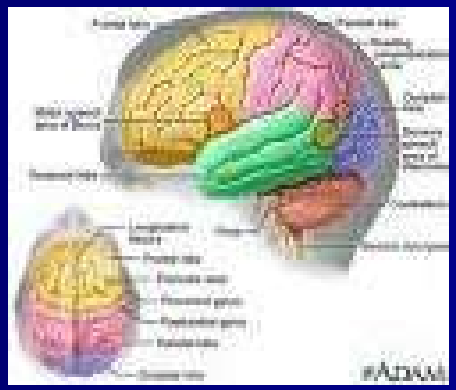
Concurrent Chemoradiotherapy in CNS tumors – Guidelines and Evidence



Dr. R. K. Vyas

Deputy Director and HOD

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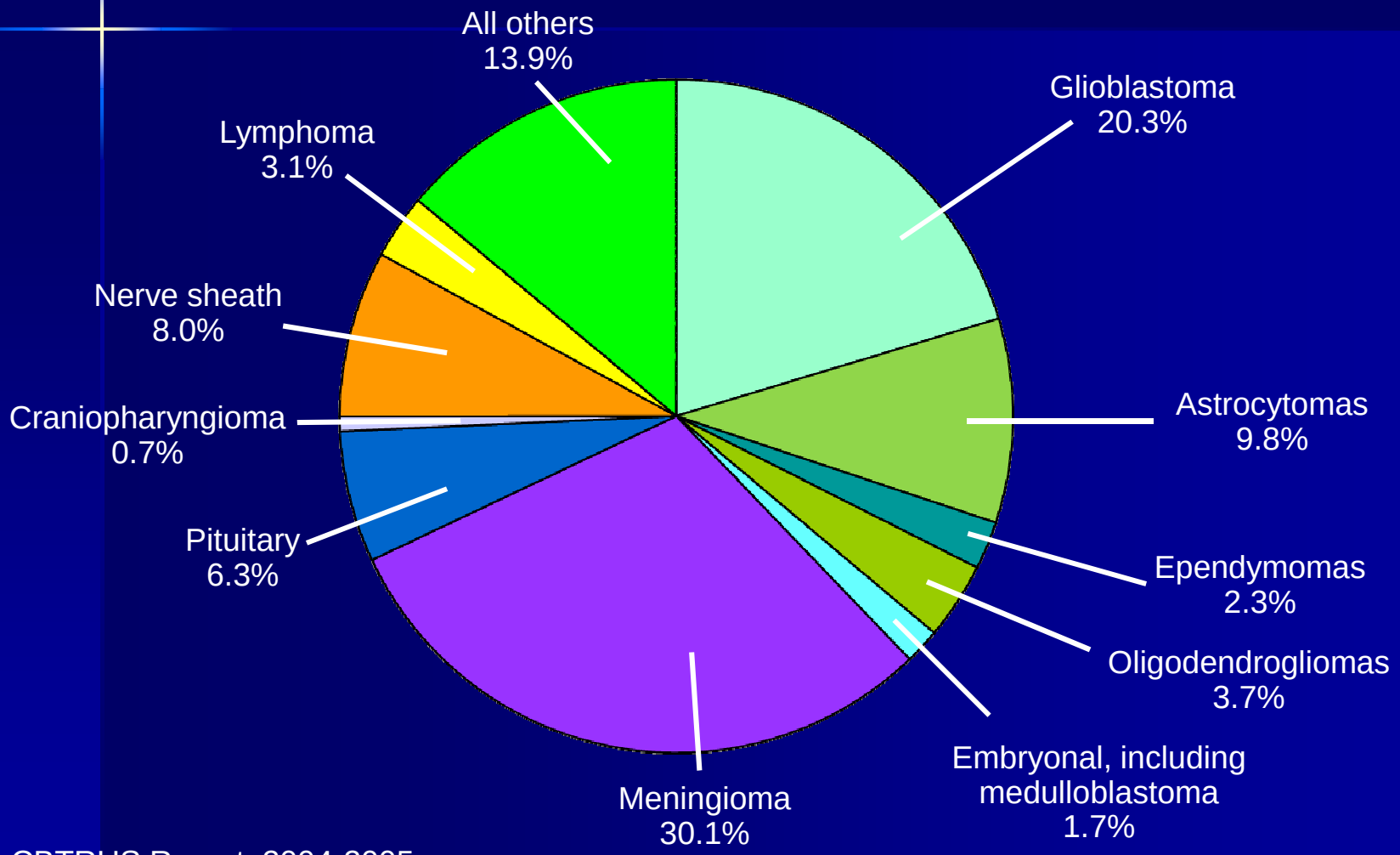
Gujarat Cancer & Research Institute, Ahmedabad

Distribution of primary CNS Tumors by Histology



CBTRUS Report, 2004-2005.

Prognostic Classification

- WHO classification system
  - Released in 1993; updated in 2007
  - Tumors classified by cell origin and level of aggression (grades 1-4)[1,2]

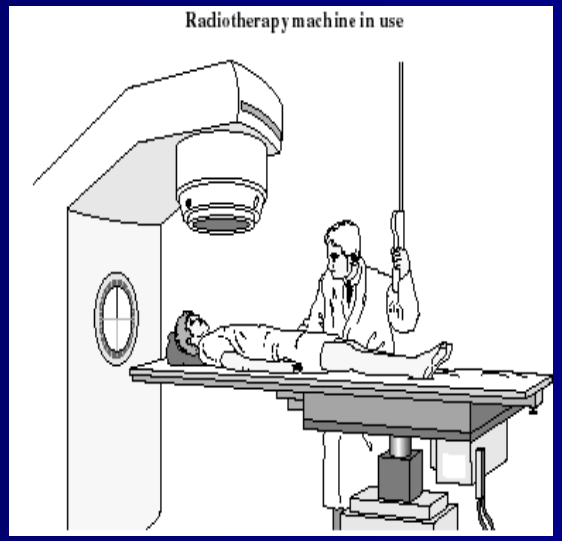
Grade	Histology	Median Survival, Yrs[2]
1	Pilocytic astrocytoma	>10
2	Well-differentiated astrocytoma	>5
3	Anaplastic astrocytoma	3
4	Glioblastoma multiforme	1

1. Wen PY, et al. N Engl J Med. 2008;359:492-507.
2. DeAngelis LM. N Engl J Med. 2001;344:114-123.

Treatment Modalities

Surgery

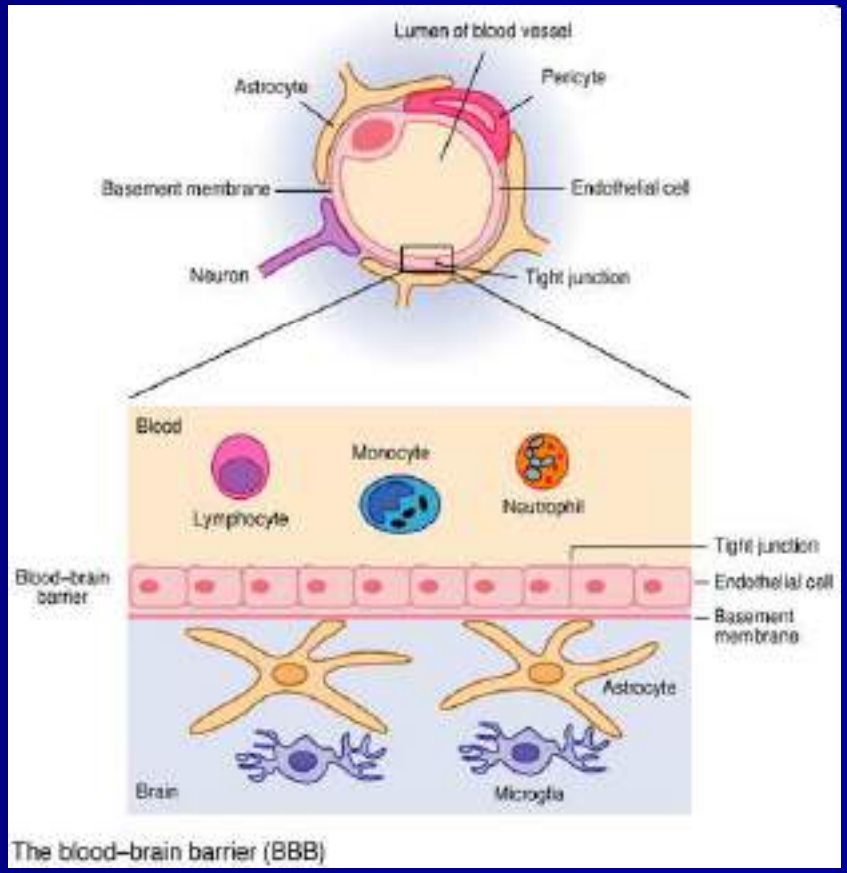
Radiotherapy



Chemotherapy

Challenges to treatment

- Biologically aggressive
- Drug delivery
  - Blood brain barrier
- Toxicity to normal brain
- Infiltration of malignant cells into brain parenchyma



The blood–brain barrier (BBB)

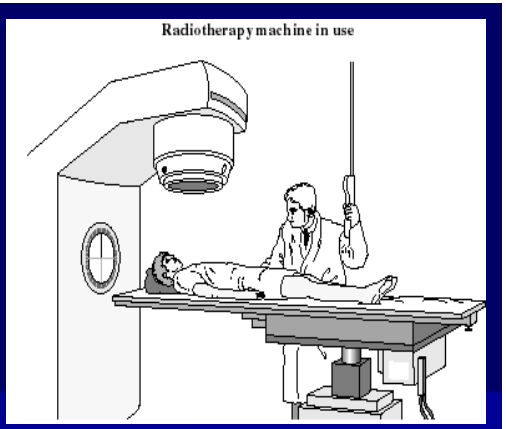
A bit of history..

- Surgery and radiation mainstays of treatment (and still are)
- Chemotherapy options
  - PCV standard of care for many years
    - **P**rocarbazine
    - **C**armustine (BCNU)
    - **V**incristine
      - Significant side effects
  - Single agent nitrosurea (lomustine/carmustine) equivalent

Types of Surgery

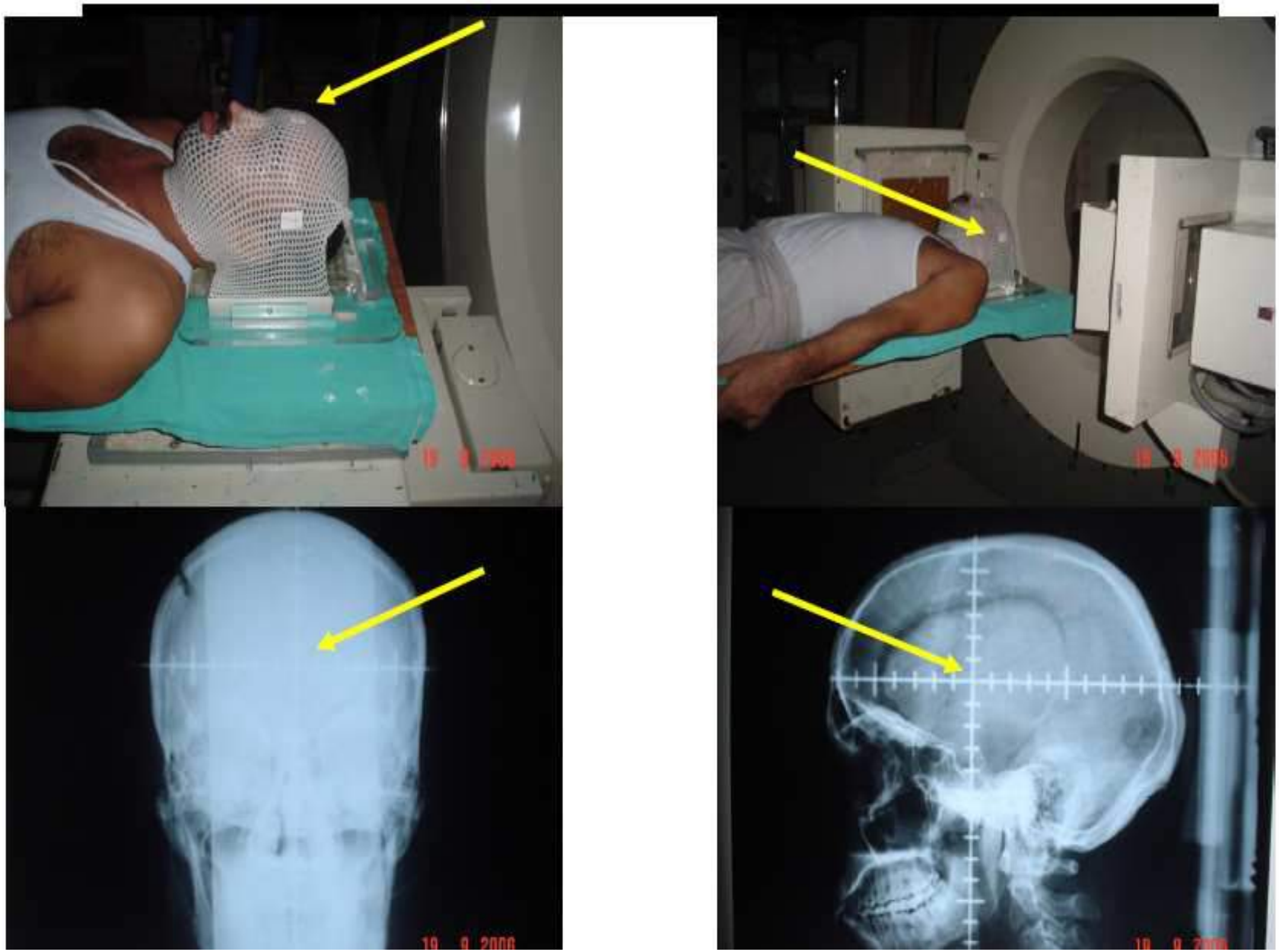
Complete Resection
Near Total Resection
Subtotal Resection
Debulking
Biopsy only
No Biopsy

Radiotherapy :

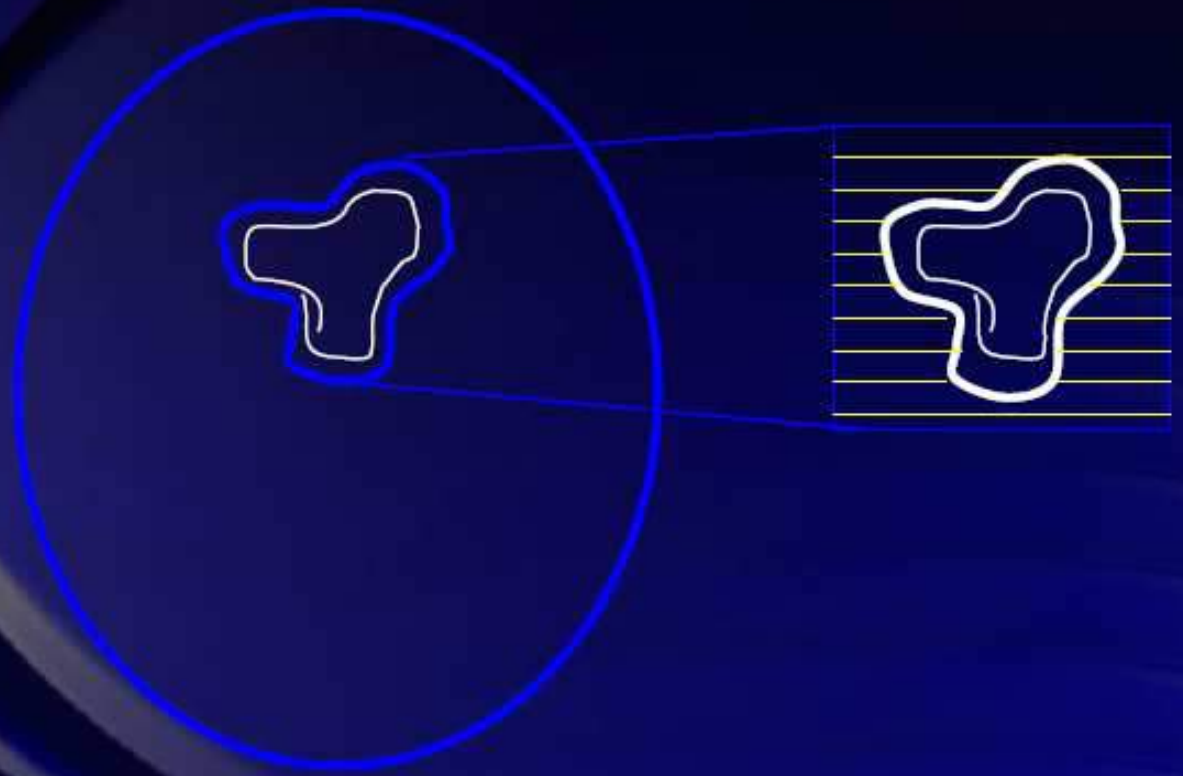


- Curative (PORT) : Low grade, High grade Gliomas, Ependymomas
- Paediatric tumors: Medulloblastoma
- SRT & SRS
- Intracranial Brachytherapy
- Palliative Radiotherapy

Conventional orthogonal plain film planning

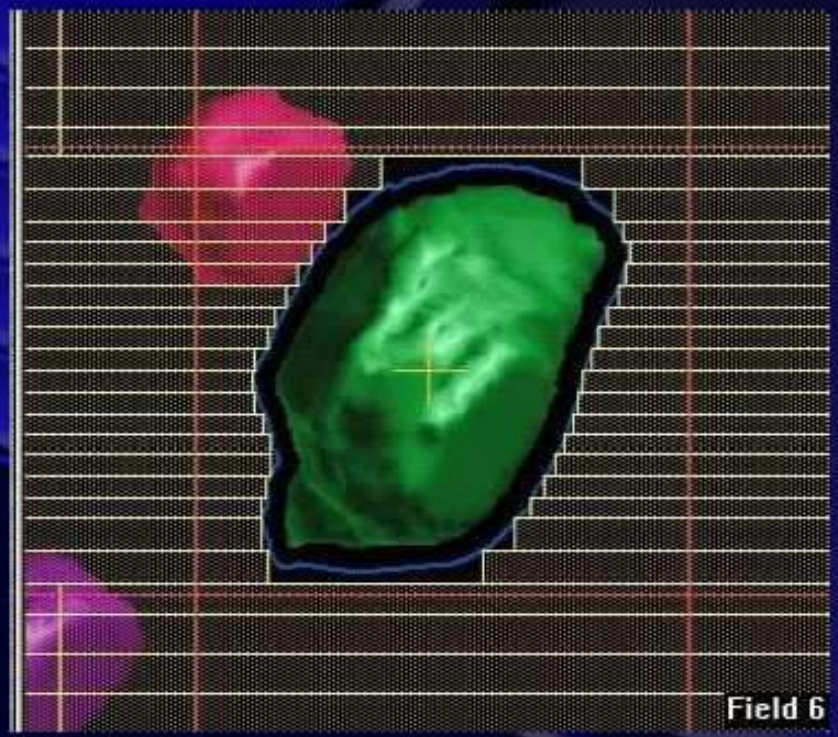


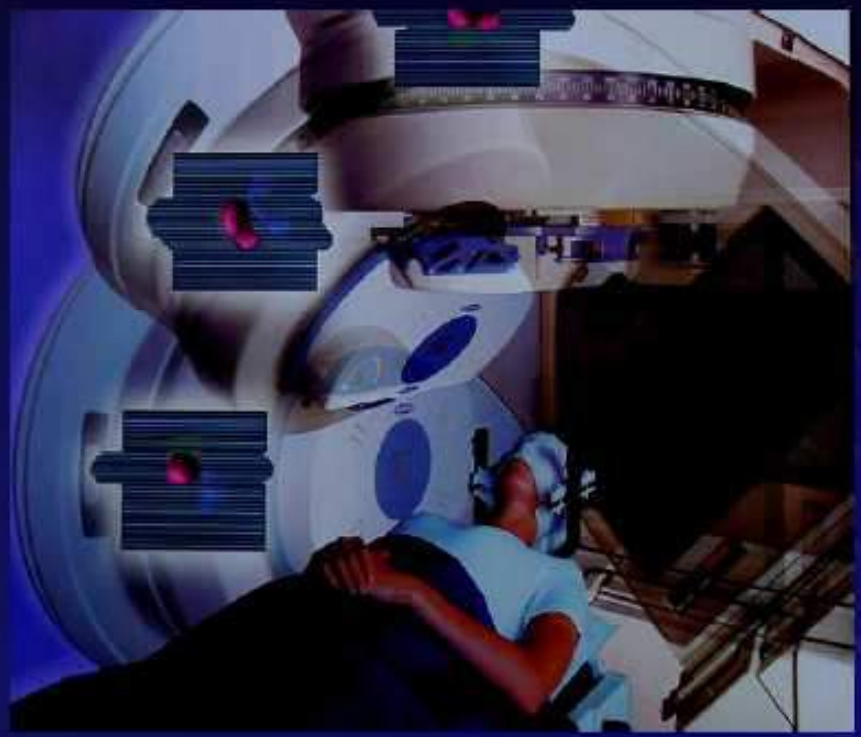
Conformal Radiotherapy



Excellent conformation

Multileaf collimators (MLC)





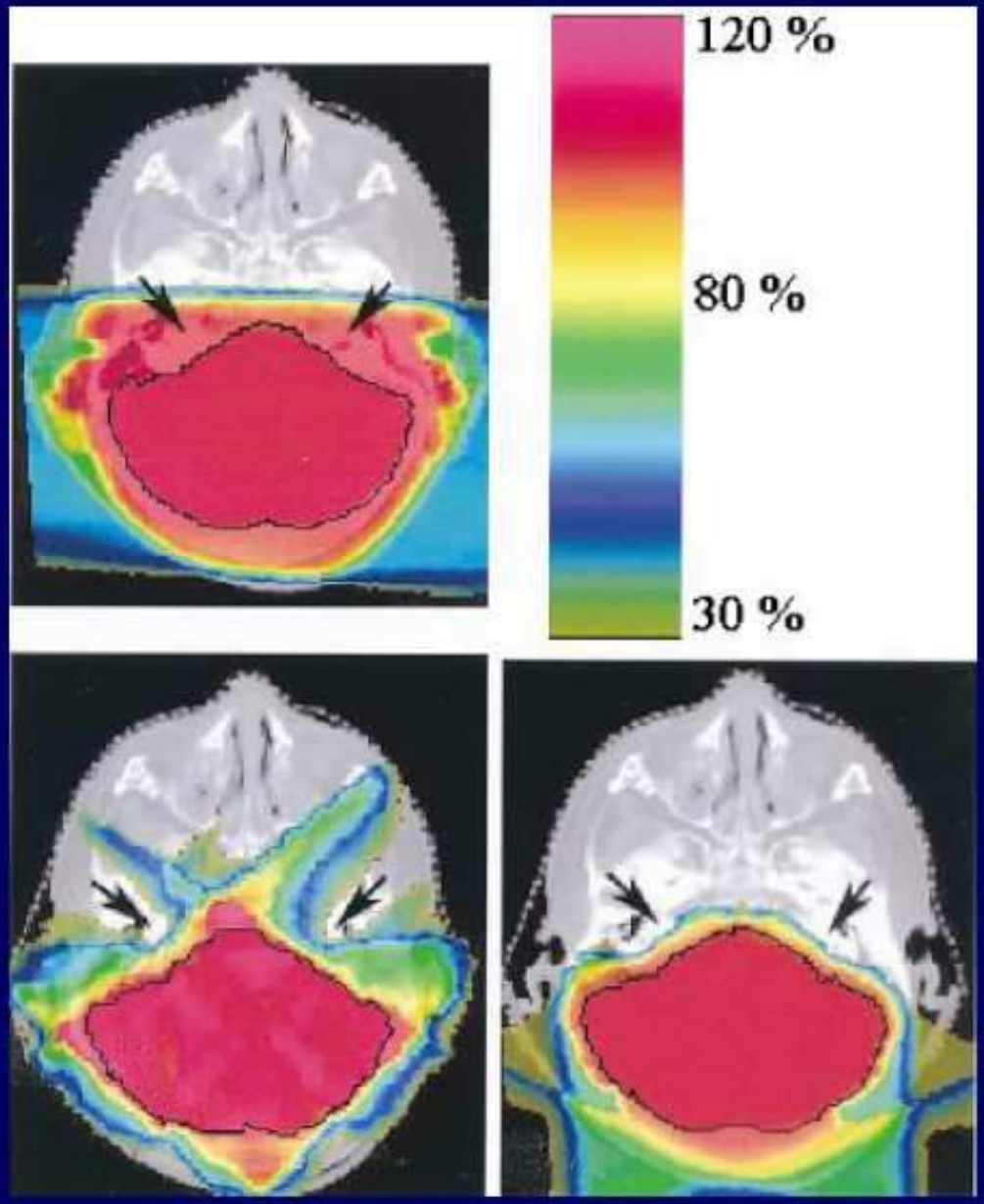
Stereotactic Radiation

- Radiosurgery
- SRT
- Stereotactic IMRT

Proton Beam Therapy: The ultimate in conformal therapy *(St Clair, IJROBP '04)*

Conventional

Bilateral Photons



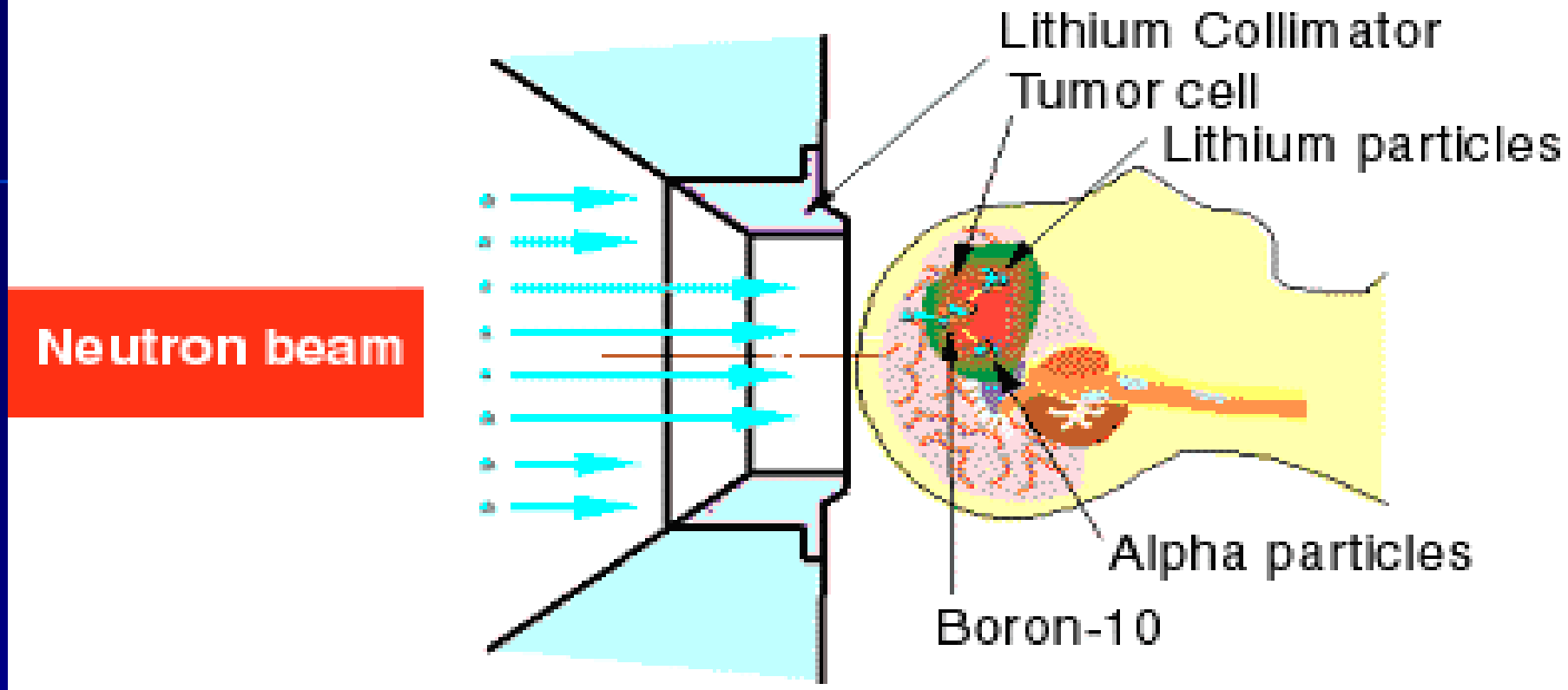
Dose to Cochlea, Pituitary Hypoth. axis etc significantly less with Protons

IMRT Photons

3 Field

PROTONS

Boron Neutron Capture Theory



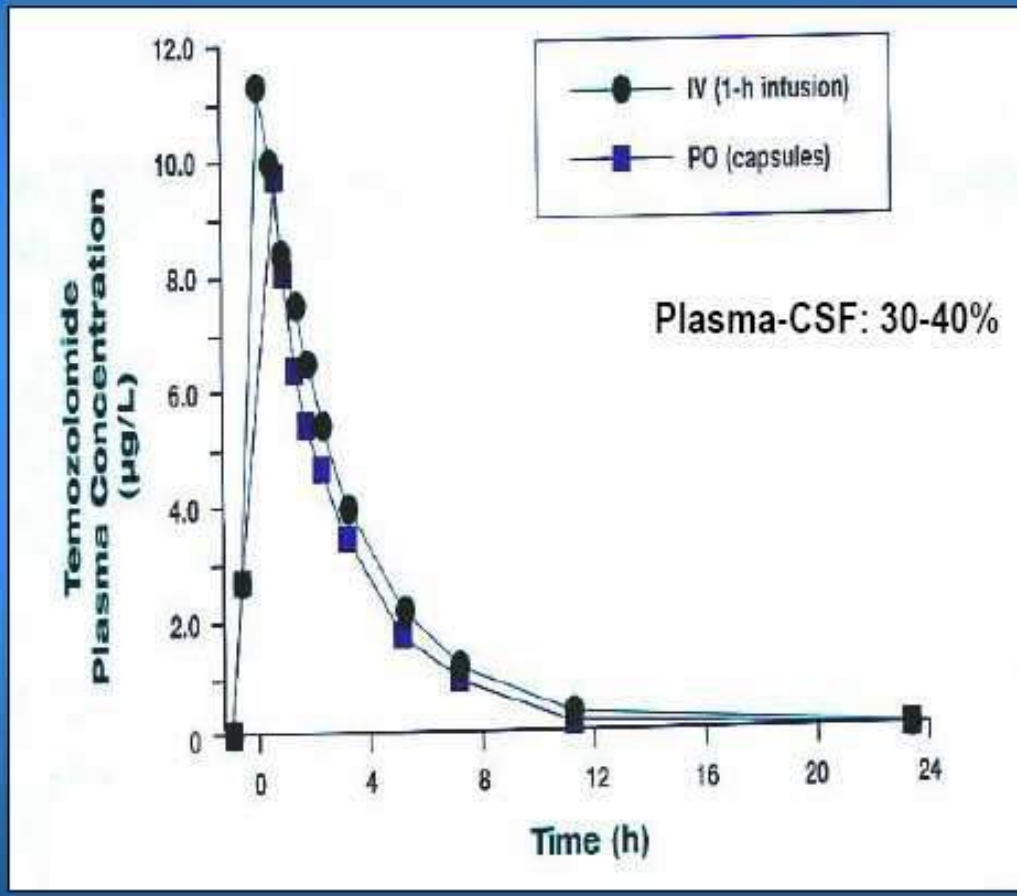
The Boron Neutron Capture Therapy (BNCT) consists of the injection of boron compounds into the human body, collecting them in tumor cells and then irradiating them with thermal neutrons in order to destroy these cells.

Timing of chemotherapy

- Adjuvant
  - After surgery or radiation
  - Defined number of cycles
  - Aim
    - prolong time to recurrence
- Recurrence
  - Number of cycles limited by side effects
  - Aim
    - improve symptoms, quality of life and slow progression

Temozolomide (TMZ)

- Oral administration
- excellent concentration in CNS
- encouraging antitumour activity
- favourable toxicity profile
- synergism with radiotherapy and other agents



The NEW ENGLAND JOURNAL of MEDICINE

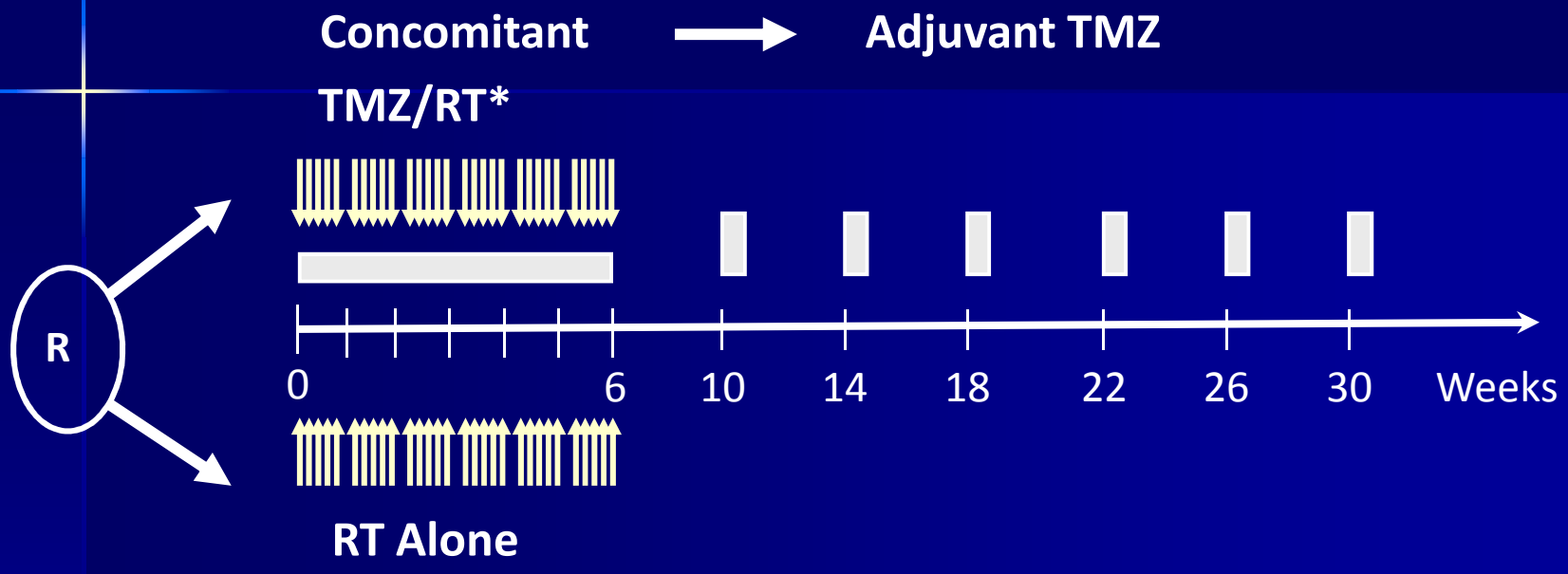
ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

NEJM 2005

Stupp Treatment Schema

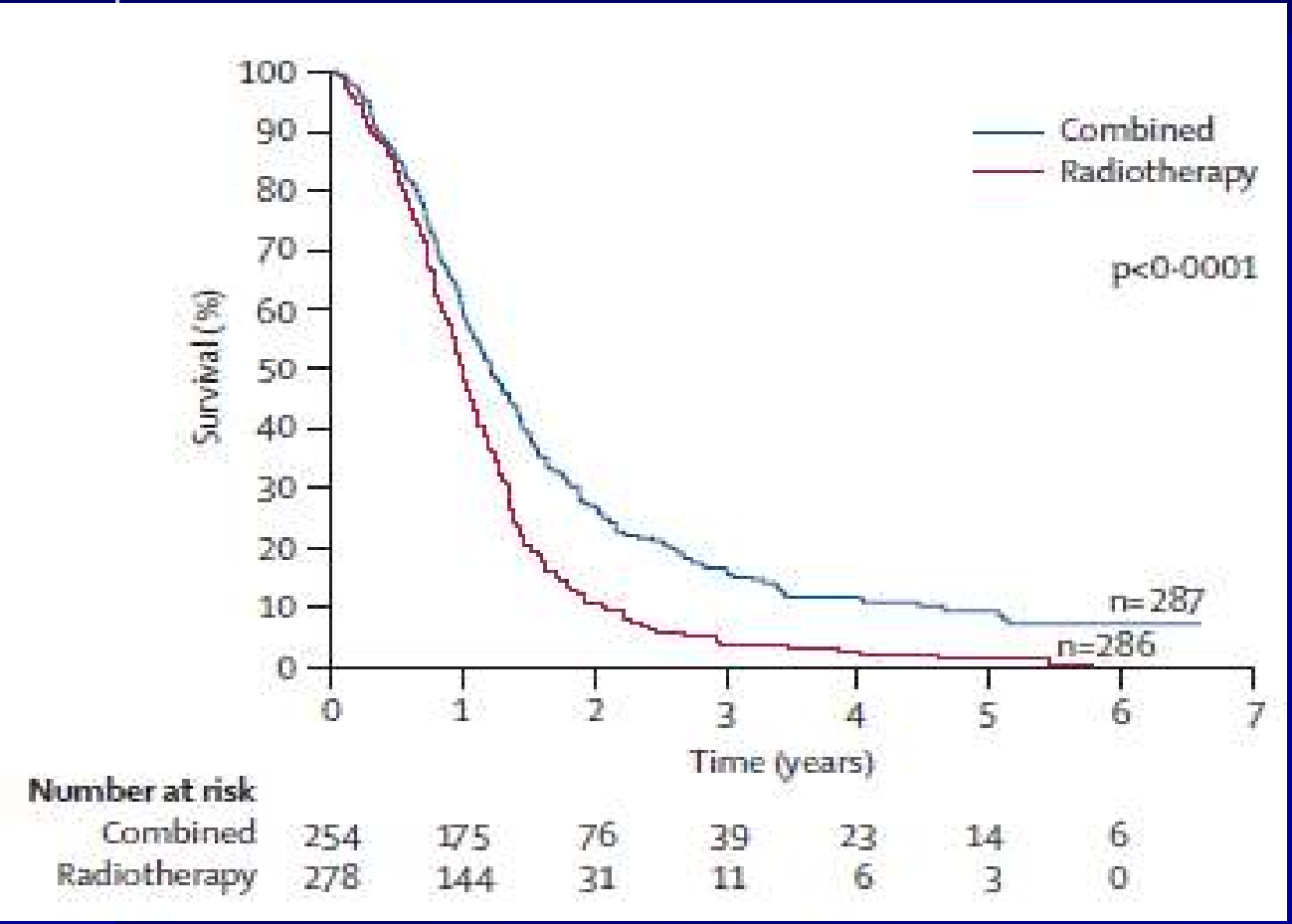


Temozolomide 75 mg/m^2 po qd for 6 weeks,
then 150–200 mg/m^2 po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

Significant improvement in survival



Survival	RT	RT + TMZ
Median, mos	12.1	14.6
2 yr, %	10.9	27.2
3 yr, %	4.4	16.0
4 yr, %	3.0	12.1%
5 yr, %	1.9	9.8

Stupp et al. Lancet Oncology 2009

Temozolomide + RT in newly diagnosed GBM

NEW STANDARD OF CARE

Throughout the world

Clin Cancer Res. 2005 Oct

Food and Drug Administration Drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme.

N Engl J Med. 2005

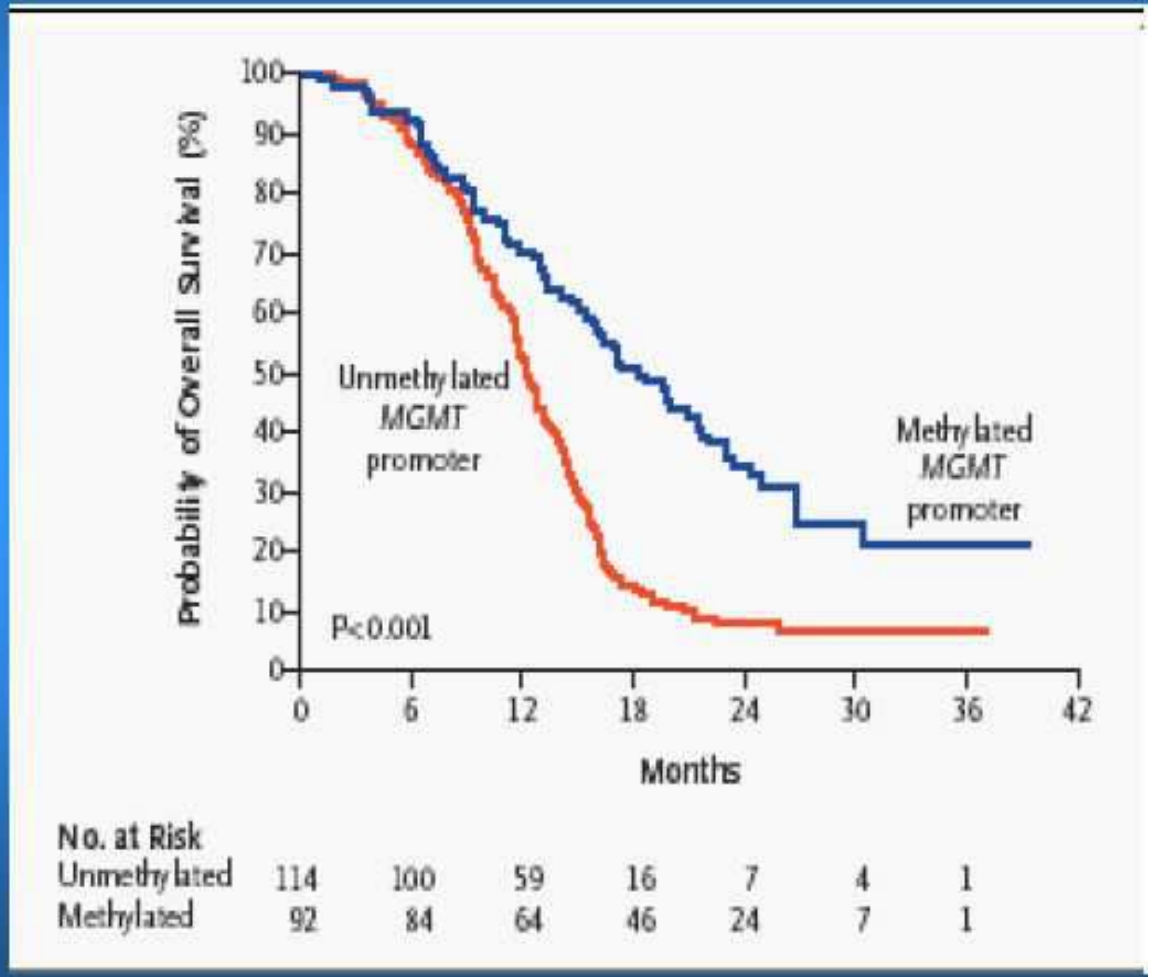
MGMT gene silencing and benefit from temozolomide in glioblastoma.

CONCLUSIONS:

Patients with glioblastoma containing a methylated MGMT promoter benefited from temozolomide, whereas those who did not have a methylated MGMT promoter did not have such a benefit.

MGMT (Methylguanine DNA methyltransferase) and TMZ Resistance

- 573 specimens
- 307 Methylation specific PCR.
- 206/307 paraffin blocks could be studied adequately.
- Studied in two groups as original design of EORTC and NCIC study (Stuup et al)



Hegi et al NEJM, 2005

Annals of Oncology 2004
European Society for Medical Oncology

- **Dose-dense regimen** of temozolomide given every other week in patients with recurrent central nervous system tumors

→**RECOMMENDED DOSE:-**

- ✓ On days 1–3 and 14–16 every 28 days (**ONE CYCLE**).
- ✓ The starting daily dose was 200 mg/m2 with subsequent increments of 50 mg/m2 until unacceptable toxicity was reached.

→**CONCLUSION:**

- ✓ TMZ can be given safely using a dose-dense regimen of 300 mg/m2/day for 3 consecutive days every 2 weeks in patients with recurrent brain tumors.

Journal of Clinical Neuroscience
Volume 13, January 2006

Phase II study of two-weekly temozolomide in patients with high-grade gliomas

- ✓ Overall, two-weekly temozolomide is an active & well tolerated schedule, but does not appear to improve on the activity of temozolomide using the standard 5-day schedule.

Meeting: 2006 ASCO Annual Meeting

Alternative schedules of adjuvant temozolomide in glioblastoma multiforme: A 6-year experience.

→**Conclusions:**

✓ Continuous daily dose of 75 mg/m2 was more advantageous than a standard monthly or a biweekly regimen, as it resulted in the highest OS with the lowest hematologic toxicity.

Journal of Clinical Oncology, *2007*

American Society of Clinical Oncology

- Efficacy and Tolerability of Temozolomide in an **Alternating Weekly Regimen** in Patients With Recurrent Glioma

- Purpose: Evaluation of toxicity and efficacy of an alternating weekly regimen of temozolomide administered 1 week on and 1 week off in patients with **recurrent glioma.**

→**Conclusion:**

- ✓ Feasible
- ✓ Safe
- ✓ Effective
- ✓ Less toxic
- ✓ Also active in patients lacking MGMT gene promoter methylation.

J Neurooncol. 2008

- Temozolomide **three weeks on and one week off** as first line therapy for patients with **recurrent or progressive low grade gliomas.**

→Conclusion:

- ✓The prolonged temozolomide schedule considered in the present study is followed by a high response rate; toxicity is acceptable.
- ✓Further randomized trials should therefore be conducted to confirm the efficacy of this regimen as first-line therapy in patients with progressive low grade glioma.

Multi-Institutional Trial of BID Regimen of Temozolomide for Recurrent Malignant Gliomas

→**Conclusions:**

✓**BID regimen** of Temozolomide is tolerated will by most patients. Response rates are promising.

Journal of Clinical Oncology, 2008: American Society of Clinical Oncology.

- MGMT Promoter Methylation Status Can Predict the Incidence and Outcome of "**Pseudoprogression"** After Concomitant Radiochemotherapy in Newly Diagnosed Glioblastoma Patients

GRADE II/III Tumors

- ✓ Anaplastic Tumors

Cancer Invest. 2007

→GRADE II/III GLIOMAS

- ✓ Newly launched and planned phase III trials - overall survival in grade II/III as well as the prognostic and predictive value of 1p/19q analyses and MGMT promotor methylation status.

Role of chemotherapy

- Temozolamide in progressive LGG
- n= 41 (16 = 35% astrocytomas)
- newly diagnosed or previously Rx (52% resected, 22% prior chemo, 15% prior RT)
- 200mg/m^2/day x 5days q28 days x 12 cs
- 70% ENHANCING on CT / MR
- MR every 8 weeks, Macdonald's criteria

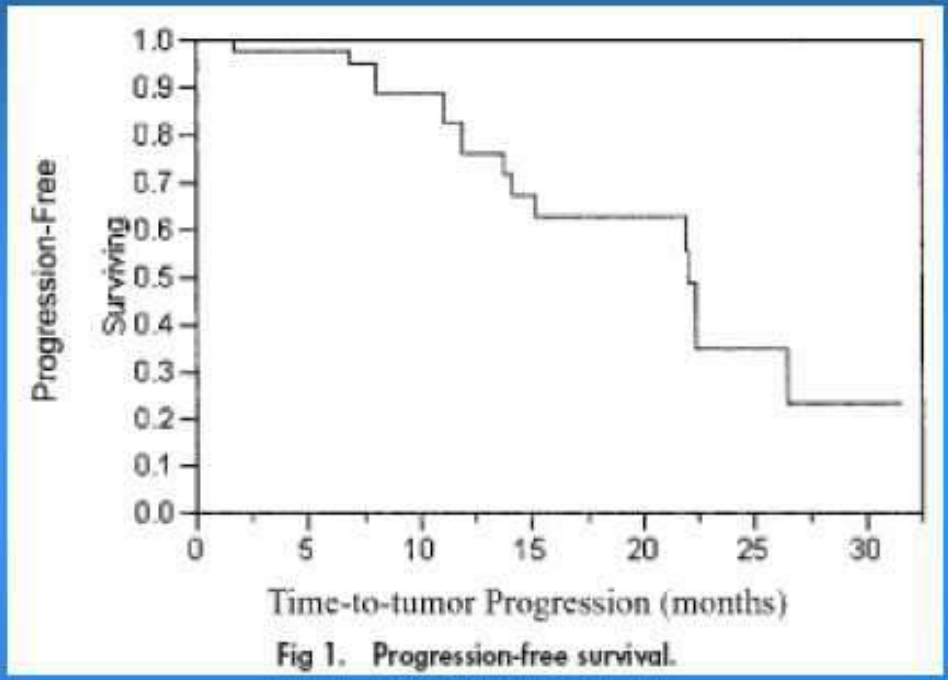


Fig 1. Progression-free survival.

Overall Median PFS 22 months, 12 mo PFS 73% for astrocytoma
Overall CR = 24% (31% for astrocytoma)
Overall PR = 37% (38% for astrocytoma)
Overall CR + PR = 61% (69% for astrocytoma)

Cancer Invest. 2007

- Temozolomide and radiation in low-grade and anaplastic gliomas: "TEMORADIATION"

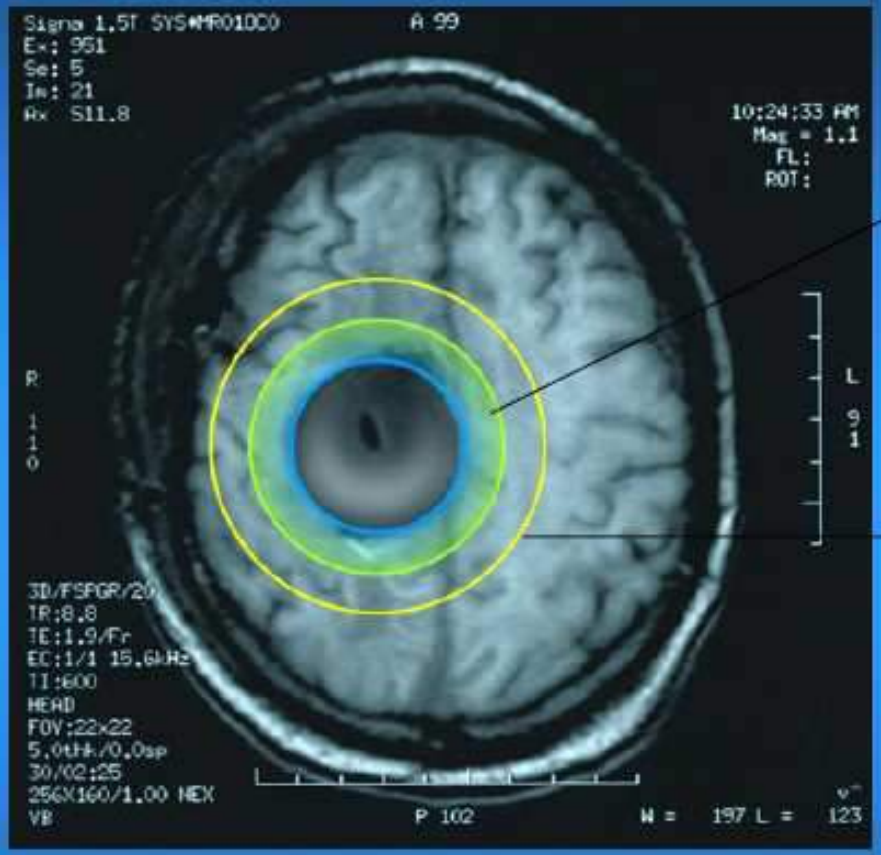
Treatment options at recurrence

- Surgery
  - Re-resection
  - BCNU (Carmustine) wafer
- Repeat radiation
- Chemotherapy
  - Temozolomide rechallenge
  - Nitrosoureas (CCNU, BCNU)
  - Bevacizumab
  - Clinical trial

Gliadel Wafers

- Gliadel wafers at time of surgery (carmustine soaked) in completely resected high grade glioma (3 or 4)

Gliasite: MRI and Treatment Plan



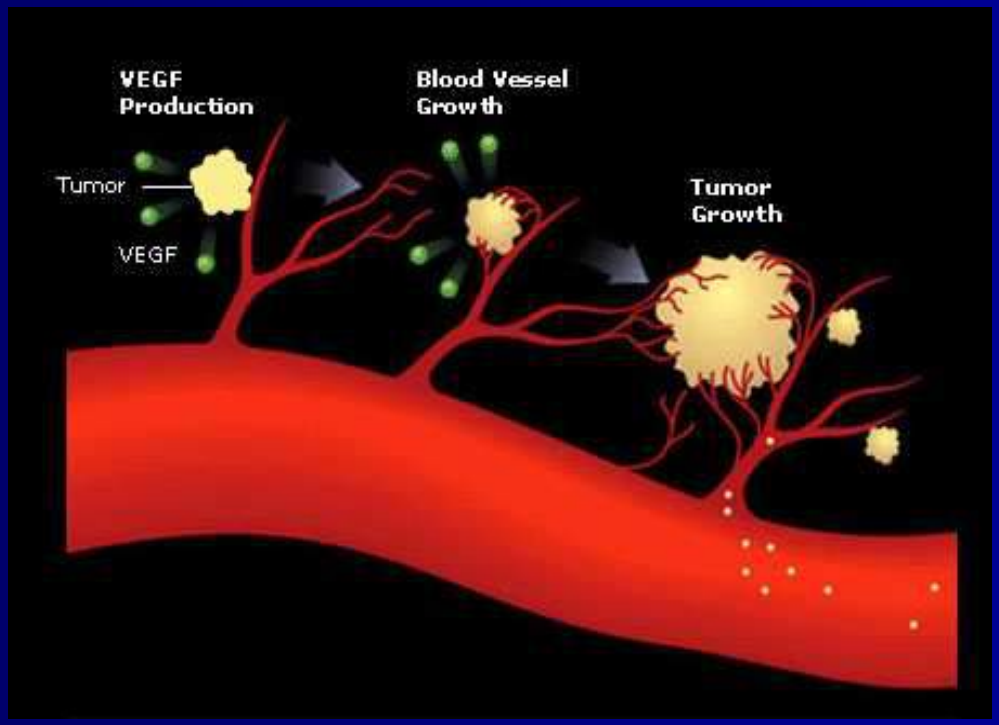
Target area receives at least 100% of the prescribed dose. Typically 40-60 Gy.

Rapid dose drop-off outside the target volume due to low energy photons of I-125.

1. Dosimetry issues, clinical data not encouraging

Bevacizumab (Avastin)

- VEGF inhibitor
- Targets angiogenesis



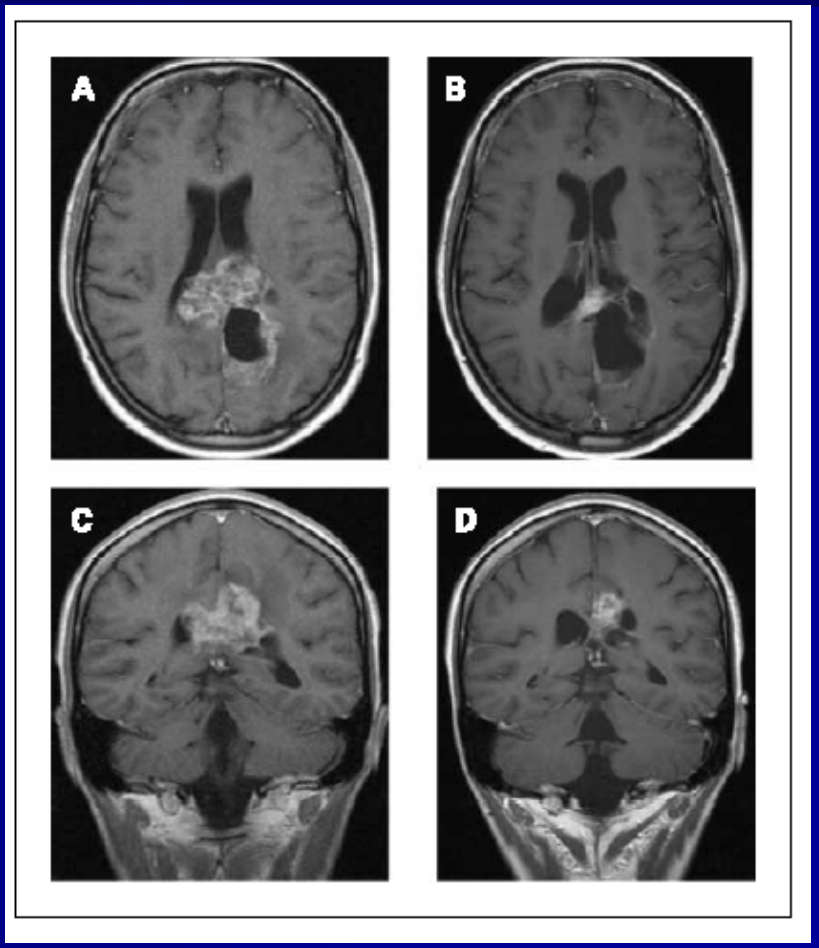
Bevacizumab (Avastin)

- To date mainly investigated in Phase II trials
- Usually in combination with irinotecan chemotherapy
- TGA approved for use in relapsed glioma
- Not approved on PBS
  - Requires co-payment (~$20,000)
- No trials have demonstrated a survival benefit

Bevacizumab ± Irinotecan in Recurrent GBM

- Phase II study in 167 patients

	Bevacizumab (n = 85)	Bevacizumab + Irinotecan (n = 82)
Response %	28.2	37.8
6-mo PFS %	42.6	50.3
Survival (months)	9.2	8.7

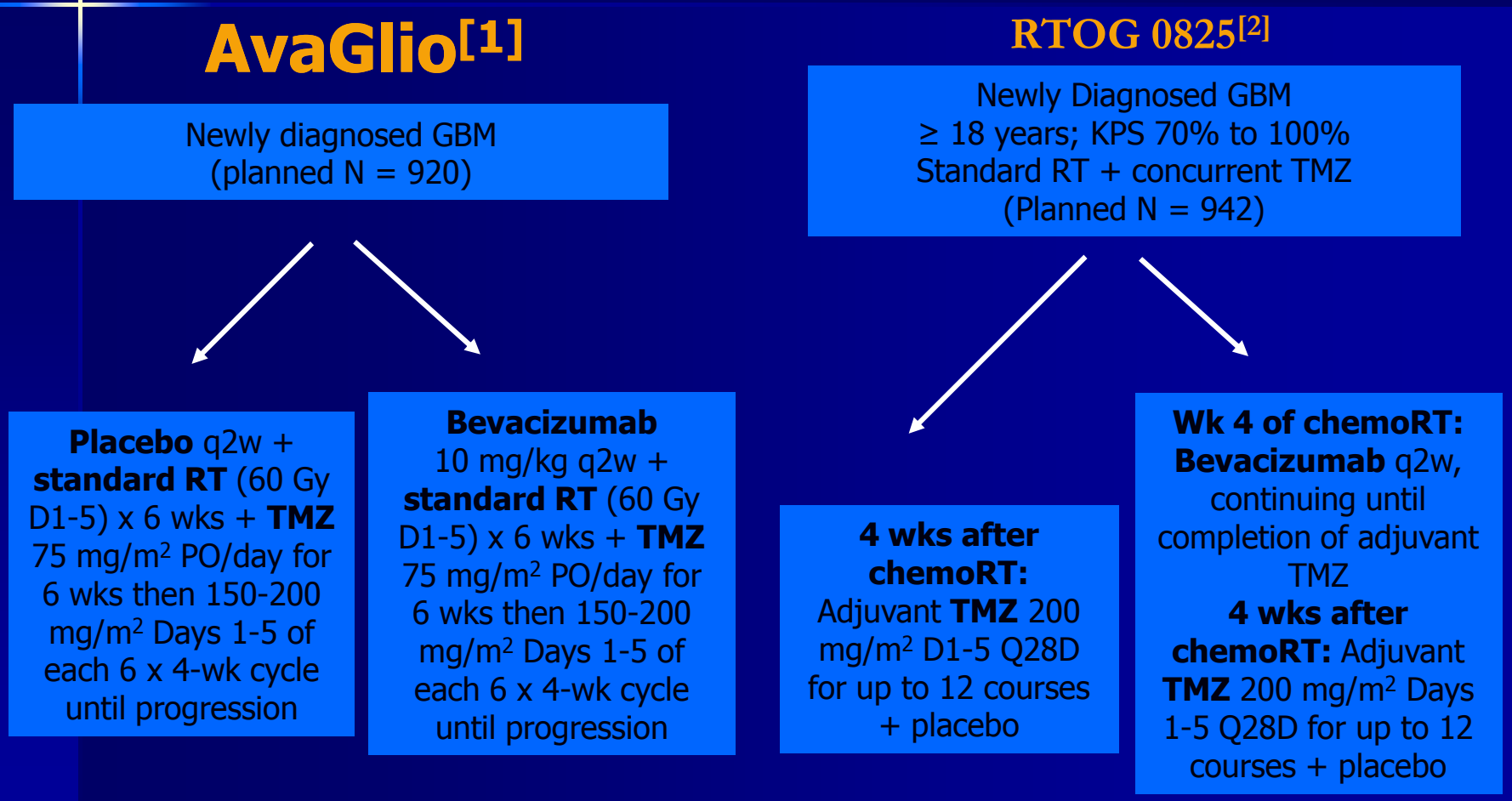


Friedman HS, et al. JCO 2009

Bevacizumab adverse events

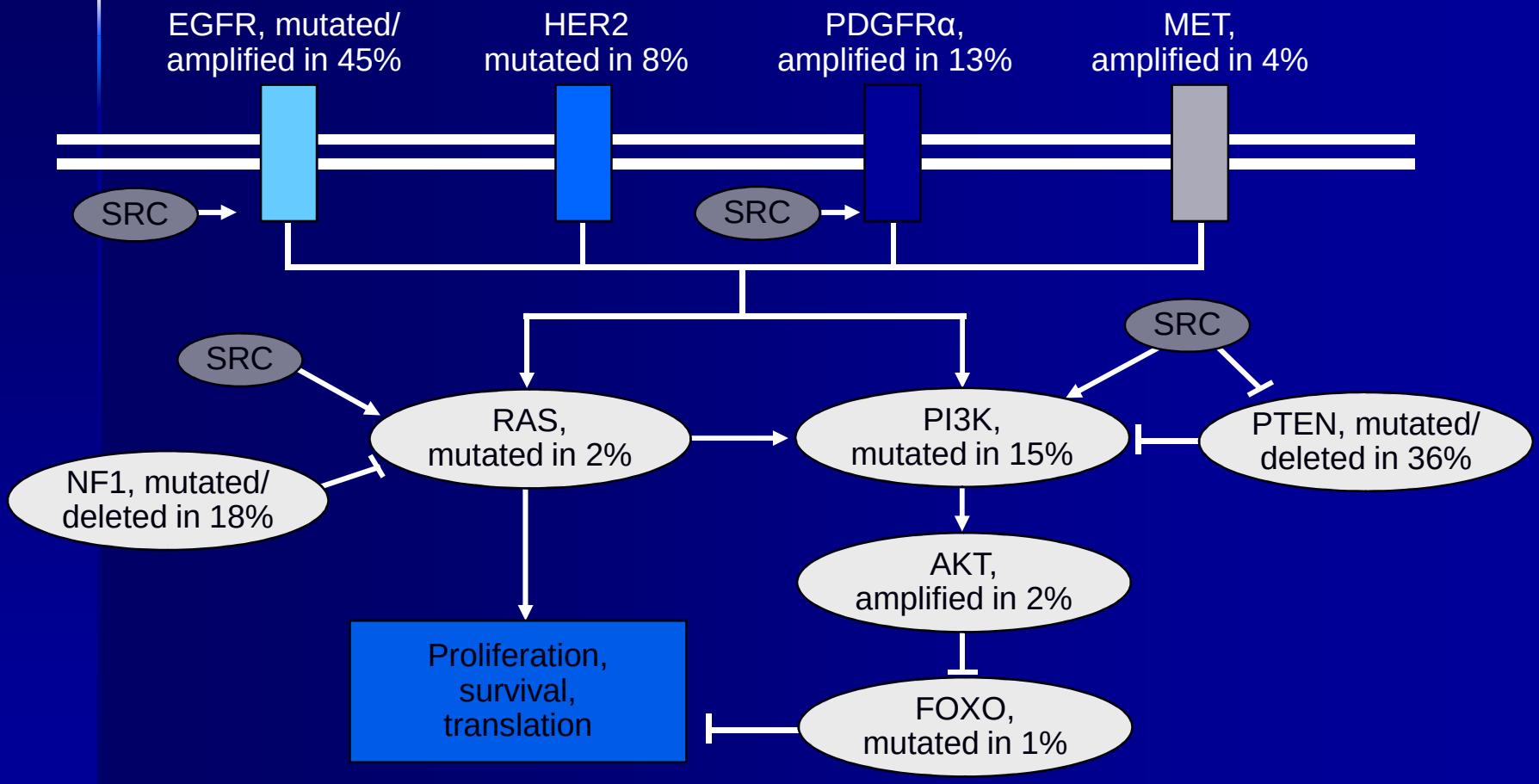
- Side effects include
  - Hypertension (9%)
  - Delayed wound healing (2%)
  - Bowel perforation (2%)
  - Intracranial haemorrhage (2%)
  - Venous and arterial clots (4%)

Phase III Trials of Bevacizumab in newly diagnosed GBM



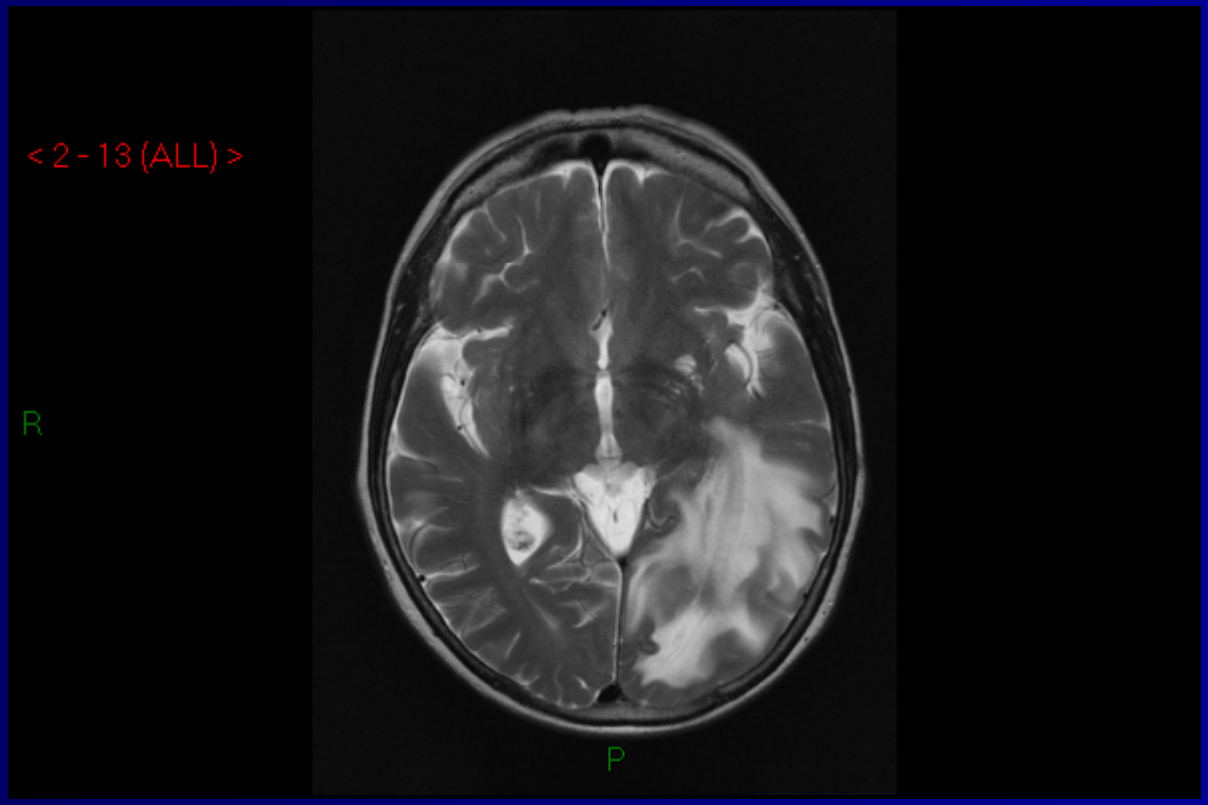
1. ClinicalTrials.gov. NCT00943826. 2. ClinicalTrials.gov. NCT00884741.

Genetic Targets in Glioblastoma



Wick W, et al Neuro-Oncol. 2011

Primary CNS Lymphoma



Primary Cerebral Lymphoma

- Primary cerebral lymphoma – HIV related
- Steroids
- Chemo (methotrexate based)+/- XRT
- Cognitive impairment
- Poor outcomes

Medulloblastoma -Chemotherapy when & What?

- A range of alkylator and platimum based regimens available
- Adjuvant VCP=Adjuvant VLP
- Other effective regimens:VLCP,VC, VJPE, MICE

Standard-Risk: New Standard

- GTR
- Reduced dose CSI (23.4Gy)
- Adjuvant chemotherapy

High-Risk: Standard of care

- GTR
- CSI (36Gy)+PF boost19.8Gy
- Adjuvant chemotherapy
- Chemotherapy improves survival by 15-20% c/t RT alone historical cohorts

Recurrent brain stem gliomas

- Individualise, symptomatic care/steriods
- Re-irradiation rarely ever possible/helpful
- Chemo largely ineffective
- Temozolomide, Tamoxifen, interferons, Iressa, etc – several small phase II studies - investigational

Large study material – learnt what does not work

Something very original/innovative needed

Chemotherapy Pediatrics

- Role unknown
- Randomised trial of RT Vs RT + adj V, CCNU & P – no benefit (MPO 1996;27:8-14)
- CCG trial – V, CCNU, P Vs 8-in-1 chemo: no difference (JNS 1999;88:695-03)
- Could consider for children < 5 years with 40% not requiring RT for 2 years (JCO 2001)
- Role needs to be crystallised

ONKOLOGIE

Editorial

Onkologie 2007;30:350–351
DOI: 10.1159/000103366

Published online: June 13, 2007

Radiochemotherapy for Brain Metastasis: How to Define a Role for Temozolomide

Michael Weller

Department of General Neurology, Center for Neurology, University of Tübingen Medical School, Germany

Brain Metastasis

- ✓ Lung Tumors
- ✓ Breast Tumors

- ? ????Malignant Melanoma

Journal of Clinical Oncology, 2004
American Society of Clinical Oncology

→**CONCLUSION:**

✓Temozolomide was well tolerated and demonstrated activity in the treatment of brain metastases from MM. Further evaluation of temozolomide combination therapy is warranted.

Conclusion

- Current standard of care
  - TMZ + RT followed by 6 months of TMZ
- Recurrence
  - Treatment options unsatisfactory
  - TMZ / nitrosurea / bevacizumab
- Involvement in clinical trials encouraged
- Multiple new therapies under development