UNIVERSITÀ DEGLI STUDI FIRENZE

11.20 - 12.20 **WORKSHOP**

La re-irradiazione nei tumori del Sistema Nervoso Centrale

Moderatori: C. Baiocchi, M. Buglione di Monale

Perché si? - **S. Scoccianti**

Perché no? - **G. Minniti**

Imaging multimodale - **M.F. Osti**

Discussione

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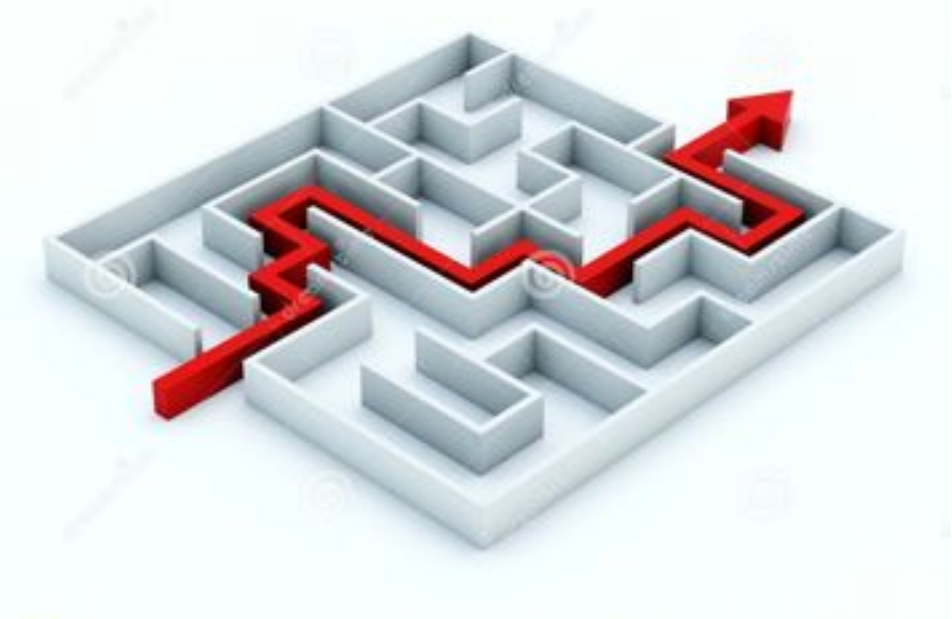
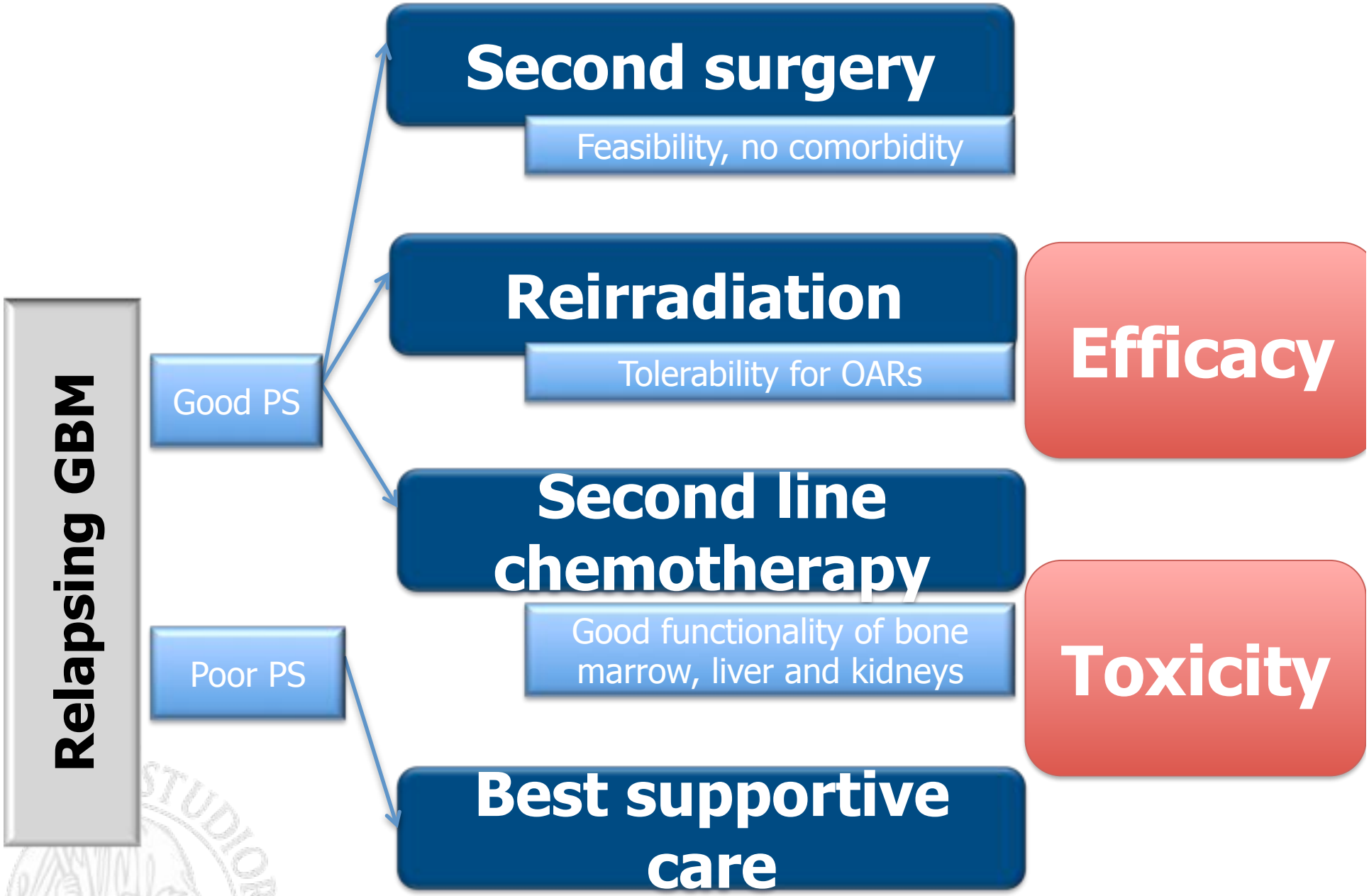
Reirradiation in GBM



- Efficacy and toxicity: findings from literature
- Practical considerations for treatment planning
- Comparisons with other therapeutic options

Therapeutic options



Pitfalls

Most studies are retrospective and with few patients

Some series included TMZ-naïve patients

Lack of data about QoL

Selected patients

Pseudoprogression

Lack of biological data

inhomogeneity in the endpoints of the different series

Findings from literature

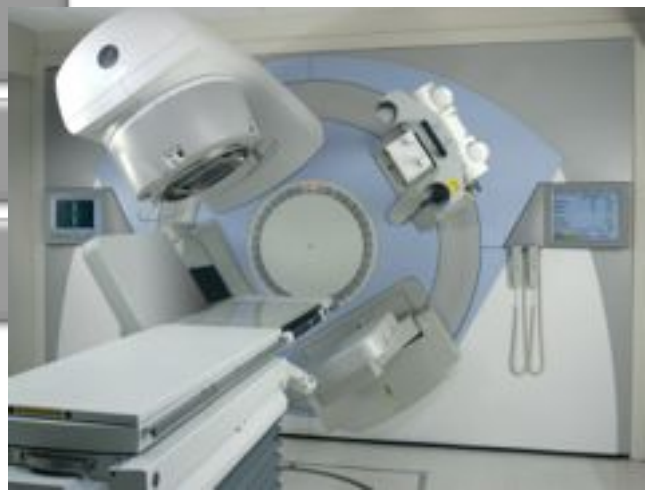
Relapsing GBM

Good PS

Reirradiation

Tolerability for OARs

- **RS**
- **HFSRT**
- **FSRT**
- **3dCRT**



Radiosurgery as second RT

Median dose: 12.2-24 Gy
Median survival: 8-14.3 months
PFS@1y 20.5%
Severe toxicity: 9.8-31%

Author	Pt. Number	Histology	Median Dose (Gy)	Tumor size (ml; median)	Median survival (months)	Rate of Severe Toxitic/ Reoperation rate (%)
Chamberlain et al, 1994	20	5 GBM, 10 AA, 5 other	13.4	17	8	-
Cho et al., 1999	46	27 GBM/19 AA	17	10	11	22%
Combs et al., 2005	32	GBM	15	10	10	-
Hall et al., 1995	35	26 GBM, 9 AA	20	28	8	31%
Kondziolka et al., 1997	23	AA	15.6	6	31	23%
Kondziolka et al., 1997	19	GBM	15	6.5	30	19%
Shrieve et al., 1995	86	GBM	13	10.1	10.2	22%
Hsieh et al.,2005	51	51 GBM	24	13.6	14.3	29%	_
Kohshi et al.; 2007	25	14 AA, 11 GBM	22	8.7	19 (AA), 11 (GBM)	16%	_
Kong et al; 2008	114	96 AA, 264 GBM	16	10,6	26 (AA), 13 (GBM)	24,4% (radionecrosis)	PFS@1y 20.5% GBM; 49.4% AA
Patel et al; 2009	26	GBM	18	10,4	8,5	_	_
Elliott et al., 2010	26	16 GBM,10 AA	15	< 12	13.5	11.5%	
Torok et al; 2011	14	GBM	24	6,97	10	_	TTP 5 months
Skeie et al; 2012	51	GBM	12,2	12,4	12	9,8%	_
Martínez-Carrillo M et al 2014	87	46 GBM, 41 AA	18	8,7	17 AA 7,5 GBM	_	_

HFSRT as second RT

Median dose: 20-50 Gy (3-7 Gy per fractions) PFS@1 y 22%
Median survival : 6-13.5 months Severe toxicity: 0-36%

Table 3: Series of patients with recurrent gliomas treated with hypofractionated stereotactic radiotherapy (H-FSRT).

Author	Pt. Number	Histology	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)	PFS
Ernst-Stecken et al., 2006	15	GBM	22.4	35	7	-	0%	75% @6m
Hudes et al., 1999	19 (1)	GBM (AA)	12.6	30	3	10.5	0%	-
Laing et al., 1993	22	GBM	-	30–50 (range)	5–6 (range)	-	-	-
Selch et al., 2000	15 (3;3)	GBM (AA/LGG)	12	25	4–6 (range)	6.7	0%	-
Shepherd et al., 1997	29 (7)	GBM/AA (LGG)	24	20–50 (range)	5	11 (GBM/AA)	36%	-
Vordermark et al., 2005	10 (19)	II or III	15	30	5	13.5	26%	-
Vordermark et al., 2005	9 (19)	IV	15	30	5	7.4		-
Fokas et al.; 2009	53	53 GBM	35	30 Gy	3 Gy	9	No	22% @1y
Kim et al. *; 2010	8	5 GBM, 3 AA	69.5	25 Gy	5 Gy	7.6	0	-
Fogh et al.; 2010	147	105 GBM, 42 AA	22	35 Gy	3.5 Gy	11 (AA) 8 (GBM)	0.7%	-
McKenzie JT et al. 2013	35	4 AA, 29 GBM	-	30 Gy	5 Gy	8,6	9%	62%@6m
Ogura et al, 2013	30	24 GBM/6 LGG	-	35 Gy	7	10,2	6.1%	19%@6m

Conventionally fractionated SRT as second RT

Median dose: 36 Gy
Median survival : 11-21 months
Severe toxicity 12%

Table 2: Series of patients with recurrent gliomas treated with fractionated stereotactic radiotherapy (FSRT).

Author	Pt. Number	*Histology*	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)	mPFS (months)
Cho et al., 1999	15 (10)	GBM (AA)	74	37.5	2.5	11	12%	12
Combs et al., 2005	42	AA		36	2	50		8
Combs et al., 2005	59	GBM		36	2	21		5

Conventionally fractionated 3dCRT as second RT

Median dose: 36-46 Gy
Median survival : 6.9-9 months
PFS@1y 30%
Severe toxicity 2-6%

Kim et al.; 1997	7 GBM/ 20	GBM, AA, LGG	-	36	1.8	9	0	-
Nieder et al.; 1999	21 GBM/ 32	GBM, AA	-	45.5	1.3-1.5	8.5	6% necrosis	-
Veninga et al.; 2001	29 HGG/ 39	HGG, OD	-	46	2	6.9 (GBM)	2.6% necrosis	8.6 m (30% @ 12m)

Reirradiation + temozolomide

Median dose: 36 in 2Gy; 30 Gy in 5/6Gy; 20 Gy in RS PFS@1y 24%
Median survival : 8-12.4 months Severe toxicity 8-40%

Author	RT technique	CHT	PZ	Histology	Tumor size (ml)	Median dose (Gy)	Median Fraction size (Gy)	Median survival (months)	Toxicity	PFS
Grosu et al;2005	SFRT	TMZ 200 mg/ m2/day for 5 days	44	GBM (AA)	5-45	30	5	8	No G3-G4	-
Combs et al.; 2008	FSRT	TMZ 50 mg/mq daily	8 (17)	GBM (AA)	50	36	2	8 6mOS 84%	0	5 6mPFS 48%
Minniti et al.; 2011	FSRT	TMZ 75 mg/mq	36	GBM	13.1	37.5	2.5	9.7 6mOS 84%	8%	5 6mPFS 42%
Conti et al.; 2012	CybKn RS or HFSRT	TMZ 75 mg/mq/ d for 21/28 d	23	GBM	< 30	20	20	12	Bone marrow G>3 40%	7 6mPFS 66.7%
						20	10			
Minniti et al.; 2013	HFSRT	TMZ 75mg/mq	38 (16)	GBM (AA)	Max Ø < 4 cm	30	6	12.4	Bone marrow G>3 18%	12mPFS 24%

Reirradiation + bevacizumab

Median dose: 36 in 2Gy; 41.6 in 2.66; 30 in 6Gy; 15 Gy in RS PFS@1y 13-20%
Median survival : 8.4-12.5 months Severe toxicity 6-14%

Authors	Tech-nique	BEV	Pt number	Histology	Tumor size	Median Dose (Gy)	Median Fraction Dose (Gy)	Median Survival (months)	Rate of severe toxicity (%)	Median PFS (months)
Gutin et al.; 2009	HFSRT	25	25 (20 GBM)	HGG	-	30	6	12.5 12mOs 54%	12	6mPFS 65%
Cuneo et al.; 2012	GKn RS	51/ 63	63 (49 GBM)	HGG	4.8	15	15	10 12mOS 50%	10-14	6 6mPFS 38%
Shapiro et al.; 2013	HFSRT	24	24 (20 GBM)	HGG	35	30	6	12.2	11	6.8 12mPFS 20%
Niyazi et al.; 2012	3DCRT	20	30 (21 GBM)	HGG LGG	-	36	2	10.3	6	6.3 6mPFS 16%
Hundsberger et al.; 2013	3DCRT/ IMRT	10	14 (8 GBM)	HGG LGG	-	41.6	2.66	8.4	14	5.7 12mPFS 13%
Flieger M et al; 2014	3DCRT	57	71	GBM	-	36	2	8	-	6.8 6mPFS 42%

Radiosurgery

Median survival: 7.5-14.3 months	PFS@1y 20.5%	Severe toxicity: 9.8-31%

HFSRT

Median survival: 6-13.5 months	PFS@1 y 22%	Severe toxicity: 0-36%

Conventionally fractionated RT

Median survival: 6.9-21 months	PFS@1y 30%	Severe toxicity 2.6-12%

Reirradiation + temozolomide

Median survival: 8-12.4 months	PFS@1y 24%	Severe toxicity 0-40%

Reirradiation + bevacizumab

Median survival: 8.4-12.5 months	PFS@1y 13-20%	Severe toxicity 6-14%

RTOG 1205

Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

SCHEMA (4/15/14)

Bevacizumab-Naïve Recurrent GBM Patients:

Accrual (actual/required): 62/178

STRATIFY	Age 1. <50 2. ≥50 Karnofsky performance status 1. 60 2. 70-80 3. 90-100 Recent resection 1.Yes 2. No/biopsy only	**RANDOMIZE**	Arm 1: Bevacizumab alone q 2 weeks (control arm) Arm 2: Hypofractionated radiotherapy 35 Gy in 10 fractions with concurrent Bevacizumab q 2 weeks (experimental arm)

Principal Investigator: Christina Tsien, MD

Primary Objective:
To establish an improvement in overall survival in recurrent GBM patients receiving bevacizumab and re-irradiation compared with patients receiving bevacizumab alone.

Patient Population:
Patients with recurrent glioblastoma or variant (gliosarcoma or giant cell glioblastoma etc).

Dose

Volume

Efficacy

Reirradiation of GBM: doses

HFSRT	Vordermark, 2005: **≥30 Gy (5 Gy per fraction)** Hudes 1999; Fogh, 2010: **≥35 Gy (3.5 Gy per fraction)**

RS	**≈18 Gy ?**
2 Gy per fraction	**36 Gy ?**

Reirradiation of GBM: volume definition

HFSRT	Vordermark, 2005; Ernst-Stecken, JNO 2007; Gutin, IJROBP 2009; Fokas, 2009; Fogh, 2010; McKenzie, 2013
FSRT	Coombs, JNO 2008; Minniti, JNO 2011
3DCRT	Niyazi, IJROBP 2012 Flieger, JNO 2014

GTV = contrast-enhanced lesion in the T1w Gd MRI

CTV = GTV

Retreatment constraints to the OARs

Toxicity

Brain parenchyma and QUANTEC

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.091

QUANTEC: ORGAN SPECIFIC PAPER — Central Nervous System: Brain

RADIATION DOSE–VOLUME EFFECTS IN THE BRAIN

Yaacov Richard Lawrence, M.R.C.P.,* X. Allen Li, Ph.D.,† Issam el Naqa, Ph.D.,‡ Carol A. Hahn, M.D.,† Lawrence B. Marks, M.D.,¶ Thomas E. Merchant, D.O. Ph.D.,‡ and Adam P. Dicker, M.D. Ph.D.*

2 Gy per fraction	Incidence of radionecrosis
BED 120 Gy (range, 100–140)	5%
BED 150 Gy (range, 140-170)	10%

The incidence and severity is **dose and volume dependent** and can also be increased by *chemotherapy, age, diabetes, and spatial factors*

$BED_{60\ Gy\ in\ 2\ Gy\ fractions}$ 120 Gy

For large fraction sizes (>2.5 Gy), the incidence and severity of toxicity is unpredictable.

Retreatment constraints to the brain parenchyma

CLINICAL INVESTIGATION **Brain**

REIRRADIATION TOLERANCE OF THE HUMAN BRAIN

RAMONA MAYER, M.D., M.SC.,* AND PETER SMINIA, PH.D.†

	$NTD_{cumulative}$
Conventional RT reirradiation series	81.6–101.9 Gy
FSRT reirradiation series	90–133.9 Gy
RS reirradiation series	111.6–137.2 Gy

-No correlation between the time interval between the initial and reirradiation course and the incidence of radionecrosis

- **Radiation-induced normal brain tissue necrosis is found to occur at $NTD_{cumulative}$** (cumulative normalized total dose) **>100 Gy**

- Modern conformal treatment options, because of their limited volume of normal brain tissue exposure, allow brain reirradiation for palliative treatment of recurrent high grade glioma with an acceptable probability of radionecrosis

-BED = D (1 + d / [α/β])[Gy], with d = fraction dose [Gy], n = number of fractions, D = total physical dose [Gy], and α/β = tissue repair capacity [Gy].

–α/β = 2

-NTD being defined as **the total dose delivered in 2-Gy fractions at appropriate α/β ratio**. The NTD is the ratio of the BED and RE.

With RE = (1 + d/[α/β]), d = 2 Gy and an α/β ratio of 2 Gy, **NTD = BED/2**

$NTD_{cumulative}$ <100 Gy= BED <200 Gy

Postoperative RT 60 Gy in 2 Gy fractions

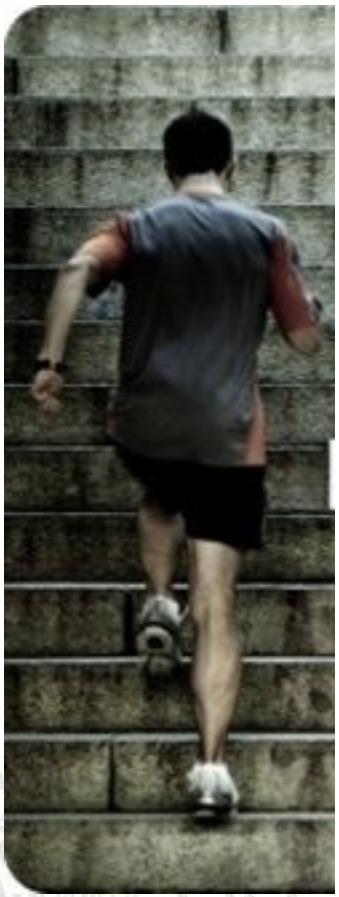
$BED_{first\ RT}$ 120 Gy

$BED_{second\ RT}$ 80 Gy

Reirradiation: ≤40 Gy in 2 Gy fractions

$NTD_{cumulative}$ <100 Gy= BED <200 Gy

$BED_{second\ RT}$ 80 Gy



HFSRT	BED
≥30 Gy (5 Gy per fraction)	105 Gy
≥35 Gy (3.5 Gy per fraction)	96.3 Gy

Brainstem and QUANTEC

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S36–S41, 2010

0360-3016/10/$ – see front matter

doi:10.1016/j.ijrobp.2009.08.078

QUANTEC: ORGAN-SPECIFIC PAPER **Central Nervous System: Brain Stem**

RADIATION ASSOCIATED BRAINSTEM INJURY

CHARLES MAYO, PH.D.,* ELLEN YORKE, PH.D.,† AND THOMAS E. MERCHANT, D.O., PH.D.‡

*Department of Radiation Oncology, University of Massachusetts Medical School, Worcester, MA, †Department of Medical Physics, Memorial Sloan Kettering Hospital, New York, NY, and ‡Division of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, TN

Entire brainstem	54 Gy	1.8/2 Gy
1-10 ml	59 Gy	1.8/2 Gy

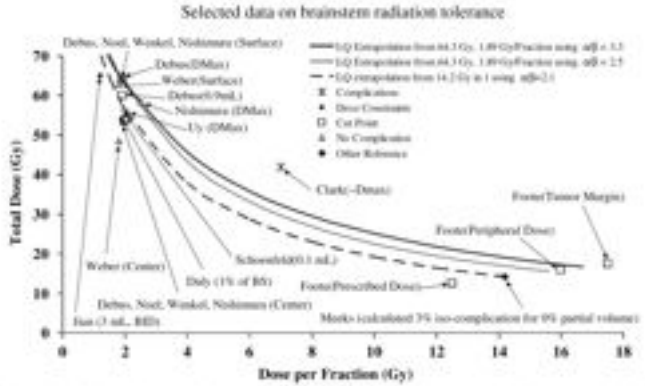


Fig. 1. Comparison of selected data on brainstem tolerance and dose constraints compared to linear quadratic (LQ) model extrapolations. Data points are marked with the corresponding author and dose parameter considered in parenthesis (*e.g.*, surface or maximum dose). Center, 0.9 mL, 0.1 mL, and 3 mL refer to the minimum dose to that hottest volume. Some data were estimated from the cited articles. Cut points illustrate thresholds determined by authors to correlate with significant increase in incidence of brainstem necrosis or neuropathy. Little quantitative data on brainstem doses is available in the dose range of stereotactic radiosurgery and hypofractionation. BID = twice daily; BS = Brain Stem; Dmax = maximum dosage.

"the apparent safety of the higher doses may be an artifact of the poor survival"

$\alpha / \beta = 3$ Gy

"There is no evidence that the tolerance of the pediatric patients differs from the adults"

Retreatment constraints for brainstem

Reirradiation after radical treatment for Nasopharynx cancer

	Constraints for brainstem	toxicity
Chen CC, 2011 Med Dosim	**Dmax <15 Gy** in 2 Gy fractions	-
Chua DTT, 2005 RO	**V10<10%** in 2 Gy fractions	Cranial neuropathy 10%
Chua DTT, 2003 RO	**Dmax <5 Gy** in radiosurgery	0%

	Dose to brainstem	toxicity
Zwicker F, 2011 Head Neck	- **Median cumulative maximum dose 62.7 Gy** ; - In 10 cases cumulative maximum dose **60-70 Gy** - in 11 cases cumulative maximum dose **71-86 Gy**	Cranial neuropathy 8%
Roeder F, 2011 Rad Onc	- **Median retreatment maximum dose 30 Gy** (10-**49**)	Cranial neuropathy 5.9%

Optic pathways and QUANTEC

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S28–S35, 2010

0360-3016/10/$ – see front matter

QUANTEC: ORGAN-SPECIFIC PAPER Central Nervous System: Optic Nerve/Chiasm

RADIATION DOSE–VOLUME EFFECTS OF OPTIC NERVES AND CHIASM

CHARLES MAYO, PH.D.,* MARY K. MARTEL, PH.D.,† LAWRENCE B. MARKS, M.D.,‡ JOHN FLICKINGER, M.D.,§ JIHO NAM, M.D.,‡ AND JOHN KIRKPATRICK, M.D., PH.D.¶

For treatment with rapid dose gradients, one would expect to observe injury to a part of the nerve, with a resultant **visual field defect**, rather than necessarily a large field defect. The latter might occur if the injury was mediated by a more global process (e.g., a vascular insult causing a more general nerve injury).

Dose	Incidence of RION
50 Gy	near to 0
50-55 Gy	unusual
55-60 Gy	3-7%
>60 Gy	7-20%

Minimal data have been derived from pts receiving hypofractionated schedules: care should be taken in that setting.

Antiangiogenetic agents as **Bevacizumab** as a potential treatment of RION

"There is no evidence that the tolerance of the pediatric patients differs from the adults"

Retreatment constraints for optic pathways

Reirradiation after radical treatment for nasopharynx cancer

	Constraints for optic pathways	toxicity
Chua DTT, 2005 RO	**V8<5%** in 2 Gy fractions	0%
Chua DTT, 2003 RO	**Dmax <4 Gy** in radiosurgery	0%

	Dose to optic pathways	toxicity
Roeder F, 2011 Rad Onc	-Median dose in 2 Gy fractions R optic nerve 25 Gy (1-43) L optic nerve 20 (1-43) chiasma 11 Gy (1-39)	0%

Retreatment and OARs: practical recommendations

- Preventive **sparing of OARs in the first line treatment**

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 15, NUMBER 1, 2014

Preventive sparing of spinal cord and brain stem in the initial irradiation of locally advanced head and neck cancers

Paolo Farace,[1,2a] Sara Piras,[1] Sergio Porru,[1] Federica Massazza,[1] Giuseppina Fadda,[1] Ignazio Solla,[1] Denise Piras,[1] Maria Assunta Deidda,[1] Maurizio Amichetti,[2] Marco Possanzini[1]

-For a proper re-irradiation planning, the following dcm files of the initial treatment are mandatory:

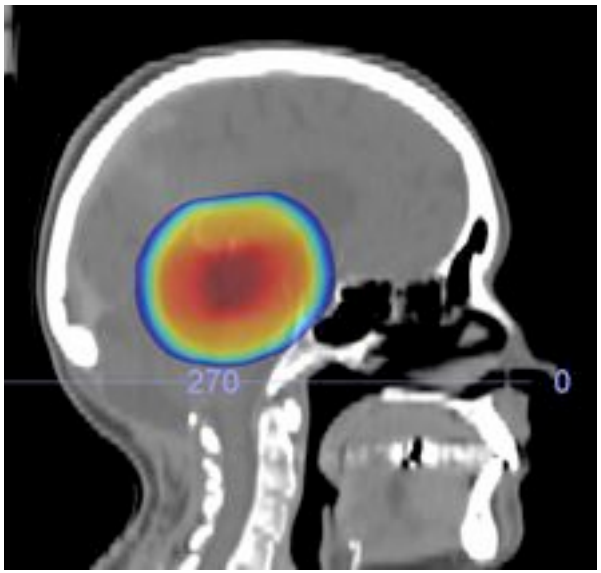
simulation CT
RT-plan
RT-structure file
RT-dose file

- Differentiating different portions of the OARs

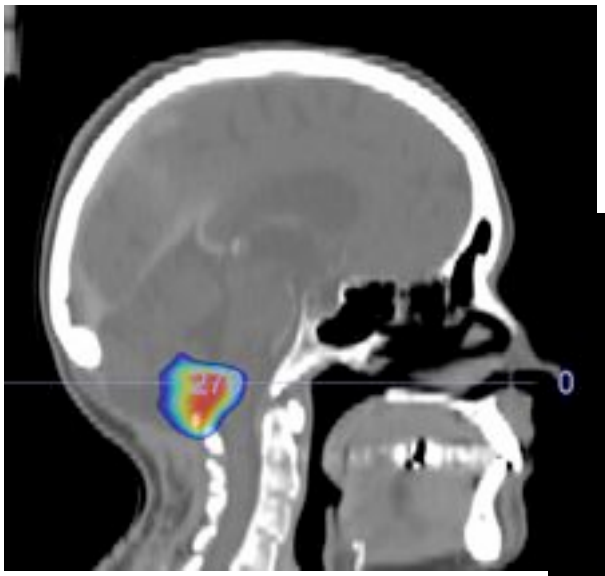
Year : 2009 | Volume : 5 | Issue : 1 | Page : 36-40

Importance of contouring the cervical spine levels in initial intensity-modulated radiation therapy radiation for head and neck cancers: Implications for re-irradiation

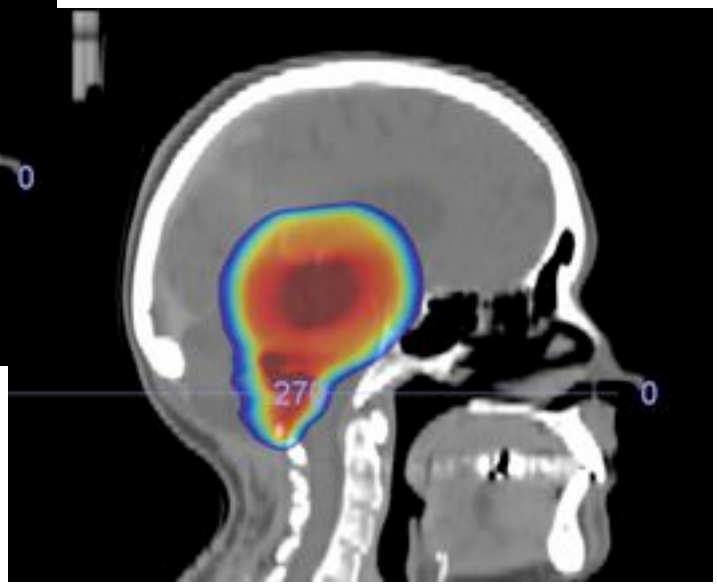
Bhupesh Parashar[1], Chi Kuo[1], David Kutler[2], William Kuhel[2], Albert Sabbas[1], Gabriella Wernicke[1], Dattatreyudu Nori[1]



first treatment

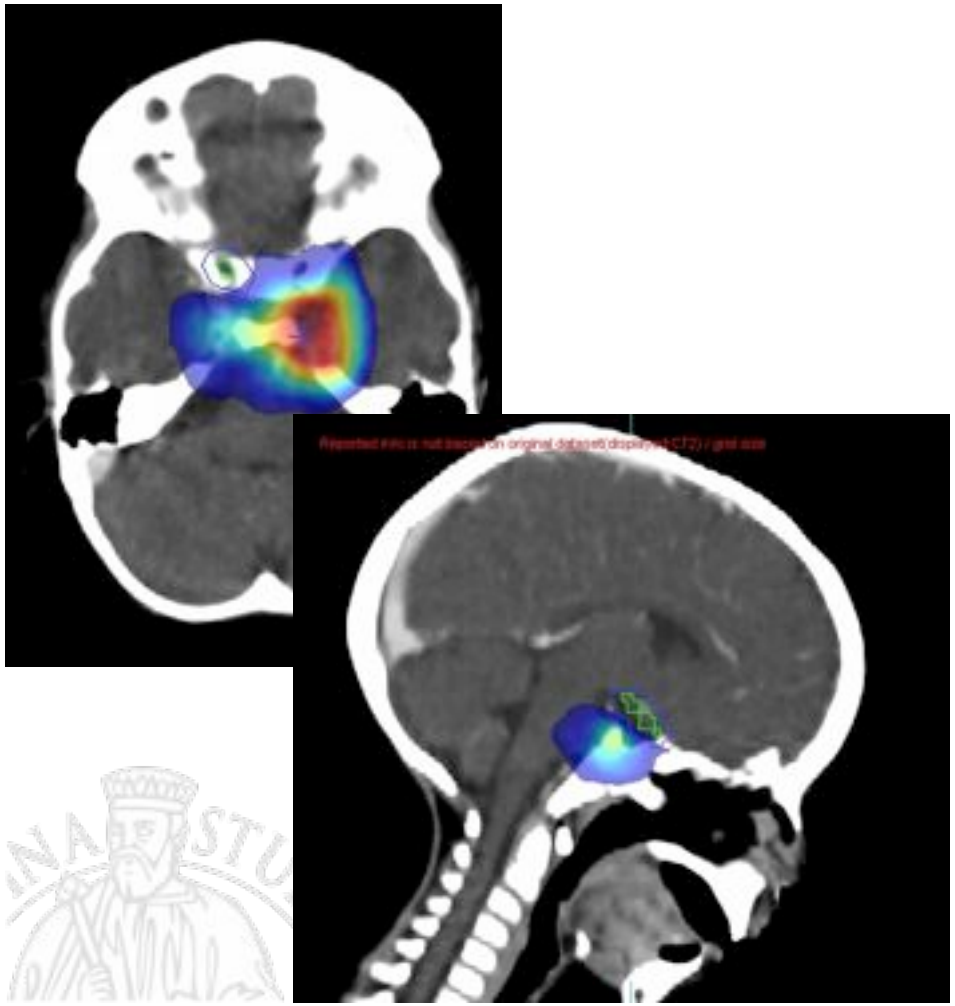


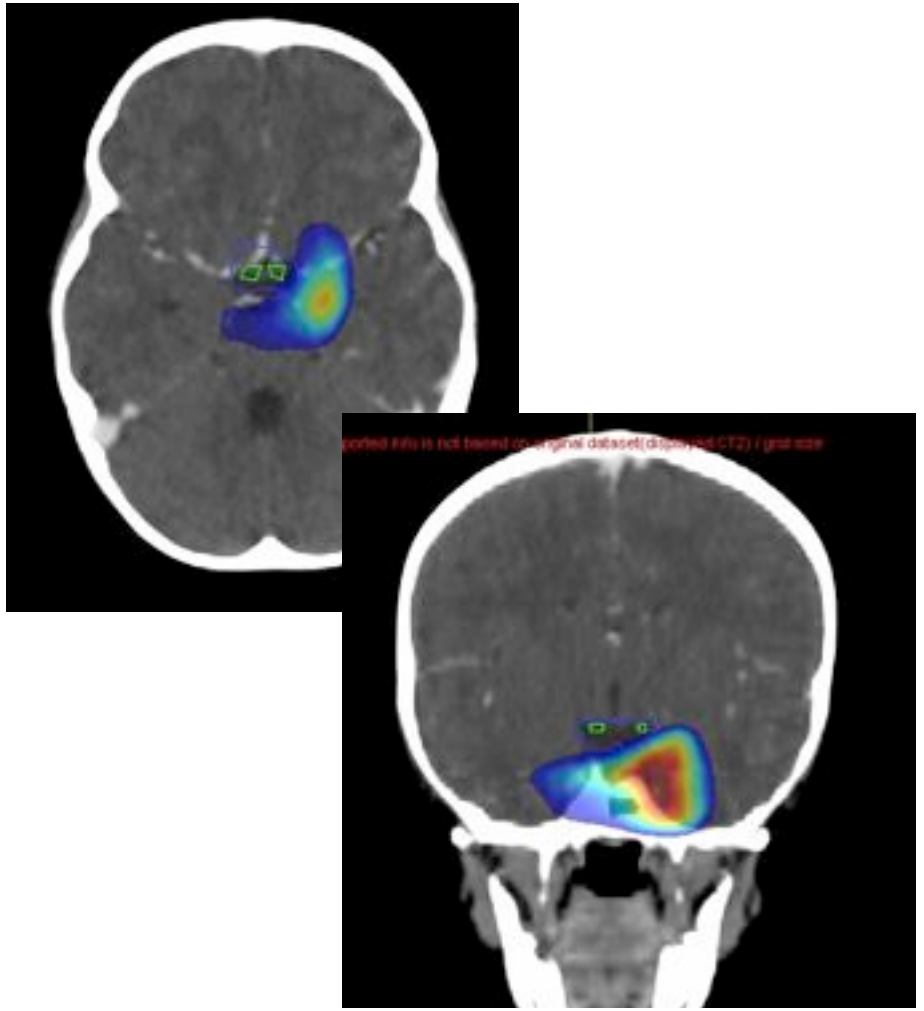
reirradiation

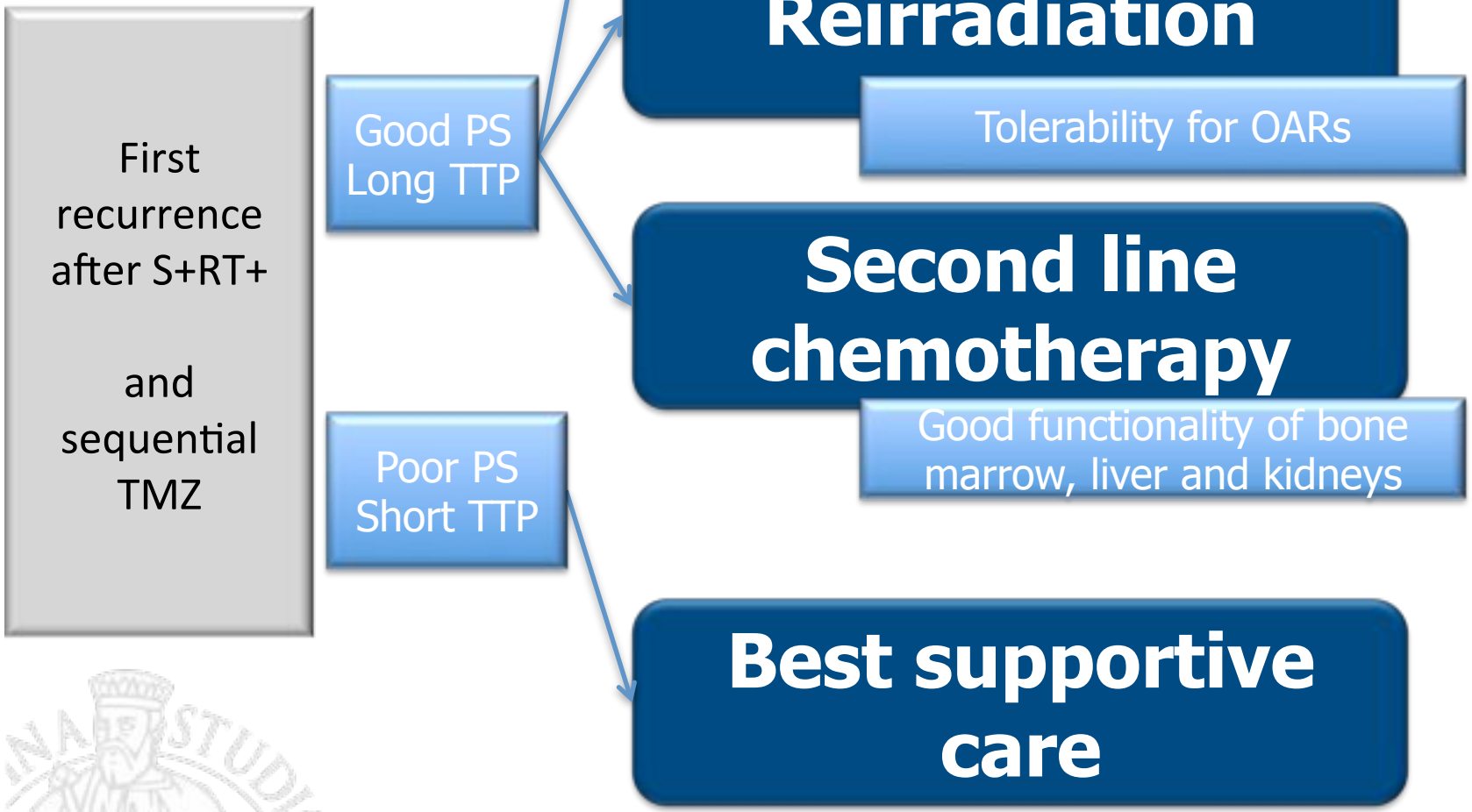


cumulative plan

- Differentiating different portions of the OARs






First recurrence after S+RT+
and sequential TMZ
Good PS Long TTP
Poor PS Short TTP
Second surgery
Feasibility, no comorbidity
Reirradiation
Tolerability for OARs
Second line chemotherapy
Good functionality of bone marrow, liver and kidneys
Best supportive care

REVIEW

Reoperation for Recurrent High-Grade Glioma: A Current Perspective of the Literature

Shawn L. Hervey-Jumper, MD
Mitchel S. Berger, MD

- Median **OS** 8.6 months (5-9)
- Perioperative **mortality** up to 5%
- **Morbidity** up to 33% (permanent morbidity up to 15%)

	mOS (months)	mPFS (months)	actuarial PFS	Severe Toxicity
RS	7,5-14.3	5	@6m 37%	9,8-31%
HFSRT §	6-13.5	-	@6m 75%	0-36%
2 Gy per fraction	6.9-21	5-12	-	2.6-12%
ReIrrad + TMZ §	8-12,4	5-7	@6m 42-66.7%	0-40%
ReIrrad + Beva §	8.4-12,5	5.7-6.8	@6m 16-65%	6-14%
TMZ *	5.1-13	2.1-12.4	@6m 18-48%	0-39%
FTM *	6-11.1	5.7-11	@6m 21-61%	2-14.8%
Beva *	6.5-9.2	2.8-4.2	@6m 25-42.6%	12.5-46.4%
TMZ+Beva*	3.7-8.7	2.4-3.7	@6m 6.7-18.8%	30%
FTM+Beva*	9.1	5.3	@6m 44%	7.4-22%
Lomu+Beva*	12	4	@6m 42%	7-25%

§ some evidence from prospective studies * prospective studies only

Good selection of patients

- **Good PS** (Voynov 2002; Nieder 2008; Fokas 2009)
- **Age** (Fogh 2010; Niyazi 2012; Scholtyssek 2013)

- **Long TTP** (Combs 2013)

- **Monofocality** (Ogura 2013)
  - **Size**
  - **Site**

- **Patient's wish**

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Reirradiation is posh!!!!!

Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial

Walter Taal, Hendrika M Oosterkamp*, Annemiek M E Walenkamp*, Hendrikus J Dubbink*, Laurens V Beerepoot, Monique C J Hanse, Jan Buter, Anfke H Honkoop, Dolf Boerman, Filip Y F de Vos, Winand N M Dinjens, Roelien H Enting, Martin J B Taphoorn, Franchette W P J van den Berkmortel, Rob L H Jansen, Dieta Brandsma, Jacoline E C Bromberg, Irene van Heuvel, René M Vernhout, Bronno van der Holt, Martin J van den Bent

	Bevacizumab (n=50)	Lomustine (n=46)	BevBEV/LOM 110 (n=8)	BEV/LOM 90 (n=44)
Progressed and/or dead at analysis	50	46	7	42
Some kind of salvage therapy*	26/50 (52%)	24/46 (52%)	4/7 (57%)	16/42 (38%)
Re-irradiation	10/50 (20%)	11/46 (24%)	–	10/42 (24%)
Surgery	–	7/46 (15%)	–	1/42 (2%)
Chemotherapy	20/50 (40%)	9/46 (20%)	3/7 (43%)	3/42 (7%)
Temozolomide	3/50 (6%)	8/46 (17%)	2/7 (29%)	3/42 (7%)
Lomustine	19/50 (38%)	–	1/7 (14%)	–
Other	–	1/46 (2%)	–	–
Bevacizumab	–	1/46 (2%)	–	–
Other	2/50 (4%)	5/46 (10%)	2/7 (29%)	4/42 (10%)
Unknown	–	–	–	1/42 (2%)

Data are n or n/N (%). BEV/LOM 110=bevacizumab plus lomustine 110mg/m^2. BEV/LOM 90=bevacizumab plus lomustine 90 mg/m^2. *Many patients received more than one line of salvage therapy.

Table 4: **Number of patients in each group that had progressed or died at the time of analysis, and numbers of patients receiving the various salvage therapies after progression in the BELOB trial**

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