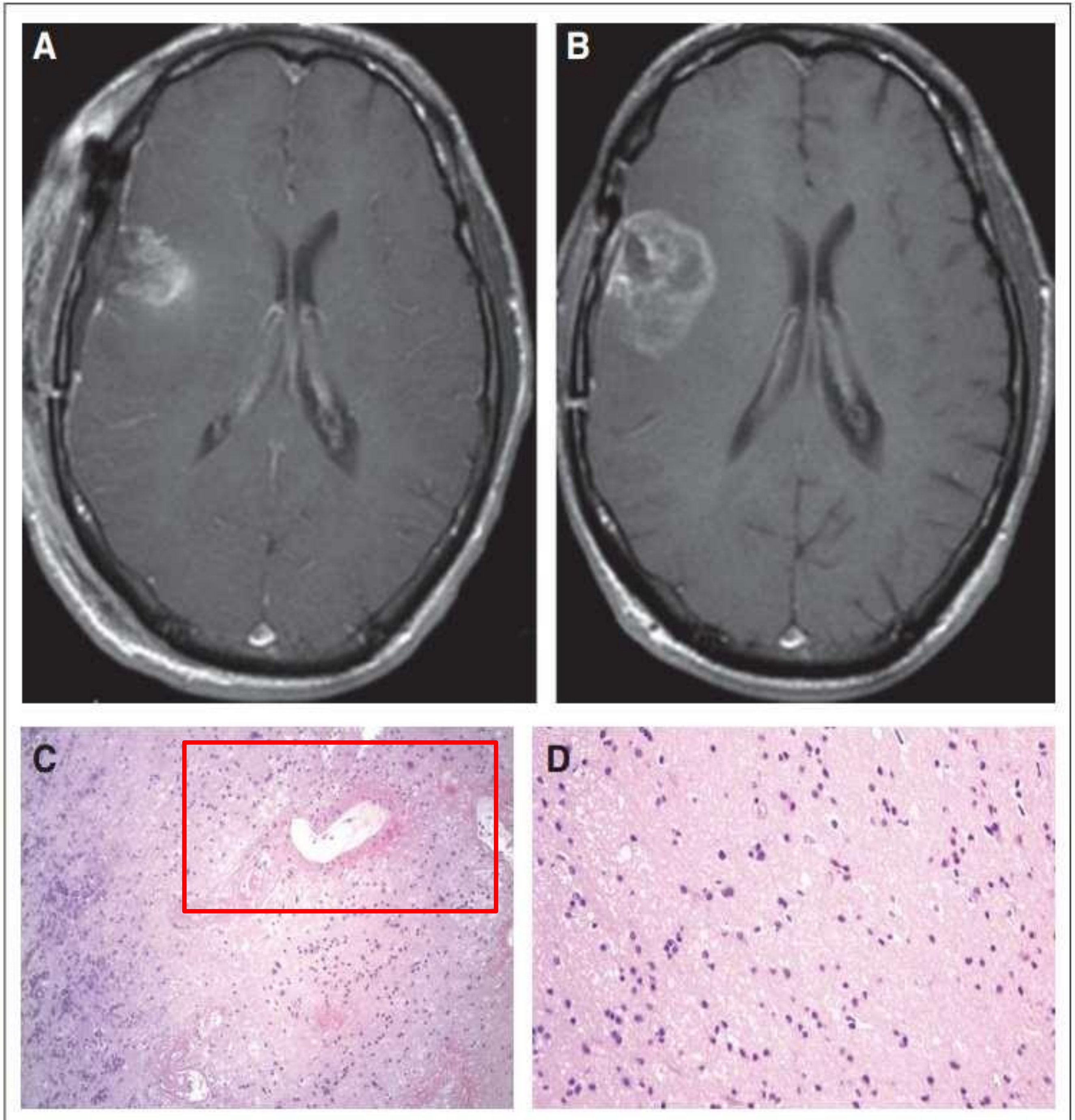


Fig 1. Representative patient with glioblastoma multiforme treated with concurrent temozolomide and radiation. T1 postgadolinium magnetic resonance imaging at (A) baseline and (B) 3 months after treatment showed a significant increase in contrast-enhancing lesion. At resection, pathology was notable for (C) fibrinoid radiation necrosis involving blood vessel wall and (D) predominantly gliotic brain parenchyma with no viable neoplasm, consistent with pseudoprogression.

Approach to Re-Irradiation

- Rule out pseudo progression and post RT necrosis.
- Use of contrast enhanced MRI and functional imaging to characterize progression
- Patient performance status
- Feasibility of reresection
- Interval from last RT or CTRT
- Previous volume, dose, fractionation, technique
- OAR doses
- Feasibility of further prolonging gap by chemotherapeutic agent.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Scale to Predict Survival After Surgery for Recurrent Glioblastoma Multiforme

John K. Park, Tiffany Hodges, Leopold Arko, Michael Shen, Donna Dello Iacono, Adrian McNabb, Nancy Olsen Bailey, Teri Nguyen Kreisl, Fabio M. Iwamoto, Joohee Sul, Sungyoung Auh, Grace E. Park, Howard A. Fine, and Peter McL. Black

The factors associated with poor postoperative survival were

- ➢ Tumor involvement of prespecified eloquent/critical brain regions (P= .021)
- ➢ Karnofsky performance status (KPS) <80 (P= .030)
- ➢ Tumor volume 50 cm3 (P= .048)

- Non of the factors - best survival (median 9.2 months)
- All 3 factors : worst survival (median 1.9 months)

- Whenever feasible resurgery should be attempted.

Re-irradiation after Gross Total Resection of Recurrent Tumor

- Controversial

- Some evidence supporting RE-RT in both paediatric and adult ependymoma.

  Rogers et al J Neurosurg 2005;102: 629-636

- Straube et al: Spatial recurrence patterns after GTR of recurrent GBM
  - 70% of cases, second recurrence in the region of the first recurrence

- Recommended : PORT resection cavity + contrast enhancing lesion and a 5-10 mm CTV margin.

Prognostic factor for Re-irradiation

Heidelberg prognostic score for re-irradiation of recurrent glioma

Prognostic factor	Subgroups	Value for prognostic score
Histology	WHO grade IV	2
	WHO grade III	1
	WHO grade II	0
Age	<50 years	0
	≥ 50 years	1
Time between primary radiotherapy and re-irradiation	≤ 12 months	1
	>12 months	0

- Scoring 0-2 best survival
- Scoring 3-4 had lower survival after re-irradiation.

Modified Combs' group scoring: Yet to be validated

- PTV volume (>47/47 ml)
- Karnofsky performance status (<80%/80%)
- Whether or not re-resection had been carried out

Combs SE, Edler L, Rausch R, Welzel T, Wick W, Debus J. Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. Acta Oncol 2012;52: 147-152.

Prognostic factors for Re-irradiation

- MGMT promoter methylation status was significant on both univariate and multivariate analyses.

Kessel KA, et al. Modification and optimization of an established prognostic score after re-irradiation of recurrent glioma. PLoS One 2017;12:e0180457

- On 18F-FET PET significant prognostic factors:
  - Uptake kinetics of the radioisotope
  - Biological tumour volume at baseline imaging

Niyazi M et al. Re-irradiation in recurrent malignant glioma: prognostic value of [18F]FET-PET. J Neurooncol 2012;110: 389-395.

RT Technique for RE-RT

- CONVENTIONAL
- FSR
- SRS
- BRACHYTHERAPY
- TTF

Target Volume Delineation

- Review the plan and dose details for the primary treatment.
- Specifically: Serial organ
- 11C-methionine-PET (MET-PET) imaging can be beneficial.
- NOA 10 study is looking at whether target volume definition with amino acid PET is beneficial.
- Contour the GTV using T1Gd-MRI + FET-PET.
- PTV margin as per immobilization and institutional protocol.

Dose Limitation

- Cumulative EQD2 around 100 Gy with conventional technique and slightly higher with conformal and SRT.

Combs SE: Stereotactic radiosurgery (SRS): treatment option forrecurrent glioblastoma multiforme (GBM). Cancer 2005, 104:2168-2173.

- SRS and interstitial brachytherapy are not favored
  - Higher toxicity (20-30%)
  - Suitability only for very small tumours (<30 cc)

Combs, S et al Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: Long-term results in 172 patients in a single insitution. J. Clin. Oncol. 2005;23: 8863–8869

Dose Limitation

- Normalised tissue dose (NTD) cumulative of > 100Gy for conventional fractionation was associated with radiation induced white matter necrosis.

- Smaller volumes and FSR –
  - NTD cumulative doses (90–133.9 Gy for FSRT, 111.6–137.2 Gy for SRS).

- No correlation between time interval of the radiotherapy courses and incidence of complications

Mayer R Reirradiation Tolerance of the Human Brain. IJROBP2008;70(5):1350–60.

Dose & Fractionation

- No large phase III randomized data.

- Evidence base for fractionated radiotherapy comes almost exclusively from single institutional retrospective case series.

Fractionated radiotherapy case series

Year	Cases	Technique	Dose	Equivalent dose (2 Gy/fraction)	Median PTV	Median overall survival after re-irradiation	Neurological toxicity
2017	5 GBM 2 G3	HFSRT	36–39 Gy in 3 Gy/fraction	45–48.75 Gy	30.2 cm^3	9 months	No RN clinically or radiologically
1993	12 GBM 7 G3 3 LGG	HFSRT	30–50 Gy in 5 Gy/fraction	52.5–87.5 Gy	Range 61–180 cm^3	9.8 months	22.7% steroid-responsive late toxicity
1997	36 HGG	HFSRT	20–50 Gy in 5 Gy/fraction	35–87.5 Gy	NR TV 24 cm^3	11 months	36% late radiation-induced damage (clinical)
1999	19 GBM 1 G3	HFSRT	24–35 Gy in 3.0–3.5 Gy/fraction	30–48.13 Gy	NR TV 12.7 cm^3	10.5 months	No RN
2000	15 GBM 3 G3 3 others	HFSRT	Median 25 Gy in 4–6 Gy/fraction		12.7 cm^3	6.7 months	No RN
2001	42 HGG/LGG	2D fields	Median 46 Gy in 2 Gy/fraction	46 Gy	NR	10.9 months	4.8% RN
2005	20 GBM 2 G3	FSRT (63.6%) HFSRT (36.4%)	45–54 Gy in 2–3 Gy/fraction 30 Gy in 5 Gy/fraction	54–56.25 Gy 52.5 Gy	154.4 cm^3 41.7 cm^3	7 months	No RN
2005	59 GBM 42 G3 71 LGG	FSRT	Median 36 Gy in 2 Gy/fraction	36 Gy	49.3 cm^3	8 months (GBM) 16 months (G3) 22 months (LGG)	0.6% RN (histologically confirmed)
2005	14 GBM 5 G3	HFSRT	Median 30 Gy in 4–10 Gy/fraction	30–60 Gy	15 cm^3	9.3 months	No RN
2007	11 GBM 3 G3	HFSRT	35 Gy in 7 Gy/fraction	78.75 Gy	22.4 cm^3	12 months (est)	NR
2009	53 GBM	HFSRT	Median 30 Gy in 2–5 Gy/fraction	30–60 Gy	35.01 cm^3	9 months	No radiological evidence of RN
2009	29 GBM 2 G3	3D CRT	Median 20 Gy in 5 Gy/fraction	35 Gy	52.7 cm^3	10.2 months	No clinically detected RN
2010	105 GBM 42 G3	HFSRT	Median 35 Gy in 3.5 Gy/fraction	48.13 Gy	22 cm^3	10 months	0.7% late neurological toxicity
2011	5 GBM 3 G3	HFSRT	25 Gy in 5 Gy/fraction	43.75 Gy	69.5 cm^3	7.6 months	12.5% RN
2012	89 GBM 52 G3 92 LGG	FSRT	Median 36 Gy in 2 Gy/fraction	36 Gy	47 cm^3	8 months (GBM) 20 months (G3) 24 months (LGG)	0.4% RN (histologically confirmed)
2013	15 GBM	HFSRT	25 Gy in 5 Gy/fraction	43.75 Gy	NR	9.5 months	13.3% had neurological deterioration managed with steroids

Dose Escalation

- Dose-escalation with FSR

- Re-irradiation dose of >40 Gy (5 Gy/fraction, EQD2 70 Gy)

  - Significant predictor of radiation damage

  - Having 6.4 times the risk compared with those receiving 40 Gy.

Shepherd et al. Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. IJROBP: 1997;37:393e398

Dose Escalation

Hudes RS et al. 1999;43:293-298

- Dose-escalation with salvage SRT was delivered using daily 3.0–3.5 Gy/#
- 24.0 Gy/8 # vs 30.0 Gy/10 # vs 35.0 Gy/ 10 #
- Median tumor volume 12.66 cc (0.89–47.5 cc).
- Dose response relationship, with increasing dose being associated with a response.
    - ➢ Clinical neurology
    - ➢ Reduction in steroid requirement
    - ➢ Imaging response.
- The cut-off for improving overall survival was about 30-35 Gy @ 3-3.5 Gy/#

SRS Case Series

Year	Cases	SRS platform	Dose	Median treatment volumes	Median overall survival after re-irradiation	Neurological toxicity
1995	26 GBM 9 G3	Linac	Median 20 Gy to 50% isodose	28 cm^3	8 months	14% RN
1999	46 HGG	Linac	Median 17 Gy to 50% isodose	30 cm^3	11 months	13% clinical RN
2000	23 GBM	Linac (56.5%) Gamma knife (43.5%)	Median 15 Gy to 60% isodose	9.9 cm^3	10.3 months	4.3% RN
2005	32 GBM	Linac	Median 15 Gy to 80% isodose	10 cm^3	10 months	No RN
2005	41 GBM	Linac	NR	4.7 cm^3	11 months	14.6% RN
2008	65 GBM 49 G3	Gamma knife	Median 16 Gy to 50% isodose	10.6 cm^3	13 months (GBM) 26 months (G3)	24.4% RN on imaging, mostly asymptomatic
2009	26 GBM	Linac	Median 18 Gy to 90% isodose	10.4 cm^3	8.5 months	7.7% RN
2009	26 GBM	CyberKnife	D_{max} 25.8 Gy	7.0 cm^3	7 months	NR
2011	16 GBM 10 G3	Gamma knife	Median 15 Gy to 50% isodose	2.15 cm^3	13.5 months	9.1% RN
2011	13 GBM	NR	Median 17 Gy	5.3 cm^3	11 months	23% asymptomatic RN
2011	19 GBM	Linac	Median 16 Gy to 80–95% isodose	13 cm^3	9.3 months	No acute toxicity
2012	18 GBM	Gamma knife	20 Gy	C: 15 cm^3 E: 13 cm^3 C: Conventional SRS, no margin E: Extended SRS, 0.5–1 cm margin	C: 10.5 months E: 9 months	C: 6.5% asymptomatic RN E: 29% RN requiring steroids
2012	51 GBM	Gamma knife	12.2 Gy Median margin dose	NR	12 months	9.8%
2013	22 GBM 7 G3	Gamma knife	17.5 Gy to 50% isodose	4.8 cm^3	15.8 months (GBM) 34.8 months (G3)	13.8% RN
2014	35 GBM 20 G3	Gamma knife	Median 20 Gy to 44% isodose	5.20 cm^3	11.3 months (GBM) 24.2 months (G3)	25% symptomatic
2014	46 GBM 41 G3	Linac	Median 18 Gy	6 cm^3	10 months	No RN
2015	29 GBM	Gamma knife	Median 14 Gy to 49% isodose	11.4 cm^3	7.9 months	5.6% RN
2015	24 GBM 14 G3	Gamma knife	Median 16 Gy to 50% isodose	6.05 cm^3	22.8 months	NR
2015	88 GBM 40 G3	CyberKnife	Median 15 Gy to 80% isodose Some received median 23 Gy/3 fractions	5.2 cm^3	11.5 months	6% RN

BRACHYTHERAPY

Table IV. Re-irradiation studies employing brachytherapy.

First author, year	Patients, n	KPS[a]	WHO grade (n)	Treatment type	Source activity[a], mCi	Total dose[a], Gy	Dose rate[a], cGy/h	Post-OS time, weeks	Post-PFS time, weeks	PTV[a], ml	Prognostic factor	Rate of severe toxicity, %	(Ref.)
Simon *et al*, 2002	42	80 (50-100)	IV (42)	Temp + LDR + ^{192}Ir implant	NR	50 (15-60)	37 (16-73)	50 (8-207)	NR	23 (1.6-122)	KPS, pre-implant volume	24-33.3	(51)
Tatter *et al*, 2003	21	80 (60-100)	IV (15) III (6)	Temp + LDR + ^{125}I GliaSite	73-459	40-60	41-61	12.7 months (17.9 months for non-GBM; 8 months for GBM)	NR	NR	NR	19.0	(53)
Larson *et al*, 2004	38	90 (60-100)	IV (38)	Perm + LDR + ^{125}I implant	0.67 (0.40-0.93)	300 (150-500)	15 (7-24)	52	16	21 (1-68)	KPS, age, tumor volume	10.5	(17)
Chan *et al*, 2005	24	80 (50-100)	IV (24)	Temp + LDR + ^{125}I GliaSite	NR	53.1 (29.9-80)	52.7	9.1 months (1.3-23.6 months)	NR	≤30	KPS	8	(54)
Gabayan *et al*, 2006	95	80 (40-100)	GBM (80) non-GBM (15)	Temp + LDR + GliaSite	369 (90-950)	60 (38-72.5)	52.3	36.3 (OS-12, 31.1%) (35.9 for GBM; 43.6 for non-GBM)	18.7 (TTP)	NR	KPS	2.1	(55)
Tselis *et al*, 2007	84	80 (50-100)	IV (84)	Temp + HDR + ^{192}Ir implant	NR	40 (30-50)	5.0 Gy twice a day	37	NR	51 (3-207)		3.6	(56)
Darakchiev *et al*, 2008	34	80 (60-100)	IV (34)	Perm + LDR + ^{125}I implant + BCNU wafers	0.67/seed	120	NR	69 (OS-6, 82%; OS-12, 66%)	47 (PFS-12, 32%)	34 (8-90)	KPS, Iseed activity, age	35.3	(18)
Fabrini *et al*, 2009	21	80	III (3) IV (18)	Temp + HDR + ^{192}Ir balloon-shaped applicator	219 GBq (106-323)	18	6171.4[b]	8 months (4.0-18.5 months)	(PFS-6, 42%) NR	13.8 (9.7-19.8)	KPS	9.5	(57)
Archavlis *et al*, 2013	50	90	IV (50)	Temp + HDR + ^{192}Ir implant	NR	40 (30-50)	5.0 Gy twice a day	37	32 (PFS-6, 64%)	46 (3-207)	TTP1, TTP2	10	(11)
Kickingereder *et al*, 2014	98	90 (60-100)	IV (98)	LDR + ^{125}I implant	16.1 (2.1-63.3)	60	7.53	10.4 months (OS-3, 95.8%; OS-6, 85.2%; OS-12, 39.0%)	5.9 months (PFS-3, 77.6%; PFS-6, 48.8%; PFS-12, 16.2%)	17.4 (1.6-70.0)	KPS, age, adjuvant chemotherapy	NR	(58)
Archavlis *et al*, 2014	17	90 (80-100)	IV (17)	Temp + HDR + ^{192}Ir implant	NR	40	5.0 Gy twice a day	8 months	7 months	38.1	NR	35	(61)

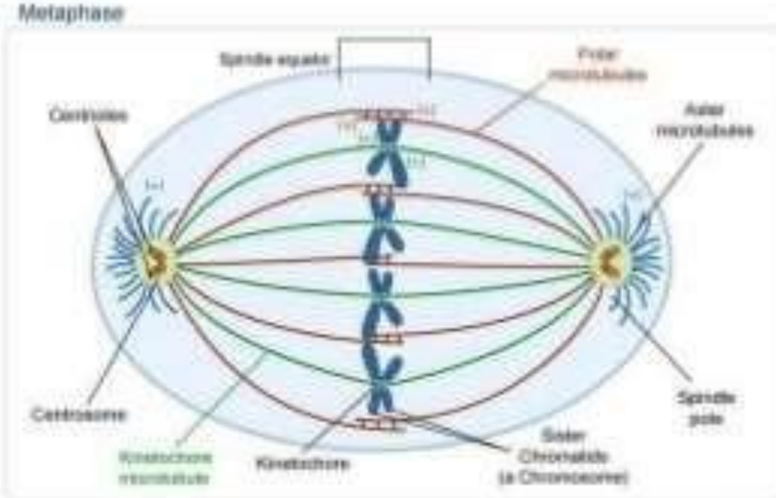
[a]Data presented as the median (range); [b]calculated from information provided. KPS, Karnofsky performance status; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival; post-OS, median OS after re-irradiation; post-PFS, median PFS after re-irradiation; OS-6, 6-month OS rates; OS-12, 12-month OS rate; OS-24, 24-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PFS-24, 24-month PFS rate; TTP1, time to progression after initial irradiation; TTP2, time to progression after re-irradiation; RPA, recursive partitioning analysis; NR, data not reported; ; BCNU, carmustine; GBM, glioblastoma multiforme; perm, permanent; temp, temporary; LDR, low-dose rate; HDR, high-dose rate; I, iodium; Ir, iridium.

Combinations with Systemic Therapy and Re-irradiation

- Bevacizumab has been most studied.
- Several series have suggested an improvement in OS and PFS with bevacizumab + radiotherapy
- Combination with gamma knife SRS, bevacizumab also results in a lower risk of adverse radiation effect. Park et al J Neurooncol 2012;107:323-333
- Anecdotal evidence for concurrent temozolamide.
- More recent work has involved combining RT with panobinostat (a histone deacetylase inhibitor). Shi W et al J Neurooncol 2016;127:535-539.

Novocure (TTF):

- Uses **electric fields** within the human body that disrupt the rapid cell division exhibited by cancer cells.
- Disrupt **mitotic spindle microtubule** assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis.
- Affect only **one cell type** at a time; The frequency used for a particular treatment is specific to the cell type being treated.
- TTF therapy has not been shown to affect cells that are not undergoing division.



ELSEVIER

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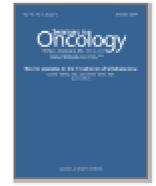

Response Patterns of Recurrent Glioblastomas Treated With Tumor-Treating Fields ☆, ☆☆

Josef Vymazal [a, b], Eric T. Wong [c]

- Overall response rate across was 15%

- Responses to TTF Therapy
  - Slow: (median time to response, 5.2 months)
  - Durable (median duration, 12.9 months)

➢ Response duration was highly correlated with OS (*P*<.0001)

Thank You