# SYLLABUS

TC25: Neurooncology

Monday, November 14, 2011 14:45 - 18:15 Hall 3

Marrakesh, Morocco, November 12-17, 2011

XX$^{th}$ WORLD CONGRESS OF NEUROLOGY

XX$^{th}$ WCN 2011 MARRAKESH World Congress of Neurology

WFN

SMN SOCIETE MAROCAINE DE NEUROLOGIE

WCN Education Program

Monday, 14 November, 2011

14:45-18:15

# NEUROONCOLOGY

Chairperson: **Riccardo Soffietti**, *Italy*

**MALIGNANT GLIOMAS: STANDARD OF CARE AND NEW DEVELOPMENTS**
**Michael Weller**, *Switzerland*

**MANAGEMENT OF LOW GRADE GLIOMAS: RISK GROUPS AND ROLE OF SURGERY, RADIOTHERAPY AND CHEMOTHERAPY**
**Riccardo Soffietti**, *Italy*

**NEUROLOGICAL COMPLICATIONS OF CANCER: BRAIN, LEPTOMENINGEAL AND SPINAL METASTASES**
**David Schiff**, *USA*

*16:15-16:45 Coffee Break*

# Malignant Glioma
## Standards of care
## And new developments
## Marrakesh, November 14, 2011

Michael Weller
Department of Neurology
University Hospital Zurich
Switzerland

## Standard of care in the treatment of gliomas

- **Pilocytic astrocytoma (WHO grade I)**
  **Surgery, at recurrence second surgery, rarely radiotherapy or chemotherapy**
- **Diffuse astrocytoma, oligoastrocytoma, oligodendroglioma (WHO grade II)**
  **Surgery, radiotherapy (or chemotherapy) or *wait-and-see***
- **Anaplastic astrocytoma, oligoastrocytoma, oligodendroglioma (WHO grade III)**
  **Surgery, radiotherapy or chemotherapy (or combination)**
- **Glioblastoma (WHO grade IV)**
  **Surgery, radiotherapy and chemotherapy**

1-12

## Facts and developments

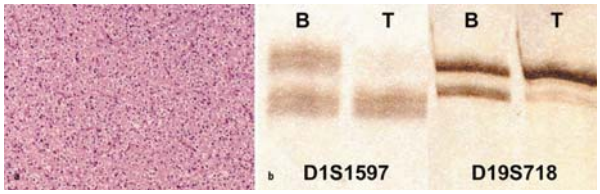
- **Extent of resection is a favorable prognostic factor for all histological variants of glioma**
- **Radiotherapy prolongs progression-free survival in all glioma variants, but is no curative treatment**
- **Chemotherapy (with temozolomide) is established for newly diagnosed glioblastoma (grade IV) and for recurrence after radiotherapy in all types of glioma (grades II-IV)**
- **Chemotherapy competes with radiotherapy or radiochemotherapy in grade II/III gliomas**

1-12

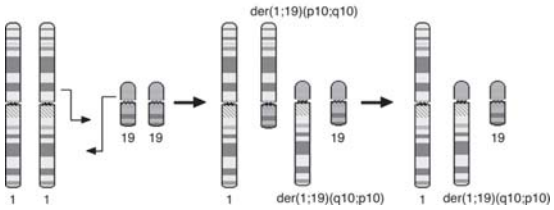
# Malignant glioma
## What is new?

- **New molecular markers:**
  1p/19q codeletion
  *MGMT* promoter methylation
  *IDH*-1/2 mutations
- **Inhibitors of angiogenesis**

# 1p/19q codeletion




A. von Deimling, Heidelberg

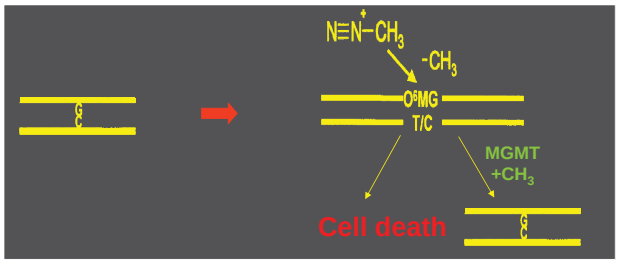



Griffin et al. JNEN 2006;65:988-94

*MGMT* promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi
*Nat. Rev. Neurol.* 6, 39–51 (2010)

**$O^6$-Methylguanin-methyltransferase (MGMT, AGAT), a DNA repair enzyme, counteracts the effect of alkylating agents:**



## *MGMT* promoter methylation in malignant gliomas: ready for personalized medicine?

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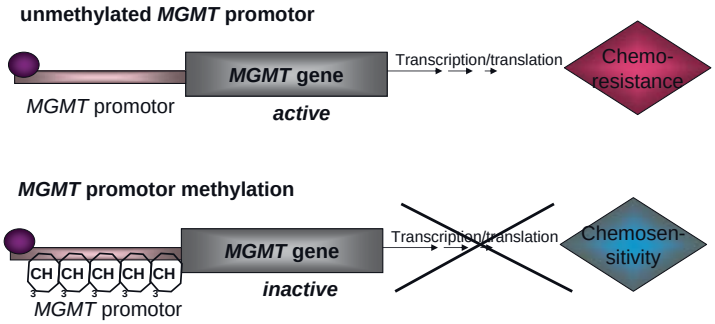
UniversitätsSpital Zürich

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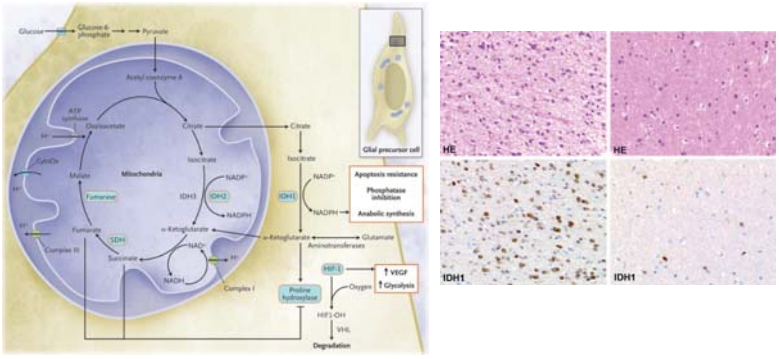
## Isocitrate dehydrogenase mutations

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## Standards of care in newly diagnosed glioblastoma

- **Surgery**
  **Histology**
  **Impact on survival in elderly patients**
  Vuorinen et al. Acta Neurochir 2003;145:5-10
  **Higher rate of complete resections improves progression-free survival rate at 6 months**
  Stummer et al. Lancet Oncol 2006;7:392-401

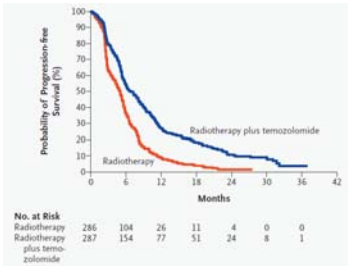
- **Radiotherapy**
  **Doubling of median survival**
  Review, Laperriere et al. Radiother Oncol 2002;64:259-273

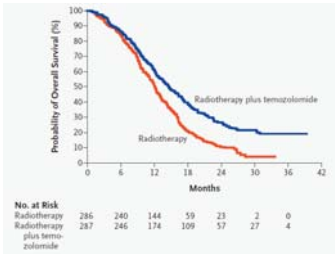
- **Pharmacotherapy**
  **Temozolomide** Stupp et al. NEJM 2005;352:987-996
  ***Nitrosoureas (Gliadel, Westphal et al. JNO 2003;5:79-88, Metaanalysis, systemic therapy, Lancet 2002;359:1011-1018)***

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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

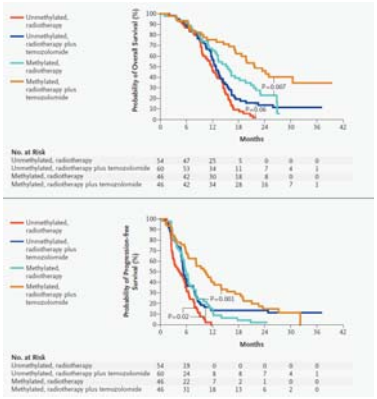



ORIGINAL ARTICLE

*MGMT* Gene Silencing and Benefit from Temozolomide in Glioblastoma

N Engl J Med 2005;352:997-1003.




## It is not standard:

- to withhold temozolomide from patients without *MGMT* promoter methylation
- to give more than 6 cycles of adjuvant temozolomide
- to dose-intensify temozolomide up-front
- to give temozolomide to children or elderly patients (> 70) or patients in reduced performance status
- to “stupp”-ardize all glioma patients according to “one size fits all”
- to believe that every famous neurooncologist must develop his own site-specific temozolomide regimen

## (No) standards of care in recurrent glioblastoma

- **Surgery**
  positive effect on survival in retrospective series
- **Radiotherapy**
  positive effect on survival in highly selected patient populations
- **Pharmacotherapy**
  ***Temozolomide superior to procarbazine***
  ***Yung et al. Br J Cancer 2000;83:588–593***
  ***Gliadel superior to placebo (?)***
  ***Brem et al. Lancet 1995;345:1008-1012***
  ***Bevacizumab (?)***
  ***Friedman et al. J Clin Oncol 2009;27:4733-4740, Fine et al. J Clin Oncol 2009;27:740-745***

## CCNU (Lomustin)

| | Treatment | CR + PR (%) | Median progression-free survival (weeks) | Progression-free survival at 6 months (%) | Median survival (weeks) |
|---|---|---|---|---|---|
| Van den Bent et al. 2009[1] (n=56) | BCNU or TMZ (n=56, 29/27) | 10 | 10 | 24 | 31 |
| | Erlotinib (n=54) | 4 | 8 | 11 | 33 |
| Wick et al. 2010[2] | CCNU (n=92) | 4 | 7 | 19 | 30 |
| | Enzastaurin (n=174) | 3 | 6 | 11 | 28 |
| Batchelor et al. 2010[3] | CCNU (n=65) | 9 | 12 | 25 | 42 |
| | Cediranib (n=131) | 15 | 13 | 16 | 34 |
| | CCNU + Cediranib (n=129) | 17 | 18 | 35 | 40 |

[1]JCO 2009;27:1268-1274, [2]JCO 2010;28:1168-1174 , [3]ESMO 2010

## Efficacy of *Temozolomide Rechallenge* by time interval to first-line temozolomide

| | Treatment | CR + PR (%) | Median progression-free survival (weeks) | Progression-free survival at 6 months (%) | Median overall survival (weeks) |
|---|---|---|---|---|---|
| **Progression during TMZ** | | | | | |
| Perry et al. 2010 (n=33) | TMZ 28/28 | 3 | 15 | 27 | nd |
| Wick et al. 2009 (n=19) | TMZ Diverse | 0 | 18 | 26 | 23 |
| **Progression after TMZ** | | | | | |
| Perry et al. 2010 (n=28) | TMZ 28/28 | 11 | 16 | 36 | nd |
| Wick et al. 2009 (n=28) | TMZ Diverse | 17 | 21 | 29 | 29 |

# Bevacizumab

| | Treatment | CR + PR (%) | Median progression-free survival (weeks) | Progression-free survival at 6 months (%) | Median survival (weeks) |
|---|---|---|---|---|---|
| Van den Bent et al. 2009 (n=56) | BCNU/TMZ | 10 | 10 | 24 | 31 |
| Wick et al. 2010 (n=92) | CCNU | 4 | 7 | 19 | 30 |
| **Kreisl et al. 2009 (n=48)** | **Bevacizumab** | **35** | **16** | **29** | **31** |
| **Friedman et al. 2009 (n=85)** | **Bevacizumab** | **28** | | **43** | **39** |
| *Friedman et al. 2009 (n=82)* | *Bevacizumab +Irinotecan* | *38* | | *50* | *37* |
| Sorensen et al. 2009 (n=31) | Cediranib 10-45 mg | | 17 | 26 | 32 |
| Reardon et al. 2008 (n=40) | Cilengitide 2000 mg | 13 | 8 | 15 | 43 |
| Wick et al. 2010 (n=174) | Enzastaurin | 3 | 6 | 11 | 28 |

NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

*Wolfgang Wick, Christian Hartmann, Corinna Engel, Mandy Stoffels, Jörg Felsberg, Florian Stockhammer, Michael C. Sabel, Susanne Koeppen, Ralf Ketter, Richard Meyermann, Marion Rapp, Christof Meisner, Rolf D. Kortmann, Torsten Pietsch, Otmar D. Wiestler, Ulrike Ernemann, Michael Bamberg, Guido Reifenberger, Andreas von Deimling, and Michael Weller*

*J Clin Oncol 27:5874-5880.*

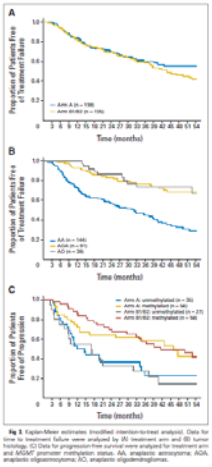


**Table 4.** Complete Model of Major Prognostic Factors As Determined in a Multivariate Cox Regression Analysis for the Primary End Point of Time to Treatment Failure

| Variable | Hazard Ratio | 95% CI | *P* |
|---|---|---|---|
| Anaplastic astrocytoma *v* anaplastic oligoastrocytoma/ anaplastic oligodendroglioma | 1.95 | 1.1 to 3.5 | .0237 |
| *IDH1*, wild-type *v* mutated | 2.0 | 1.2 to 3.3 | .0128 |
| 1p/19q retained *v* 1p/19q deleted | 1.8 | 0.9 to 3.4 | .0718 |
| *MGMT* promoter, unmethylated *v* methylated | 1.9 | 1.1 to 3.4 | .0172 |
| Age, > 50 *v* ≤ 50 years | 2.6 | 1.5 to 4.3 | .0004 |
| Extent of resection | | | |
| Incomplete *v* complete resection | 1.6 | 0.9 to 3.0 | |
| Biopsy *v* incomplete resection | 2.1 | 1.1 to 4.0 | .0006 |
| Biopsy *v* complete resection | 3.5 | 1.8 to 7.0 | |

# Soft standards of care in malignant gliomas

- **Always tell the truth, but do it in fractions …**
- **Check the need for steroids**
- **Check the need for anticonvulsants**
- **Watch out for treatment-related side effects**
- **Watch out for vascular complications: deep venous thrombosis, pulmonary embolism, hemorrhage, stroke**
- **Listen and watch for alternative treatment use**
- **Keep the patient in focus and not the relatives and not your trials…**

# References


Brada et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. J Clin Oncol 2010;28:4601-8

Hegi et al. MGMT gene silencing and response to temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003.

Keime-Guibert et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527–35

Louis et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109

Stupp et al. Radiotherapy plus concomitant and adjuvant temozolomide for patients with newly diagnosed glioblastoma. N Engl J Med 2005;352:987–96

Stummer et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7:392–401

Weller et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nature Rev Neurol 2010;6:39-51

Wick et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. J Clin Oncol 2009;27:5874-80

Wen et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963-72

Yan et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.

# MANAGEMENT OF LOW GRADE GLIOMAS : RISK GROUPS AND ROLE OF SURGERY, RADIOTHERAPY AND CHEMOTHERAPY

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World Congress of Neurology, Marrakesh , November 14, 2011

## GENERAL CONCEPTS ON OUTCOME OF LOW GRADE GLIOMAS

- The natural history and pattern of care of $LGG_s$ has changed over time with an increase of survival
- The 5- year overall survival and progression-free survival rates (RTOG and EORTC trials) range from 58% to 72% and 37% to 55% respectively
- Median survival is ~ 5 years for astrocytomas , 9-10 years for oligodendrogliomas , being oligoastrocytomas in between
- Up to 25% of patients survive for 20 years (Claus and Black, 2006)
- $LGG_s$ grow continously over time , and this process can last many years (Mandonnet et al, 2003)

## MALIGNANT TRANSFORMATION

- The risk in $LGG_s$ is high (up to 70%)
- The process is different in astrocytomas and in oligodendrogliomas, both in terms of molecular pathways and clinical aspects
- It is more frequent in older patients (>40 – 45 years) with astrocytoma
- At diagnosis it is unpredictable in the individual patients

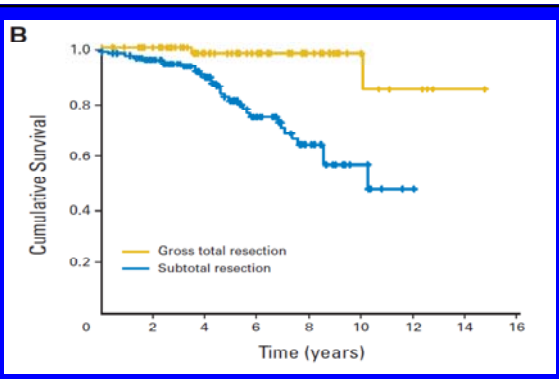
## Clinical favorable prognostic factors

- Age < 40 yrs
- Seizures at presentation
- Absence of neurological deficits
- High performance status (Karnofsky ≥ 70)
- Absence of enhancement on CT/MRI
- Preoperative tumor size < 5-6 cm
- Tumor not crossing the midline

*Baumann et al, 1999; Pignatti et al, 2002; Kaloshi et al, 2009; Schomas et al,2009*

## MOLECULAR FACTORS OF POSITIVE PROGNOSTIC / PREDICTIVE VALUE

- 1 p /19q codeletion
- MGMT methylation
- IDH-1 mutation




Smith JS et al, J Clin Oncol. 2008, 26 (8):1338-45.

D. J. Englot et al.

**TABLE 3: Predictors of seizure freedom after CCM resection**

| Parameter | OR | 95% CI | p Value |
|---|---|---|---|
| CCM size <1.5 cm | 15.4 | 5.2–45.4 | <0.001 |
| single CCM only | 2.02 | 1.13–3.60 | <0.02 |
| seizures medically controlled | 2.38 | 1.29–4.39 | <0.01 |
| partial seizures only | 3.33 | 2.09–5.30 | <0.001 |
| seizures for ≤1 yr | 1.83 | 1.30–2.58 | <0.001 |
| gross-total lesionectomy | 36.6 | 8.5–157.5 | <0.001 |

DOI: 10.3171/2011.7.JNS11536

Englot et al, J Neurosurg, April 29, 2011

## EXTENT OF SURGERY AS A PROGNOSTIC FACTOR

Gross total resection, in combination with age < 40 or even alone, is now used to define low-risk patients

↓

Observation with MRI

## Early versus Delayed Radiotherapy: EORTC 22485

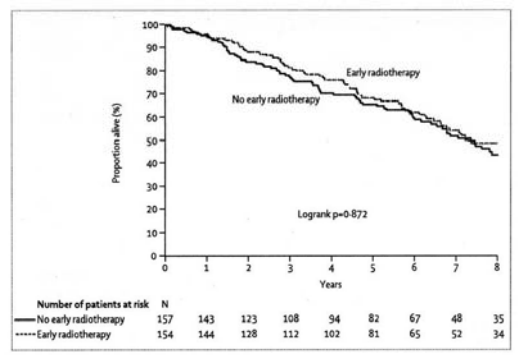



**Figure 2: Overall survival by intention-to-treat analysis**
Number of events: O=80 for control group; O=76 for early radiotherapy group.

Van den Bent et al, Lancet. 2005, 17-23;366(9490):985-90.

## Early versus Delayed Radiotherapy: EORTC 22485

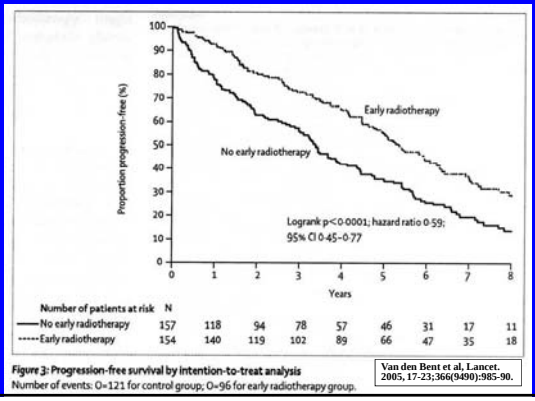



*Figure 3:* **Progression-free survival by intention-to-treat analysis**
Number of events: O=121 for control group; O=96 for early radiotherapy group.

Van den Bent et al, Lancet. 2005, 17-23;366(9490):985-90.

## RADIATION VOLUME

- Whole-brain radiotherapy yields a significant risk of long-term leukoencephalopathy and dementia (O. Surma-aho *et al*, 2001).
- Conformal radiotherapy with doses of 1.8-2 Gy is safe (Taphoorn *et al*,1994; Klein *et al*, 2002; Brown *et al*, 2003; Laack *et al*, *2005*), but risk of cognitive and radiological compromise in long-term survivors still exists (Douw et al, 2009)

## COGNITIVE DEFICITS IN LOW GRADE GLIOMAS

- Patient characteristics ( location of the tumor , disease duration ,presence and severity of epilepsy, treatment with antiepileptic drugs, psycologic stress or a combination of these factors ) play an important role in long-term decline in cognitive function.

*Taphoorn, 2003*

**Effect of cranial irradiation on seizure frequency in adults with low-grade astrocytoma and medically intractable epilepsy**

**Article abstract**—We report the effect of cranial irradiation on seizure frequency in five adults with unresected (biopsy-proven) cerebral hemisphere low-grade astrocytoma and medically intractable epilepsy. Seizures were refractory to standard antiepileptic drugs for 7 months to 27 years. Treatment with 5,400 cGy to 6,120 cGy focal radiation reduced seizure frequency by more than 90% in three patients (one of whom became seizure-free) and by more than 75% (but less than 90%) in one patient. One patient had no response. Brain CT or MRI showed a partial tumor response to radiation in three of the four patients with reduced seizure frequency. In three patients, the reduced seizure frequency continued to the most recent follow-up of 1 to 1.5 years. In the patient who became seizure-free, seizures recurred at 8.2 years and were associated with tumor progression. Irradiation can reduce seizure frequency in some patients with unresected cerebral hemisphere low-grade astrocytoma and medically intractable epilepsy.

NEUROLOGY 1993;43:1599-1601

Lisa R. Rogers, DO; Harold H. Morris, MD; and Kathy Lupica, RN

## Final report of Radiation Therapy Oncology Group (RTOG) protocol 9802: radiation therapy (RT) versus RT + procarbazine, CCNU and vincristine (PCV) chemotherapy for adult low grade glioma (LGG)

- Median OS and PFS not reached for RT +PCV compared to 7.5 years and 4.4 years for RT alone
- Both OS and PFS similar for patients treated with RT+PCV or RT between years 0-2
- Beyond 2 yrs the OS and PFS curves separated significantly favouring RT+PCV (PFS at 5 years 63% vs 46%, p<0.005)
- Histology (oligos vs astros) the strongest prognostic factor
- 1p/19q analysis ongoing
- More myelotoxicity with chemotherapy

Shaw et al, ASCO 2008

## LESSONS LEARNED FROM STUDIES ON CHEMOTHERAPY ALONE AS INITIAL TREATMENT

- Complete responses are generally lacking, minor responses prevail over partial responses (PR + MR up to 53%).
- Maximum tumor shrinkage can be delayed as long as 24-30 months.
- Evaluation of response on conventional MRI (T2 weighted and/or FLAIR images) difficult in nonenhancing tumors → need for new imaging techniques

Studies with PCV: *Mason et al, 1996; Soffietti et al, 2001; Buckner et al, 2003; Biemond-ter Stege et al, 2005; Lebrun et al, 2007*

Studies with TMZ: *Brada et al, 2003; Hoang-Xuan et al, 2004; Kaloshi et al, 2007*

## Seizure response to chemotherapy in low-grade gliomas

| *Author* | *N° pts with seizures/N° of total pts* | *Chemotherapy regimen* | *Seizure response* |
|---|---|---|---|
| Mason et al,1996 | 6/9 | PCV | 100% |
| Soffietti et al, 1998 | 12/26 | PCV | 50% |
| Frenay et al, 2005 | 8/10 | PCV | 87% |
| Lebrun et al, 2007 | 22/33 | PCV | 53%. |
| Pace et al, 2003 | 31/43 | TMZ standard | 48% |
| Brada et al, 2003 | 27/29 | TMZ standard | 55% |
| Hoang-Xuan et al, 2004 | 60* | TMZ standard | Up to 51% |
| Kaloshi et al, 2007 | 149* | TMZ standard | Up to 58% |
| Soffietti et al, 2008 *(ongoing study)* | 17/31 | TMZ dose-dense | 65% |

PCV: Procarbazine, CCNU, Vincristine
TMZ: temozolomide
*Number of pts with epilepsy not reported

Rudà et al, Curr Opin Oncol 2010;22(6):611-20

J Neurosurg 114:1617–1621, 2011

Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas

Clinical article

Jonathan H. Sherman, M.D.,[1] Krisztina Moldovan, B.S.,[2] H. Kwang Yeoh, M.B.Ch.B.,[1] Robert M. Starke, M.D., M.Sc.,[1] Nader Pouratian, M.D., Ph.D.,[1] Mark E. Shaffrey, M.D.,[1] and David Schiff, M.D.[1,3,4]

*Departments of [1]Neurological Surgery, [3]Neurology, and [4]Medicine, University of Virginia Health System; and [2]University of Virginia School of Medicine, Charlottesville, Virginia*

## ONGOING PHASE III TRIALS IN HIGH RISK/PROGRESSIVE LOW GRADE GLIOMAS

- Chemotherapy with dose-dense TMZ versus RT alone
  ( phase III trial EORTC 22033-26033)
- Association of RT and concomitant/adjuvant standard TMZ versus RT alone
  (ECOG/RTOG phase III trial)

*Cancer Therapy: Clinical*

## Phase II Study of Protracted Daily Temozolomide for Low-Grade Gliomas in Adults

Santosh Kesari,[1,2,6] David Schiff,[9] Jan Drappatz,[1,2,6] Debra LaFrankie,[1] Lisa Doherty,[1] Eric A. Macklin,[6,7] Alona Muzikansky,[6,7] Sandro Santagata,[3,6] Keith L. Ligon,[3,6,8] Andrew D. Norden,[1,2,6] Abigail Ciampa,[1] Joanna Bradshaw,[1] Brenda Levy,[1] Gospova Radakovic,[9] Naren Ramakrishna,[1,4,6] Peter M. Black,[1,5,6] and Patrick Y. Wen[1,2,6]

**Abstract** **Purpose:** Resistance to temozolomide chemotherapy is partly mediated by $O^6$-methylguanine-DNA methlytransferase (MGMT). Protracted treatment with temozolomide potentially overcomes MGMT resistance and improves outcome. We conducted a phase II study of protracted daily temozolomide in adults with low-grade gliomas.
**Experimental Design:** Patients with newly diagnosed oligodendroglioma or oligoastrocytoma with a MIB-1 index of ≥5% or recurrent low-grade gliomas received temozolomide (75 mg/m$^2$/day in 11-week cycles of 7 weeks on/4 weeks off). Treatment continued for a total of six cycles or until tumor progression or unacceptable toxicity. Primary end point was best overall response rate; secondary end points were progression-free survival, overall survival, and toxicity. We correlated response with MGMT promoter methylation and chromosome 1p/19q deletion status.
**Results:** Forty-four patients were treated (14 female, 30 male) with a median follow-up of 39.4 months. Median age was 43 years (range, 20–68 years) and median Karnofsky performance status was 90 (range, 70–100). The regimen was well tolerated. No patients had a complete response (0%), 9 had partial response (20%), 33 had stable disease (75%), and 2 had progressive disease (5%). A total of 21 patients eventually progressed with an overall median progression-free survival of 38 months. Patients with methylated MGMT promoter had a longer overall survival ($P = 0.008$). Deletion of either 1p or 19q chromosomes also predicted longer overall survival (hazard ratio, 0.17; 95% confidence interval, 0.03–0.93; log-rank $P = 0.02$).
**Conclusions:** A protracted course of daily temozolomide is a well-tolerated regimen and seems to produce effective tumor control. This compares favorably with historical data on the standard 5-day temozolomide regimen.

Clin Cancer Res 2009;15(1) January 1, 2009

### Translational Relevance

The optimal management of progressive low-grade gliomas is controversial because of a lack of data from prospective randomized trials. The standard treatment for low-grade glioma is surgical resection and radiotherapy. There is increasing evidence that conventional chemotherapeutic agents used for malignant gliomas, such as temozolomide, are active in low-grade glioma. We report the first use of a protracted temozolomide regimen (75 mg/m$^2$/day in 11-week cycles of 7 weeks on/4 weeks off) in patients with low-grade glioma. This regimen was well tolerated and had significant activity comparing favorably with historical data on the standard 5-day temozolomide regimen. Tumor $O^6$-methylguanine-DNA methlytransferase (MGMT) promoter methylation and 1p/19q chromosome deletion status correlated with overall survival. An increase in progression-free survival among patients with tumors with unmethylated MGMT promoters relative to studies using standard temozolomide dosing suggests that this regimen may potentially overcome MGMT-mediated temozolomide resistance. This protracted temozolomide regimen is a feasible treatment option for patients with low-grade glioma.

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**EFNS GUIDELINES/CME ARTICLE**

## Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force

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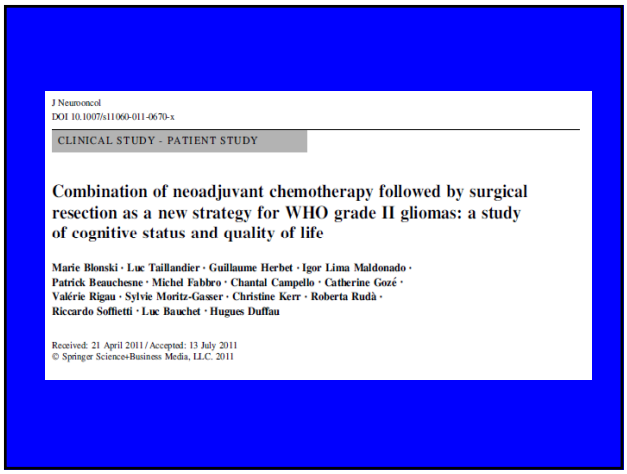

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CLINICAL STUDY - PATIENT STUDY

**Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life**

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# Neurological Complications of Cancer: Brain, Leptomeningeal and Spinal Metastases

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## Brain Mets – Clinical Presentation

- 90% known cancer, 10% synchronous (2/3 lung)
- Common symptoms
  - Headache 50%
  - Focal weakness 30%
  - Mental status changes 32%
  - Gait ataxia 20%
  - Seizures 20%
- Common signs
  - Hemiparesis 60%
  - Mental status changes 60%
- MRI superior to CT
  - # lesions: 25% 1, 25% 2-3, 50% 4+
- Single lesion
  - Hx cancer: 90% likely metastatic
  - No hx cancer: 15% chance metastasis
    - CT C/A/P vs. body PET
- DDx: 1º BT, infection, demyelination

## Brain Metastases: Prognosis

- Median survival 4 mo
- Most deaths 2º systemic disease
- RTOG RPA classes
  - **1** (7.1 mo): age < 65, 1º controlled, no extracranial mets, KPS > 70
  - **2** (4.2 mo): Not Class 1 or 3
  - **3** (2.3 mo): KPS ≤ 70

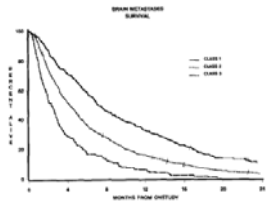

Fig. 3. Survival curves for Class I, II, III.

L Gaspar, IJROBP, 1997

## Brain Mets: Whole Brain Radiotherapy

- Treats all mets, visible and microscopic
  - Choice of schedules
- Inexpensive and technologically simple
- Most effective for radiosensitive histologies
- ≈ 60% CR/PR rate
- Drawbacks
  - Fatigue
  - Leukoencephalopathy and risk of dementia
  - Eventual local relapse

## Brain Mets: Craniotomy/Resection

- Improves survival c/w WBRT for single brain met in better prognosis pts (Patchell NEJM)
  - <65, controlled systemic disease, good PS
- After metastatectomy, WBRT ↓s the risk of both local and remote brain failure (Patchell JAMA)
- Current interest in following metastatectomy with focal RT to tumor bed

## Brain Mets: Radiosurgery (RS)

- Multiple convergent beams/arcs to met
  - Gamma Knife, LINAC, protons
- Best for mets ≤ 3 cm median diameter
- Can treat surgically inaccessible mets
- Local control 70-90% at one year
  - Much better than WBRT for radioresistant mets
- As add-on to WBRT
  - ↑s local control
  - Improves OS for pts with single brain met

## Brain Mets: RS alone or with WBRT?

- 3 published randomized studies
  - Restricted to pts with 1 to 3-4 brain mets
- Consistent conclusions
  - WBRT improves local control at RS sites
  - WBRT improves remote intracranial control
    - More salvage therapy needed in RS alone group
  - WBRT does not improve overall survival
    - <30% of brain met pts die from brain mets
- No evidence yet that WBRT improves cognitive function or QoL (modest evidence to contrary)

## LMD: Clinical Features

- 1-8% of patients on autopsy studies
- Breast, lung, lymphoma, leukemia, melanoma
- Usually with known metastatic disease
- Brain met hx in 70% of solid tumor pts Multifocal subacute neurologic dysfunction
  - Cerebral hemispheres (HA, HC, encephalopathy)
  - Cranial nerves/posterior fossa
  - Spinal cord/nerve roots
- Diagnosis: CSF cytology and/or MRI
  - MRI of entire neuraxis for LM enhancement
    - More sensitive for solid tumor than heme LMD
    - Occasionally unequivocally diagnostic
  - CSF: Most diagnostic but limited sensitivity
    - ≈ 2/3 have + cytology with two LPs
    - CSF is rarely completely normal with LMD

## LMD Treatment: Radiation and Systemic Chemotherapy

- Craniospinal RT rarely indicated
- RT palliative
  - Generally reserved for symptomatic/bulky sites
    - Skull base for CN palsies
    - Cerebral convexities for HC, encephalopathy
    - Spine, as needed
- Theoretical benefit: treats systemic tumor
- For success, requires
  - Drug that penetrates BBB
  - Drug active against tumor
- HD MTX, ara-C achieve good CSF levels
- Capecitabine, temozolomide, thiotepa cross and are occasionally useful

## LMD Treatment: Intrathecal Chemo

- Via LP or intraventricular (Ommaya) reservoir
- Minimizes systemic side effects
- Achieves high intra-CSF levels
- Little penetration into bulky deposits
- CSF block may → neurotoxicity
  - Radionuclide flow studies useful
- All agents may cause aseptic meningitis
  - Leukoencephalopathy, rarely transverse myelopathy
- Drugs: MTX, thiotepa, ara-C, liposomal ara-C

## LMD: Prognosis & Recommendations

- Median survival ≈ 1 mo w/o, 2-3 mo w/Rx
- Sensitive tumors (heme, breast) better prognosis, but 1 yr survival 15%
- Belief that treatment palliates symptoms
- RT for bulky/symptomatic disease
- IT or systemic chemo depending on tumor type, prior Rx, systemic disease

## Epidural Spinal Cord Compression (ESCC)

- Compression of thecal sac that may deform spinal cord or cauda equina
- Affects 3-5% of pts with cancer
- May arise from any cancer
  - Breast, lung, prostate 15-20% each
  - NHL, myeloma, RCC other common causes
- In 20%, initial manifestation of cancer
  - Lung, NHL, myeloma
- 60% in thoracic and 30% lumbosacral spine
- 90% vertebral mets; 10% paraspinous mass

## ESCC: Symptoms and Signs

- Back pain: 90-95%, typically for 2-3 mo
  - Gradually worsening, may ↑ w/recumbency
  - Often, radicular component over time
  - Abrupt worsening suggests compression fracture
- Motor: Weakness in 65-80% at diagnosis
  - Usually symmetric; findings depend on level
- Sensory loss: Majority of patients
  - Requires careful history and exam
  - Level typically 1-5 levels below anatomic compression
  - Saddle loss in cauda compression
- Bowel/bladder dysfunction: Late finding
  - Rarely the sole symptom of ESCC
- Majority of patients non-ambulatory at diagnosis

## ESCC: Radiographic Diagnosis

- MRI the best
  - Images cord, leptomeninges, bone, paraspinal tissues
  - Coagulopathy, low platelets, spinal block not concerns
- CT-myelography
  - Alternative when MRI contraindicated
  - May be adjunct in (radio)surgical planning
  - May be easier for pts with severe pain
- CT: Good for bone destruction but doesn't show cord, epidural space
- Plain x-rays: not sensitive enough for screening tool
  - Vert collapse or pedicle erosion highly predictive of ESCC
- One-third of pts have multiple ESCCs

## ESCC: Fractionated RT

- Standard of care for most patients
- Potential side effects
  - Radiation myelopathy
  - Gastrointestinal
  - Myelosuppression
- Pre-treatment ambulatory status
  - 80-100% amb post-Rx if amb pre-Rx
  - 1/3 amb post-Rx if paraparetic pre-Rx
  - 2-6% amb post-Rx if paraplegic pre-Rx
- Tumor type
- Rapidity of onset of deficits also a factor
  - Rapid onset of deficits over $\leq 48^{o}$ bodes poorly
- Degree of spinal block (↓↓ importance)
- ≈ 50% alive at one year still ambulatory

## ESCC: RT Dose & Schedule

- RCT of 1600 cGy/2 fx vs 3,000 cGy/8 fx
  - Randomized 300 pts with life expectancy < 6 mo.
  - No differences in efficacy or toxicity
- 3,000/10 vs 4,000/20
  - Prospective but Rx assigned based on appt availability
  - No difference in post-Rx motor fx or % ambulatory
- 1,300 pts on 5 schedules (800/1 to 4,000/20)
  - Retrospective
  - All regimens gave similar functional results
  - More protracted schedules had fewer in-field recurrences
  - Recommended 800/1 for poor prognosis and 3,000/10 for good prognosis

Maranzone JCO 2005, Rades Cancer 2004, Rades JCO 2005

## ESCC: Surgery

- Laminectomy w/o stabilization best avoided
- Replaced by radical resection + stabilization
- Case series suggested best initial Rx for
  - Spinal instability
  - Retropulsed bone in spinal canal
  - Deterioration during/after RT
  - Radioresistant tumor and otherwise good prognosis

## ESCC: Surgery + RT vs. RT

- RCT for non-radiosensitive metastatic ESCC
  - Direct circumferential tumor resection + RT vs RT only
  - 101 pts
  - RT 3,000 cGy in 10 fractions
  - Steroids standardized
  - RT only arm could cross over to S for worsening
  - $1^{o}$ endpoint time ambulatory after treatment
- Single ESCC, life expectancy 3+ mo, no paraplegia > $48^{o}$
- Surgical complication rate 12%
- 9/16 non-ambulatory pts in S/RT group regained ability to walk c/w 3/16 in RT group
- 20% of RT group crossed over to S/RT because of deterioration during RT

## ESCC: Radiosurgery

- A.k.a. stereotactic body radiotherapy
- Precision allows ↑ tumor dose while sparing cord
- Requires immobilization, control for respiratory movement, incorporation of CT scanner and LINAC
- Particularly useful for radioresistant tumors
  - RCC, sarcoma, melanoma
- Achieves long-term tumor control in ≈ 90% w/o neuro deficits or spinal instability
- However, larger tumors producing high-grade cord compression can't be safely and effectively treated without first debulking
- Reasonable 1st option in low-grade ESCC from radioresistant tumor w/o spinal instability

## ESCC: Managing Recurrence

- 20% recur at median of 7 mo
  - Half at initial site of ESCC
  - Half of 2-yr survivors of ESCC have 2nd episode
- Radiosurgery good option if lesion small
- Standard RT reasonably effective especially if life expectancy < 1 yr
- Surgical decompression if prognosis adequate
- Systemic therapy?

## Prognosis after ESCC

- Retrospective multivariate analysis of 1852 patients treated with radiotherapy.
- Local control is associated with favorable histology (breast, prostate, heme) and long-course RT.
- Survival is associated with:
  - Favorable histology,
  - Absence of visceral and other bone mets
  - ↑ing time between tumor and ESCC dx
  - Ambulatory before RT
  - Slow development of motor deficits pre-RT
- 1-year survival 43%

Rades, J Clin Oncol 2006