# Toxicity Considerations in Brain Tumours and Reirradiation in Brain Tumours

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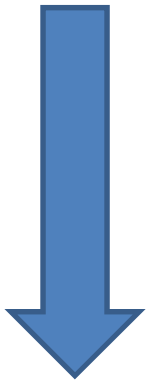
# Toxicity Considerations in Brain Tumour Radiation

- Brain: Symptomatic necrosis
- Brain Stem: Necrosis or Cranial neuropathy
- Optic nerves: Optic neuropathy
- Retina: Blindness
- Cochlea: Hearing loss
- Hippocampus & left temporal lobe: neurocognition and memory deficits

# Transition from Emami to QUANTEC Cranial Radiation---- Toxicity

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |

**IMRT,SRS,CT+RT, ALTEREDFRACTIONATION**



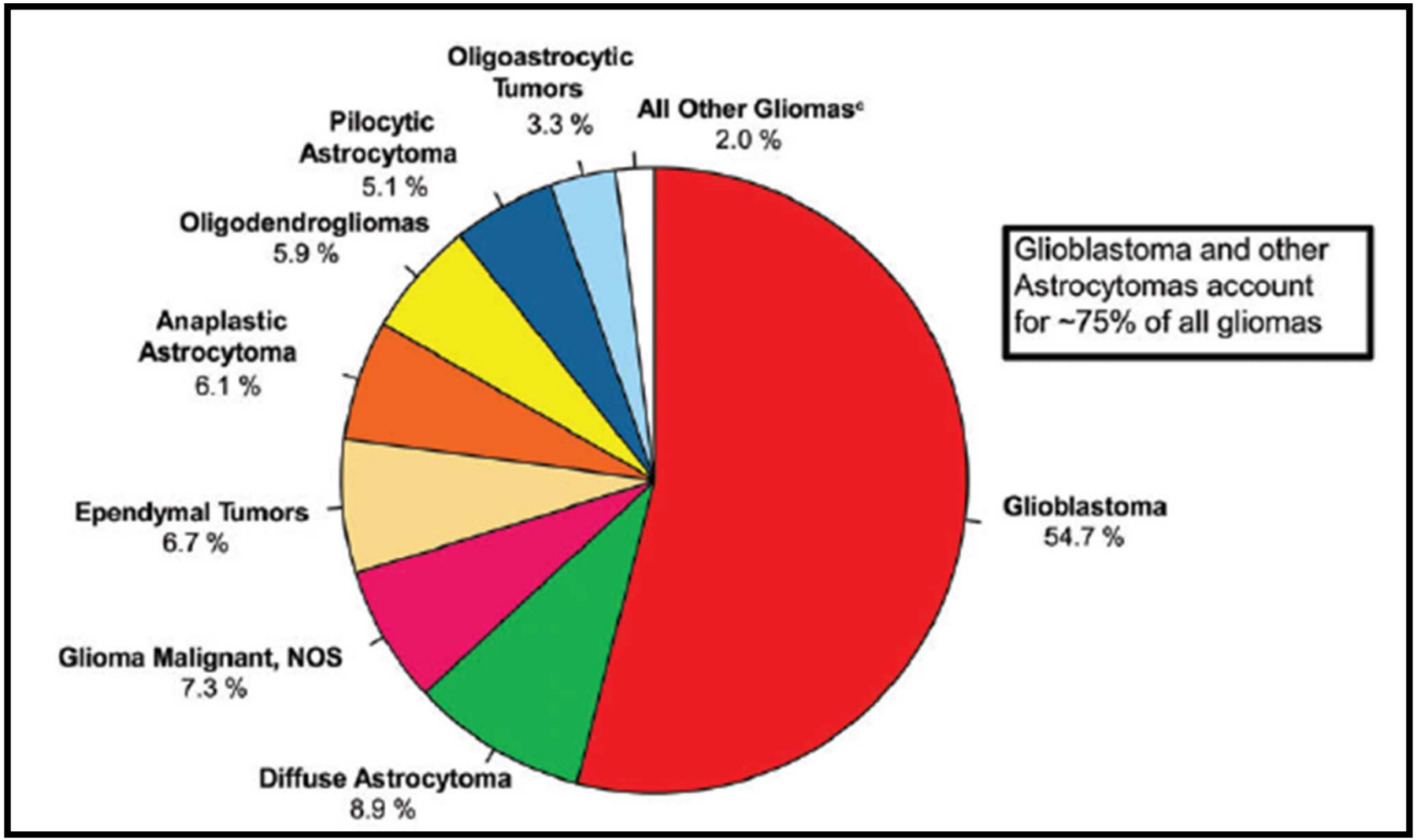
**QUANTEC**

# QUANTEC

| organ | endpoint | technique | rate | Dose-volume parameters | Dmax(Gy) | Dmaen(Gy) |
|---|---|---|---|---|---|---|
| Brain | Necrosis | Conventional<br>SRS | 5% | <br>5-10cc <12Gy | 72Gy | |
| Brain Stem | Necrosis | Conventional<br>SRS | 5% | 0.3cc <60Gy | <12.5Gy | 54Gy |
| Optic nerve & chiasm | Optic neuropathy | Conventional<br>SRS | | 0.3cc <54-60 Gy | | <50gy<br><8Gy |
| Cochlea | Hearing loss | Conventional<br>SRS | | | 12-14Gy | 45Gy(35) |

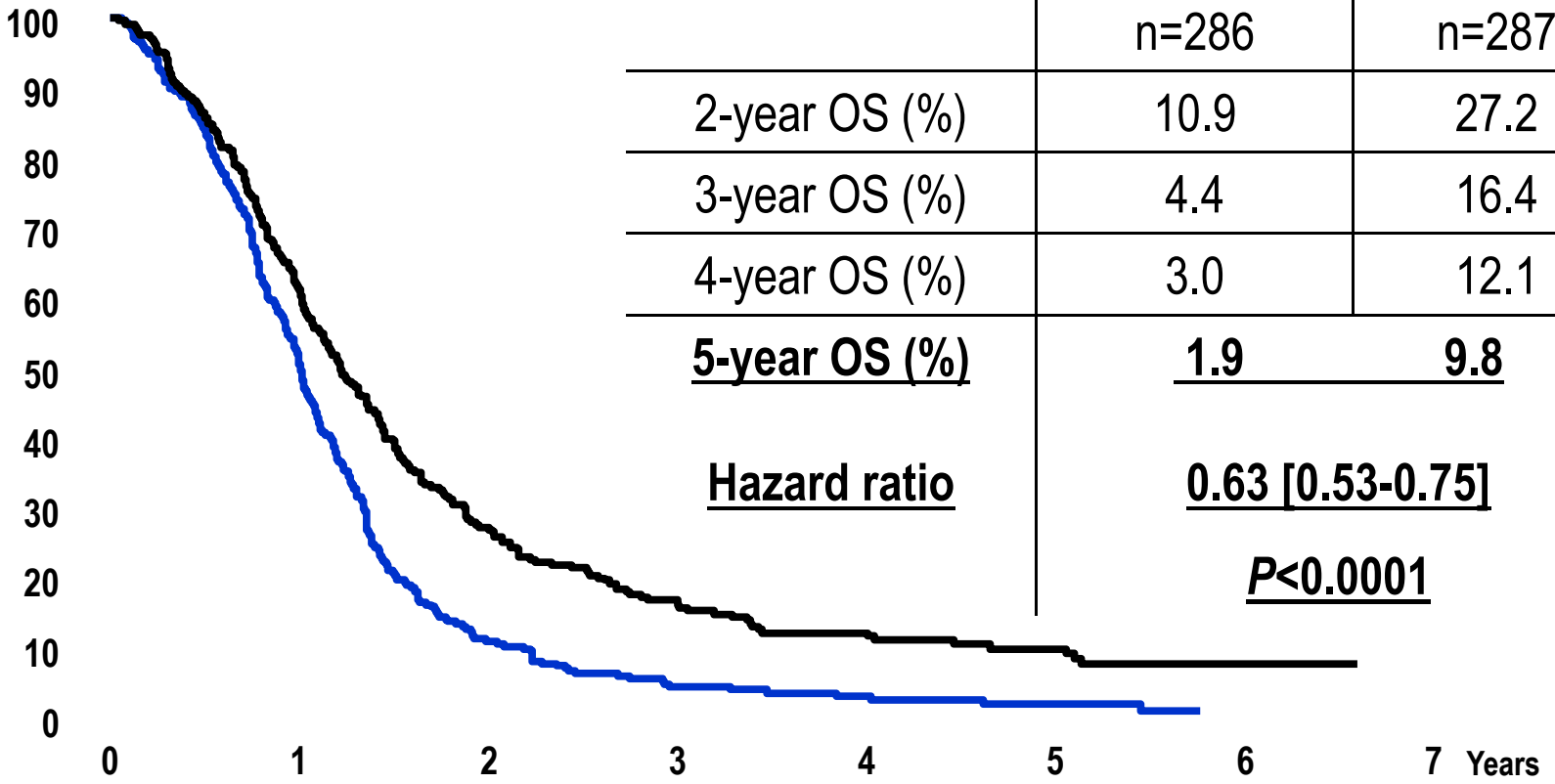
# Re-irradiation in brain tumors

# Stats about primary brain tumors




*Ostrom et al, CBTRUS 2007-2011, Neuro Oncol 2014*

# Récurrences: Hallmark in GBM




| 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** | |

0

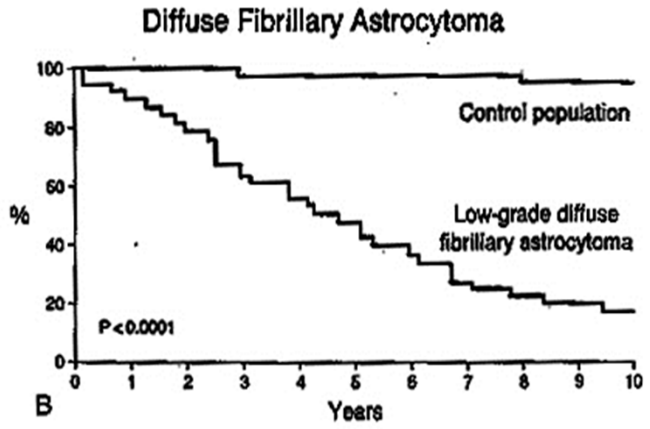
Stupp et al NEJM 2005

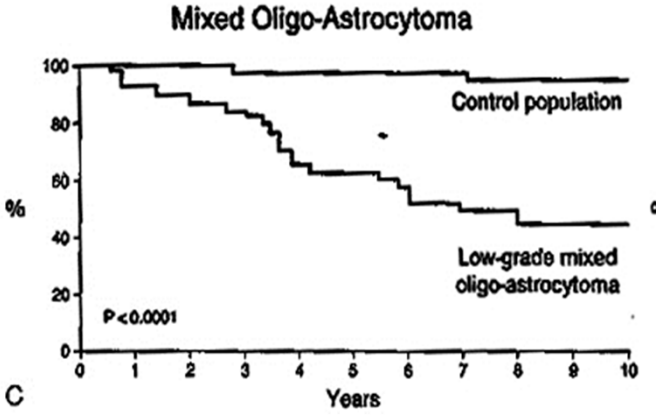
Stupp et al Lancet Oncol 2009

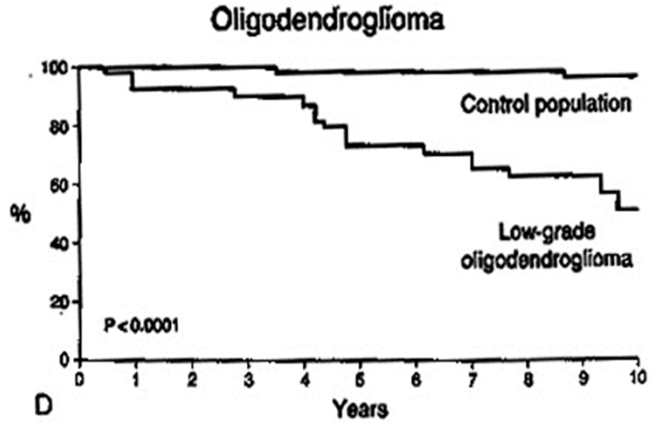
# Recurrences in LGG

| Survival Astrocytomas | Oligo-Astros | Oligodendrogliomas |
|---|---|---|
| Median (yr) 4.7 | 7.1 | 9.8 |
| 2-yr (%) 80 | 89 | 93 |
| 5-yr (%) 46 | 63 | 73 |
| 10-yr (%) 17 | 33 | 49 |
| 15-yr (%) 17 | 17 | 49 |

*Shaw E, 2000*



# We are still Hesitant to Reirradiate

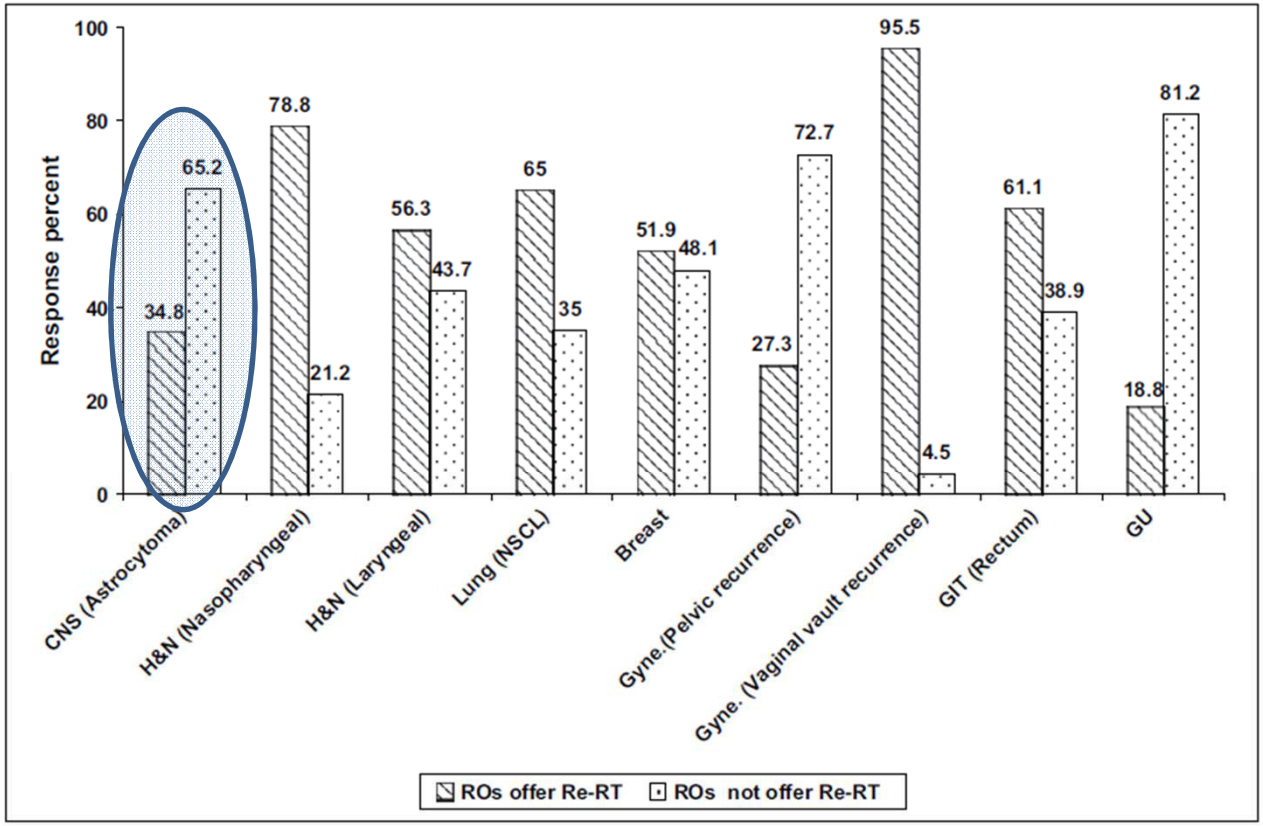



Fig. 1. Poll of radiation oncologists' (ROs) opinions for case scenarios of patients referred for reirradiation (Re-RT). *Abbreviations:* CNS = central nervous system; H&N = head and neck; NSCL = non–small-cell lung cancer; gyne = gynecologic; GIT = gastrointestinal; GU = genitourinary.

Joseph,, IJROBP 2008

# And Here's Why…

- **Patients are complicated.**
- **planning is complicated.**
- **Toxicity concerns usually dominate, especially concern for late toxicity.**
- **Liability is high.**
- **success rates are thought to be low.**
- **uncertainty is great.**
- **Saying "No" is usually the easiest course.**

# Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles

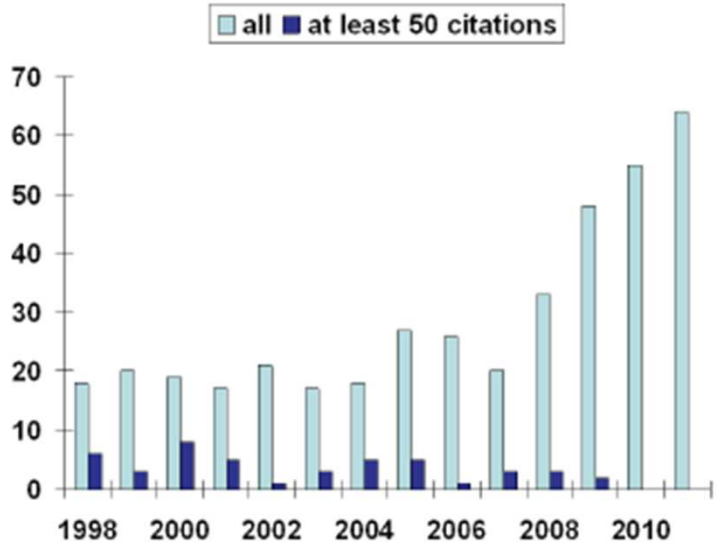



Figure 1. Number of articles and highly cited articles published per year.

## Leading sites for re-irradiation

- Head-Neck Cancers (37%)
- Brain Tumors (36%)
- Bone metastases (13%)

***Nieder et al, Am J Cancer Res 2013***

# How to justify re-irradiation in brain tumors?

# Rationale of reirradiation in brain tumors

- **Large majority of brain tumors still remain localized at recurrence (within 2cm)**

  RT is an ***effective local treatment*** for brain tumors (provides good local control)

- **Recurrent brain tumors are associated with significant morbidity & mortality**

  ReRT has some proven efficacy ***(symptom relief & prolongation of survival)***

- **Alternative options if any are neither very effective, nor very affording**

  ***Limited benefit*** of chemotherapy (TMZ) or targeted therapy (Bevacizumab) alone

**Despite significant advances in neurosurgery, radiotherapy, chemotherapy, and targeted therapy, outcomes of recurrent brain tumors continue to remain dismal**

# Common brain tumors types where reirradiation is offered at recurrence/progression

- **Recurrent high-grade glioma**

  *Most common indication & by far most widely studied*

- **Recurrent ependymoma**

  *Tumor type where reirradiation probably is most effective*

- **Recurrent medulloblastoma**

  *Emerging role of reirradiation as salvage therapy*

# Techniques of reirradiation in brain tumors

- Conventional Radiation Therapy (CRT)
- Fractionated Stereotactic Radiation Therapy (FSRT)
- Stereotactic Radio-Surgery (SRS)
- Intensity Modulated Radiation Therapy (IMRT)
- Brachytherapy
- Proton Therapy

**IMRT either conventionally fractionated or hypofractionated with image-guidance has become increasingly popular in recent times**

# Fractionation at reirradiation in brain tumors

- **Conventionally fractionation radiation therapy (CFRT)**

  *Standard **1.8-2Gy per fraction**, 5 fractions per week over 4-6 weeks*

- **Hypofractionated Radiation Therapy (HypoRT)**

  Large dose ***(>2.5-3Gy) per fraction***, 3-5 fractions per week over 2-5 weeks

- **Stereotactic Radio-Surgery (SRS)**

  Large dose typically ***>12-15Gy*** given as a ***single fraction***

- **Hyperfractionated Radiation Therapy (HFRT)**

  Small dose ***(1-1.2Gy per fraction)***, 2 #s daily (6 hrs apart) over 5-6 weeks

# Factors affecting tolerance of brain to reirradiation

- **Cumulative biological dose of radiation to the brain**

  *Lesser the cumulative dose, better the tolerance*

- **Time interval from initial course of RT to reirradiation**

  *Longer the time interval, better the tolerance*

- **Volume of reirradiation**

  *Smaller the volume(s) of irradiation, better the tolerance*

- **Concurrent systemic therapy during reirradition**

  *Chemotherapy potentially increases biological dose*

## How much of cumulative biological dose is safe?

- Conventional fractionation
- FSRT
- SRS

# Assumptions and Calculations

- Low repair capacity of brain tissue assumed ($\alpha/\beta=2$)
- Linear Quadratic (LQ) model used for radiobiology calculations
- BED=nd(1+d/[$\alpha/\beta$]); d=dose/fx, n=number of fx, $\alpha/\beta$=tissue repair capacity
- Converted to equivalent dose in 2Gy fractions (EQD2) for easy understanding
- Cumulative BED calculated as BED (cumulative) = BED (RT1) + BED (RT2)

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 5, pp. 1350–1360, 2008

0360-3016/08/$–see front matter

ELSEVIER

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**CLINICAL INVESTIGATION** **Brain**

# REIRRADIATION TOLERANCE OF THE HUMAN BRAIN

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**Purpose:** To give an overview of current available clinical data on reirradiation of glioma with respect to the tolerance dose of normal brain tissue.

**Methods and Materials:** Clinical brain reirradiation studies from January 1996 to December 2006 were considered on radiation-induced late adverse effects—*i.e.*, brain tissue necrosis. The studies were analyzed by using the linear quadratic model to derive information on the cumulative biologic effective tolerance dose ($BED_{cumulative}$) and equivalent doses in 2-Gy fractions (normalized total doses, $NTD_{cumulative}$) for the healthy human brain.

**Results:** The $NTD_{cumulative}$ in conventional reirradiation series ($NTD_{cumulative}$ of 81.6–101.9 Gy) were generally lower than in fractionated stereotactic radiotherapy (FSRT) ($NTD_{cumulative}$ of 90–133.9 Gy.) or LINAC-based stereotactic radiosurgery series ($NTD_{cumulative}$ of 111.6–137.2 Gy). No correlation between the time interval between the initial and reirradiation course and the incidence of radionecrosis was noted. The analysis showed the prescribed $NTD_{cumulative}$ to increase with decreasing treatment volume, which is allowed by modern conformal radiation techniques.

**Conclusion:** Radiation-induced normal brain tissue necrosis is found to occur at $NTD_{cumulative}$ >100 Gy. The applied reirradiation dose and $NTD_{cumulative}$ increases with a change in irradiation technique from conventional to radiosurgery re-treatment, without increasing the probability of normal brain necrosis. Taken together, 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. © 2008 Elsevier Inc.

Reirradiation, Tolerance dose, Brain, Late side effects, Normalized total dose.

**Seminal publication on reirradiation tolerance of the human brain includes data from 21 studies of CNS reirradiation from 1996-2006**

*Cancers* **2012**, *4*, 379-399; doi:10.3390/cancers4020379

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*Review*

# External Beam Radiotherapy of Recurrent Glioma: Radiation Tolerance of the Human Brain

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**Updated publication from the same authors includes a total of 30 studies of reirradiation in brain tumors (published data till 2011 )**

# Studies of Reirradiation using Conventional RT

**Table 1.** Clinical data on brain re-irradiation by conventional radiotherapy: Physical dose and equivalent total dose in 2 Gy fractions (EQD2), survival and toxicity.

| Authors | | First course | | | Interval | Re-irradiation | | | Cumulative | Survival | Toxicity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [Ref.; symbol] | n/Grade | Total dose (Gy) | Fraction size (Gy) | EQD2 (Gy) | (mo) | Total dose (Gy) | Fraction size (Gy) | EQD2 (Gy) | EQD2 (Gy) | (mo) | Acute | Late |
| | | | | | median | | | | | | | |
| Kim *et al.* [9; □] | 7 GM 13 AA/LG | 59.4 | 1.8 | 56.4 | 38 | 36 | 1.8 | 34.2 | 90.6 | 9 | No severe | No severe |
| Hayat *et al.* [10;□] | 21 Glioma | 45 | 2.25 | 47.8 | 31 | 30 | 2.5 + Lomustine | 33.8 | 81.6 | 22 | No severe | na |
| Arcicasa *et al.* [11;□] | 24 HG | 60 | 2 | 60 | 14 | 34.5 | 1.5 + Lomustine | 30.2 | 90.2 | 13.7 | No severe n = 4 Gr.3/4 hematol. | na |
| Nieder *et al.* [12;■;■] | 21 GM 11 AA/other | 58.5 | 1.3 (bid) | 48.3 | 20 | 45.5 (n = 19) 45 (n = 13) | 1.3 (bid) 1.5 (bid) | 37.6 39.4 | 85.8 87.7 | 8.5 | 9% neurol. tox. | 6% necrosis |
| Veninga *et al.* | 29 Astrocytoma | 50–60 | 2 | 55 | 33 | 46 | 2 | 46 | 98.8 | 6.9 | 1 severe | 1 clinical necrosis |
| [13;■; □] | 10 OD | | | 52 | 55 | | | 51.3 | 101.9 | 27.5 | edema | 1 cognitive decline EQD2 cum >102 Gy |
| Henke *et al.* [14;□;□] | 29 GM | 59 | 2 | 59 | 18 | 20 (n = 19) 20 (n = 10) | 5 4 | 35 30 | 94 89 | 10.2 | No severe | No severe |
| | 2 AA/LG | | | | | 25 (n = 2) | 5 | 43.8 | 102.8 | | | |
| Niyazi *et al.* [15;□] | 22 GM 8 AA TMZ in 16 pts | 60 | 2 | 60 | n.a. | 36 | 2 + Bevacizumab in 20 pts. | 36 | 96 | 187 days * with 367 days without Bevacizumab | Gr. 4 wound dehiscence (n = 1) Gr. 3 deep vein thrombosis (n = 1) Gr. 2 Hypertension (n = 1) | No clin. necrosis Radionecrosis on imaging (n = 2) |

GM: Glioblastoma multiforme; AA: Anaplastic astrocytoma; bid: twice a day; n.a.: not stated.

EQD2 cumulative: 81Gy-103 Gy

# Studies of reirradiation using FSRT

**Table 2.** Clinical data on brain re-irradiation by fractionated stereotactic radiotherapy: physical dose and equivalent total dose in 2 Gy fractions (EQD2), survival and toxicity.

| Authors [Ref.;symbol] | n/Grade | First course | | Interval | | Re-irradiation | | | | Cumulative | Survival | Toxicity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total dose (Gy) | Fraction Size (Gy) | EQD2 (Gy) | (mo) | Total dose (Gy) | Fraction Size (Gy) | EQD2 (Gy) | Volume (cc) | EQD2 (Gy) | (mo) | Acute | Late |
| | | | | | | median | | | | | | | |
| Shepherd *et al.* | 29 AA | 55 | | 52.2 | 29 | 35 | 5 [1] | 61.3 | 24 | 113.5 | 11 | No severe | 12% "clinical" necrosis |
| *dose escalation* | 4 AO/Ep | | | | | | | | | | | | 6% necrosis |
| [16; ▲] | 3 LG | | | | | | | | | | | | |
| Cho *et al.* | 15 GM | 60 | 1.8 | 57 | 19 | 37.5 | 2.5 [1] | 42.2 | 25 | 99.2 | 12 | 8% | 1 clinical necrosis |
| [17; Δ] | 10 grade III | | | | | | | | | | | | No path. necrosis |
| Hudes *et al.* [18; Δ] | 19 GM | 60 | | 57 | 3 | 24,30,35 | 3–3.5 [1] | 48.2 max | 13 | 105.2 max | 10.5 | No severe | No necrosis |
| *dose escalation* | 1 AA | | | | | | | | | | | | |
| Lederman *et al.* | 88 GM | 60 | 1.8 | 56.4 | 6.3 | 24 | 6 [2] | 48 | 32.7 | 104.4 | 7 | No severe | 8% necrosis |
| [19; ▲] | | | | | | | + Paclitaxel | | | | 9.4 (+Chemo) | | 2% mixed tum/necrosis |
| Voynov *et al.* | 5 GM | 59.7 | 1.8–2 | ~57 | 6.3 | 30 | 5 [1] | 52.5 | 34.7 | ~109.5 | 10.1 | na | 10% necrosis |
| [20; ▲] | 5 AA | | | | | | | | | | | | 10% mixed tum/necrosis |
| | | | | | | | | | | | | | 40% "clinical" necrosis |
| Grosu *et al.* | 35 GM | 60 | 1.8–3 | 57–75 | 16 | 30 | 5 [1] | 52.5 | 18 | 109.5–127.5 | 6 | No severe | 13% mixed tum/necrosis |
| [21; ▲] | 9 AA | | | | | | (+TMZ n = 29) | | | | 11 (+Chemo) | | |

EQD2 cumulative: 99Gy-127Gy

# Studies of reirradiation using SRS

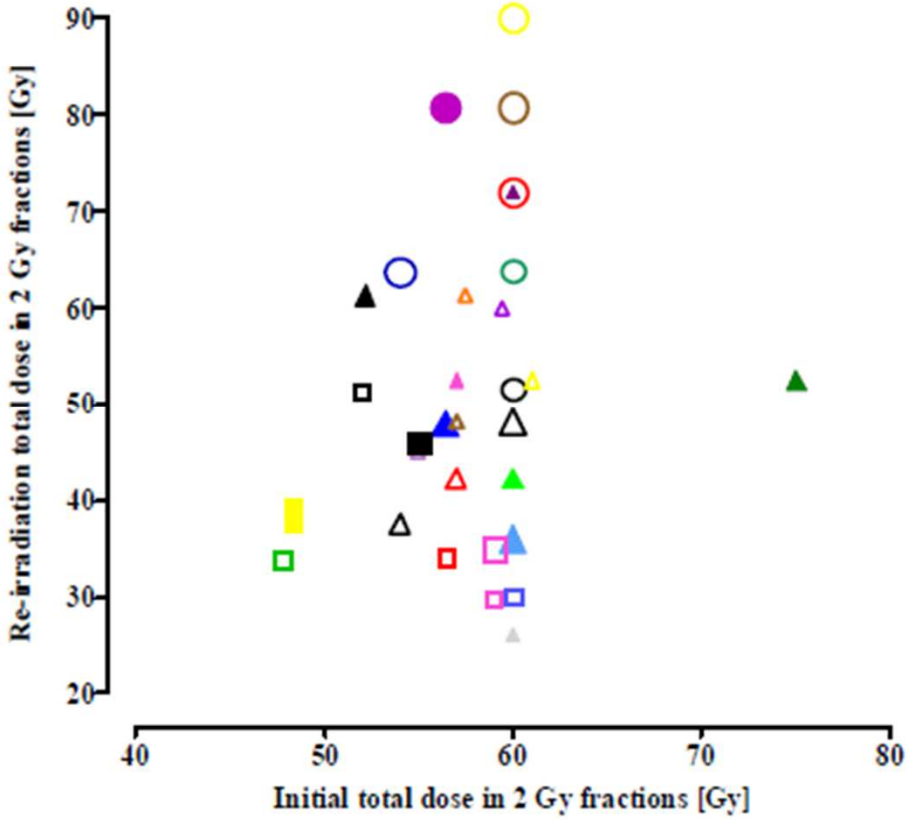
**Table 3.** Clinical data on brain re-irradiation by stereotactic radiosurgery: physical dose and equivalent total dose in 2 Gy fractions (EQD2), survival and toxicity.

| Authors [Ref. No; symbol] | n/Grade | First course | | | Interval | Re-irradiation | | | Cumulative | Survival | Toxicity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total dose (Gy) | Fraction Size (Gy) | EQD2 (Gy) | (mo) | Total dose = fraction size (Gy) median | EQD2 (Gy) | Volume (cc) | EQD2 (Gy) | (mo) | Acute | Late |
| Chamberlain *et al.* [32;O] | 5 GM<br>15 Astro | 60 + CT | 2 | 60 | 11 | 13.4 | 51.6 | 17 | 111.6 | 8 | 7 increased intra-cranial pressure<br>1 Death with 24 h | 1 Hypervommolence |
| Van Kampen *et al.* [33;O] | 27 GM | 60 | 2 | 60 | 9.6 | 16 | 72 | 21 | 132 | 9 | No severe | No necrosis |
| Cho *et al* [17;●] | 27 GM<br>19 AA | 60 | 1.8 | 56.4 | 10 | 17 | 80.8 | 30 | 137.2 | 11 | 41% transient progr. of neurological symptoms | 17% necrosis<br>13% "clinical" necrosis |
| Combs *et al.* [34; O] | 32 GM | 54 | 2 | 54 | 10 | 15 | 63.8 | 10 | 117.8 | 10 | No severe | No necrosis |
| Patel *et al.* [31;O] | 26 GM<br>? | 50–60 +CT | | ~60 | 12.5 | 18 | 90 | 10.4 | ~150 | 8.4 | No severe | 1 necrosis<br>1 mixed tumor\necrosis |
| Biswas *et al.* [35;O] | 18 GM | 60 ± CT | 1,8–2 | 60 | 9.1 | 15 | 63.8 | 8.4 | 123.8 | 5.3 | no > grade 2 | No necrosis |
| Pouratian *et al.* Gamma knife [36;O] | 26 GM | 60 | 2 | ~60 | n.a. | 17 | 80.8 | 21.3 | 140.8 | 9.4 | no significant toxicity | no necrosis |

EQD2 cumulative: 111Gy-150 Gy

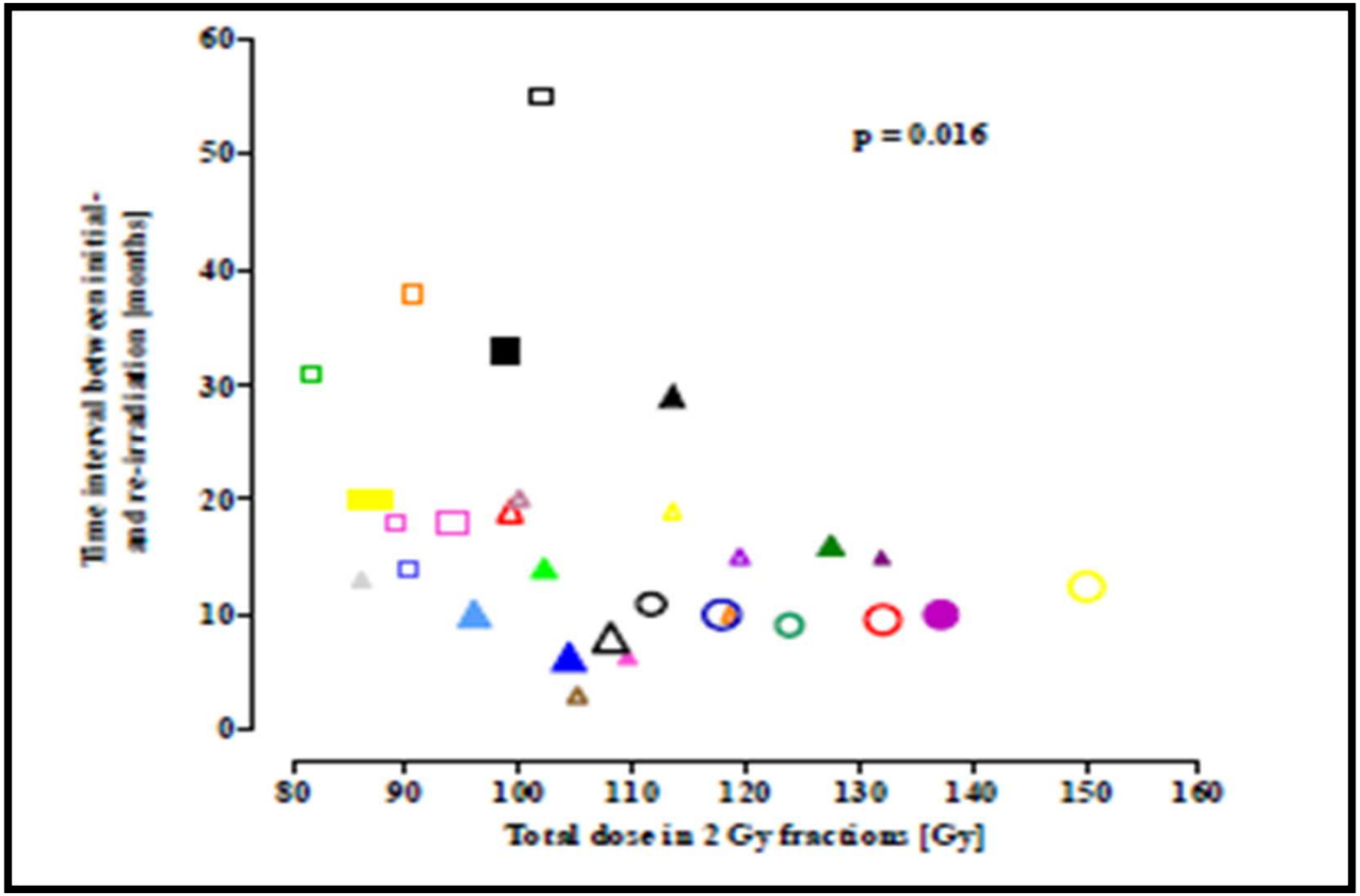
**How much does initial dose matter for one to reirradiate the brain again?**

# Correlation of the Initial dose and Re-irradiation dose



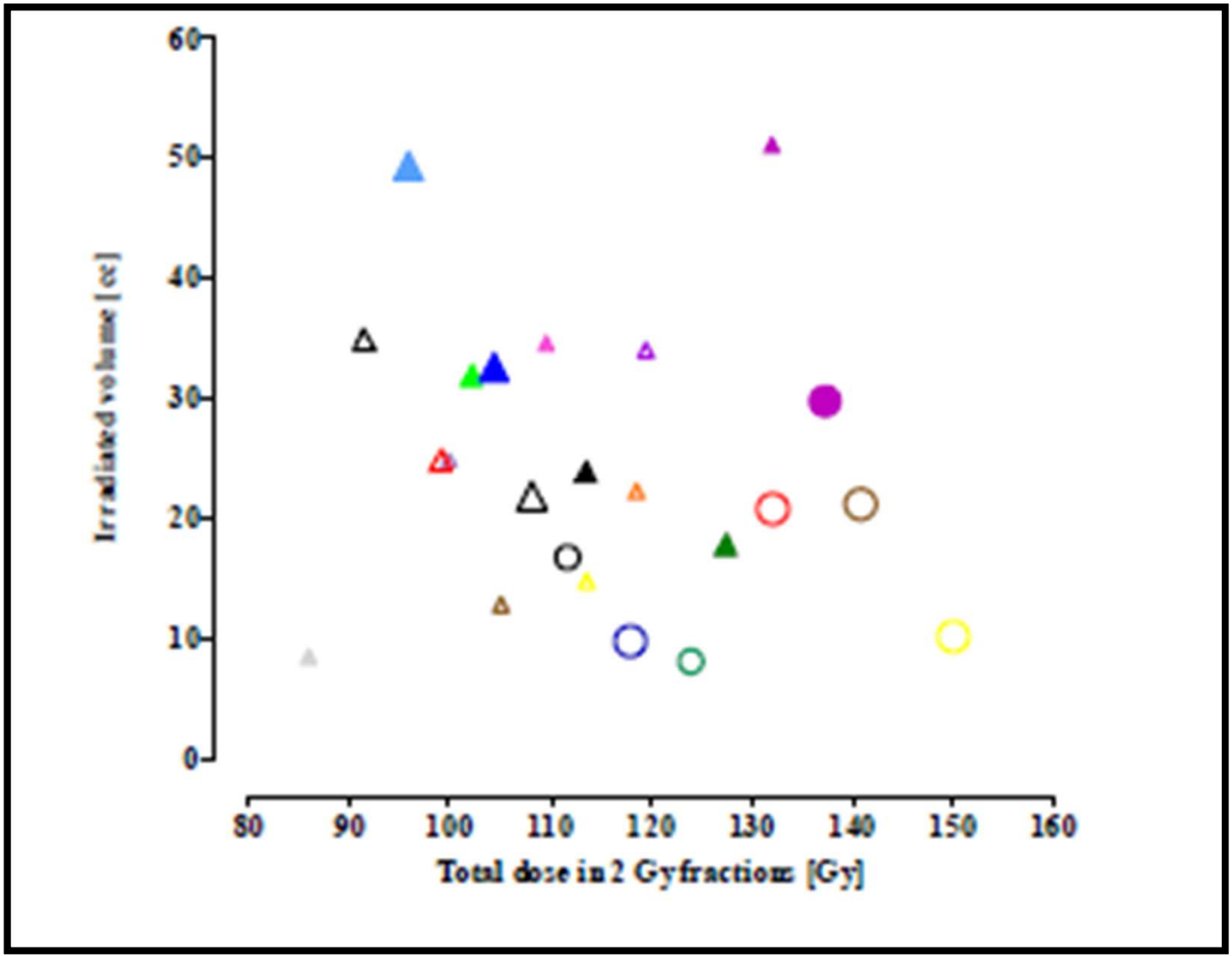
**How soon can one irradiate the brain again?**

# Inverse Correlation between time interval between two courses of irradiation and cumulative biological dose



# Does volume at Reirradiation matter?

# Significant inverse correlation between volume at reirradiation and cumulative biological dose



# Summary of Reirradiation tolerance of human brain

| Re-irradiation procedure | $EQD2_{cumulative}$ [Gy] | Time interval between initial radiotherapy and re-irradiation [months] | Mean treatment volume [cc] |
|---|---|---|---|
| Conventional radiotherapy | 92.6 ± 6.8 (81.6–102.8) | 29.9 ± 14.1 (14–55) | No data |
| Fractionated stereotactic radiotherapy | 109.9 ± 13.8 (86.1–133.9) | 16.7 ± 11.1 (3–48) | 27.6 ± 11.9 (8.7–51.1) |
| Stereotactic radiosurgery | 130.5 ± 13.5 (111.6 to ~150) | 10.4 ± 1.2 (9.1–12.5) | 16.9 ± 7.9 (8.4–30) |

***Sminia & Mayer 2012, eCancers 2012***

**Can you prognosticate reliably?**

VOLUME 23 · NUMBER 34 · DECEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Efficacy of Fractionated Stereotactic Reirradiation in Recurrent Gliomas: Long-Term Results in 172 Patients Treated in a Single Institution

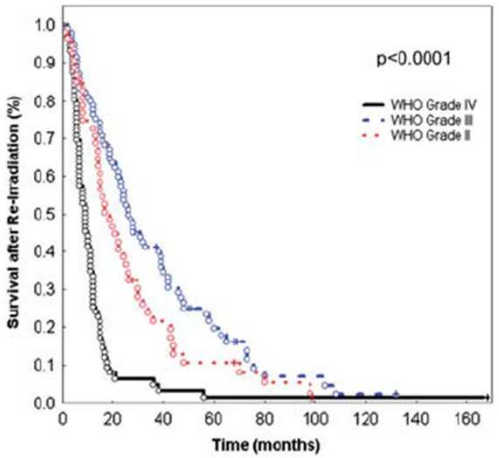
*Stephanie E. Combs, Christoph Thilmann, Lutz Edler, Jürgen Debus, and Daniela Schulz-Ertner*

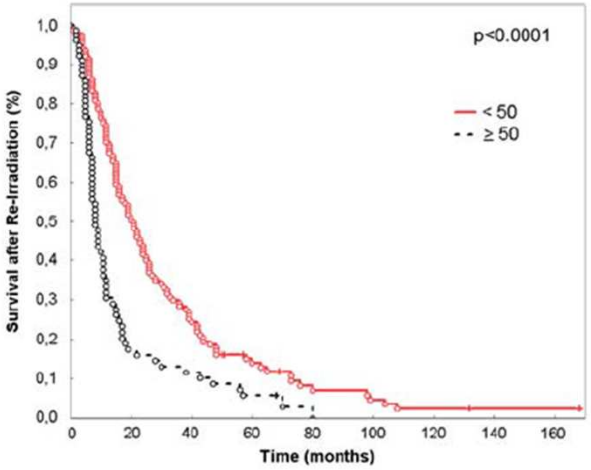
| CHARACTERISTIC | WHO GRADE II | WHO GRADE III | WHO GRADE IV (GBM) |
|---|---|---|---|
| No. of patients | 71 | 42 | 59 |
| Median age at primary diagnosis | 35 years | 39 years | 54 years |
| Histopathological diagnosis | -Astrocytoma : 57<br>-Oligoastrocytoma : 7<br>-Oligodendroglioma : 7 | -Astrocytoma : 24<br>-Oligoastrocytoma : 8<br>-Oligodendroglioma : 10 | GBM |
| Neurosurgical treatment at diagnosis<br>Total resection : 54 (31.4 %) Subtotal resection : 78 (45.3 %) -Biopsy : 40 (23.3 %) | | | |
| Median RT Dose received for primary RT : 60 Gy (conventional #) | | | |

# Results

| CHARACTERISTIC | WHO GRADE II | WHO GRADE III | WHO GRADE IV (GBM) |
|---|---|---|---|
| At final analysis : No. of patients alive : 22 No. of patients dead : 150 | | | |
| Median F / U after FSRT | 23 months | 13 months | 7 months |
| Median OS after primary diagnosis | 111 months | 50 months | 21 months |
| Median OS after re-RT | 22 months | 16 months | 8 months |
| PFS after Re-RT | 12 months | 8 months | 5 months |
| Toxicities after Re-RT :<br>- alopecia<br>- headaches<br>- nausea/vomiting<br>- skin erythema<br>- radiation-induced necrosis (1 patient) | | | |

# Heidelberg Prognostic Score for Reirradiation in Gliomas (N=233)



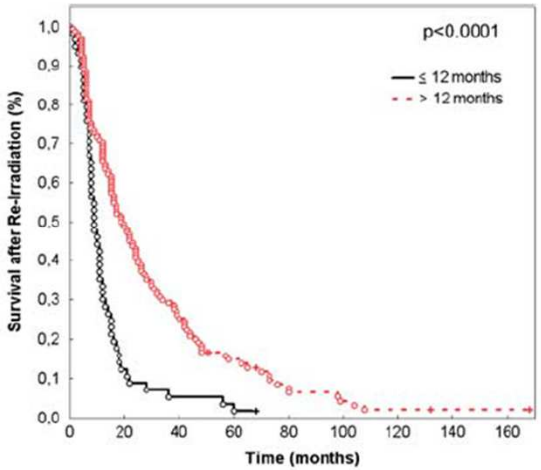
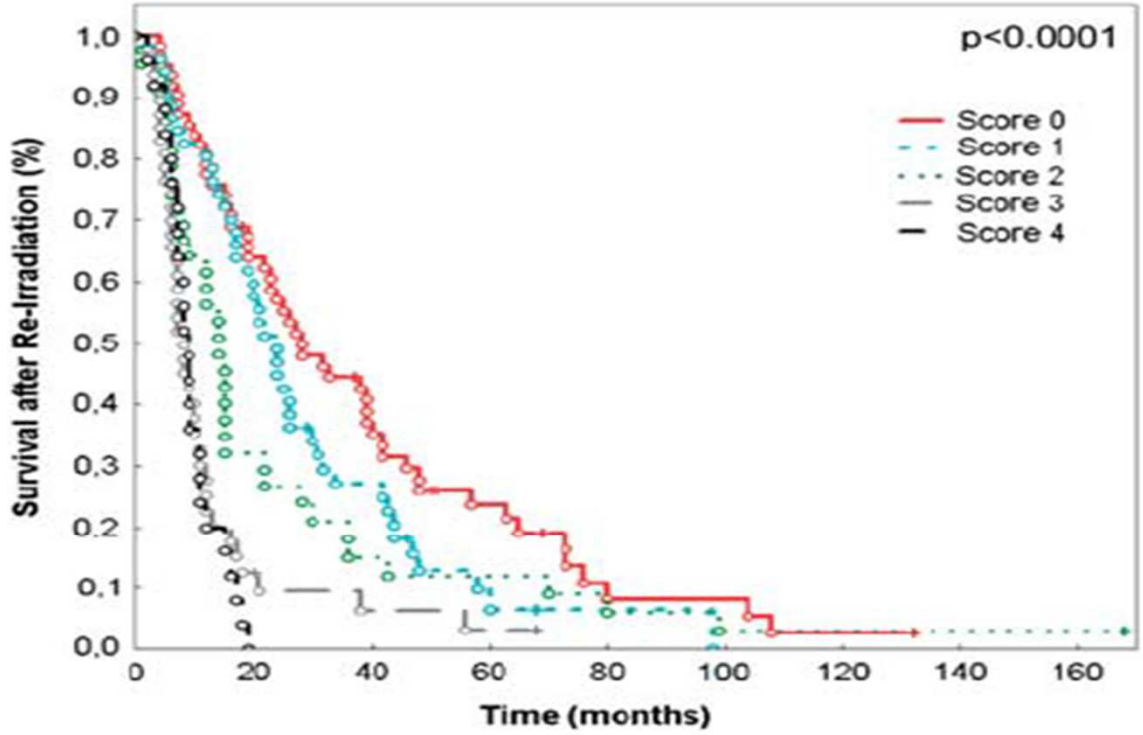




Table II. Factors identified as signficiantly influencing survival after re-irradiation used for the generation of the prognostic score.

| Prognostic factor | Subgroups | Value for prognostic score |
|---|---|---|
| Histology | WHO Grade IV | 2 |
| | WHO Grade III | 1 |
| | WHO Grade II | 0 |
| Age | < 50 years | 0 |
| | ≥ 50 years | 1 |
| Time betweeen RT and re-RT | ≤ 12 months | 1 |
| | > 12 months | 0 |

**Stephanie Combs; acta oncologica;2013**

# OS after reirradiation stratified by Heidelberg Score




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

*Stephanie Coombs et al, Acta Oncol 2013*

# Validation of the Heidelberg prognostic scoring system

No convincing correlation of the Heidelberg prognostic score with overall survival after reirradiation

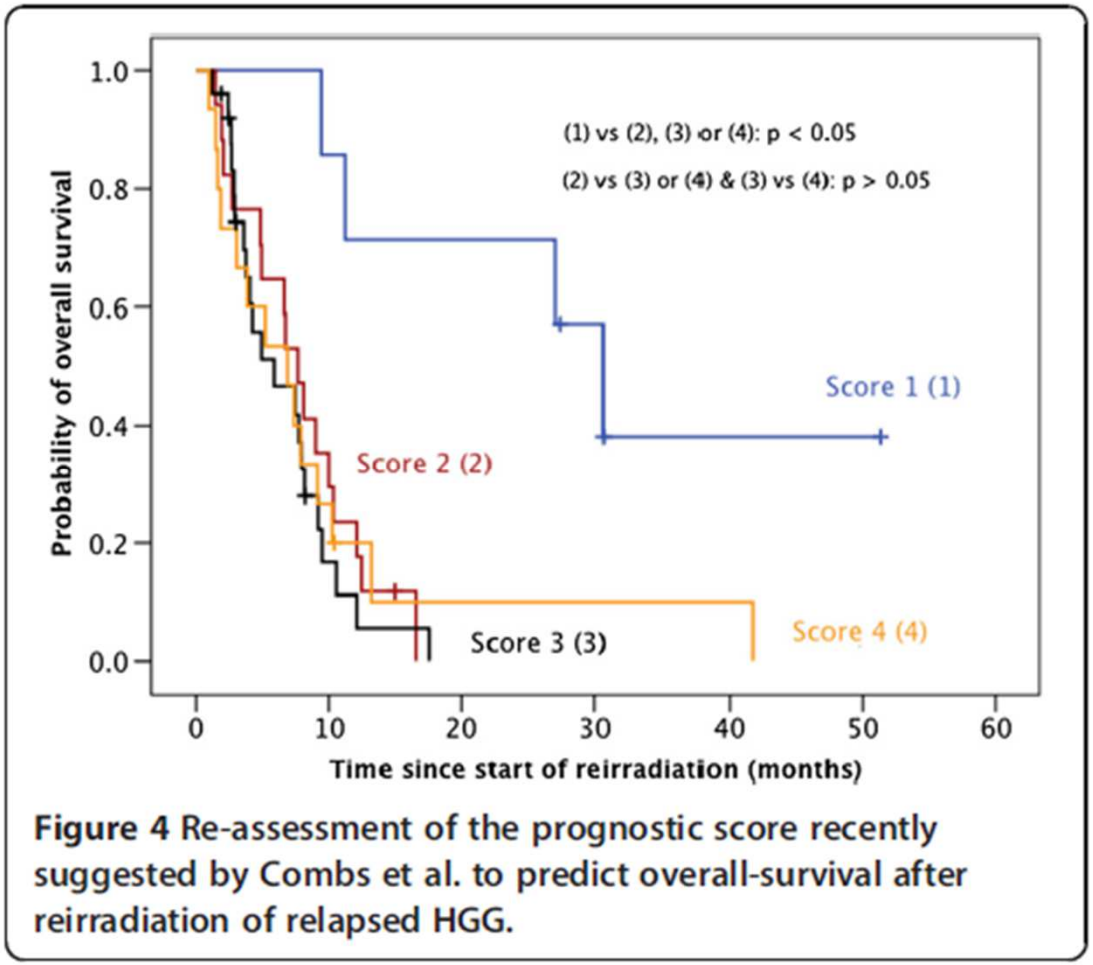



**Figure 4** Re-assessment of the prognostic score recently suggested by Combs et al. to predict overall-survival after reirradiation of relapsed HGG.

***Scholltyssek et al, Radiat Oncol 2013***

# What is the appropriate target volume?

# Guidelines for target volume delineation in patients with newly diagnosed glioblastoma

| Guideline | Phases and dose | GTV | CTV | PTV |
|---|---|---|---|---|
| **WHO grade IV glioma** | | | | |
| EORTC (from EORTC 22981/ 26981/NCIC CE.3) [3] | Single phase (60 Gy in 30 fractions) | Surgical cavity + T1 gd abnormality | CTV + 2–3 cm | Not stated |
| RTOG (from RTOG 0825) [12] | Phase 1 (46 Gy in 23 fractions) | GTV1 = surgical cavity + T1 gd abnormality + T2/FLAIR abnormality | CTV1 = GTV1 + 2 cm (if oedema present) or GTV1 + 2.5 cm (if no oedema) | PTV1 = CTV1 + 3–5 mm, depending on centre's reproducibility. |
| | Phase 2 (14 Gy in 7 fractions) | GTV2 = surgical cavity + T1 gd abnormality | CTV2 = GTV2 + 2 cm | PTV2 = CTV2 + 3–5 mm |

***Cannot be applied blindly for reirradiation***

**TRUTH is that we do not really KNOW**

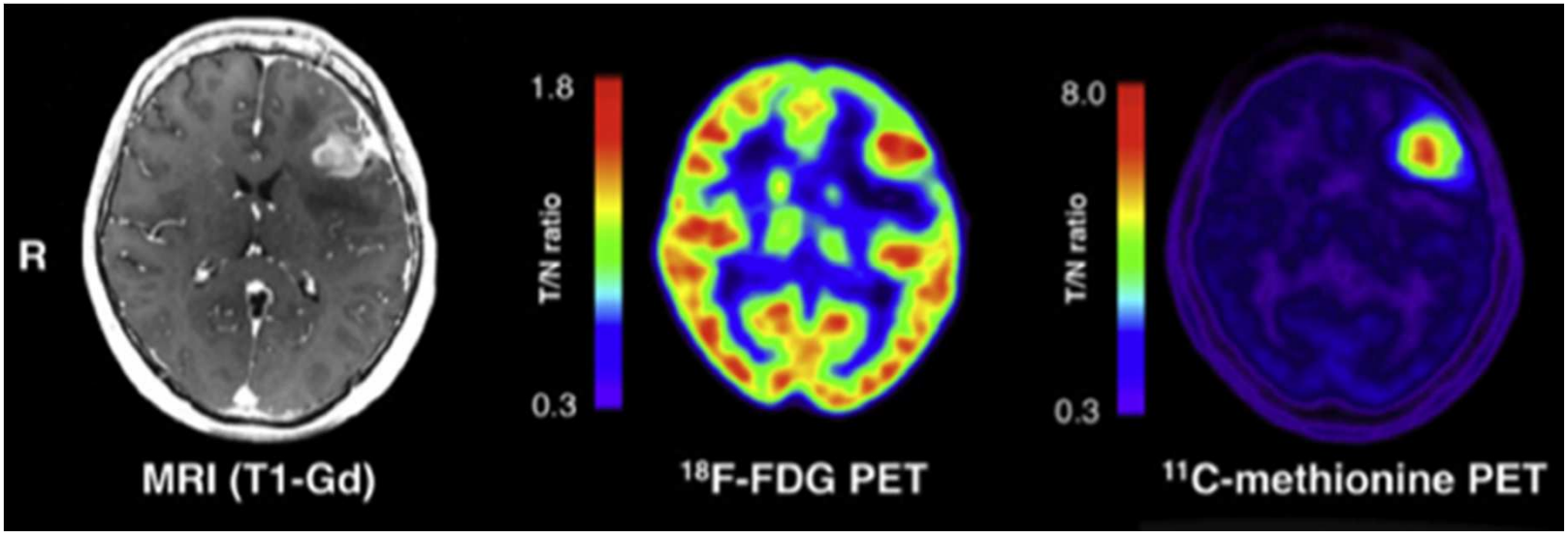
## Personal philosophy: be conservative (but not overly)

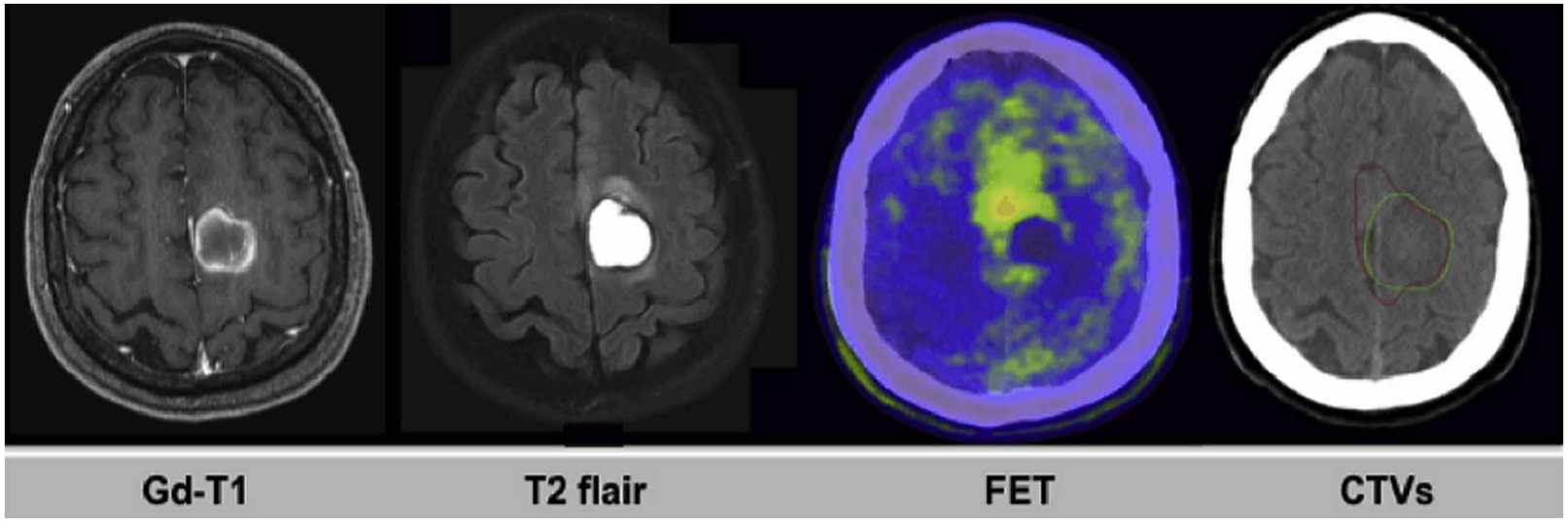
- GTV = Gross infiltrative tumor + resection cavity (2$^{nd}$ surgery)
- CTV = GTV + 1-1.5cm (3D-isotropic expansion)
- Edit away CTV from natural anatomic barriers (bone, falx)
- Expand CTV where difficult to distinguish from edema/gliosis
- PTV = CTV + 2-5mm (technique & institutional set-up)
- In SRS, CTV margins do not apply (GTV = CTV)

**Does advance imaging help define/refine target volumes?**

**Role of functional imaging**

# Amino Acid PET can improve target volume delineation



# DTI predicts pattern of Recurrence

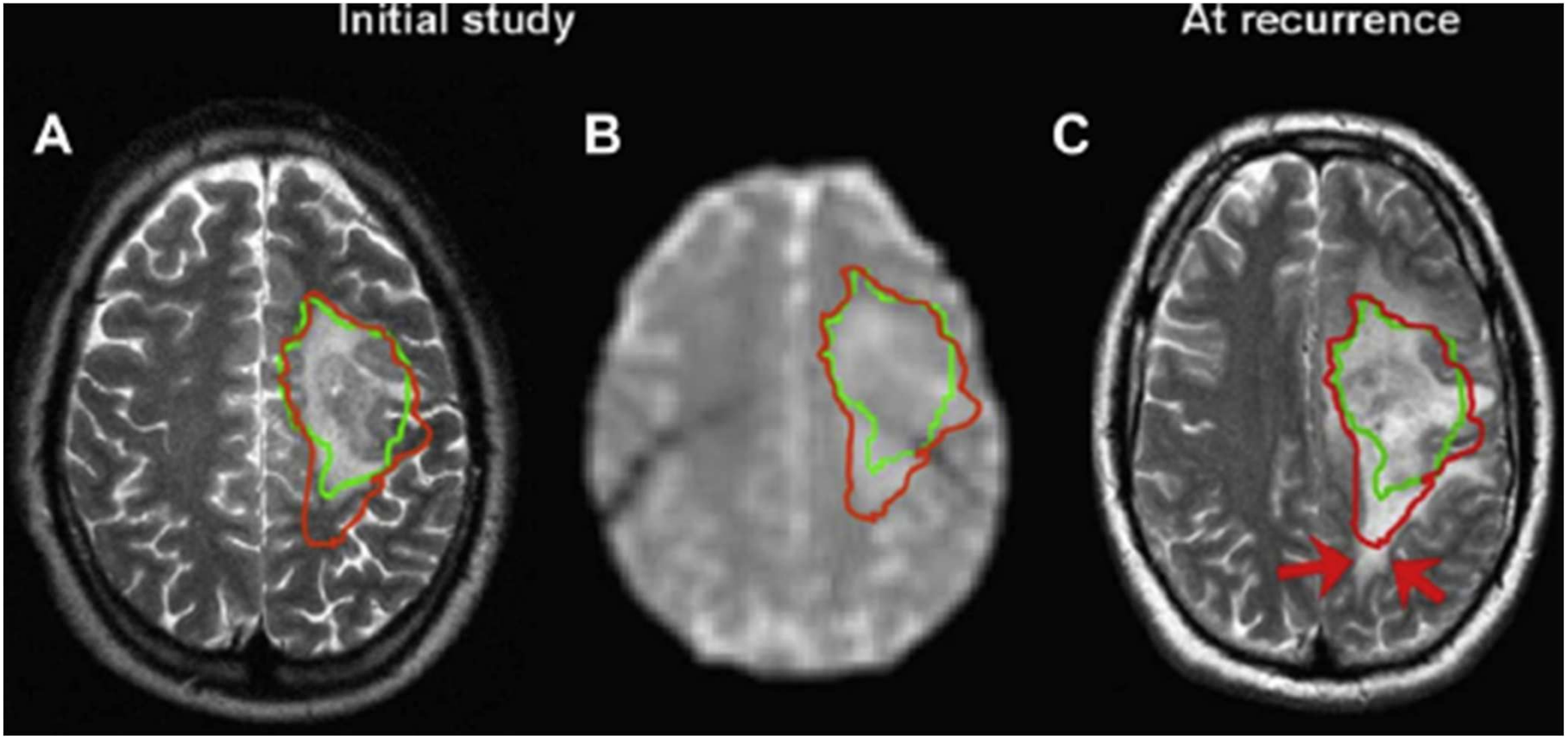



**Fig 1.** An example of the use of diffusion tensor imaging (DTI) to predict patterns of recurrence. This patient with a glioblastoma developed localised recurrence whose position was predicted by the DTI. The images show a T2-weighted image of the tumour before radiotherapy (A), a map of the isotropic component of the DTI carried out at the same time (B) and a T2-weighted image carried out after tumour progression (C). These images have been co-registered with the isotropic (green) and anisotropic (red) tensor abnormalities. There is a mismatch posteriorly where the anisotropic abnormality is greater than the isotropic abnormality. Imaging showed recurrence with a localised growth pattern in this

***Whitfield et al, Clin Oncol 2014***

# How best to integrate systemic therapies?

# Before, After, or Concurrently?
# Personal Philosophy

## *ChemoRx-naïve patient (transformed from an erstwhile LGG)*

- Give 6-12 cycles of monthly temozolomide as salvage to defer ReRT
- Follow-up with concurrent temozolomide during ReRT
- In patients with known 1p/19q deletion, PCV may be offered instead of TMZ

## *Patient progressed after prior chemoRx (either PCV/TMZ)*

- <6 months from last exposure to chemoRx: Not much rationale of chemoRx
- 6-12 months from last exposure to chemoRx: Value judgement
- >12 months from last exposure to chemoRx: Rechallenge with chemoRx

## *Bevacizumab-naïve patient (but received multiple chemoRx)*

- Consider ReRT with concurrent bevacizumab followed by maintenance Rx

## *Patient progressed after prior chemoRx + Bevacizumab*

- Enter patient into a clinical trial (either IND or combining IND + ReRT)

# What happens when bevacizumab is combined with reirradiation?

**Table 2 Univariate analysis (log-rank test/Cox regression), influence on post-recurrence survival (PRS) and post-recurrence progression-free survival (PR-PFS)**

| Variable | Univariate p-value PRS/PR-PFS |
|---|---|
| Age (< 50 y, ≥ 50 y) | ns (p = 0.717)/ns (p = 0.854) |
| KPS (< 70, ≥ 70) | ns (p = 0.156)/ns (p = 0.095) |
| MGMT (meth/not meth) | ns (p = 0.897)/ns (p = 0.711) |
| Initial WHO grade (II/III/IV) | ns (p = 0.996)/ns (p = 0.922) |
| Bevacizumab (no/yes) | p = 0.027/ns (p = 0.396) |
| Adjuvant/Salvage chemotherapy (no/yes) | ns (p = 0.108)/ns (p = 0.054) |
| Sex (male/female) | ns (p = 0.410)/ns (p = 0.304) |
| Time interval (≤ 12 y, > 12 y) | ns (p = 0.672)/ns (p = 0.349) |

**Table 3 Outcome data concerning PRS stratified by the Heidelberg score; subgroups with and without bevacizumab are shown**

| Heidelberg score/group | Entire cohort, PRS [months] | Bevacizumab, PRS [months] | No bevacizumab, PRS [months] |
|---|---|---|---|
| Excellent | 7 | 7 | – |
| Good | 7 | 8 | 2 |
| Moderate | 9 | 9 | – |
| Poor | 7 | 8 | 6 |
| P-value | ns (p = 0.664) | ns (p = 508) | ns (p = 0.316) |

A "poor" score consists of patients with score values of 3 or 4.

***The applicability and validity of Heidelberg Prognostic Score becomes suspect with addition of bevacizumab to reirradiation***

***Niyazi et al, Radiat Oncol 2014***

# First ever randomized controlled trial involving re-irradiation in gliomas

- APG101: i.v. CD95 ligand-binding fusion protein and synergistic activity with RT
- 84 Recurrent GB patients
- RT vs. RT+APG
- OS: no difference (11.5 m)
- CD95: negative prognostic biomarker

*Wick et al, ECCO 2013 & ASCO 2014*

# How to select patients appropriately for reirradiation?

# Case selection for reirradiation in brain tumors

- Age: Younger patients (<50 years) likely to do better
- Performance status: KPS>60 (at least) or NPS <2 (at worst)
- Location: Preferably away from deep or eloquent brain structures
- Spread: No leptomeningeal or ependymal dissemination
- Size: Should preferably be small volume (limited to one side)
- Morphology: Circumscribed & not very diffusely infiltrating

**Need to select favorable subset for improved outcomes**

# Reirradiation in ependymoma

- Retrospective analysis from St Jude Children's Research Hospital

- 38 children with localized ependymoma at initial diagnosis

Median time to failure after 1$^{st}$ course of RT: 19 mths (range 3-73 mths)

- ReRT for local (n=21), metastatic (n=13), or combined failure (n=4)

- Median age of study cohort at reirradiation: 4.8 yrs (range 2-16.9 yrs)

- Median interval between both courses of RT: 21.9 mths (range 7.5-67.7 mths)

- ReRT included CSI (n=19), focal fractionated RT (n=13), or SRS (n=6)

# Disease outcomes after reirradiation

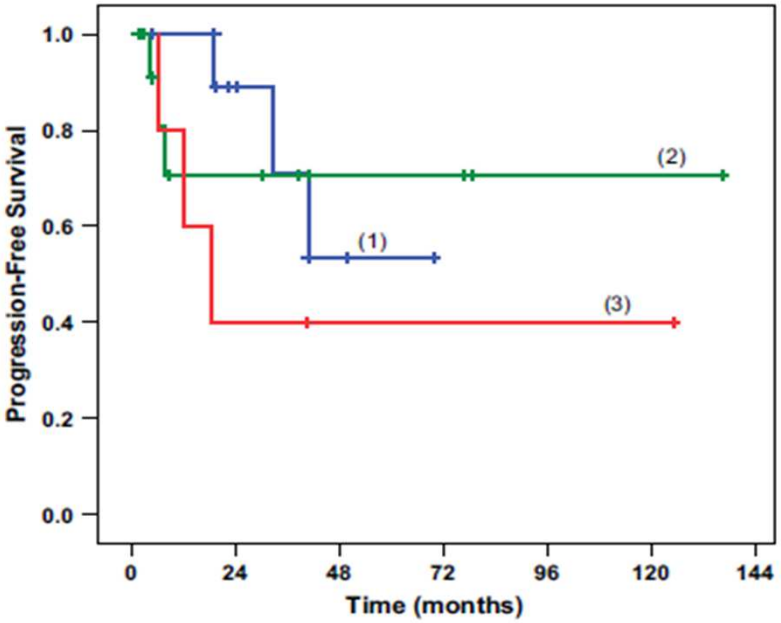



Fig. 4. Progression-free survival after reirradiation according to treatment method and initial tumor pattern failure (blue (1) = 12 patients with metastatic failure treated with craniospinal reirradiation; green (2) = 13 patients with local failure retreated with focal fractionated irradiation; red (3) = 5 patients with local failure treated with radiosurgery).

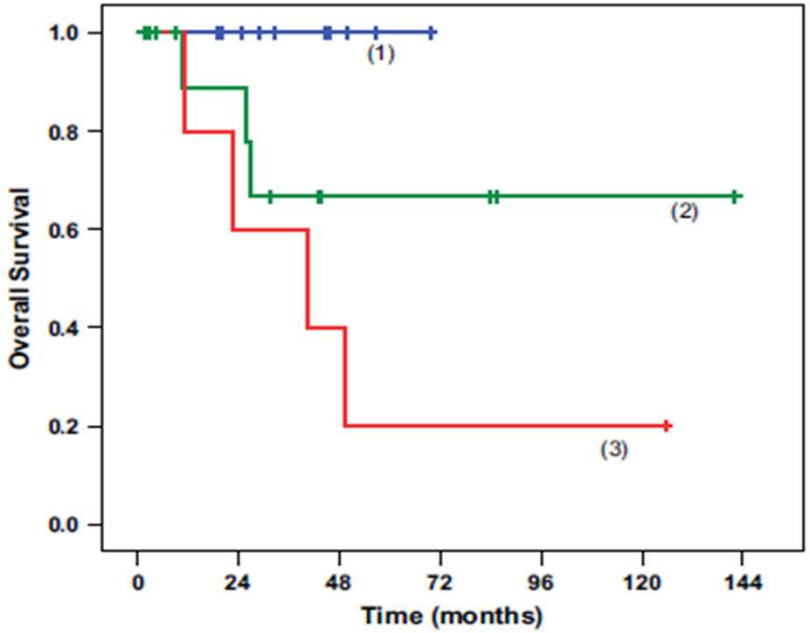



Fig. 5. Overall survival dated from the start of reirradiation according to treatment method and initial tumor pattern failure (blue (1) = 12 patients with initial metastatic failure treated with craniospinal reirradiation; green (2) = 13 patients with local failure retreated with focal fractionated irradiation; red (3) = 5 patients with local failure treated with radiosurgery).

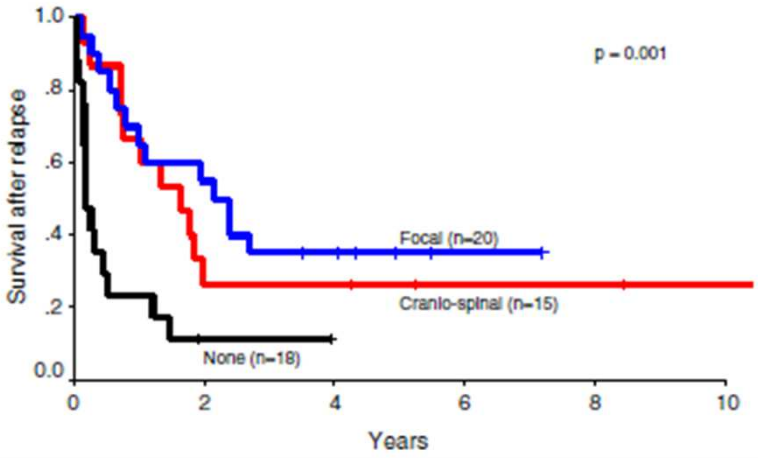
**Conclusion: Patients with locally recurrent EP experience durable local tumor control, but remain at risk of metastasis. Patients with metastatic EP failure may receive salvage therapy that includes a component of CSI. Durability of disease control and long-term effects from this approach require further follow-up.** 

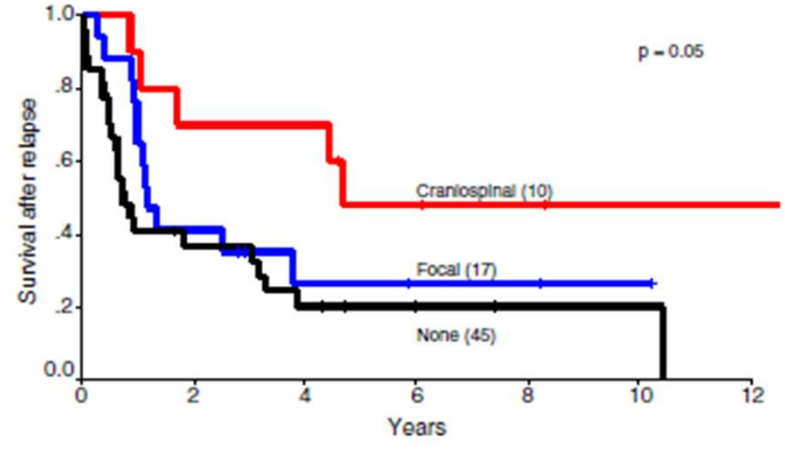
***Merchant et al, IJROBP 2008***

# Relapsed intracranial ependymoma in children in the UK: Patterns of relapse, survival and therapeutic outcome

**Table 2 – Site of relapse in Groups A and B.**

| | Group A | Group B | Total |
|---|---|---|---|
| Local | 44 | 37 | 81 (75%) |
| Local + other sites in CNS | 3 | 7 | 10 (9%) |
| Spine with no local relapse | 2 | 3 | 5 (5%) |
| Other CNS site–no local relapse | 5 | 7 | 12 (11%) |

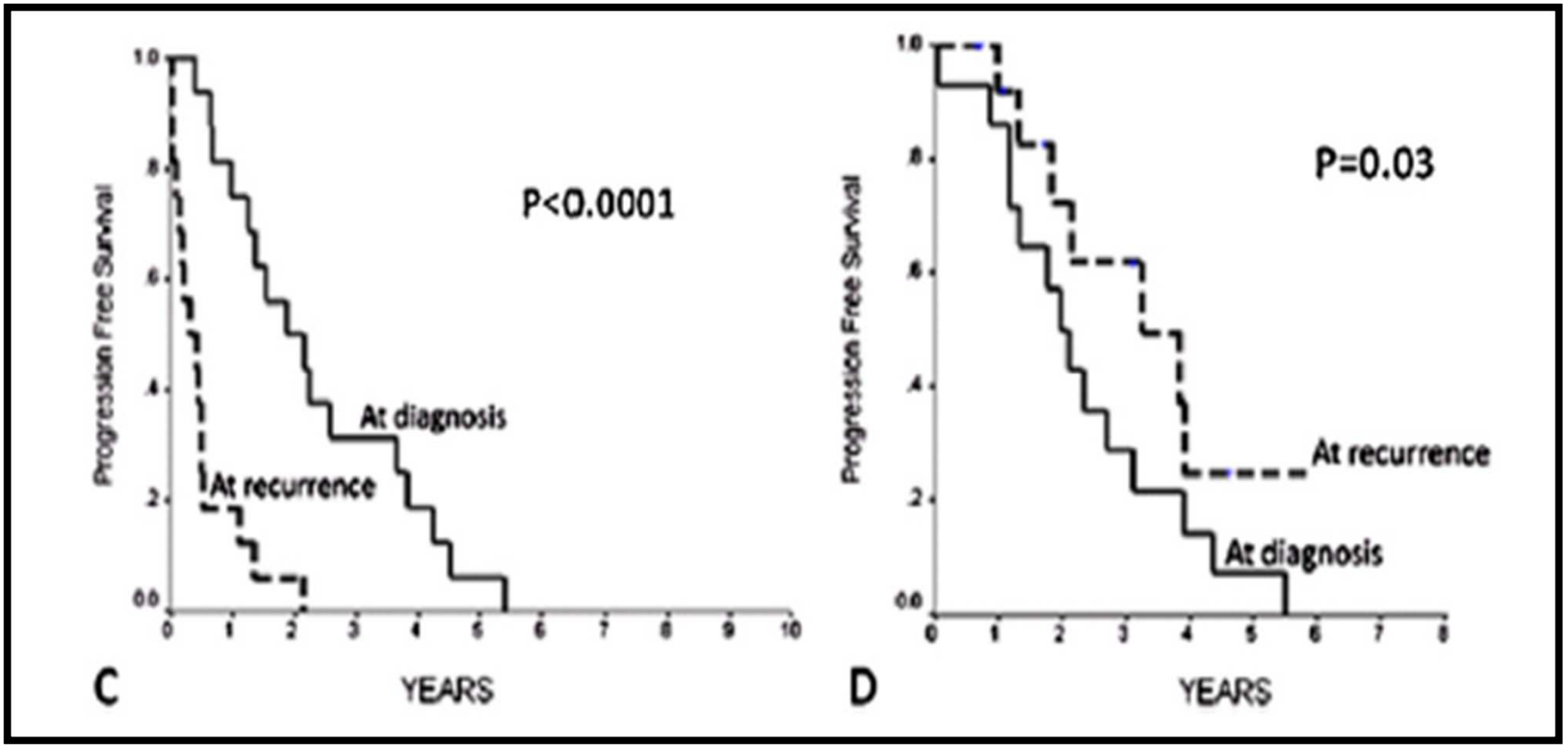



Relapse was associated with poor outcome in both age groups. A survival advantage conferred by both radiotherapy and surgery at relapse is independently significant.

***Messahel et al, EJC 2009***

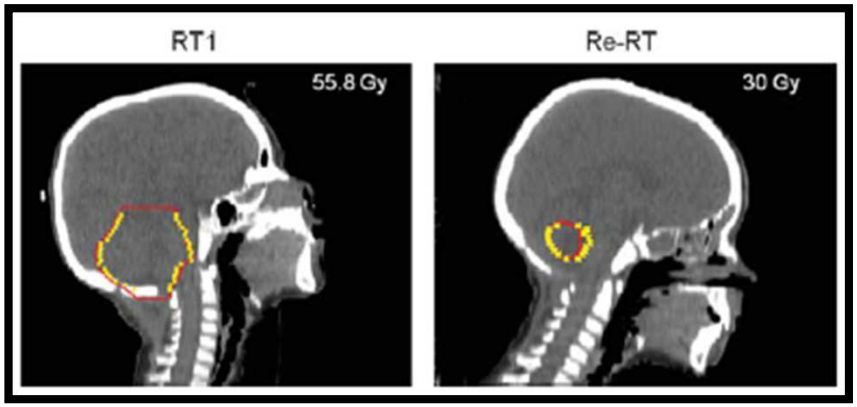
# Significant survival benefit of reirradiation in ependymoma




**Conclusions:** Reirradiation is an effective treatment that may change the natural history of recurrent ependymoma in children. However, this change may be associated with increased neurocognitive toxicity. Additional follow-up is needed to determine the risk of late recurrence, secondary radiation-induced tumors, and long-term functional outcome of these patients.

***Bouffet et al, IJROBP 2012***

# Reirradiation in Medulloblastoma




- 13 children treated with ReRT
- Sx and/or CTh at relapse in all
- Median time RT1 to RT2: 57 mths
- ReRT included local, spinal, & CSI
- Median ReRT dose: 30Gy (19.8-45Gy)
- Median # size: 1.5Gy (1-1.8Gy)
- Median Cum Dose: 84Gy (65-98.4Gy)
- Median FU: 30 mths (1-176 mths)

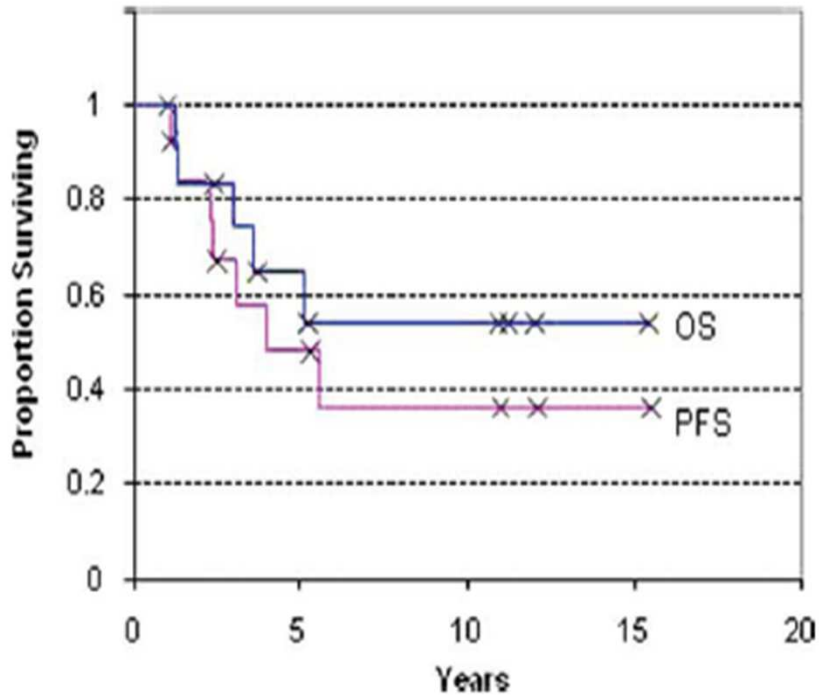



**Figure 2.** Progression-free survival (PFS) and overall survival (OS) since time of initial recurrence are shown.

***Bakst et al, Cancer 2011***

**TABLE 3.** Major Toxicities Observed in Relapsed Medulloblastoma Patients According to the Use of Irradiation

| Toxicity | Nonirradiated Patients and Toxicity (%) | Irradiated Patients and Toxicity (%) | *P* |
|---|---|---|---|
| Hemorrhage (grade 1) | 15/24 (62.5%) | 9/14 (64.3%) | 1.00 |
| Hypopituitarism | 8/24 (33.3%) | 8/14 (57.1%) | .187 |
| Necrosis (grades 1, 2) | 7/24 (29.2%) | 9/14 (64.3%) | .047 |
| Hypothyroidism | 7/24 (29.2%) | 7/14 (50.0%) | .298 |

**CONCLUSIONS:** The use of irradiation as a component of salvage therapy for relapsed MB may prolong survival.

***Wetmore et al, Cancer 2014***

# Our own experience of reirradiation in brain tumors

- More than 100 patients treated with re-irradiation since 2008
- Histology includes high-grade glioma, ependymoma, medulloblastoma, others
- Image-guided IMRT (mostly tomotherapy) used for reirradiation
- CFRT used in vast majority (≈95%); occasionally (≈5%) HFRT for CSI as reirradiation
- Doses range from 36-55.8Gy; minimum 2-year interval from 1$^{st}$ course of irradiation
- Most gliomas received concurrent TMZ in addition to neoadjuvant or adjuvant TMZ
- Few patients have received bevacizumab with reirradiation (in recent times)
- ReRT generally well tolerated, but few patients developed symptomatic necrosis

**Ongoing prospective study evaluating QOL in patients being treated with reirradiation as part of MD Dissertation**

## In summary: is there a magic formula?

- Select cases appropriately for reirradiation (age, KPS, histology)
- Keep cumulative biological doses <100Gy EQD2
- Have atleast 12 months interval between primary RT and re RT
- Avail functional/metabolic imaging  to refine target volumes
- Use modern technology to reduce volume of reirradiation
- Add systemic therapies judiciously to/with reirradiation

**The simple answer is NO**

# *Thank You*