Does radiotherapy technique, doses,fractionation really matter?

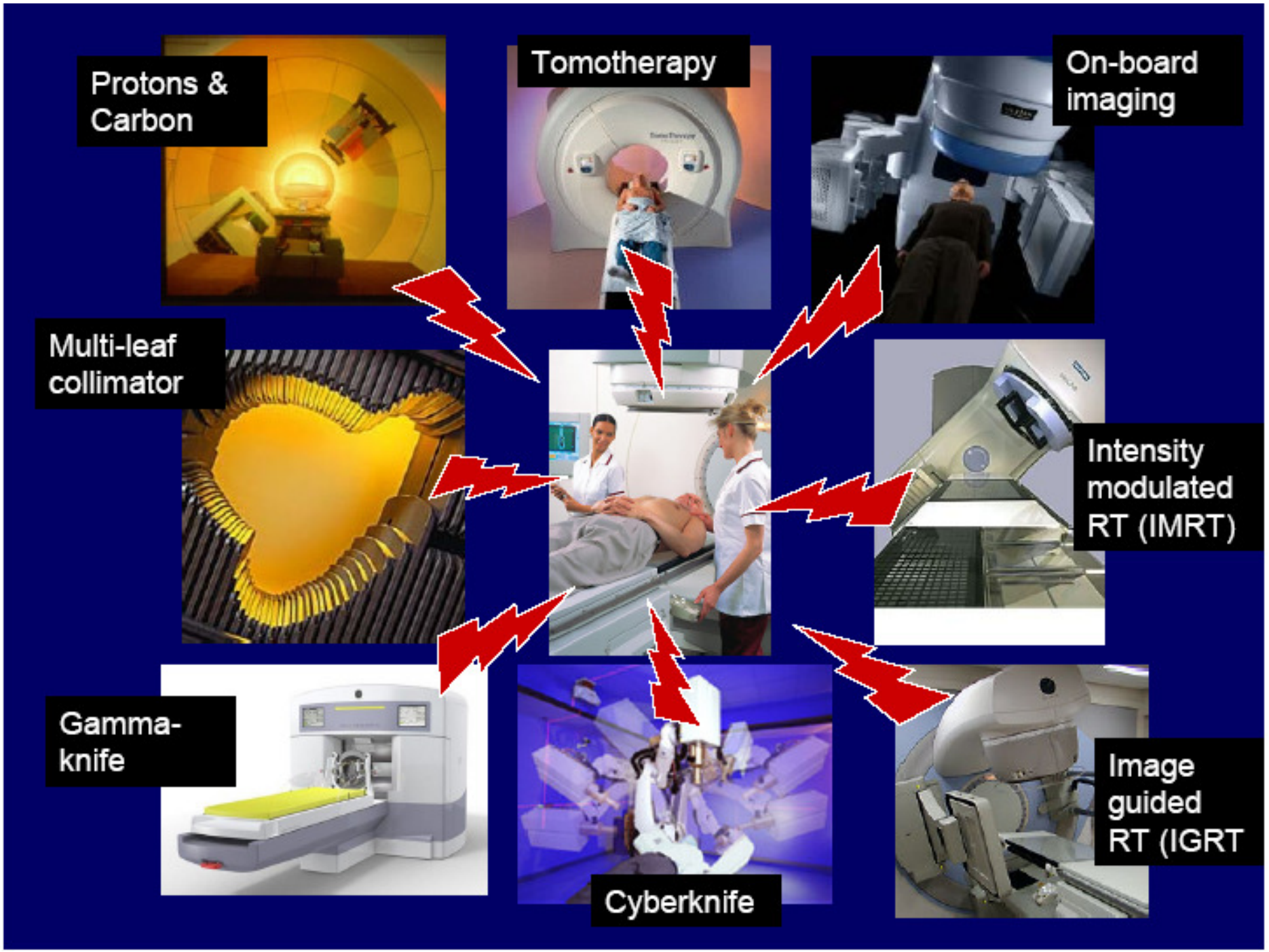
No

N.Giaj Levra, U.Ricardi

Department of Oncology, Radiation Oncology Unit
University of Turin

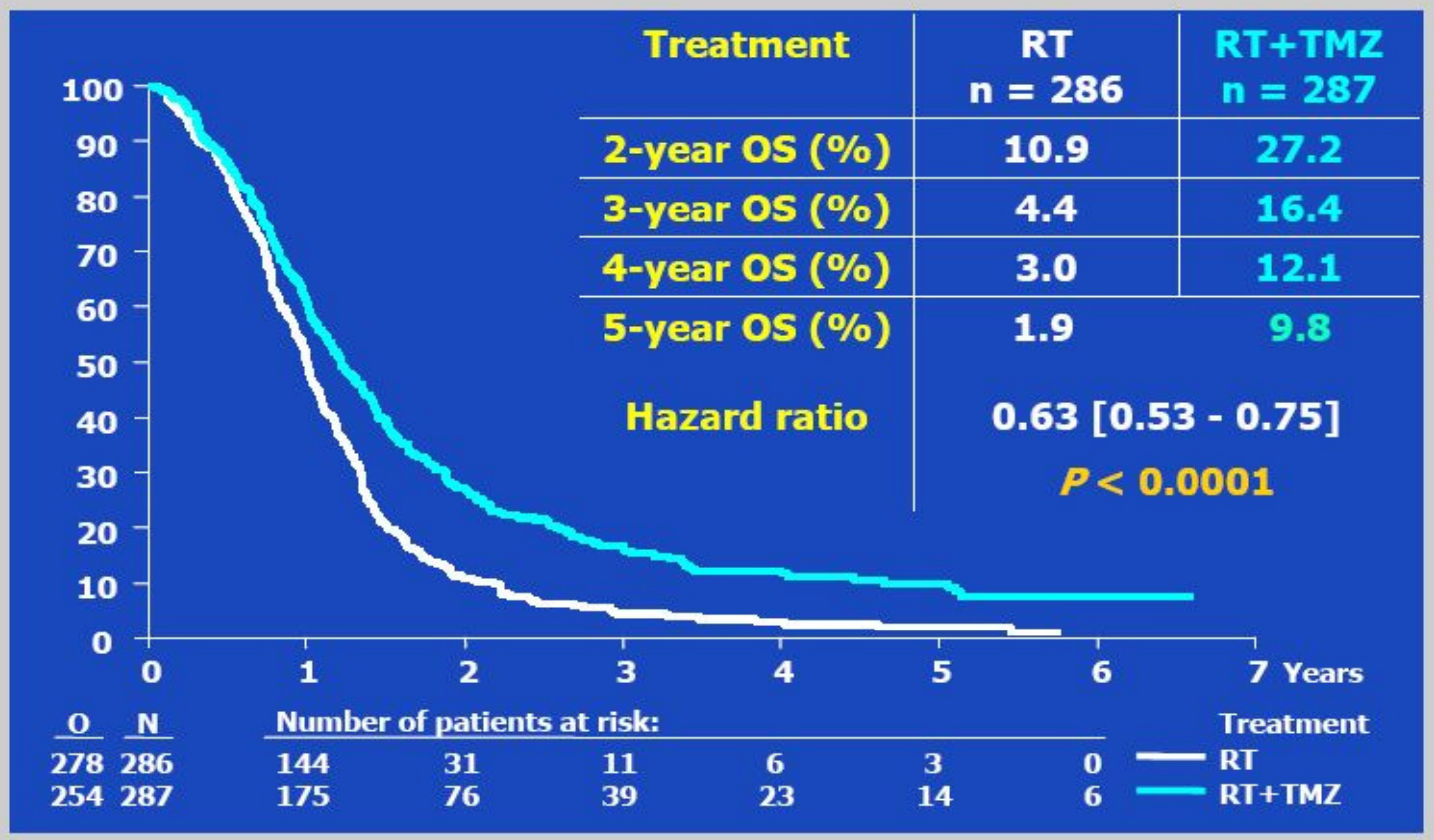
Radiotherapy and Primary CNS tumour

- Radiotherapy technique
  - 3D-CRT
  - IMRT
  - Brachytherapy
  - Particle (Proton, Carbon)
  - SRS techniques
- Radiation Dose
  - Standard dose
  - High dose
  - Simultaneous Integrated Boost
- Fractionation
  - Conventional
  - Alterated (Hyper/hypofractionation)


Protons & Carbon
Tomotherapy
On-board imaging
Multi-leaf collimator
Intensity modulated RT (IMRT)
Gamma-knife
Cyberknife
Image guided RT (IGRT

3D-CRT (+ TMZ) High Grade Glioma

Results : Overall Survival

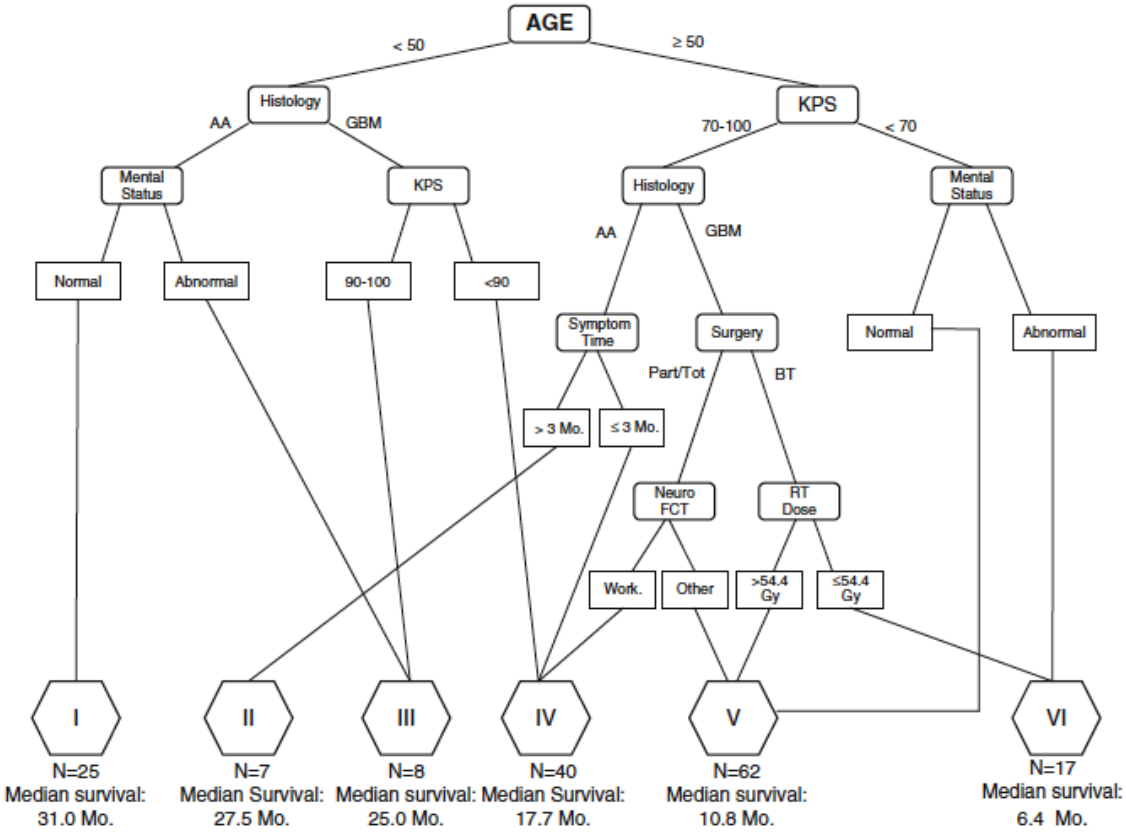


Treatment	RT n = 286	RT+TMZ n = 287
2-year OS (%)	10.9	27.2
3-year OS (%)	4.4	16.4
4-year OS (%)	3.0	12.1
5-year OS (%)	1.9	9.8
Hazard ratio	0.63 [0.53 - 0.75]	
	P < 0.0001	

Stupp R et al NEJM 2005

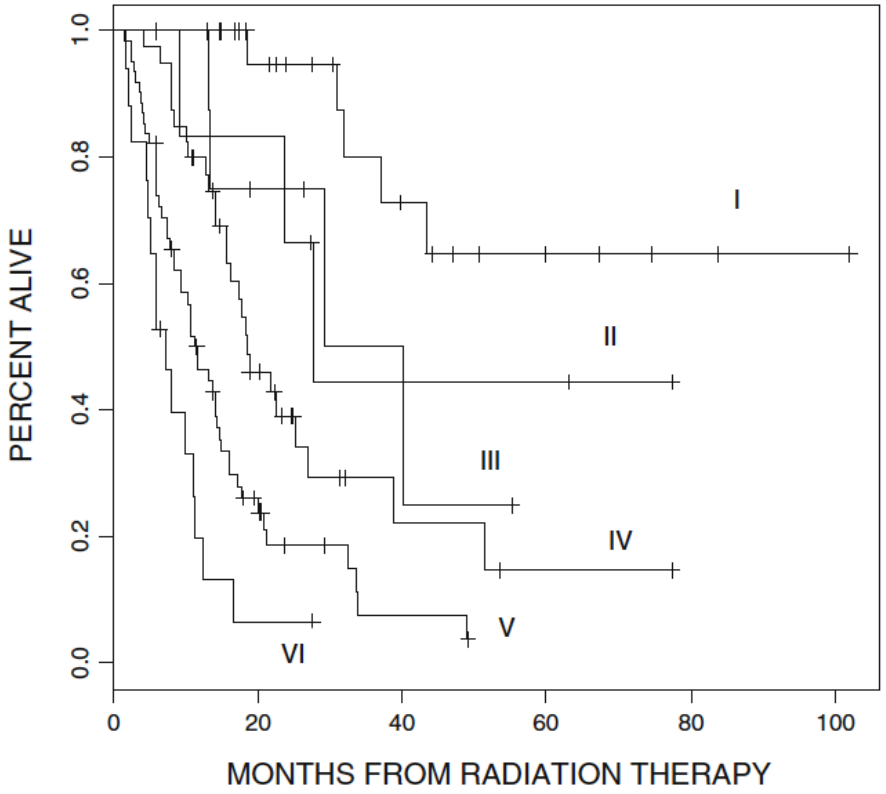
RTOG and High Grade Glioma

Radiotherapy and temozolomide for newly diagnosed glioblastoma and anaplastic astrocytoma: validation of Radiation Therapy Oncology Group-Recursive Partitioning Analysis in the IMRT and temozolomide era



Paravati et al J Neuurooncol 2011

IMRT (+ TMZ) High Grade Glioma



Class (159)	Median survival (months)	2-Year survival %
I (25)	31.0 (18.7–47.2)	93.8
II (7)	27.5 (16.4–45.6)	66.7
III (8)	25.0 (17.4–32.0)	66.7
IV (40)	17.7 (12.4–23.7)	31.3
V (62)	10.8 (5.9–16.9)	11.5
VI (17)	6.4 (4.9–11.2)	6.3

More 50% patients were over class III and median survival is poor

Paravati et al J Neuurooncol 2011

Radiotherapy in low grade glioma

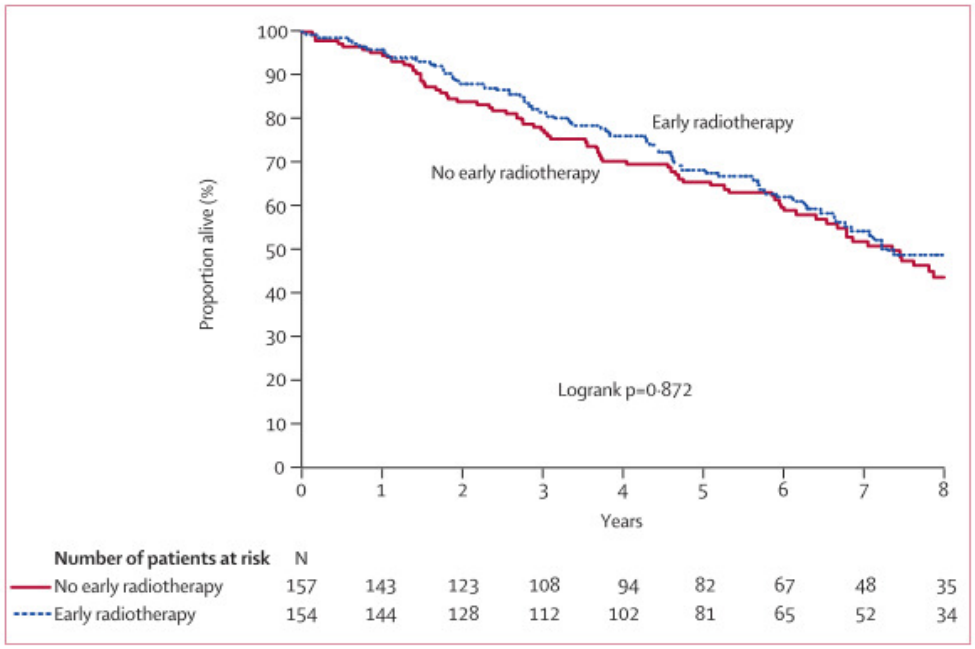


Figure 2: **Overall survival by intention-to-treat analysis**
Number of events: O=80 for control group; O=76 for early radiotherapy group.

Median survival :

7.4 years in the RT group

Vs.

7.2 years in the control group
(p=0.872)

Van den Bent MJ et al; Lancet,2005:366:985-990

Patients after a radiation treatment have a long survival time and consequently an higher possibility to develop neurological toxicity.

In this group, especially when close to critical structure, is useful to offer an IMRT treatment

Dose tolerance – Organ at risk

	Mean dose (Gy)	Maximum dose (Gy)
Lens of eye	10	-
Retina	-	50
Optic nerve/ Chiasm	-	54
Spinal cord	-	45
Brain stem	-	54
Cochlea	-	45

Dose tolerance – Organ at risk

Brainstem

Smaller volumes of the brainstem (1–10 cc) may be irradiated to maximum doses of 59 Gy for dose fractions ≤2 Gy but the risk appears to increase markedly at doses **>64 Gy**.

Chiasm/ Optic nerve

At 5 years the risk increases (**3–7%**) in the region of **55–60 Gy** and becomes more substantial (>7–20%) for doses >60 Gy when fractionations of 1.8–2.0 Gy are used

Mayo C. et al IJROBP 2010

Radiotherapy and Oncology 97 (2010) 361–369

Contents lists available at ScienceDirect

Radiotherapy and Oncology

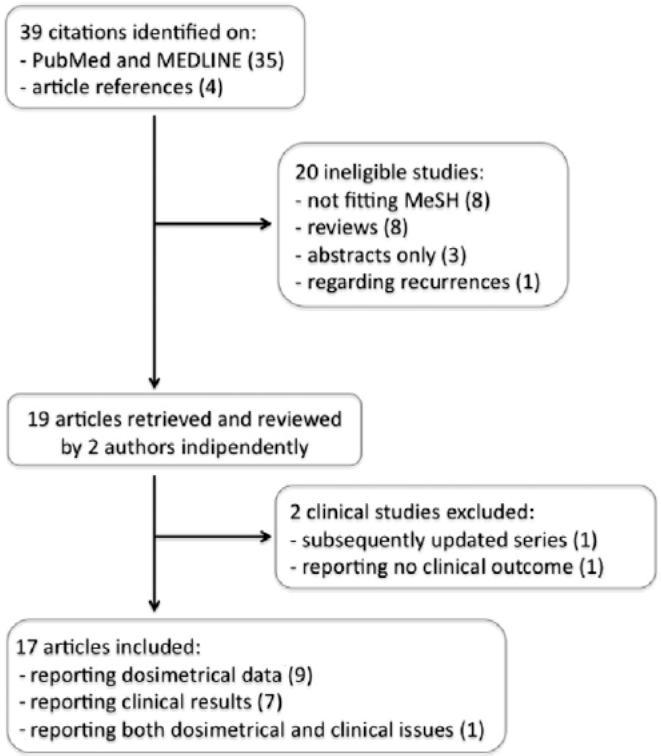
journal homepage: www.thegreenjournal.com

Systematic review

Intensity-modulated radiation therapy in newly diagnosed glioblastoma: A systematic review on clinical and technical issues

Dante Amelio [a,*], Stefano Lorentini [a,b], Marco Schwarz [a], Maurizio Amichetti [a]

[a] ATreP – Provincial Agency for Proton Therapy, Trento, Italy; [b] Medical Physics School, University of Padua, Italy



Systematic review

Radiotherapy and Oncology 97 (2010) 361–369

Intensity-modulated radiation therapy in newly diagnosed glioblastoma: A systematic review on clinical and technical issues

- 3D-CRT and IMRT techniques provide similar results in terms of target coverage

- IMRT is some what better than 3D-CRT in reducing the maximum dose to the organs at risk; IMRT is clearly better than 3D-CRT in terms of dose conformity and sparing of the healthy brain

Radiotherapy and Oncology 97 (2010) 361–369

Systematic review

Intensity-modulated radiation therapy in newly diagnosed glioblastoma: A systematic review on clinical and technical issues

IMRT in GBM

- From a clinical point of view this means including patients with better prognosis (i.e. lower age, receiving a gross total resection, with high performance status) for which the preservation of QOL is a much more relevant concern as well.

- From a dosimetrical point of view, the smaller the distance between target and (one or more) OARs the greater the difficulty in achieving target coverage and OAR sparing.

Innovative treatment techniques

- IMAT (Intensity Modulated Arc Therapy): multiple rotations of a gantry (complete or partial arcs), with dynamic movement of MLC

- VMAT (Volumetric Modulated Arc Therapy)

- Rapid Arc

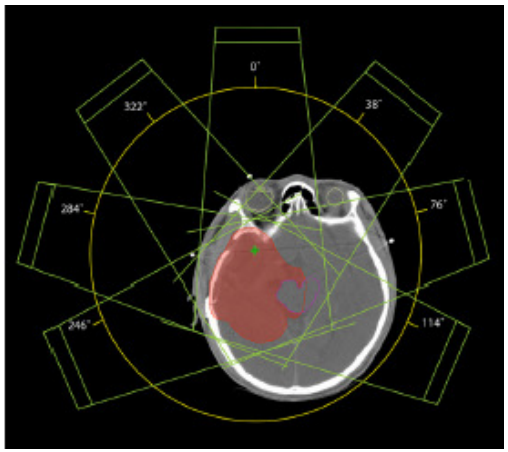
single gantry revolution through the simultaneous variation of the rotation speed, the beam opening through the movement of MLC leaves, the dose-rate

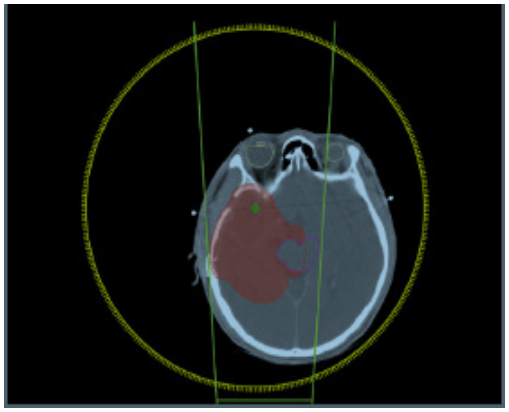
Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 4, pp. 1177–1184, 2010

CLINICAL INVESTIGATION **Brain**

A COMPARISON OF VOLUMETRIC MODULATED ARC THERAPY AND CONVENTIONAL INTENSITY-MODULATED RADIOTHERAPY FOR FRONTAL AND TEMPORAL HIGH-GRADE GLIOMAS

Richard Shaffer, M.B.B.S.,* Alan M. Nichol, M.D.,* Emily Vollans, M.Sc.,† Ming Fong, B.Sc.,‡ Sandy Nakano, B.Sc.,‡ Vitali Moiseenko, Ph.D.,† Moira Schmuland, M.Sc.,† Roy Ma, M.D.,* Michael McKenzie, M.D.,* and Karl Otto, Ph.D.†





- 10 previously treated patients were replanned with cIMRT and VMAT

- There was equivalent PTV coverage, homogeneity, and conformality; VMAT significantly reduced maximum and mean retinal, lens, and contralateral optic nerve doses compared with IMRT ($p < 0.05$).

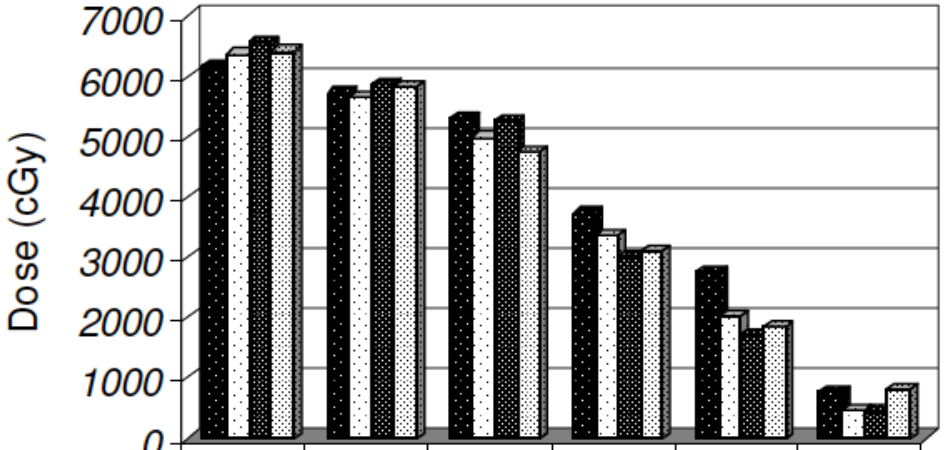
-VMAT spared lateralized OARs better, required fewer monitor units, and had shorter treatment times.

- However, for both cIMRT and VMAT, mean doses to parallel OARs compared unfavorably with those for non-coplanar IMRT in published planning studies.

A dosimetric comparison of four treatment planning methods for high grade glioma

Comparison with four different RT approach in HGG

- 3D-CRT
- IMRT (with or without boost)
- **Tomotherapy**



	Ipsi lateral SVZ	Brain Stem	Contra lateral	Optic Chiasm	Ipsi lateral globe	Contra lateral
3D	6176	5733	5319	3737	2758	756
IMRT	6380	5675	4999	3383	2024	480
IB	6593	5887	5269	3036	1706	443
TOMO	6425	5842	4750	3117	1837	796

Conclusion: No single treatment planning method is superior to all other

Zach L et al Rad Oncol 2009

Radiotherapy and CNS tumours

A limited number of patients with specific molecular feature (= longer overall survival), clinical condition and critical position (= near OAR) can justify the use of sophisticate RT technique.

- ✓ MGMT methylation
- ✓ 1p/19q codelation
- ✓ IDH1 positive
- ✓ P53 negative
- ✓ LGG
- ✓ Temporal/Frontal lobes
- ✓ Optic chiasm
- ✓ Optic nerve
- ✓ Not elderly (not all!)

Brachytherapy and HHG

Author	Isotope (dose, T/P)	# (1/2)	Histology	MS	Comp	Reoperation
Halligan [36]	125I (54–65, P)	18 (2)	GBM	16 months	5%	0%
		4 (2)	AA	17		
Patel [37]	125I (120–160, P)	40 (2)	GBM	11.7	5	0
Kitchen [63]	125I (50, T)	23 (2)	GBM:AA	6.3		9
Bernstein [145]	125I (70 ,T)	44 (2)	GBM(32):AA(12	11.5	11	26
Chamberlain [14]	125I (50, T)	14 (2)	GBM(11):AA(3)	9.5	6	56
Malkin [10]	125I (60, T)	20 (1)	GBM	22	20 (2%)	43
		36 (2)	GBM(24):AA(12	10		
Lucas [156]	192Ir (48, T)	13 (1,2)	GBM	10	12	9
		7 (1)	AA	22		
		13 (2)	AA	16		
Scharfen [11]	125I (56, T)	106 (1)	GBM	22	6 (<1%)	40
		66 (2)	GBM	12.3		
		52 (1)	AA*	35.5		
		45 (2)	AA*	13		
Wen [62]	125I (50, T)	56 (1)	GBM	18	13	64
Gutin [46]	125I (60, T)	34 (1)	GBM	22	0	48
		29 (1)	AA	39.3		
Fernandez [38]	125I (102, P)	18 (1)	GBM	23		45
		40 (1)	AA	>31		
Videtic [139]	125I (104, P)	53 (1)	GBM	16		
Laperriere [13]	125I (60, T)	63 (1)	GBM	15.7	4.8	31
Ryken [157]	125I (60, T)	20 (2)	GBM(11):AA(9)	6		
Ostertag [25]	125I (60, T)	34 (1)	GBM	6	4	

Proton Therapy

- Protons have been evaluated in a number of other intracranial tumors, including a prospective study in glioblastoma multiforme (23 patients).

- Dose escalation with protons has not demonstrated convincing survival benefit in malignant glioma other than the benefit that would be expected as a result of patient selection

- Low-grade astrocytoma (27 patients) do not allow for conclusion about superiority over photons

Proton therapy for glioma patients appears to have at least as favourable an outcome as photons, but the rates of radiation necrosis are higher.

Brada M. et al JCO 2007

Carbon Therapy

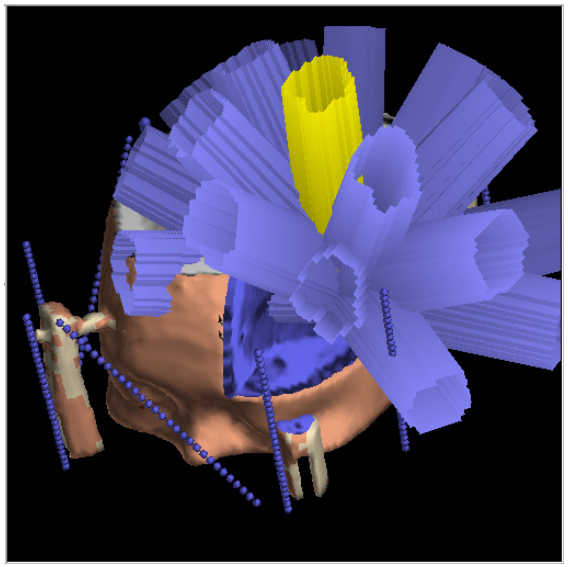
- Theoretically, carbon ion therapy is also expected to improve the prognosis in glioma patients, owing to its physiological and biological advantages.

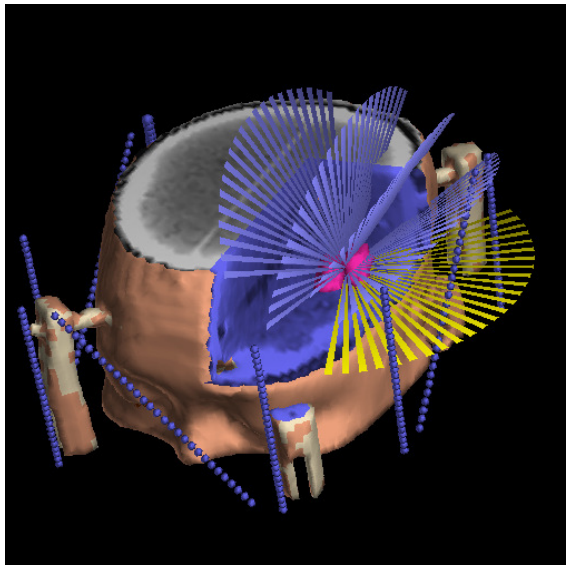
- Preclinical study demonstrated that carbon ion is more effective in killing GBM cells compared with photons.

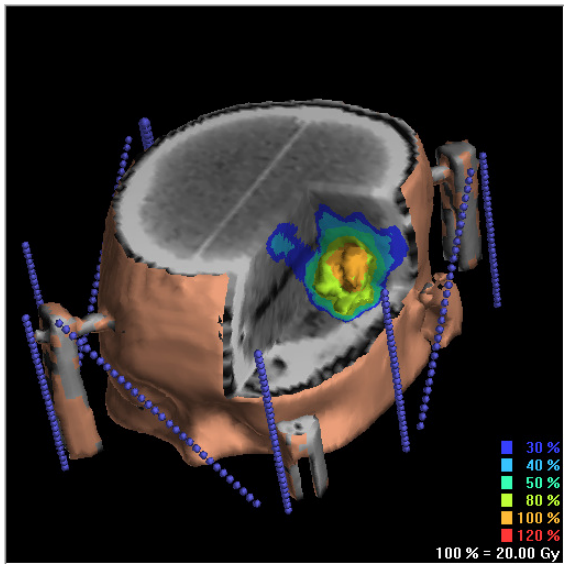
The efficacy of carbon ion therapy and TMZ has not yet been demonstrated in clinical study

Hadziahmetovic M et al. Future Oncology 2011

Radiosurgery in HGG







	n. of cases	*EBRT dose (Gy)*	*SRS dose (Gy)*	*Median OS months*	*2 yr survival %*
Maryland	*31*	*59.7*	*17*	*25*	*40+*
Wisconsin	*31*	*60*	*18*	*9.5*	
Pittsburg	*64*	*60*	*18*	*26*	*51*
Gainesville	*11*	*60*	*12.5*	*17*	
Arizona	*17*	*59.4*	*10*	*13.9*	*25*
Heidelberg	*35*	*54 Hfr*	*15*	*10.1*	*6*
Boston	*78*	*60*	*18*	*22.3*	*35.9*

STEREOTACTIC RADIOTHERAPY IN GLIOMA
RTOG 9305

Phase III Trial comparing SRS followed by conventional XRT + BCNU versus conventional XRT + BCNU for GBM

203 pts/186 analyzable

60 Gy / 30 fr + BCNU (80 mg/m2 days 1,2, 3 of RT then q 8 weeks for a total of 6 cycles) vs.
60 Gy / 30 fr + BCNU preceded by SRS (15-24 Gy)

Eligibility:
1. Supratentorial GBM < 4 cm max diameter, unifocal
2. Age > 18, KPS >60, Hgb >10, ANC >1500, Plt >100 K

STEREOTACTIC RADIOTHERAPY IN GLIOMA
RTOG 9305

- Median follow-up 44 months
- Median Survival: 14.1 vs 13.7 months
- Median Survival for RPA III/IV: 14.7 vs 14.2 months
- 2 yr survival: 22 vs 16%
- > 90% pts had local failure on both arms
- General QoL & cognitive function comparable

RADIOSURGERY NOT PROVEN TO PROLONG SURVIVAL IN GBM

Souhami, ASTRO 2004

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 1, pp. 47–55, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.05.024

ASTRO REPORT

THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) EVIDENCE-BASED REVIEW OF THE ROLE OF RADIOSURGERY FOR MALIGNANT GLIOMA

MAY N. TSAO, M.D., MINESH P. MEHTA, M.D., TIMOTHY J. WHELAN, M.D., DAVID E. MORRIS, M.D., JAMES A. HAYMAN, M.D., JOHN C. FLICKINGER, M.D., MICHAEL MILLS, PH.D., C. LELAND ROGERS, M.D., AND LUIS SOUHAMI, M.D.

The American Society for Therapeutic Radiology and Oncology, Fairfax, VA

Conclusions: For patients with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU. The use of radiosurgery boost is associated with increased toxicity. For patients with malignant glioma, there is insufficient evidence regarding the benefits/harms of using radiosurgery at the time progression or recurrence. There is also insufficient evidence regarding the benefits/harms in the use of stereotactic fractionated radiation therapy for patients with newly diagnosed or progressive/recurrent malignant glioma.

Review

Radiotherapy and Oncology 98 (2011) 1–14

Therapeutic options for recurrent malignant glioma

Maximilian Niyazi [a], Axel Siefert [a], Silke Birgit Schwarz [a], Ute Ganswindt [a], Friedrich-Wilhelm Kreth [b], Jörg-Christian Tonn [b], Claus Belka [a,*]

[a] *Department of Radiation Oncology; and* [b] *Department of Neurosurgery, Ludwig-Maximilians-University Munich, München, Germany*

Selected studies on SRS in recurrent malignant glioma

Author(s)	Year	N	Grading	Median dose (Gy)	Median tumor size (ml)	Endpoints	Toxicity
Biswas et al.	2009	18	IV	15	8.4	mOS 5.3 mo	No acute > grade 2, 1 pt grade 4 late toxicity
Chamberlain et al.	1994	5/10/5	IV/III/other	13.4	17	mOS 8 mo	–
Cho et al.	1999	27/19	IV/III	17	10	mOS 11 mo	22%
Combs et al.	2005	32	IV	15	10	mOS 10 mo	No late toxicity
Hall et al.	1995	26/9	IV/III	20	28	mOS 8 mo	31% re-operation rate
Kondziolka et al.	1997	19/23	IV/III	15/15.6	6.5/6	mOS 30/31 mo	19%/23% Re-operation
Kong et al.	2008	49/65	IV/III	–	–	mPFS 4.6 mo/8.6 mo	
Masciopinto et al.	1995	31	IV	19.72	16.4	mOS 9.5 mo	–
Patel et al.	2009	26	IV	18	10.4	mOS 8.4 mo	Necrosis in 2 pts
Shrieve et al.	1995	86	IV	13	10.1	mOS 10.2 mo	22% necrosis
van Kampen et al.	1998	27	IV	17	20.9	mOS 9 mo	Alopecia, no necrosis

SRS for recurrent glioma is possible, but with higher tumor volumes the risk of side effects increases.
A clear volume cut-off cannot be deduced from the literature at present.
Patient selection has to be performed very cautiously

Review

Radiotherapy and Oncology 98 (2011) 1–14

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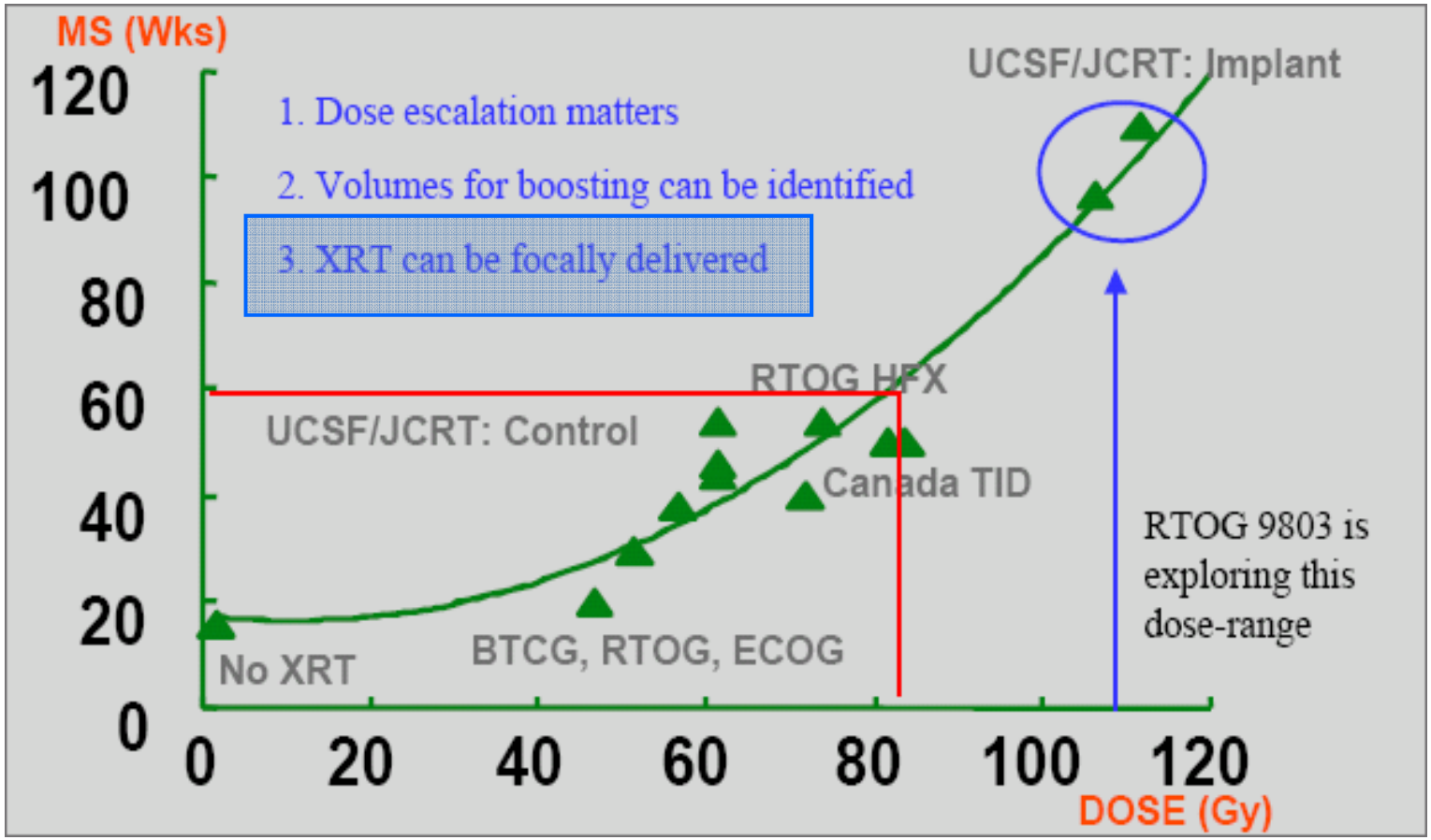
[a] *Department of Radiation Oncology; and* [b] *Department of Neurosurgery, Ludwig-Maximilians-University Munich, München, Germany*

Selected studies on FSRT in recurrent malignant glioma

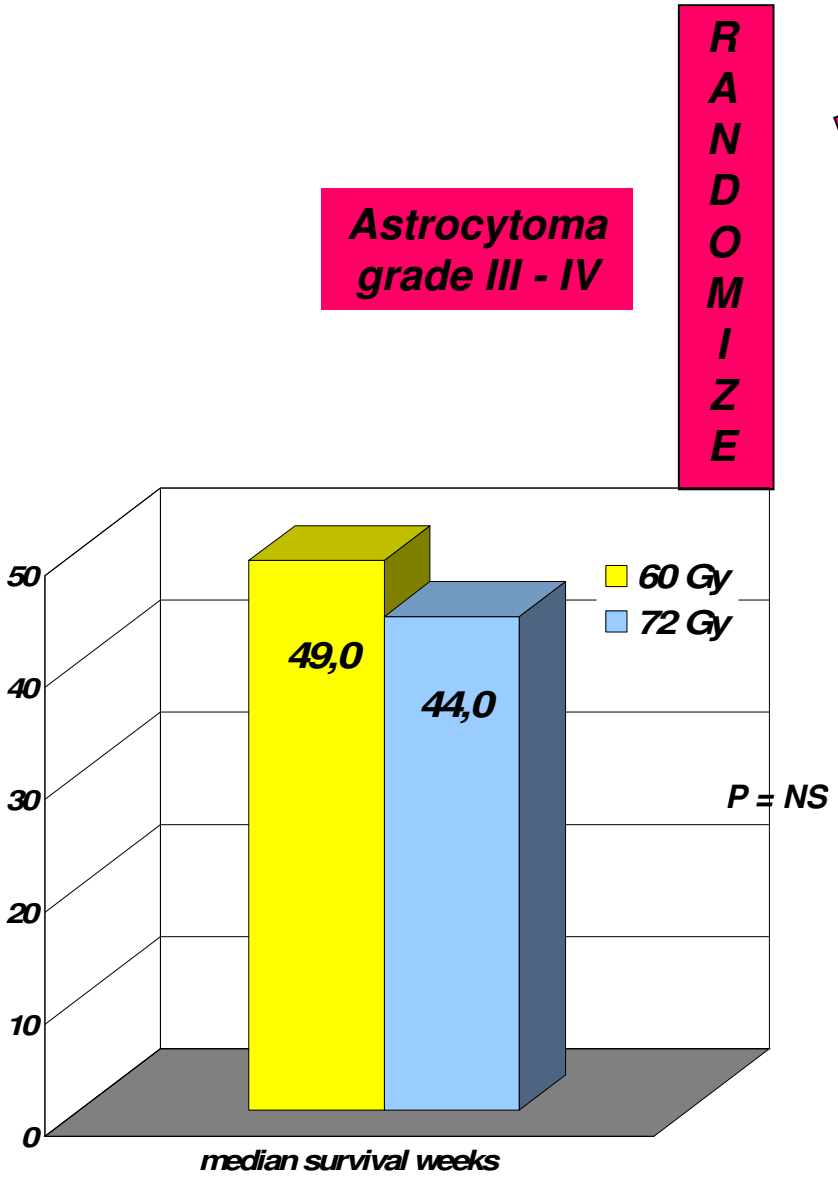
Author(s)	Year	*N*	Grading	Median dose (Gy)	Median tumor size (ml)	Median fraction size (Gy)	Endpoint	Toxicity
Cho et al.	1999	15 (10)	IV (III)	37.5	74	2.5	mOS 11 mo	12% severe
Combs et al.	2005	53	IV	36.0	49.3	2.0	mOS 8 mo	–
Ernst-Stecken et al.	2007	11/4	IV/III	35	22.4	7	PFS-6/-12 75%/53%	No re-operation
Fokas et al.	2009	53	IV	30	35.01	3	mOS 9 mo	No ⩾ grade 2
Henke et al.	2009	29/2	IV/III	20	55	5	mOS 10.2 mo	2 necroses
Hudes et al.	1999	19/1	IV/III	30	12.6	3	mOS 10.5 mo	–
Kim et al.	1997	7/7	IV/III	36	–	1.8	mOS 9 mo	No necrosis
Laing et al.	1993	22	IV	30–50	25	5–6	mOS 9.8 mo	–
Selch et al.	2000	15/3	IV	25	12	4–6	mOS 6.7 mo	–
Shepherd et al.	1997	29	IV/III	20–50	24	5	mOS 11 mo (IV/III)	36%
Vordermark et al.	2005	10/9	II or III/IV	30	15	5	mOS 13.5/7.4 mo	26%

FSRT is a safe and feasible option in the treatment for recurrent MG, even for larger tumors (again, there is no clear cutoff-volume), and shows adequate efficacy

GBM – Dose escalation



RTOG 9006: study design and results

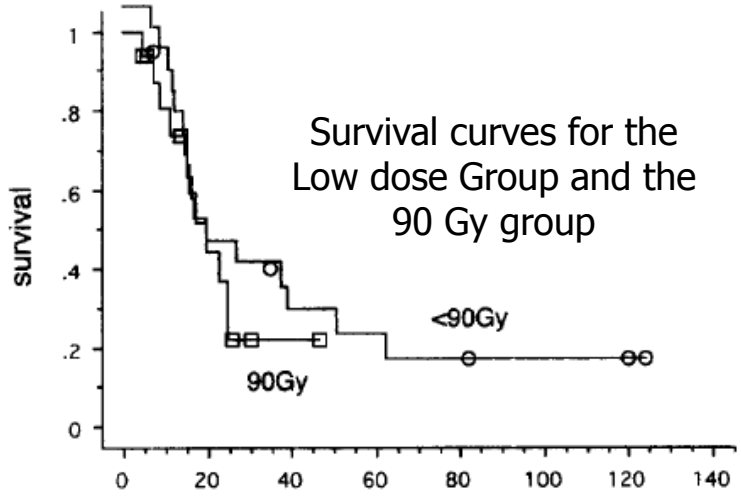


712 pts were included in the study.

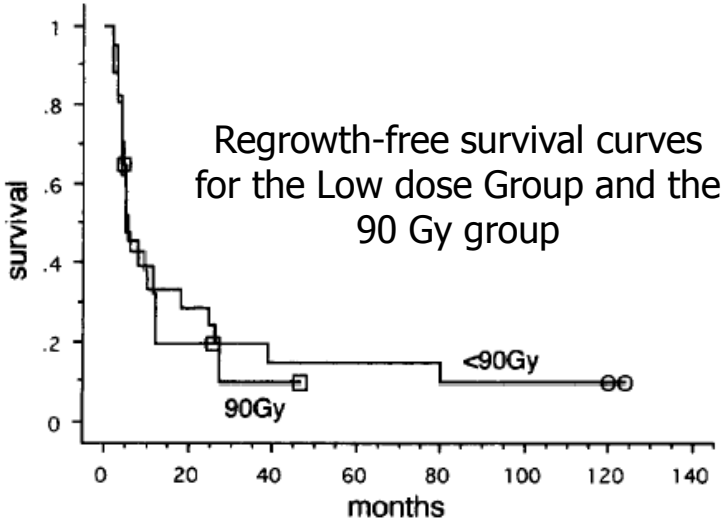
There was no significant difference between the 2 treatment groups.

(Scott CB et al.: Proc Ann Meet Am Soc Clin Oncol 17: 401a, 1998)

High dose conformal RT did not improve survival in Glioblastoma multiforme



Survival curves for the Low dose Group and the 90 Gy group

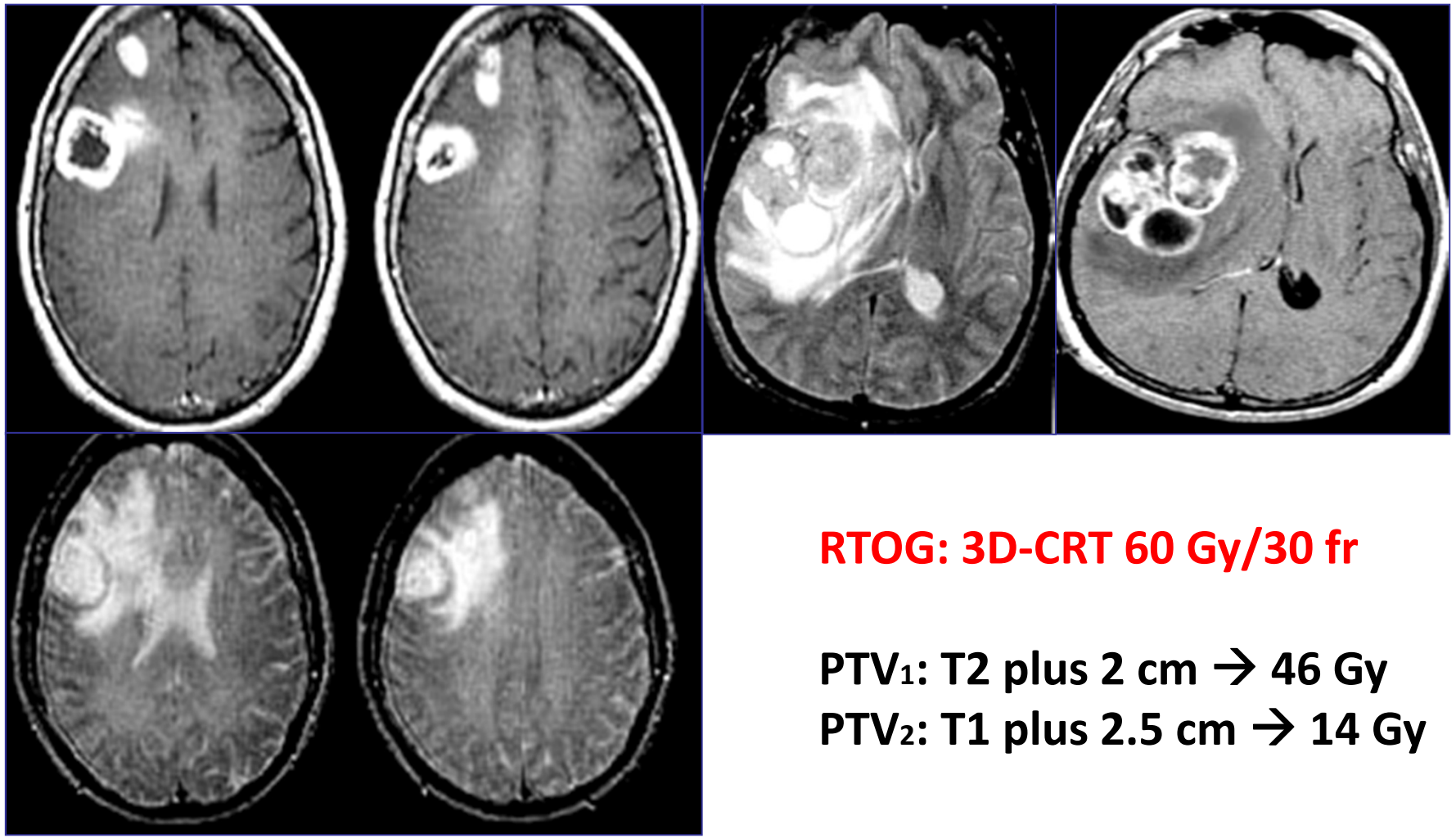


Regrowth-free survival curves for the Low dose Group and the 90 Gy group

- 38 pts with Glioblastoma treated using the rotational MLC conformal therapy
- All underwent surgical resection (1 biopsy, 13 partial resection, 21 subtotal resection, 3 gross total resection)
- Radiation dose ranged from 60 Gy to 80 Gy in 21 pts, and 90 Gy in 17 pts

Nakagawa, et al, IJROBP, 1998

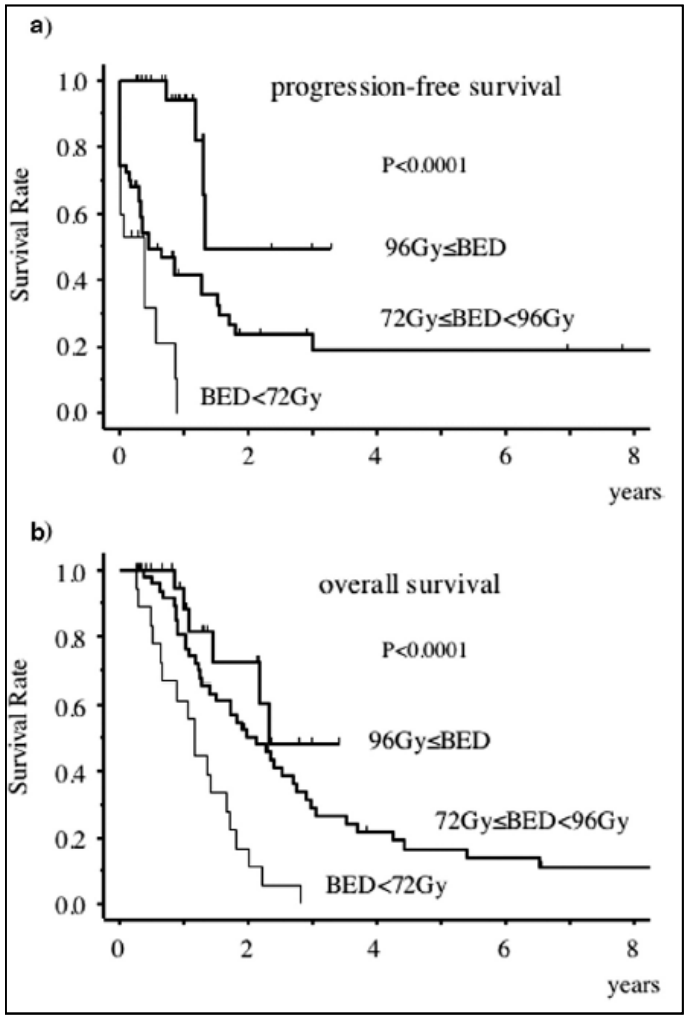
Target volumes in HGG

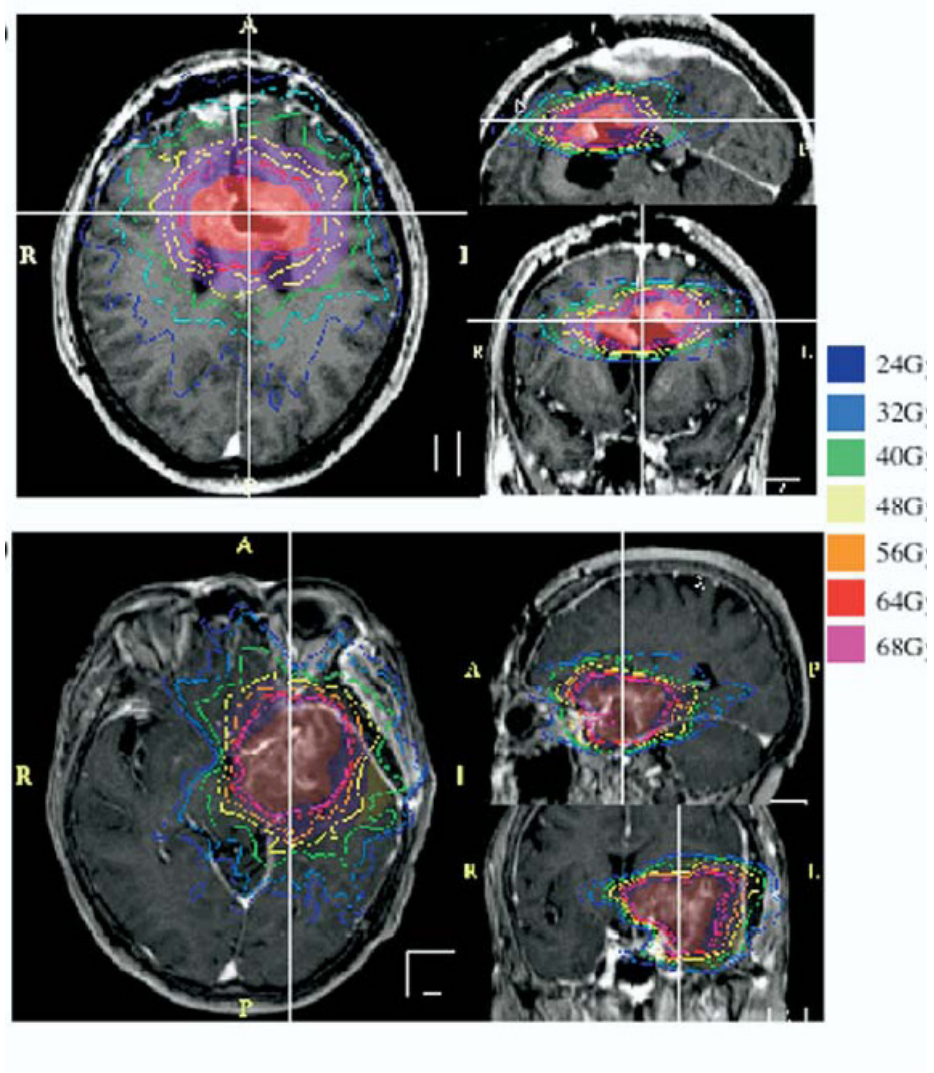


RTOG: 3D-CRT 60 Gy/30 fr

PTV_1: T2 plus 2 cm → 46 Gy
PTV_2: T1 plus 2.5 cm → 14 Gy

IMRT – Dose escalation





Iuchi, et al; IJROBP,2006

IMRT Planning: the use of IMRT poses new questions related to fractionation

Simultaneous Integrated Boost (SIB)

- Higher dose per fraction to GTV compared to CTV

Advantages: Accelerated RT (shortening overall treatment time)

Concerns: Healthy tissues exposed to higher fraction sizes

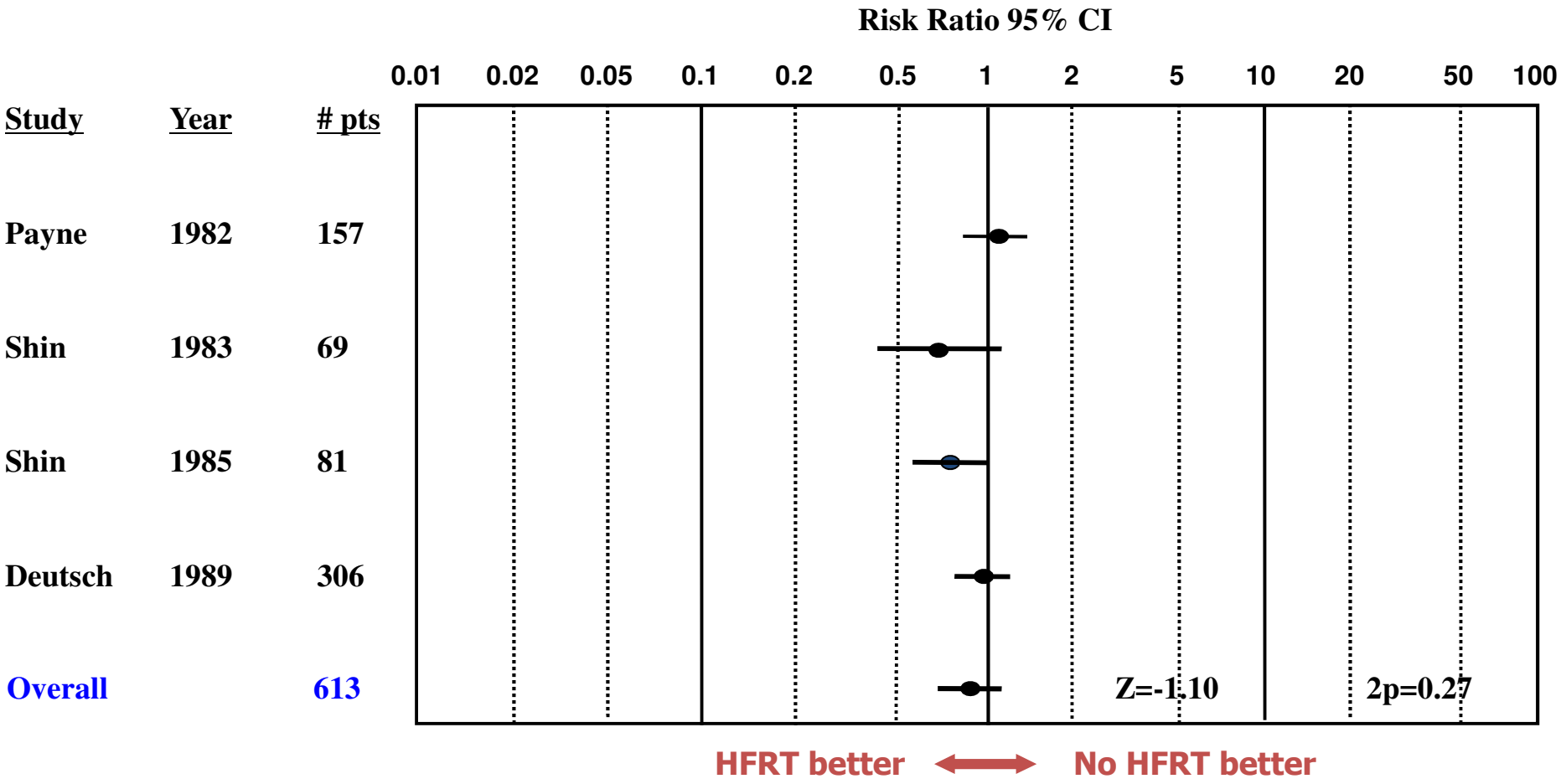
SIB-IMRT studies

Author	N° pt	N° of grade III/IV	Target volume: RT (Gy/fx) BED	N° pt CT (Yes/no)	Median PFS (%)	Median OS (%)	1 yr (%)	2 yr (%)	Local Failure (%)
Sultanem	25	0/25	GTV(60/20),72.5; GTV+15mm: (40/20)	ND	5.2	9.5	40	-	84
Iuchi	25	2/23	GTV+5mm(48-68/8),77.9-126.9; GTV+20 mm (40/8); Edema: (32/8)	19/6	IV:14	IV:24	71	56	24
Nakamatsu	13	5/8	GTV+5mm(70/28), 77.5: edema: (56/28)	11/2	III:7.5 IV:8.0		77	31	100
Panet-Raymond	35	0/35	GTV:(60/20), 72.5;GTV+15mm (40/20)	29/6	7.7	14.4	57	9	60
Cho	40	14/26	GTV+5mm: (60/25), 66.1 Edema+10mm: (50/25)	25/15	33.5 8.2	NR 12.4	78 56	65 31	III: 29 IV: 50

Radiation dose fractionation

- Hyperfractionation
- Accelerated fractionation
- Hypofractionation

Pooled results of hyperfractionated versus conventional RT randomized trials



Overall risk ratio = 0.89 (95% CI 0.73 to 1.09; p=0.27)

Radiotherapy for High-Grade Gliomas

Does Altered Fractionation Improve the Outcome?

1.414 patients from 21 studies (with two phase III study)

Dose per fraction were :

- 1.2- 1.8 Gy in 17 studies
- 1.9-2.65 Gy in 4 studies

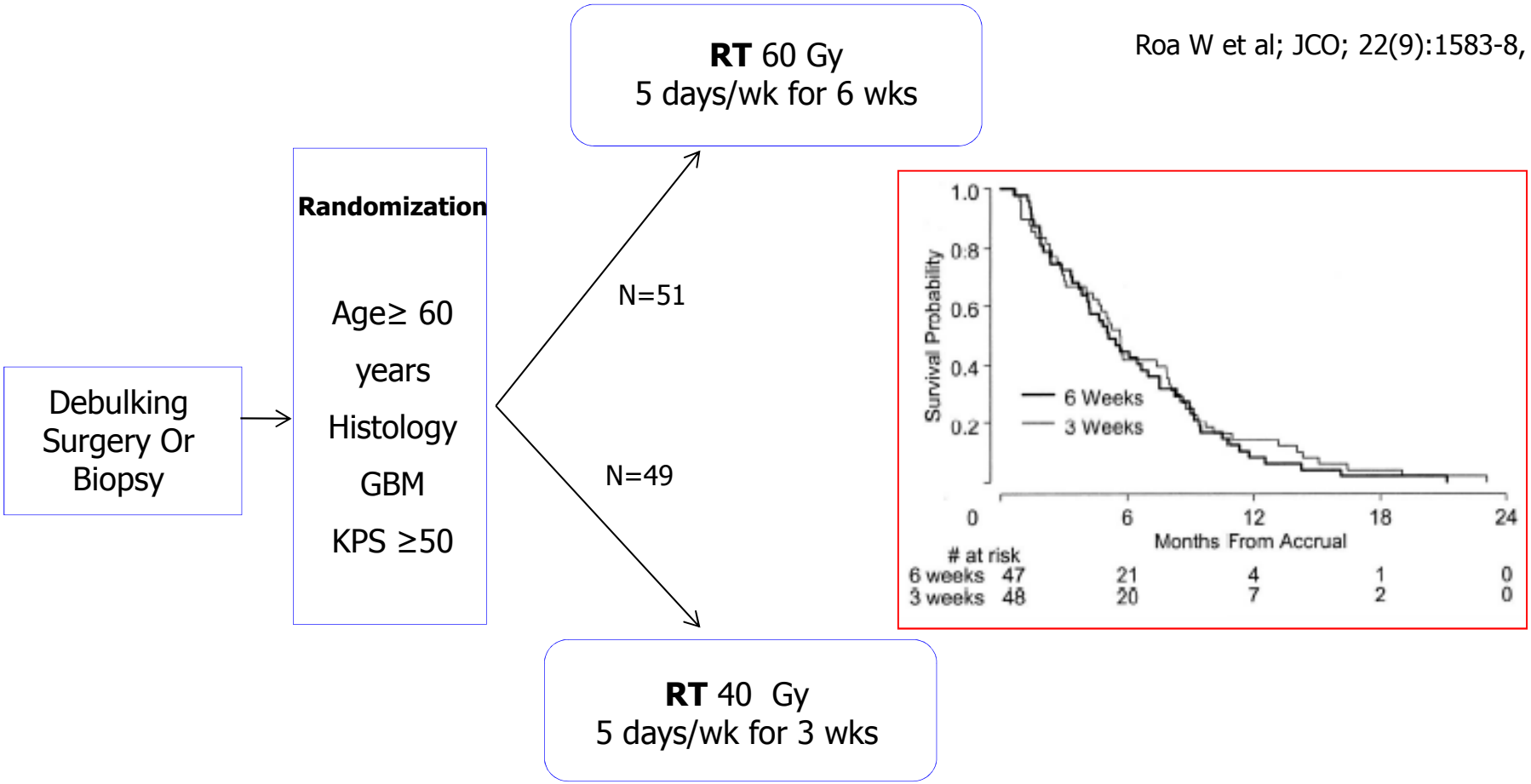
Doses of 60–70 Gy do not appear to improve survival compared to 50–60 Gy

Altered fractionation shortens treatment time.
However, there is not a significant survival improvement.

Nieder C. et al. Strahlen und Onkologie, 2004

Glioblastoma in the elderly and radiotherapy

Roa W et al; JCO; 22(9):1583-8, 2004



• No difference in survival between two arms. In view of the similar KPS scores, decreased increment in corticosteroid requirement, reduced treatment time.

• Abbreviated course of RT seems to be a reasonable treatment option for older (>60 yrs) patients with GBM.

Hypofractionation and HGG

NOA-08 trial

373 pts

(11% GIII glioma)

> 65 years

- RT (60Gy/30fr)
- Dose dense TMZ (1w. on/1w. off)

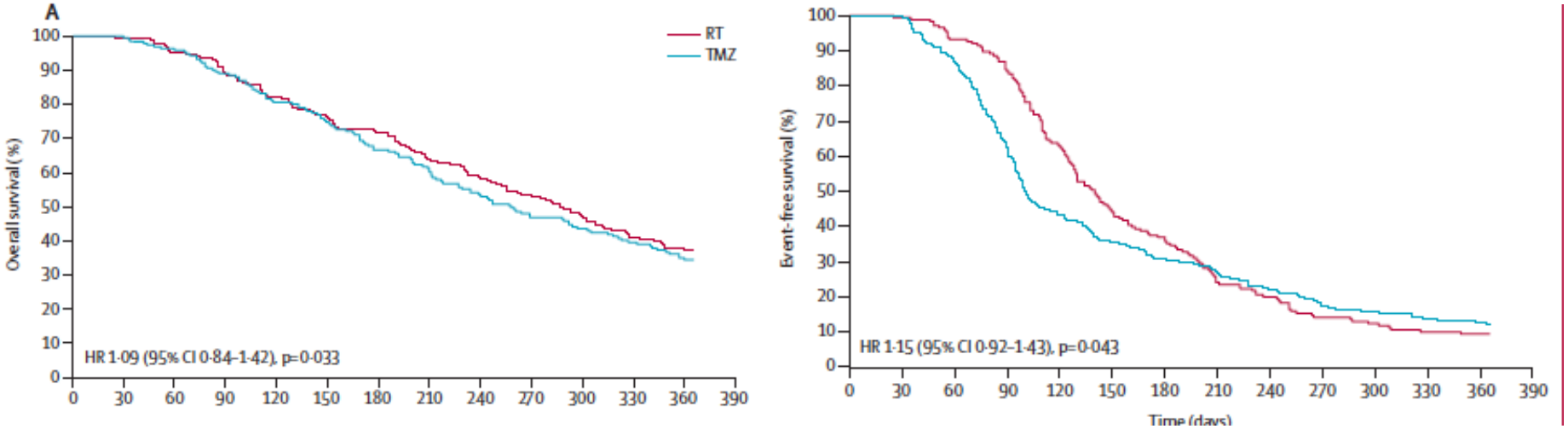
Nordic Brain Tumor Group Trial

342 pts

>60 years

- RT (60Gy/30fr)
- HypoRT (34Gy/10fr)
- Standard TMZ (5 out of 28 days)

NOA08 Trial



Temozolomide alone is non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma

Wich Wet al. Lancet Oncol, 2012

Nordic Brain Tumor Group Trial

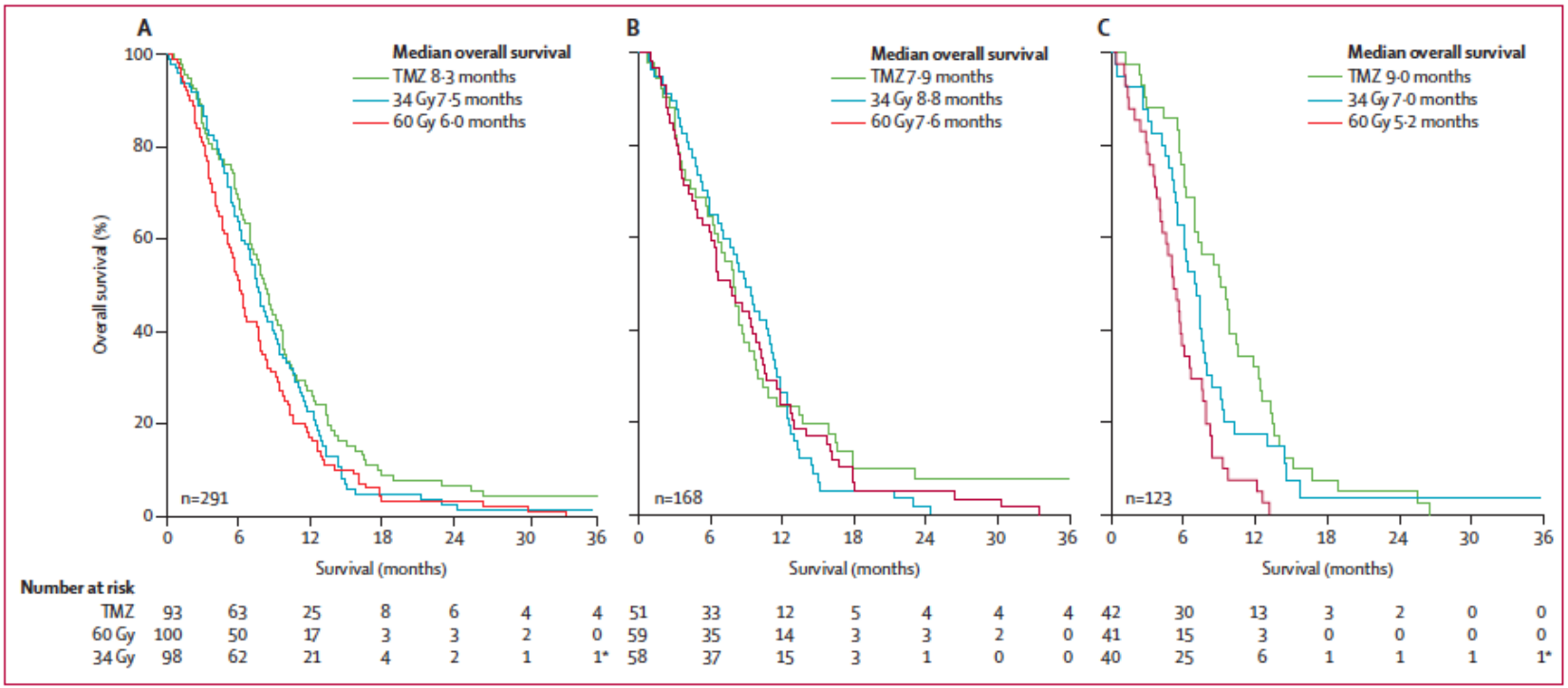


Figure 2: **Kaplan-Meier analysis of overall survival in patients randomised across three treatment groups**
(A) All patients. (B) Patients aged 60–70 years. (C) Patients older than 70 years. TMZ=temozolomide. 34 Gy=hypofractionated radiotherapy. 60 Gy=standard radiotherapy. *Patient censored at 35 months.

Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma

Malmström A et al. Lancet Oncol, 2012

Conclusion

- Radiotherapy technique: there is not a clear evidence of benefit with the use of modern RT approach and increase in overall survival rates.
- In limited case (i.e LGG, molecular feature selection) it is possible to purpose IMRT in order to reduce late neurological toxicity (i.e neurocognitive and hormonal)
- There is not a significant survival improvement with the use of alterated fractionation, SIB or SRS in HGG .
- There is an evidence with the use of hypofractionation and HGG in elderly patients or in patient with a poor PS.
- Evaluate cost and benefit in every specific case