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Observation vs Radiotherapy vs Chemotherapy after surgery for the treatment of low-grade glioma: less treatment, same outcome, less toxicity?

Silvia Scoccianti
Radioterapia
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Brescia Meeting in Radiation Oncology, 2014

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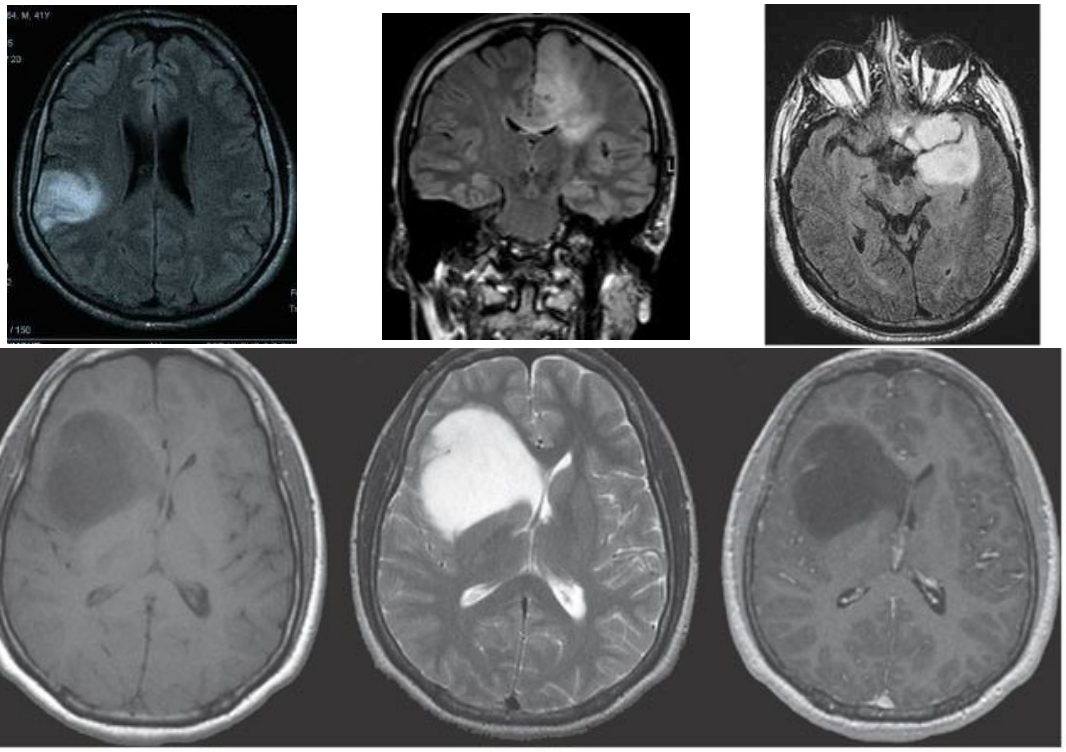

EORTC 22845: 5y-OS 65-68%; 5y-PFS 35-55%

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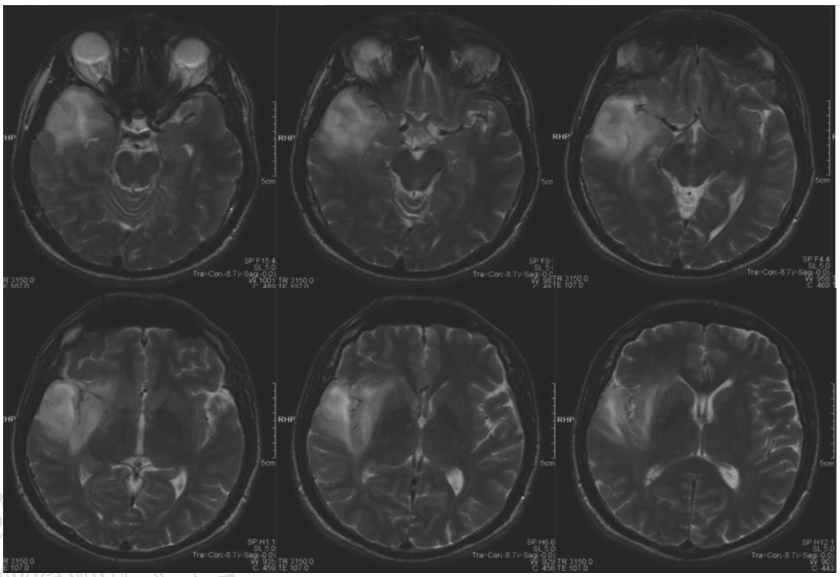
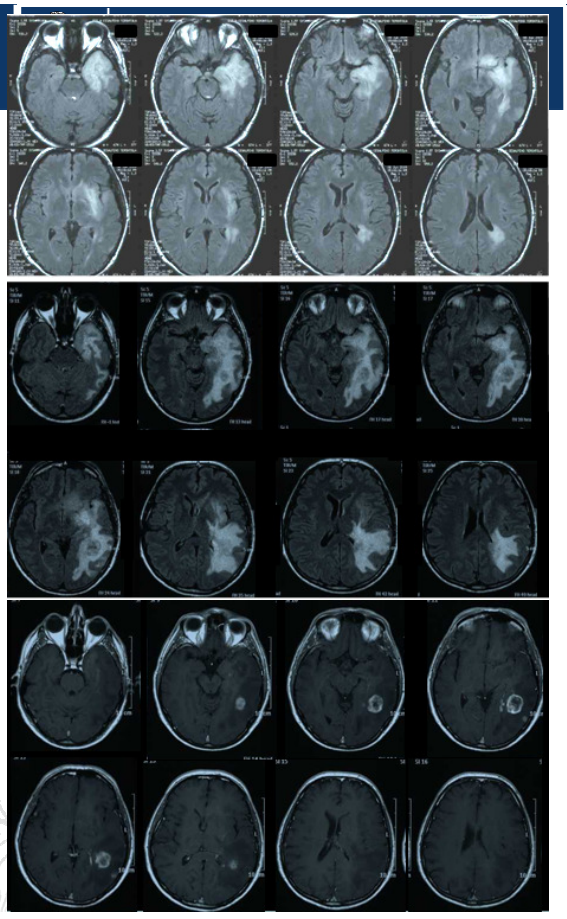
Good reasons why adjuvant treatment in Low Grade Gliomas should be given



LGG have infiltrative growth pattern



♂, 58 y,
Astrocytoma

09/06/2009

LGG often display an aggressive pathological behavior

05/11/2011

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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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Postoperative Radiotherapy

Efficacy
Neurotoxicity

THE DILEMMA OF LOW GRADE GLIOMA

I R Whittle

J Neurol Neurosurg Psychiatry 2004;**75**(Suppl II):ii31–ii36. doi: 10.1136/jnnp.2004.040501

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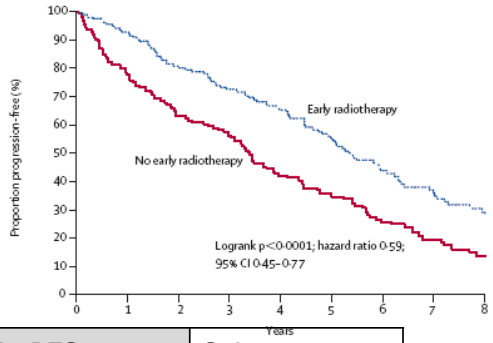
Efficacy of postoperative Radiotherapy

Lancet 2005; 366: 985–90

Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial

MJ van den Bent, D Afra, O de Witte, M Ben Hassel, S Schraub, K Hoang-Xuan, P-O Malmström, L Collette, M Piérart, R Mirimanoff, A B M F Karim, for the EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council



314 pts with LGG	mOS	5y-OS	mPFS	5y-PFS	Seizure control @1 y
Early RT (54 Gy)	7.4 y	68.4%	5.3 y	55%	75%
Delayed RT	7.2 y	65.7%	3.4 y	35%	59%

p<0.0001

p=0.03

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Take home message

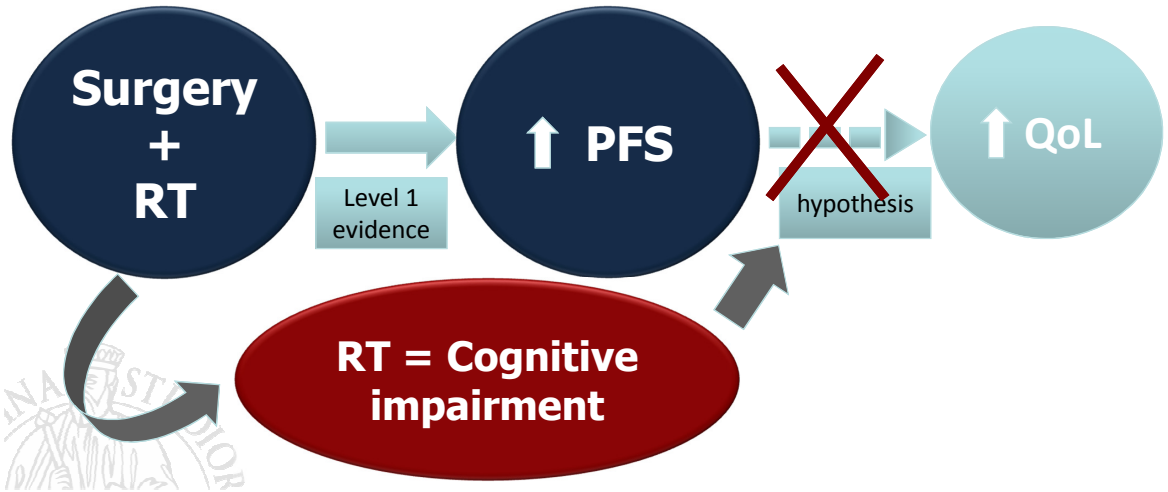
Efficacy of postoperative Radiotherapy
Level 1 evidence:
Early RT increases PFS

THE DILEMMA OF LOW GRADE GLIOMA

I R Whittle

J Neurol Neurosurg Psychiatry 2004;75(Suppl II):ii31–ii36. doi: 10.1136/jnnp.2004.040501

Efficacy of postoperative Radiotherapy
Level 1 evidence:
Early RT increases PFS



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Neurocognitive effects of Radiotherapy

Quality of Life after Radiation Therapy of Cerebral Low-grade Gliomas of the Adult: Results of a Randomised Phase III Trial on Dose Response (EORTC Trial 22844)

G.M. Kiebert,[1] D. Curran,[2] N.K. Aaronson,[3] M. Bolla,[4] J. Menten,[5] E.H.J.M. Rutten,[6] E. Nordman,[7] M.E. Silvestre,[8] M. Pierart,[2] A.B.M.F. Karim[2] on behalf of the EORTC Radiotherapy Co-operative Group

A PROSPECTIVE STUDY OF COGNITIVE FUNCTIONS FOLLO' CONVENTIONAL RADIOTHERAPY FOR SUPRATENTORIAL GL IN YOUNG ADULTS: 4-YEAR RESULTS

MARIA-CLAUDIA VIGLIANI, M.D.,* NICOLE SICHEZ, PH.D.,† MICHEL POISSON M.D.* AND JEAN-YVES DELATTRE, M.D.*

Long-term outcome of low-grade oligodendroglioma and mixed glioma

Jon D. Olson, MD; Elyn Riedel, MA; and Lisa M. DeAngelis, MD

Short-Term Effects of Radiotherapy on Attention and Memory Performances in Patients with Brain Tumors

Arja M. Lilja, M.A.[1,2] Raija I. Portin, Ph.D.[1,3] Päivi I. Hämäläinen, Ph.D.[2] Eeva K. Salminen, M.D.[4]

CME **Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients**

O. Surma-aho, MSc; M. Niemelä, MD, PhD; J. Vilkki, PhD; M. Kouri, MD, PhD; A. Brander, MD, PhD; O. Salonen, MD, PhD; A. Paetau, MD, PhD; M. Kallio, MD, PhD; J. Pyykkönen, LicPhil; and J. Jääskeläinen, MD, PhD

Radiotherapy-induced cerebral abnormalities in patients with low-grade glioma

Abstract—Abnormalities on CT or MRI and neuropsychological performance in patients with low-grade glioma, with (n = 23) or without (n = 16) prior cerebral radiotherapy, were evaluated. Cerebral atrophy was observed in 14 of 23 patients (61%) treated with prior radiotherapy, and in 1 of 16 patients (6%) without prior radiotherapy. White matter abnormalities were observed in six patients, all of whom were treated with prior radiotherapy. These radiologic cerebral abnormalities correlated with cognitive performance.

NEUROLOGY 2002;59:123–125

T.J. Postma, MD; M. Klein, PhD; C.C.P. Verstappen, MD; J.E.C. Brumberg, MD; M. Swennen, MD; J.A. Langendijk, MD; M.J.B. Taphoorn, MD; P. Scheltens, MD; B.J. Slotman, MD; H.M. van der Ploeg, PhD; N.K. Aaronson, PhD; and J.J. Heimans, MD

CME **Late cognitive and radiographic changes related to radiotherapy**

Initial prospective findings

C.L. Armstrong, PhD; J.V. Hunter, MD; G.E. Ledakis, PhD; B. Cohen, PhD; E.M. Tallent, BA; B.H. Goldstein, PhD; Z. Tochner, MD; R. Lustig, MD; K.D. Judy, MD; A. Pruitt, MD, J.E. Mollman, MD; E.M. Stanczak, PhD; M.Y. Jo, PsyD; T.L. Than, BS; and P. Phillips, MD

Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study

M Klein, J J Heimans, N K Aaronson, H M van der Ploeg, J Grit, M Muller, T J Postma, J J Mooij, R H Boerman, G N Beute, G J Ossenkoppele, G W van Imhoff, A W Dekker, J Jolles, B J Slotman, H Struikmans, M J B Taphoo

Effects of Radiotherapy on Cognitive Function in Patients With Low-Grade Glioma Measured by the Folstein Mini-Mental State Examination

By Paul D. Brown, Jan C. Buckner, Judith R. O'Fallon, Nancy L. Iturria, Carise A. Brown, Brian P. O'Neill, Bernd W. Scheithauer, Robert P. Dinapoli, Robert M. Arusell, Walter J. Curran, Ross Abrams, and Edward G. Shaw

The neurocognitive effects of radiation in adult low-grade glioma patients[1]

Paul D. Brown,[2] Jan C. Buckner, Joon H. Uhm, and Edward G. Shaw

Division of Radiation Oncology (P.D.B.), Division of Medical Oncology (J.C.B.), and Division of Neuro-Oncology (J.H.U.), Mayo Clinic, Rochester, MN 55905, USA; and Department of Radiation Oncology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA (E.G.S.)

Delayed radiation toxicity after focal or whole brain radiotherapy for low-grade glioma

M.H.J. Swennen[1], J.E.C. Bromberg[1], Th.D. Witkamp[2], C.H.J. Terhaard[3], T.J. Postma[4] and M.J.B. Taphoorn[1]
[1]Department of Neurology, [2]Department of Radiology, [3]Department of Radiotherapy, University Medical Centre Utrecht; [4]Department of Neurology, Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

COGNITIVE FUNCTION AFTER RADIOTHERAPY FOR SUPRATENTORIAL LOW-GRADE GLIOMA: A NORTH CENTRAL CANCER TREATMENT GROUP PROSPECTIVE STUDY

NADIA N. LAACK, M.D.,* PAUL D. BROWN, M.D.,* ROBERT J. IVNIK, PH.D.,† ALFRED F. FURTH, M.S.,† KARLA V. BALLMAN, PH.D.,‡ JULIE E. HAMMACK, M.D.,† ROBERT M. ARUSELL, M.D.,* EDWARD G. SHAW, M.D.,*¶ AND JAN C. BUCKNER, M.D.¶

Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits

Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong

FACTORS INFLUENCING NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH BENIGN AND LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL RADIOTHERAPY

RAKESH JALALI, M.D.,* INDRANIL MALLICK, M.D.,* DEBNARAYAN DUTTA, M.D.,* SAVITA GOSWAMI, M.SC.,† TEJPAL GUPTA, M.D.,* ANUSHEEL MUNSHI, M.D.,* DEEPAK DESHPANDE, PH.D.,† AND RAJIV SARIN, F.R.C.R.*

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Radiotherapy = Neurocognitive Impairment

Table 1 Existing literature that found a relationship between radiotherapy and neurocognitive impairment in patients with low grade gliomas

Author	Study type	RT+ patients	Evaluable patients for cognitive outcome	Radiotherapy			Cognitive assessment	Cognitive outcome	Follow-up
				Total dose	Dose per fraction	Volume			
Olson [12]	Retrospective	62/106 (33% received RT after malignant trasformation) (20 postoperative RT, 6 postoperative RT+ CHT, 36 delayed RT)	NA	Median D 59.4 Gy (up to 65 Gy)	NA	NA	Clinical evaluation	Cognitive impairment in 13/62 RT+ patients (21%)	Median 6 years
Surma-aho [13]	Retrospective	28/51 postoperative RT	51/51	Median D 60 Gy (up to 68 Gy)	1.8 or 2 Gy	WBRT for 40 Gy + boost up to 20–28 Gy 67.8% Limited volume 32.2%	Standardized tests [Digit Span, Similarities, Block design and Digit Symbol subtests (Wechsler Adult Intelligence Scale) Modified Benton Visual Retention Test]	RT+ pts performed significantly worse in cognitive tests regarding performance IQ visual memory and attention	Mean 7 years
Postma [14]	Retrospective	23/39 postoperative RT	NA	Median D 54 Gy (up to 64 Gy)	up to 2.5 Gy	WBRT + boost 17.4% Limited volume 82.6%	Standardized tests (Letter-Digit Substitution Test, Visual verbal Learning Test, Stroop Color-Word Test, Concept Shifting Test)	Cerebral atrophy in 14/23 RT+ patients (61%) and in 1/16 RT− patients (6%). Brain atrophy was significantly related to graphomotor speed, information processing capacity and memory performance. White matter changes in 6/23 RT+ patients (26.1%) and in none of RT− patients.	NA

J Neurooncol (2012) 108:291–308
DOI 10.1007/s11060-012-0821-8

Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy

Silvia Scoccianti · Beatrice Detti · Samantha Cipressi · Alberto Iannalfi · Ciro Franzese · Giampaolo Biti

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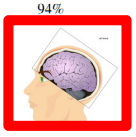
Radiotherapy = Neurocognitive Impairment

Author	Study type	RT+ patients	Evaluable patients for cognitive outcome	Radiotherapy			Cognitive assessment	Cognitive outcome	Follow-up
				Total dose	Dose per fraction	Volume			
Correa [15]	Retrospective	6/25 (5 RT, 1 RT+ CHT)	15/25 were available for long-term follow-up	54–68.4 Gy	1.8 or 2 Gy	Limited volume	Standardized tests (Brief test of attention, Trail making test, Verbal fluency, Hopkins verbal learning test, Brief visual spatial memory, Grooved pegboard test, Beck depression inventory, Functional assessment of cancer therapy-brain)	Long-term follow-up: RT contributed to a mild decline in verbal fluency, mood and quality of life.	Median 8 years
Douw [5]	Retrospective	65/65	65/65	Mean D 56.6 Gy, 38% of patients received a boost (mean dose 14 Gy)	1.6–2.5 Gy (9% 2.5 Gy)	WBRT 6% Limited volume 94%	Standardized tests (Letter-digit substitution test, Concept shifting test, Stroop color-word test, Visual verbal learning test, Memory comparison test and Categoric word fluency)	RT+ patients did worse in executive functioning, information processing speed and attention.	Mean 12 years

RT radiotherapy, *RT+ patients* patients who received radiotherapy, *RT− patients* patients who did not receive radiotherapy, *CHT* chemotherapy, *D* dose, *NA* not available, *WBRT* whole brain radiotherapy, *y* years



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EFFECTS OF STANDARD OF ART TREATMENT

Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy

Silvia Scoccianti · Beatrice Detti · Samantha Cipressi · Alberto Iannalfi · Ciro Franzese · Giampaolo Biti

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Radiotherapy ≠ Neurocognitive Impairment

Author	Study type	RT+ patients	Evaluable patients for cognitive outcome	Radiotherapy			Cognitive assessment	Cognitive outcome	Follow-up
				Total dose	Dose per fraction	Volume			
Klein [7]	Retrospective	104/195	195/195	Median D 55.6 Gy	1.8–2 Gy (82.7%) >2 Gy (17.3%)	Limited volume 48.1% Limited volume + boost 42.3% WBRT 1.9% WBRT + boost 7.7%	Standardized tests (Dutch adult reading test, Line bisection test, Facial recognition test, Judgment of line orientation test, Letter-digit substitution test, Visual verbal learning test, Working memory task, Stroop color-word test, Categoric word fluency task, Concept shifting test)	Logistic regression showed that the use of RT was not associated with cognitive disability. Impairment in the memory domain was found only in patients who received fraction doses >2 Gy.	Mean 6 years
Vigliani [16]	Prospective	17/31	29/31 patients were evaluable 12 months after the end of treatment	54–55.8 Gy	1.8 Gy	Limited volume	Standardized tests (Stroop color-word test, WAIS subtest code, Reaction time, Verbal and visual span, Raven progressive matrices, Wechsler memory scale, Recall of a word/design series, Recall of Rey-osterrieth complex figure)	No significant difference was found over time between the RT+ and RT− patients.	6–48 m
Armstrong [17]	Prospective	26/48	37/48	Mean D 55.6 Gy	1.8–2 Gy	Limited volume	Standardized tests (Praxis/finger/tapping test, Bells test, Continuous performance test, Sentence repetition test, Controlled oral word association test, Animal naming test, Paced auditory serial addition test, symbol digit modalities test, Digit/word span test,	RT without other risk for morbidity does not carry a burden of cognitive decline in adults for at least 4 years after treatment.	Mean 3 years

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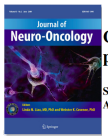

Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy

Silvia Scoccianti · Beatrice Detti · Samantha Cipressi · Alberto Iannalfi · Ciro Franzese · Giampaolo Biti

Radiotherapy ≠ Neurocognitive Impairment

Author	Study type	RT+ patients	Evaluable patients for cognitive outcome	Radiotherapy			Cognitive assessment	Cognitive outcome	Follow-u
				Total dose	Dose per fraction	Volume			
Brown [18]	Prospective	203/203	88/203 patients were evaluable 12 months after the end of treatment	50.4 or 64.8 Gy	1.8 Gy	Limited volume	MMSE	Most patients maintained a stable neurocognitive status after focal RT (5% of patients had a clinically significant decrease in score 5 years after the end of treatment). Patients with abnormal MMSE were more likely to have an improvement in cognitive abilities than deterioration after RT	Median 7.4 yea
Torres [19]	Prospective	20/22	15/22	Mean D 54 Gy (45–63 Gy)	1.8 Gy	Limited volume	Standardized tests (Selective reminding test, Spatial recall test, Symbol digit modality test, Shipley scale. Wechsler adult intelligence scale-revised test, Trail making test, Symptom Checklist-90-revised global severity index scale)	Decline in memory and attention only if disease progressed	Mean 2 years
Laack [4]	Prospective	20/20	20/20	50.4 or	1.8 Gy	Limited volume	Standardized tests (Wechsler adult intelligence scale-revised test, Auditory-verbal learning test, Benton visual retention test, Trail making test, Stroop color-word test, Controlled oral word association test)	Cognitive function was stable after RT	Mean 3 years

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EFFECTS OF STANDARD OF ART TREATMENT

Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy

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Neurocognitive impairment in LGG have a multifactorial genesis

Baseline alterations	Laack 2005
Older age	Crossen JCO 1994, Klein 2002, Douw 2009
Comorbidities	Peterson 1993, Armstrong 2002, Swennen 2004
The tumor itself	Taphoorn 1994, Hahn 2000, Klein 2002, Laack 2003, Torres 2003, Correa 2007, Merchant 2009, Douw 2009
Surgery	Recht 1992, Reijneveld 2001, Merchant 2009, Douw 2009
Radiotherapy	**Dose >2Gy**: Corn 1994, Crossen 1994, Klein 2002 **High total dose**: Crossen 1994, Kiebert 1998, Klein 2002 **Large volume**: Asai 1989, Kleinberg 1993, Gregor 1996, Surma-aho 2001, Swennen 2004, Merchant 2009
Chemotherapy	Crossen 1994, Keime-Guibert 1998
Antiepilectic Drugs	Klein 2002, Correa 2007, Correa 2009, Douw 2009
Psychological Experience	Cull 1996

Take home message

There are no evidenced-based data to exclude or confirm neurocognitive effects of "modern" RT

Strategies for reducing the toxicity of RT

Selection for pts to be treated with immediate RT

How to reduce the potential neurotoxicity of radiotherapy

Use high **conformal** technique		
Keep your **volume** as small as possible	GTV: high intensity area on T2w MRI + CE CTV=GTV +**1**(-2) cm	EORTC 22033: Fairchild 2012 Merchant 2009
Keep **total dose** as low as possible	45/50.4/(54Gy)	EORTC 22844: Karim 1996 RTOG: Shaw 2002
Use always **conventional fractionation**	1.8/2 Gy	

"..with modern RT techniques, the risk of cognitive decline is probably low.."

Taphoorn, ASCO Proceedings 2009

Consider hippocampal sparing RT	Pinkham 2013

Hippocampal-sparing radiotherapy: The new standard of care for World Health Organization grade II and III gliomas?

M.B. Pinkham [a,e,*], K.C. Bertrand [e], S. Olson [b], D. Zarate [f], J. Oram [b,c], A. Pullar [a,e], M.C. Foote [a,d,e]

Associazione Italiana Radioterapia Oncologica
Gruppo di Lavoro Neoplasie Cerebrali

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Unfavorable prognostic factors

Clinical factors	Disease related factors	Treatment related factors
Age ≥40 y*	Astrocytoma*	Partial removal or biopsy
Low PS	High proliferative index	
Neurological deficits *	No LOH 1p/19q	
	Large diameter*	
	Tumor crossing the midline*	
	Contrast enhancement	

*****Confirmed by EORTC data, Pignatti 2002

Decision on treatment

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

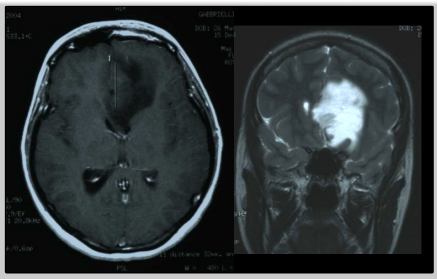
J Clin Oncol 20:2076-2084

Age	<40 vs ≥40 y
Headache	No vs Yes
Epilepsy	No vs Yes
Epilepsy only	No vs Yes
Mental disturbances	No vs Yes
Motor disturbances	No vs Yes
Neurologic deficit	No vs Yes
Largest diameter	<6 cm vs ≥6 cm
Tumor crossing the midline	No vs Yes
N of lobes involved	<1 vs>1
Ventricles involved	No vs Yes
Surgery	Biopsy vs<50% removal vs 50-89% removal vs 90-100%
Histology subtype	OD/OA vs A

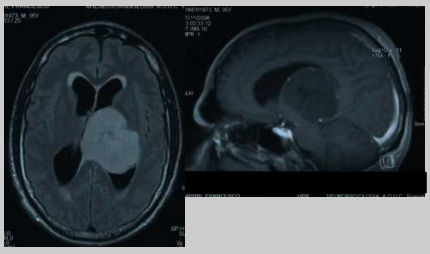
Age	<40 vs ≥40 y
Neurologic deficit	No vs Yes
Largest diameter	<6 cm vs ≥6 cm
Tumor crossing the midline	No vs Yes
Histology subtype	OD/OA vs A

Prognostic score
0
1
2
3
4
5

Risk Groups	
Low risk	0-2
High risk	3-5



Tumor crossing the midline

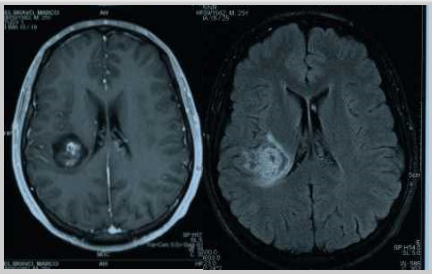


Max diameter > 6 cm

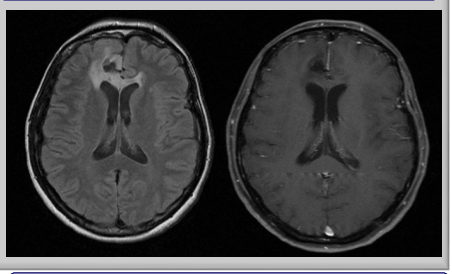
Age ≥ 40 y

Neurological deficit (with exception of well-controlled seizures)

Astrocytoma

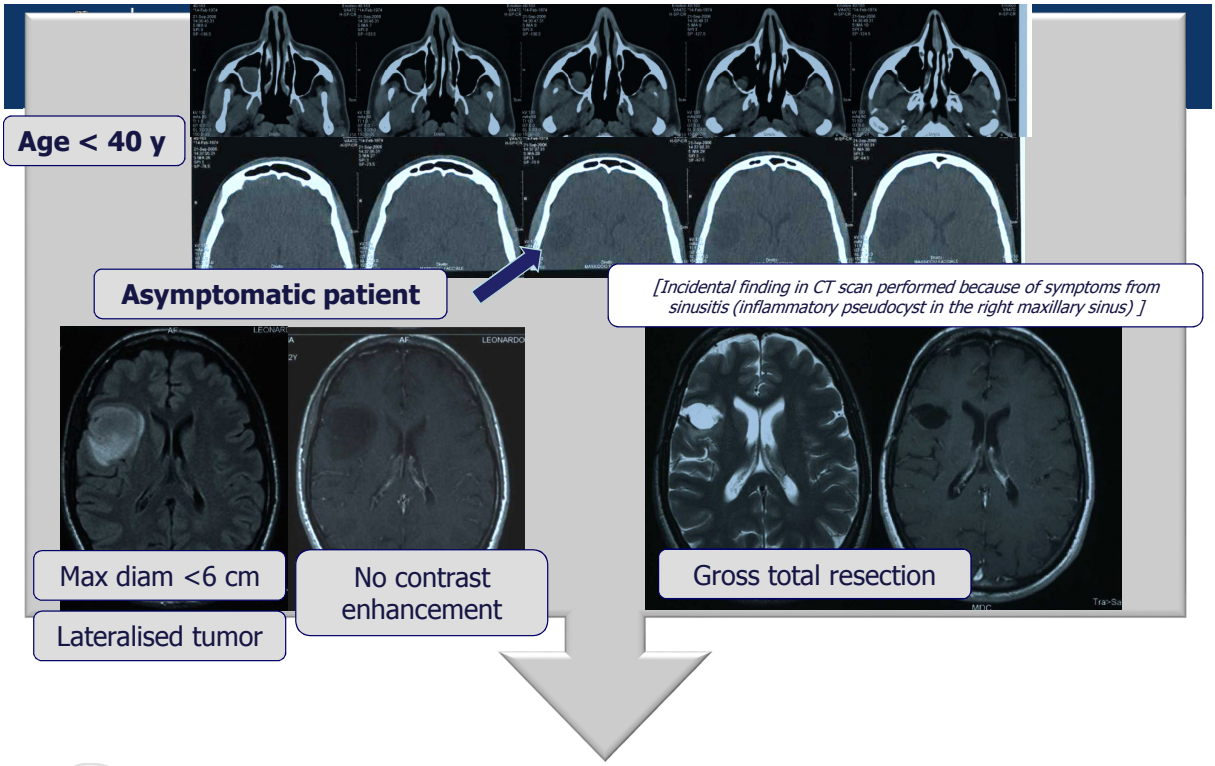


Contrast enhancement



Partial resection

RADIOTHERAPY WITHOUT DELAY



OBSERVATION
withholding radiotherapy until progression

Take home messages

1) Efficacy of postoperative Radiotherapy
Level 1 evidence:
Postoperative RT increases PFS

2) Neurotoxicity of Radiotherapy
There are no evidence-based data to neither exclude nor confirm neurocognitive effects of modern RT

3) Adequate selection of patients
Patients with poor prognostic factors should receive postoperative RT

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Can Chemotherapy replace Radiotherapy in the postoperative management of LGG?

1.Phase II studies on exclusive cht
2.EORTC trial 22033/26033

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Phase II studies on exclusive cht

Author	n	Histotypes	Chemo	Newly diagn/rec	OS	PFS	RR
Mason Neurology 1996	8/9	OD	PCV	Newly diagn	n.a.	mPFS 25 m	PR 75%
Soffietti Neurosurgery 1998	15/26	OD+OA	PCV	Onlyrec	n.a.	mPFS 24 m*	CR 12%* SD 31%* PR 50%* PD 8%*
Brada Ann Oncol 2003	30	A+OD+OA	TMZ	Both	3y OS 82%	3y PFS 66%	SD 38% PR 58% PD 3%
Hoang-Xuan JCO 2004	60	OD+OA	TMZ	Only rec	n.a.	1y PFS 73%	SD 61% PR 31% PD 8%
Lebrun Eur JNeurol 2007	33	OD	PCV	Newlydiagn	2y OS 85%	1y PFS 90%	CR 3% SD 55% PR 24% PD 18%
Tosoni JNO 2008	30	A+OD+OA	3 weeks on, 1 week off TMZ	Only rec	2y OS 79%	2y PFS 43%	SD 56,7% PR 30% PD 13,3%
Kesari Clin Cancer Res 2009	32/44	OD+OA	7 weeks on, 4 weeks off TMZ	Both	3y OS 12%*	3y PFS 57%*	SD 75%* PR 20%* PD 5%*

* Results for untreated+pretreated pts

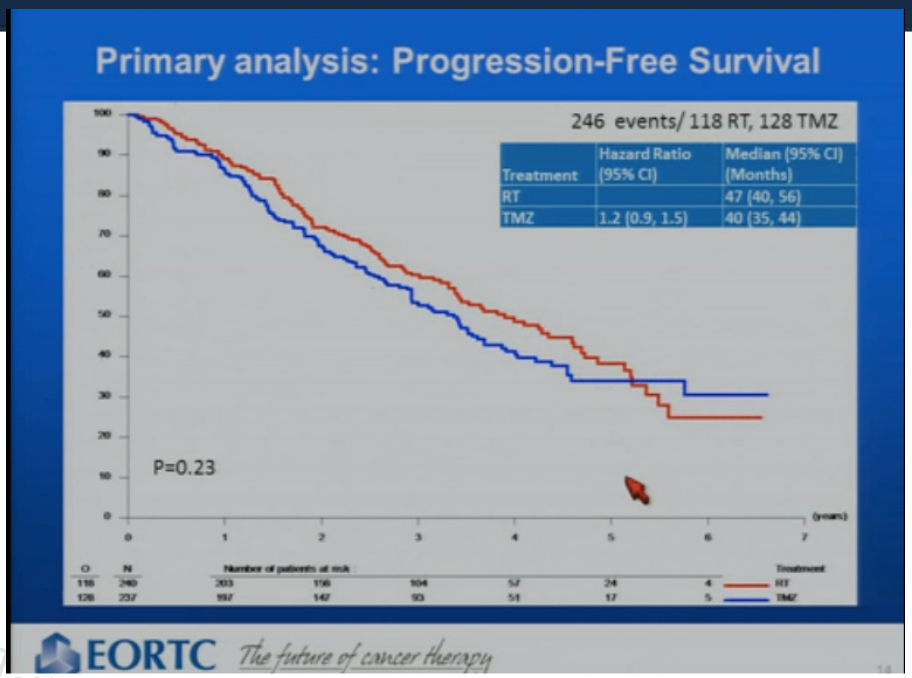
EORTC 22033-26033 phIII trial

Newly diagnosed high risk patients or progressive Low Grade Gliomas

Treatment	Endpoint
® → **50,4 Gy** → 75 mg/m2/day, d1-21, q28 **TMZ** (up to 12 courses or until progression)	**PRIMARY ENDPOINT:** PFS (differences to be detected: improvement of 13% to 58% in PFS at 5 years for the TMZ arm; HR: 0.68,2-sided,5% sign.level) **SECONDARY ENDPOINTS:** OS QoL and MMSE **Neurocognitive measures** (only in some centers) Toxicity

Stratification: 1p mutation, contrast enhancement on MRI, age, PS,

EORTC 22033-26033 phIII trial



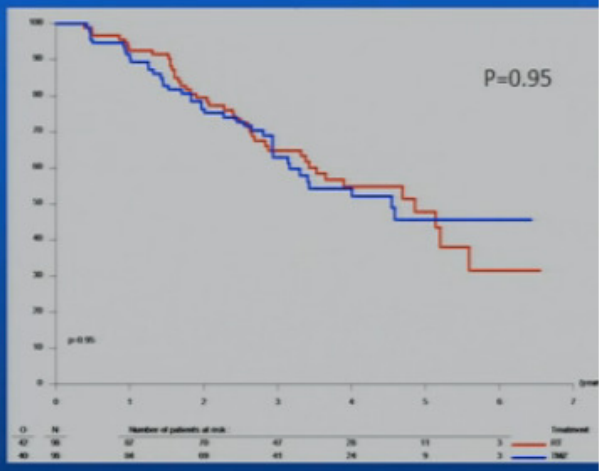
707 pts registered, **477 pts randomized**, first analysis after 246 progression events, median Fup 45.5 months

1p status: Progression-Free Survival

1p normal: 121 events/ 55 RT, 66 TMZ

Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		41 (32, 55)
TMZ	1.4 (1.0, 2.0)	30 (24, 40)

1p deleted: 82 events/ 42 RT, 40 TMZ



Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		58 (41, 67)
TMZ	1.01 (0.7, 1.6)	76 (66, 83)

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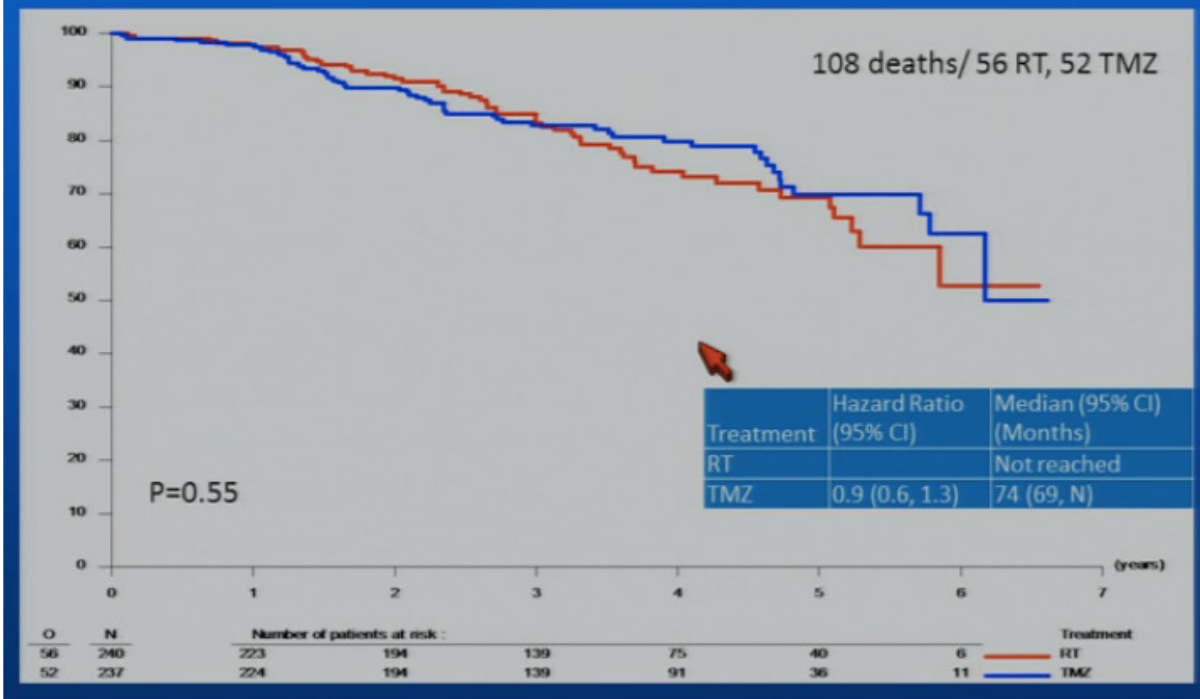
Overall Survival
(Immature data, Follow-up < 5 years)



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G4 hematological toxicity	
Radiotherapy	0%
TMZ	5.5%

	RT (N=228)(%)		TMZ (N=235)(%)		
	Grade 2	Grade 3	Grade 2	Grade 3	Grade 4
WBC	2 (0.9%)	-	61 (26.0%)	8 (3.4%)	1 (0.4%)
ANC	1 (0.4%)	1 (0.4%)	28 (11.9%)	6 (2.6%)	4 (1.7%)
Platelets	-	-	4 (1.7%)	4 (1.7%)	7 (3.0%)
Haemoglobin	-	-	7 (3.0%)	1 (0.4%)	1 (0.4%)

22033-26033: General toxicity

	RT (N=238) (%)			TMZ (N=235) (%)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Allergy, immuno.				1 (0.4)		
Auditory, ear	4 (1.8)			1 (0.4)		
Blood				14 (6.0)	3 (1.3)	
Cardiac (general)				2 (0.9)		1 (0.4)
Constitutional symptoms	8 (3.5)			15 (6.4)	1 (0.4)	
Dermatology/skin	1 (0.4)			4 (1.7)		
Gastrointestinal	4 (1.8)			10 (4.3)		
Hepato./pancreas	2 (0.9)					
Infection	2 (0.9)			7 (3.0)	1 (0.4)	
Lymphatics	1 (0.4)					
Metabolic/laboratory	2 (0.9)		1 (0.4)			
Neurology	25 (11.0)	2 (0.9)			34 (14.5)	5 (2.1)
Pain	6 (2.6)				7 (3.0)	
Pulmonary/upper respiratory	1 (0.4)		1 (0.4)		1 (0.4)	
Renal/Genitourinary	2 (0.9)					
Second. malignancy	1 (0.4)		1 (0.4)		2 (0.9)	3 (1.3)
Sexual/reproductive function					4 (1.7)	
Vascular	1 (0.4)		1 (0.4)		1 (0.43)	

G4 toxicity	
RT	0.9%
TMZ	22.9%
G5 toxicity	
RT	1.7%
TMZ	3.8%

Take home message

Can Chemotherapy replace Radiotherapy in the postoperative management of high risk LGG?

- First line treatment with TMZ compared to RT did not improve PFS
- Severe toxicity in patients treated with TMZ was more frequent

Neurocognitive evaluation

Molecular analysis
(19q, MGMT, IDH, genome-wide methylation)

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Take home messages

- **Make a proper selection of patients for observation or treatment**
- **Treat high risk patients with postoperative highly conformal RT**
- **Wait for the definitive results of EORTC 22033-26033**

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