LOW GRADE GLIOMAS : STATE OF ART AND FUTURE DIRECTIONS

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GENERAL CONCEPTS ON NATURAL HISTORY 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%), being the process different in astrocytomas and in oligodendrogliomas
- It is more frequent in older patients (>40 – 45 years) with astrocytoma
- At diagnosis it is unpredictable in the individual patients
- Overall, low grade gliomas are an heterogeneous populations in terms of outcome

CLINICAL AND RADIOLOGICAL UNFAVORABLE PROGNOSTIC FACTORS

- Age > 40 yrs
- Presence of neurological deficits and/or absence of seizures at onset
- Low performance status (Karnofsky < 70)
- Preoperative tumor diameter > 4-5-6 cm and/or tumor crossing the midline
- Astrocytoma histology
- Contrast enhancement on MRI still uncertain

Baumann et al, 1999; Pignatti et al, 2002; Daniels et al, 2011;

TABLE 4

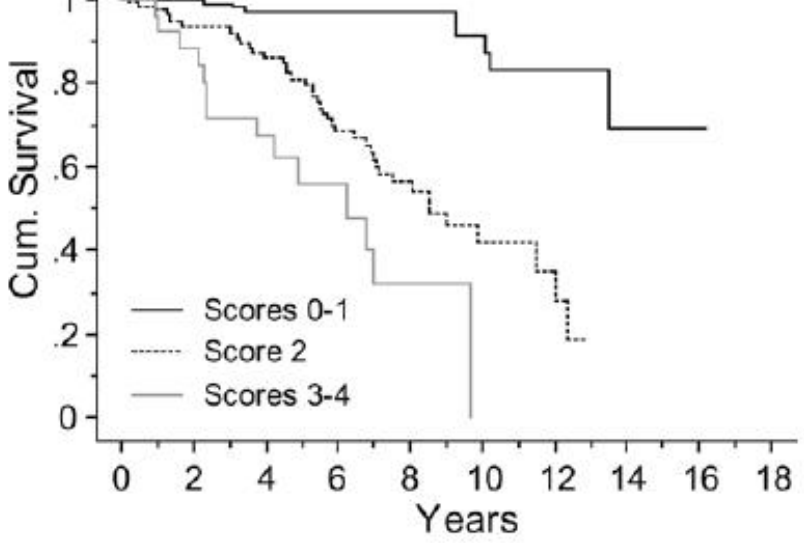
Low-grade glioma scoring system (UCSF)

	(Y/N)
age >50 yrs	(1/0)
KPS ≤80	(1/0)
eloquent location (presumed)	(1/0)
diameter (max) >4 cm	(1/0)

total score = sum of above (range 0–4)

J. Neurosurg. / Volume 109 / November 2008

Chang et al, J Neurosurg 2008



Progression-Free Survival

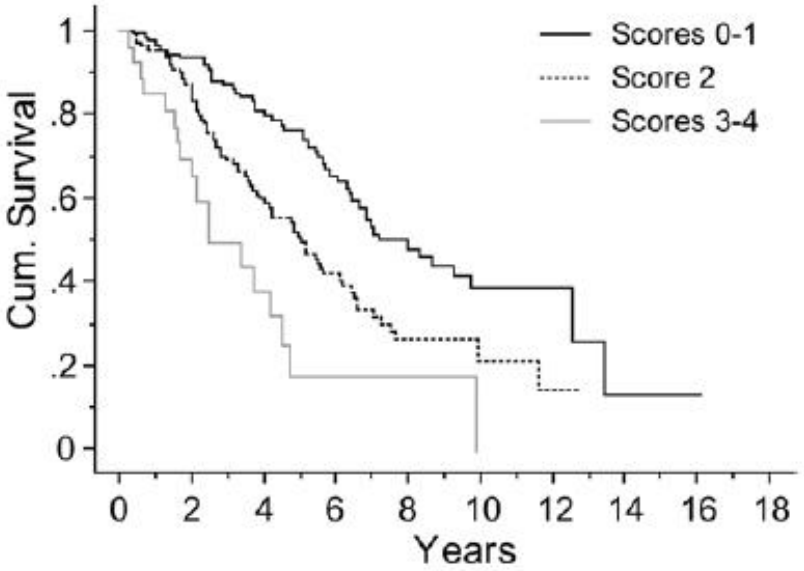


FIG. 2. Graphs showing long-term OS *(upper)* and PFS *(lower)* in patients after resection of LGG. Cum. = Cumulative.

Chang et al, J Neurosurg, 2008

ADVANCED NEUROIMAGING UNFAVORABLE PROGNOSTIC FACTORS : TO BE VALIDATED IN CLINICAL TRIALS

- High speed of volumetric increase or velocity of diametric expansion (VDE)
- Elevated cerebral blood volume (CBV) values
- High uptake of methionine on PET

Ribon et al, 2001; Laws et al, 2008;

Rees et al, 2009; Caseiras et al,2010

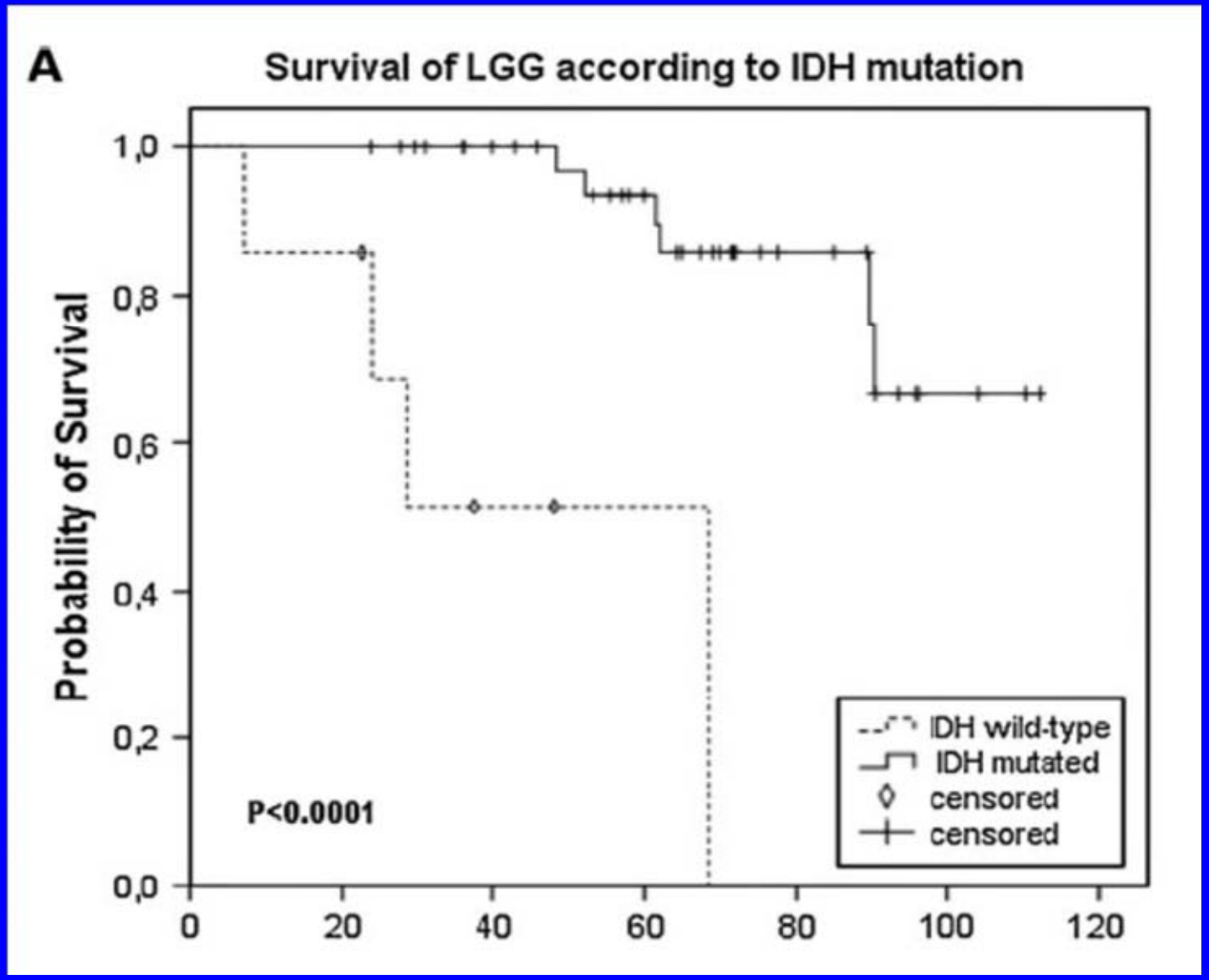
MOLECULAR FACTORS OF PROGNOSTIC VALUE: 1p/19q STATUS

- 1p deletion or 1p/19q co-deletion, that are commonly associated with the oligodendroglial phenothype, predict longer overall survival (Smith et al, 2000; Fallon et al, 2004; Kujas et al, 2005; Walker et al, 2005; Mariani et al, 2006).

- 1p/19q co-deletion does not confer any prognostic advantage in terms of progression-free survival in patients with oligodendroglial tumors after surgery alone (Weller et al, 2007;)

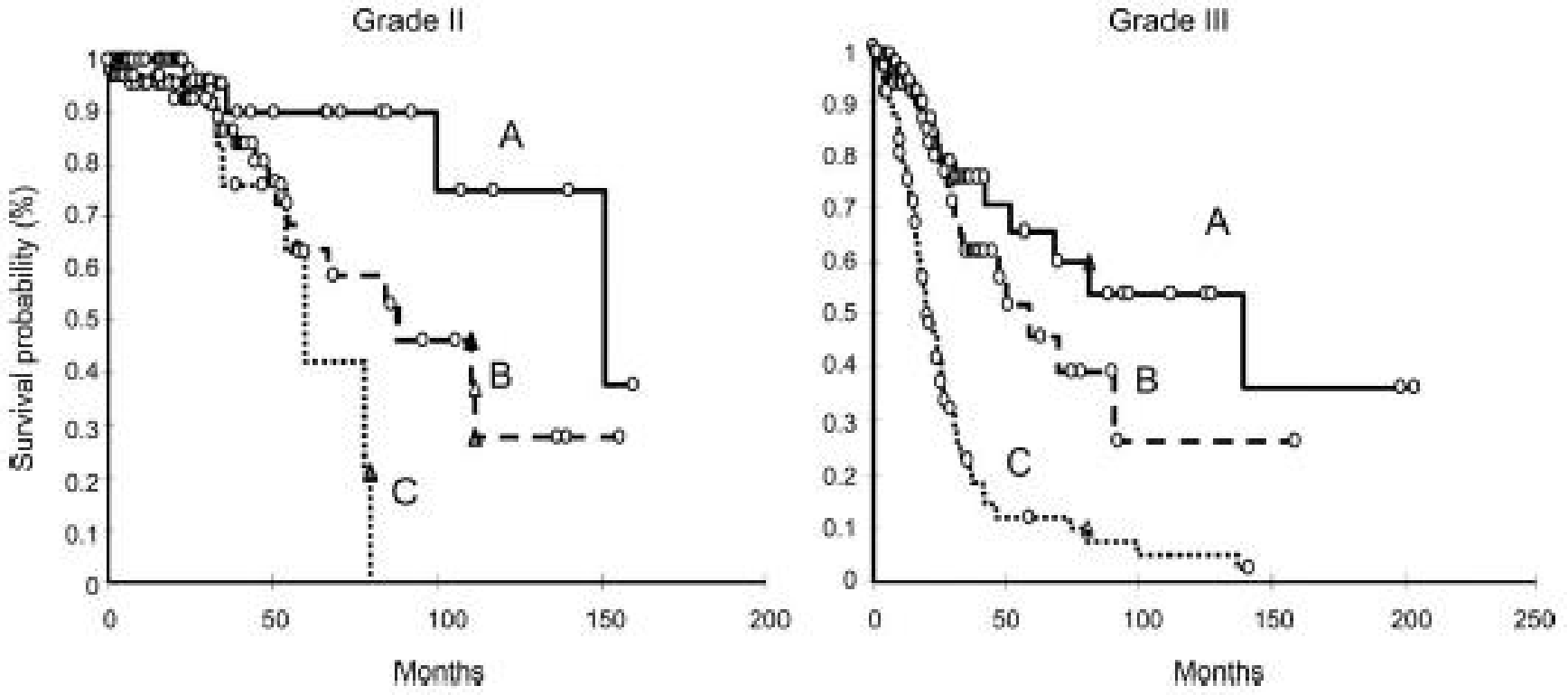
MOLECULAR FACTORS OF PROGNOSTIC VALUE: MGMT STATUS

- MGMT promoter methylation predicts shorter progression-free survival in diffuse astrocytomas (WHO grade II) after surgey alone (Komine et al, 2005)



Metellus et al, Acta Neuropathologica 120:719-729, 2010

Figure 2 Overall survival in grade II and III gliomas according to 1p19q and IDH1/IDH2 status identifies 3 prognostic subtypes: Complete 1p19q codeletion (A), no complete 1p19q codeletion but IDH1/2 mutation (B), no complete 1p19q codeletion and no IDH1/2 mutation (C)



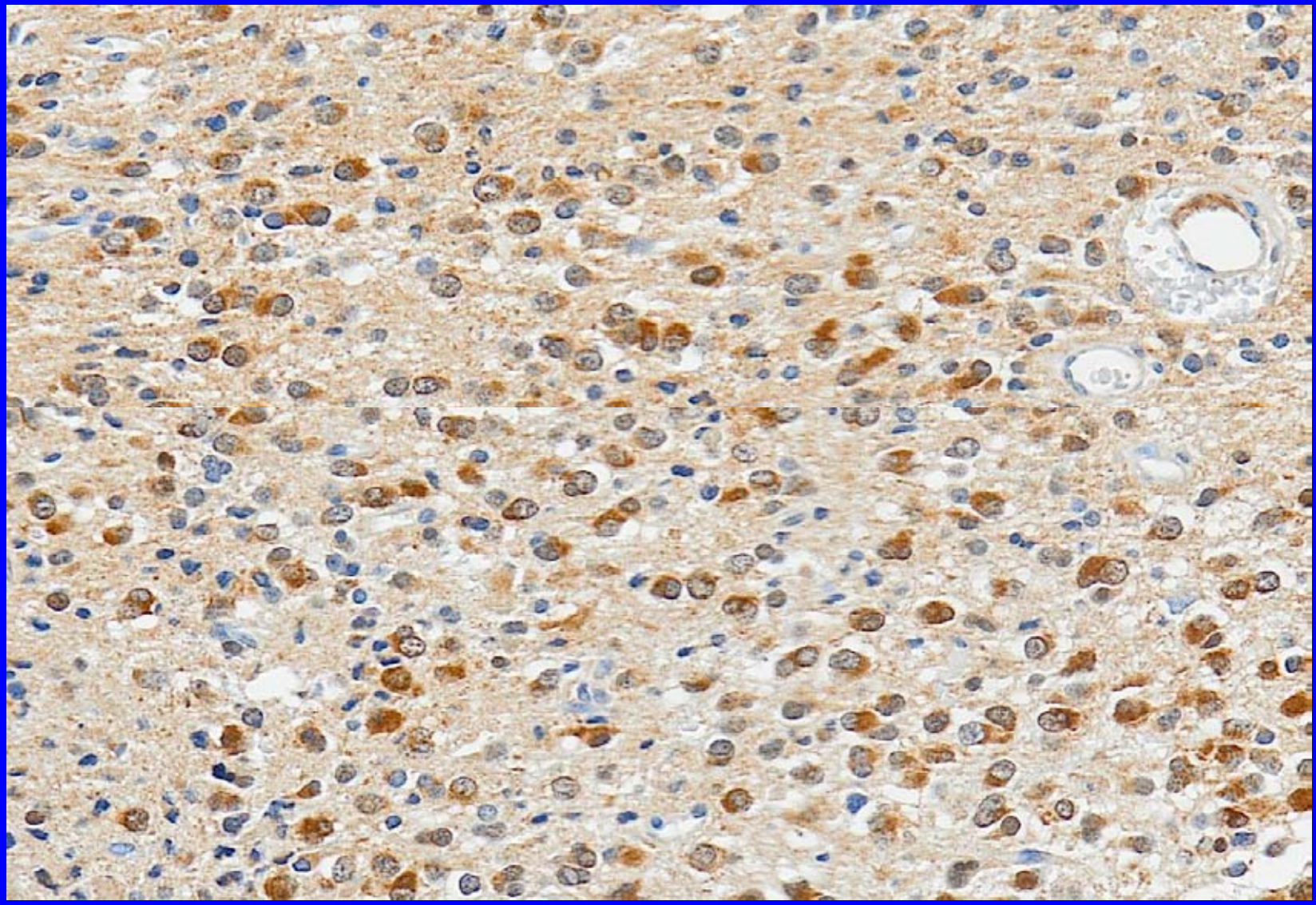
In these 3 categories, median overall survival is as follows: for grade II, 151 months (100–∞), 88 months (58–∞), 60 months (54–80), $p = 0.012$; and for grade III, 139 months (51–∞), 59 months (33–∞), 20 months (17–26), $p < 10^{-4}$.

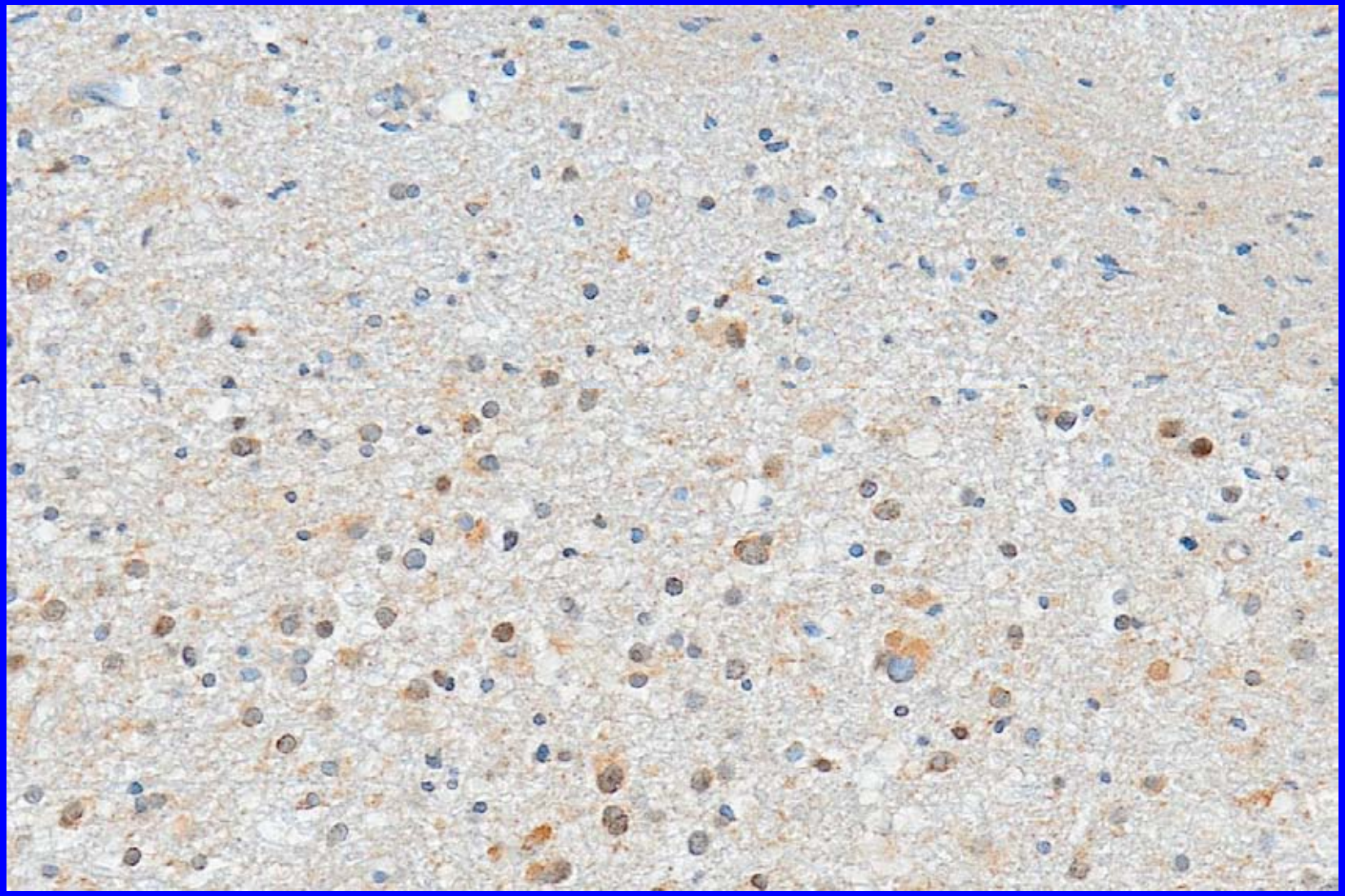
Labussiere et al, Neurology, 74 , 1886 - 2010

IMMUNOHISTOCHEMISTRY FOR IDH-1 MUTATIONS IN THE DIAGNOSTIC SETTING

- To distinguish diffuse grade II gliomas from entities, such as pilocytic astrocytoma, central neurocytoma, DNET and ependymoma.
- To distinguish diffuse grade II and III gliomas from reactive gliosis
- To detect single neoplastic cells in small samples or in specimens originating from the infiltrating tumor edge

Caffer et al, 2010;Von Deimling et al, 2010; Preusser et al, 2011





Pregnancy Increases the Growth Rates of World Health Organization Grade II Gliomas

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Denys Fontaine, MD,[3,6] Mathilde Badoual, PhD,[5]
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Hugues Duffau, MD,[3,13]
and Luc Taillandier, MD[3,14]; for the Club de Neuro-Oncologie de la Société Française de Neurochirurgie (SFNC) and the Association des Neuro-Oncologues d'Expression Française (ANOCEF)

Twelve pregnancies in 11 adult women harboring World Health Organization (WHO) grade II gliomas (GIIGs) prior to pregnancy were reviewed to address whether pregnancy affects tumor growth using a quantitative approach of the radiological velocity of diametric expansion (VDE) on successive magnetic resonance images. VDE was significantly increased during pregnancy as compared to prepregnancy ($p < 0.001$) and to postdelivery ($p = 0.012$) periods. Pregnancy increases the radiological growth rates of GIIGs. An increase in seizure frequency was observed concomitantly in 40% of cases and further oncological treatment was started after delivery in 25% of cases.

ANN NEUROL 2010;67:398–404

Pallud et al, Ann Neurol, 2010

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2608-1338/$20.00

DOI: 10.1200/JCO.2007.13.9337

ABSTRACT

Purpose
The prognostic role of extent of resection (EOR) of low-grade gliomas (LGGs) is a major controversy. We designed a retrospective study to assess the influence of EOR on long-term outcomes of LGGs.

Patients and Methods
The study population (N = 216) included adults undergoing initial resection of hemispheric LGG. Region-of-interest analysis was performed to measure tumor volumes based on fluid-attenuated inversion-recovery (FLAIR) imaging.

Results
Median preoperative and postoperative tumor volumes and EOR were 36.6 cm^3 (range, 0.7 to 246.1 cm^3), 3.7 cm^3 (range, 0 to 197.8 cm^3) and 88.0% (range, 5% to 100%), respectively. There was no operative mortality. New postoperative deficits were noted in 36 patients (17%); however, all but four had complete recovery. There were 34 deaths (16%; median follow-up, 4.4 years). Progression and malignant progression were identified in 95 (44%) and 44 (20%) cases, respectively. Patients with at least 90% EOR had 5- and 8-year overall survival (OS) rates of 97% and 91%, respectively, whereas patients with less than 90% EOR had 5- and 8-year OS rates of 76% and 60%, respectively. After adjusting each measure of tumor burden for age, Karnofsky performance score (KPS), tumor location, and tumor subtype, OS was predicted by EOR (hazard ratio [HR] = 0.972; 95% CI, 0.960 to 0.983; $P < .001$), log preoperative tumor volume (HR = 4.442; 95% CI, 1.601 to 12.320; $P = .004$), and postoperative tumor volume (HR = 1.010; 95% CI, 1.001 to 1.019; $P = .03$), progression-free survival was predicted by log preoperative tumor volume (HR = 2.711; 95% CI, 1.590 to 4.623; $P \leq .001$) and postoperative tumor volume (HR = 1.007; 95% CI, 1.001 to 1.014; $P = .035$), and malignant progression-free survival was predicted by EOR (HR = 0.983; 95% CI, 0.972 to 0.995; $P = .005$) and log preoperative tumor volume (HR = 3.826; 95% CI, 1.632 to 8.969; $P = .002$).

Conclusion
Improved outcome among adult patients with hemispheric LGG is predicted by greater EOR.

J Clin Oncol 26:1338-1345. © 2008 by American Society of Clinical Oncology

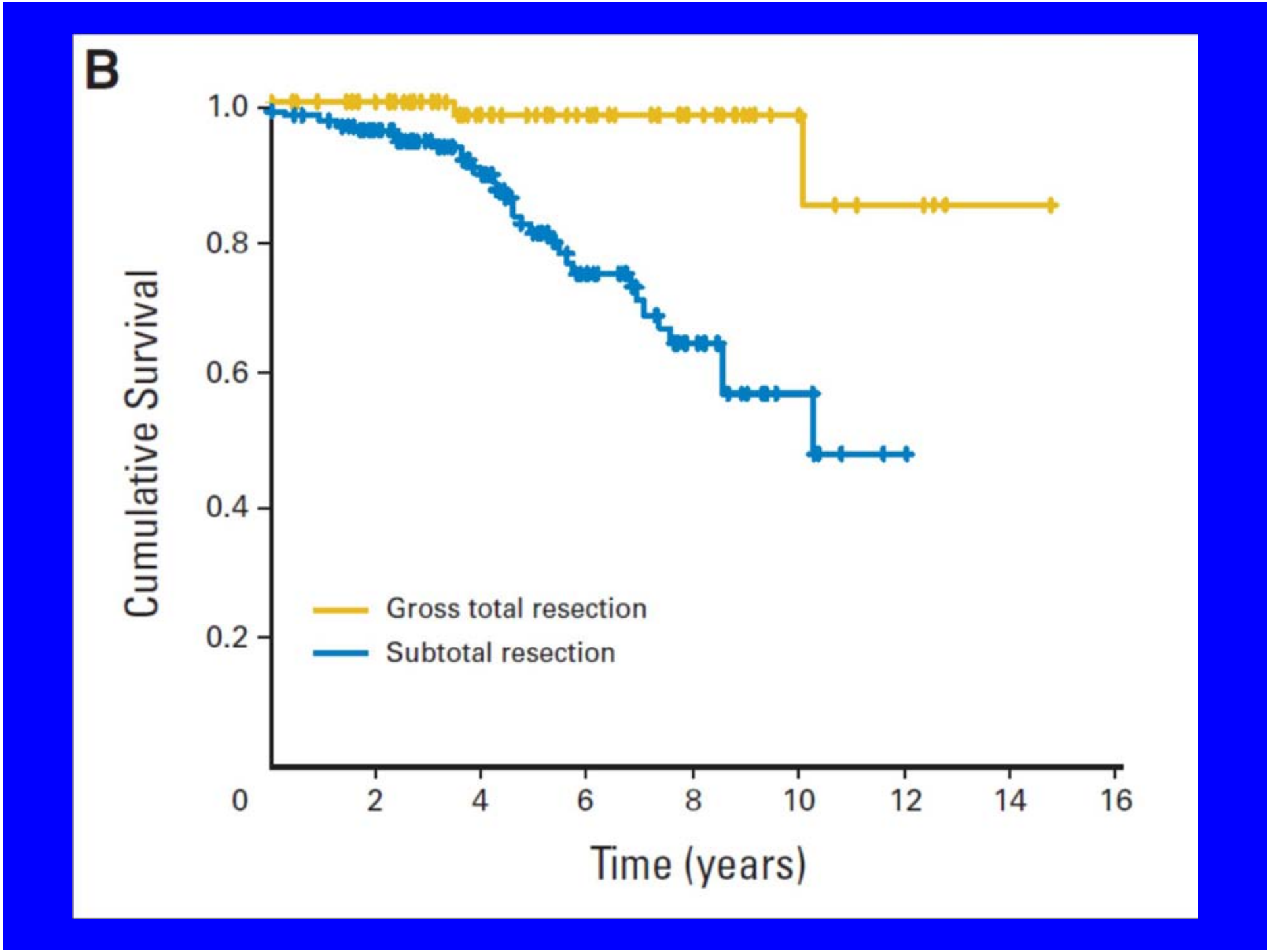
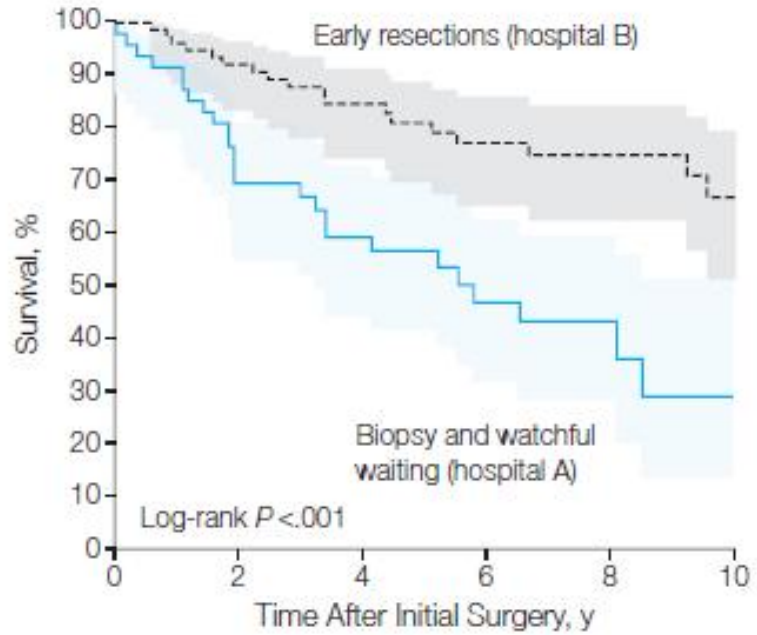

B
1.0
0.8
0.6
0.4
0.2
Cumulative Survival
Gross total resection
Subtotal resection
0
2
4
6
8
10
12
14
16
Time (years)

Figure 3. Survival When Treated in Accordance With Favored Strategy



No. of patients at risk						
Biopsy	47	30	23	14	6	3
Resection	75	67	48	39	22	13

This analysis excludes patients who initially received treatment different from the local favored strategy (excluding the 19 patients with initial resections at hospital A and the 12 patients who were only initially biopsied at hospital B). A survival benefit of resection was seen with median survival of 5.8 years (95% CI, 3.0-8.7) at hospital A while median survival was not reached at hospital B ($P<.001$). Shaded areas indicate 95% CIs.

Jakola et al, JAMA 2012

See the corresponding editorial in this issue, pp 230–231.

J Neurosurg 115:232–239, 2011

Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection

Clinical article

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J Neurosurg 108:227–235, 2008

Seizure characteristics and control following resection in 332 patients with low-grade gliomas

Edward F. Chang, M.D.,[1] Matthew B. Potts, M.D.,[1] G. Evren Keles, M.D.,[1] Kathleen R. Lamborn, Ph.D.,[1,2] Susan M. Chang, M.D.,[1,2] Nicholas M. Barbaro, M.D.,[1] and Mitchel S. Berger, M.D.[1,2]

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Object. Seizures play an important role in the clinical presentation and postoperative quality of life of patients who undergo surgical resection of low-grade gliomas (LGGs). The aim of this study was to identify factors that influenced perioperative seizure characteristics and postoperative seizure control.

Methods. The authors performed a retrospective chart review of all cases involving adult patients who underwent initial surgery for LGGs at the University of California, San Francisco between 1997 and 2003.

Results. Three hundred and thirty-two cases were included for analysis; 269 (81%) of the 332 patients presented with $\geq$ 1 seizures (generalized alone, 33%; complex partial alone, 16%; simple partial alone, 22%; and combination, 29%). Cortical location and oligodendroglioma and oligoastrocytoma subtypes were significantly more likely to be associated with seizures compared with deeper midline locations and astrocytoma, respectively ($p = 0.017$ and 0.001, respectively; multivariate analysis). Of the 269 patients with seizures, 132 (49%) had pharmacoresistant seizures before surgery. In these patients, seizures were more likely to be simple partial and to involve the temporal lobe, and the period from seizure onset to surgery was likely to have been longer ($p = 0.0005$, 0.0089, and 0.006, respectively; multivariate analysis). For the cohort of patients that presented with seizures, 12-month outcome after surgery (Engel class) was as follows: seizure free (I), 67%; rare seizures (II), 17%; meaningful seizure improvement (III), 8%; and no improvement or worsening (IV), 9%. Poor seizure control was more common in patients with longer seizure history ($p < 0.001$) and simple partial seizures ($p = 0.004$). With respect to treatment-related variables, seizure control was far more likely to be achieved after gross-total resection than after subtotal resection/biopsy alone (odds ratio 16, 95% confidence interval 2.2–124, $p = 0.0064$). Seizure recurrence after initial postoperative seizure control was associated with tumor progression ($p = 0.001$).

Conclusions. The majority of patients with LGG present with seizures; in approximately half of these patients, the seizures are pharmacoresistant before surgery. Postoperatively, $>$ 90% of these patients are seizure free or have meaningful improvement. A shorter history of seizures and gross-total resection appear to be associated with a favorable prognosis for seizure control. *(DOI: 10.3171/JNS/2008/108/2/0227)*

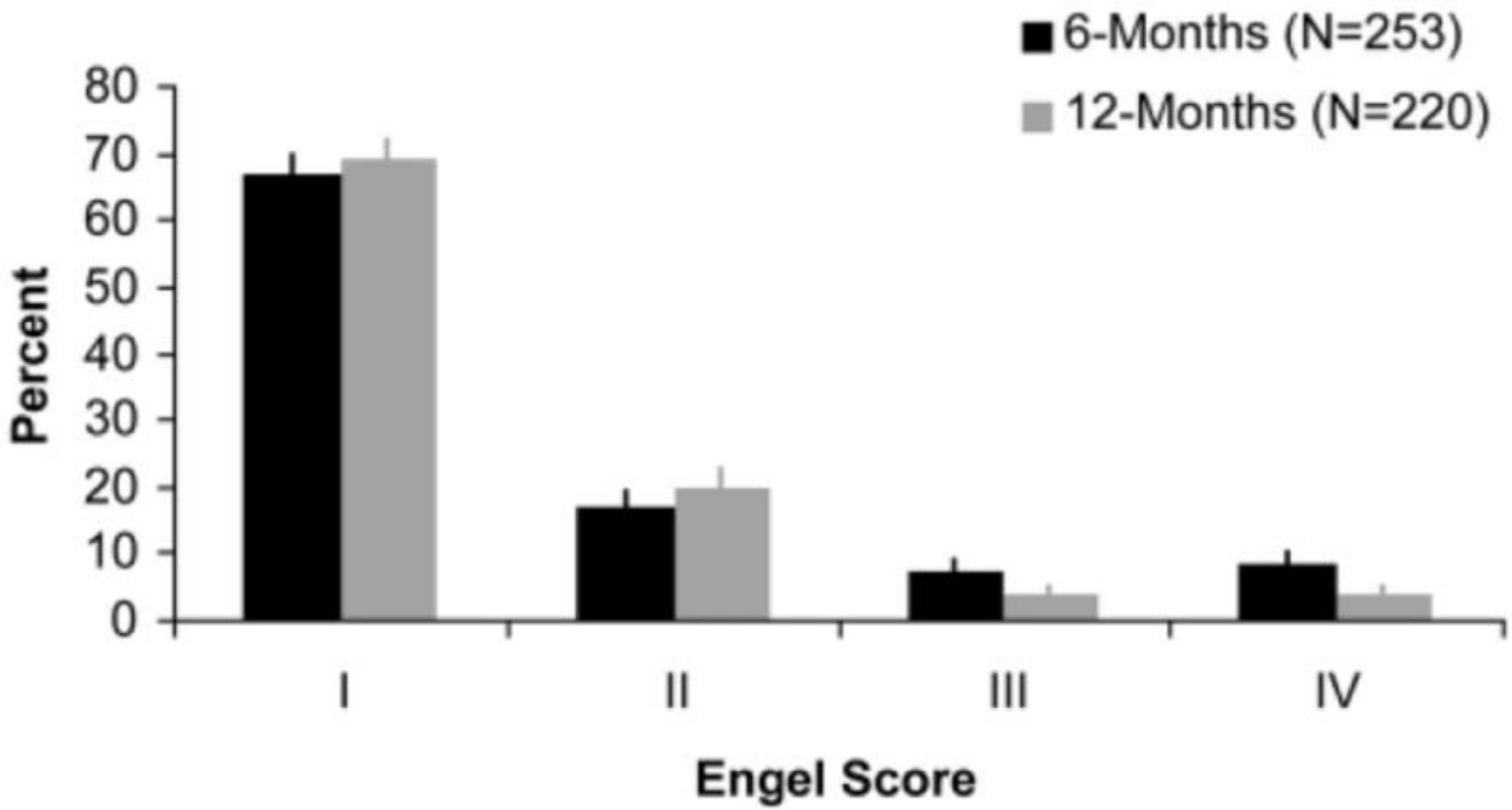


FIG. 1. Graph illustrating seizure control (Engel class) at 6 and 12 months after surgery in patients who had a preoperative history of seizures (controlled or uncontrolled). N = number of patients.

TABLE 3: Predictors of seizure freedom after tumor resection*

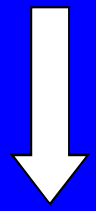
Factor	OR	95% CI	p Value
medically controlled seizures	2.12	1.33–3.38	0.002
simple partial seizures	0.46	0.26–0.80	0.007
seizures for ≤1 yr	1.85	1.22–2.79	0.003
gross-total resection	3.41	2.36–4.93	<0.001

* Results of binary logistic regression analysis.

Englot et al, J Neurosurg, April 29, 2011

LOW RISK PATIENTS : DEFINITION

patients with gross total resection and/or age <40



Observation with MRI

J Neurosurg 109:835–841, 2008

Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial

Clinical article

Edward G. Shaw, M.D.,[1] Brian Berkey, M.S.,[2] Stephen W. Coons, M.D.,[3] Dennis Bullard, M.D.,[4] David Brachman, M.D.,[5] Jan C. Buckner, M.D.,[6] Keith J. Stelzer, M.D., Ph.D.,[7] Geoffrey R. Barger, M.D.,[8] Paul D. Brown, M.D.,[9] Mark R. Gilbert, M.D.,[10] and Minesh Mehta, M.D.[11]

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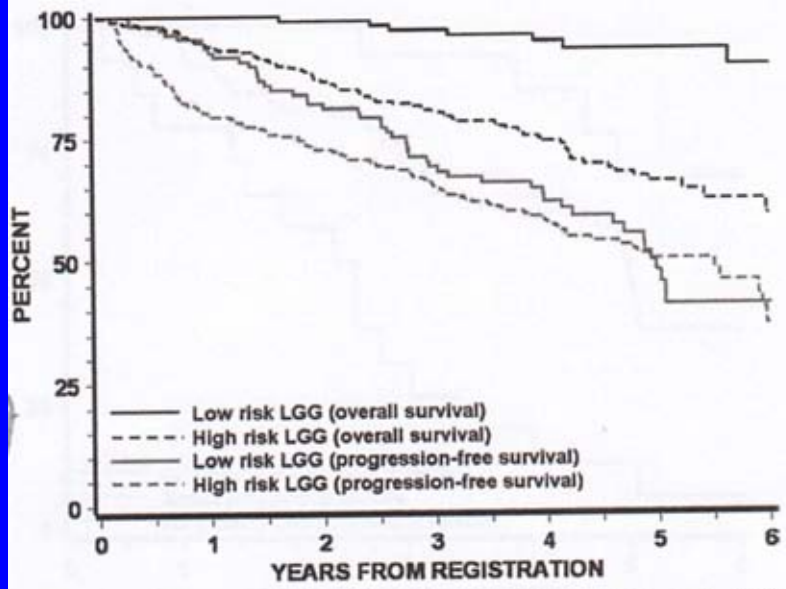

FIG. 2. Line graph showing the overall survival and PFS curves for the 111 patients with favorable (low risk) LGG and the 251 patients with unfavorable (high risk) LGG.

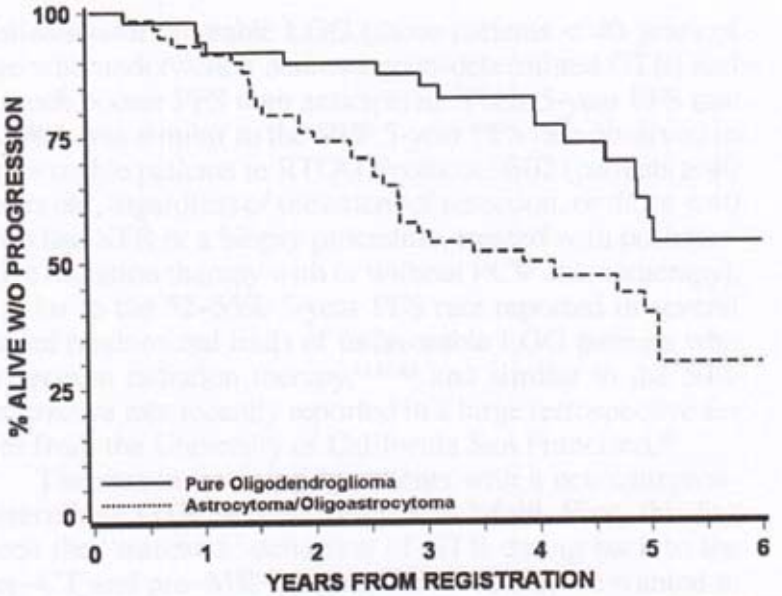

FIG. 4. Line graph showing patient PFS according to histological type (pure oligodendroglioma vs astrocytoma and mixed oligoastrocytoma).

Shaw et al, J Neurosurg 109: 835-841, 2008

EARLY VERSUS DELAYED RADIOTHERAPY: EORTC 22485

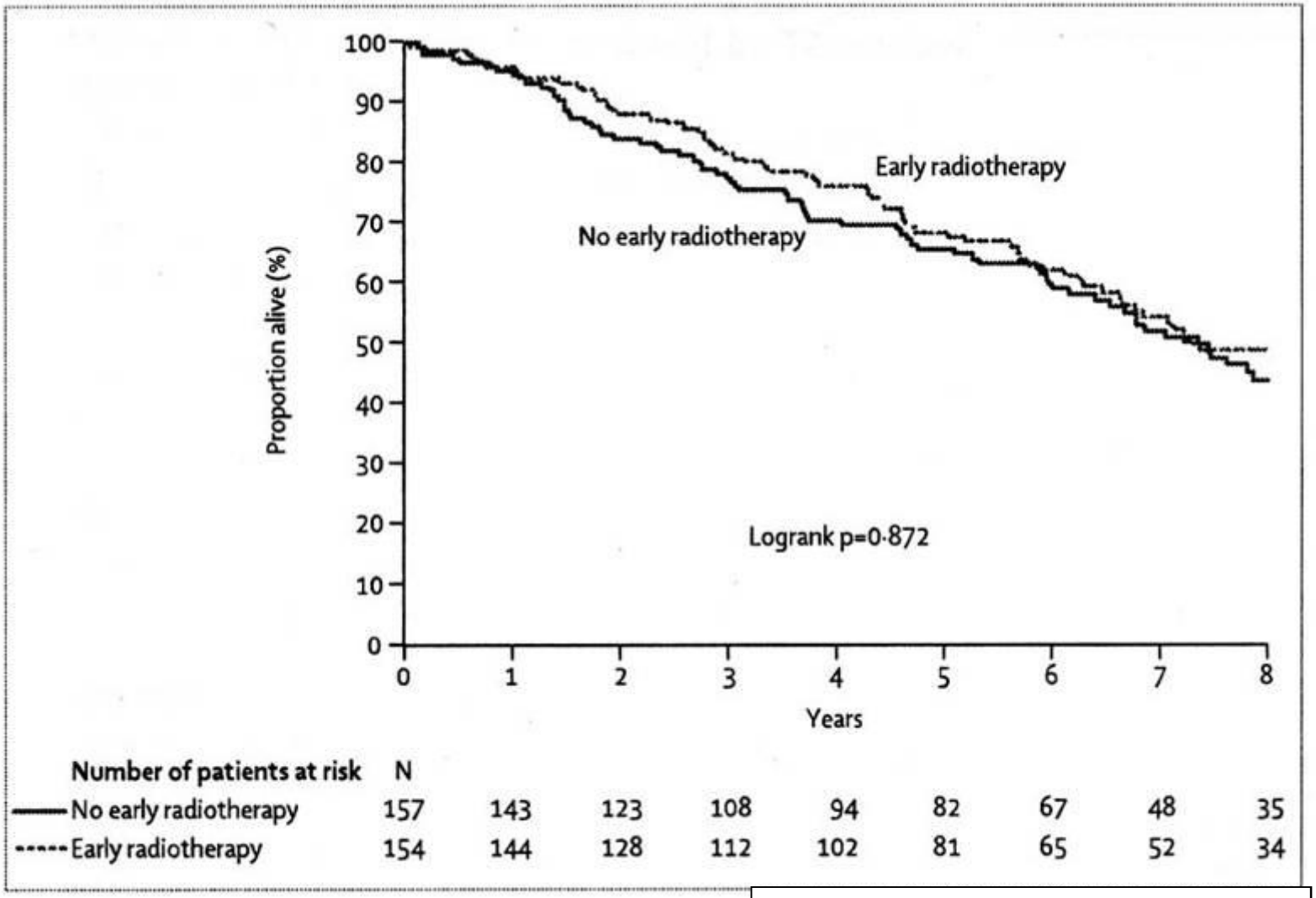

Figure 2: **Overall survival by intention-to-treat analysis**
Number of events: O=80 for control group; O=76 for early radiotherapy group.

Van den Bent *et al*, Lancet 2005

EARLY VERSUS DELAYED RADIOTHERAPY: EORTC 22485

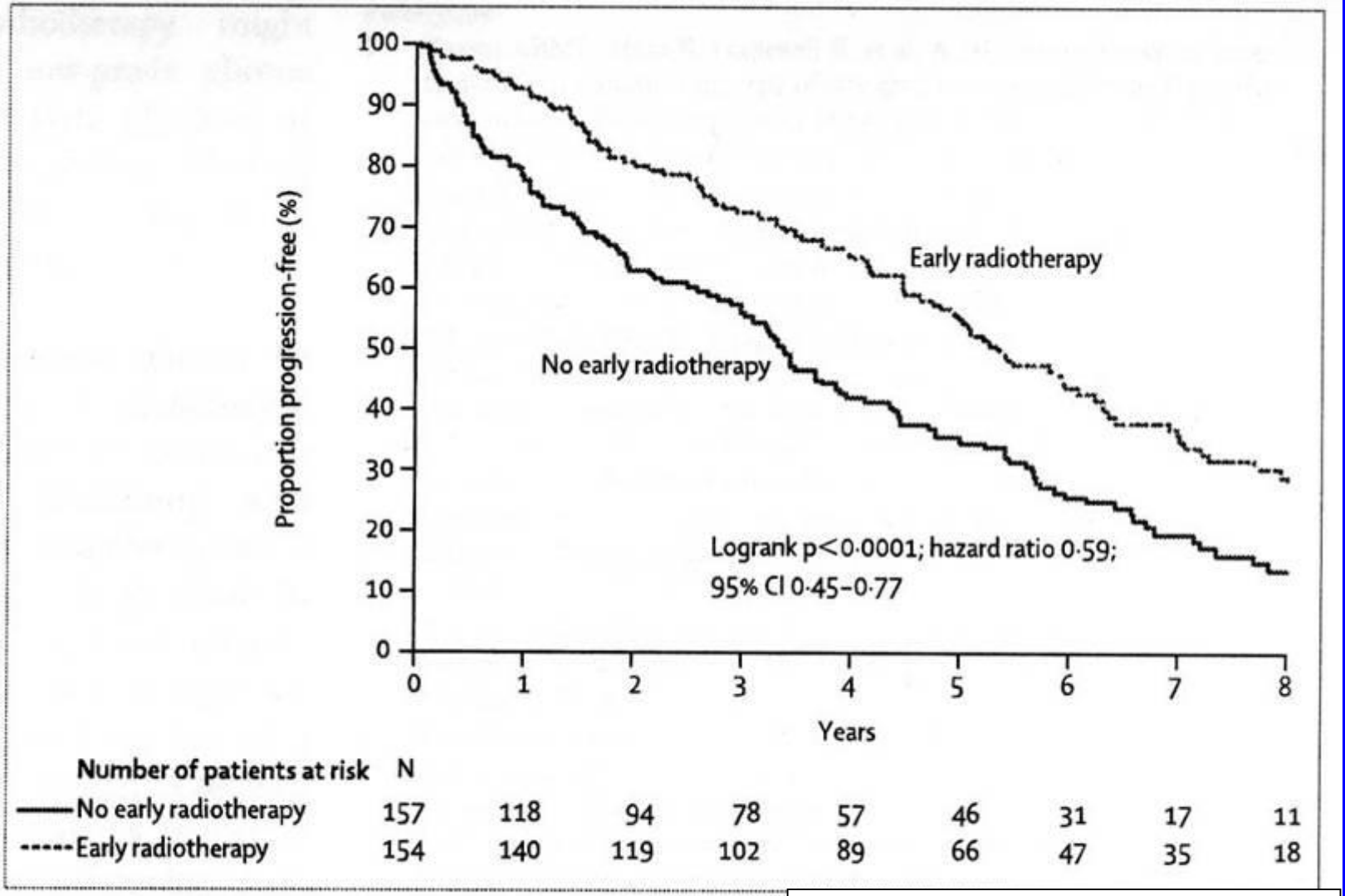

Figure 3: **Progression-free survival by intention-to-treat analysis**
Number of events: O=121 for control group; O=96 for early radiotherapy group.

Van den Bent *et al*, Lancet 2005

RADIATION DOSE

- Low doses (45-50.4 Gy) are as efficacious as high doses (59.4-64.8 Gy) (EORTC22844 *Karim et al, 1996;* RTOG *Shaw et al, 2002)*
- Radiation necrosis is more frequent after high doses (10% vs 2%)
- Shortly after RT, radiation-induced changes may mimic tumor progression (“pseudo-tumor progression”)

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

Seizure control following radiotherapy in patients with low-grade gliomas: a retrospective study

	>50% seizure reduction
At 3 months after radiotherapy	25/33 (75.8%)
At 12 months after radiotherapy	19/25 (76%)

Engel classes	After 6 months from RT	After 12 months from RT
Seizure free (class I)	10/33 (30%)	8/25 (32%)
Rare seizures (class II)	1/33 (3%)	1/25 (4%)
Meaningful improvement in seizures (class III)	14/33 (43%)	10/25 (40%)
No improvement or worsening (class IV)	8/33 (24%)	6/25 (24%)

•Rudà et al., Neuro Oncol July 2013

Seizure control following radiotherapy in patients with low-grade gliomas: a retrospective study

Conclusions :

- This study confirms in a larger series of patients that conventional radiotherapy can reduce the seizure frequency in a significant proportion of patients with grade II astrocytomas

- Seizure reduction may begin early during radiotherapy (as already shown after interstitial radiotherapy)

- It does not seem to exist a correlation between the seizure reduction and tumor response on CT or MRI

Rudà et al, Neuro Oncol July 2013

WHICH ARE THE PATIENTS WHO MAY BENEFIT FROM CHEMOTHERAPY?

HIGH RISK PATIENTS

- Residual tumor after surgery
- Persisting seizures
- Age ?º40-45 years
- Progression on MRI

OPTIMIZATION OF CHEMOTHERAPY IN LOW GRADE GLIOMAS (LGGs) : ISSUES

- Best timing
- Best regimen and duration
- Role of molecular factors to predict response and outcome
- Role of standard and advanced neuroimaging to predict response and outcome

CHEMOTHERAPY FOR RECURRENT LGGs AFTER SURGERY AND RADIOTHERAPY

- At time of recurrence most cases are no longer LGGs but anaplastic gliomas with contrast enhancement.
- The usefulness of chemotherapy is well established, with more data available for oligodendrogliomas and oligoastrocytomas.
- PCV and temozolomide yield similar response rates (CR+PR) on MRI (45% - 62%) and duration of response (10-24 months), with a toxicity profile favouring temozolomide.

Soffietti et al, 1998, 2004; van den Bent et al, 1998, 2003a-b; Pace et al, 2003; Quinn et al, 2003

CHEMOTHERAPY FOR NEWLY DIAGNOSED HIGH RISK LOW-GRADE GLIOMAS

- Chemotherapy has been investigated either in association with radiotherapy or alone as an upfront treatment, delaying radiotherapy at the completion of chemotherapy or more commonly at tumor progression.

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.35.8598

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Trial of Radiation Therapy Plus Procarbazine, Lomustine, and Vincristine Chemotherapy for Supratentorial Adult Low-Grade Glioma: Initial Results of RTOG 9802

Edward G. Shaw, Meihua Wang, Stephen W. Coons, David G. Brachman, Jan C. Buckner, Keith J. Stelzer, Geoffrey R. Barger, Paul D. Brown, Mark R. Gilbert, and Minesh P. Mehta

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ABSTRACT

Purpose
A prior Radiation Therapy Oncology Group (RTOG) clinical trial in anaplastic oligodendroglioma suggested a progression-free survival benefit for procarbazine, lomustine, and vincristine (PCV) chemotherapy in addition to radiation therapy (RT), as have smaller trials in low-grade glioma (LGG).

Patients and Methods
Eligibility criteria included supratentorial WHO grade 2 LGG, age 18 to 39 years with subtotal resection/biopsy, or age ≥ 40 years with any extent resection. Patients were randomly assigned to RT alone or RT followed by six cycles of PCV. Survival was compared by using the modified Wilcoxon and log-rank tests.

Results
In all, 251 patients were accrued from 1998 to 2002. Median overall survival (OS) time and 5-year OS rates for RT versus RT + PCV were 7.5 years versus not reached and 63% versus 72%, respectively (hazard ratio [HR]; 0.72; 95% CI, 0.47 to 1.10; $P = .33$; log-rank $P = .13$). Median progression-free survival (PFS) time and 5-year PFS rates for RT versus RT + PCV were 4.4 years versus not reached and 46% versus 63%, respectively (HR, 0.6; 95% CI, 0.41 to 0.86; $P = .06$; log-rank $P = .005$). OS and PFS were similar for all patients between years 0 and 2. After 2 years, OS and PFS curves separated significantly, favoring RT + PCV. For 2-year survivors (n = 211), the probability of OS for an additional 5 years was 74% with RT + PCV versus 59% with RT alone (HR, 0.52; 95% CI, 0.30 to 0.90; log-rank $P = .02$).

Conclusion
PFS but not OS was improved for adult patients with LGG receiving RT + PCV versus RT alone. On post hoc analysis, for 2-year survivors, the addition of PCV to RT conferred a survival advantage, suggesting a delayed benefit for chemotherapy.

J Clin Oncol 30.

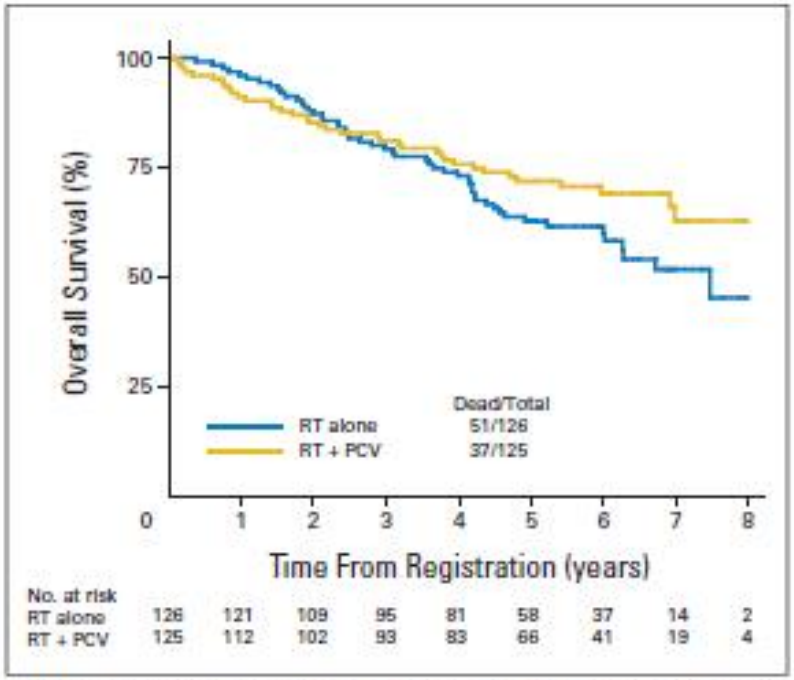


Fig 2. Overall survival for all patients from date of registration/random assignment. PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

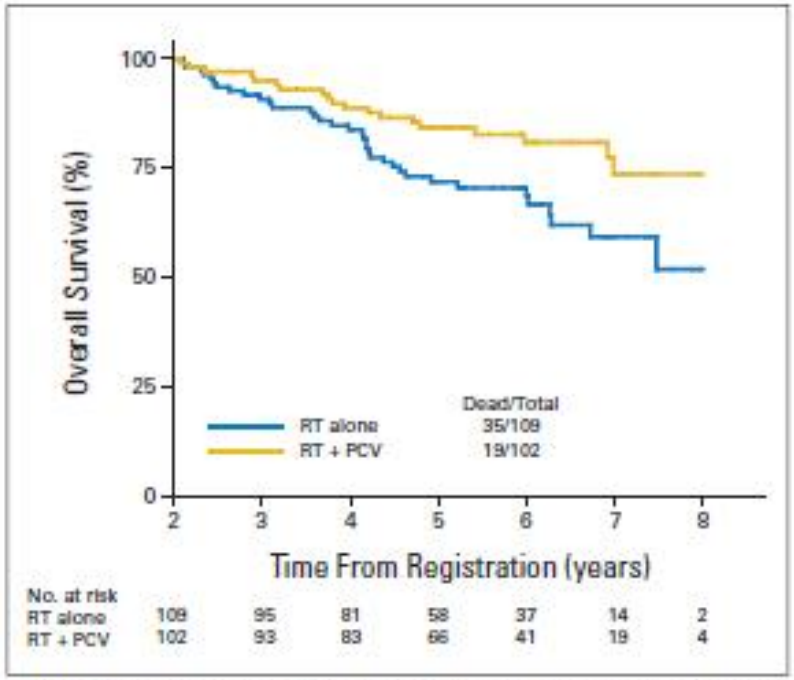


Fig 4. Overall survival for patients surviving to 2 years. PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

Shaw EG et al, JCO 2012

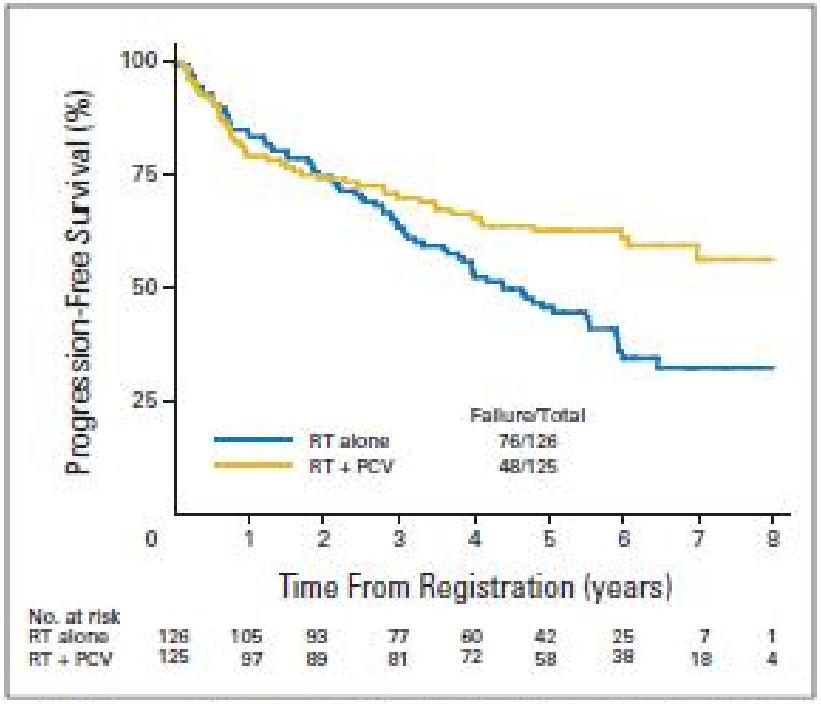


Fig 3. Progression-free survival for all patients from date of registration/random assignment. PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

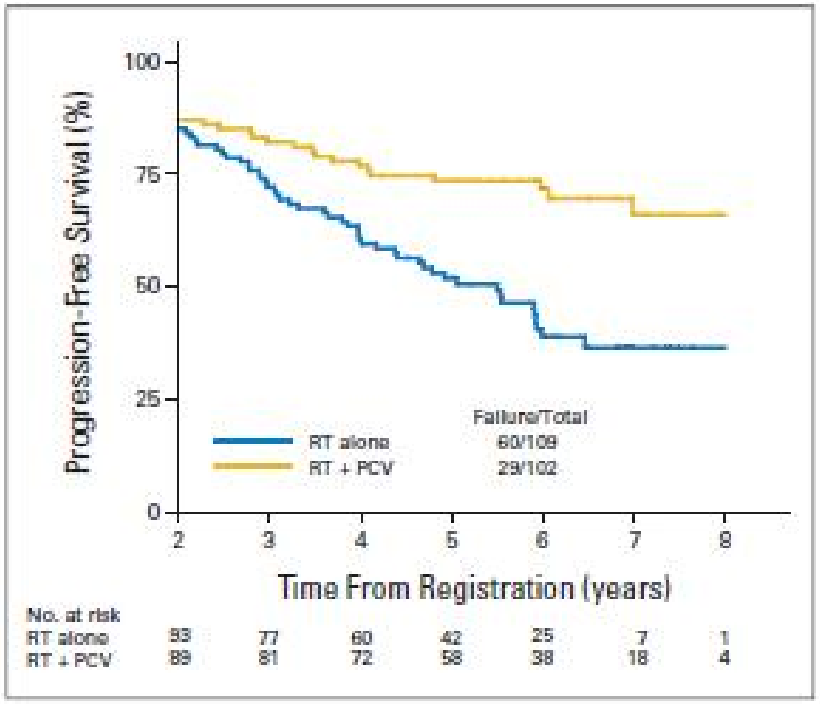


Fig 5. Progression-free survival for patients surviving to 2 years. PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

Shaw EG et al, JCO 2012

DATA FROM RTOG 9802 ARE NOT MATURE BECAUSE:

- With OS as the primary endpoint, 65% of patients are still alive
- Only 30% of patients who were treated with RT+PCV experienced progression
- No molecular analysis is available.

JCO January 7, 2013 : correspondence from Chamberlain and van den Bent et al.

LESSONS LEARNED FROM STUDIES ON CHEMOTHERAPY ALONE AS INITIAL TREATMENT

- Most tumors are non-enhancing or minimally enhancing on MRI, thereby response is evaluated on T2 / FLAIR images
- Complete responses are generally lacking, minor responses prevail over partial responses (PR + MR up to 53%).
- Responses are usually slow and progressive.
- Maximum tumor shrinkage can be delayed, as long as 24-30 months, and prolonged after the end of treatment.

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 ; Peyre et al, 2010

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

LESSONS LEARNED FROM STUDIES ON CHEMOTHERAPY ALONE AS INITIAL TREATMENT

- Median duration of response ranges between 24-48 months
- Astrocytic tumors can respond as well as oligodendrogliomas.
- Most patients with seizures have a clinical benefit even in the absence of a radiological change on MRI.

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%
Sherman et al, 2011	69	TMZ standard	59%

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

Rudà et al, Curr Opin Oncol 2010;22(6):611-20
Rudà et al, Neuro Oncol. 2012;14, Suppl 4:iv55-iv64

Studies of “upfront” chemotherapy for low-grade gliomas

Study	N° of patients	Radiological response (PR/MR)			PFS
		PCV	TMZ standard	TMZ dose-dense	
Buckner et al. 2003*	28	52%/NA	-	-	n.r.
Lebrun et al. 2007	33	27%/NA	-	-	12-mo: 90%
Peyre et al. 2010	21	38%/42%	-	-	n.r.
Pace et al. 2003	43	-	46%/37%	-	6-mo: 76% 12-mo: 39%
Brada et al. 2003	30	-	10%/48%	-	2-yr: 76% 3-yr: 66%
Hoang-Xuan et al. 2004	60	-	17%/14%	-	12-mo:73,4%
Kaloshi et al. 2007	149	-	15%/38%	-	Median: 28 mo
Pouratian et al. 2007	25	-	-	24%/28%	6-mo: 92% 12-mo: 72%
Tosoni et al. 2008	30	-	-	30%/NA	
Kesari et al. 2009	44	-	-	20%/NA	Median: 38 mo
Range		27%-80%	31%-58%	20%-58%	

CORRELATIONS BETWEEN RESPONSE TO TEMOZOLOMIDE AND 1P/19Q LOSS

Objective response rate higher in the 1p/19q loss group than in the 1p/19q intact group (72% vs 46%)

Duration of response longer in the 1p/19q deleted responders than in the 1p/19q intact responders (> 40 vs 20 months)

a proportion (up to 29%) of patients with 1p/19q intact do respond to chemotherapy

Buckner et al, 2003; Biemond-ter Stege et al, 2005; Levin et al, 2006;

Walker et al, 2006; Kaloshi et al, 2007;

CORRELATIONS BETWEEN RESPONSE TO TEMOZOLOMIDE AND MGMT METHYLATION AND IDH1 MUTATION

- MGMT promoter methylation predicts longer progression-free survival

  (*Everhard et al, 2006; Levin et al, 2006; Ochsenbein et al, 2011*).

- Uncertain whether IDH1 mutation predicts response.

  (*Dubbink et al, 2009; Houllier et al, 2010).*

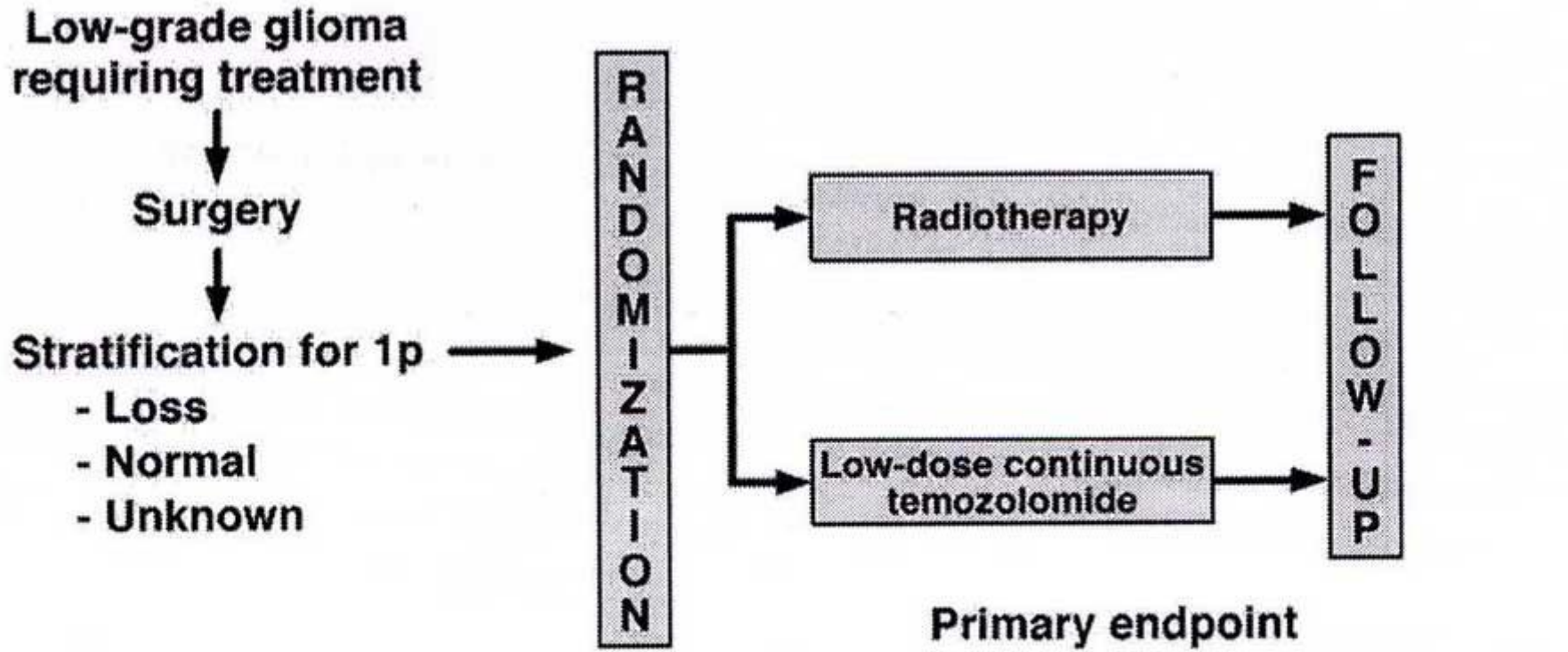
RECOMMENDATIONS OUTSIDE CLINICAL TRIALS

- Chemotherapy is indicated for patients recurrent after surgery and radiation therapy (Level B).
- Chemotherapy is an option as initial treatment in patients with large residual tumor after surgery to delay the risk of late neurotoxicity from radiotherapy, and this could be particularly true when 1p/19q loss is present (Good Practice Point). Nonetheless one must be aware that data regarding the efficacy of radiotherapy, when postponed at progression after chemotherapy, are still lacking.
- Up to date, the presence or absence of 1p/19q loss should not be used as the sole criterion for treatment decisions.

Soffietti et al, Eur J Neurol, 2010 (EANO Guidelines)

QUESTIONS TO BE ANSWERED BY CLINICAL TRIALS

- Which is the best initial treatment after surgery (radiotherapy or chemotherapy with TMZ)? ?*ƒ* phase III EORTC 22033-26033.
- Is the association of temozolomide with radiotherapy (Stupp regimen) superior over radiotherapy alone? ?F phase III RTOG trial.
- Is dose-dense temozolomide superior over standard temozolomide? (phase II AINO study).
- Is preoperative chemotherapy effective in terms of clinical (response, PFS) and surgical end-points? ?ú French and Italian pilot studies



Primary endpoint
- Progression-free survival

Secondary endpoints
- Quality of life
- Cognitive functions

Phase III EORTC 22033-26033

Phase III EORTC 22033-26033

Conclusions

- First line treatment with TMZ compared to RT did not improve PFS in high risk LGG (40 vs 47 mo respectively); however, they may be considered an equivalent alternative strategy
- Molecular analysis is ongoing (1p-19q, IDH1, etc) and may identify subgroups of patients who benefit mostly from one or other treatment strategy

Baumert et al, ASCO, Chicago 2013

DOSE-DENSE TEMOZOLOMIDE IN LGGs

- Protracted low-dose TMZ offers potential advantages over standard TMZ, including greater cumulative drug exposure and depletion of MGMT, theoretically overcoming intrinsic chemoresistance
- Two retrospective studies and one phase II trial reported results apparently similar to those obtained with the classical regimen.
- The phase II study suggested a preferential activity in patients with unmethylated MGMT promoter
- Protracted low-dose TMZ has a distinct spectrum of toxicity (ie, lymphopenia grade 3-4 : 20%-43%) that needs to be fully evaluated

Pouratian et al, 2007;Tosoni et al, 2008; Kesari et al, 2009

Dose-dense temozolomide as initial treatment for progressive low grade oligodendroglial tumors: a multicenter phase II study of the AINO (Italian Association of Neuro-Oncology)

R. Rudà[1], L. Bertero[1], E. Trevisan[1], A. Pace[2], C. Carapella[3], C. Dealis[4], M. Caroli[5], M. Faedi[6], C. Bomprezzi[7], R. Soffietti[1]

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ASCO, Chicago 2012; EANO, Marseille 2012

SNO, Washington 2012

ENDPOINTS

- Primary
  - Response rate according to modified Macdonald's criteria (centrally reviewed)

- Secondary
  - Median progression-free survival
  - PFS at 12 months
  - Overall survival
  - Toxicity (CTC criteria)
  - Correlation between molecular alterations (1p/19q, MGMT promoter methylation, IDH1 mutation) and response/outcome
  - Correlation between PET with Methionine and response/outcome

RESPONSE ON MRI-FLAIR IMAGES

Median number of cycles:	**11 (range 2 – 18)**

Type of response:	
- CR:	0/60
- PR:	21/60 (35%)
- MR:	14/60 (23%)
- SD:	21/60 (35%)
- PD:	4/60 (7%)

CLINICAL OUTCOME

Seizure improvement:	
- Significant (>50% reduction of frequency):	29/34 (85%)
- Not significant:	5/34 (15%)
- Increase in seizure frequency:	0/34

- Significant reduction of AEDs in 7/29 (24%)
- Withdrawal of AEDs in 2/29 (7%).
- Seizure-free at the end of treatment: 18/34 (53%)
- No significant correlations between seizure response and tumor site, seizure type, frequency and duration of seizures before treatment.

CORRELATIONS BETWEEN SEIZURE RESPONSE AND RADIOLOGICAL RESPONSE

Seizure improvement:		**Response on FLAIR MRI**		
		PR or MR	SD	PD
- Significant:	29/34 (85%)	20/29 (69%)	9/29 (31%)	0/29
- Not significant:	5/34 (15%)	1/5 (20%)	3/5 (60%)	1/5 (20%)

TIMING TO MAXIMUM RESPONSE

Time to maximum radiological response:	
- 3 cycles:	9.5%
- 6 cycles:	44%
- 9 cycles:	12.5%
- >9 cycles:	34%

Time to maximum clinical response:	
- < or = 3 cycles:	52%
- 6 cycles:	30%
- 9 cycles:	9%
- >9 cycles:	9%

CORRELATIONS BETWEEN 1p-19q CODELETION AND MRI RESPONSE

1p and 19q deletion available in:	**52/60 (87%)**
- Codeletion of 1p and 19q:	22/52 (42%)

Patients with codeletion:	**Patient without codeletion:**
- PR: 8/22 (36%)	- PR: 10/30 (33%)
- MR: 7/22 (32%)	- MR: 5/30 (17%)
- SD: 7/22 (32%)	- SD: 12/30 (40%)
- PD: 0	- PD: 3/30 (10%)

TOXICITY

Haematologic	
- Lymphopenia gr. 3	47%
- Neutropenia gr. 3	5%
- Neutropenia gr. 4	2%
- Thrombocytopenia gr. 3	7%
- Thrombocytopenia gr. 4	8%
Non haematologic	
- Fatigue	25%
- Infections*	18%
- Nausea	22%
- Weight loss	8%

- Minor infections except one patient who developed a pneumonia by Pneumocystis Jirovecii
- One patient developed a possible secondary Burkitt's lymphoma and died
- 18% of patients were shifted to TMZ standard because of toxicity while TMZ was stopped in 8%
- 28% of patients completed the entire course of therapy (18 cycles)

WHICH IS THE OPTIMAL DURATION OF CHEMOTHERAPY?

- In patients with LGGs treated with temozolomide a prolonged duration of treatment might be important to achieve a prolonged response

  (Hoang-Xuan et al, 2004)

- A dynamic volumetric study demonstrated that when temozolomide is discontinued in the absence of progression (after a median of 18 cycles), 60% of LGGs resume their growth within 1 year *(Ricard et al, 2007).*

WHICH IS THE OPTIMAL DURATION OF CHEMOTHERAPY?

- In patients with LGGs treated with PCV a dynamic volumetric study demonstrated that a prolonged (> 2 years) and persistent response after chemotherapy discontinuation was achieved despite the duration of PCV chemotherapy was shorter than that of temozolomide.

  (Peyre et al, 2010).

HOW TO ASSESS THE RADIOLOGICAL RESPONSE?

- Modified McDonald's criteria have been used to assess the response to chemotherapy, taking into account the product of perpendicular diameters of the lesion on $T_{2/FLAIR}$ images ("tumor area") (*Viaccoz et al, 2012*)
- These criteria have been formalized by the RANO group (*van den Bent et al, 2011*).
- A more precise quantification of tumor volume or mean tumor diameter seem more sensitive to detect the magnitude and duration of chemotherapy effects over time (*Ricard et al, 2007; Pallud et al, 2012*).

British Journal of Cancer (2011) 104, 1854 – 1861

www.bjcancer.com

Translational Therapeutics

Predicting the outcome of grade II glioma treated with temozolomide using proton magnetic resonance spectroscopy

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BACKGROUND: This study was designed to evaluate proton magnetic resonance spectroscopy (^{1}H-MRS) for monitoring the WHO grade II glioma (low-grade glioma (LGG)) treated with temozolomide (TMZ).

METHODS: This prospective study included adult patients with progressive LGG that was confirmed by magnetic resonance imaging (MRI). Temozolomide was administered at every 28 days. Response to TMZ was evaluated by monthly MRI examinations that included MRI with volumetric calculations and ^{1}H-MRS for assessing Cho/Cr and Cho/NAA ratios. Univariate, multivariate and receiver-operating characteristic statistical analyses were performed on the results.

RESULTS: A total of 21 LGGs from 31 patients were included in the study, and followed for at least $n = 14$ months during treatment. A total of 18 (86%) patients experienced a decrease in tumour volume with a greater decrease of metabolic ratios. Subsequently, five (28%) of these tumours resumed growth despite the continuation of TMZ administration with an earlier increase of metabolic ratios of 2 months. Three (14%) patients did not show any volume or metabolic change. The evolutions of the metabolic ratios, mean $(Cho/Cr)_n$ and mean$(Cho/NAA)_n$, were significantly correlated over time (Spearman $\rho = +0.95$) and followed a logarithmic regression ($P > 0.001$). The evolutions over time of metabolic ratios, mean$(Cho/Cr)_n$ and mean$(Cho/NAA)_n$, were significantly correlated with the evolution of the mean relative decrease of tumour volume, mean$(\Delta V_n/V_o)$, according to a linear regression ($P < 0.001$) in the 'response/no relapse' patient group, and with the evolution of the mean tumour volume (meanV_n), according to an exponential regression ($P < 0.001$) in the 'response/relapse' patient group. The mean relative decrease of metabolic ratio, mean$(\Delta(Cho/Cr)_n/(Cho/Cr)_o)$, at $n = 3$ months was predictive of tumour response over the 14 months of follow-up. The mean relative change between metabolic ratios, mean$((Cho/NAA)_n - (Cho/Cr)_n)/(Cho/NAA)_n$, at $n = 4$ months was predictive of tumour relapse with a significant cutoff of 0.046, a sensitivity of 60% and a specificity of 100% ($P = 0.004$).

CONCLUSIONS: The ^{1}H-MRS profile changes more widely and rapidly than tumour volume during the response and relapse phases, and represents an early predictive factor of outcome over 14 months of follow-up. Thus, ^{1}H-MRS may be a promising, non-invasive tool for predicting and monitoring the clinical response to TMZ.

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Published online 24 May 2011

Keywords: MRI; ^{1}H-MRS; low-grade glioma; temozolomide; tumour response

J Neurol (2007) 254:668–669
DOI 10.1007/s00415-006-0321-x

Ulrich Roelcke
Matthias Wyss
Esther Bärtschi
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Metabolic deactivation of low-grade glioma during chemotherapy

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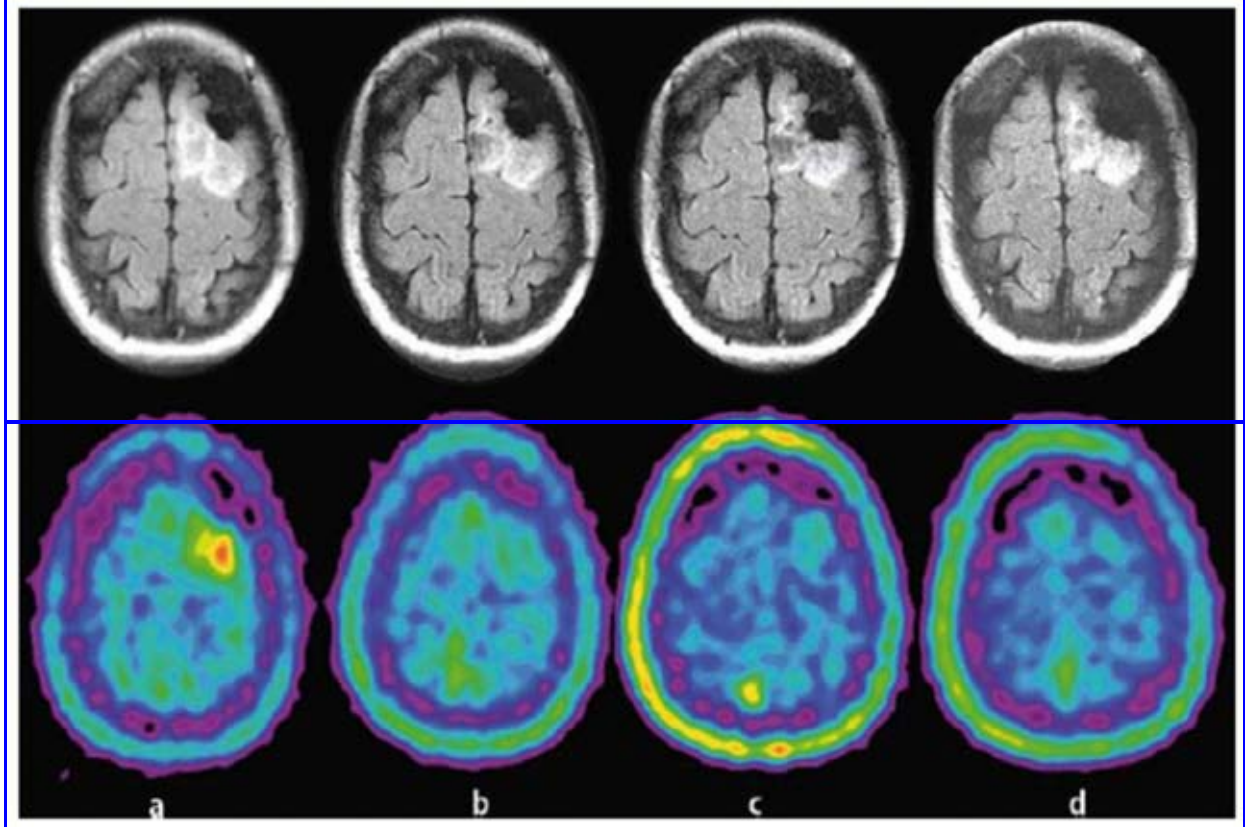
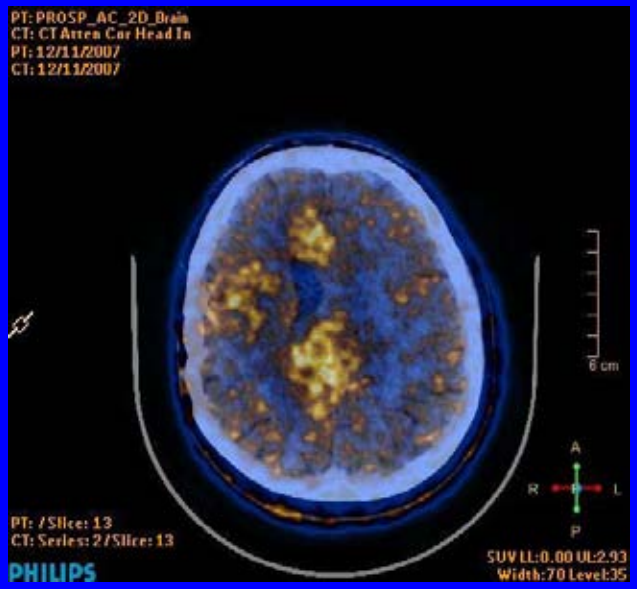


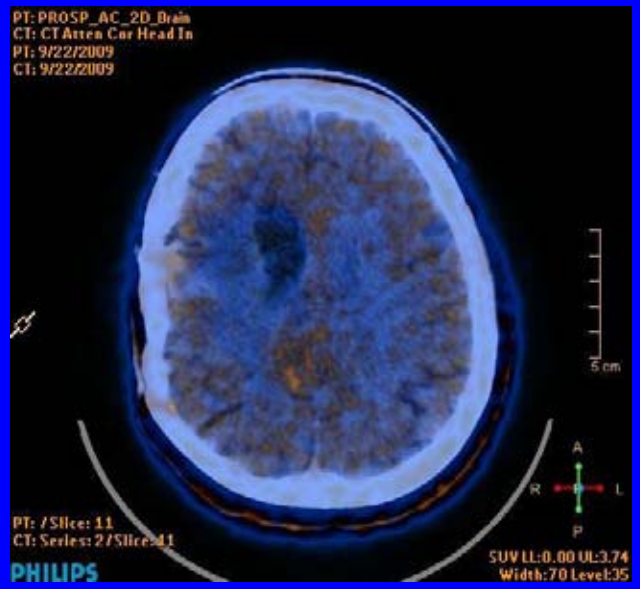
Fig. 1 Axial planes of fluid-attenuated inversion recovery MRI (FLAIR) (top) and FET PET images (bottom). A: before chemotherapy; B, C: at six and 12 months during continuous temozolomide chemotherapy; D: six months after termination of chemotherapy. The FET tumor:contralateral cortex ratio as a measure of amino acid transport upregulation was 1.39 at baseline, and declined to 1.13 and 0.97 at six and 12 months respectively. The tumor volume reduction on MRI was 12% at six months, and 22% at 12 months

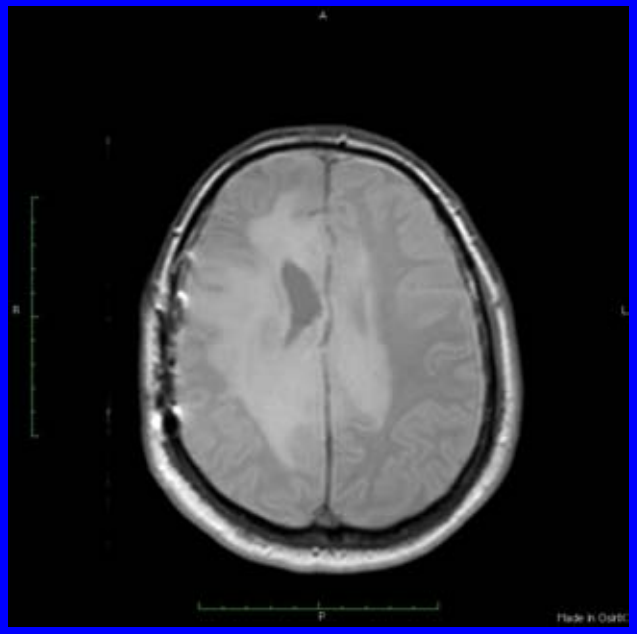
METABOLIC RESPONSE (AINO study)

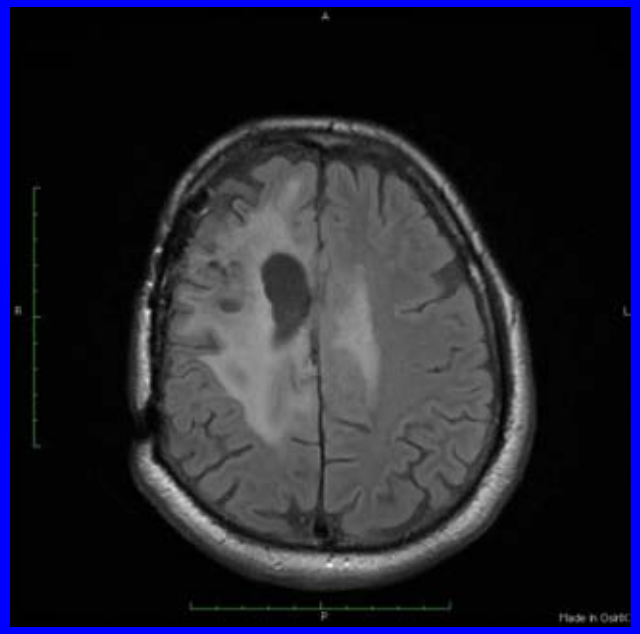
Response on PET with methionine:	
- Disappearance of uptake:	3/17 (18%)
- Decrease of uptake:	7/17 (41%)
- Stable uptake:	5/17 (29%)
- Increase of uptake:	2/17 (12%)

In 2 patients with a significant reduction of seizures and SD on FLAIR-MRI, PET with methionine showed a significant reduction of uptake.









•PET images courtesy of Dr. Crippa,

•National Cancer Institute, Milan, Italy

Aminoacid PET in non-enhancing low- grade gliomas : challenging the duration of chemotherapy

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•[1] Aarau, [2] Innsbruck, [3] Torino, [4] Milano, [5]Zurich

Ongoing retrospective multicenter study on progressive or recurrent non-enhancing LGG treated with upfront temozolomide. The active tumor size on PET images was defined as the volume of pixels exceeding 110% of cerebellar tracer uptake.

Onset of PET response was observed as early as 2 months after initiation of chemo while initial MRI responses were observed after 5 months. The stabilization of the response on PET was observed 6 to 14 months earlier as compared to MRI. In these patients the total administered dose and duration of chemo did not correlate with the progression-free survival (PFS).

If shorter courses of chemo are not inferior to chemo given until tumor progression in terms of PFS, the stabilization of a metabolic response may determine the individual duration of chemo.

EANO, Marseille 2012; SNO, Washington 2012

PREOPERATIVE CHEMOTHERAPY : A NEW OPTION?

Rationale

- In the recent literature, the extent of resection has been demonstrated to have a significant impact on the natural history of LGG : reduction of malignant transformation and improvement of PFS and OS *(Berger et al, 1994;Duffau et al, 2005; Smith et al, 2008; Chaicana et al, 2010; Englot, 2011)*

- Preoperative chemotherapy can reduce tumor infiltration and thus improve the surgical resectability (*Duffau et al, 2006; Spena et al, 2010*)

J Neurooncol
DOI 10.1007/s11060-011-0670-x

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

Marie Blonski · Luc Taillandier · Guillaume Herbet · Igor Lima Maldonado · Patrick Beauchesne · Michel Fabbro · Chantal Campello · Catherine Gozé · Valérie Rigau · Sylvie Moritz-Gasser · Christine Kerr · Roberta Rudà · Riccardo Soffietti · Luc Bauchet · Hugues Duffau

Received: 21 April 2011 / Accepted: 13 July 2011

MR-DTI AND BRAIN TUMORS

- *Diffusion Tensor Imaging (DTI)* can reveal tumoral and peritumoral abnormalities in gliomas that are *not apparent on conventional MR imaging*.
- By extracting and quantifying the information in the diffusion tensor, it is possible to obtain two maps: isotropic (p) and anisotropic (q)
- These maps allow a better characterization of LGG invasion along white matter tracts.

Price et al, AJNR 2006; Price et al, Eur Radiol 2007 ; Wang et al, 2009

Preoperative chemotherapy: a pilot Italian study

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AIM OF THE STUDY

- To assess if preoperative chemotherapy can reduce tumor extension/infiltration close to critical areas and thus improve surgical resectability

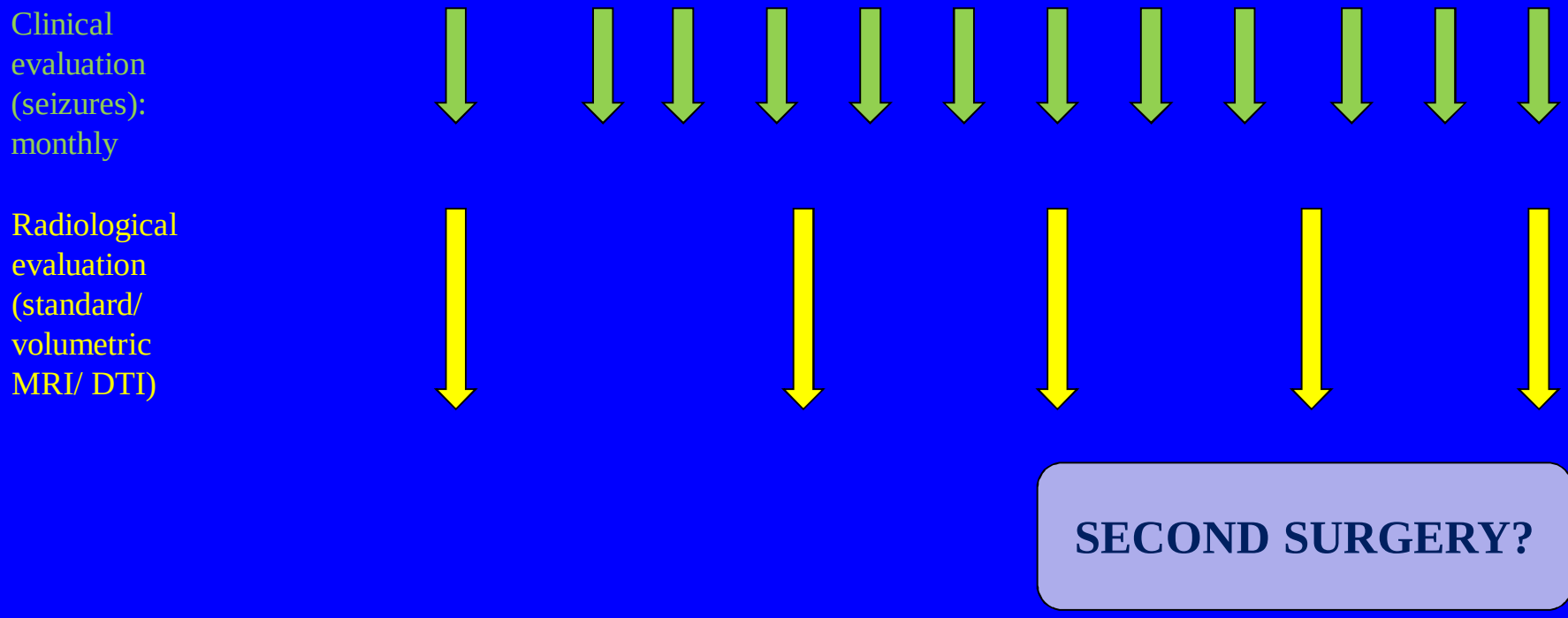
- To evaluate whether MR-DTI is able to detect, particularly in patients with stable disease, changes in peripheral tumor areas,along the infiltrative margings of the tumor

ELIGIBILITY CRITERIA

- Histologically proven grade II WHO astrocytoma or oligodendroglioma or oligoastrocytoma
- Age > 18
- Karnofsky > 70
- Patients with suspected low grade glioma unresectable or candidate to a partial resection only who have undergone a biopsy
- Patients who had a partial resection at previous surgery and have progressed clinically and/or radiologically

METHODS

Cycles (1 cycle = TMZ 150mg/m^2/die 1 week-on/1 week-off on 4 weeks)	0	3	6	9	12



RESULTS

21 PATIENTS ENROLLED SO FAR

Cycles (1 cycle = TMZ 150mg/m^2/die 1 week-on/1 week-off for 4 weeks)	3	6	9	12

3 patients ongoing

3 patients ongoing

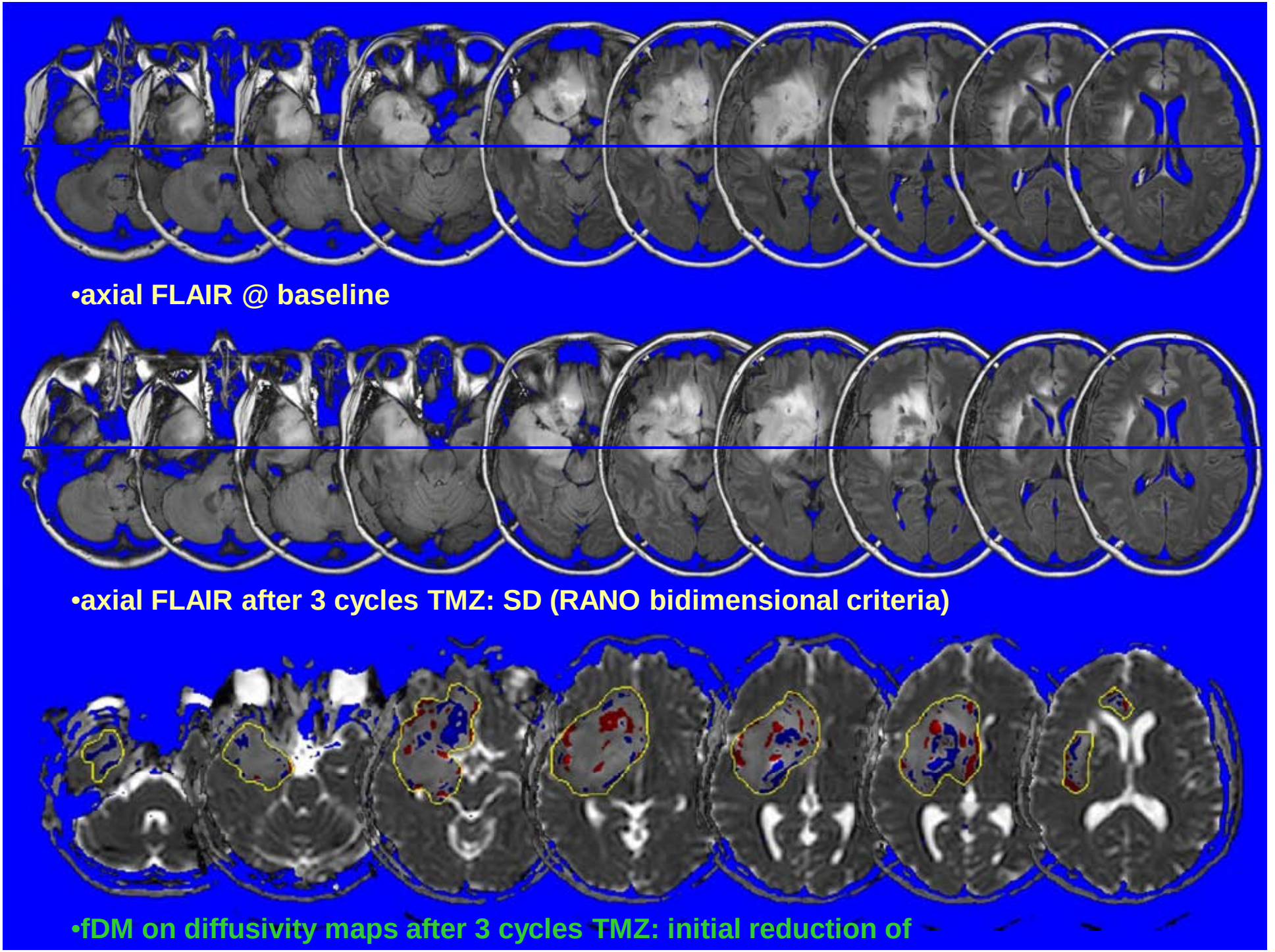
Second Surgery:

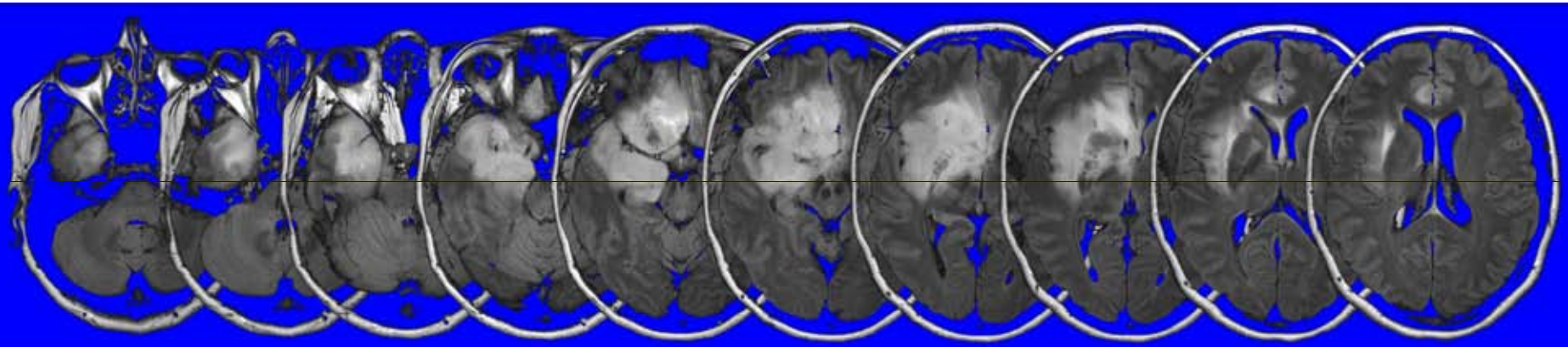
10/21

4/21

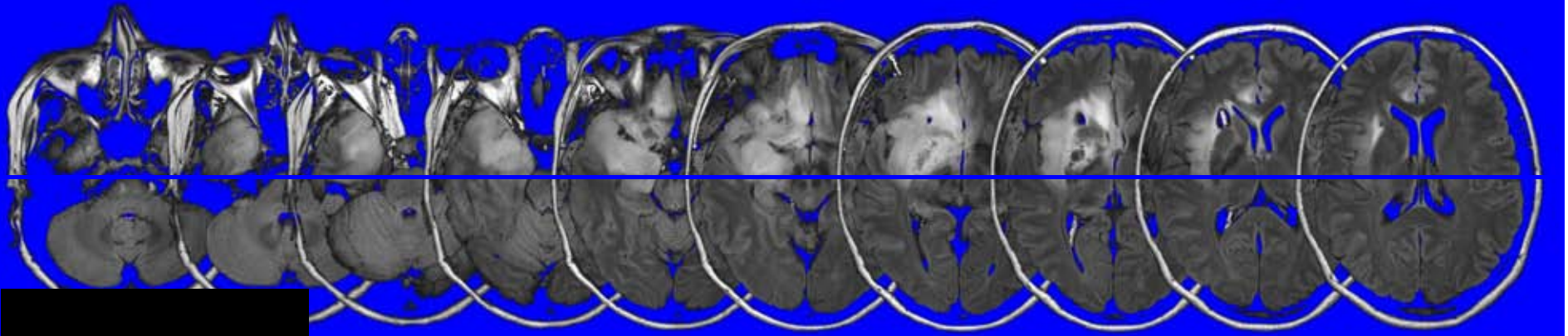
1/21

In 7/21 second surgery was total/near total (>95% volumetric measurement)

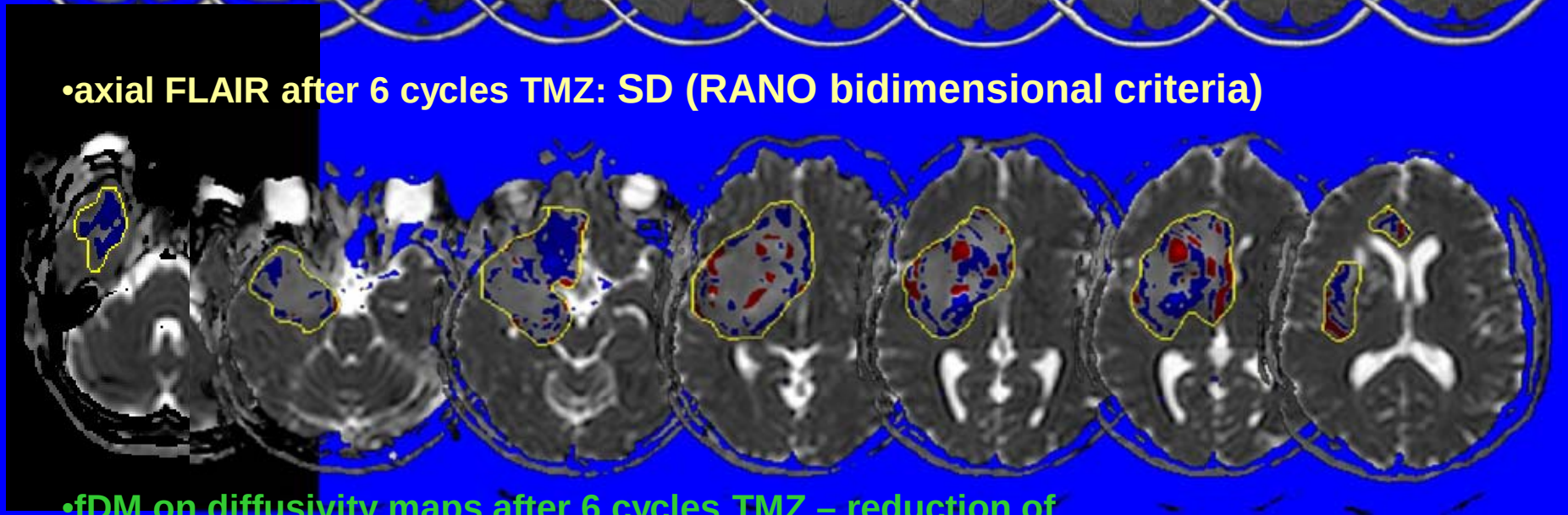

•axial FLAIR @ baseline
•axial FLAIR after 3 cycles TMZ: SD (RANO bidimensional criteria)
•fDM on diffusivity maps after 3 cycles TMZ: initial reduction of isotropy



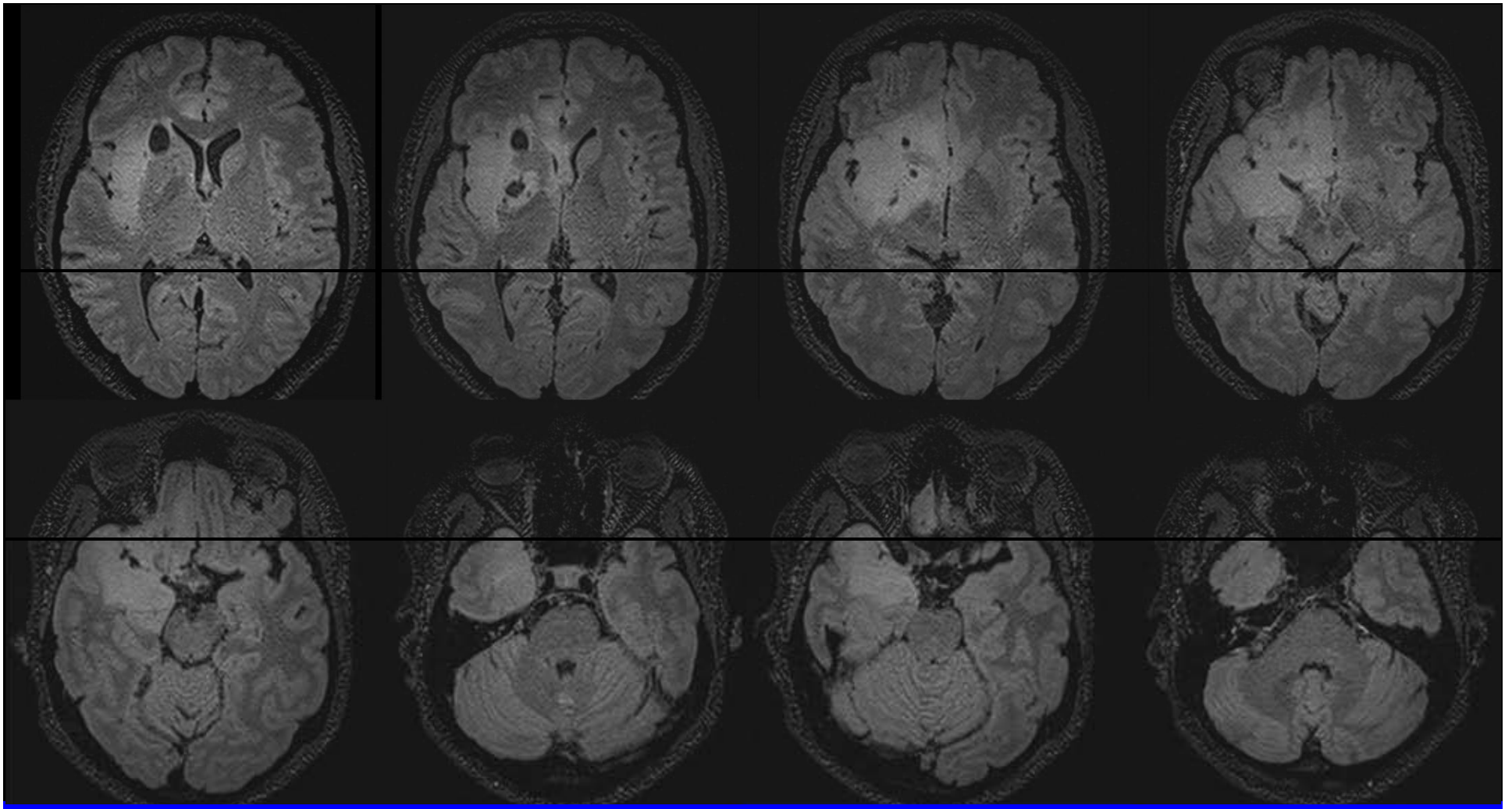
•axial FLAIR @ baseline



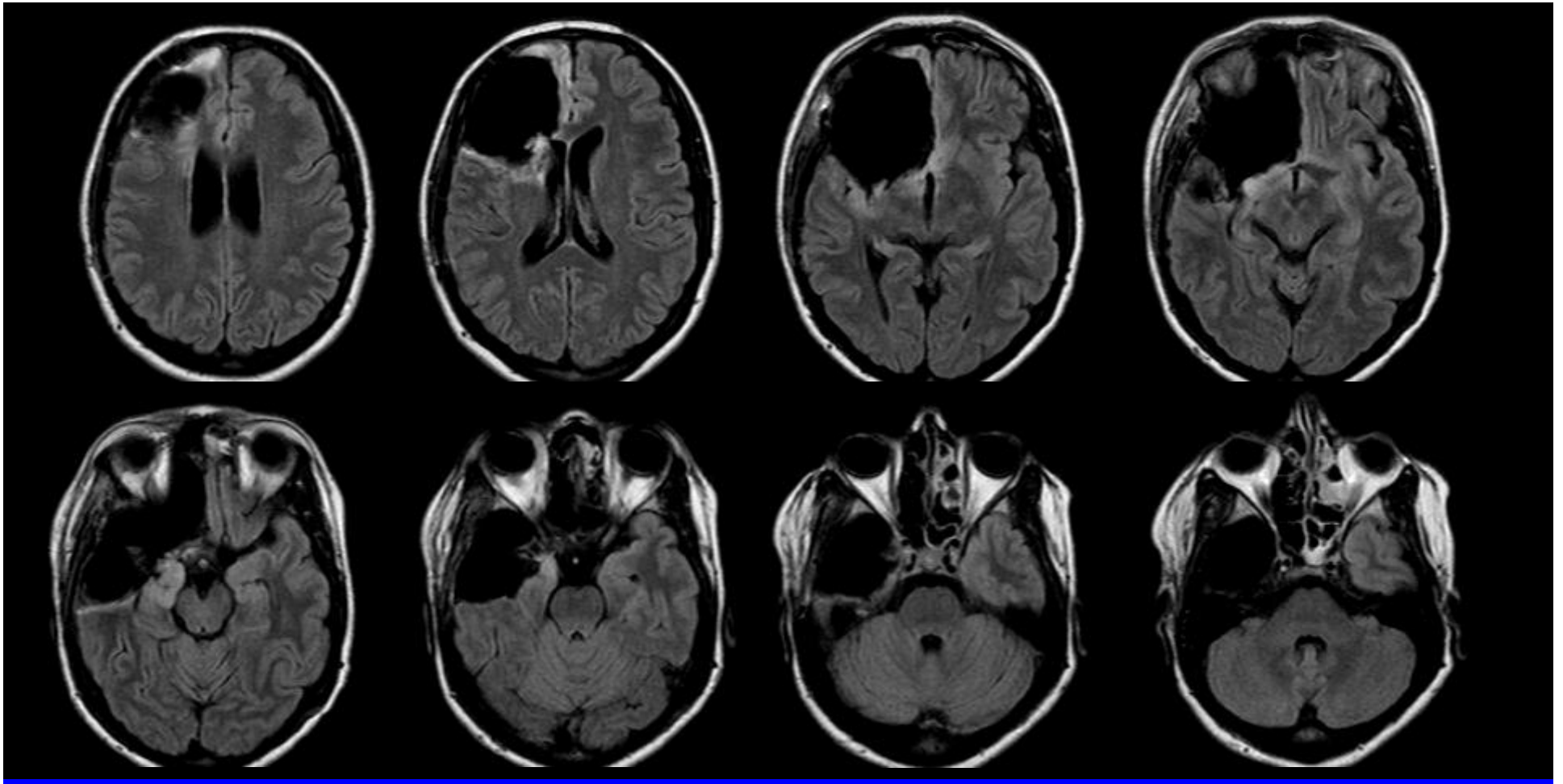
•axial FLAIR after 6 cycles TMZ: SD (RANO bidimensional criteria)



•fDM on diffusivity maps after 6 cycles TMZ – reduction of isotropy



Axial volumetric FLAIR @ surgery



Axial FLAIR 2 months since surgery

OPEN ISSUES :

- Better define the predictive value of molecular markers (MGMT, IDH1 mutation, etc) and of advanced neuroimaging
- Evaluate the role of target therapies in addition or in lieu of standard options (m-TOR inhibitors, specific IDH1/2 inhibitors)
- Different treatment strategies for different molecular subgroups of patients?