The association of Temozolomide to radiation therapy and a prospect on other drug-radiation combinations for CNS Tumors

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B2B

(no, not the Dotcom Nonsense...)

Glioblastoma:
Prime example of the *Bedside-to-Bench-to-Bedside* paradigm...
...with some considerable success!

Let‘s put things into perspective:
What‘s the problem?
Patients die of

-Local recurrence around resection site

-Diffuse/Distant in-brain recurrence

Table 1. Importance of Prognostic Factors Demonstrated in Cooperative Group Trials

Study	Patient variables				Morphology	Extent of Resection
	Age	PS	Symptoms	Mental Status		
BTSG						
Walker et al, 1978[2]	Yes	Yes	Yes	NA	NA	Yes
Walker et al, 1980[3]	Yes	Yes	Yes	NA	Necrosis	NA
Green et al, 1983[4]	Yes	Yes	Yes	NA	GBM *v* other	Yes
NCCTG						
Dinapoli et al, 1993[5]	Yes	Yes	NA	NA	NA	Yes
Elliott et al, 1997[6]	Yes	Yes	NA	NA	NA	Yes
Buckner et al, 2001[7]	Yes	+/−	NA	Yes*	Tumor grade	Yes
RTOG RPA						
Curran et al, 1993[8]	Yes	Yes	NA	Yes	GBM *v* AAF	Yes

Abbreviations: PS, performance status; BTSG, Brain Tumor Study Group; NA, not available; GBM, glioblastoma multiforme; NCCTG, North Central Cancer Treatment Group; RTOG, Radiation Therapy Oncology Group; RPA, recursive partitioning analysis; AAF, astrocytomas with anaplastic or atypical foci.

*Mini mental status examination.

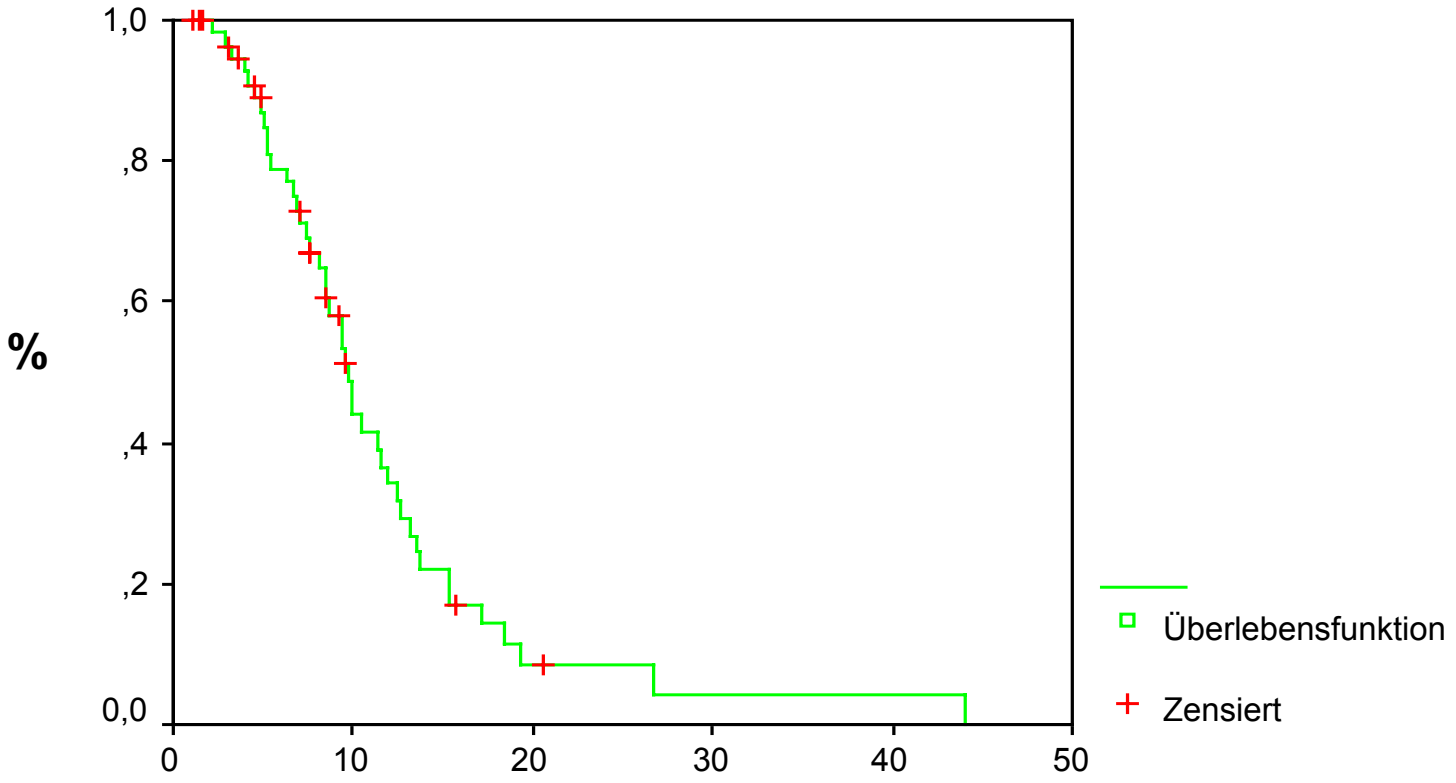
Factors Influencing Survival in High-Grade Gliomas

Semin Oncol 30 (suppl 19):10-14.

Jan C. Buckner

malignant gliomas: conventional view conventional results

overall survival in pts with GBM (n = 89) pOP+RT+/-Chemo



Kaufmann Med Diss 2004

3D-recurrence-patterns of gliobastomas after CT-planned postoperative irradiation

Ulrich Oppitz*, Dirk Maessen, Hildegard Zunterer, Susanne Richter, Michael Flentje

Radiotherapy and Oncology 53 (1999) 53–57

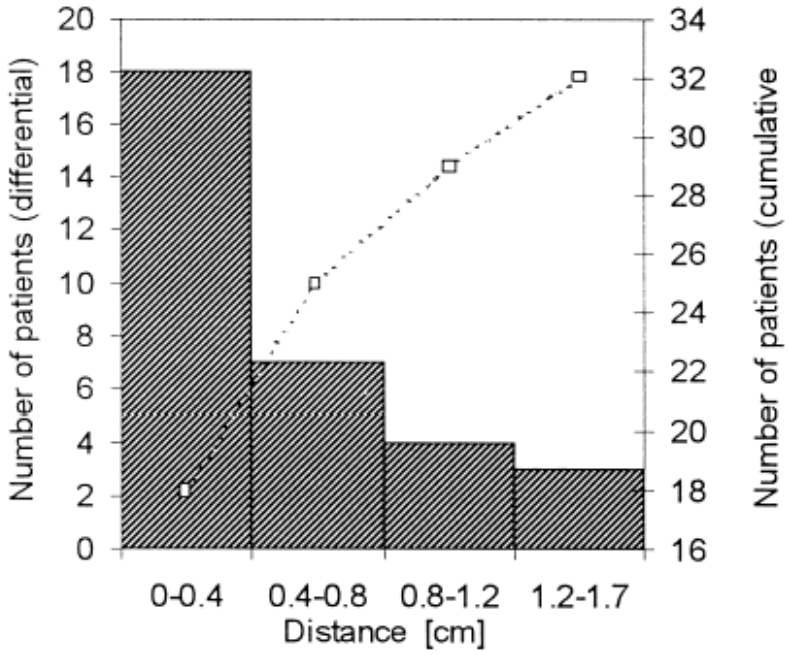


Fig. 2. Minimal distance between the 90%-isodose- and the recurrent tumour-surface ($n = 32$), differential (hatched columns) and cumulative (dotted line).

Dose-Escalated Conformal Radiotherapy of Glioblastomas – Results of a Retrospective Comparison Applying Radiation Doses of 60 and 70 Gy

Reinhold Graf[a] Bert Hildebrandt[b] Wolfgang Tilly[a] Geetha Sreenivasa[a] Renate Ullrich[a]
Klaus Maier-Hauff[c] Roland Felix[a] Peter Wust[a]
Onkologie 2005;28:325–330

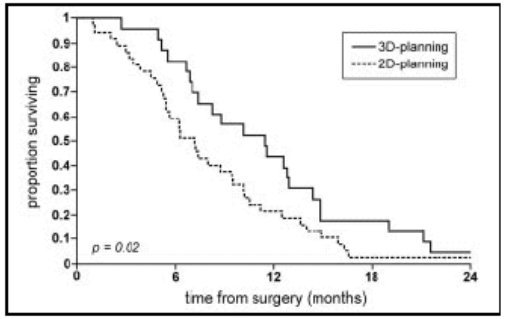


Fig. 1. Kaplan-Meier 2-year survival curves for 65 patients with glioblastoma according to planning scheme (2-D-planning vs. 3-D-planning).

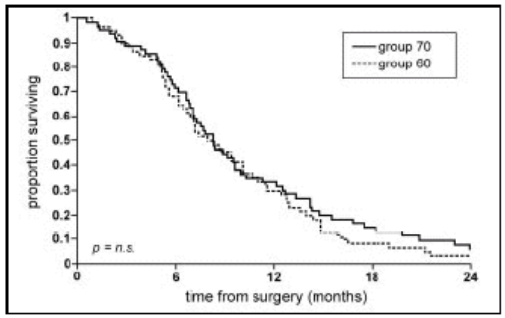


Fig. 2. Kaplan-Meier 2-year survival curves for 135 patients with glioblastoma according to prescribed dose (group 60: prescribed dose 60 Gy, group 70: prescribed dose 70 Gy).

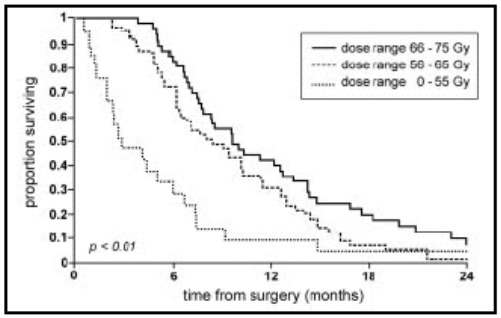
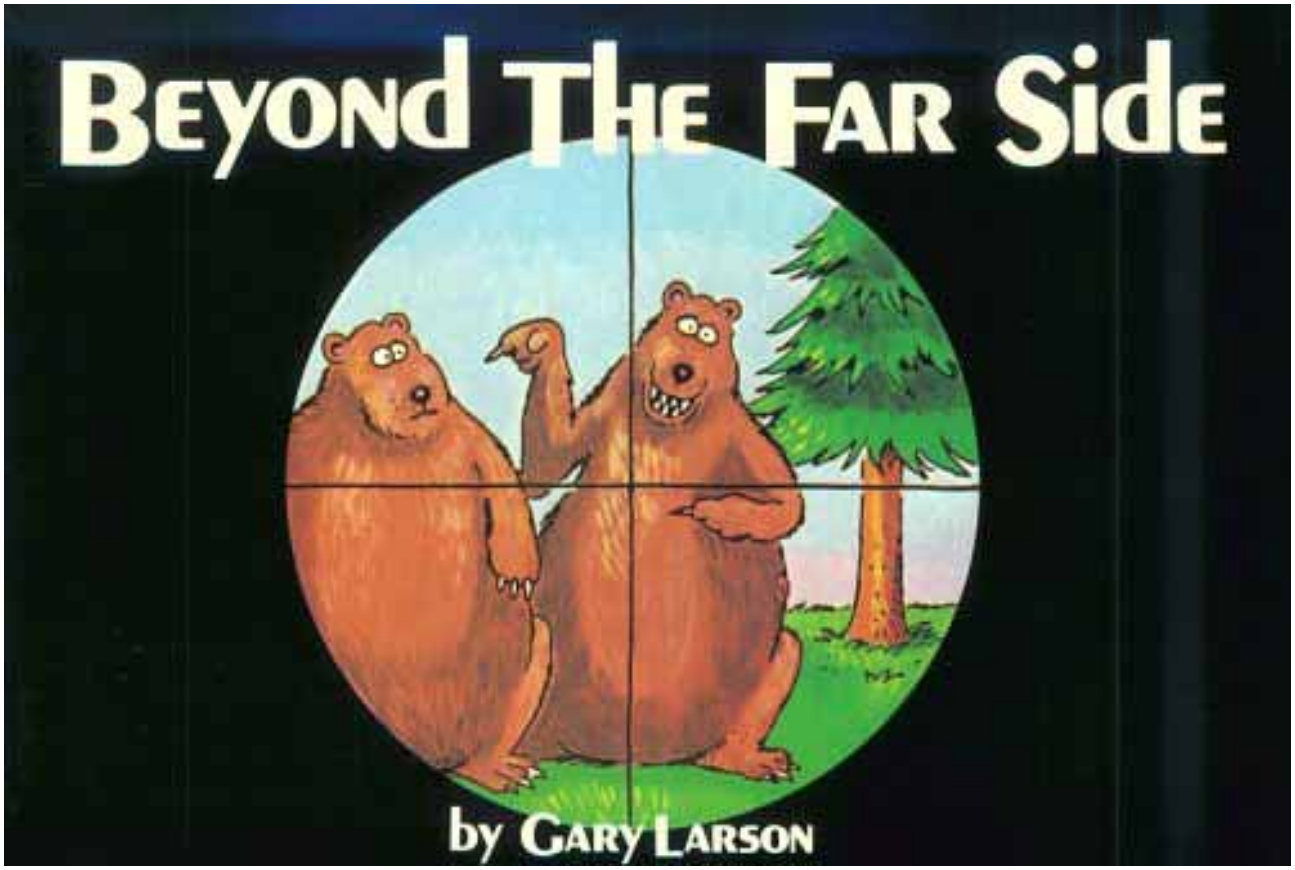


Fig. 3. Kaplan-Meier 2-year survival curves for 135 patients with glioblastoma according to applied dose range (0–55, 56–65 and 66–75 Gy).

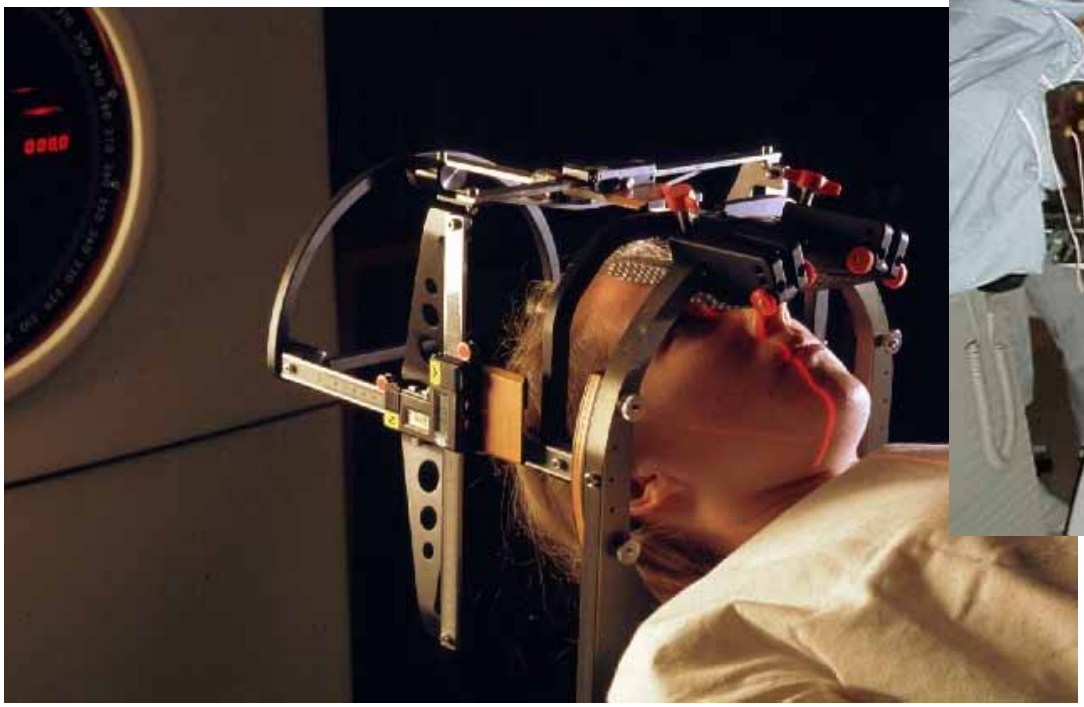
Only *five* things to do to improve Glioblastoma therapy.....

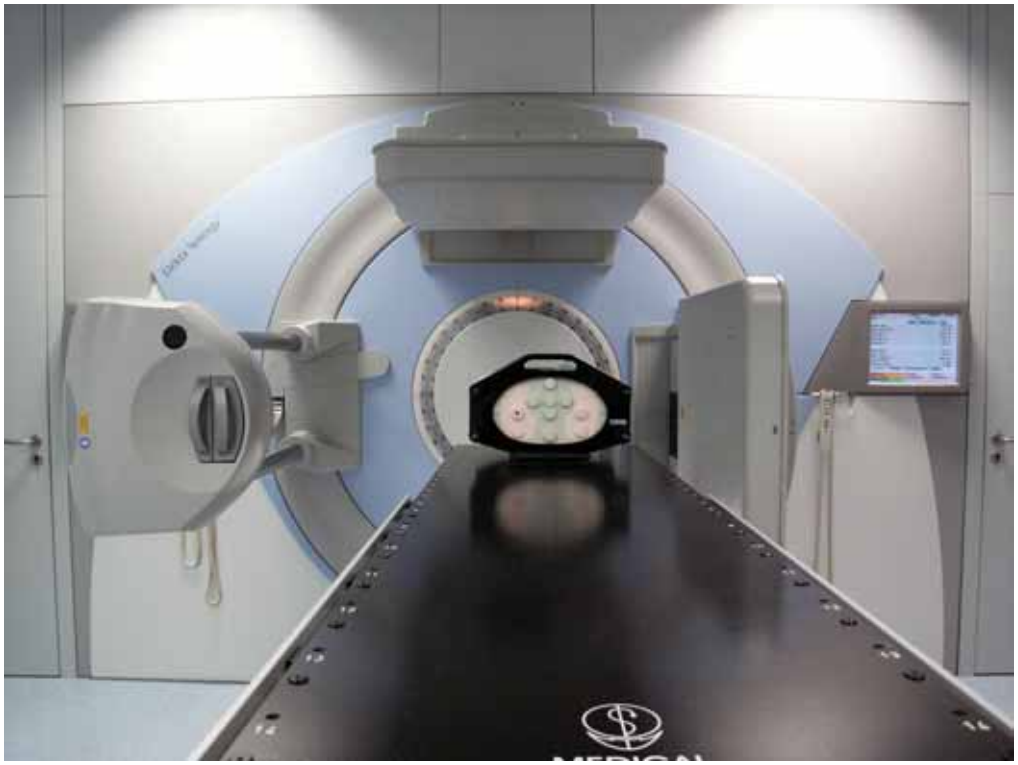
First Task:
Improvement of Therapy Precision

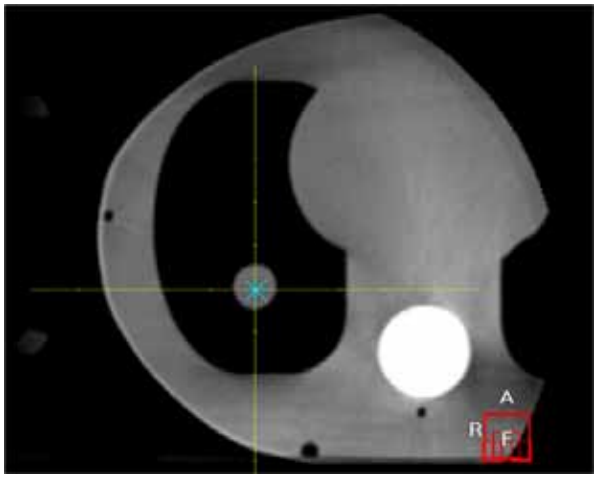
targeted therapy works only when the target is there
radiation works only when it reaches the target



targeting is the key



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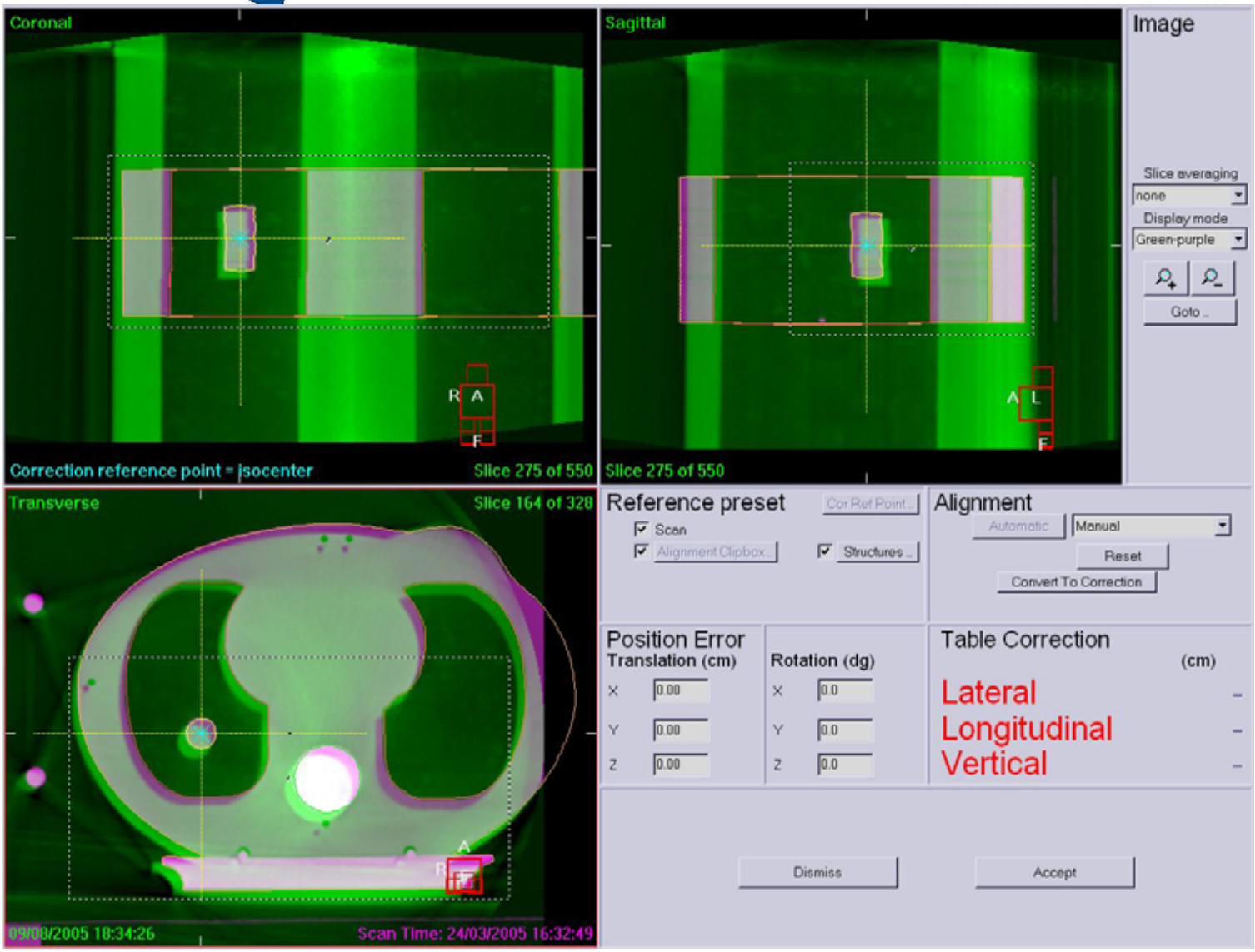
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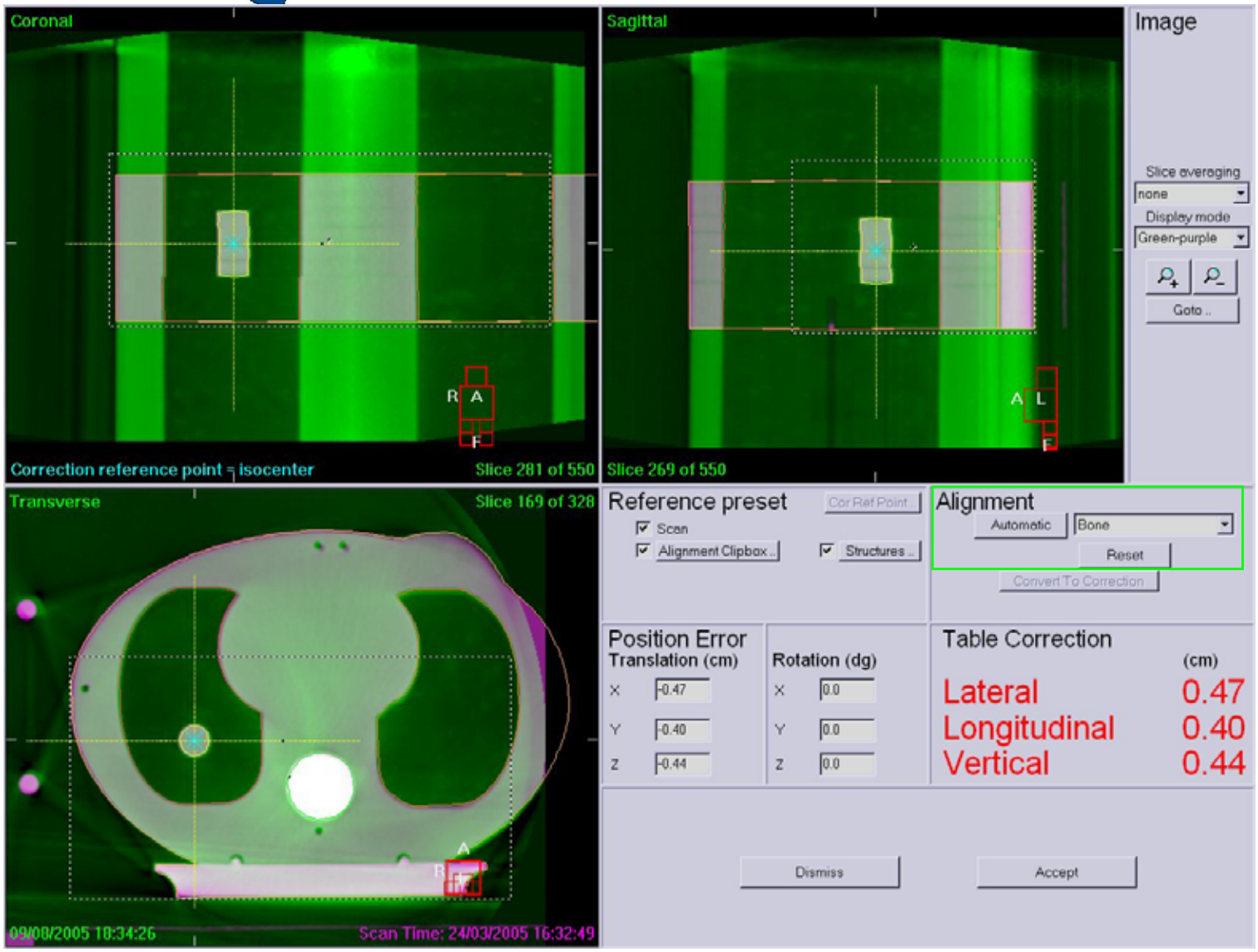
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Goto ..
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09/08/2005 18:34:26
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Structures ..
Alignment
Automatic
Bone
Reset
Convert To Correction
Position Error
Translation (cm)
Rotation (dg)
X -0.47
Y -0.40
Z -0.44
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Y 0.0
Z 0.0
Table Correction
(cm)
Lateral 0.47
Longitudinal 0.40
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Dismiss
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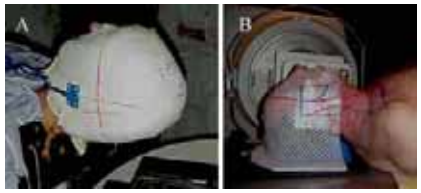
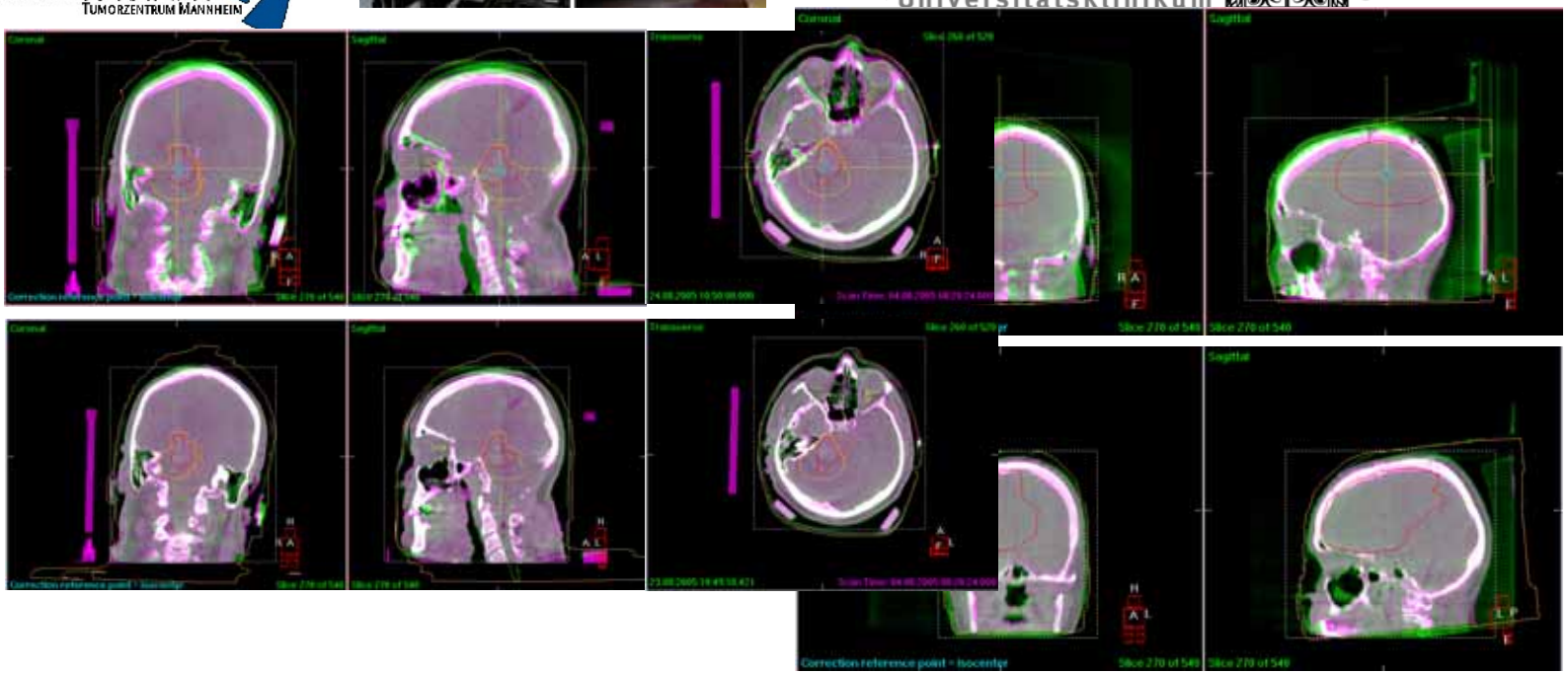




	Translation (MV±SD, cm)				Rotation (degrees)		
	x	y	z	**Vector (cm)**	x	y	z
Delta-Cast™ (Intracranial)	0.039±0.175	0.083±0.232	0.005±0.174	**0.312±0.152**	0.073±1.018	0.13±1.653	-0.25±0.0881
Thermoplastic masks (intracranial)	-0.02±0.227	0.23±0.233	-0.154±0.277	**0.472±0.174**	-1.47±1.75	-0.13±1.921	-0.06±2.18
Delta-Cast™ (neck)	-0.158±0.207	0.225±0.241	0.179±0.479	**0.586±0.294**	1.027±3.527	1.013±2.556	1.257±3.008
Thermoplastic masks (neck)	0.205±0.298	0.407±0.516	0.142±0.393	**0.726±0.445**	-0.2±2.31	-1.3±2.69	-1.09±2.02

Table 1. Results with the example of automatic bony registration

J. Boda-Heggemann, IJROBP, 2006

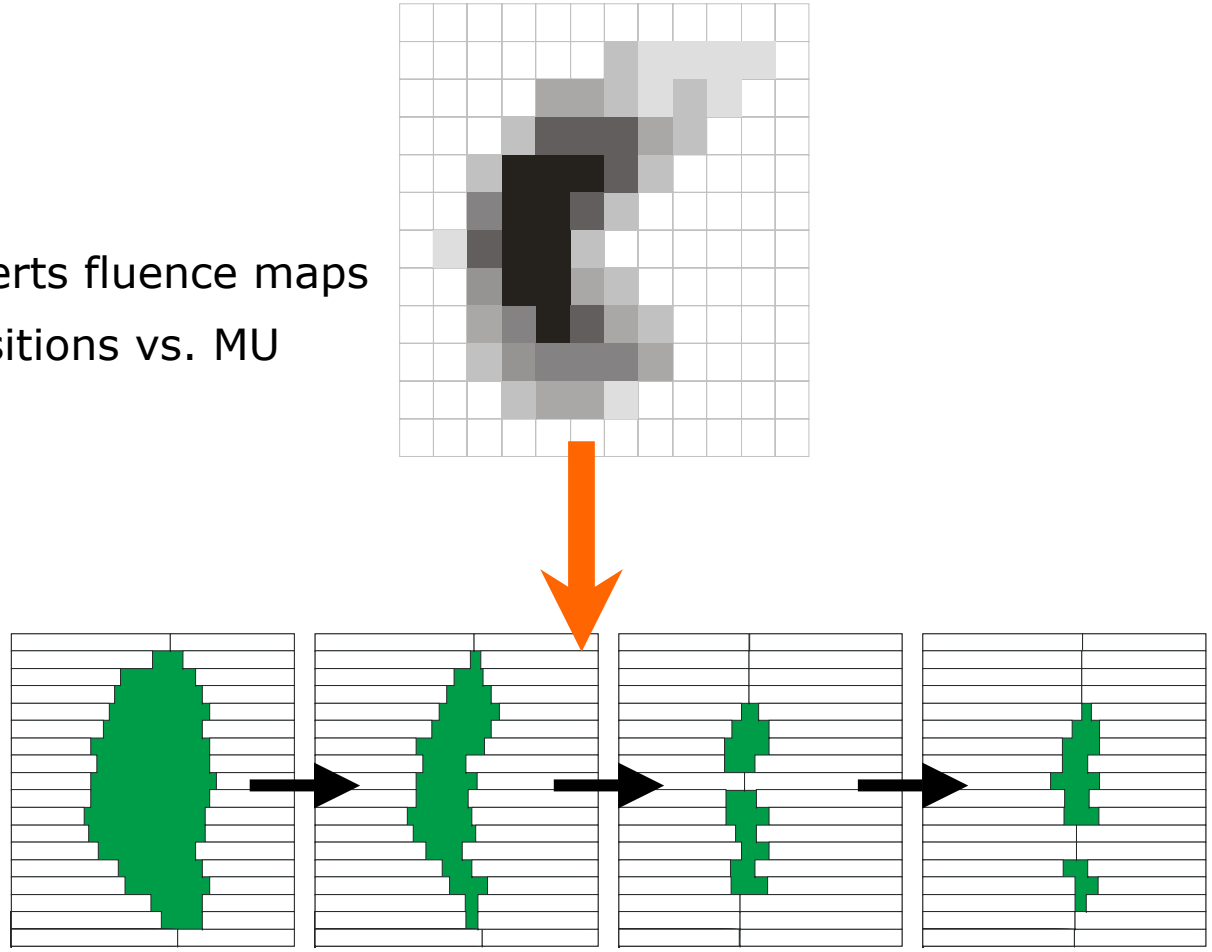
Done !!

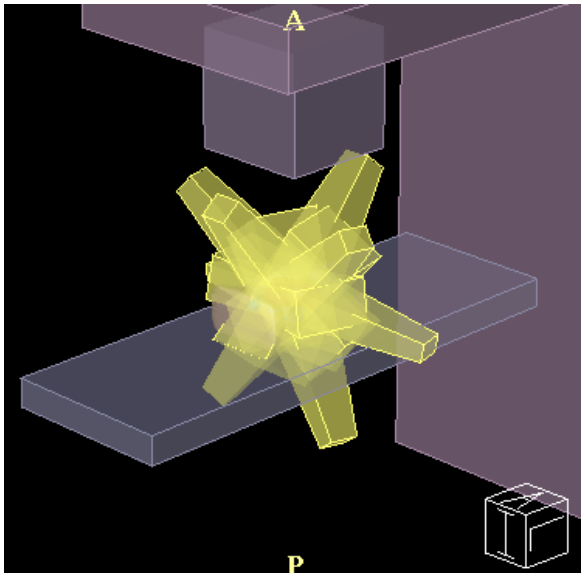
Not much room for improvement left

Second Problem:
Improvement of Therapy Conformality

> **Leaf Sequencers**

+ Software converts fluence maps to MLC leaf positions vs. MU

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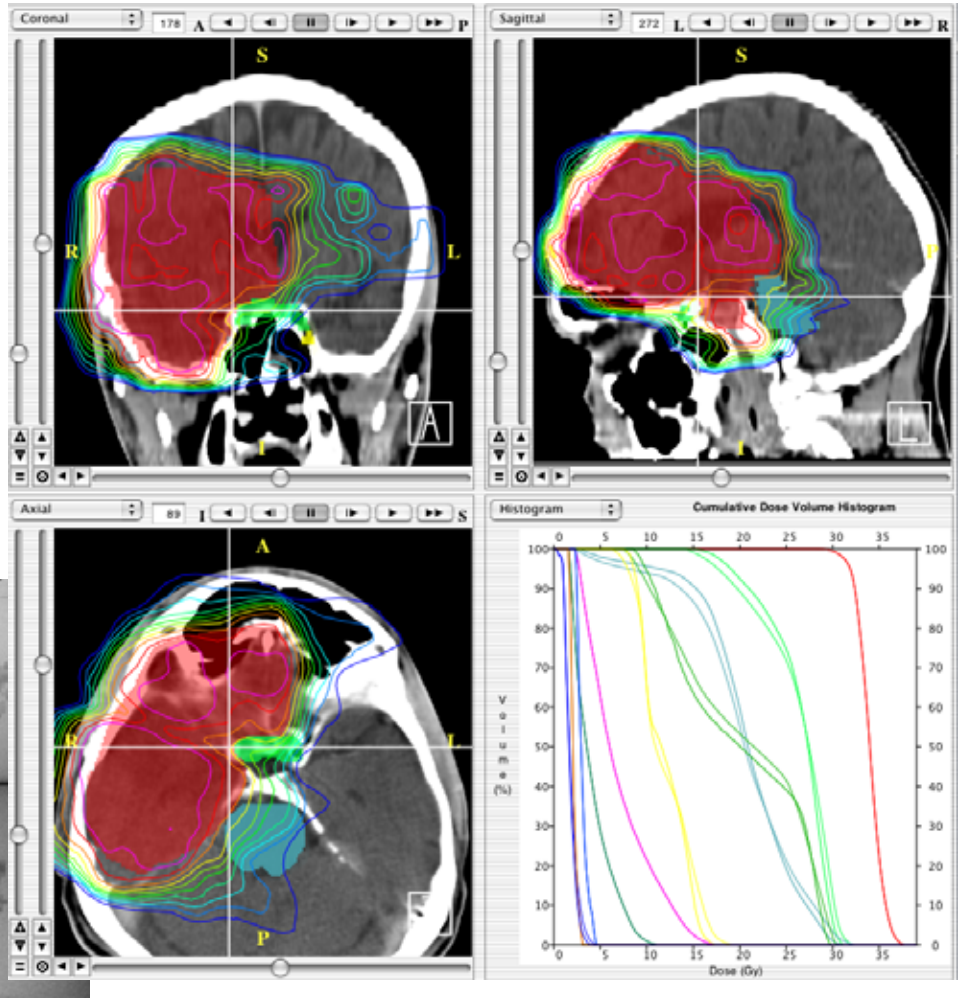
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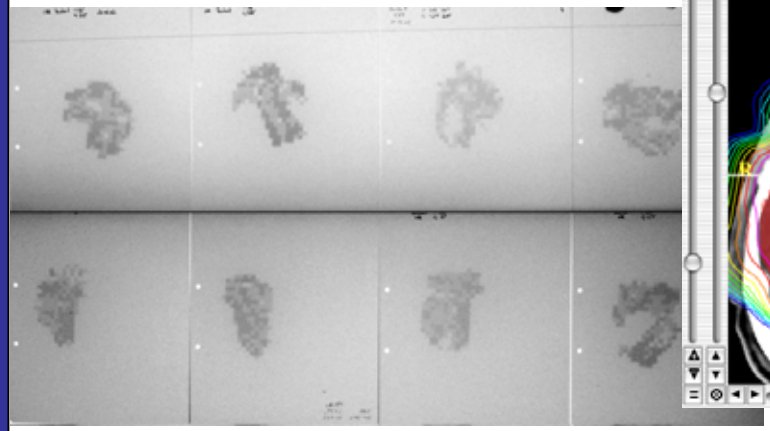
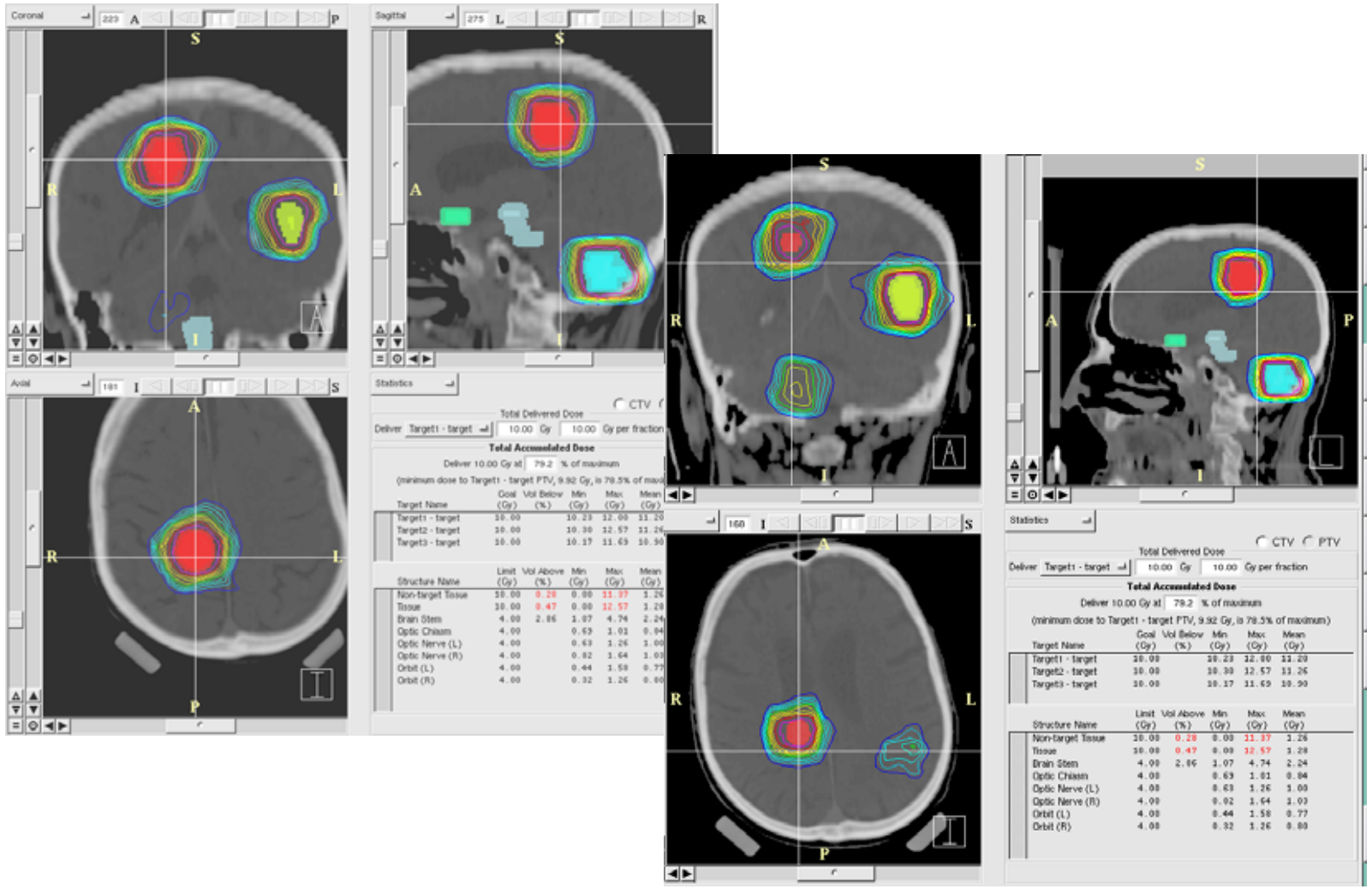
Sagittal
Axial
Histogram
Cumulative Dose Volume Histogram
Dose (Gy)

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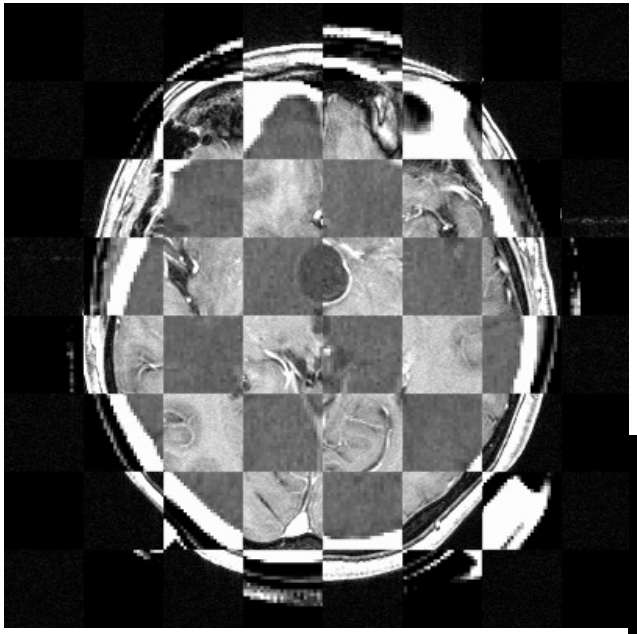
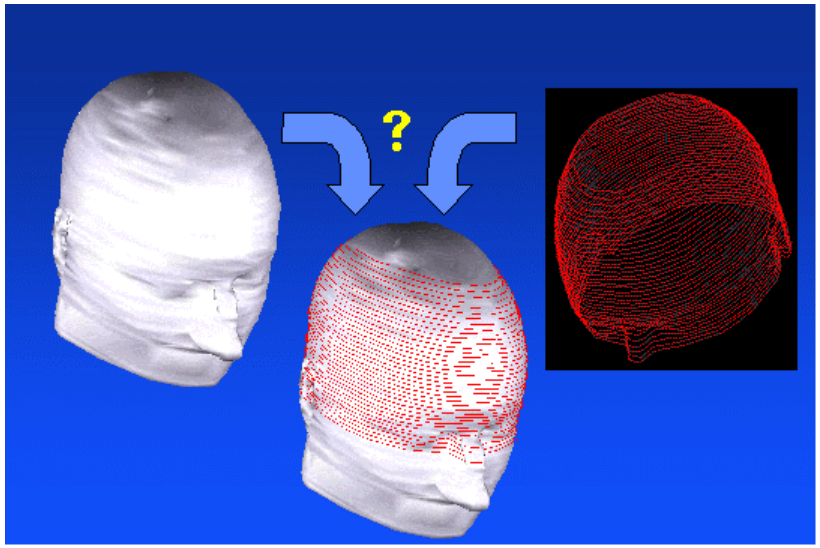
Sagittal
Axial
Statistics
CTV
PTV
Total Delivered Dose
Total Accumulated Dose
Target Name
Structure Name

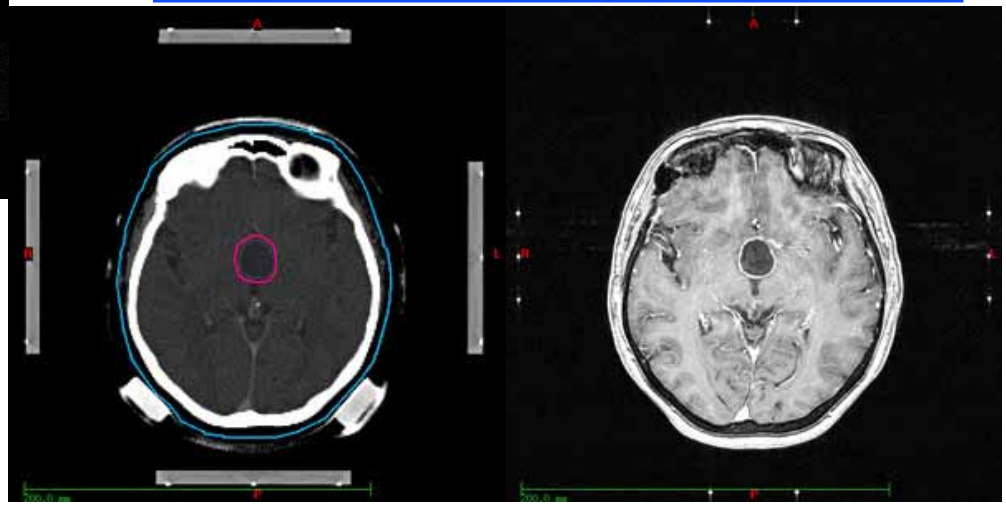
Done !!

Not much room for improvement left beyond IMRT and Particle Therapy

Third Problem:
Knowing WHAT to hit.....







3D MRSI FOR RESECTED HIGH-GRADE GLIOMAS BEFORE RT: TUMOR EXTENT ACCORDING TO METABOLIC ACTIVITY IN RELATION TO MRI

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 1, pp. 126–137, 2004

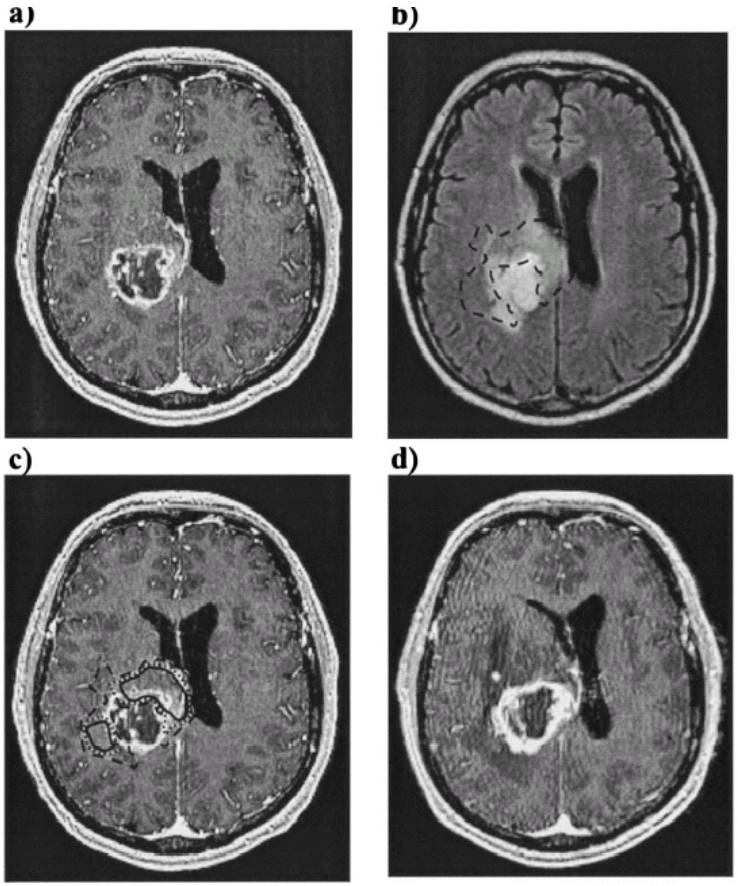


Fig. 5. Patient with right central GBM after surgical resection. (a) T_1-weighted MRI post gadolinium showing contrast-enhancing residual tumor around RC and toward falx cerebri. (b) T_2-weighted MRI (FLAIR) showing abnormal hyperintense signal corresponding to the area of contrast enhancement; superimposed CNI2 (broken line) reveals metabolic activity within and beyond FLAIR abnormality. (Note lateral extension of CNI2 beyond hyperintensity). (c) T_1-weighted MRI post gadolinium with superimposed spectroscopic contours CNI2, CNI3, and CNI4 (from outside to inside). (Note, CNI contours reveal metabolic activity mainly outside/beyond contrast enhancement.) (d) Follow-up T_1-weighted MRI post gadolinium showing thickening of contrast-enhancing rim around RC and a new focus of contrast enhancement at 1.2 months after course of conventional RT with 60 Gy.

Still a long way to go !!

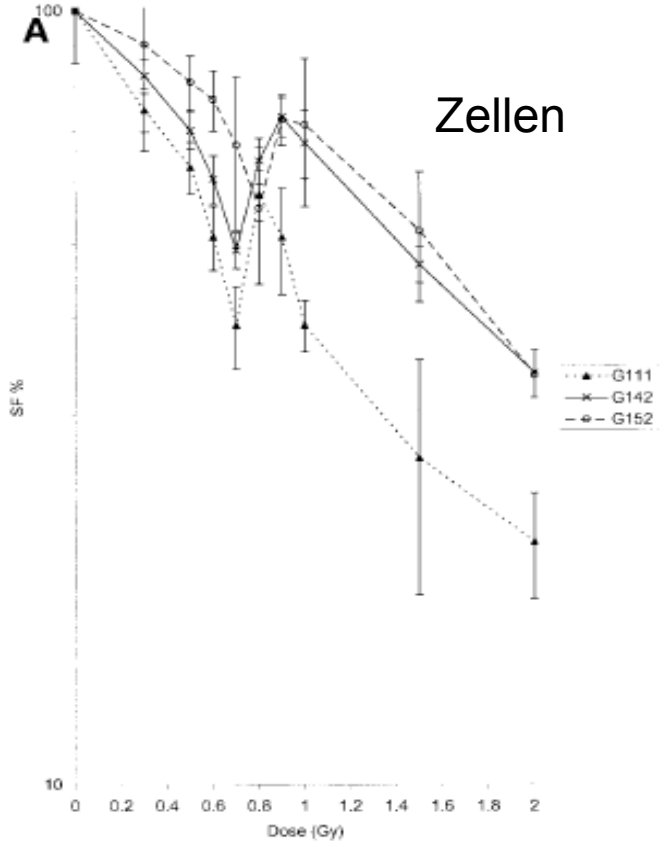
-PET

-Diffusion weighted MRI

-New Contrast Agents

-....

Fourth Problem:
Knowing WHEN to hit.....
(and this is where B2B starts....)



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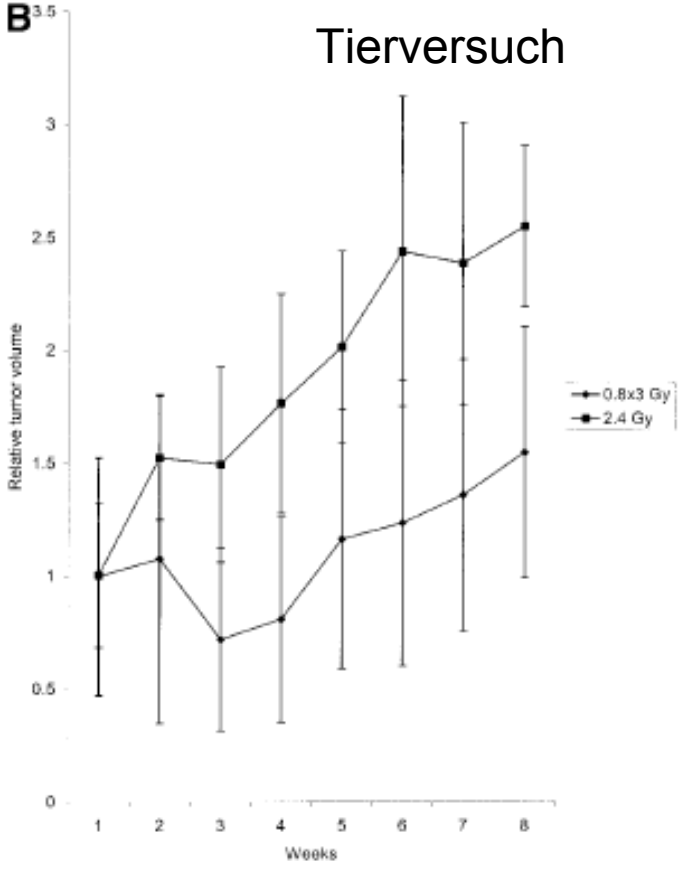

Beauchesne, Int J Cancer, 2003

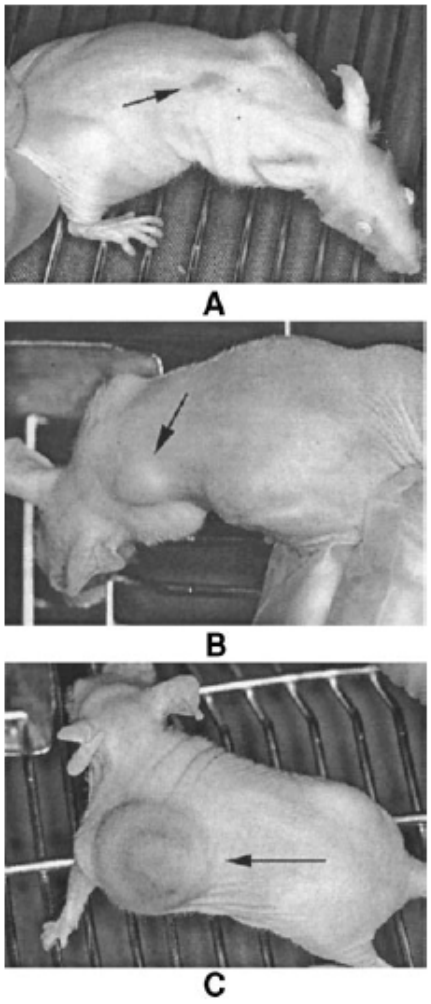

FIGURE 4 – Effect of irradiation on xenograft glioma tumor. Glioma tumors *s.c.*-grafted in mice treated with either the ultrafractionated regimen *(a)* or the conventional, single dose per day radiation regimen *(b)* or not treated *(c)*.

Beauchesne, Int J Cancer, 2003

dose more explicit we define:

$$\alpha_d \equiv \alpha_r \left[1 + \left(\frac{\alpha_s}{\alpha_r} - 1\right) \exp\left(-\frac{d}{d_c}\right)\right] \quad (2)$$

Substituting Equation (2) into Equation (1), we can write the surviving fraction in its more conventional form:

$$SF(d) = \exp\left(-\alpha_d d - \beta d^2\right) \quad (3)$$

Now let us use Equation (3) to study the effect of breaking up the therapy dose per fraction into m sub-fractions of dose δ that are separated by a fixed time interval δT. The effective dose rate is then given by $\dot{\delta} = \delta / \delta T$. Hence by breaking up the dose per fraction d into m subfractions of dose δ each, separated by fixed time intervals δT, one can achieve an effective reduced dose-rate of $\dot{\delta}$. If δ=0.2 Gy and δT=3 min then the effective reduced dose rate is $\dot{\delta}$=0.0667 Gy/min. The surviving fraction after a pulse δ is delivered is given by:

$$SF(\delta) = \exp\left(-\alpha_\delta \delta - \beta \delta^2\right) \quad (4)$$

From this we find the surviving fraction corresponding to the delivery of m pulses straightforwardly as:

$$SF_m^\delta(d) \equiv (SF(\delta))^m = \exp\left(-\alpha_\delta m\delta - \beta m\delta^2\right) \quad (5)$$

Depending on the value of α_δ the surviving fraction $SF_m^\delta(d)$ may be larger or smaller than the surviving fraction $SF_1^d(d)$. More explicitly, we have that:

$$\begin{aligned} &If\ \alpha_\delta > \alpha_d \Rightarrow SF_m^\delta(d) < SF_1^d(d) \\ &If\ \alpha_\delta < \alpha_d \Rightarrow SF_m^\delta(d) > SF_1^d(d) \end{aligned} \quad (6)$$

Hence, subdividing the dose per fraction into pulses separated by fixed time intervals is only beneficial if the tumour treated exhibits HRS. Now using the fact that $d = m\delta$ we can rewrite Equation (5) as follows:

$$SF_m^\delta(d) = \exp\left(-\alpha_\delta d - \frac{\beta}{m} d^2\right) \quad (7)$$

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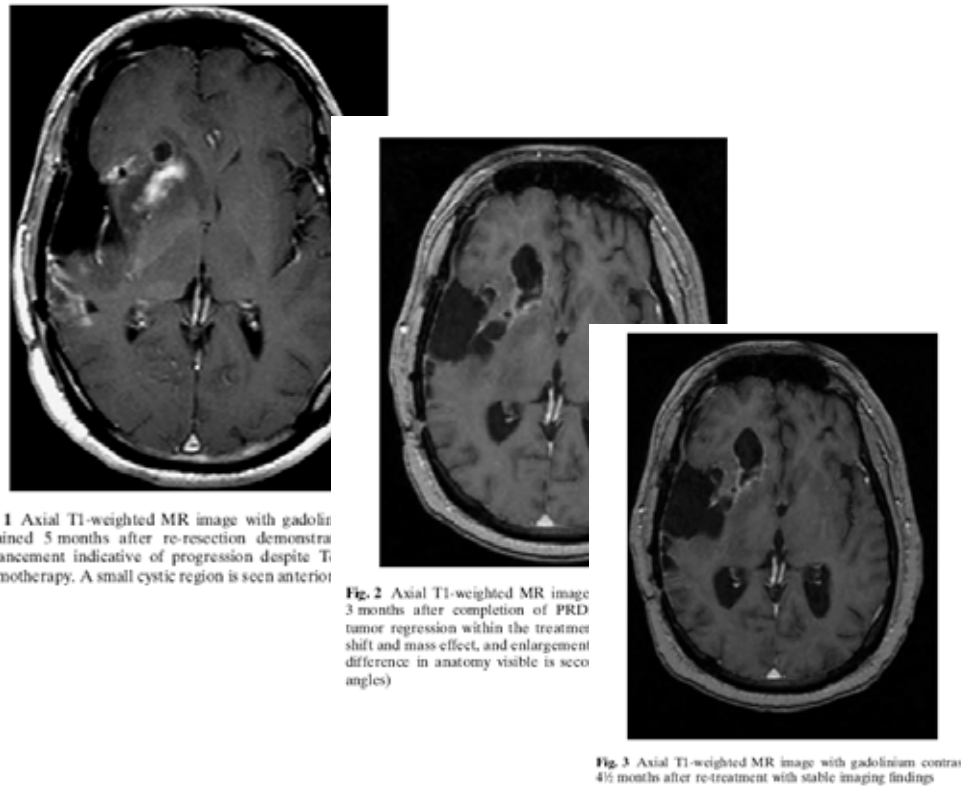

Fig. 1 Axial T1-weighted MR image with gadoli
obtained 5 months after re-resection demonstra
enhancement indicative of progression despite T
chemotherapy. A small cystic region is seen anterio

Fig. 2 Axial T1-weighted MR image
3 months after completion of PRD
tumor regression within the treatme
shift and mass effect, and enlargement
difference in anatomy visible is seco
angles)

Fig. 3 Axial T1-weighted MR image with gadolinium contrast 4½ months after re-treatment with stable imaging findings

Tomé et al., Br. J. Radio, 2007
Cannon/Tomé et al., J Neuroonc 2007

2069 Pulsed Reduced Dose-Rate Radiotherapy: A Novel Re-Treatment Strategy in the Management of Large Volume Recurrent Glioma

W. A. Tome, **J. Atkinson, H. I. Robins, K. Rassmussen, J. S. Welsh, P. Mahler, S. P. Howard**

University of Wisconsin, Department of Human Oncology, Madison, WI

Background and Purpose: Radiotherapy delivered below standard dose-rates reduces normal tissue toxicity and can induce significant tumor regression in some tumor types. Early clinical studies suggested that fractionated reduced dose-rate external beam radiotherapy could achieve an improved therapeutic ratio. The factors and mechanisms that determine the response of normal cells and tumors to reduced dose-rate irradiation remain largely unknown. In conventional radiotherapy a dose of 2 Gy is delivered at a dose rate of 4–6 Gy/min, which means that the delivery of this dose requires only a few minutes. By reducing the effective doserate and increasing the treatment time, it becomes possible for repair processes to be active during irradiation. A reduced dose-rate can either be obtained by using a continuous reduced dose-rate irradiator, or by dividing the standard 2 Gy fractions into a number of equal sub-fractions that are delivered in a pulsed manner separated by a fixed time interval, allowing for repair during each subfraction.

This is done by delivering treatment in a series of 0.2 Gy pulses separated by 3-minute time intervals, creating an apparent dose rate of 0.0667 Gy/min. We have termed this re-irradiation technique pulsed reduced dose-rate radiotherapy (PRDR). This pulsed approach will preferentially protect normal tissue and have almost the same effect in terms of tumor cell kill because repair capacity is greater in late responding normal tissues than tumors.

Materials/Methods: Between January 1999 and March 2007, 99 patients with recurrent gliomas were re-irradiated using PRDR (mean dose 50 Gy) delivered in 1.8–2.0 Gy fractions. Prior to the initiation of PRDR, all patients had received conventional radiotherapy, 68 had multiple surgeries, 14 radiosurgery, 4 GliaSite brachytherapy and 78 received conventional chemotherapy and/or one or more experimental therapies. MRI-CT fusion with 3-dimensional planning was used for all patients. The treatment volume was the volume of the contrast-enhancing lesion and surrounding edema on pre-treatment MRI plus a 2 cm margin. Due to the complexities of MRI interpretation; overall survival at six months was used as the study end point.

Results: Thirty-one (31.3%) of these 99 heavily pretreated patients had an overall survival of six months or greater.

A PHASE II TRIAL OF RE-IRRADIATION USING PULSED REDUCED DOSE-RATE EXTERNAL BEAM RADIOTHERAPY FOR THE TREATMENT OF RECURRENT SUPRATENTORIAL HIGH GRADE GLIOMAS.

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H. Ian Robins, MD

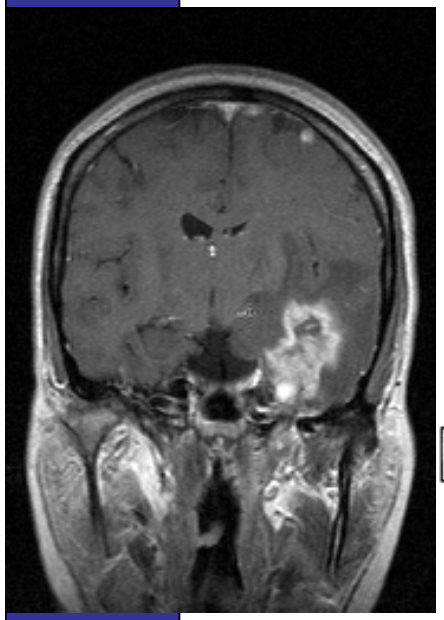
Neuro-Radiology:
Howard Rowley MD

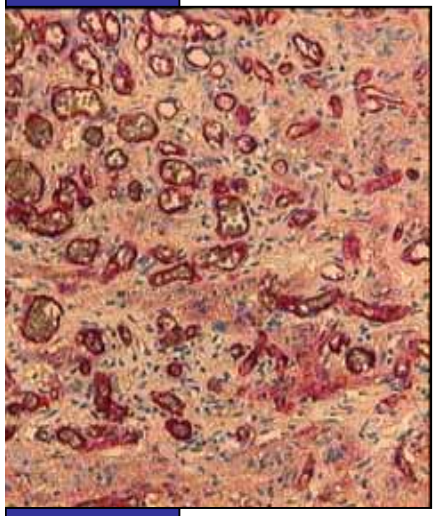
Medical Physics and Bio-mathematical Modeling:
Wolfgang Tomé, PhD

Radiation Oncology:
James S. Welsh, MS, MD

Fifth and last (and biggest) Problem: Knowing WHAT else to do.....

clinical-radiologic and biologic characterization of malignant gliomas: a help to define prognosis and treatment





astrocytoma

TP53 mutation / chromosome 17p loss
PDGFα and PDGFαR overexpression
chromosome 22q loss

	second	prim
	40%	60%
	<50yrs	>50yrs
p53mut	65%	10%
EGFR		+++
MDM2		++
PDGF	60%	

anaplastic astrocytoma

CDKN2A (and CDKN2B) deletion / chromosome 9p loss
RB mutation / chromosome 13q loss
CDK4 amplification
chromosome 19q loss
chromosome 11p loss

PTEN mutation / chromosome 10q loss
chromosome 10p and 10q loss
EGFR amplification and rearrangement
MDM2 amplification

CDKN2A (and CDKN2B) deletion / chromosome 9p loss
RB mutation / chromosome 13q loss
CDK4 amplification

EGFR amplification

glioblastoma

glioblastoma

1. Secondary glioblastoma
2. Glioblastoma in younger adults
3. Giant cell glioblastoma
4. Brain stem glioblastoma in children

1. Rapidly progressive glioblastoma
2. Primary glioblastoma
3. Glioblastoma in older adults

dense cellularity, cell proliferation, microvascular proliferation, focal necrosis

a) Thank God there‘s Temodal!
(and I really mean it)

Neuro-Oncology Working Group 01 Trial of Nimustine Plus Teniposide Versus Nimustine Plus Cytarabine Chemotherapy in Addition to Involved-Field Radiotherapy in the First-Line Treatment of Malignant Glioma

Journal of Clinical Oncology, Vol 21, No 17 (September 1), 2003: pp 3276-3284

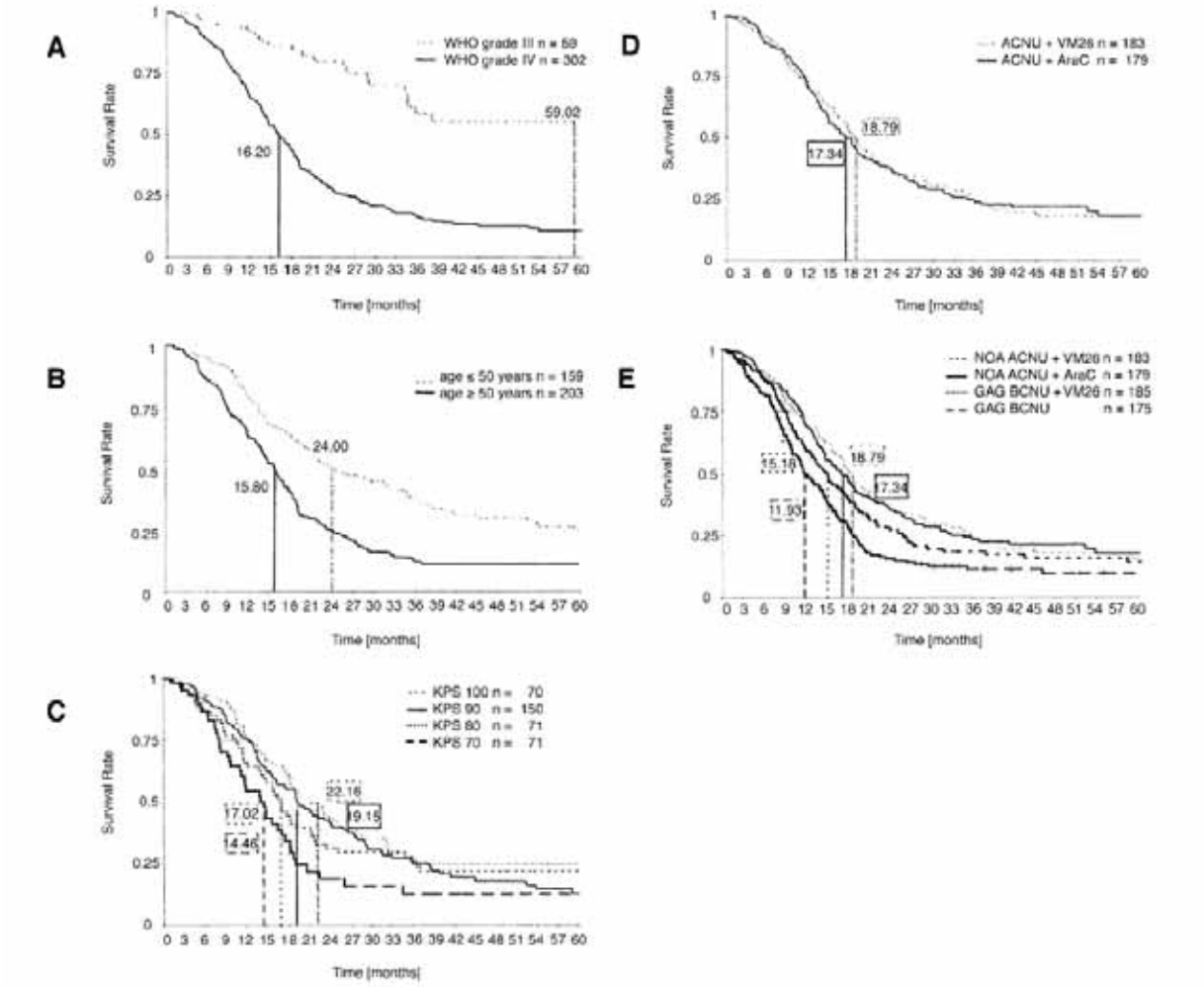


Fig 1. Survival in the Neuro-Oncology Working Group (NOA)-01 trial. (A) World Health Organization (WHO) grade 3 versus WHO grade 4 glioma; (B) effect of age (≤ 50 versus > 50 years); (C) effect of Karnofsky performance score (KPS; 70, 80, 90, and 100 compared), (D) nimustine (ACNU) + teniposide (VM26) versus ACNU + cytarabine (Ara-C); and (E) comparison of the NOA-01 and German-Austrian Glioma (GAG) trials. BCNU, carmustine.

Rationale for Combination of TEM and RT:

The simple:
TEM worked in Glioblastoma !!

The more elaborate:
TEM silences MGMT which repairs DNA-Damage
and may be induced by RT

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Stupp et al.

N Engl J Med 2005;352:987-96.

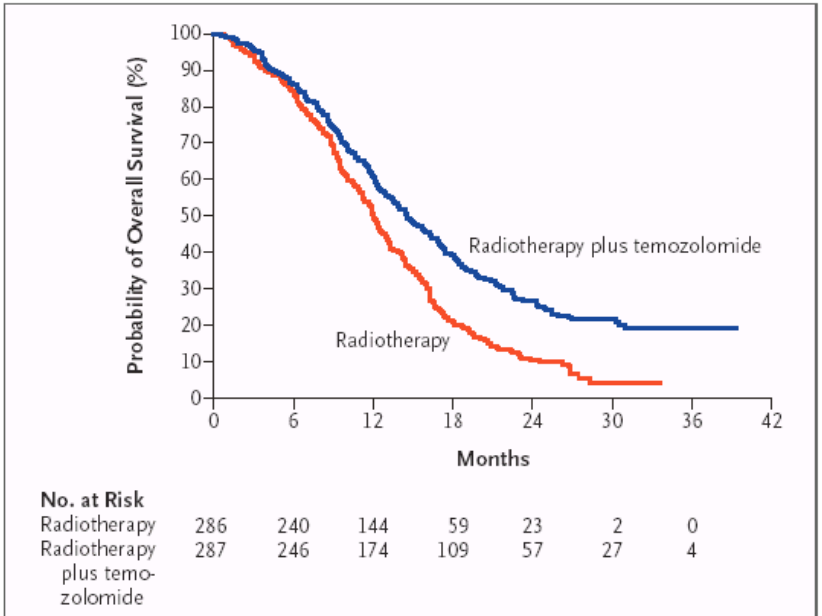


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

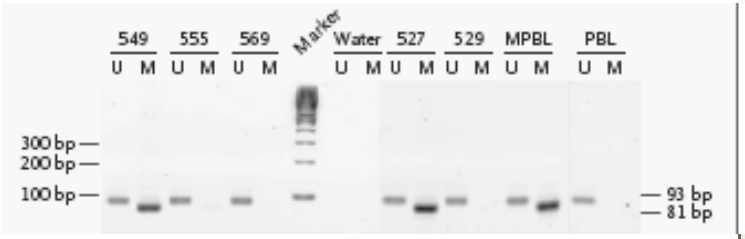
The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

TREATMENT AFTER DISEASE PROGRESSION

If disease progression occurred, further treatment was at the physician's discretion. At the cutoff date (May 10, 2004), 512 patients — 268 in the radiotherapy group (94 percent) and 244 in the radiotherapy-plus-temozolomide group (85 percent) — had disease progression. At the time of progression, 23 percent of patients in both treatment groups underwent a second surgery, and 72 percent of patients in the radiotherapy group and 58 percent in the radiotherapy-plus-temozolomide group received chemotherapy. Salvage chemotherapy consisted of temozolomide in 60 percent of patients in the radiotherapy group and 25 percent of patients in the radiotherapy-plus-temozolomide group. The response to salvage chemotherapy was not recorded as part of our study.

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.



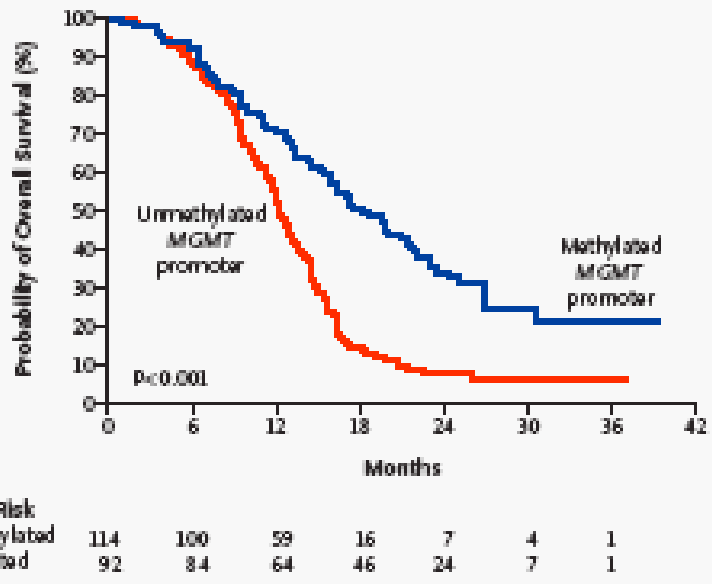


Figure 2. Kaplan–Meier Estimates of Overall Survival, According to *MGMT* Promoter Methylation Status.

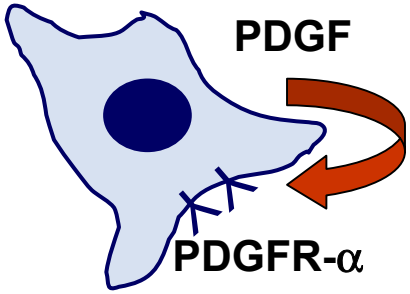
The difference in survival between patients with a methylated *MGMT* promoter (92 patients, 65 of whom died) and those with an unmethylated *MGMT* promoter (114 patients, 105 of whom died) was highly significant ($P<0.001$ by the log-rank test), indicating that the *MGMT* methylation status has prognostic value. In the group of patients with a methylated *MGMT* promoter, there was a risk reduction of 55 percent (hazard ratio for death, 0.45; 95 percent confidence interval, 0.32 to 0.61), as compared with the group with an unmethylated *MGMT* promoter.

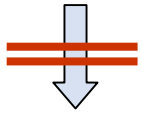
b) What else really works?
And how well?
Glivec(/CCNU)
Tarceva
Temodal again, but differently....
Avastin(/Topotecan)
Erbitux (?)

Glivec

Overexpression of PDGF/PDGFRs in malignant Glioma

Tumor cell compartment





PDGFR Blockade
(z.B. Imatinib, SU6668)

Antiproliferative

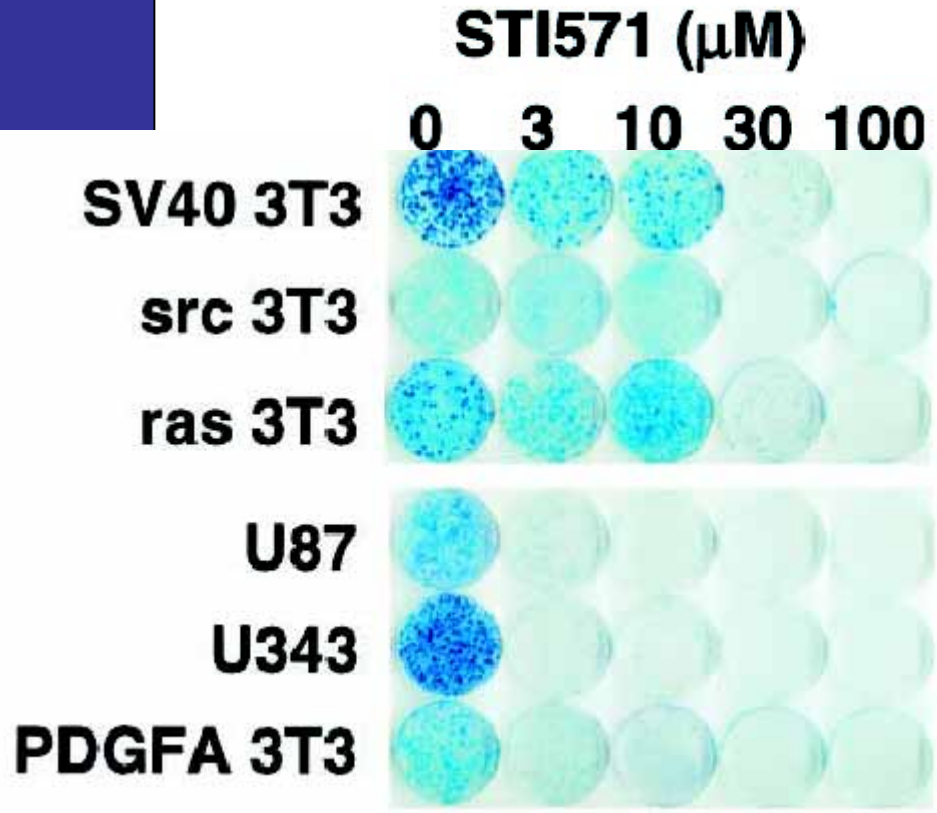
Intracranial Inhibition of Platelet-derived Growth Factor-mediated Glioblastoma Cell Growth by an Orally Active Kinase Inhibitor of the 2-Phenylaminopyrimidine Class[1]

[CANCER RESEARCH 60, 5143–5150, September 15, 2000]

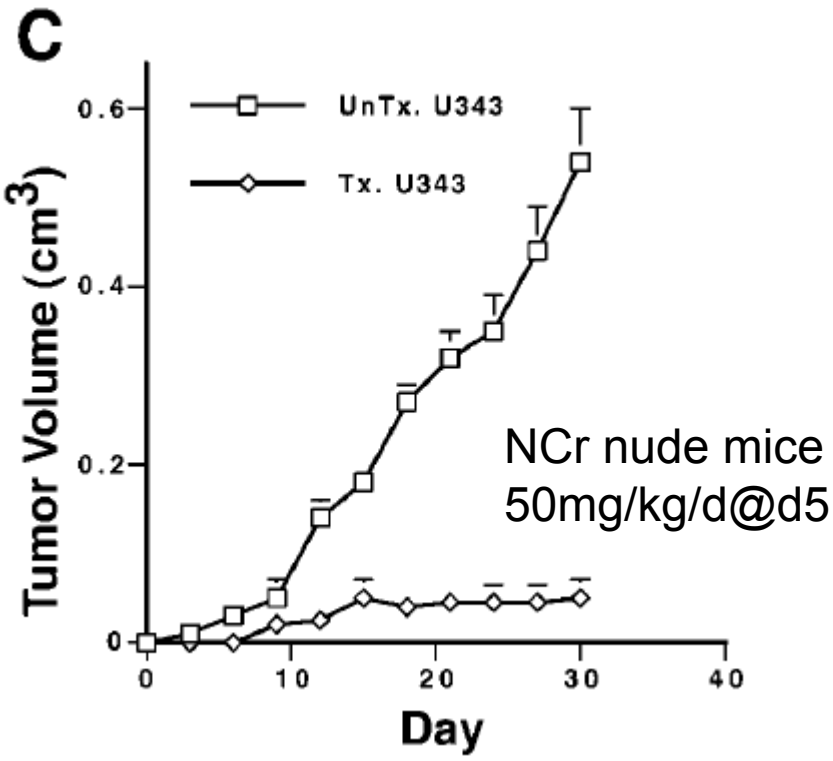
Turker Kilic,[2,3] John A. Alberta,[2] Pawel R. Zdunek,[4] Melih Acar,[5] Palma Iannarelli, Terence O'Reilly, Elisabeth Buchdunger, Peter M. Black, and Charles D. Stiles[6]

STI571 selectively inhibits …

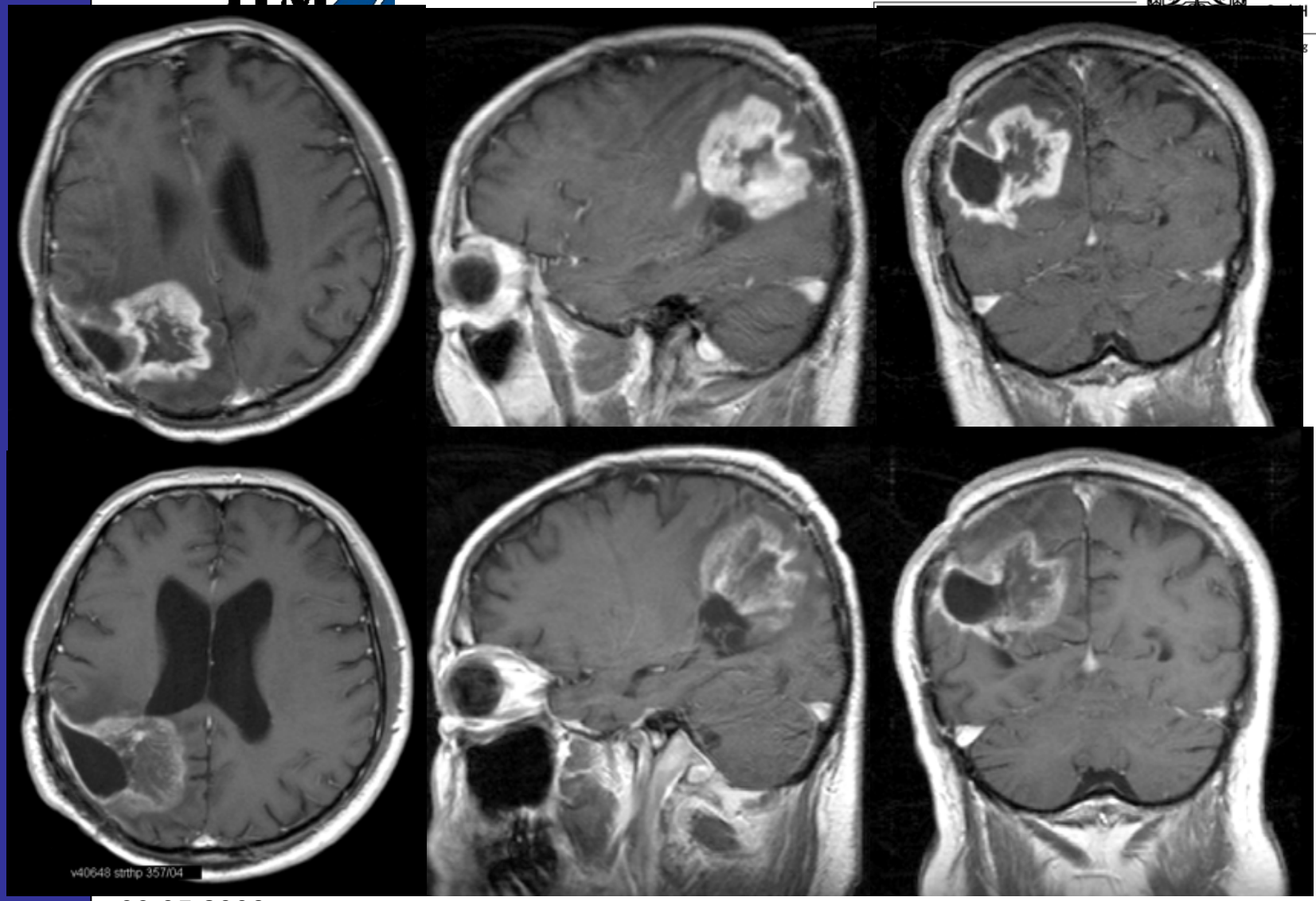
the growth of cells that express PDGF receptor autocrine loops



tumor formation from cells that express PDGF receptor autocrine loops



Open label Phase II evaluation of hypofractionated stereotactic radiotherapy combined with antiproliferative chemotherapy with imatinib mesylate for inoperable or macroscopically incompletely resected Glioblastoma multiforme

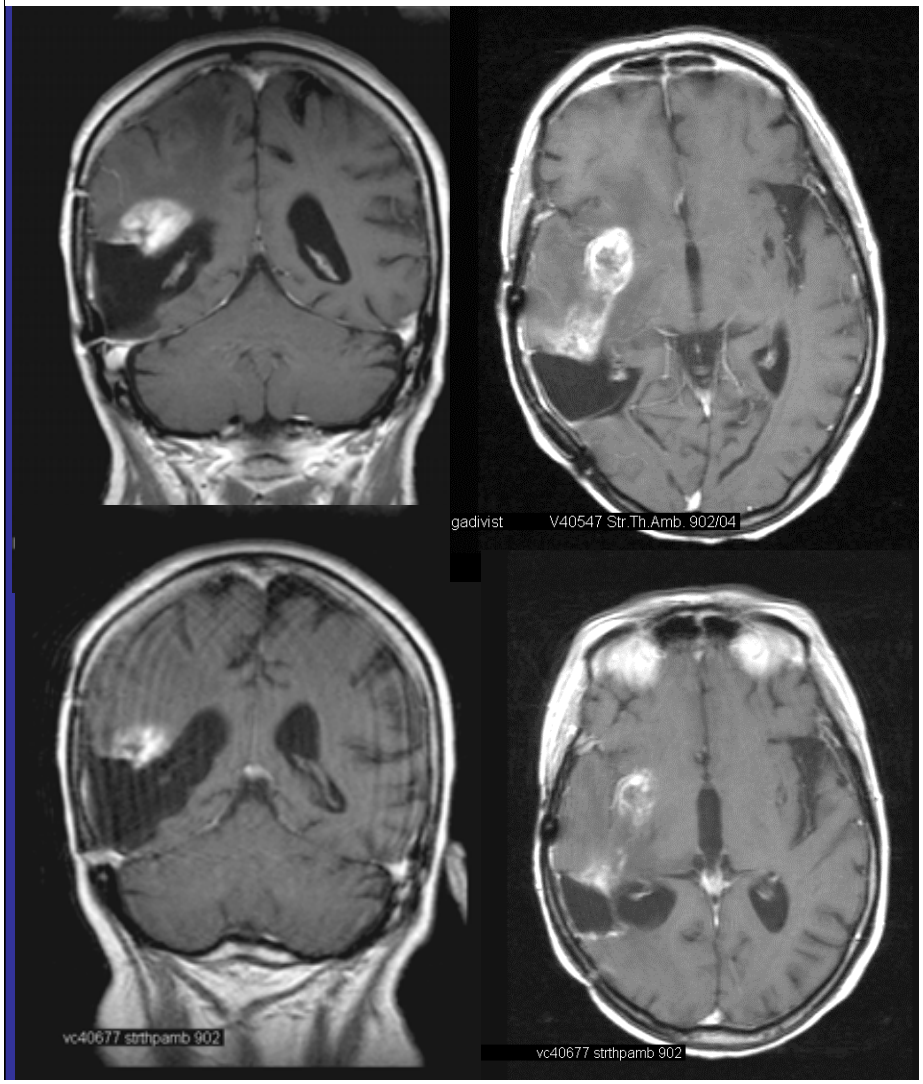


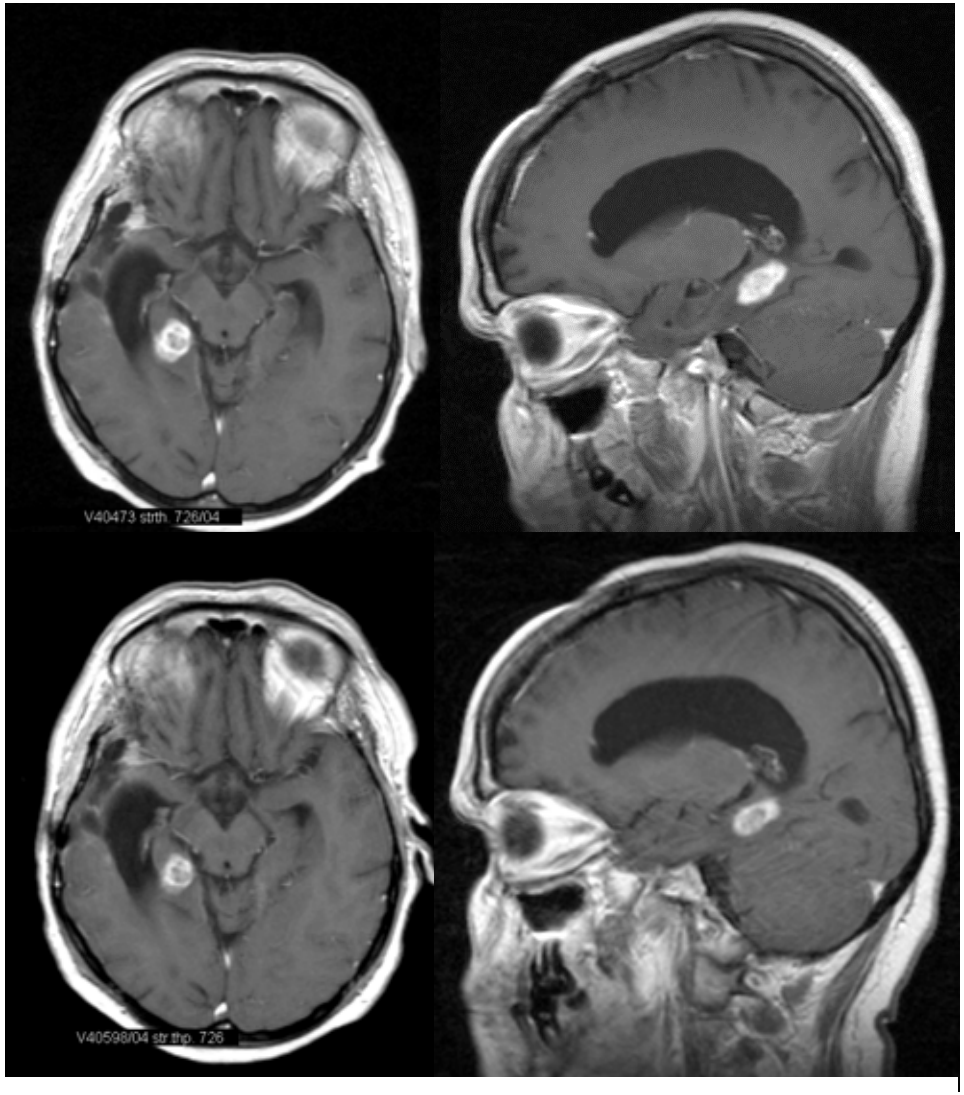
01/04

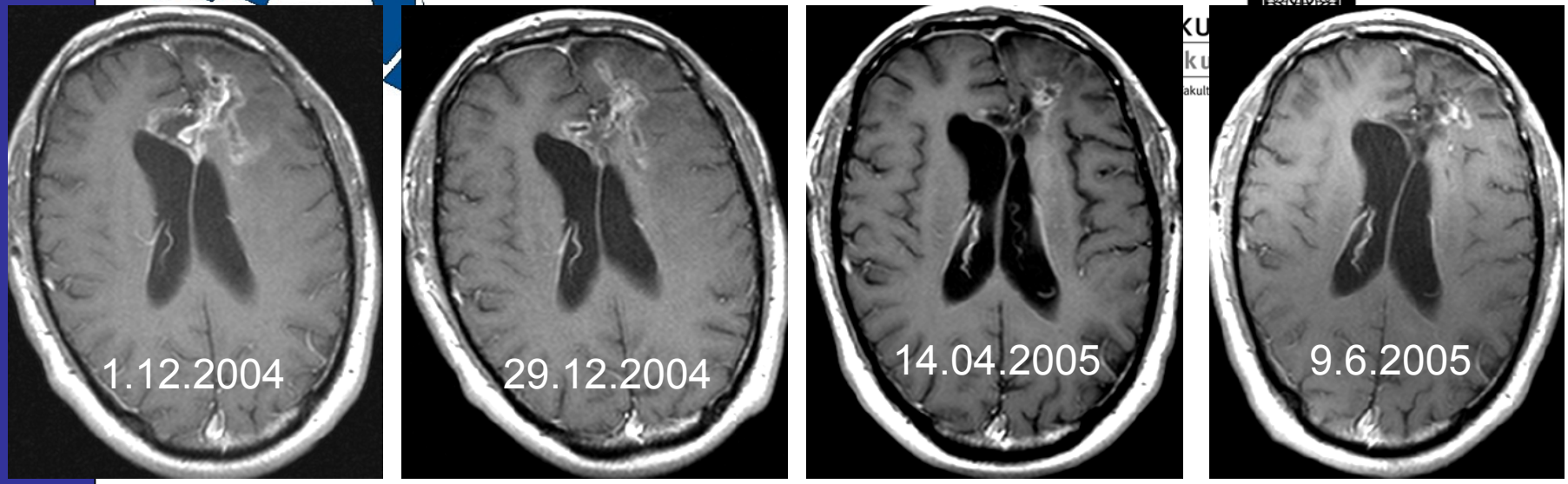
03/04

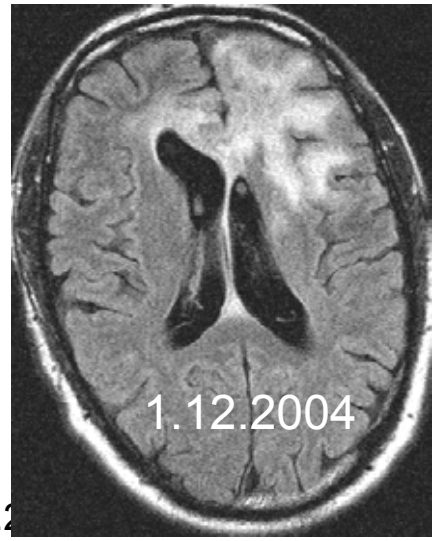
OP 5/03, RT 54 Gy 5-6/03, recurrence 8/03, SRS 16 Gy 08/03, recurrence 2 x BCNU 11-12/03, 1-/04 STI

Open label Phase II evaluation of hypofractionated stereotactic radiotherapy combined with antiproliferative chemotherapy with imatinib mesylate for inoperable or macroscopically incompletely resected Glioblastoma multiforme






1.12.2004
29.12.2004
14.04.2005
9.6.2005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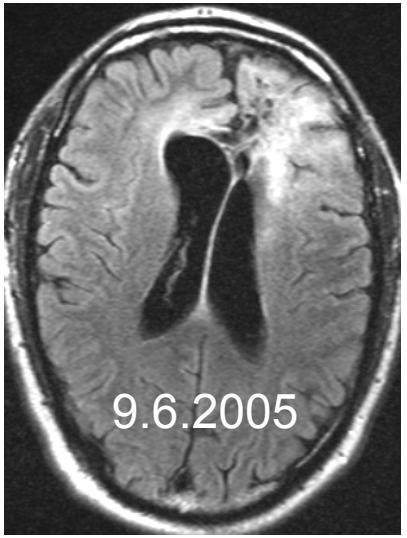

9.6.2005

Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series

G. Dresemann

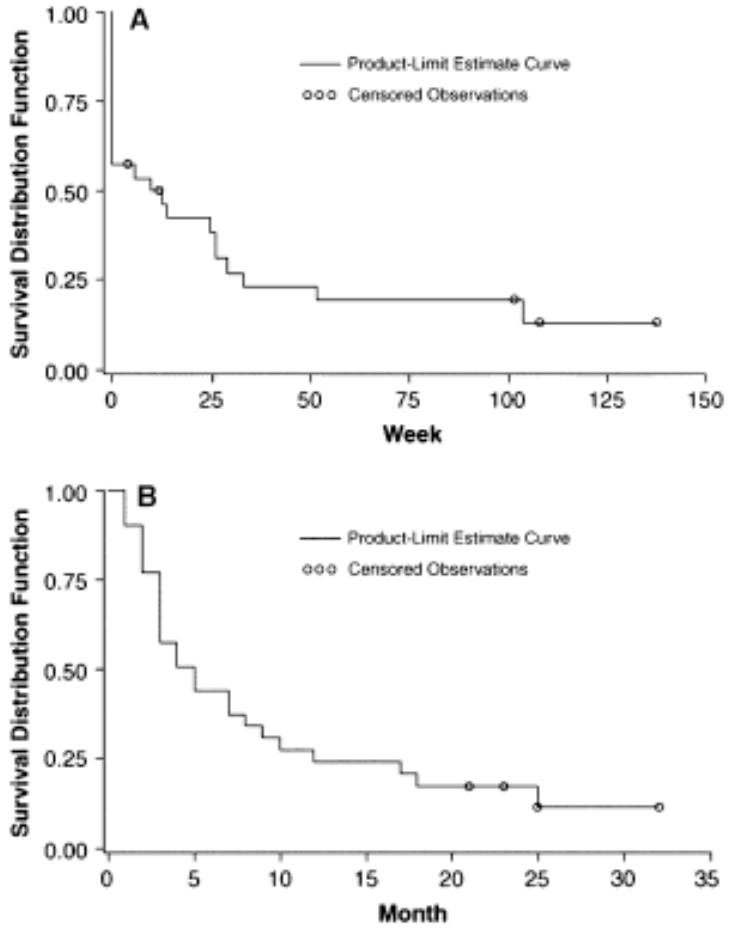
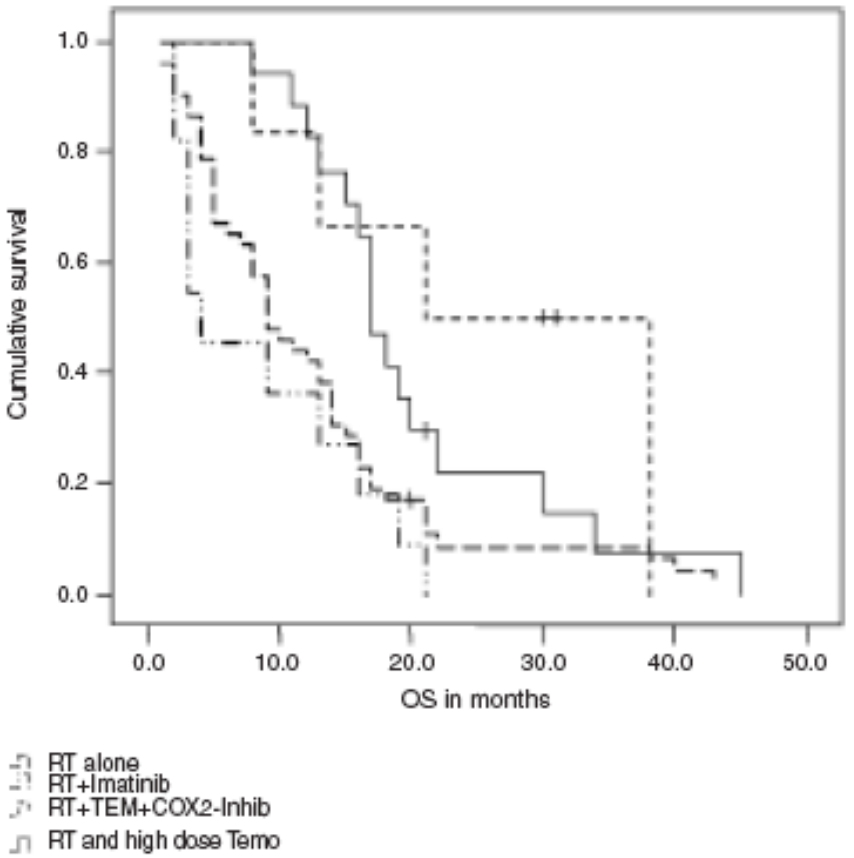


Figure 3. Survival of 30 progressive glioblastoma multiforme (GBM) patients treated with imatinib and hydroxyurea. (**A**) Progression-free survival (**B**) and overall survival.

EFFICACY OF DIFFERENT REGIMENS OF ADJUVANT RADIOCHEMOTHERAPY FOR TREATMENT OF GLIOBLASTOMA

Antonella Scheda[1], Janvier Kaba Finjap[1], Jochen Tuettenberg[2], Marc Alexander Brockmann[3], Andreas Hochhaus[4], Ralf Hofheinz[4], Frank Lohr[1], and Frederik Wenz[1]

[1]Klinik für Strahlentherapie und Radioonkologie, [2]Neurochi Onkologisches Zentrum, Universitätsklinikum Mannheim, G



30% initial Responses based on imaging
(not necessarily correlating with a clinical response)

10 % Clinically Useful Responses

Glivec plus.....
well, Temodal of course....

Safety and pharmacokinetics of dose-intensive imatinib mesylate plus temozolomide: Phase 1 trial in adults with malignant glioma

David A. Reardon [1*], Annick Desjardins [2], James J. Vredenburgh [2], Sith Sathornsumetee [2], Jeremy N. Rich [3], Jennifer A. Quinn [3], Theodore F. Lagattuta [4], Merrill J. Egorin [4], Sridharan Gururangan [1], Roger McLendon [5], James E. Herndon II [6], Allan H. Friedman [7], August J. Salvado [8], Henry S. Friedman [1]

Imatinib doses up to 1,000 mg/day for 8 consecutive days are well tolerated when combined with standard TMZ dosing for MG patients

Tarceva

Molecular Determinants of the Response of Glioblastomas to EGFR Kinase Inhibitors

Ingo K. Mellinghoff, M.D., Maria Y. Wang, M.D., Ph.D., Igor Vivanco, Ph.D.,

KLINIKUM MANNHEIM gGmbH
Universitätsklinikum
Medizinische Fakultät Mannheim der Universität Heidelberg

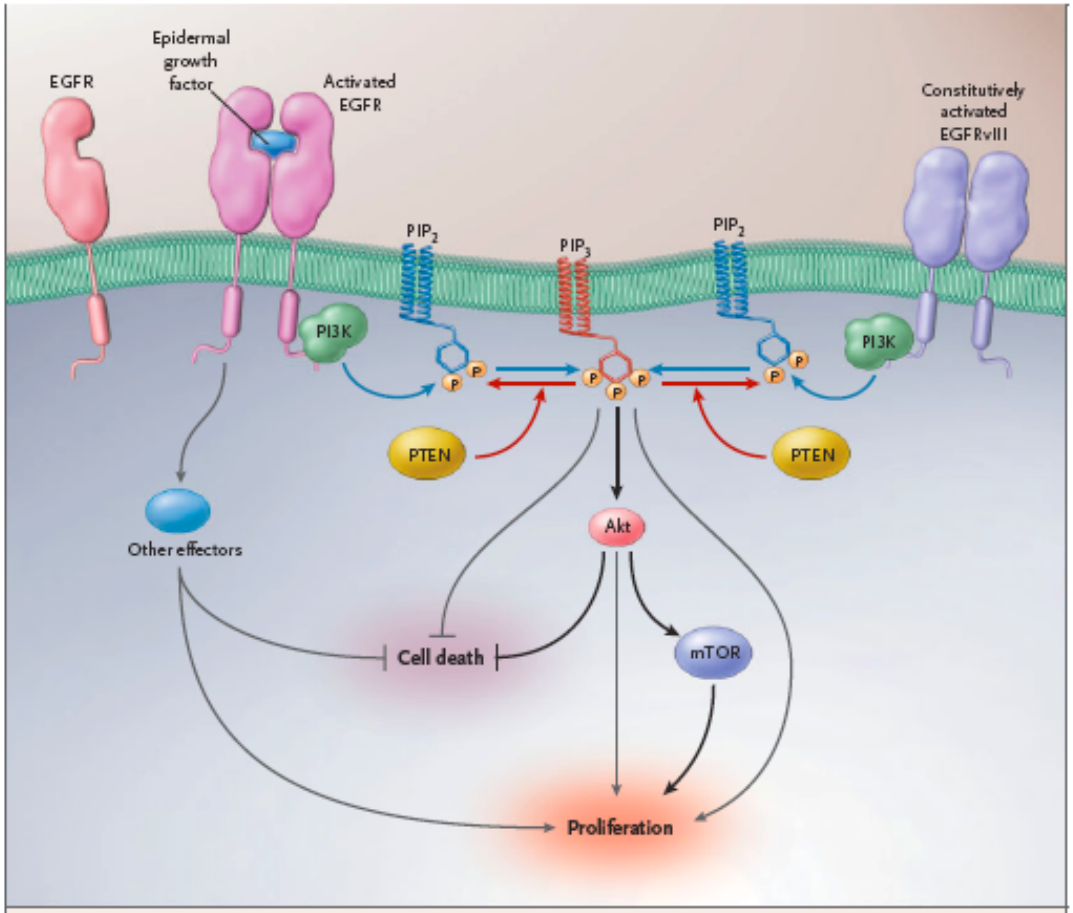


Figure 1. The PI3K–Akt Signaling Pathway.

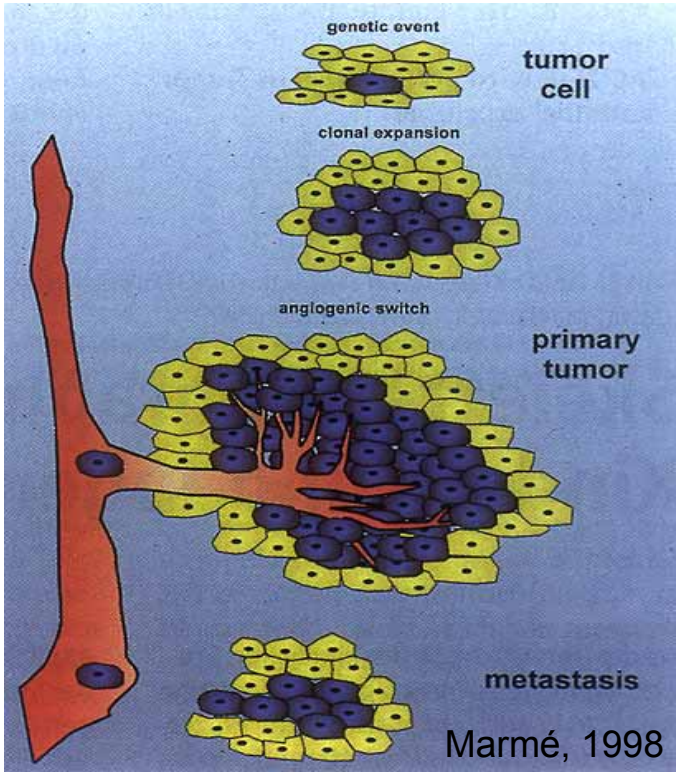
The EGFR becomes activated on binding to epidermal growth factor and recruits PI3K to the cell membrane. PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP_2) to the second-messenger molecule PIP_3 (blue arrows). This second messenger then activates downstream effector molecules, such as Akt and the mammalian target of rapamycin (mTOR), which help induce cellular proliferation and block apoptosis. PTEN terminates the PIP_3 signal (red arrows). The mutant receptor EGFRvIII is persistently activated in the absence of ligand, owing to an in-frame deletion within the extracellular ligand-binding domain.

The greatest likelihood of a clinical response to EGFR kinase inhibitors was associated with coexpression of EGFRvIII and PTEN

10-15 % Clinically Useful Responses in unselected patients

Temodal again.....

Angiogenesis:

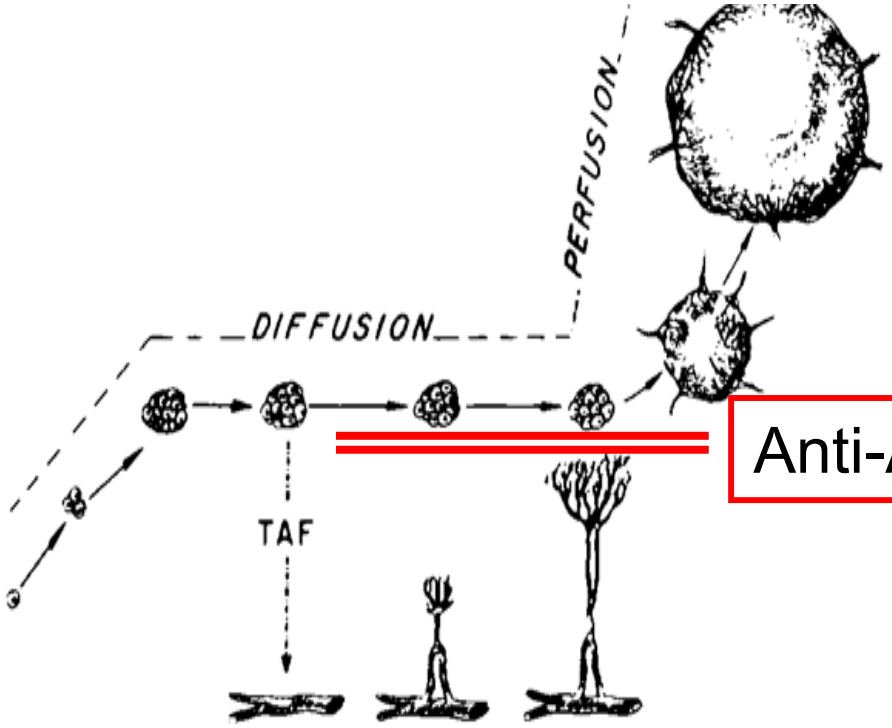


Tasks:

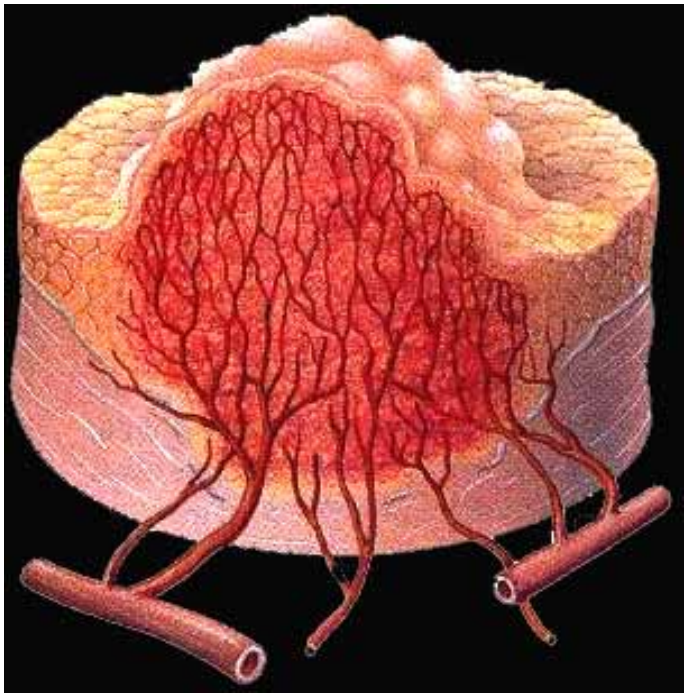
- Oxygen Supply
- Nutrient Supply
- Removal of „Waste“
- (Metastases)

Tumor Growth and Angiogenesis

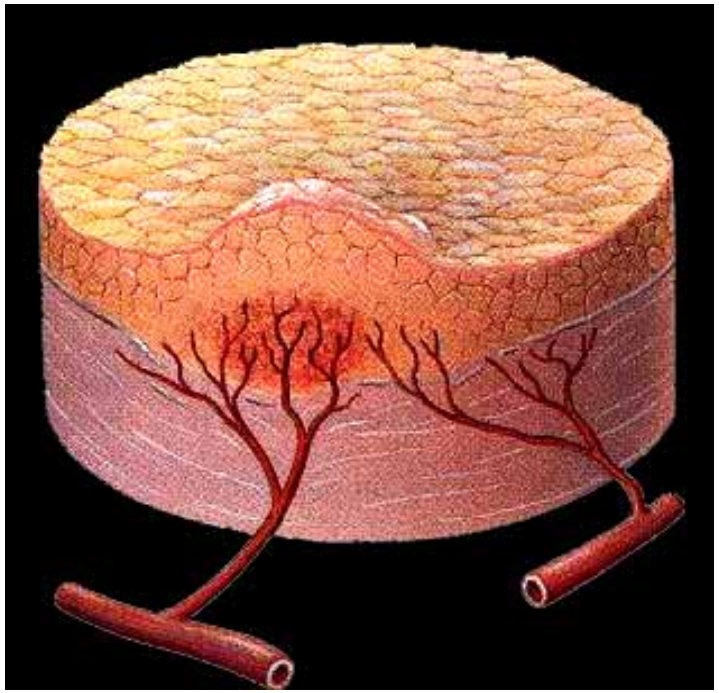
(Folkman, NEJM 1973)



Anti-Angiogenese

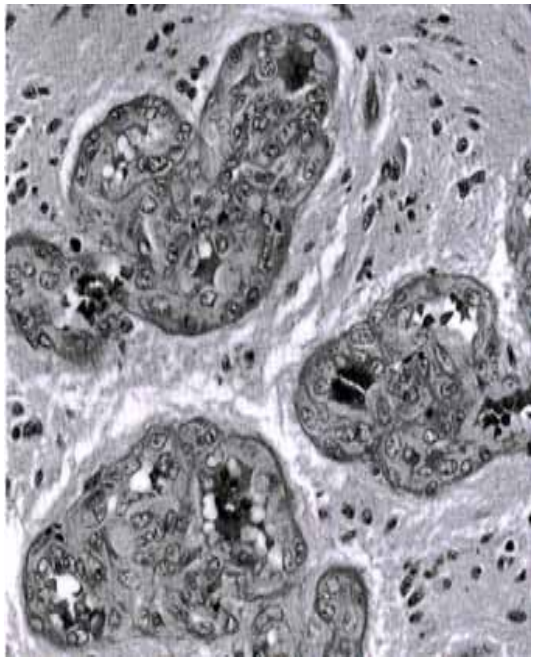


untreated

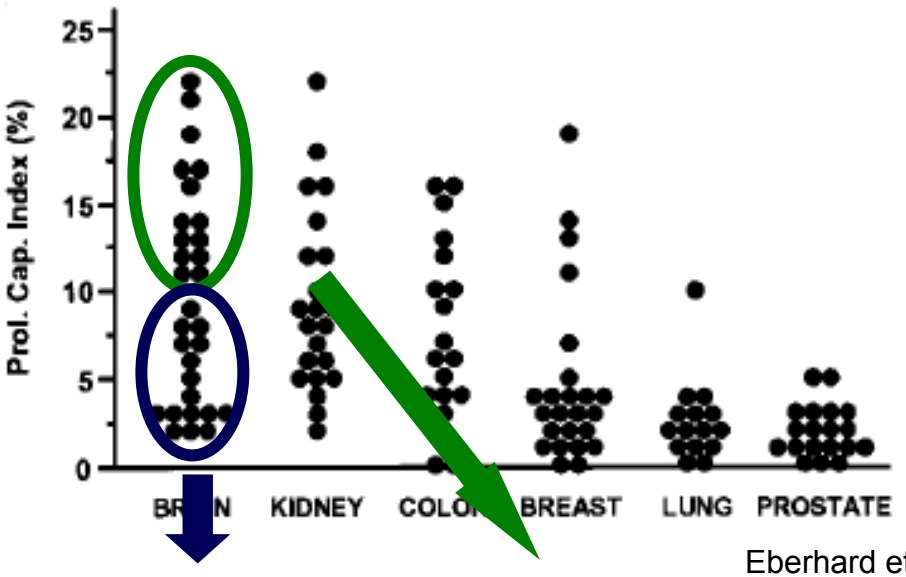


treated

Glioblastom – Prototype of an angiogenic tumor



Neovaskularisierung



Eberhard et al., 2000

Prognosis

Leon et al., 1996

Anti-angiogenic Chemotherapy:

Concept

- every cytostatic drug has antiangiogenic properties
- Endothelial cells more susceptible than tumor cells
- Blood-Brain-Barrier no problem
- Endothelial cell not prone to development of resistance

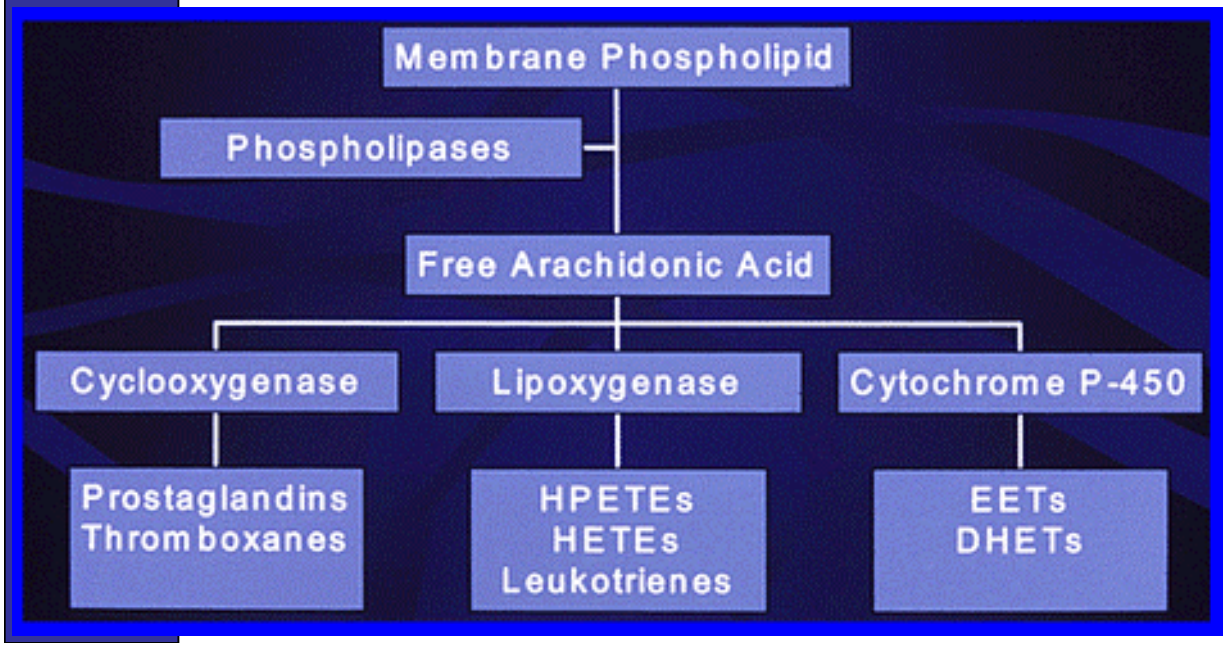
Continuous low dose chemotherapy with temozolomide as an anti-angiogenic approach in patients with primary glioblastoma multiforme

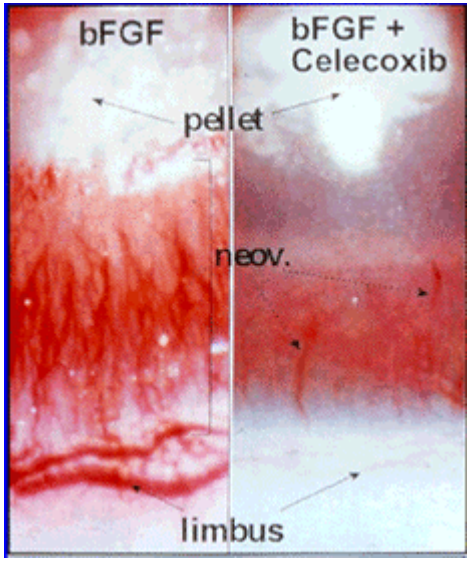
Tuettenberg J, Grobholz R, Korn T, Wenz F, Erber R, Vajkoczy P, submitted

TMZ:
antiangiogenic scheduling
continuous low dose

effective in GBM
well tolerated
orally available

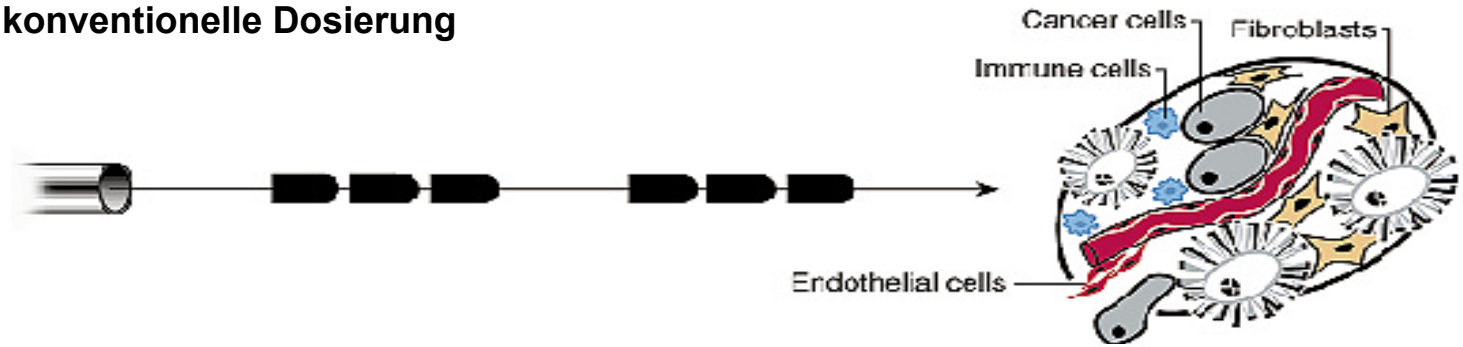
COX2 Inhibitors:
downregulate VEGF
block endothel cell proliferation
induce endothel cell apoptosis
widely expressed in GBM
well tolerated
orally available



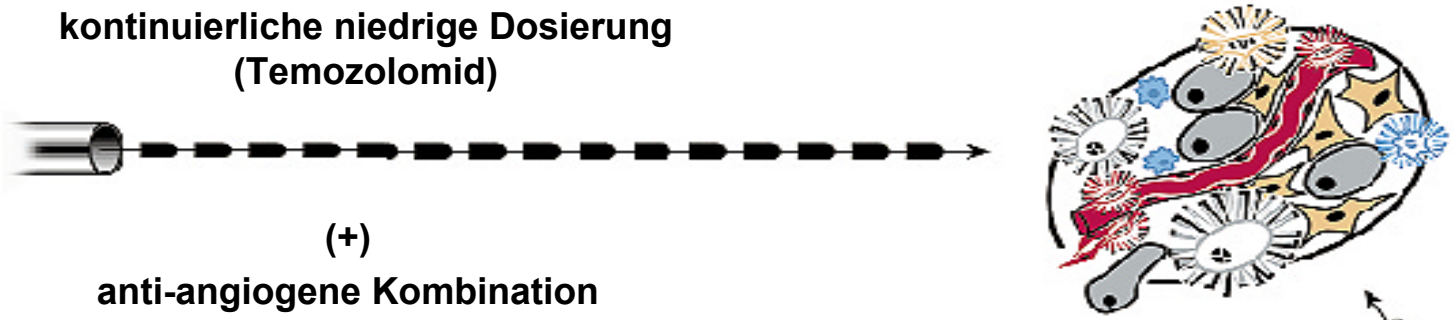


Dannenberg ASCO 2002

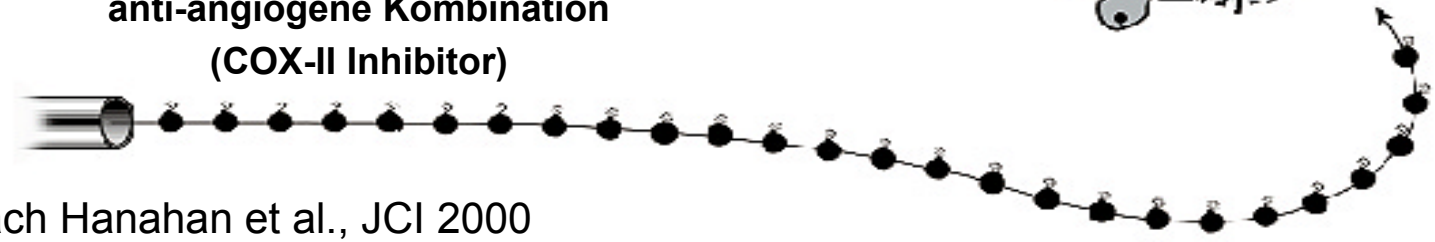
konventionelle Dosierung



kontinuierliche niedrige Dosierung
(Temozolomid)



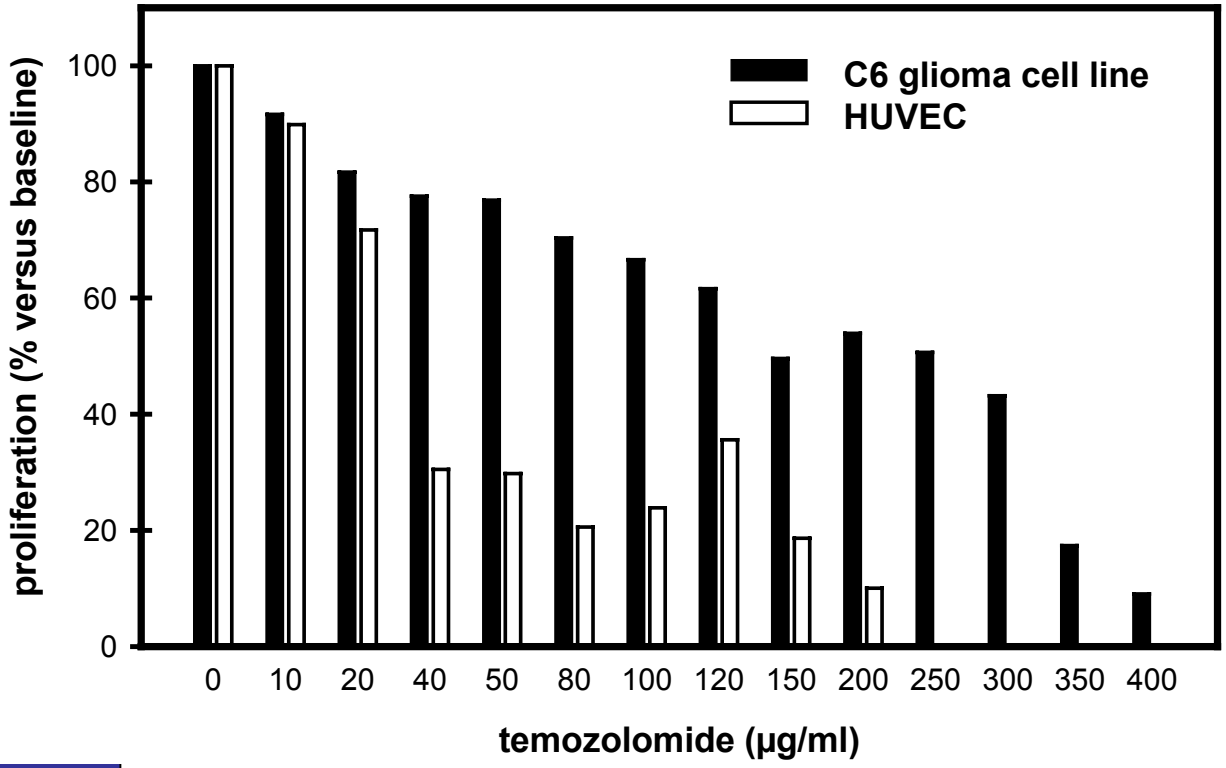
(+)
anti-angiogene Kombination
(COX-II Inhibitor)



nach Hanahan et al., JCI 2000

Continuous low dose chemotherapy with temozolomide as an anti-angiogenic approach in patients with primary glioblastoma multiforme

Tuettenberg J, Grobholz R, Korn T, Wenz F, Erber R, Vajkoczy P, submitted



TMZ for 5d, MTT assay

	IC50
C6	200 ug/ml
HUVEC	20 ug/ml

1/10 MTD
for clinical study

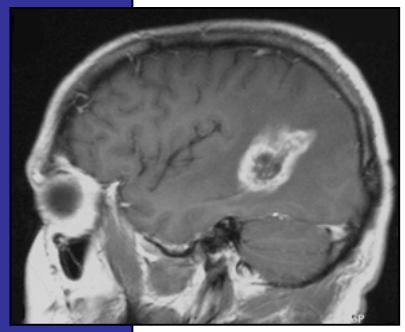
Continuous low dose chemotherapy with temozolomide as an anti-angiogenic approach in patients with primary glioblastoma multiforme

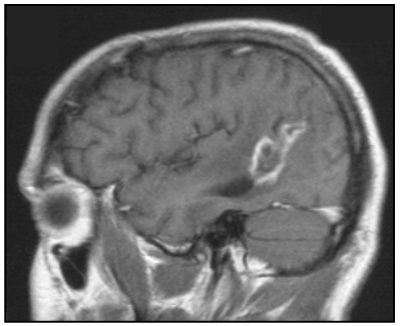
Tuettenberg J, Grobholz R, Korn T, Wenz F, Erber R, Vajkoczy P, submitted

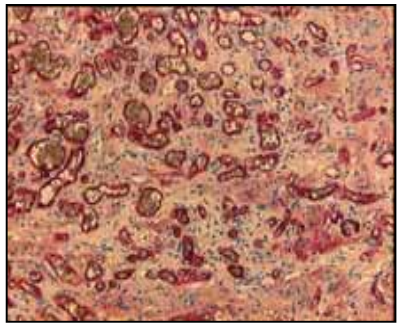
Immunohistochemistry: COX2, VEGF, VEGFR +++ in all GBMs

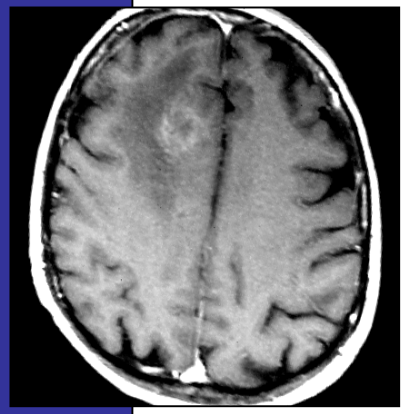
Vessel density: >3.5% vs. < 3.5% (PFS 11.7 ± 4.6 vs. 5.6 ± 1.5 months; p<0.05)

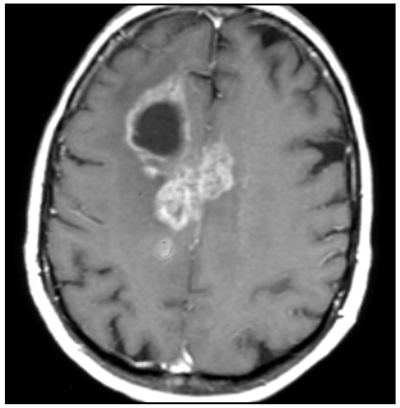
responder

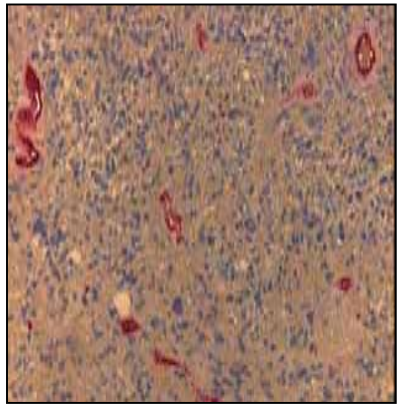


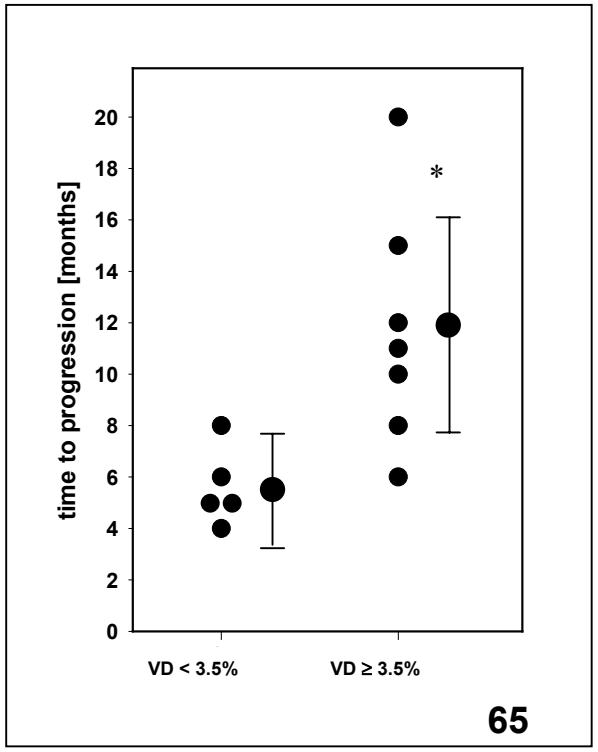








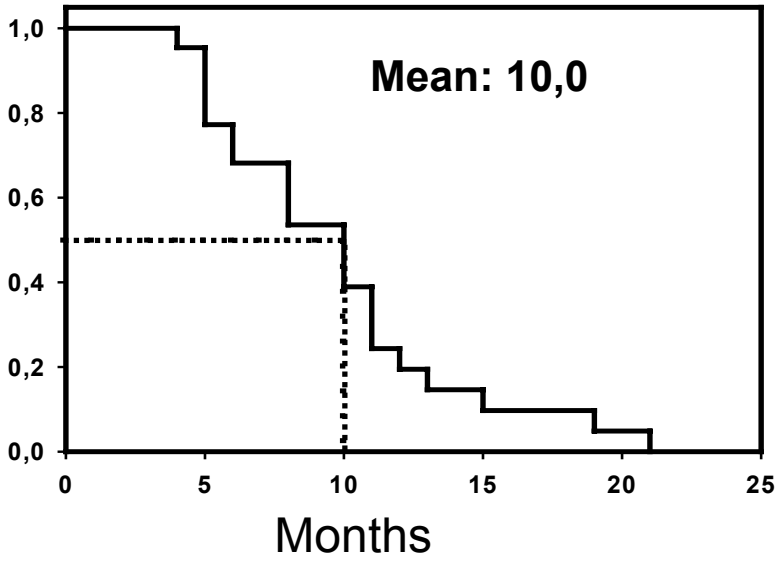




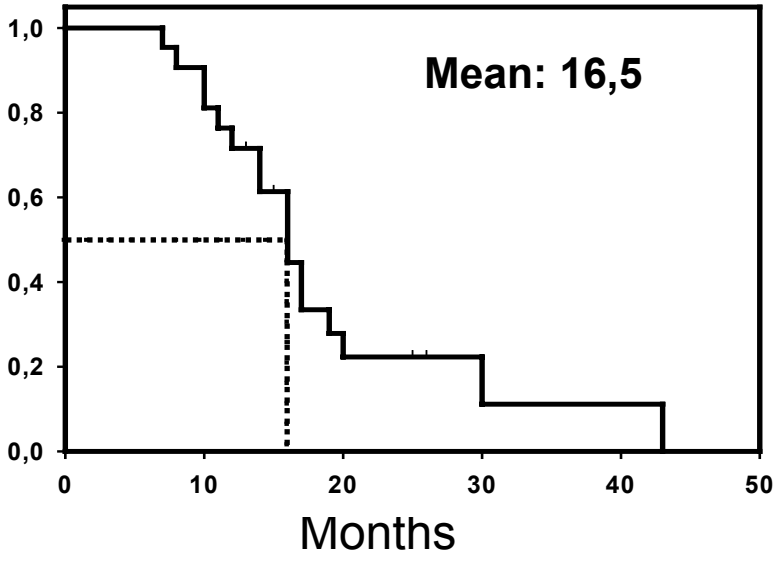
non-responder

Results (updated) (n = 32)

Progression Free Survival



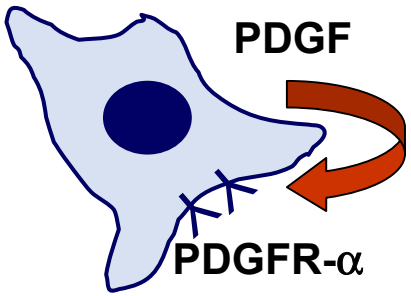
Survival



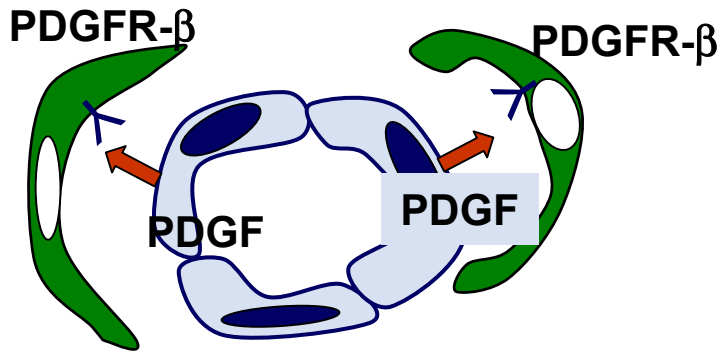
J Cancer Res Clin Oncol, 2005

Overexpression of PDGF/PDGFRs in malignant Glioma

Tumor cell compartment



Vascular compartment



PDGFR Blockade
(z.B. Imatinib, SU6668)

Antiproliferative

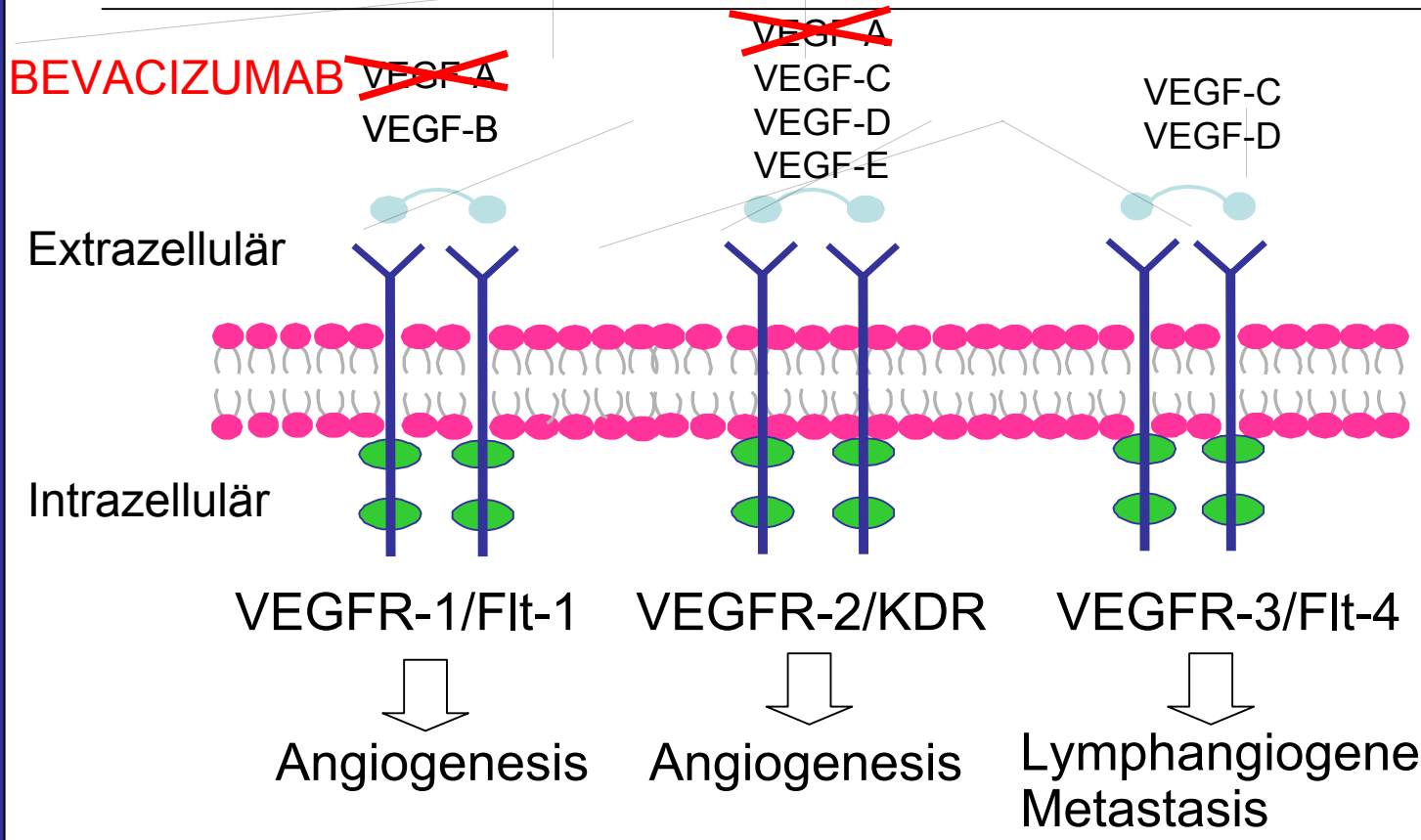
„Vessel Stabilization“

Improving BBB permeability by Radiotherapy

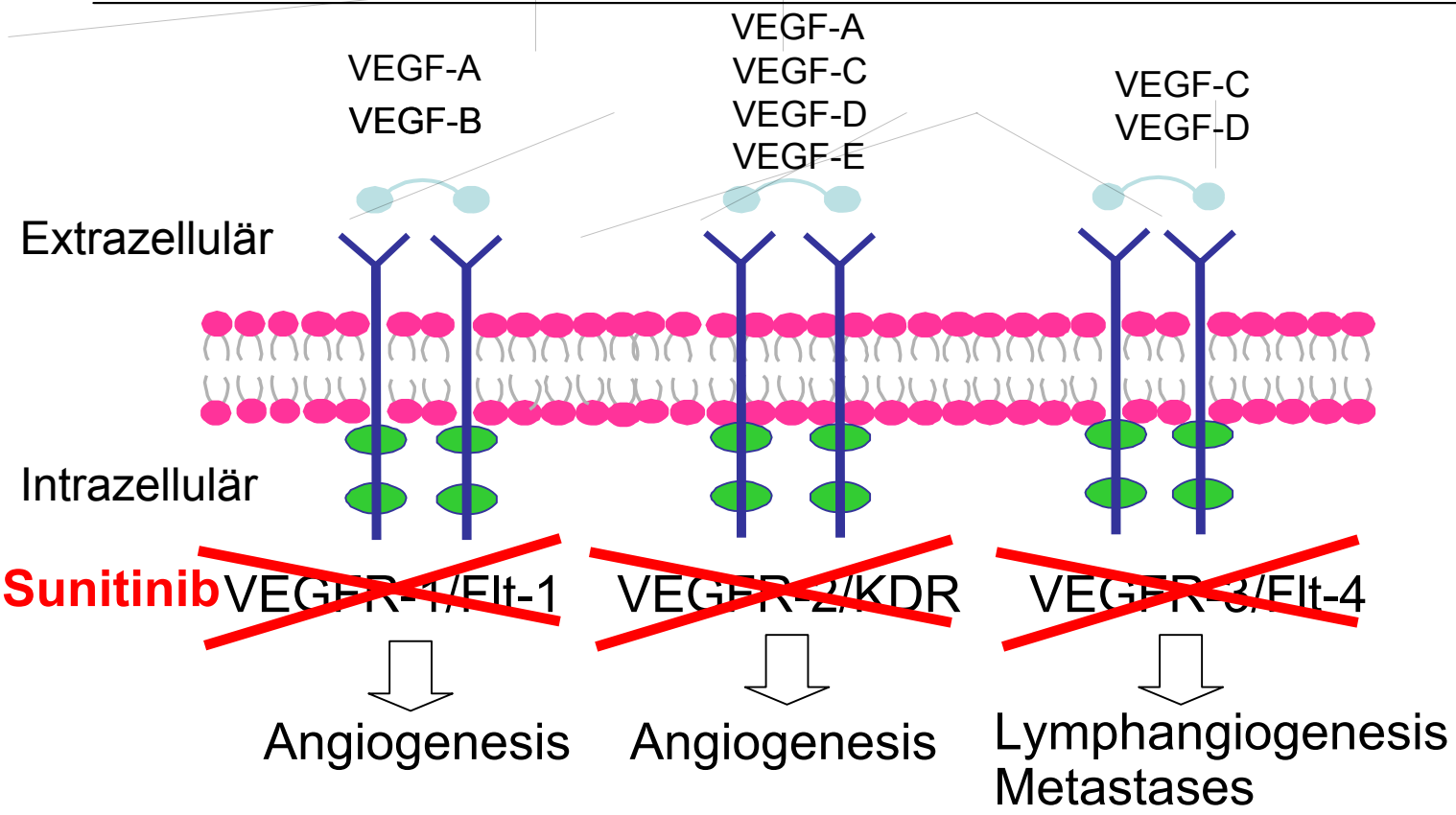
experimental C6 Glioma

Kollaboration Radiotherapie, Neurochirurgie, Medizinische Onkologie; UK Mannheim

Avastin



Adapted from Dvorak H. J Clin Oncol. 2002;20(21):4368-4380
Hsei V, et al. Pharm Res. 2002;19(11):1753-1756



Adapted from Dvorak H. J Clin Oncol. 2002;20(21):4368-4380
Hsei V, et al. Pharm Res. 2002;19(11):1753-1756

Bevacizumab + Irinotecan Phase II+III Studies:

Vredenburgh JJ et al. Clin Cancer Res 2007
Vredenburgh JJ et al. J Clin Oncol 2007

35 Patienten with relapsed Glioblastoma

24 wks mean PFS (6 Mo. PFS 46%)
42 wks mean OS

Vredenburgh JJ et al. J Clin Oncol 2007

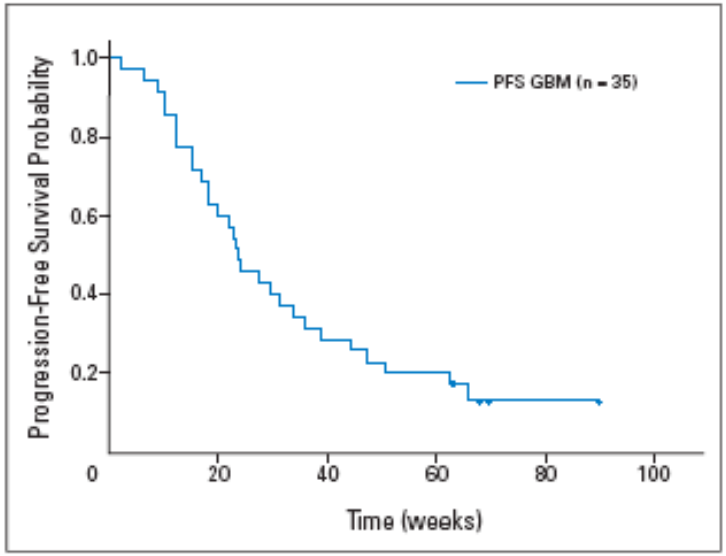


Fig 1. Kaplan-Meier progression-free survival (PFS). GBM, glioblastoma multiforme.

PFS

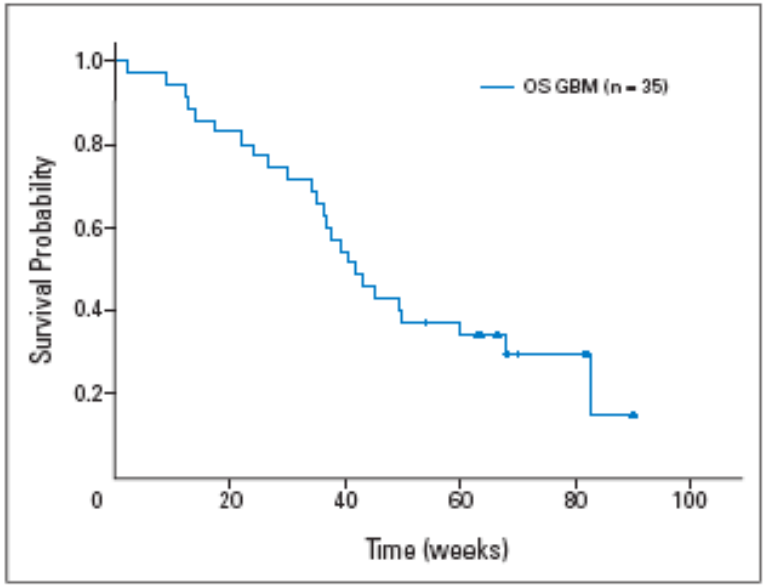


Fig 2. Kaplan-Meier overall survival (OS). GBM, glioblastoma multiforme.

OS

Sunitinib (Sutent®) for relapsed Glioblastoma

Sunitinib:

•Blocks all VEGF- and PDGF-Receptors

•Therefore blocks Angiogenesis and autocrine boosted proliferation
•oral formulation

TEM + Avastin

PHASE II PILOT STUDY OF BEVACIZUMAB IN COMBINATION WITH TEMOZOLOMIDE AND REGIONAL RADIATION THERAPY FOR UP-FRONT TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME: INTERIM ANALYSIS OF SAFETY AND TOLERABILITY

ALBERT LAI, M.D., PH.D.,* EMESE FILKA,* BRUCE MCGIBBON, M.D.,¶ PHOANH LEIA NGHIEMPHU, M.D.,* CARRIE GRAHAM,* WILLIAM H. YONG, M.D.,† PAUL MISCHEL, M.D.,† LINDA M. LIAU, M.D., PH.D.,‡ MARVIN BERGSNEIDER, M.D.,‡ WHITNEY POPE, M.D., PH.D.,§ MICHAEL SELCH, M.D.,¶ AND TIM CLOUGHESY, M.D.*

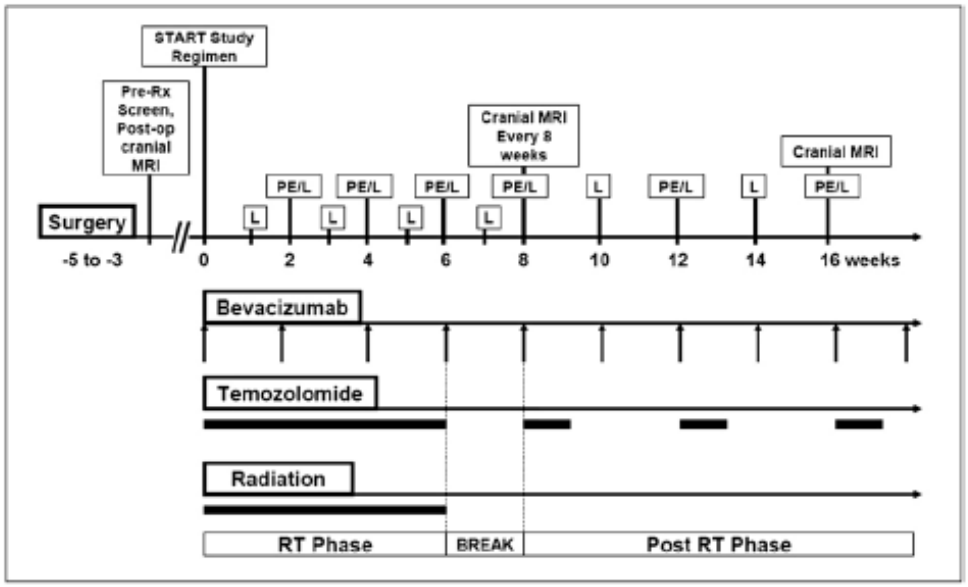


Fig. 1. Study schema. Bevacizumab (BV) is given intravenously at 10 mg/kg every 2 weeks beginning as early as 3 weeks after surgery and no later than 5 weeks. Temozolomide (TMZ) is given daily (75 mg/m^2) during radiation. After a break of 2 weeks, TMZ will be continued for up to 24 cycles given 5 days of 28 at a dose of 150 to 200 mg/m^2 on those days and BV will be continued until progression. If progression occurs after completion of 24 cycles of TMZ, BV will be continued as a single agent. Schedule of physical examination (PE), cranial magnetic resonance imaging (MRI) scans, and laboratory assessments (L) are indicated. Pre-Rx = pretreatment; Post-op = postoperative; RT = radiation therapy.

→ Feasible

Erbitux ??

.....well,.....mixed results in early clinical studies as single agent

Phase I/II Study of TEM/Erbitux under way in Heidelberg.

c) What else is on the horizon?

-Multiple Combinations
-Immune Therapy (again!?!)

Coactivation of Receptor Tyrosine Kinases Affects the Response of Tumor Cells to Targeted Therapies

Jayne M. Stommel,[1] Alec C. Kimmelman,[1,2] Haoqiang Ying,[1] Roustem Nabioullin,[3] Aditya H. Ponugoti,[3] Ruprecht Wiedemeyer,[1] Alexander H. Stegh,[1] James E. Bradner,[4] Keith L. Ligon,[1,5] Cameron Brennan,[6] Lynda Chin,[1,3,7] Ronald A. DePinho[1,3,8,*]

Combination of Vascular Endothelial Growth Factor Receptor/ Platelet-Derived Growth Factor Receptor Inhibition Markedly Improves Radiation Tumor Therapy

Carmen Timke,[1,2] Heike Zieher,[1,2] Alexandra Roth,[1,2] Kai Hauser,[4,5] Kenneth E. Lipson,[1,2] Klaus J. Weber,[1,2] Jürgen Debus,[1,2] Amir Abdollahi,[1,2,3] and Peter E. Huber[1,2,3]

Antitumor Vaccination of Patients With Glioblastoma Multiforme: A Pilot Study to Assess Feasibility, Safety, and Clinical Benefit

Hans Herbert Steiner, Marco Mario Bonsanto, Philipp Beckhove, Michael Brysch, Karsten Geletneky, Rezvan Ahmadi, Rebecca Schuele-Freyer, Paul Kremer, Golamreza Ramule, Dejana Marejic, Harald Bauer, Marika Kiessling, Stefan Kunze, Volker Schirrmacher, and Christel Herold-Mende

Interdisziplinäres Tumorzentrum Mannheim

Linikum Mannheim gGmbH
Universitätsklinikum
Medizinische Fakultät Mannheim der Universität Heidelberg

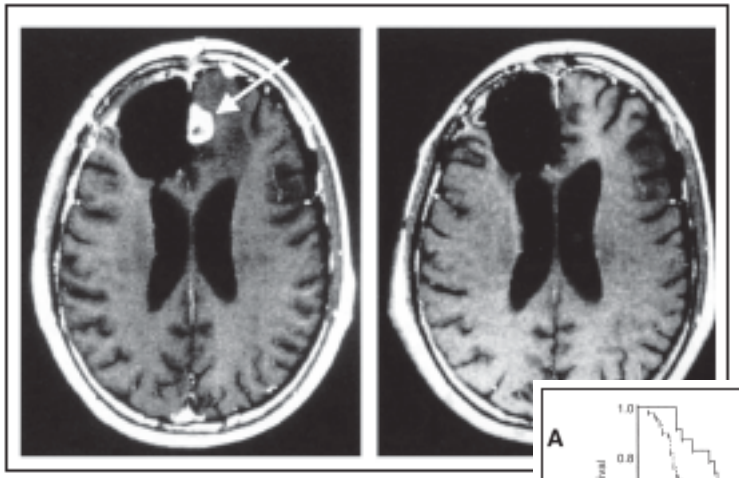


Fig 3. Tumor regression as evidenced by magnetic resonance imaging. Magnetic resonance imaging scans of the brain (T1 with gadolinium) of patient 4 after standard treatment (surgery and radiotherapy; left panel) and 6 months later after additional vaccination therapy (right panel). A tumor (arrow) that developed during radiotherapy completely disappeared after vaccination.

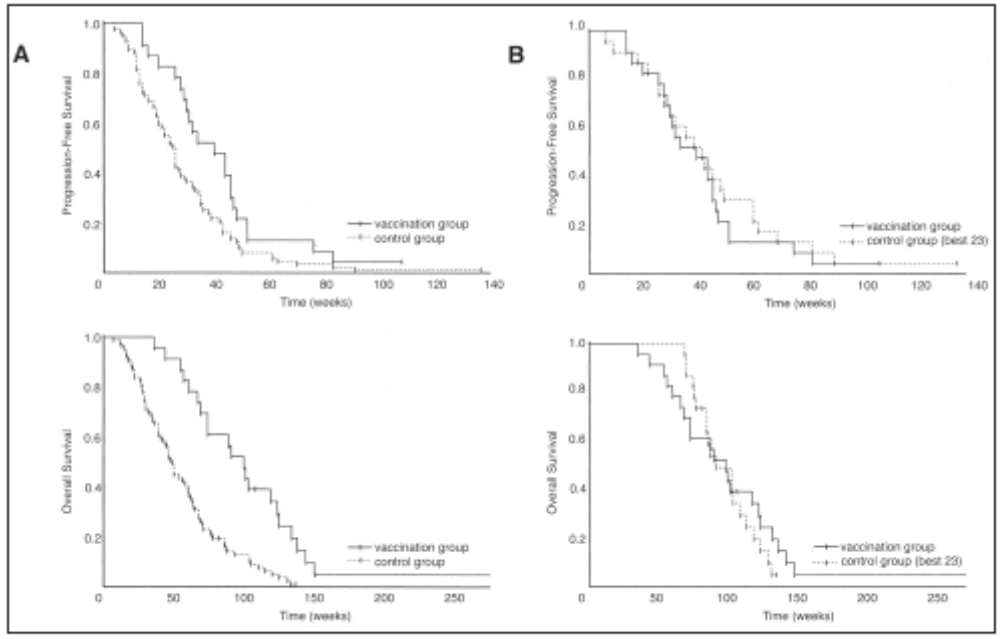


Fig 2. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS). (A) Kaplan-Meier curves for PFS and OS of vaccination group (n = 23) compared with controls (n = 87). (B) Kaplan-Meier curves for PFS and OS of vaccination group compared with 23 glioblastoma patients of the control group (shown in A) selected for the best survival (best 23 patients in control group).

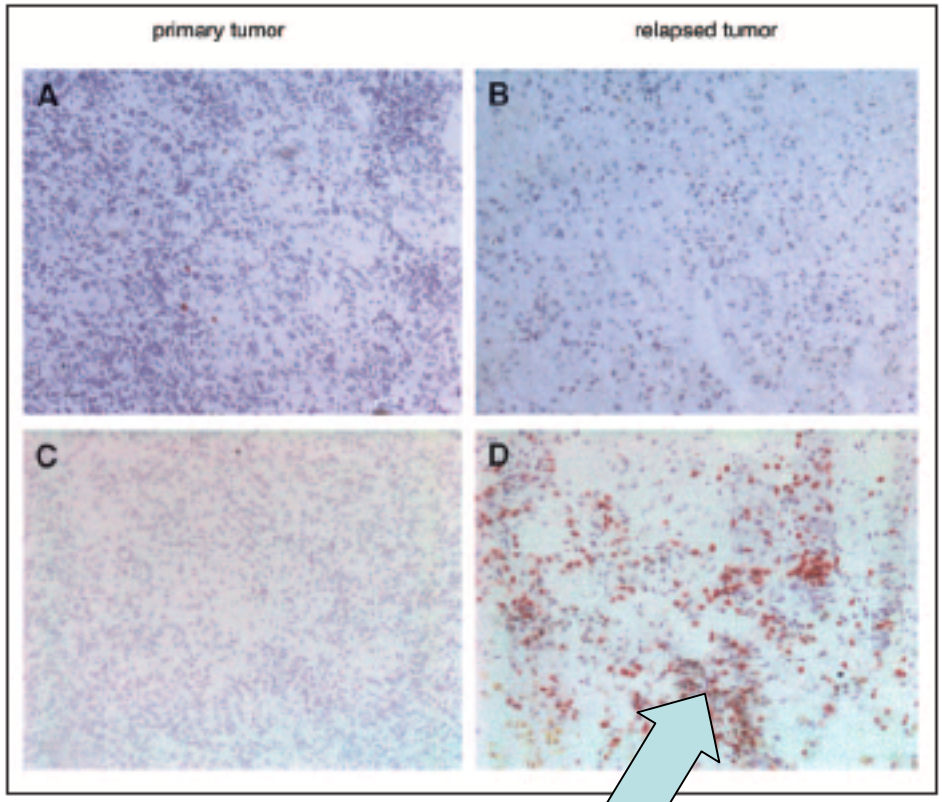


Fig 5. CD8 infiltrates in primary and relapsed tumors. Comparison of CD8 infiltrates in primary and relapsed tumors of control patient 76 (A and B) and study patient 13 (C and D) as determined by immunohistochemistry revealed a significantly increased number of $CD8^+$ T cells in the relapsed tumor of the verum patient after vaccination (D).

Response seems to be inducible

- > Boost through High-Dose RT and Agonistic Antibodies???

EGFRvIII Peptide Vaccine???

Conclusion

1. Radiotherapy is still the mainstay of adjuvant treatment for malignant glioma, is technically fully developed and can be applied with minimal strain on the patient.
2. Temodal has for the first time substantially improved survival at least for a subset of patients, at tolerable toxicity
3. Temodal has convincingly made the case for individualization of Glioma Therapy based on biological characteristics of the tumor.
4. Based on the notion the new drugs also work on subsets of patients, tailoring of therapy has to be done to substantially improve results (which will happen!).
5. Aggressive treatmetn of patients with relapse seems to be beneficial, at least for a subset of patients
6. While multiple attempts at optimizing fractionation failed, „pulsed“ RT might open new roads, also in combination with drugs