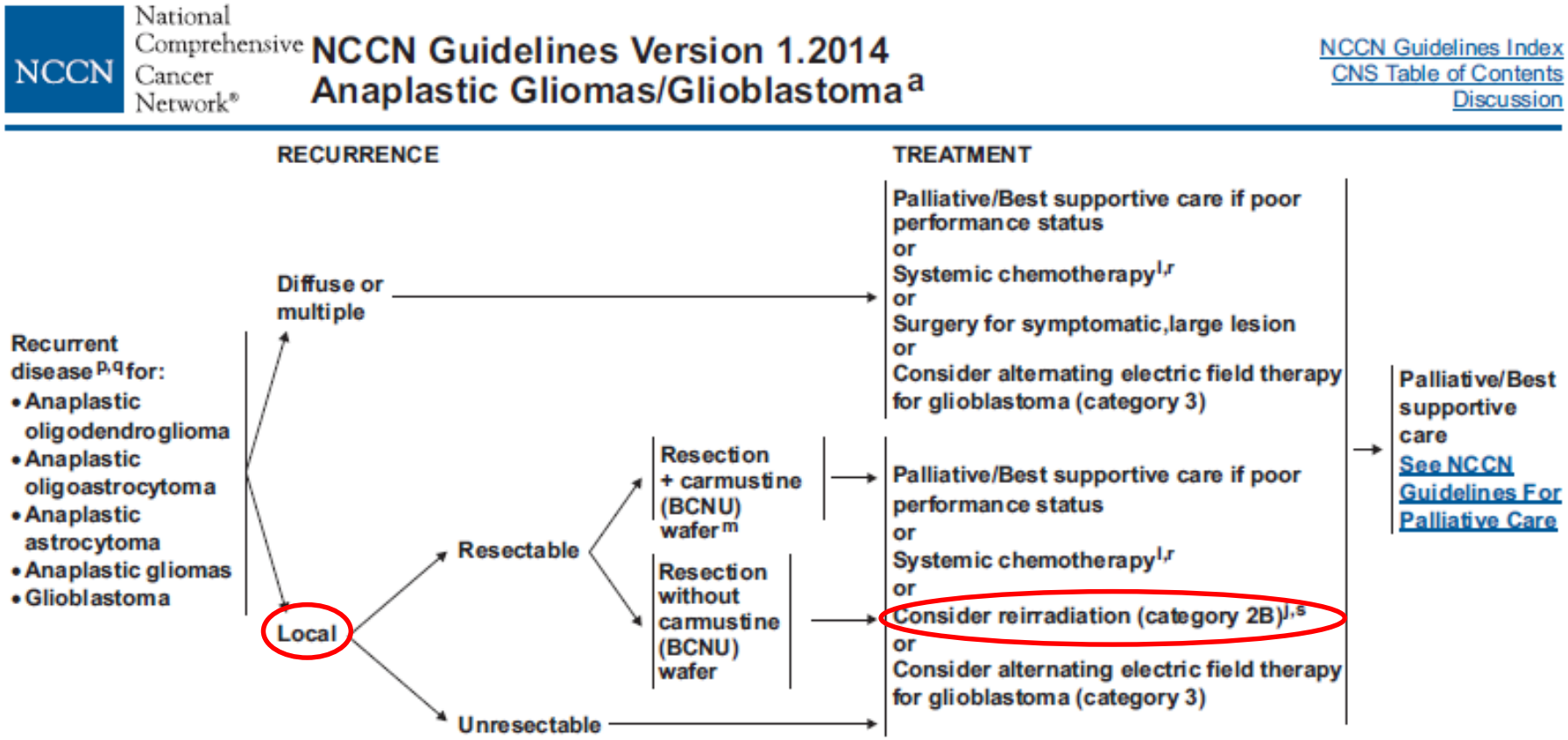
Recurrent high grade gliomas: role of RT



[s]Especially if long interval since prior RT and/or if there was a good response to prior RT.

clinical practice guidelines

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High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Re-irradiation is being considered increasingly for recurrent small tumours [IV, C], although there is considerable doubt about its benefit and the literature lacks prospective and comparative trials [62, 63]. The few limited size case series do not allow for any conclusion.

Recurrent high grade gliomas: role of RT
Introduction

- Malignant gliomas relapse in up to 90% of cases in close proximity to the resection site or the initially irradiated volume

- The high recurrence rate of approximately 100% is caused by the infiltrative growth characteristics of this tumor type, with unrelenting spread throughout the normal brain

- The tolerance dose of the healthy brain tissue is the limiting factor of the reirradiation dose that can be applied with an ucceptable late morbility profile

- Recovery capacity (→ size of the reirradiation dose) depends on:
  - Treatment volume
  - Initial BED (size of initial dose)
  - Time interval between the initial exposure and reirradiation

Recurrent high grade gliomas: role of RT
Introduction

- No experimental data available on reirradiation tolerance of the brain
- A standard protocol for reirradiation of brain tumors does not exist
- A large variety of irradiation treatment schemes is used with regard to total dose, size, and number of fractions. In most clinical reports, the physical radiation doses of both the initial and repeated radiation treatment are given.
- BED (α/β ratio of 2 Gy for the low repair capacity of the normal brain)
- Irreversible late radiation toxicity = clinically or histopatologically proved brain necrosis

Recurrent high grade gliomas: role of RT
Introduction

- Time interval is less important than the total dose (a correlation between the time interval between the initial and reirradiation course and the incidence of radionecrosis was not found)

- No data relative to QoL

- Since PFS is often difficult to determine due to the intricate patterns of imaging after radiation including edema or post-radiotherapy contrast-enhancement, as well as potential other treatment-related differences in imaging, survival after re-irradiation was chosen as a “ hard endpoint ” correlating with treatment efficacy

- The number of beams and the time interval between their application as well as the protracted treatment time may influence the effectiveness of treatment. No incomplete repair correction for loss of biologic effect could be made for those data.

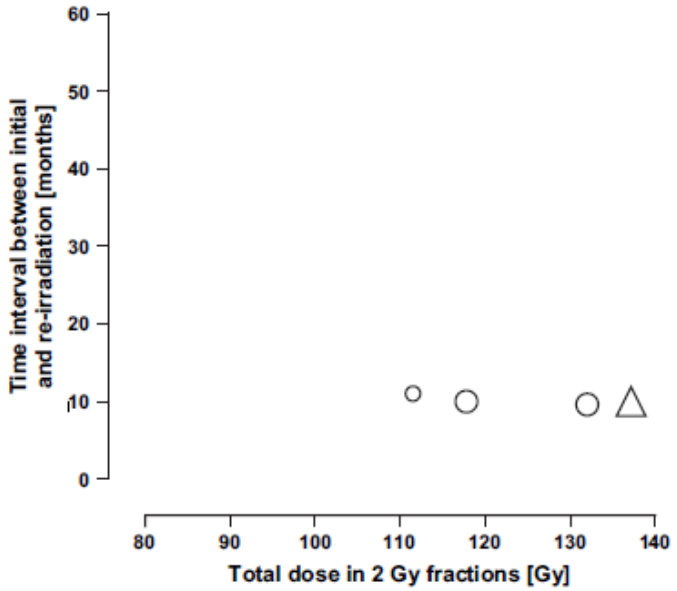

Fig. 3. The normalized total dose ($NTD_{cumulative}$) as a function of the time interval between the initial treatment and reirradiation in patients who underwent reirradiation with SRS. Open circles indicate that none of the patients in the study showed brain necrosis; open triangles indictates patient(s) with radionecrosis in the study. Symbol size represents the number of patients in the study. Small symbols indicate <25 patients, medium symbols 26 to 50 patients, and large symbols >50 patients.

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CLINICAL INVESTIGATION — Brain

REIRRADIATION TOLERANCE OF THE HUMAN BRAIN

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The shortest time interval between the first and reirradiation of the CNS in the present overview was 3 months

Despite this short time interval, even at the maximum BED cumulative of 210 Gy, no tissue necrosis was observed, but in other reports necrosis was found at lower BED cumulative and longer time interval

For the CNS, the time interval is less important than the total dose

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Revue générale

Réirradiation cérébrale des tumeurs primitives malignes ou secondaires

Reirradiation in primary or secondary brain tumors

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CLINICAL INVESTIGATION **Brain**

REIRRADIATION TOLERANCE OF THE HUMAN BRAIN

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J Neurooncol. 2014 Jul;118(3):489-99. doi: 10.1007/s11060-013-1337-6. Epub 2014 Apr 12.

The role of radiotherapy in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline.

Ryu S[1], Buatti JM, Morris A, Kalkanis SN, Ryken TC, Olson JJ; AANS/CNS Joint Guidelines Committee.

REVIEW ARTICLE

Improvement, Clinical Course, and Quality of Life After Palliative Radiotherapy for Recurrent Glioblastoma

Carsten Nieder, MD,¶ Sabrina T. Astner, MD,† Minesh P. Mehta, MD,‡ Anca L. Grosu, MD,§ and Michael Molls, MD†*

Review

Open Access

Radiotherapeutic alternatives for previously irradiated recurrent gliomas

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Recurrent high grade gliomas: role of RT
Issues

- Selection of patients
- Dose/Fractionation scheme
- Treatment Volumes
- Radiotherapy techniques
- Association with chemotherapy

Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma

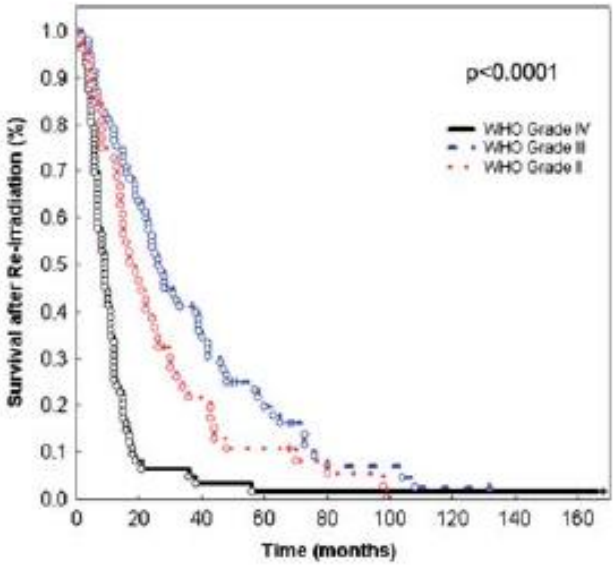
STEPHANIE E. COMBS[1], LUTZ EDLER[2], RENATE RAUSCH[2], THOMAS WELZEL[1], WOLFGANG WICK[3] & JÜRGEN DEBUS[1]

- Some " subgroups of patients " benefit from this treatment more than others

- A patient cohort: 233 patients with recurrent gliomas (38% GBL) treated between 1990 and 2010 with FSRT in a single institution

- The median PTV was 47 ml (range 3 – 758 ml)

- Re-irradiation was performed as FSRT with a median dose of 36 Gy in 2 Gy daily single fractions, 5 fractions per week, delivered by a 6 MV linear accelerator



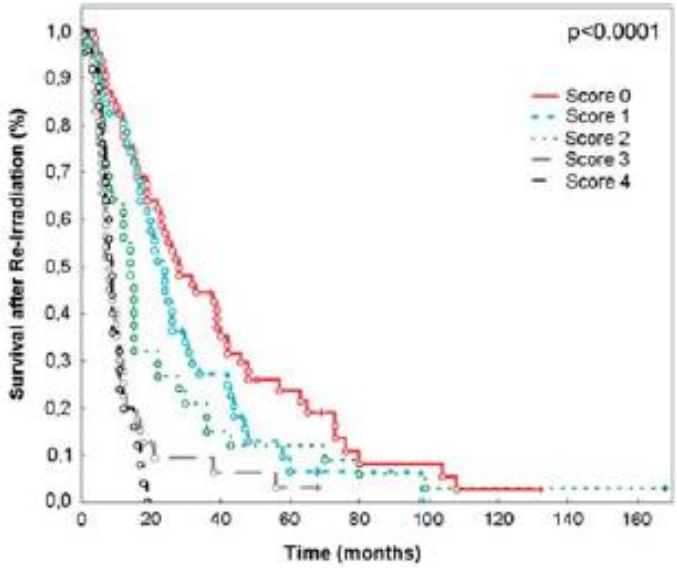
	6 months	12 months	24 months	36 months
GBM	69%	23%	5%	2%
WHO Grade III	83%	68%	41%	22%
WHO Grade II	84%	71%	46%	31%

Figure 1. Survival after re-irradiation according to primary histology. The table shows survival at 6, 12, 24 and 36 months.

- We observed radiographically diagnosed and histologically confirmed radiation-induced necrosis after re-irradiation in one patient only.
- No other severe early or late side effects CTCAE Grade 2

Table II. Factors identified as signficiantly influencing survival after re-irradiation used for the generation of the prognostic score.

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 betweeen RT and re-RT	≤ 12 months	1
	> 12 months	0



	6 months	12 months	24 months	36 months
Score 0	89%	73%	50%	35%
Score 1	82%	74%	41%	23%
Score 2	68%	50%	25%	11%
Score 3	68%	20%	6%	3%
Score 4	72%	28%	8%	4%

Figure 4. Survival after re-irradiation according the newly generated prognostic score.

Clinical data on brain reirradiation by conventional radiotherapy: Physical dose, survival and toxicity

Série	Année	Nombre de malades/type tumoral	Dose d'irradiation encéphalique en totalité antérieur/dose par fraction/BED_2 [49]	Délai médian entre les deux irradiations (mois)	Dose médiane réirradiation/dose par fraction/BED_2 [49]	Volume cible de réirradiation	Dose cumulée BED_2 [49]	Médiane de survie sans progression	Médiane de survie globale/taux de survie à un an	Complications
Bauman et al. [8]	1996	34 Gliome de haut grade : 10 Gliome de bas grade : 7 Autres : 17	54–72 Gy/1–1,8 Gy/NC	4–100	18–74 Gy/1–3 Gy/non calculée	Irradiation encéphalique en totalité : 15 patients	Non calculée	3,3 mois	8,3 mois	Déclin cognitif : 2 patients Radionécrose : 3 patients
Kim et al. [38]	1997	51 Glioblastome multiforme : 7 Astrocytome anaplasique–gliome de bas grade : 13	59,4 Gy/1,8 Gy/112,9 Gy	38 (9–234)	36 Gy/1,8 Gy/68,4 Gy	Prise de contraste gadolinium IRM + 5 mm	181,3 Gy	Non précisée	9 mois 26 %	Radionécrose : 1 patient
Hayat et al. [34]	1997	21 Gliome de bas grade : 10 Gliome de haut grade : 11	45 Gy/2,25 Gy/95,6 Gy	31 (3–100)	30 Gy/2,5 Gy/67,4 Gy + lomustine	Gliome de bas grade : prise de contraste scanographie + 1–2 cm Gliome de haut grade : œdème + 1 cm	163,1 Gy	Non précisée	22 mois gliome de bas grade : 26 mois Gliome de haut grade : 13 mois	Traitement par corticoïdes prolongé
Arcicasa et al. [5]	1999	24 Gliome de haut grade : 24	60 Gy/2 Gy/120 Gy	14	34,5 Gy/1,5 Gy/60,4 Gy + lomustine	Prise de contraste + œdème + 2 cm scanographie ou IRM	180,4 Gy	8,5 mois	13,7 mois	Non précisées
Nieder et al. [50]	1999	32 Glioblastome multiforme : 21 Astrocytome anaplasique–autres : 11	58,5 Gy/1,3 Gy × 2 par jour/96,5 Gy	20 (2–120)	45,5 Gy/1,3 Gy × 2 par jour/75,1 Gy 45 Gy/1,5 Gy × 2 par jour/78,8 Gy.	Tumeur + œdème	171,6 Gy 175,3 Gy	5 mois	8,5 mois 30 %	Radionécrose : 3 patients histologiquement prouvé : 2 patients
Veninga et al. [78]	2001	39 Astrocytome anaplasique : 29	60 Gy/2 Gy/109,9	32,8	46 Gy/2 Gy/92 Gy	Prise de contraste + œdème + 1 cm scanographie ou IRM	197,5 Gy	8,6 mois	10,9 mois	Radionécrose : 1 patient
		Oligodendrogliome : 10	50 Gy/2 Gy/103,8 Gy	54,6			203,8 Gy			Traitement par corticoïdes prolongé : 1 patient

Clinical data on brain reirradiation by FSRT: survival, and toxicity

Série	Année	Nombre de patients	Âge (ans) (min–max)	Indice de Karnofsky médian % (min–max)	Glioblastome/ Autres[c]	Dose antérieure médiane (min–max)	Intervalle traitement initiale RCS (mois)	Diamètre Volume médian (cm/cm^3) (min–max)	Survie globale médiane (mois) 1 an/2 ans (min–max)	Survie sans récidive médiane (mois) 1 an/2 ans (min–max)	Facteurs pronostiques	Complications : nombre de patients
Laing et al. [42]	1993	22	34 (14–56)	70 (50–100)	12/7	55 (40–60)	20 (3–81)	5 (1,4–7)/25 (1–93)	9,8 mois	–	–	Détérioration : 10
Glass et al. [27]	1997	20	44 (6–73)	90	13/7	–	8	–/14 (2–122)	13,7 mois	–	–	Radionécrose : 3
Shepherd et al. [67]	1997	33	37 (19–55)	80	0/29	55 (45–60)	29 (5–174)	5 (2–7)/24 (3–93)	10,7 mois	–	–	Corticothérapie prolongée : 1 ; Radionécrose : 3 ; Réopération : 2
Lederman et al. [46,47]	19982000	88	56 (21–82)	70 (50–100)	14/0	60	7,8	–/33 (1,5–150)	7 mois 17 %/3,4 %	–	GTV	Radionécrose : 7 ; Réopération : 11
Hudes et al. [36]	1999	20	NP	80 (60–100)	19/1	60 (44–72)	3 (0,7–45)	–/13 (1–47)	10,5 mois	–	Dose, GTV	Corticothérapie prolongée : 2
Cho et al. [13]	1999	25	53 (25–75)	60 (40–80)	15/5	59,4 (48–63)	19	–/25 (4–115)	12 mois 50 %/–	–	Grade, indice de Karnofsky	Corticothérapie prolongée : 41 % Radionécrose : 1 ; Réopération : 3
Selch et al. [64]	2000	21	54 (14–72)	80 (50–90)	14/7	60	9	2,5 (1–4,8)/12 (4,5–33,7)	6 mois 15 %/–	4 mois	Grade	–
Voynov et al. [80]	2002	10	48 (33–85)	80 (60–100)	4/6	59,7 (35–62,1)	19 (2–200)	–/34,7 (4,3–75)	10,1 mois 50 %/33 %	–	–	Réopération : 2
Combs et [15]	2005	172	43 (23–75)[a] 54 (18–76)[b]		59/42	60	32 (3–126)[a] 10 (3–71)[b]	–/49 (2,5–636)[e]	16 mois (1–99)[a] 8 mois (1–105) 23 %/–[b]	8 mois (1–99)[a] 5 mois (1–21)[b]	Grade	–
Vordermark et al. [79]	2005	19	50 (11–74)	90 (60–90)	9/10	(45–61)	19 (3–116)	–/15 (4–70)	9,3 mois (1,9–77,6) 26 %/16 %	4,9 mois (1,3–37,3)	Grade	Réopération : 5
Grosu et al. [29]	2005	44	50 (36–75)	80 (40–100)	33/11	60 (42–70)	16 (4–7)	(0,5–4,5)/15 (1–61)	8 mois (6–10)	–	SPECT/scanographie /IRM, chimiothérapie	–
Wurm et al. [82]	2006	25	46 (11–66)	80 (50–100)	20/5	54,4–60	–	–	14,5 mois (3–56,4)	10,5 mois (1,4–47,8)	–	–
Kohshi et al. [39]	2007	25	46 (14–81)	75 (40–100)	11/14	60 (50–72)	–	–/8,7 (1,7–159)	11 mois (4–12)[b] 19 mois (0–38)[a]	–	–	–
Ernst–Stecken et al. [24]	2007	15	49 (31–69)	80 (60–100)	10/3	57,7 (45–60)	10 (2–47)	–/5,7 (0,8–22)	85 %/–	15 mois 53 %/–	Grade	–
Schwer et al. [63]	2008	15	47 (23–65)	70 (60–90)	11/4	60 (54–61,2)	12 (3–57)	–/41,3 (8–150)[e]	10 mois (2–29).	7 mois (2–24) 40 %/–	–	–
Fokas et al. [26]	2009	53	53 (22–71)	< 70 % : 34 ≥ 70 % : 19	53/0	54 (38,5–64)	–	–/35 (3–204)	9 mois 83 %/45 %	12 mois 40 %/10 %	indice de Karnofsky	Réopération : 0
Patel et al. [61]	2009	10	44 (28–60)	90 (70–90)	10/0	50–60[d]	14,9 (3,7–31,2)	–/51,1 (16,1–123,3)	7,5 mois	–	Répondeurs	–
Gutin et al. [31]	2009	25	56 (30–80)	80 (70–100)	20/5	59,4 (54–61,2)	15 (2–292)	–/34 (2–62)	12,5 mois	7,5 mois	–	–

Clinical data on brain reirradiation by FSRT: Physical dose, biologically effective dose (BED), normalized total dose in 2-Gy fractions (NTD), survival, and toxicity

		First course			Reirradiation						Toxicity	
Authors (Reference)	*n*/Grade	Dose (Gy)	BED_2 (Gy)	Interval (mo)	Dose (Gy)	BED_2 (Gy)	Volume (cc)	Cumulative BED_2 (Gy)	NTD (Gy)	Survival (mo)	Acute	Late
					Median							
Shepherd *et al.* (21) Dose escalation	29 AA 4 AO/Ep 3 LG	55	104.3	29	35 5*	122.5	24	226.8	113.4	11	Not severe	12% "Clinical" necrosis 6% Necrosis
Cho *et al.* (22)	15 GM 10 grade III	60 1,8	114	19	37.5 2.5*	84.4	25	198.4	99.2	12	8%	1 Clinical necrosis No pathologic necrosis
Hudes *et al.* (23) Dose escalation	19 GM 1 AA	60	114	3	24, 30, 35 3–3.5*	96.3 max	13	210.3 max	105.2	10.5	Not severe	No necrosis
Lederman *et al.* (24)	88 GM	60 1.8	114	6.3	24 6† + Paclitaxel	96	32.7	210	105	7 9.4 (+Chemo)	Not severe	8% Necrosis 2% Mixed tum/necrosis
Voynov *et al.* (25)	5 GM 5 AA	59.7 1.8–2	~114	6.3	30 5*	105	34.7	219	109.5	10.1	Not reported	10% Necrosis 10% Mixed tum/necrosis 40% "Clinical" necrosis
Grosu *et al.* (26)	35 GM 9 AA	60 1.8–3	114–150	16	30 5* (+TMZ n = 29)	105	18	219–255	109.5–127.5	6 11 (+Chemo)	Not severe	13% Mixed tumor/ necrosis
Combs *et al.* (27)	63 LG	60 2	120	50	36 2*	72	44	192	96	23	Not severe	Not severe
Combs *et al.* (28)	40 AA	59.4 2	118.8	34.5	36 2*	72	56.2	190.8	95.4	16	Not severe	Not severe
Combs *et al.* (29)	53 GM	57 2	114	10	3* 2*	72	49	186	94	8	Not severe	Not severe
Vordermark *et al.* (30)	14 GM 5 AA	54-61 /1.8–2 (63%) 45/3 (11%) 54/1.8 b.i.d. (26%)	114 112.5 102.6	19	30 5	105	15 ml	207.6–229	103.8–114.5	7.9 15.4	Not severe	5% mixed tum/necrosis
Ernst-Stecken *et al.* (31)	11 GM 4 AA	57.75 1.8–2 ?	~115	10	35 5†	122.5	22.4	237.5	118.8	12	Not severe	No necrosis
Kohshi *et al.* (12)	11 GM 14 AA	60 2	120	13	22/8 fx + HBO	52.3	8.7	172.3	86.2	11 19	Not reported	28% necrosis
Laing *et al.* (32)	12 GM	55	~110	20	20–45/5* (n = 2)	70	25	180–267.7	90–133.9	11	Not severe	*n* = 5 Neurologic detoriation
Dose escalation	7 AA 3 LG	1.8-2				157.5				9		No surgery performed

Clinical data on brain reirradiation by LINAC–based SRS: Physical dose, biologically effecticve dose (BED), normalized total dose in 2-Gy fractions (NTD), survival, and toxicity

Authors (Reference)	*n*/Grade	First course			Reirradiation						Toxicity	
		Dose	BED_2 (Gy)	Interval (mo)	Dose	BED_2 (Gy)	Volume (cc)	Cumulative BED_2 (Gy)	NTD (Gy)	Survival (mo)		
		Median									Acute	Late
Chamberlain *et al.* (33)	5 GM 15 Astro	60 +CT 2	120	11	13.4	103.2	17	223.2	111.6	8	7 Increased intracranial pressure 1 Death within 24 h	1 Hypersomnolence
Van Kampen *et al.* (34)	27 GM	60 2	120	9.6	16	144	21	264	132	9	Not severe	No necrosis
Cho *et al.* (22)	27 GM 19 AA	60 1.8	112.9	10	17	161.5	30	274.4	137.2	11	41% Transient progression of neurological symptoms	17% Necrosis 13% "Clinical" necrosis
Combs *et al.* (35)	32 GM	54 2	108	10	15	127.5	10	235.5	117.8	10	Not severe	No necrosis

Clinical data on brain reirradiation by LINAC–based SRS: survival, and toxicity

Série	Année	Nombre de patients	Âge (ans) (min–max)	Indice de Karnofsky médian % (min–max)	Glioblastome/ Autres[e]	Dose antérieure de radiothérapie conformationnelle tridimensionnelle médiane (min–max) (Gy)	Intervalle traitement initial radiothérapie monofractionnée en conditions stéréotaxiques (mois)	Diamètre Volumes médians (cm/cm^3) (min–max)	Survie globale médiane (mois) 1 an/2 ans (min–max)	Survie sans récidive médiane (mois) 1 an/2 ans (min–max)	Facteurs pronostiques	Complications : nombre de patients
Alexander et Loeffler [2]	1992	25	45 (6–67)	80 (40–90)	16/9	59,4 (53,9–72)	14 (3–120)	–/10 (2–27)	> 9 mois	–	–	Radionécrose : 3
Chamberlain et al. [10]	1994	20	34 (8–62)	80 (50–100)	5/10	54-72	11	–/17 (3–53)	8 mois	–	–	Hypersomnolence 1
Schrieve et al. [69]	1995	86	46 (9–77)	80 (40–100)	72/4	–	10	–/10 (22–83)	10,2 mois 45 %/19 %	–	Âge, GTV	Épilepsie : 3 Radionécrose : 19 Réopération : 19
Larson et al. [43]	1997	132	45 (2–70)	90 (40–100)	66/27	–	> 4	–/6,5 (0,3–96)	40–53 semaines 24–68 %/12–61 %[f]	–	GTV	–
Kondziolka et al. [40]	1997	42	51 (3–72) + 45 (3–75) =	90 (50–100) + 90 (50–100) =	19/23	60 +	8	–/6,5 (0,9–31) + –/6 (0,5–20) =	30 mois (2–74) + 31 (3–47) = –/67 % =	–	Âge, score RPA	Radionécrose < 3
Van Kampen et al. [77]	1998	27	50	≥ 70	27/0	60	9,6	–	4,5 mois 38 %/13 %[h]	–	–	–
Hall et al. [32]. Cho et al. [13]	1999	46	48 (16–74)	70 (50–90)	27/4	60 (38,5–66,6)	10	–/10 (1–54)	11 mois 48 %/–	–	Grade, indice de Karnofsky	Corticothérapie prolongée : 41 % Réopération : 10 Radionécrose : 6
Park et al. [59]	2000	23	53 (36–80)[g]	80 (60–90)[g]	23	60 (48–62,9)[g]	–	–/11,5 (2,6–37,5)[c,g] –/8,9 (0,9–16,5)[d,g]	10,3 mois (1,9–20,3)[g,h]	4,7 mois (0,6–7,5)[g]		Épilepsie : 2 Réopération : 3 Corticothérapie prolongée : 9
Larson et al. [44]	2002	26	44 (24–62)[a] 53 (22–74)[b]	90 (70–100)	14/12	–	43 (7–175)[a] 12 (3–50)[b]	–/2,7 (0,4–13,4)[a] –/8 (1,6–29,7)[b]	68 semaines [a] 38 semaines [b]	29 semaines [a] 15 semaines [b]	Âge, indice de Karnofsky	Aucune
Noël et al. [51]	2004	14	52 (49–58)	90 (60–100)	10/4	59,4 (50,4–59,4)	12,5	3,8 (2,5–8,6)/7 (2–35)	11,6 mois 36 %/12 %	8,2 mois 1 an : 14 %	GTV, grade histologique	Radionécrose : 2
Ulm et al. [76]	2005	33	55 (21–80)[g]	90 (60–100)[g]	–	60[g]	–	–/10 (1–73)[g]	16,2 mois[g]	–	Score RPA, zone éloquente, récidive [g]	Réopération : 22[g] Radionécrose : 2[g]
Patel et al. [61]	2009	26	53 (25–70)	80 (50–100)	23/0	50–60[g]	12,5 (0,8–119)	–/10,4 (0,3–60,1)	8,4 mois	–	Répondeurs	Radionécrose : 2

Recurrent high grade gliomas: role of RT
Issues

- Selection of patients
- Dose/Fractionation scheme
- Treatment Volumes
- Radiotherapy techniques
- Association with chemotherapy

CLINICAL INVESTIGATION **Brain**

REIRRADIATION OF RECURRENT HIGH-GRADE GLIOMAS USING AMINO ACID PET (SPECT)/CT/MRI IMAGE FUSION TO DETERMINE GROSS TUMOR VOLUME FOR STEREOTACTIC FRACTIONATED RADIOTHERAPY

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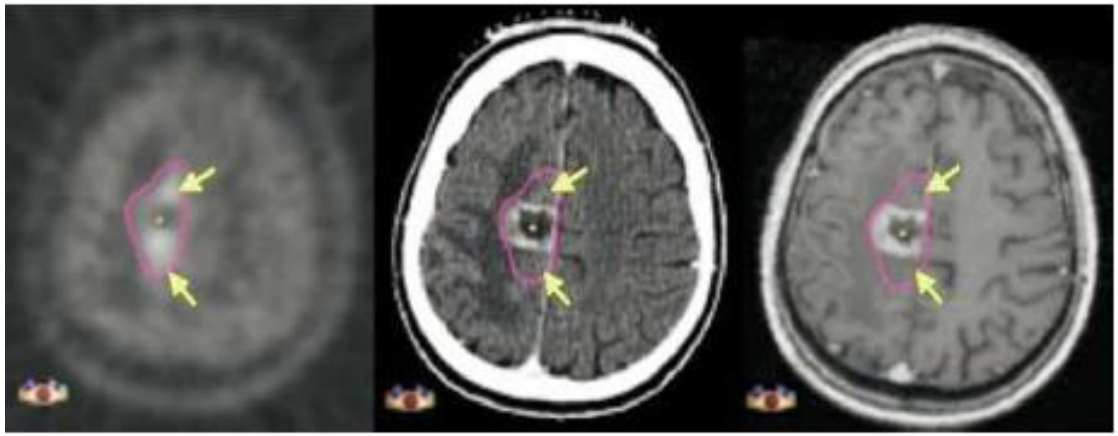
- A prospective non-randomized single-institution trial to investigate the implementation of amino-acid PET or SPECT imaging to improve re-irradiation using SFRT

- This is the first study of biologic imaging optimized SFRT plus temozolomide in recurrent HGGs showing the feasibility and safety of this approach.

- Whether treatment planning with SPECT/PET independently influences survival has to be studied in a larger series of patients



Recurrent high grade gliomas: role of RT
Issues

- Selection of patients
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Recurrent high grade gliomas: role of RT in association with chemotherapy

- To further optimize treatment results obtained by re-irradiation

- Potential increase of radiation induced toxicity, especially in substances with strong radiosensitizing potential

- Paucity of data reporting on the combination of chemotherapy and RT for recurrent gliomas

- Ongoing phase I-II trials

Recurrent high grade gliomas: role of RT
Conclusions

- In the past, a number of attempts have been made to salvage patients with recurrent gliomas with a second course of radiotherapy.

- A number of invasive and non-invasive techniques are now available; the choice as to which modality should be applied has to be made individually for each patient, reflecting possibilities, potential benefit and side effects.

- Using modern highly conformal RT techniques, precise dose application to a defined target volume is possible while the surrounding normal tissue can be spared, in a non-invasive approach.

- Re-irradiation using high precision radiotherapy offers significant benefit, at least for a subgroup of patients. For each patient, the fractionation scheme must be chosen individually.