Incontri Bresciani di Radioterapia Oncologica – Edizione 2013
Brescia Meetings in Radiation Oncology – 2013 Edition

DIFFICULT CLIMBING: TREATMENT OF GLIOMAS AND A TRIBUTE TO PROF. G.P.BITI

Brescia – October 3rd/4th, 2013

DOES RADIOTHERAPY TECHNIQUE / DOSE / FRACTIONATION REALLY MATTER? YES

Marco Krengli

Radiotherapy, Department of Translational Medicine, University of Piemonte Orientale "A. Avogadro"

THE STANDARD OF CARE

The NEW ENGLAND JOURNAL of MEDICINE

Stupp R 2005

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Which RT?

3D conformal RT (TD = 60 Gy, 2Gy / fx):

- **CTV: GTV plus 2-3 cm margin**
- **Planning on CT images**

No analysis of the pattern of recurrence

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

CNS radiotherapy

Minniti et al, 2010

Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide

- **105 Pts,** planning on CT-MRI (EORTC Guidelines)

- **Recurrence :**

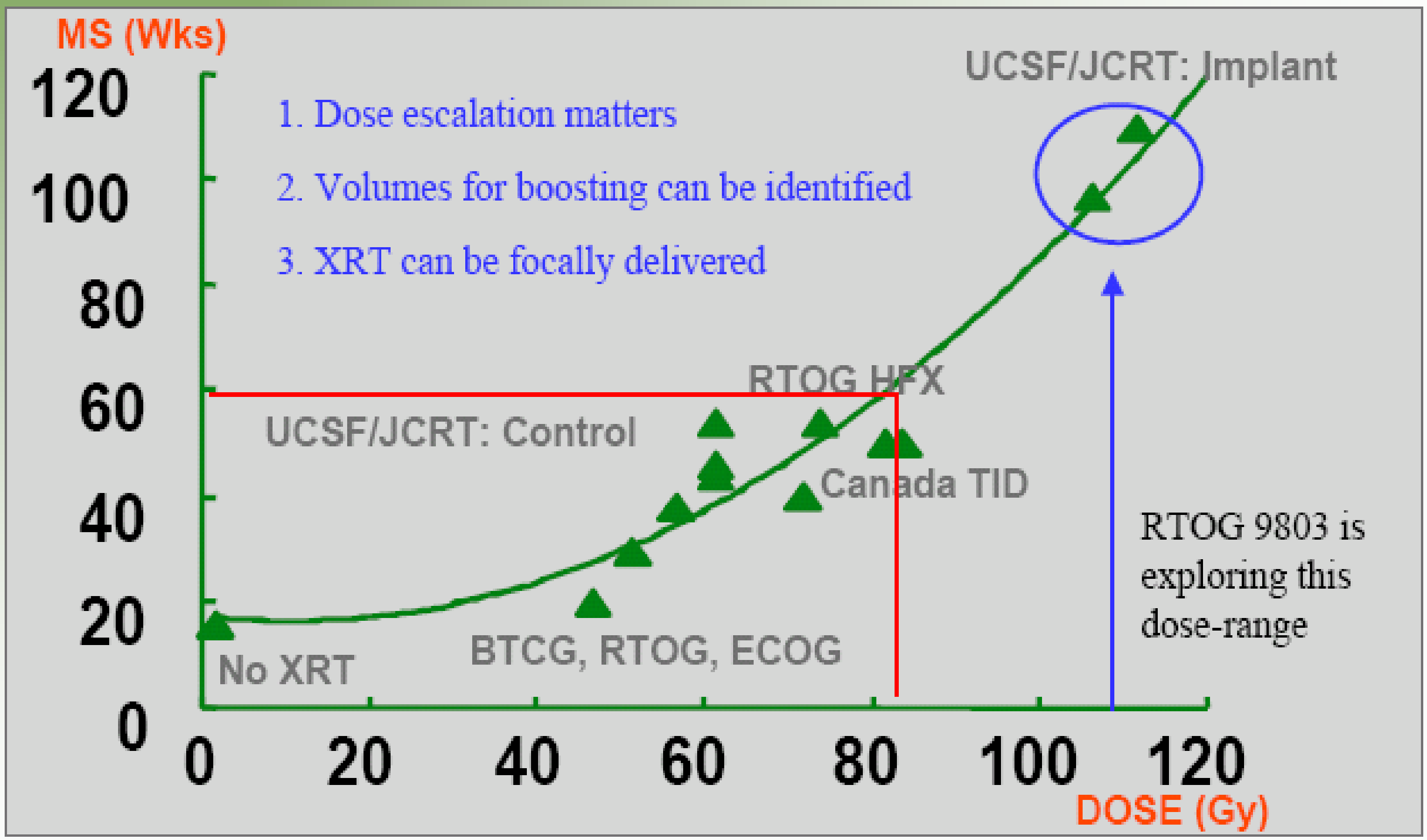
central in 79 pts	**75%**	**80.7%** (central + in-field)
in-field in 6 pts	**5.7%**	
marginal in 6 pts	**5.7%**	
outside in 14 pts	**13%**	

- **Central/in-field recurrence:** **64% of MGMT methylated pts**
  91% of MGMT unmethylated pts

Total dose

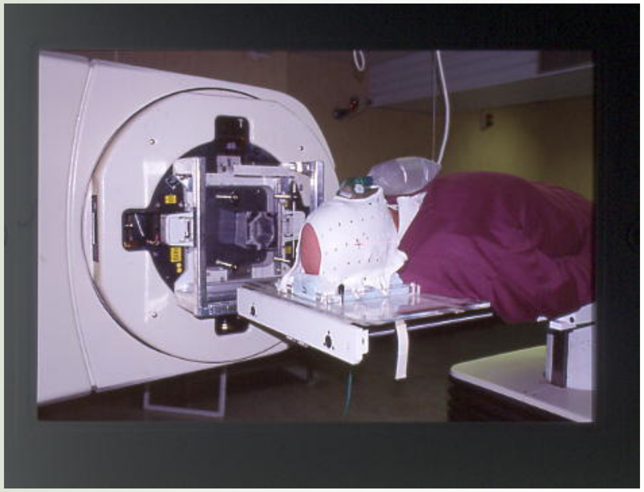
Dose / fraction

GBM- Dose escalation



HYPERFRACTIONATION

ARCON IN GLIOBLASTOMA
(EORTC 22933),
Miralbell, JCO, 1999



Pts: 115 (23 ARCO, 28 ARN, 56 ARCON)

Dose: 60 Gy Bid (1.5 x 2)

Median survival:	10.1 months	ARCO
	9.7 months	ARN
	11.1 months	ARCON

Main toxicity: gastrointestinal (Nicotinamide)

HYPOFRACTIONATION

Rationale

- ✓Dose intensification
- ✓Shorter treatment time
- ✓Less cell repopulation
- ✓Less influence of shoulder in cell survival curves
- ✓Better quality of life

Curran W, in *The Gliomas*, 1999
Glinski B, *Journal of Neuro-Oncology*, 1993
Sayin M. Y, *Medical Oncology*, 2007
Hulshof MCCM, *Radiotherapy and Oncology*, 2000

The NORDIC TRIAL

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

A. Malmstrom, Lancet Oncology 2012

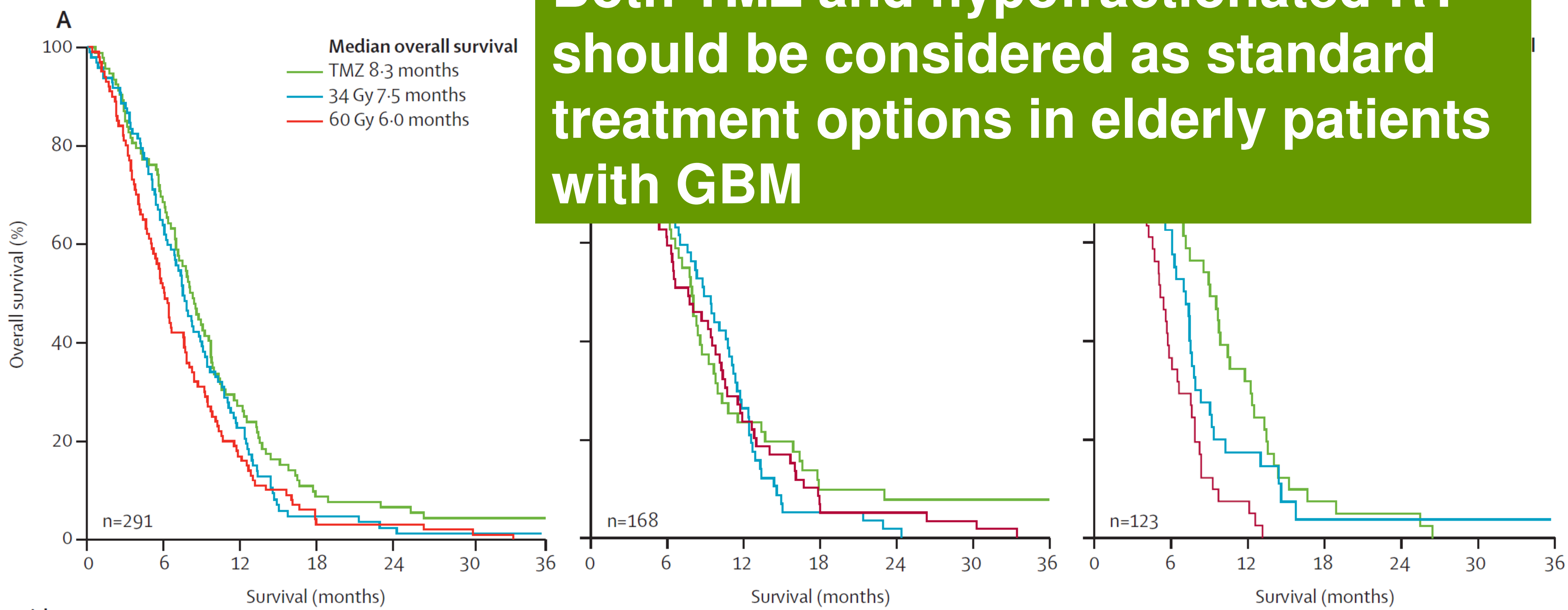
RANDOMIZATION

- 119 pts → **RT 60 Gy (2 Gy x 30)**
- 100 pts → **RT 34 Gy (3.4 Gy x 10)**
- 123 pts → **TMZ x 6 (200 mg/m^2 d 1-5 q 28 d)**

RESULTS:

Standard RT 60 Gy was in no case superior to RT 34 Gy or TMZ alone

Both TMZ and hypofractionated RT should be considered as standard treatment options in elderly patients with GBM



Number at risk

TMZ	93	63	25	8	6	4	4	51	33	12	5	4	4	4	42	30	13	3	2	0	0
60 Gy	100	50	17	3	3	2	0	59	35	14	3	3	2	0	41	15	3	0	0	0	0
34 Gy	98	62	21	4	2	1	1*	58	37	15	3	1	0	0	40	25	6	1	1	1	1*

All pts **Pts age 60-70 yrs** **Pts age > 70 yrs**

Clinical Investigation: Central Nervous System Tumor

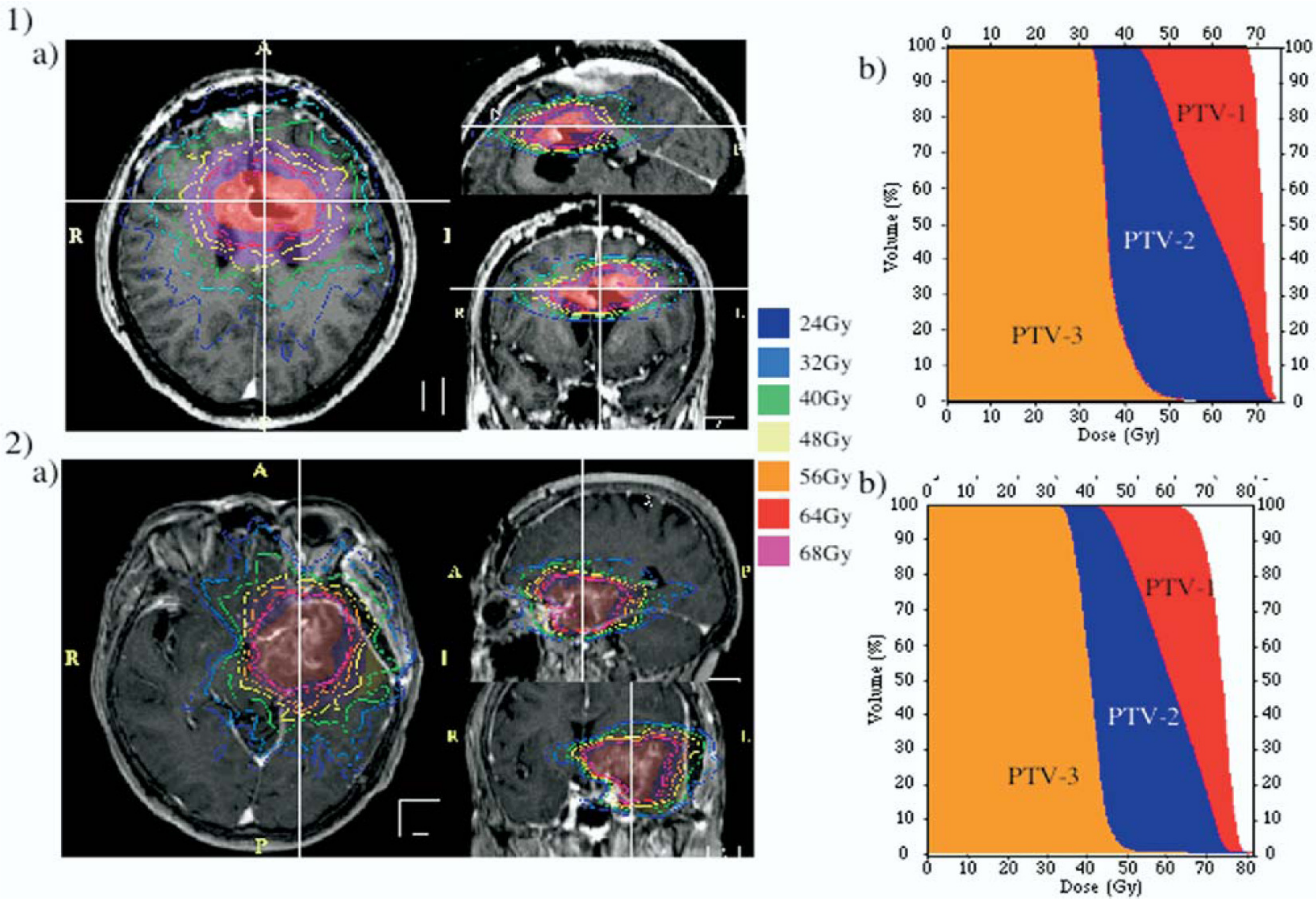
Health-Related Quality of Life in Elderly Patients With Newly Diagnosed Glioblastoma Treated With Short-Course Radiation Therapy Plus Concomitant and Adjuvant Temozolomide

Giuseppe Minniti, MD, PhD,[*,‡] Claudia Scaringi, MD,[*] Alessandra Baldoni, MD,[†] Gaetano Lanzetta, MD,[‡] Vitaliana De Sanctis, MD,[*] Vincenzo Esposito, MD,[‡] and Riccardo Maurizi Enrici, MD[*]

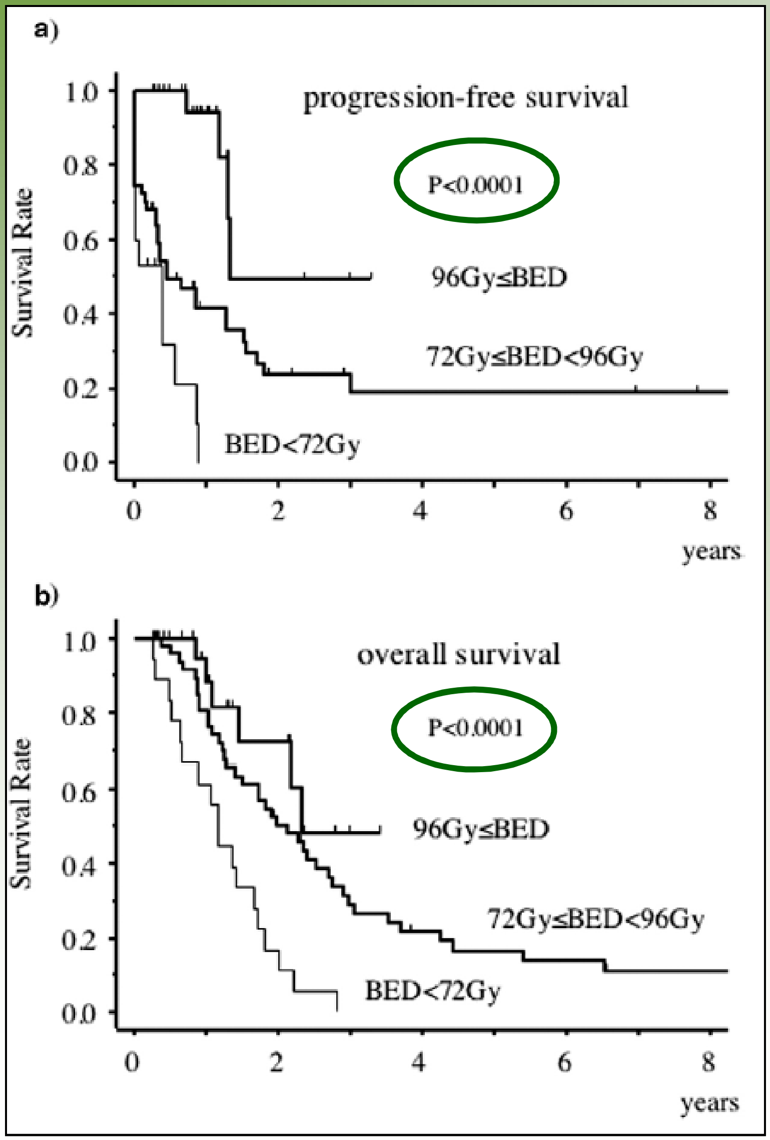
Departments of [*]Radiation Oncology and [†]Medical Oncology, Sant' Andrea Hospital, University Sapienza, Rome, and [‡]Department of Neurological Sciences, Neuromed Institute, Pozzilli (IS), Italy

In conclusion, a short course of RT in combination with TMZ was of benefit in elderly patients with GBM. The treatment was associated with improvement in, or at least preservation of, important HRQOL domains until the time of disease progression.

HYPOFRACTIONATED HIGH-DOSE IRRADIATION FOR THE TREATMENT OF MALIGNANT ASTROCYTOMAS USING SIMULTANEOUS INTEGRATED BOOST TECHNIQUE BY IMRT



IMRT – Dose escalation



The effect of dose-escalation on local control (a) and patients' survival (b).

BED<72 Gy= 60Gy
With conventional fx

Iuchi, et al; IJROBP,2006

Stereotactic radiosurgery

Table 1: Studies of stereotactic radiosurgery as adjunct treatment for newly diagnosed high-grade gliomas

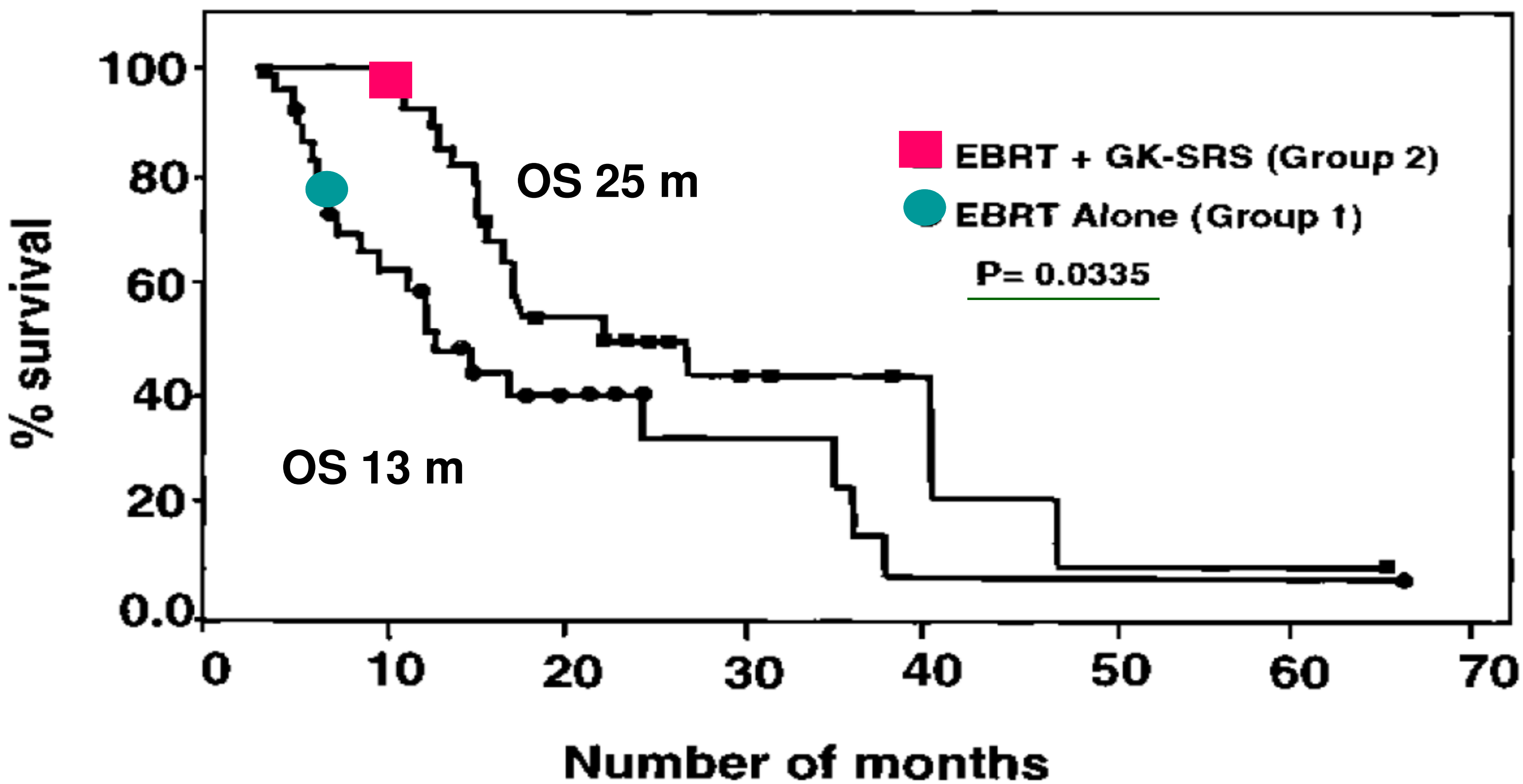
Year	Pt #	SRS tech.	Timing SRS to XRT pre, post (duration, if known)	Median dose/ range (Gy)	Median vol. (cm^3)	Median OS-Dx (months)	Ref. no.
1992	37	LIN	Post (within 4 weeks)	12–15	4.8	III: NR, IV: 26	38
1993*	10	GK	–	–	–	–	13
1994	31	LIN	Pre, post	12	17.4	10.5	46
1994	26	LIN	Post	10–20	16.4	9.6	44
1995	31	LIN	Pre, post	–	16.4	9.5	52
1995	115	LIN	Pre, post (within 4 weeks)	12	10.0	24	57
1995	30	LIN	Post (within 8 weeks)	10	24.0	13.9	20
1995	11	LIN	Post (within 2 weeks)	12.5	14.0	17	10
1996	47	GK	Post (within 16 weeks)	16–32	5.9	III: 20, IV: 10 ^	34
1997	65	GK	Post (within 6.2 months)	III: 15.2, IV: 15.5	III:6, IV:6.5	III: 56, IV: 20 ^	30
1997	14	LIN	Pre	20	–	10[and]	61
1999	78	LIN	Post (within 42 weeks#)	12	9.4	19.9	63
2002	32	LIN	Post (within 13 weeks)	10	15.0	21.4	55
2002	64	GK	Post (within 4 weeks)	17.1	18.5	25	51
2003	17	LIN	Post (within 2 weeks)	20	–	20	6
2004	186	LIN/GK	Pre	15–24	3.0	13.6	65
2005	67	LIN	Post (within 4 weeks)	15	–	–	72
2005	25	GK	–	12	23.6	11	27
2006	25	CBK	Post	20.3	19.1	20.7	79
2009	95	GK	–	14.7	–	III: 68, IV: 27	28
2009	15	LIN	Post (within 7.6 months#)	13	13.2	10.3	9
2009	20	CBK	Post (within 3 months#)	20	5.8	11.5	73

Binello E, Surgical Neurology International, Review 2012

CLINICAL STUDIES

Nwokedi E.C, Neurosurgery 2002

Gamma Knife Stereotactic Radiosurgery for Patients with Glioblastoma Multiforme



How to improve RT dose delivery ?

IMRT - IGRT

Systematic review **R&O 2010**

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*

Authors	No. of cases	Prescription and Fractionation	Site of lesions	Volumes
3D-CRT vs IMRT studies				
Chan et al. [7]	5	3D-CRT: 59.4 Gy to PTV (1.8 Gy/fx)	N/R	GTV: median 39 cc, mean 58 cc;
MacDonald et al. [9]	20	3D-CRT: 45 Gy to PTV + 14.4 Gy to PTVboost (1.8 Gy/fx)	11 frontal, 9 temporal	N/R
Piroth et al. [11]	16	3D-CRT: 60 Gy to PTV (2 Gy/fx) + 12 Gy ... to PTVboost (2.4 Gy/fx) – SIB	8 frontal, 4 temporal, 4 parietal;	PTVboost: mean (12.1 ± 18.6) cc
Comparison among different IMRT techniques (with or without 3D-CRT)				
		SIB-IMRT: 46 Gy to PTV (2 Gy/fx) and 53.8 Gy to PTVboost (2.34 Gy/fx) – SIB HT: same as SIB-IMRT		PTV: mean 432 cc, range (276–1074) cc
Shaffer et al. [14]	10	S-IMRT: 60 Gy to PTV (2 Gy/fx) VMAT: same as IMRT	N/R; overlaps with OARs	PTV: mean 343 cc

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

IMRT is better than 3D-CRT in reducing the maximum dose to the organs at risk, although to an extent that varies considerably from case to case;

IMRT is clearly better than 3D-CRT in terms of dose conformality and sparing of the healthy brain tissue at medium to low doses;

There is no case in which IMRT seems to be worse than 3DCRT,

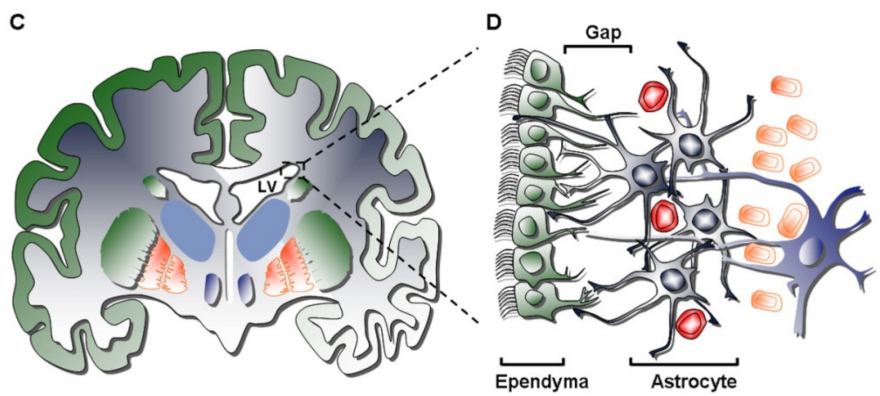
From the dosimetric point of view, IMRT appears adequate for the treatment of GBM. In GBM patients with good prognosis, SIB IMRT allows to deliver hypofractionated regimens that, in association with CHT, suggests the possibility to achieve results that are even superior to those obtainable by the standard treatment.

Clinical Investigation: Central Nervous System Tumor

Chen L, Johns Hopkins University, IJROBP 2013

Increased Subventricular Zone Radiation Dose Correlates With Survival in Glioblastoma Patients After Gross Total Resection

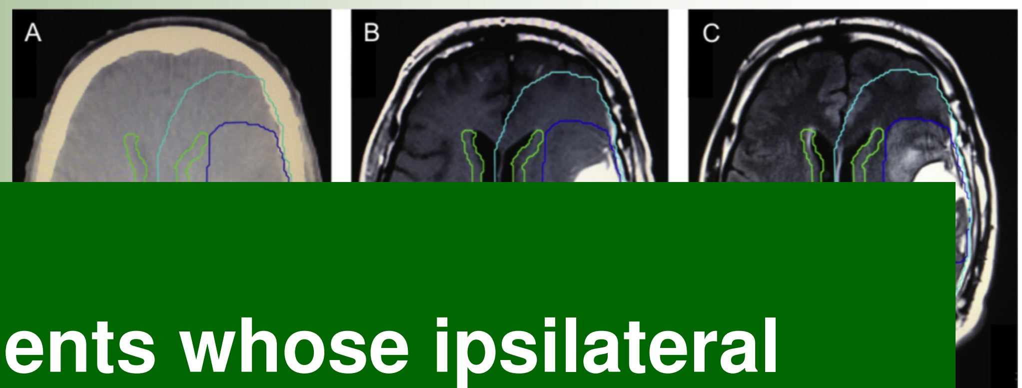
- A putative source of glioma stem cells is the subventricular zone (SVZ), the largest area of neurogenesis in the adult human brain. Multipotent neural progenitor cells (NPCs) line the lateral wall of the lateral ventricles (LVs).



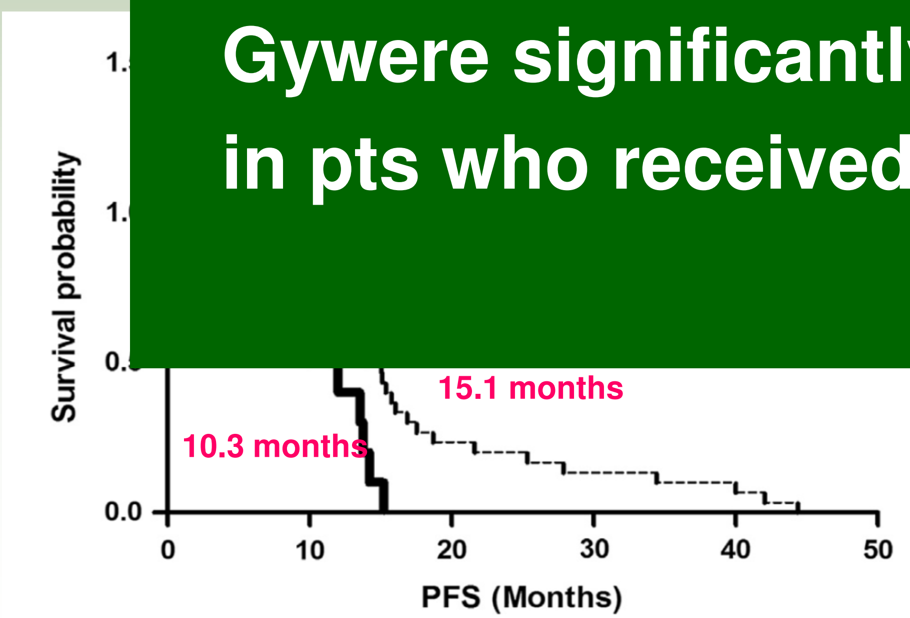
- **To analyse the relationship between RT dose to the SVZ and patient outcome (DFS and OS)**

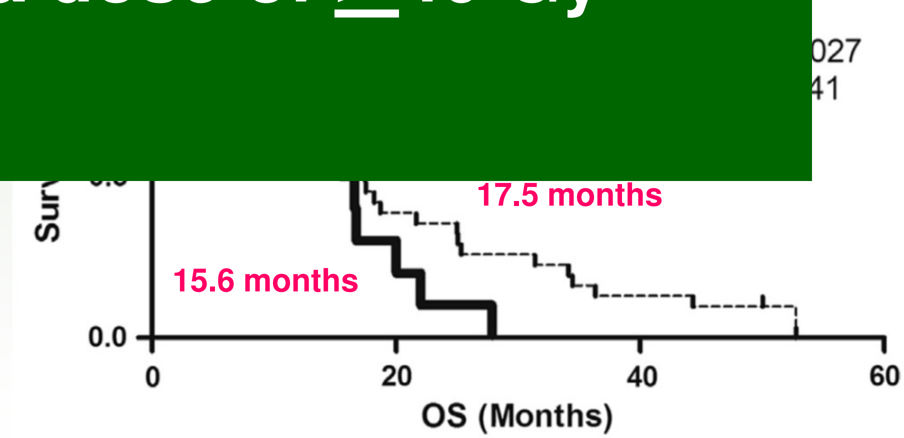
SVZ & RADIATION DOSE

- 116 GBM pts
- 41 GTR
- I

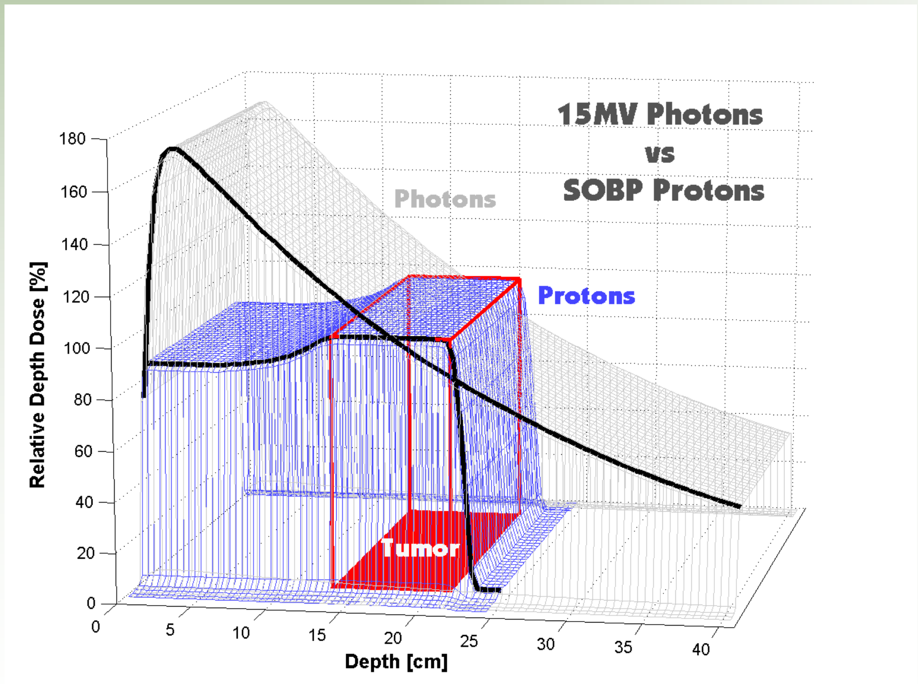


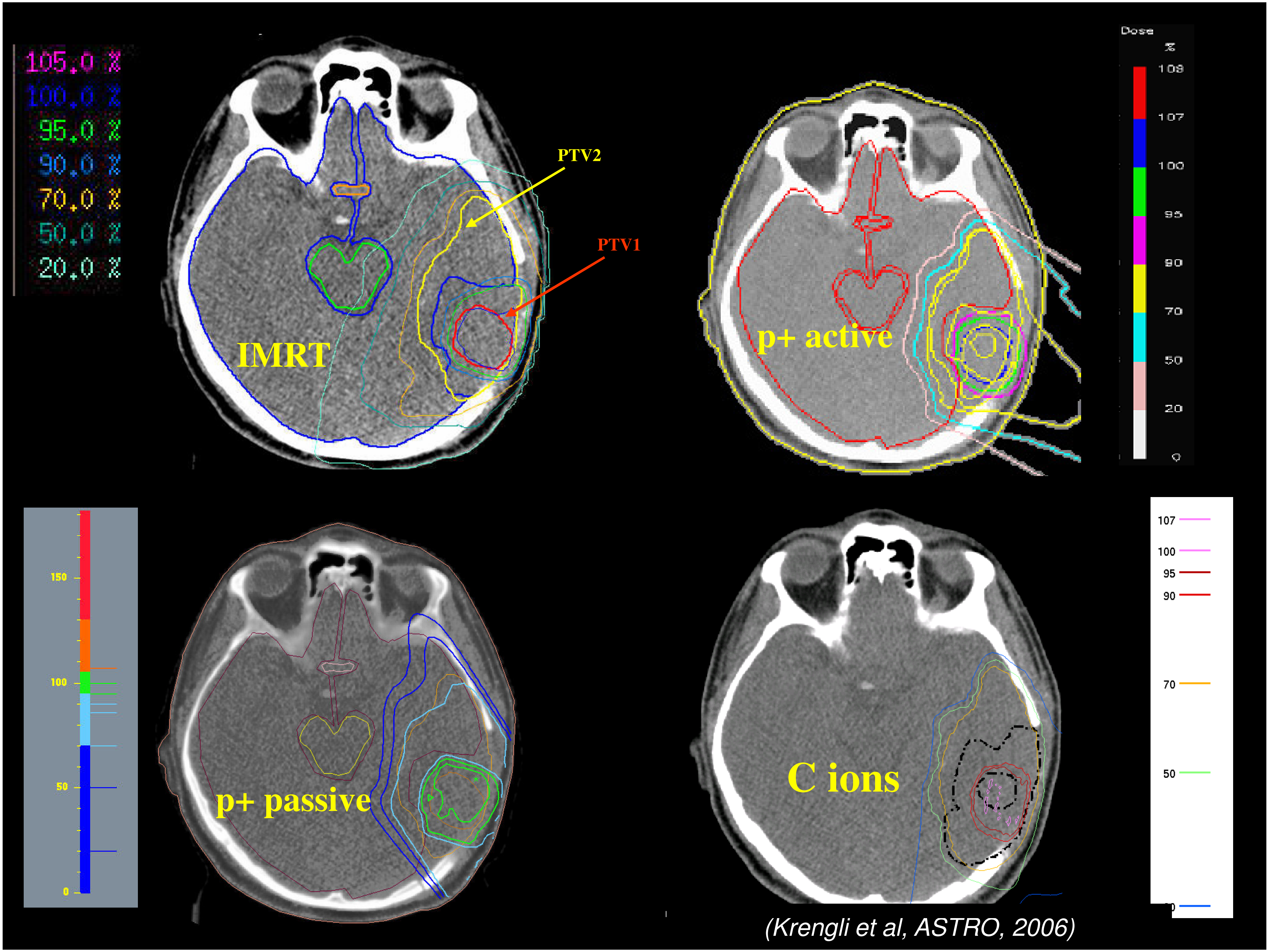
- **PFS & OS in patients whose ipsilateral subventricular zone (SVZ) received > 40 Gywere significantly different from that in pts who received a dose of ≥ 40 Gy**





Low and High - LET Charged Particles

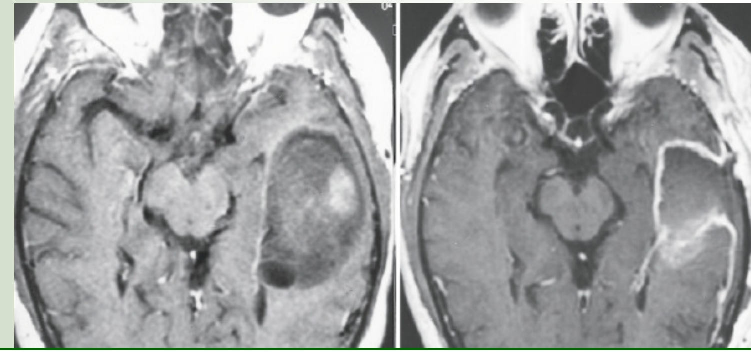



105.0 %
100.0 %
95.0 %
90.0 %
70.0 %
50.0 %
20.0 %
PTV2
PTV1
IMRT
Dose
%
108
107
100
95
90
70
50
20
0
p+ active
150
100
50
0
p+ passive
107
100
95
90
70
50
C ions
(Krengli et al, ASTRO, 2006)

PROTONTHERAPY IN GBM
(Fitzek, MGH-HCL, 1999)

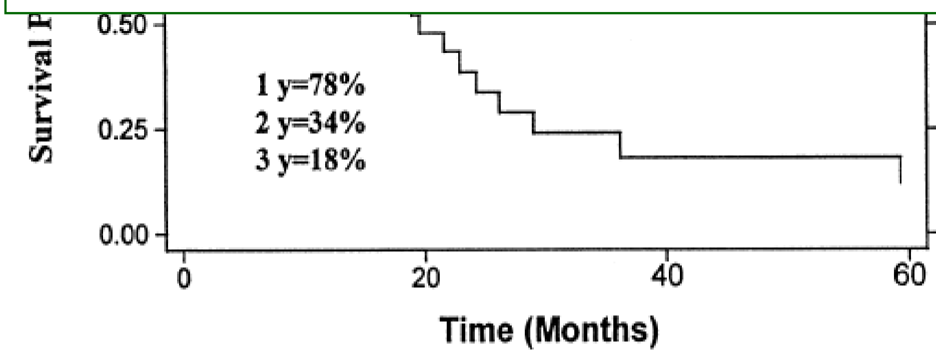
Fx: b.i.d. (1.8 GyE x 2), 50 fxs, 5 wks

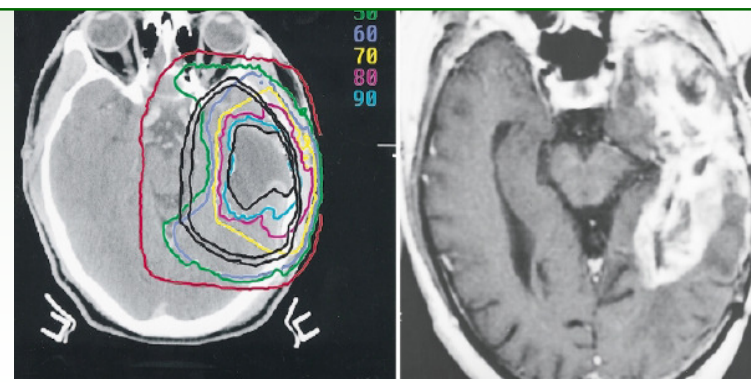
3 volumes: V1 (90 GyE), V2 (64.8 GyE)



Tumor progression: 16/23 (1 in 90 GyE volume)

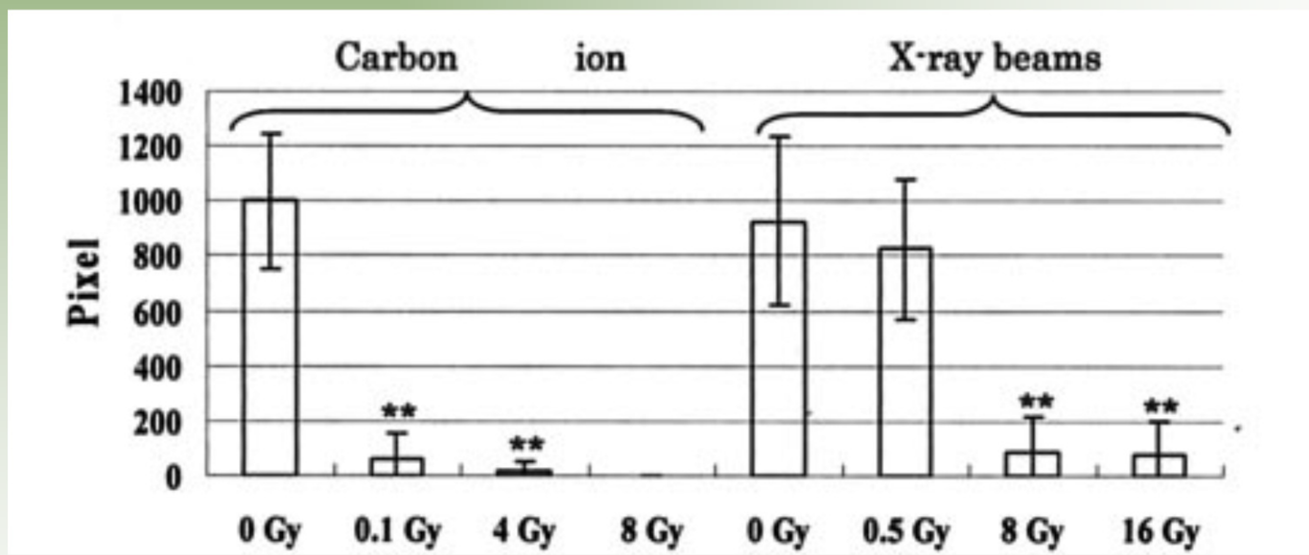
Open issue: Identification of target volume ?





Carbon ions and Angiogenesis

- Comparison of 290 MeV carbon ion beam and photons
- Carbon ions are able to inhibit angiogenic factors like matrix metalloproteinese-2 even at subclinical doses (0.1 GyE)



Effects of irradiation on the formation of capillary-like tube structures assessed in a collagen-embedded culture.

Takahashi, Cancer Res, 2003

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 2, pp. 390–396, 2007

PHASE I/II CLINICAL TRIAL OF CARBON ION RADIOTHERAPY FOR MALIGNANT GLIOMAS: COMBINED X-RAY RADIOTHERAPY, CHEMOTHERAPY, AND CARBON ION RADIOTHERAPY

Jun-Etsu Mizoe, M.D.,* Hirohiko Tsujii, M.D.,* Azusa Hasegawa, D.D.S.,* Tsuyoshi Yanagi, M.D.,* Ryo Takagi, D.D.S.,* Tadashi Kamada, M.D.,* Hiroshi Tsuji, M.D.,* and Kintomo Takakura, M.D.,† for the Organizing Committee of the Central Nervous System Tumor Working Group

*Hospital, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan; and †Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Total number	48
Histology (%)	
AA	16 (33)
GBM	32 (67)
Median age, y	53 (range, 18–78)
Age <50 (%)	22 (46)
Age >50 (%)	26 (54)
Sex (%)	
Male	29 (60)
Female	19 (40)
Extent of surgical resection (%)	
Gross total	8 (17)
Subtotal	8 (17)
Partial	27 (56)
Biopsy	5 (10)
Neurologic function (%)	
1 (Able to work)	29 (60)
2 (Able to be at home)	19 (40)
Tumor location (%)	
Frontal	22 (46)
Temporal	10 (21)
Parietal	5 (10)
Occipital	6 (13)
Others	5 (10)

Table 2. Treatment characteristics of carbon ion radiotherapy

Total number	AA (16)	GBM (32)	Total (48)
Total carbon dose (%)			
16.8 GyE	3	4	7 (15)
18.4 GyE	1	6	7 (15)
20.0 GyE	2	7	9 (19)
22.4 GyE	3	10	13 (27)
24.8 GyE	7	5	12 (25)
Clinical target volume (cm^3)			
Minimum	13.7	25.6	13.7
Maximum	188.8	285.0	285.0
Average	82.4	123.1	109.5
Number of ports (%)			
2 Ports	10	18	28 (58)
3 Ports	6	14	20 (42)

Results

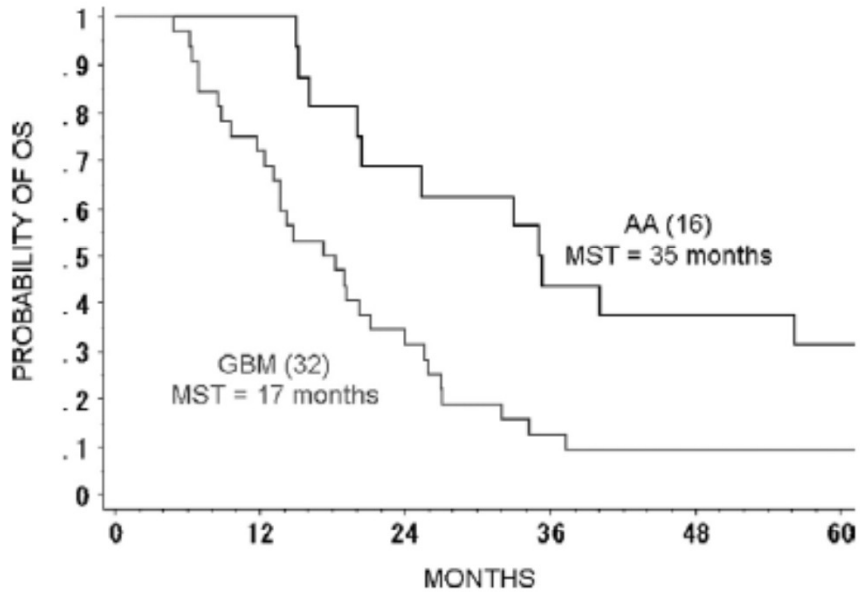


Fig. 3. Overall survival by histology. Median survival time of 16 anaplastic astrocytoma was 35 months and that of glioblastoma multiforme 17 months. There was statistical significance between two curves ($p = 0.0094$).

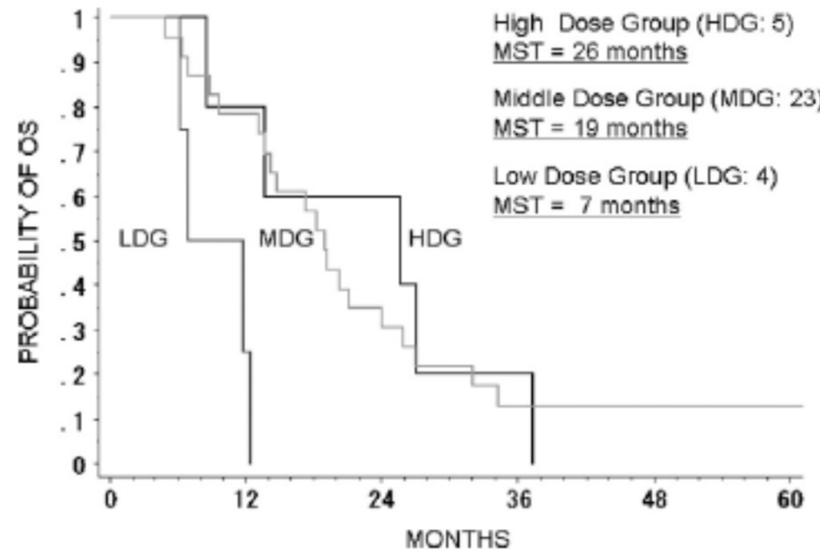


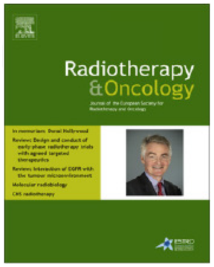
Fig. 4. Overall survival of glioblastoma multiforme by carbon ion dose. Median survival time of the low-dose group (16.8 GyE) was 7 months, that of the middle-dose group (18.4–22.4 GyE) 19 months, and that of the high-dose group (24.8 GyE) 26 months. There was statistical significance among three curves ($p = 0.0031$).

- ✓ **Prolongation of OS with higher doses**
- ✓ No grade 3-4 acute and late toxicity and no evidence of dose – toxicity correlation

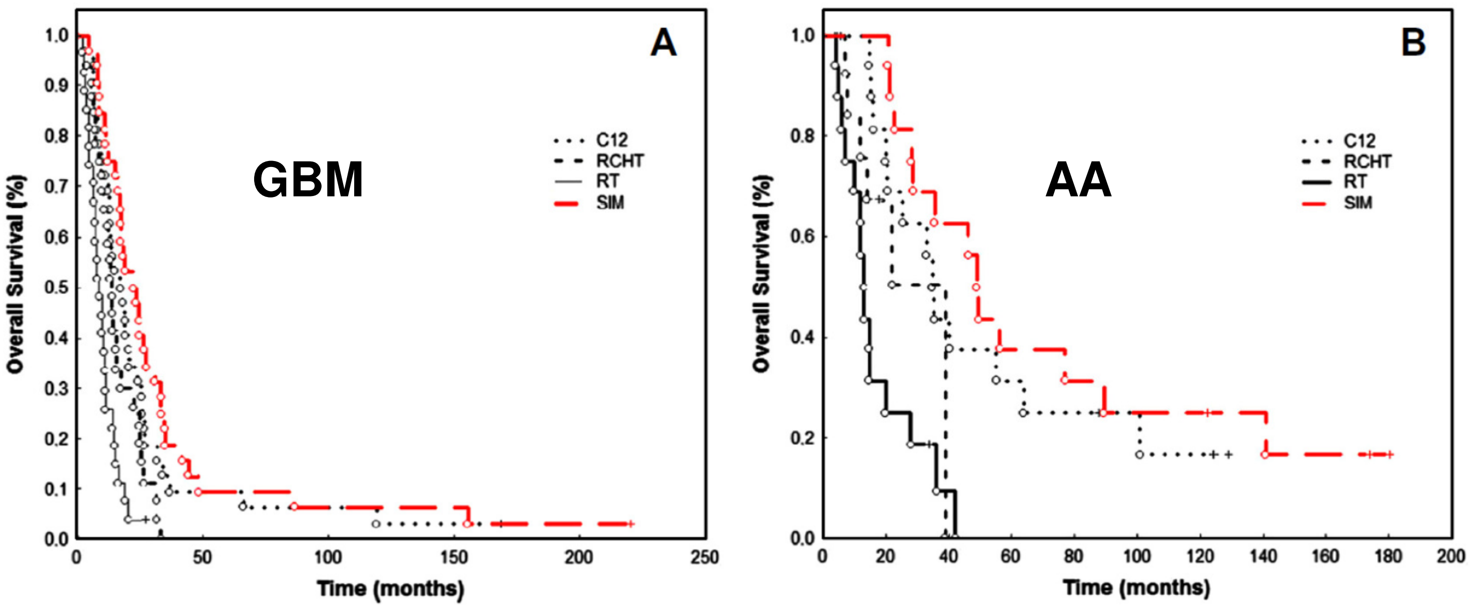
Mizoe et al., IJROBP, 2007

Radiotherapy and Oncology 108 (2013) 132–135

Comparison of carbon ion radiotherapy to photon radiation alone or in combination with temozolomide in patients with high-grade gliomas: Explorative hypothesis-generating retrospective analysis



Stephanie E. Combs [a,*], Thomas Bruckner [b], Jun-Etso Mizoe [c,d], Tadashi Kamada [c], Hirohiko Tsujii [c], Meinhard Kieser [b], Jürgen Debus [a]



	1-year	2-year	3-year	5-year
RT	7	1	0	0
RCHT	19	7	0	0
C12	23	11	4	3
SIM	25	15	6	3

	1-year	2-year	3-year	5-year
RT	11	4	2	0
RCHT	10	1	1	0
C12	16	11	7	5
SIM	16	13	10	6

Protocol for GBM @ CNAO (to be activated)

Total dose: 74 Gy[RBE], 2 Gy[RBE]/fx

Assessment: acute toxicity, local response, DFS, OS, late toxicity

Which volume ?

Which imaging ?

NCCN Guidelines Version 2.2013

PRINCIPLES OF BRAIN TUMOR RADIATION THERAPY

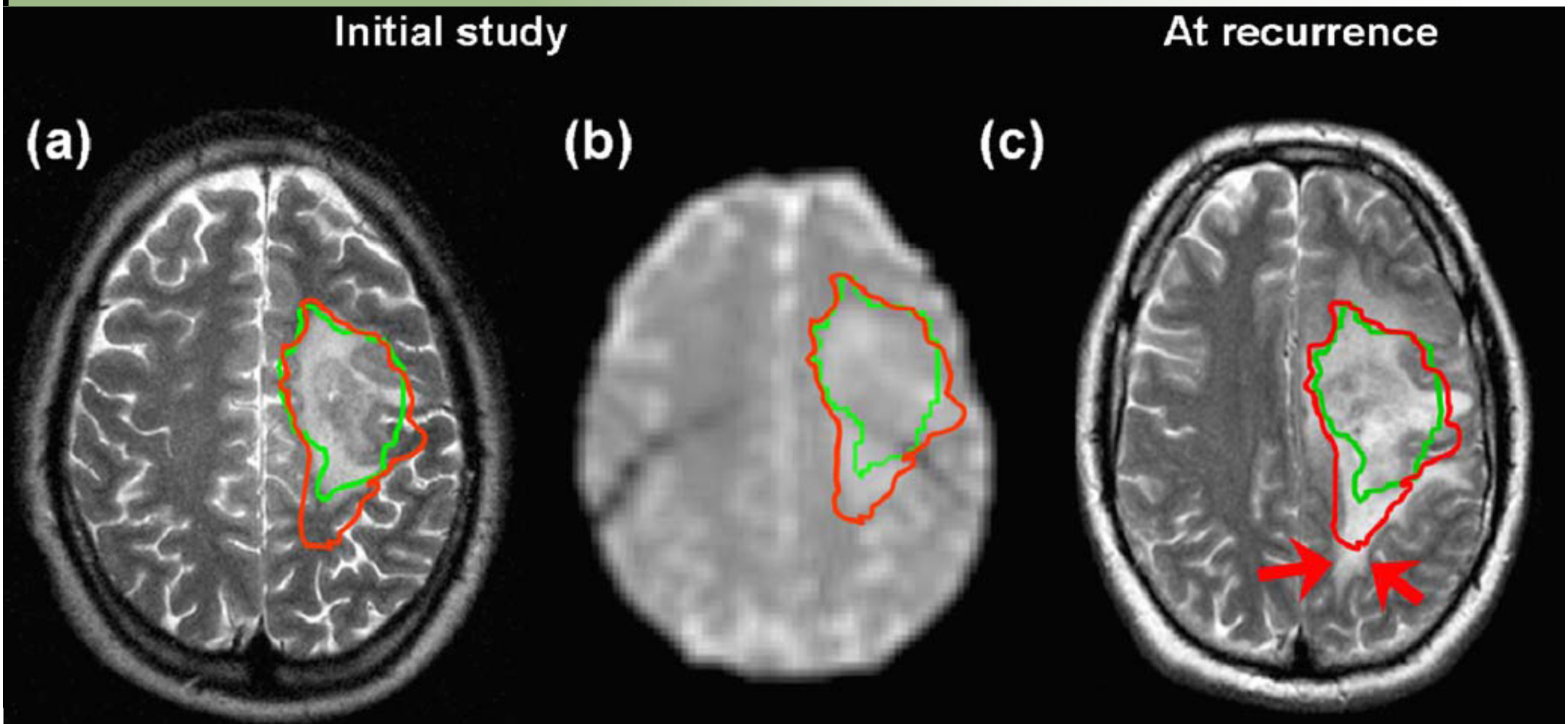
High Grade Gliomas (Grades III/IV)

- The gross tumor volume (GTV) is best defined using pre- and postoperative **MRI imaging using enhanced T1 and FLAIR/T2**. The GTV is expanded by 2-3 cm (CTV) to account for sub-diagnostic tumor infiltration. Fields are usually reduced for the last phase of the treatment (boost).

(Price, Eur Radiol 2007)

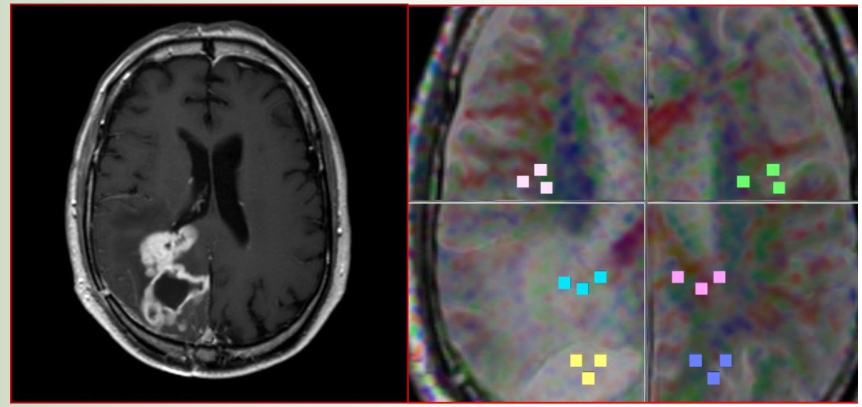
Predicting patterns of glioma recurrence using diffusion tensor imaging

Decreased anisotropy (q) = gross tumor margin
Increased isotropy (p) = infiltrating tumor margin

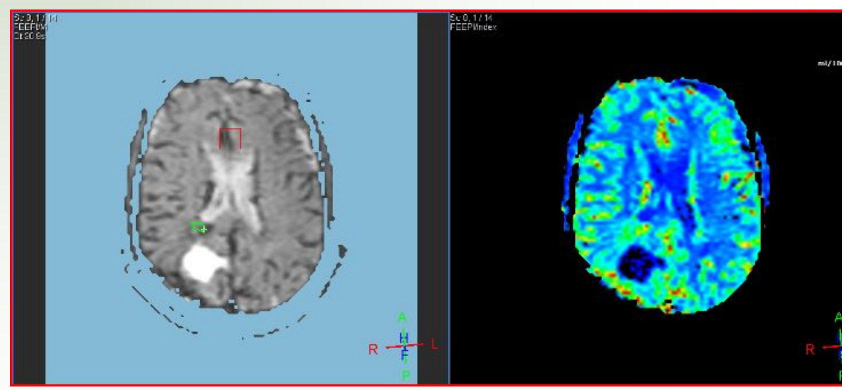


Can imaging by PW and DW MR help in identification of radiation target ?

- 17 pts: 14 M, 3 F
- surgery+RT (60 Gy) + TMZ
- Timing of image acquisition:
  - MR DWI and MR PWI pre RT (**T0**)
  - MR DWI and MR PWI after RT (2 months) and during F/U (every 4 months)
  - @ PD: MR DWI and MR PWI (**T1**)



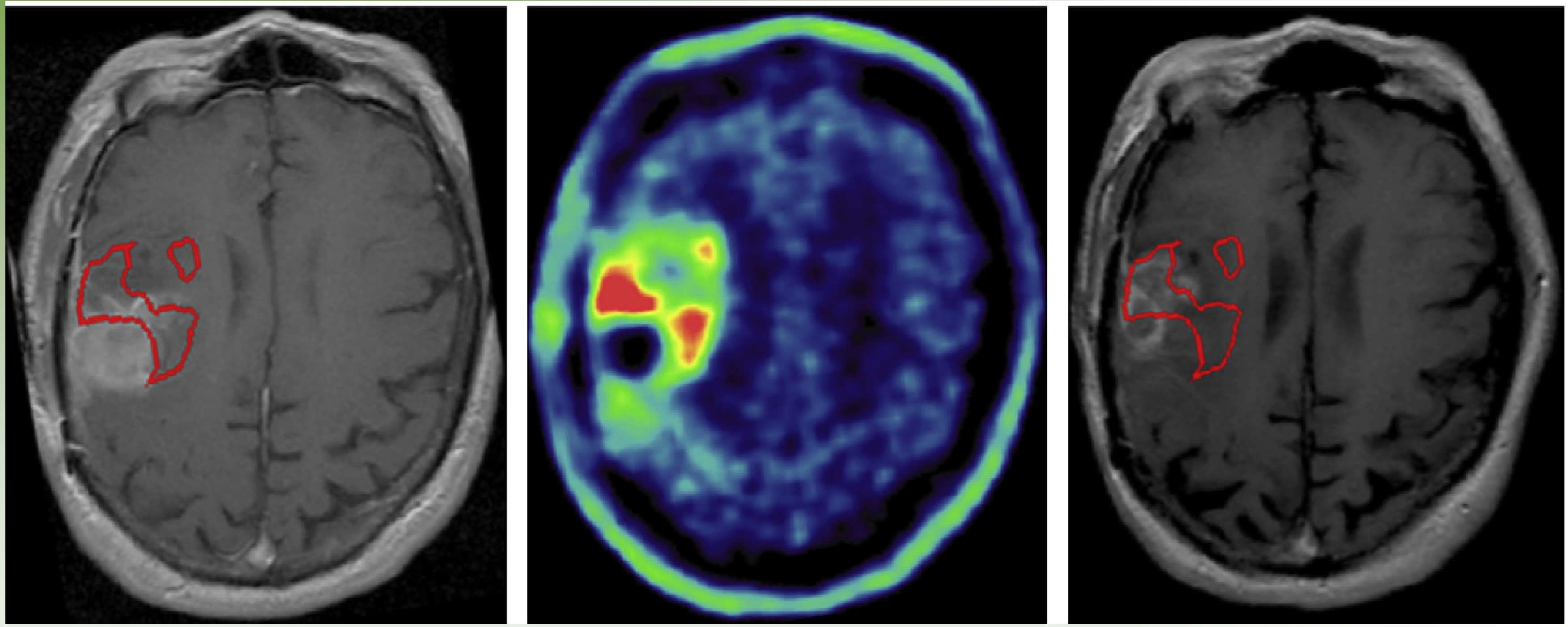
MR DWI @ T1



MR PWI @ T1

(Stecco et al, J Neurooncol, 2011)

Retrospective study on marginal recurrence with MET-PET



- 26 pts, GTV contoured with MRI, 5 had MET enhancement outside GTV;
- 5/5 marginal recurrences when the area MET+ was not included in the GTV vs. 2/21 in the others.

Lee et al. IJROBP 2009

Clinical Investigation: Central Nervous System Tumor

Einstein DB, IJROBP 2012

Phase II Trial of Radiosurgery to Magnetic Resonance Spectroscopy—Defined High-Risk Tumor Volumes in Patients With Glioblastoma Multiforme

✓The median survival was 15.8 months.

✓ **For the 16 /35 pts who received concurrent TMZ, the median survival was 20.8 months** *(historical controls of 14.6 months)*.

✓ The treatment is feasible, with acceptable toxicity and patient survivals higher than in historical controls.

FEASIBILITY STUDY OF INTENSITY-MODULATED RADIOTHERAPY (IMRT) TREATMENT PLANNING USING BRAIN FUNCTIONAL MRI

JENGHWA CHANG, PH.D., ALEX KOWALSKI, B.S., BOB HOU, PH.D., and ASHWATHA NARAYANA, M.D.

Departments of Medical Physics and Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY; and Department of Radiation Oncology, New York University Medical Center, New York, NY

Medical Dosimetry 2008

***Conclusion*:**

IMRT can reduce the RT dose to the primary motor cortex (PMC) without compromising the PTV coverage or sparing of other critical organs. IMRT planning allows a significant reduction in RT dose to the PMC regions.

(A) (B)

Fig. 2. Treatment plans for patient no. 1 (A) without and (B) with the fMRI information.

In Conclusion …

Does technique/dose/fractionation matter in Clinical Practice ?

At least in part

YES

Does technique/dose/fractionation matter in Clinical Trials ?

YES!