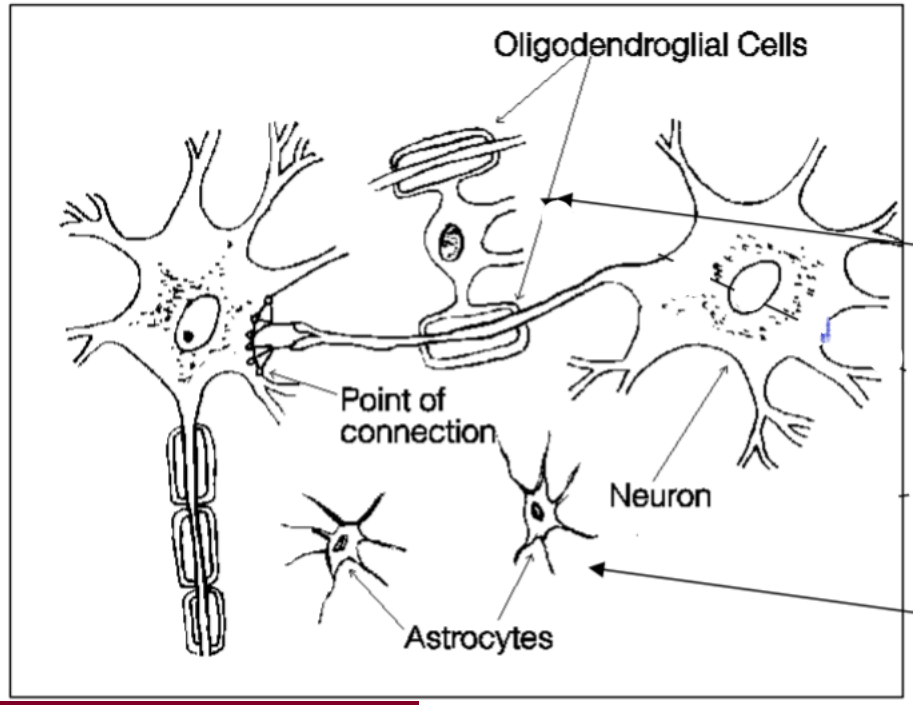
Gliomi di basso grado

Forme astrocitarie e oligodendrogliali di grado I (astrocitoma pilocitico) e grado II (astrocitomi, oligodendrogliomi e gliomi misti)

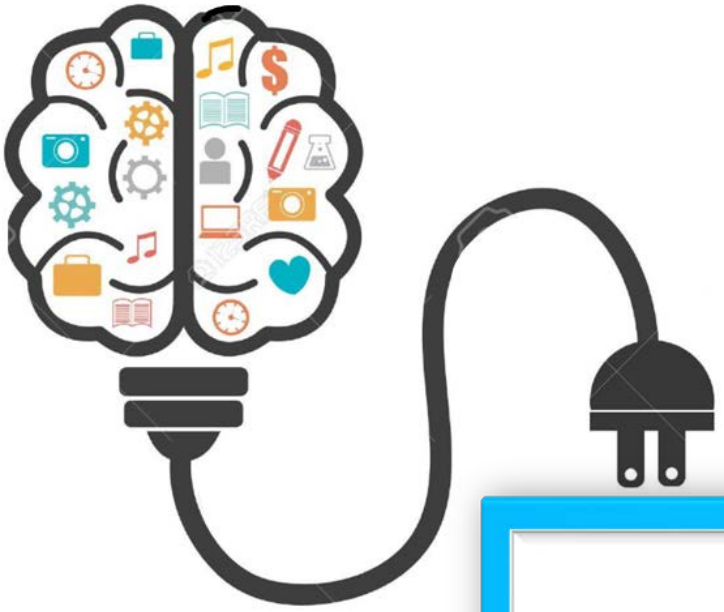


OLIGODENDROGLIOMI

ASTROCITOMI

EPIDEMIOLOGIA

- 15% dei tumori primitivi cerebrali
- 30% dei gliomi nell'adulto
- II-IV decade di vita
- 5-year OS: 58-72%
- PFS: 37-55%

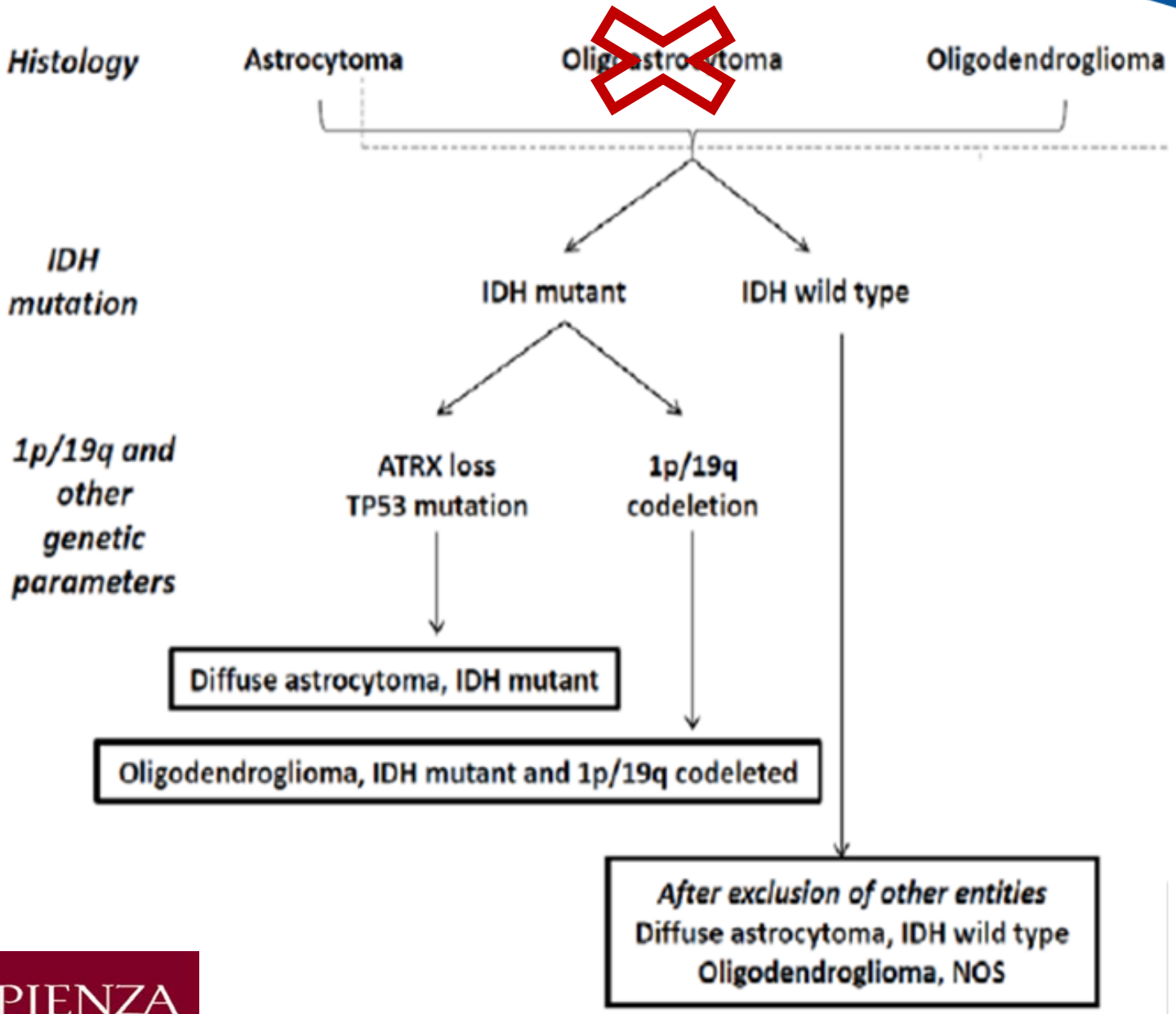


Diagnostic biomarkers

IDH1 or IDH2 mutations

Loss of nuclear **ATRX** expression

1p/19q co-deletion


Histology
Astrocytoma
Oligodendroglioma
IDH mutation
IDH mutant
IDH wild type
1p/19q and other genetic parameters
ATRX loss
TP53 mutation
1p/19q
codeletion
Diffuse astrocytoma, IDH mutant
Oligodendroglioma, IDH mutant and 1p/19q codeleted
After exclusion of other entities
Diffuse astrocytoma, IDH wild type
Oligodendroglioma, NOS

Grading of selected CNS tumors: 2016 CNS WHO

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
	III
...ellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

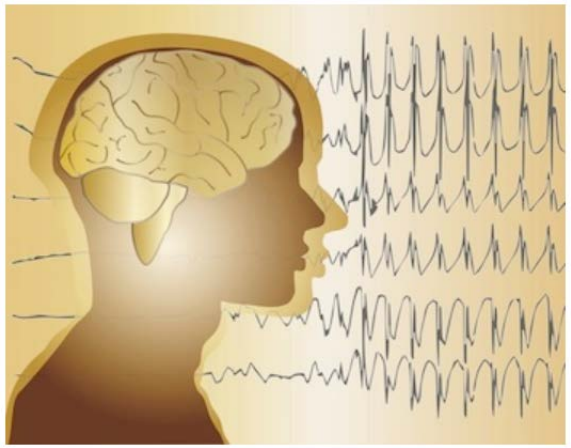
GRADING

Grado I	Basso indice di proliferazione
	Trattabili con la sola chirurgia

Grado II	Natura infiltrante
	Tendenza a recidivare
	Potenziale progressione verso forme a più alto grado di malignità (astrocitoma gemistocitico)

SEGNI e SINTOMI di PRESENTAZIONE

- **Generali**
  - cefalea
  - ipertensione
- **Focali**
  - Irritativi



  - Deficitari → Sindromi neurologiche

Eloquent areas funzione motoria, visuospaziale, memoria e linguaggio

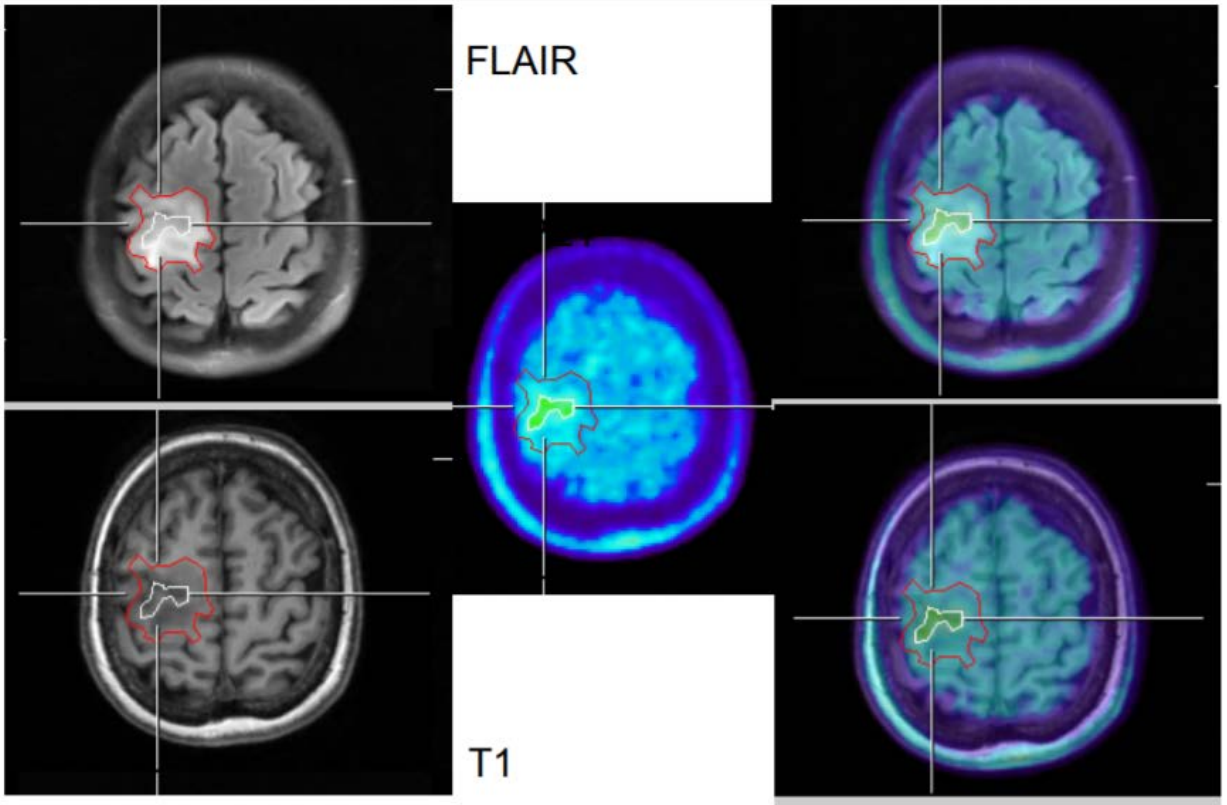
IMAGING

Morfologiche

- **TC** cerebrale con mdc
- **RMN** cerebrale con gadolinio

Non morfologiche

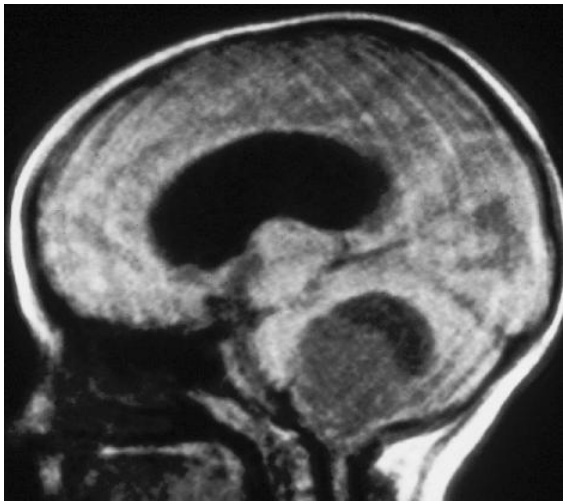
- **RM** perfusione
- **RM** Spettroscopia
- **PET**

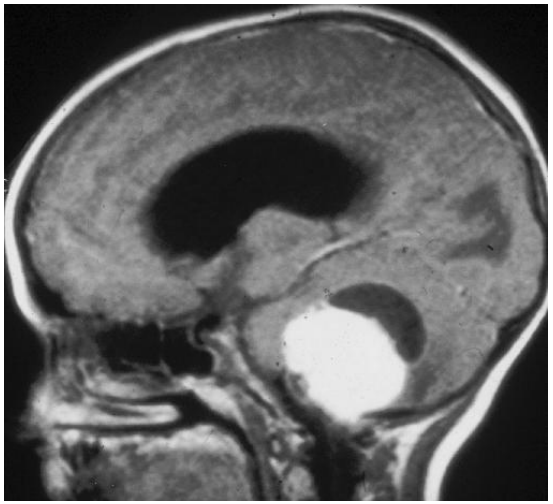


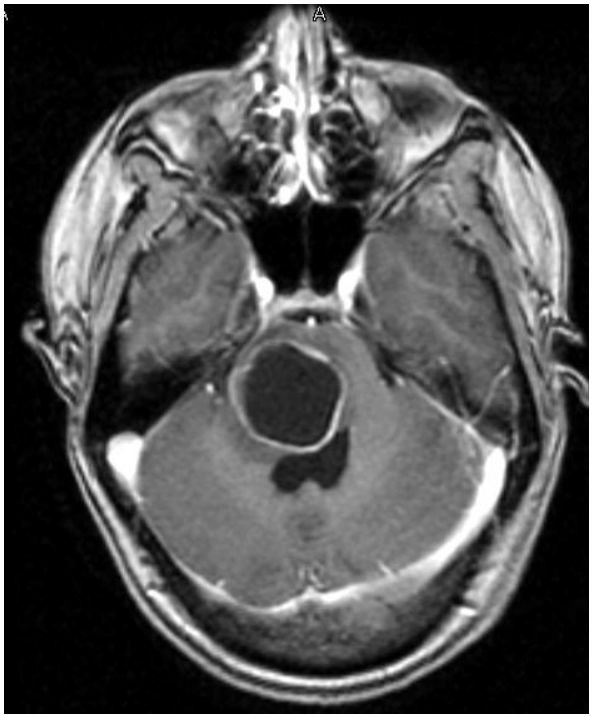
Gliomi circoscritti

Astrocitoma pilocitico

- Età infantile-giovanile
- Sede: cervelletto, tronco encefalico, diencefalo

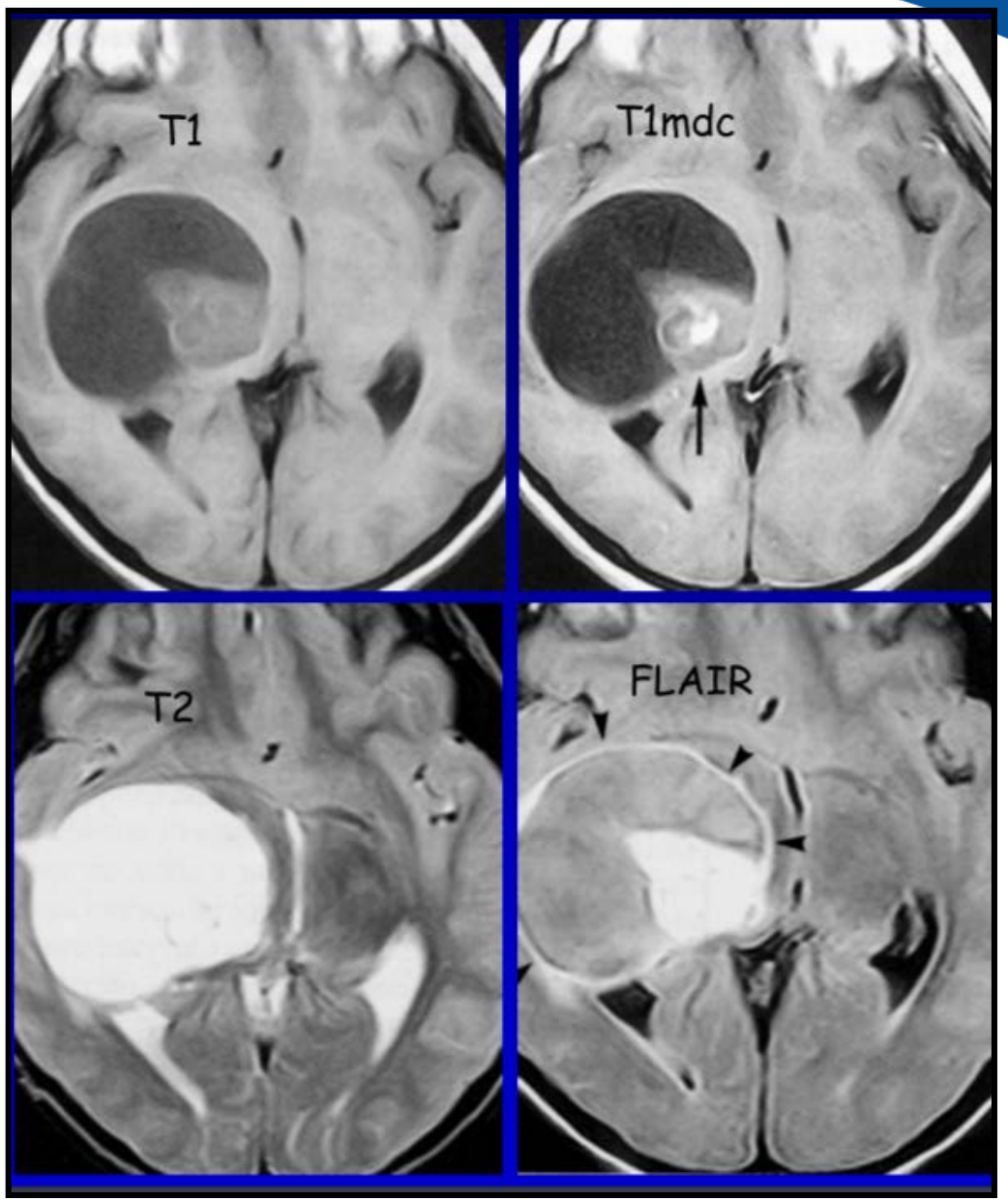






Treatment

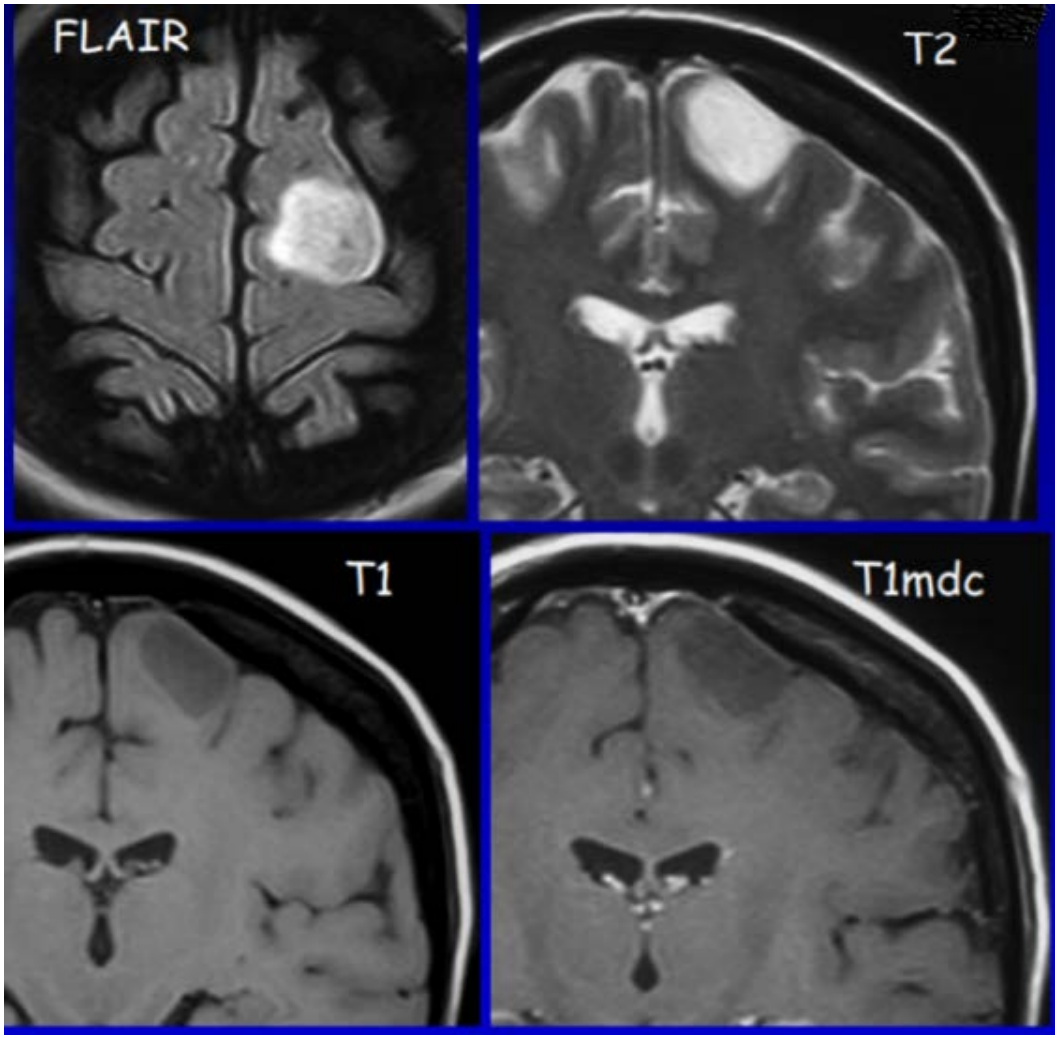
- ❑ **Surgery**
- ❑ **Consider RT**
  - Incomplete resection/biopsy
  - Significant tumor growth
  - Neurological symptoms



Gliomi infiltranti

Astrocitoma diffuso

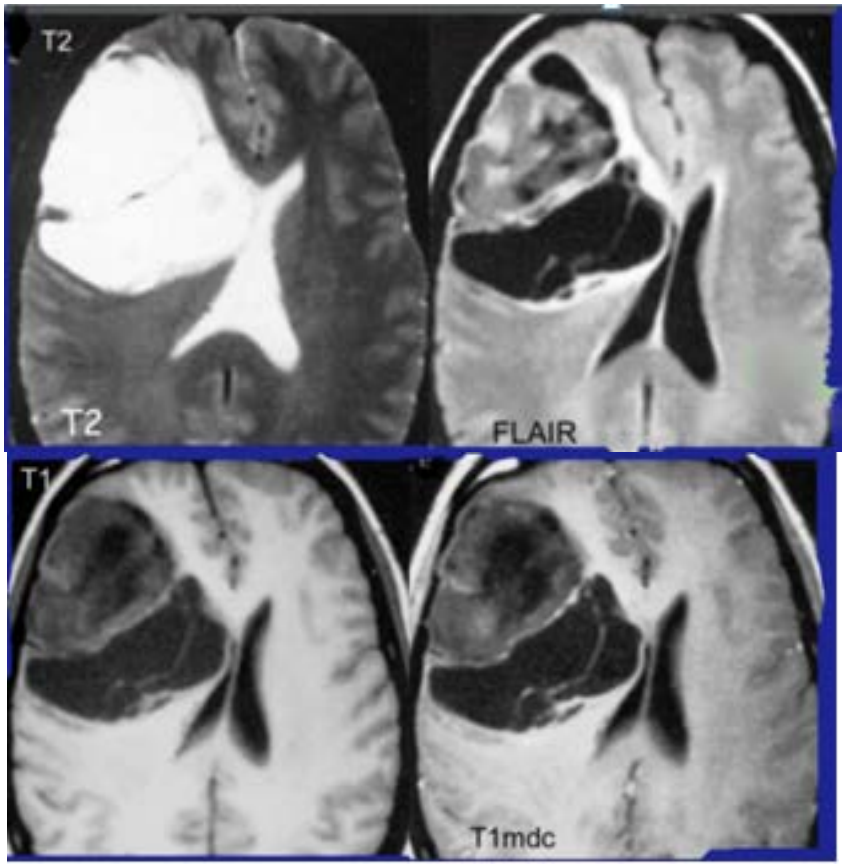
- Aspetto solido ben delimitato
- Lesione omogenea a margini apparentemente definiti
- Scarso edema perilesionale



Gliomi infiltranti

Oligodendroglioma

- Lesione disomogenea per voluminose calcificazioni
- Rare emorragie e cisti, scarso edema
- Sede: sostanza bianca fronto-parieto-temporale



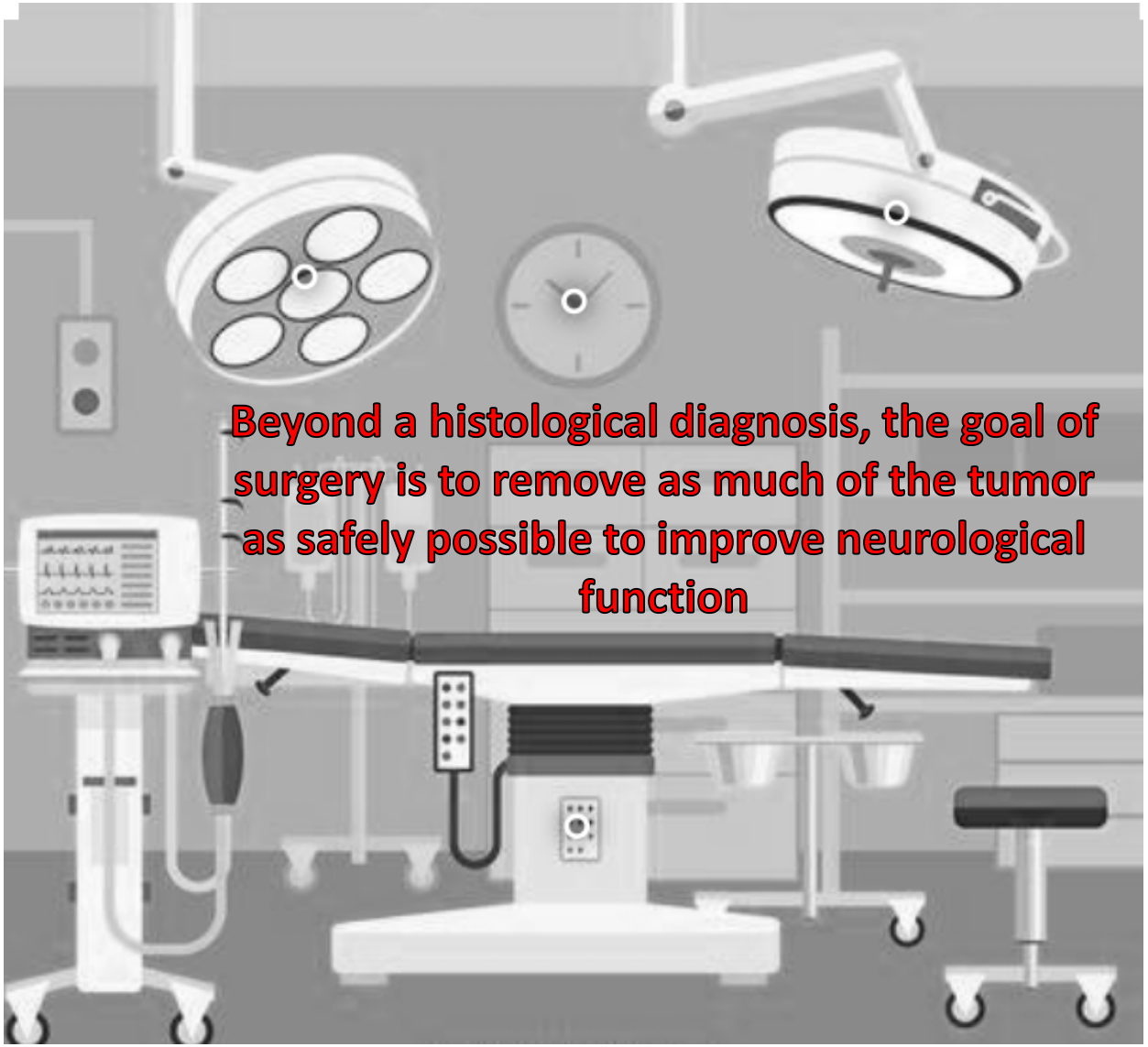
INTEGRAZIONE TERAPEUTICA

CHIRURGIA

RADIOTERAPIA

CHEMIOTERAPIA

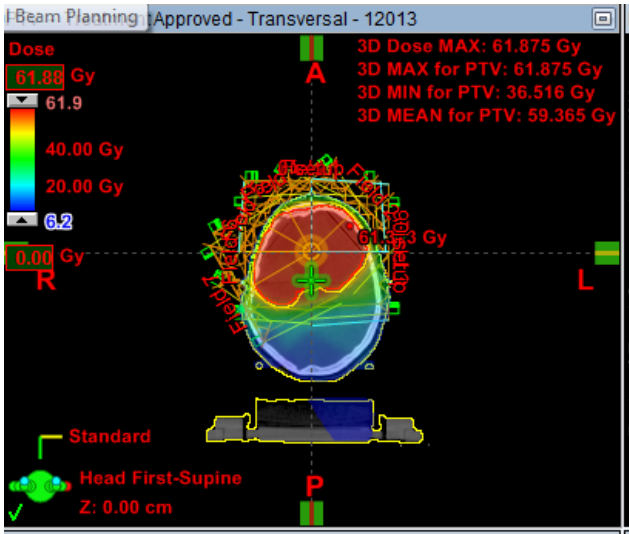
Surgery

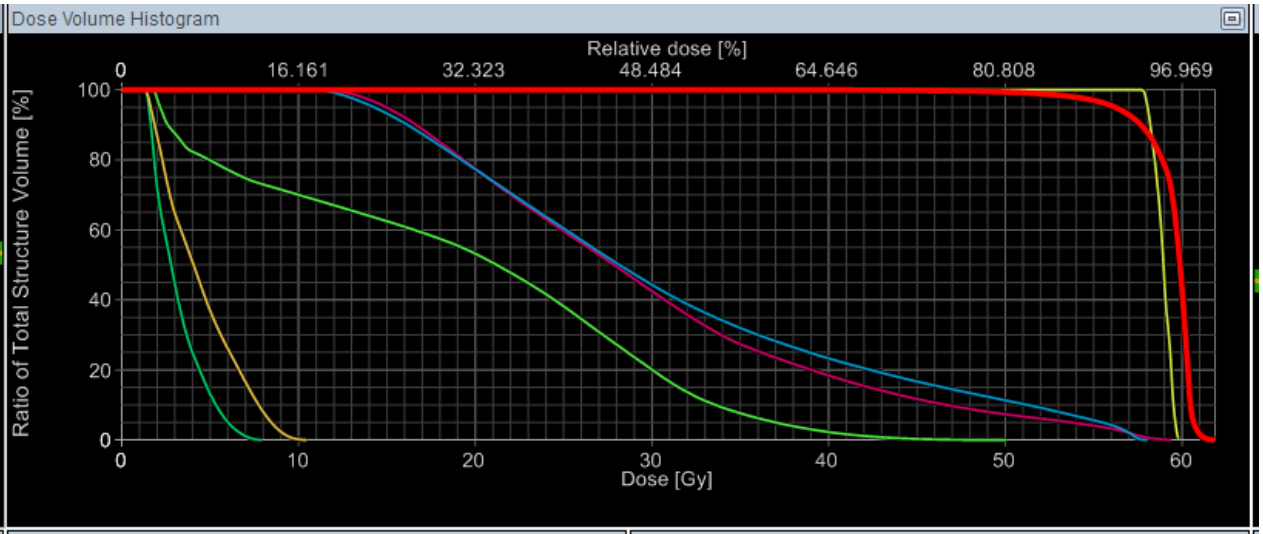

Beyond a histological diagnosis, the goal of surgery is to remove as much of the tumor as safely possible to improve neurological function

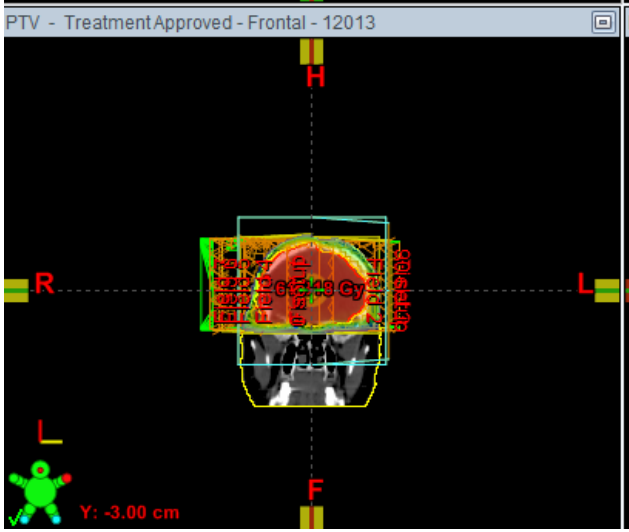
OBIETTIVI CHIRURGICI

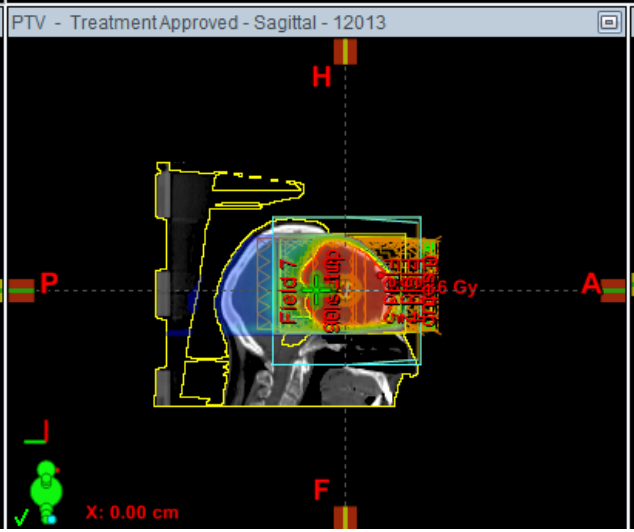
- **DIAGNOSI ISTOLOGICA**, valutazione della malignità e stato molecolare
- **GROSS TOTAL RESECTION, WHEN APPROPRIATE**: miglior outcome, maggior controllo delle crisi epilettiche

RADIOTERAPIA









The goal of radiotherapy is to improve local control at a reasonable risk benefit ratio. RT helps to preserve function and increases survival

Fattori prognostici sfavorevoli

→ ***EORTC*** *(European Organisation for Research and Treatment of Cancer)*

- Età > 40 anni
- Deficit neurologici alla diagnosi
- Diametro lesionale > 6 cm
- Superamento della linea mediana
- Istotipo astrocitario

→ ***RTOG*** *(Radiation Therapy Oncology Group)*

- Età > 40 anni
- Resezione subtotale

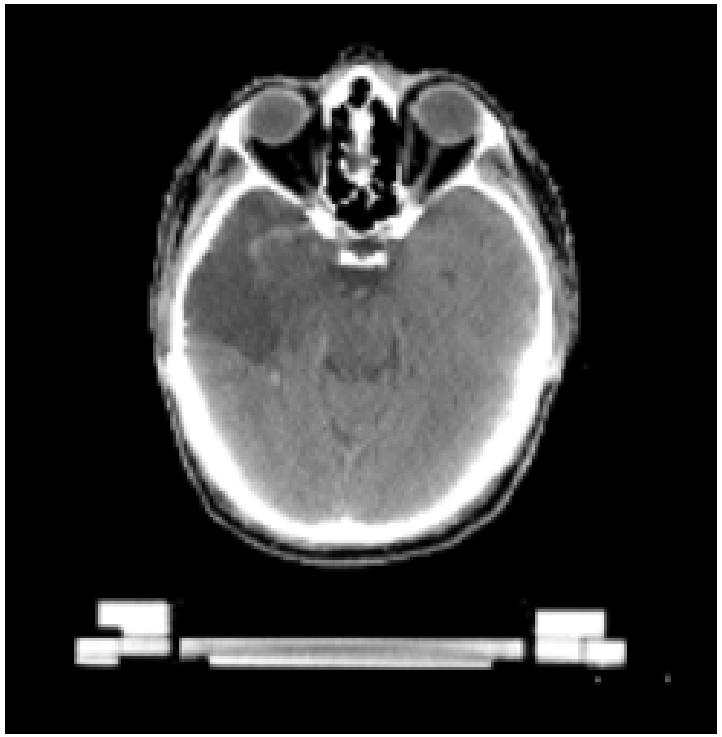
POST-SURGICAL MANAGEMENT

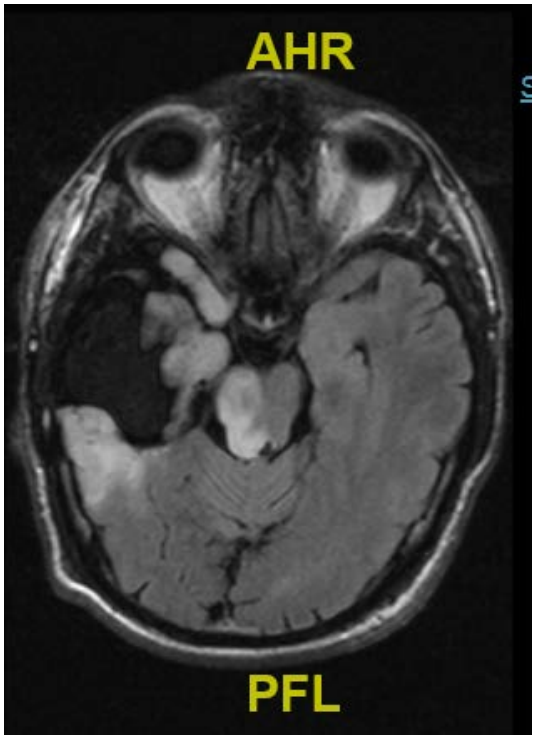
LOW RISK (gross total resection, alone or in combination with age ≤ 40 ys) → **Observation** with MRI

HIGH RISK (incomplete resection or biopsy and/or persisting seizures, and/or older patients, progression on MRI, IDH1 or 2 wild type) → Treatment required: **RT and/or CHT**

TARGET DELINEATION

Planning CT ***fused with*** PRE and POST-operative MRI

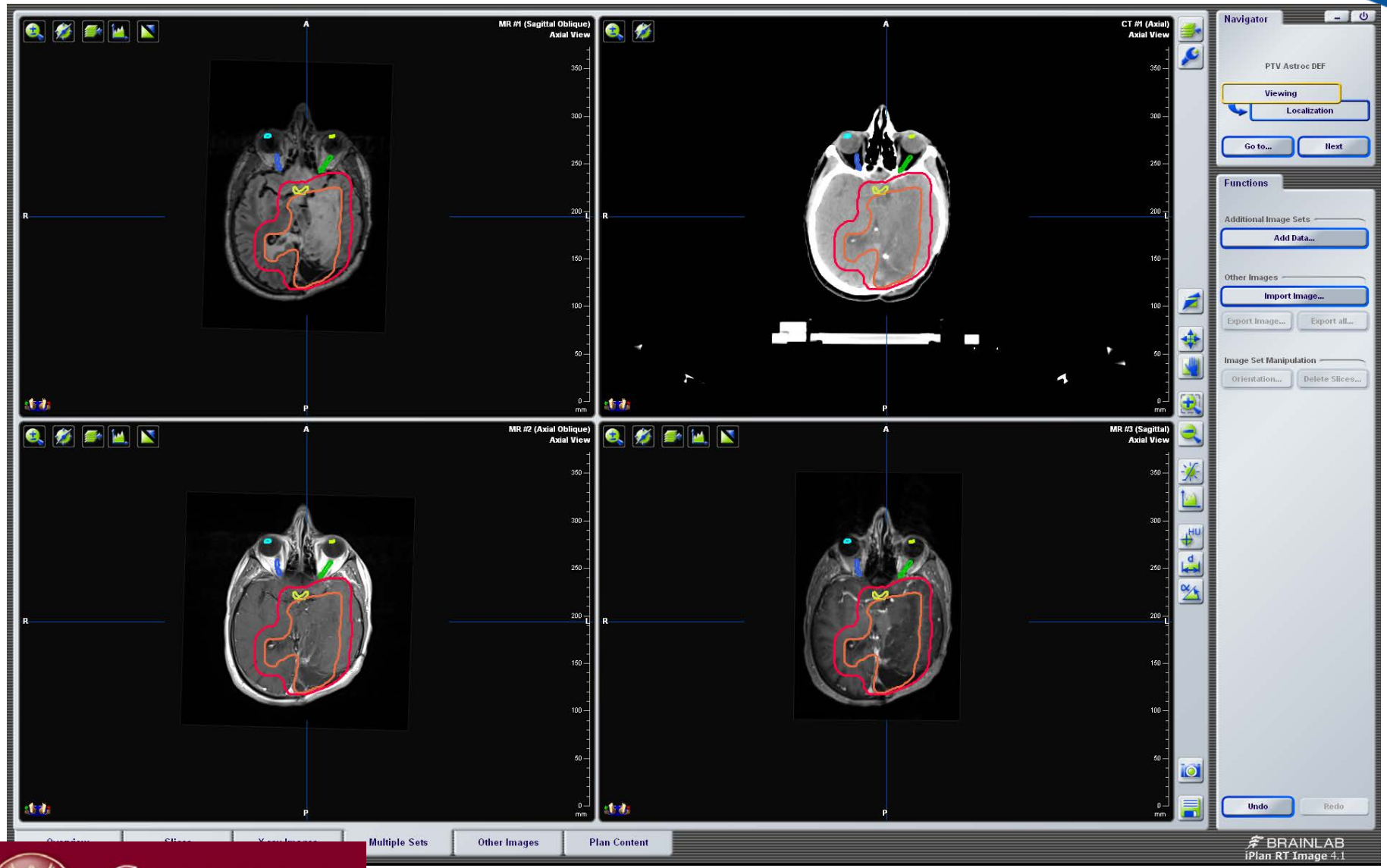




TARGET VOLUME

- **Gross Tumor Volume** (**GTV**): tumor bed + macroscopically visible disease
- **Clinical Target Volume** (**CTV**): GTV + a margin to account for microscopic spread [1-2.5 cm]
- **Planning Target Volume** (**PTV**) : CTV + uncertainties of planning, including those arising from CT-MRI fusion and patient setup. The definite margin should be based on the institutional fixation technique and quality assurance measurements [0.3-0.5 cm]

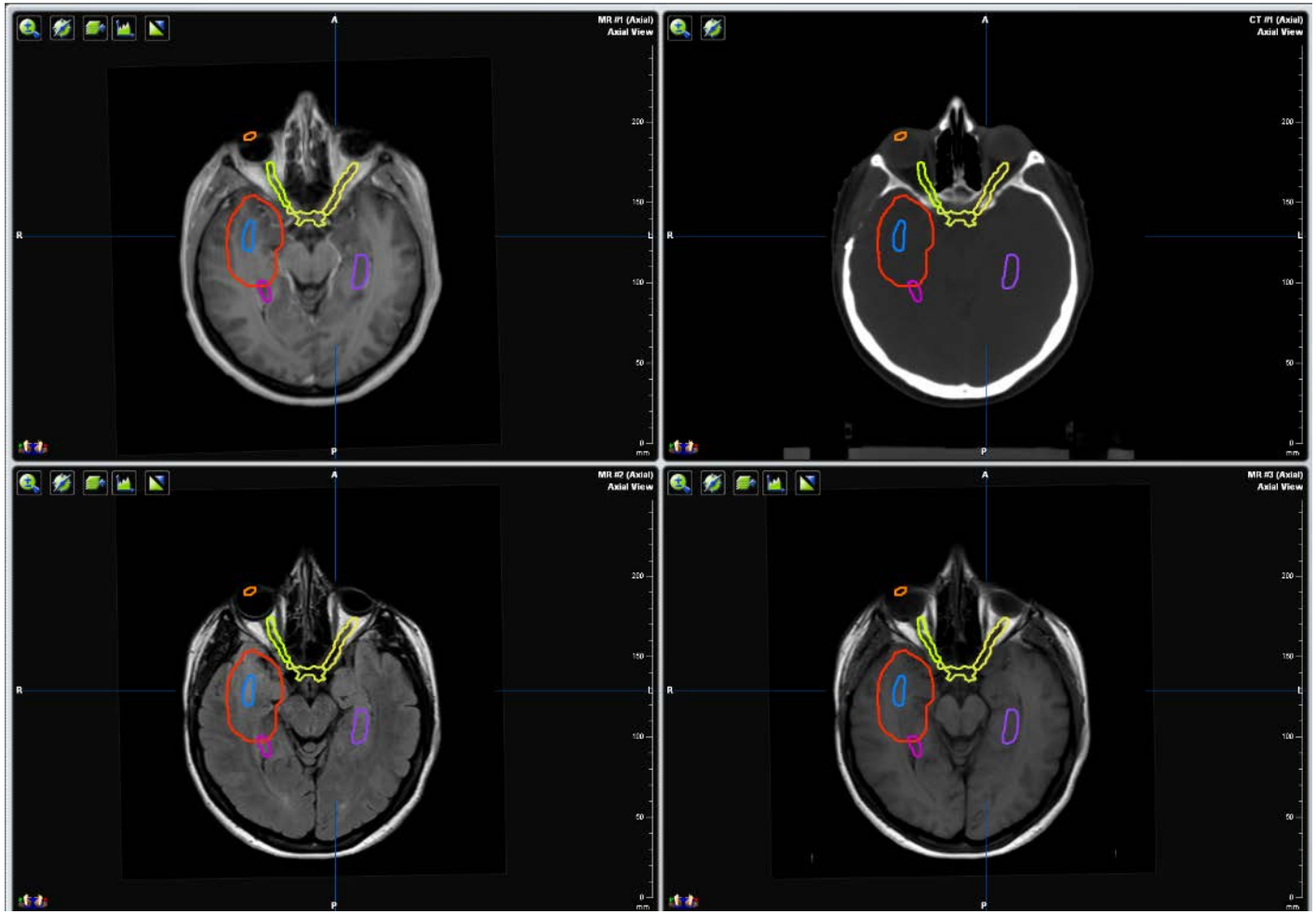
CONTOURING


MR #1 (Sagittal Oblique)
Axial View
CT #1 (Axial)
Axial View
MR #2 (Axial Oblique)
Axial View
MR #3 (Sagittal)
Axial View
Navigator
PTV Astroc DEF
Viewing
Localization
Go to...
Next
Functions
Additional Image Sets
Add Data...
Other Images
Import Image...
Export Image...
Export all...
Image Set Manipulation
Orientation...
Delete Slices...
Undo
Redo
Multiple Sets
Other Images
Plan Content
BRAINLAB
iPlan RT Image 4.1

ORGANS AT RISK

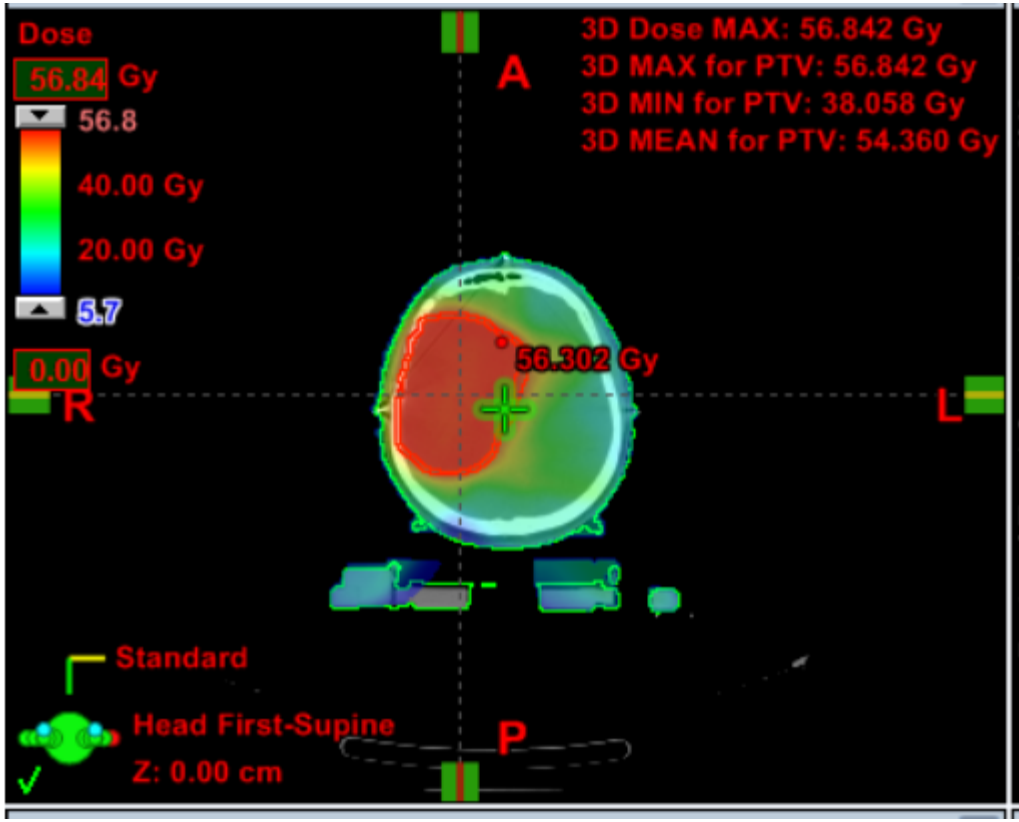
- N.Ottici
- Chiasma ottico
- Cristallino
- Brainstem
- Brain

Ipofisi
Coclea
Ippocampo

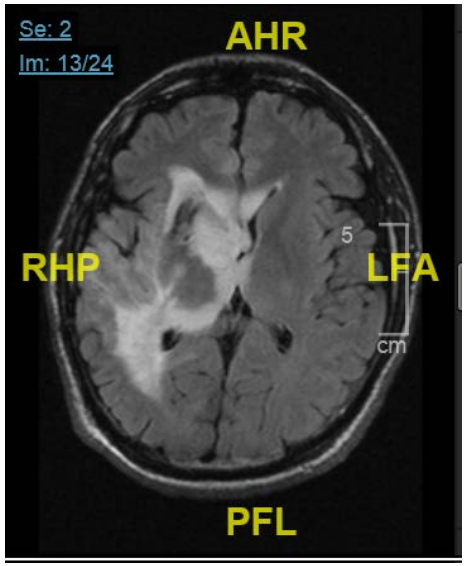


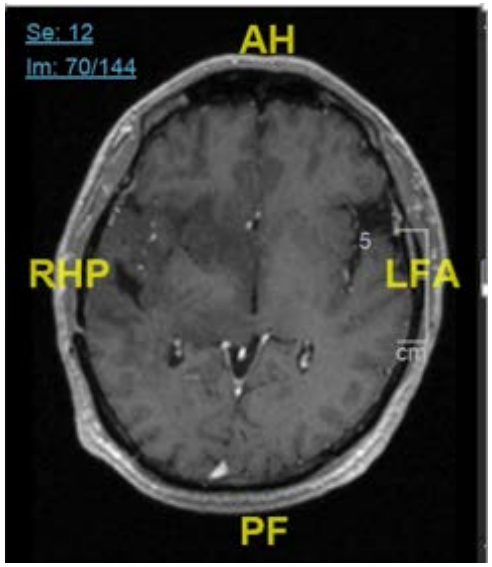
RT DOSE

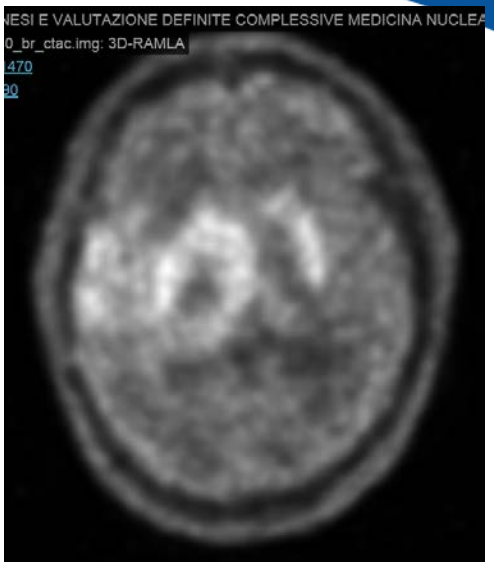
- **Dose totale: 45-54 Gy** in frazioni da 1.8-2 Gy
- Nessun vantaggio per dosi più alte ma, maggior incidenza di radionecrosi e riduzione della QoL, in particolare fatigue, insonnia e decadimento cognitivo [**EORTC 22844**]
- Valuta RT dose escalation 59.4-60 Gy per **IDH-wt LGG**



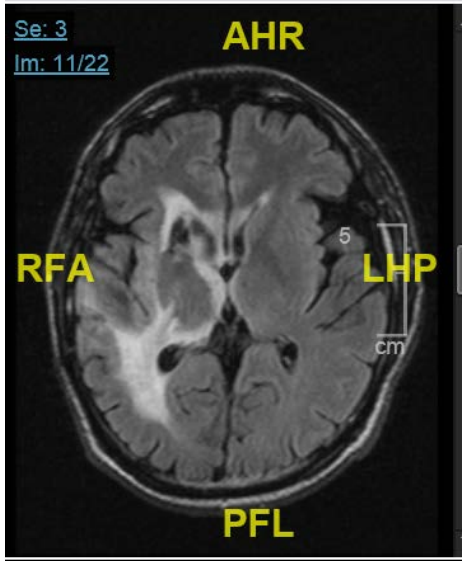
Imaging pre-RT (2011)

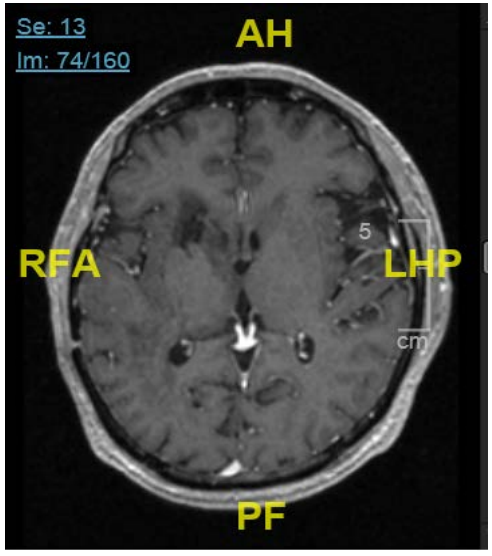


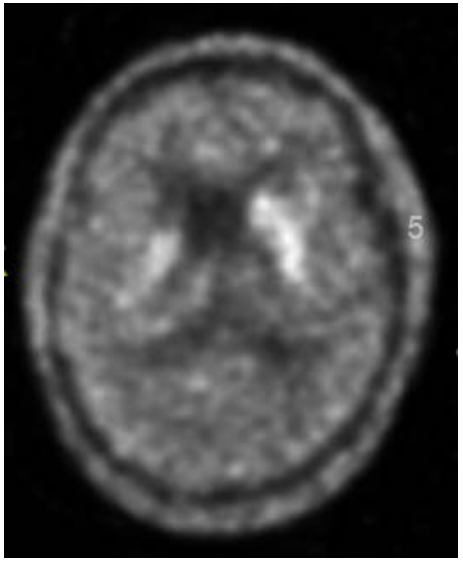




Imaging post-RT (2013)

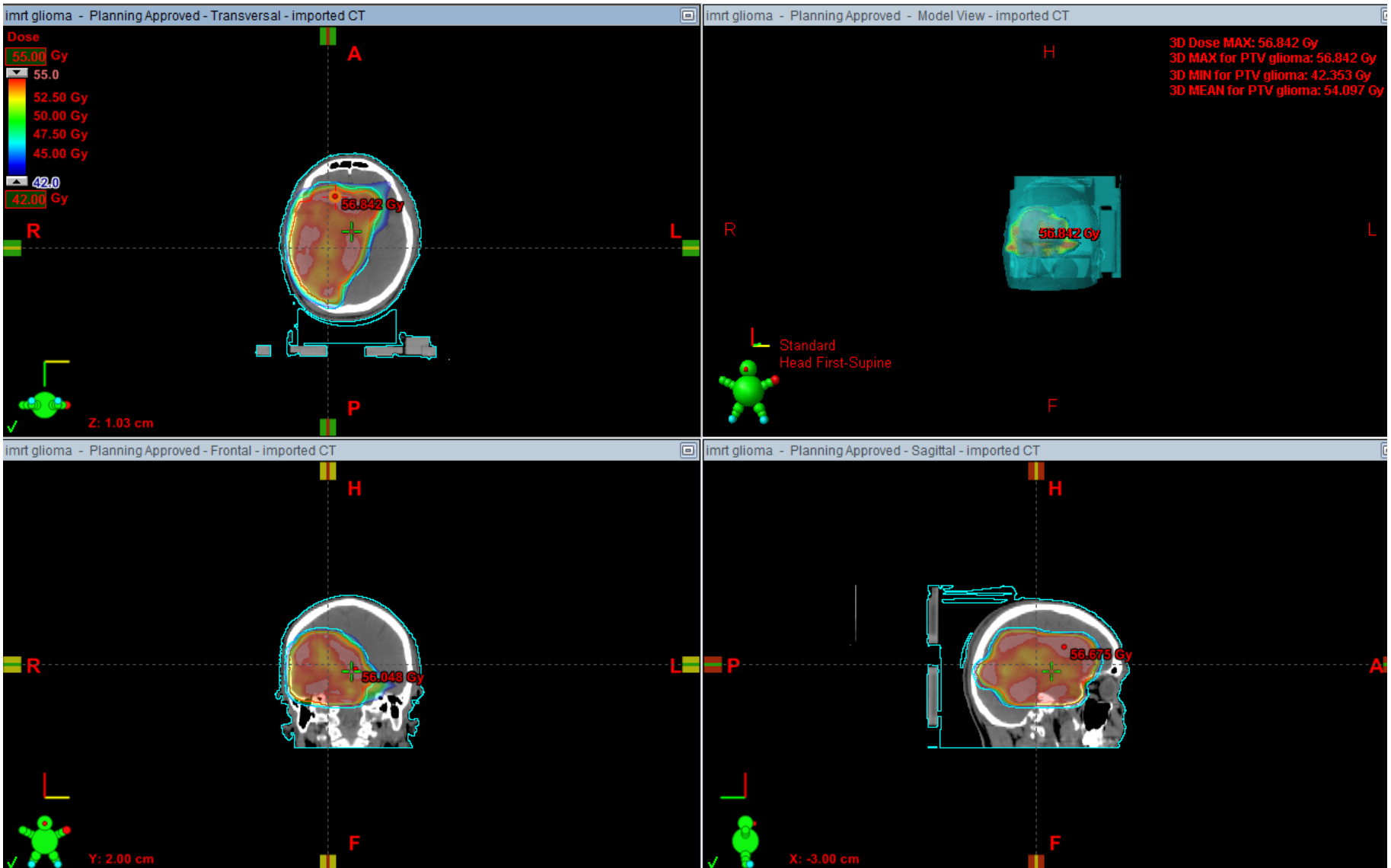






Trattamento RT-CHT concomitante con TMZ 75 mg/mq/die

Dose totale sul letto chirurgico: 54 Gy in 30 frazioni da 1.8 Gy /die (volume totale di 70.74 cc)



CHEMIOTERAPIA

Temozolomide

- 75 mg/m² orally, daily including weekends during radiotherapy
- 150–200 mg/m² orally, days 1–5, fasting in the morning every 4 weeks for six cycles of maintenance treatment

Nimustine, carmustine, lomustine, and fotemustine

- Different regimens, most commonly lomustine 110 mg/m² orally every 6 weeks

Procarbazine, loumustine, and vincristine

- Procarbazine 60 mg/m² orally, days 8–21
- Lomustine 110 mg/m² orally, day 1
- Vincristine 1·4 mg/m² intravenously (maximum 2 mg), days 8 and 29 for 6–8 weeks

Bevacizumab

- 10 mg/kg once every 2 weeks

Diffuse gliomas: benefit & timing of postsurgical management

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

M J 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

	No early radiotheraphy (n=157)	Early radiotherapy (n=154)	Hazard ratio (95% CI)
Overall survival			
Median years (95% CI)	7·4 (6·1–8·9)	7·2 (6·4–8·6)	0·97 (0·71–1·34)
Proportion alive at 5 years	65·7% (57·8–73·5)	68·4% (60·7–76·2)	
Progression-free survival			
Median years (95% CI)	3·4 (2·9–4·4)	5·3 (4·6–6·3)	0·59 (0·45–0·77)
Proportion free from progression at 5 years	34·6% (26·7–42·5)	55·0% (46·7–63·3)	

Table 2: Survival and progression-free survival

EORTC 22845: early versus delayed radiotherapy

PFS

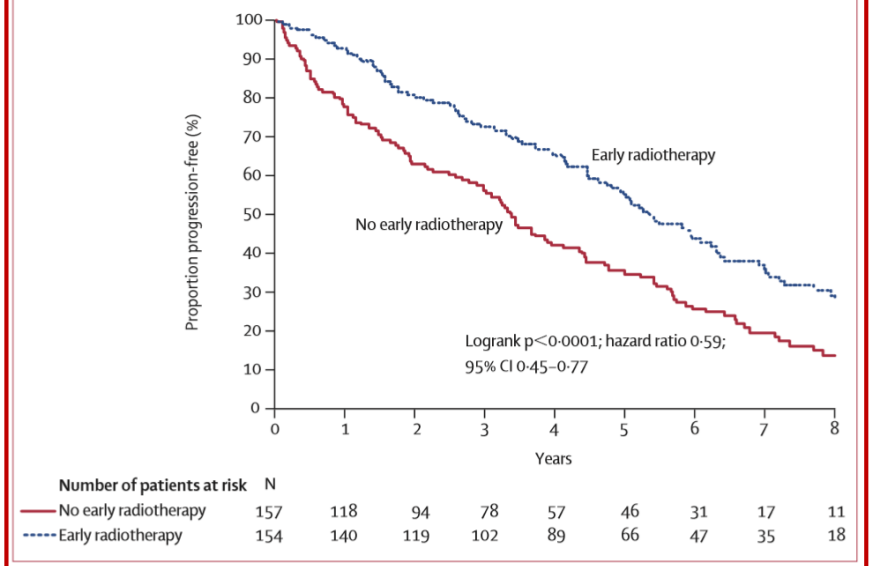


Figure 3: Progression-free survival by intention-to-treat analysis
Number of events: O=121 for control group; O=96 for early radiotherapy group.

OS

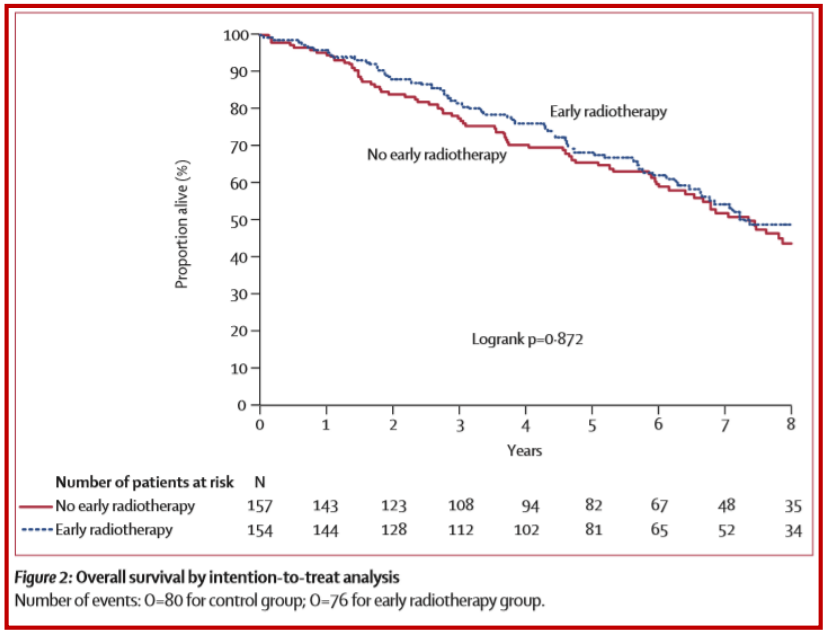


Figure 2: Overall survival by intention-to-treat analysis
Number of events: O=80 for control group; O=76 for early radiotherapy group.

www.thelancet.com Vol 366 September 17, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

Jan C. Buckner, M.D., Edward G. Shaw, M.D., Stephanie L. Pugh, Ph.D.,

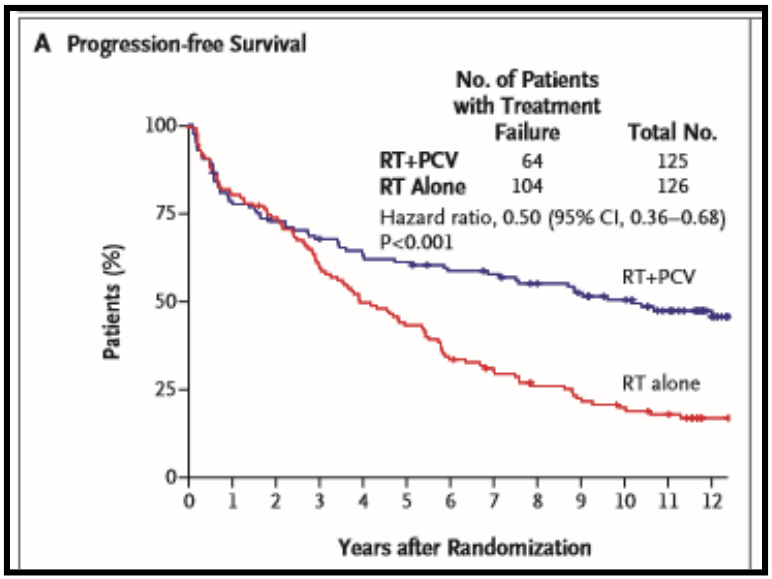
METHODS

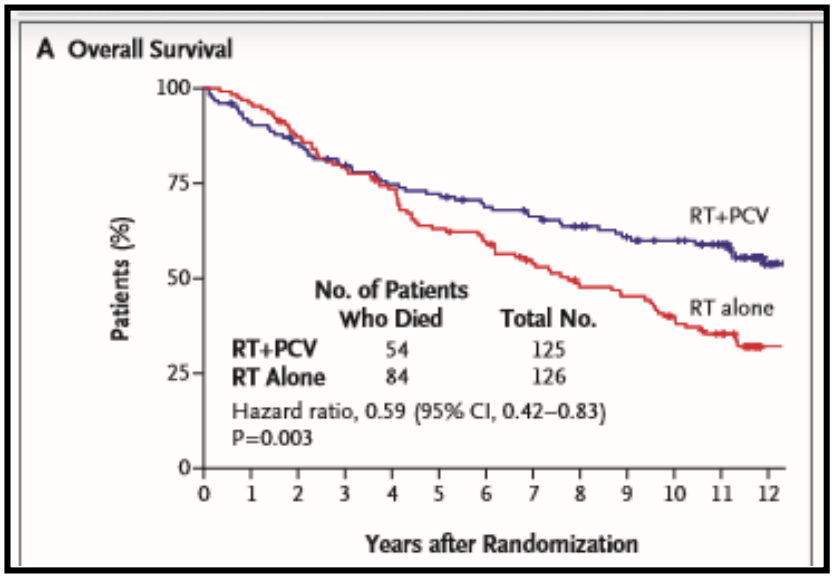
We included patients with grade 2 astrocytoma, oligoastrocytoma, or oligodendroglioma who were younger than 40 years of age and had undergone subtotal resection or biopsy or who were 40 years of age or older and had undergone biopsy or resection of any of the tumor. Patients were stratified according to age, histologic findings, Karnofsky performance-status score, and presence or absence of contrast enhancement on preoperative images. Patients were randomly assigned to radiation therapy alone or to radiation therapy followed by six cycles of combination chemotherapy.

RESULTS

A total of 251 eligible patients were enrolled from 1998 through 2002. The median follow-up was 11.9 years; 55% of the patients died. Patients who received radiation therapy plus chemotherapy had longer median overall survival than did those who received radiation therapy alone (13.3 vs. 7.8 years; hazard ratio for death, 0.59; P=0.003). The rate of progression-free survival at 10 years was 51% in the group that received radiation therapy plus chemotherapy versus 21% in the group that received radiation therapy alone; the corresponding rates of overall survival at 10 years were 60% and 40%. A Cox model identified receipt of radiation therapy plus chemotherapy and histologic findings of oligodendroglioma as favorable prognostic variables for both progression-free and overall survival.

RADIATION PLUS PROCARBAZINE, CCNU, AND VINCRISTINE IN GLIOMA





Median PFS
RT + CHT: 10.4 ys
RT alone: 4.0 ys

10 ys PFS
RT + CHT: 51%
RT alone: 21%

Median OS
RT + CHT: 13.3 ys
RT alone: 7.8 ys

10 ys OS
RT + CHT: 60%
RT alone: 40%

The NEW ENGLAND JOURNAL of MEDICINE

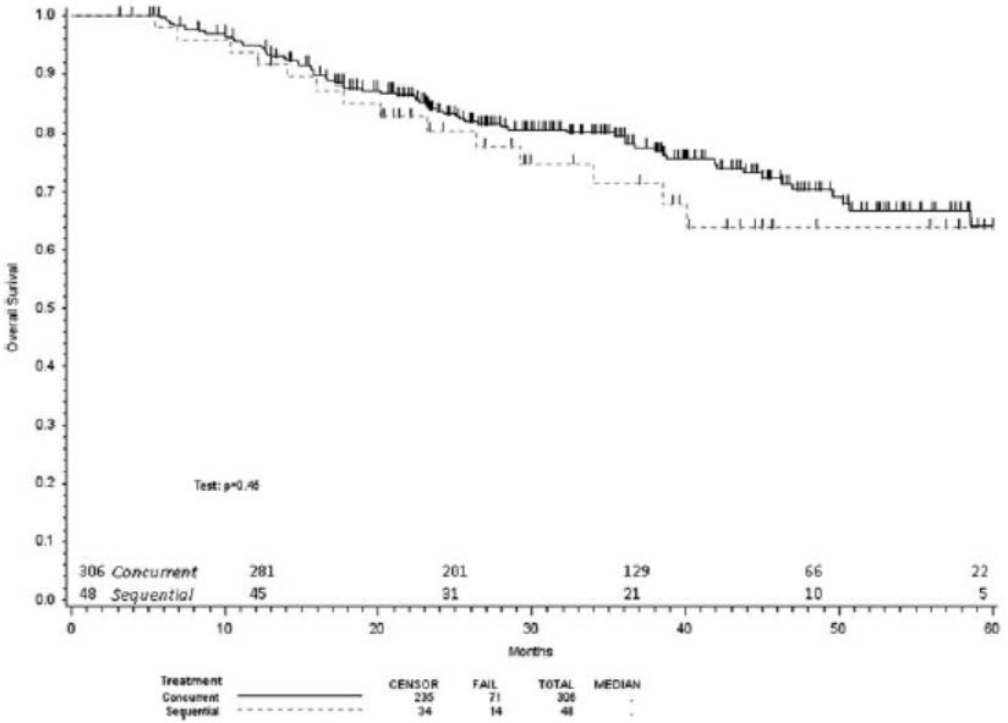
Table 2. Most Common Toxic Effects, According to Treatment Group.

Event	Radiation Therapy Alone (N=126)					Radiation Therapy plus PCV (N=125)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	no. of patients with event									
Constitutional symptoms	43	20	4	1	0	46	30	10	1	0
Fatigue	42	20	3	1	0	47	25	7	1	0
Weight loss	8	0	1	0	0	14	10	4	0	0
Blood or bone marrow disorder	2	2	1	0	0	11	20	52	12	0
Hemoglobin decreased	2	0	0	0	0	32	11	5	1	0
Packed red-cell transfusion required	0	0	0	0	0	1	0	2	0	0
Platelet count decreased	1	1	0	0	0	20	12	23	0	0
Platelet transfusion	0	0	0	0	0	0	0	0	1	0
Neutropenia	0	0	1	0	0	7	11	44	11	0
Febrile neutropenia	0	0	0	0	0	0	1	0	0	0
Infection	0	1	0	0	0	11	15	2	0	0
Lymphopenia	0	1	0	0	0	0	3	1	0	0
Gastrointestinal disorder	32	6	2	0	0	45	50	12	0	0
Anorexia	8	1	0	0	0	23	8	1	0	0
Constipation	3	0	0	0	0	18	11	0	0	0
Nausea	20	4	2	0	0	46	29	3	0	0
Vomiting	3	2	2	0	0	22	15	4	0	0
Hepatic disorder	2	0	0	0	0	27	9	3	2	0
Alanine aminotransferase increased	0	0	0	0	0	11	1	1	1	0
Aspartate aminotransferase increased	0	0	0	0	0	11	1	0	1	0

Concurrent Versus Sequential Chemoradiation for Low-grade Gliomas Meeting RTOG 9802 Criteria

Jeffrey M. Ryckman, MD, MSMP, Adams K. Appiah, MS,† Elizabeth Lyden, MS,†*
*Vivek Verma, MD,‡ and Chi Zhang, MD, PhD**

With a median FUP time of 38.3 months, ***there were no statistical differences for OS (p=0.45) between concurrent-CRT and sequential-CRT treatments groups***



Kaplan-Meier comparison of overall survival between cohorts.

American Journal of Clinical Oncology • Volume 42, Number 4, April 2019

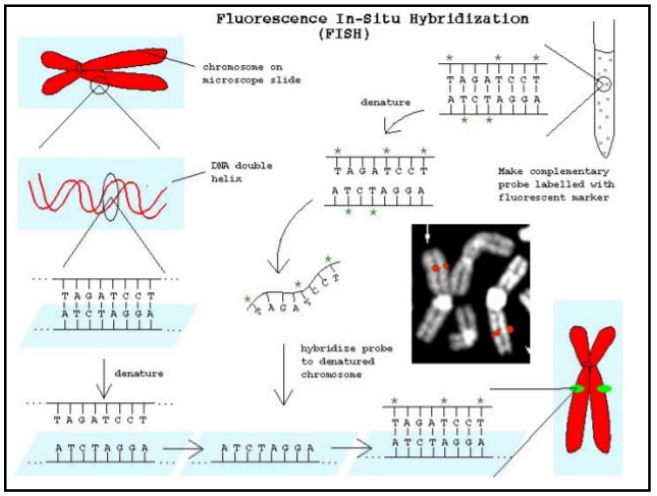
Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Brigitta G Baumert*, Monika E Hegi*, Martin J van den Bent, Andreas von Deimling, Thierry Gorlia, Khê Hoang-Xuan, Alba A Brandes, Guy Kantor, Martin J B Taphoorn, Mohamed Ben Hassel, Christian Hartmann, Gail Ryan, David Capper, Johan M Kros, Sebastian Kurscheid, Wolfgang Wick, Roelien Enting, Michele Reni, Brian Thiessen, Frederic Dhermain, Jacoline E Bromberg, Loic Feuvret, Jaap C Reijneveld, Olivier Chinot, Johanna M M Gijtenbeek, John P Rossiter, Nicolas Dif, Carmen Balana, Jose Bravo-Marques, Paul M Clement, Christine Marosi, Tzahala Tzuk-Shina, Robert A Nordal, Jeremy Rees, Denis Lacombe, Warren P Mason, Roger Stupp*

Primary endpoint: PFS

Secondary endpoints: OS, QoL, neurocognitive evaluation and association of molecular markers with outcome

- 1p/19q codeletion status
- MGMT promotor methylation status
- IDH1/2 mutations



www.thelancet.com/oncology Vol 17 November 2016

EORTC 22033-26033 - Primary Endpoint: PFS

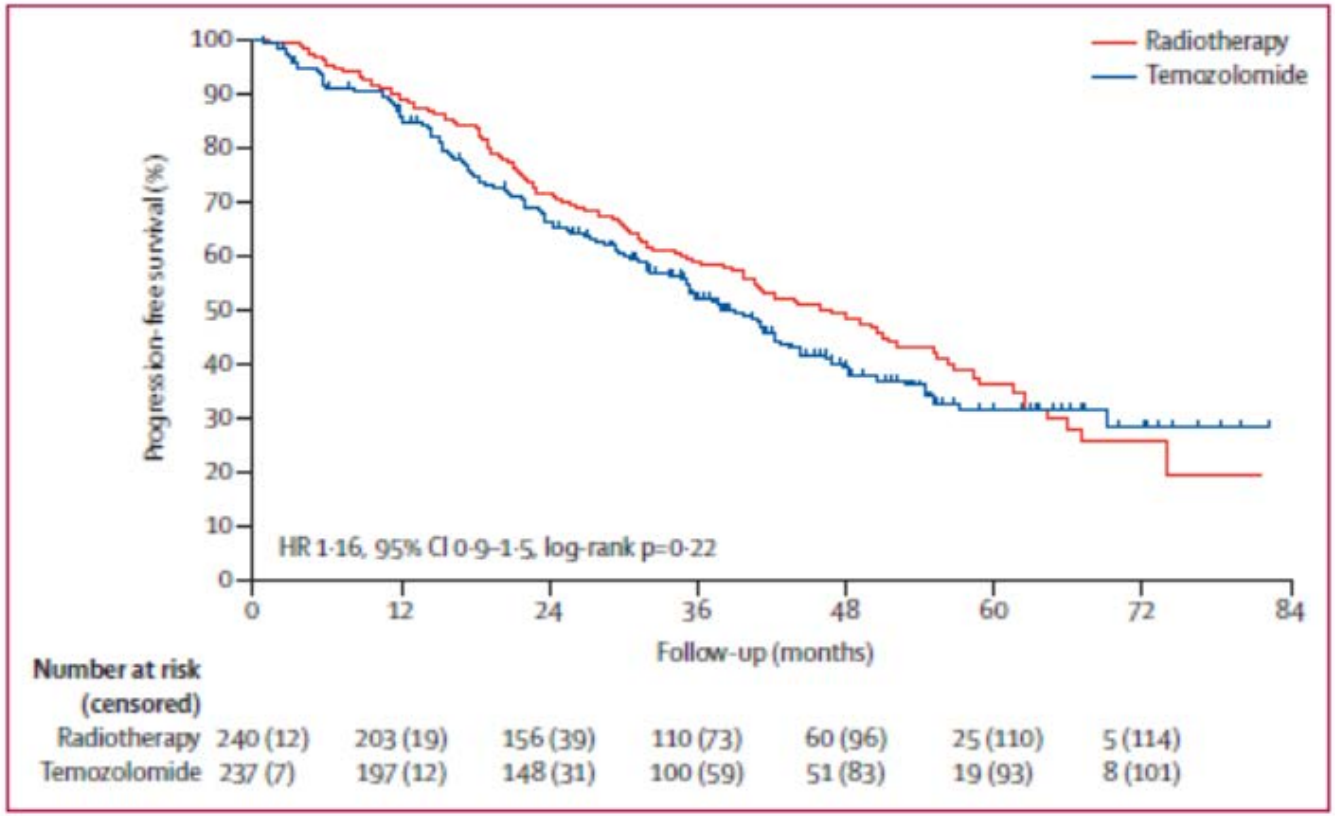
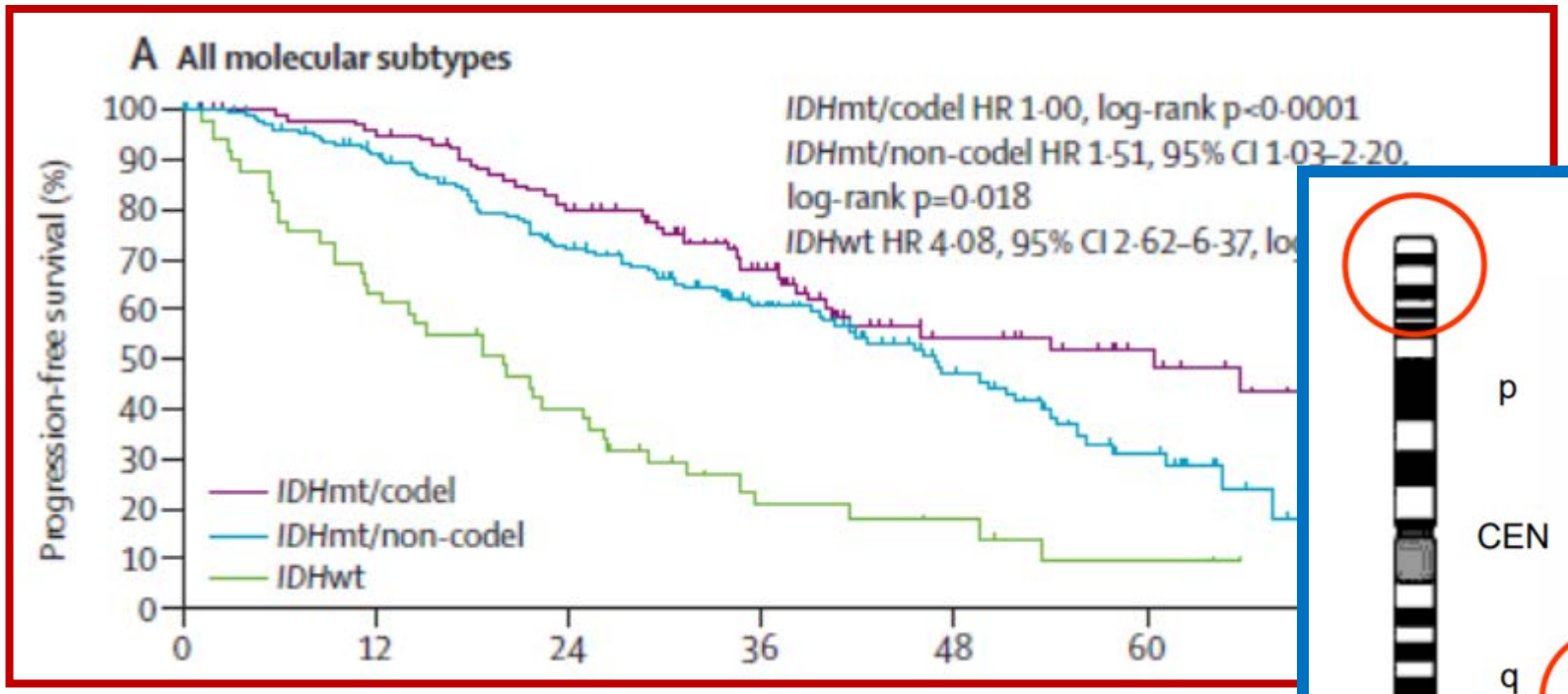
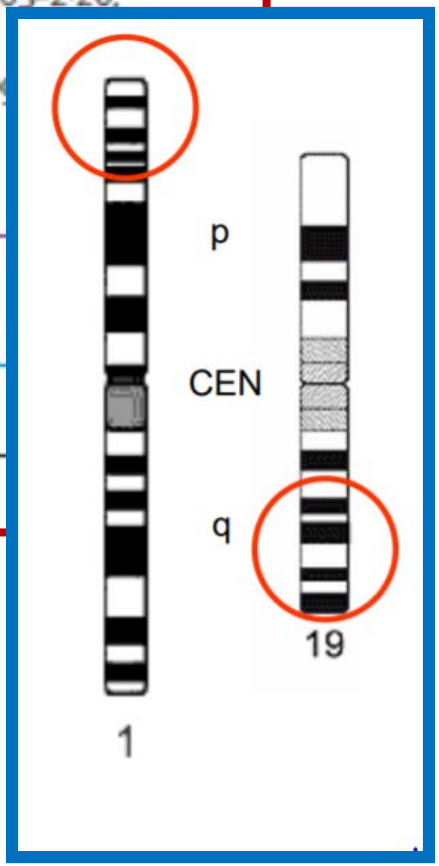


Figure 2: Progression-free survival

No significant difference in PFS in pts with LGG when treated with either radiotherapy alone or temozolomide chemotherapy alone

EORTC 22033-26033 - **Secondary Endpoint:** Molecular markers and outcome





	PFS (months)
IDHmt/codel	62
IDHmt/non-codel	48
IDHwt	20

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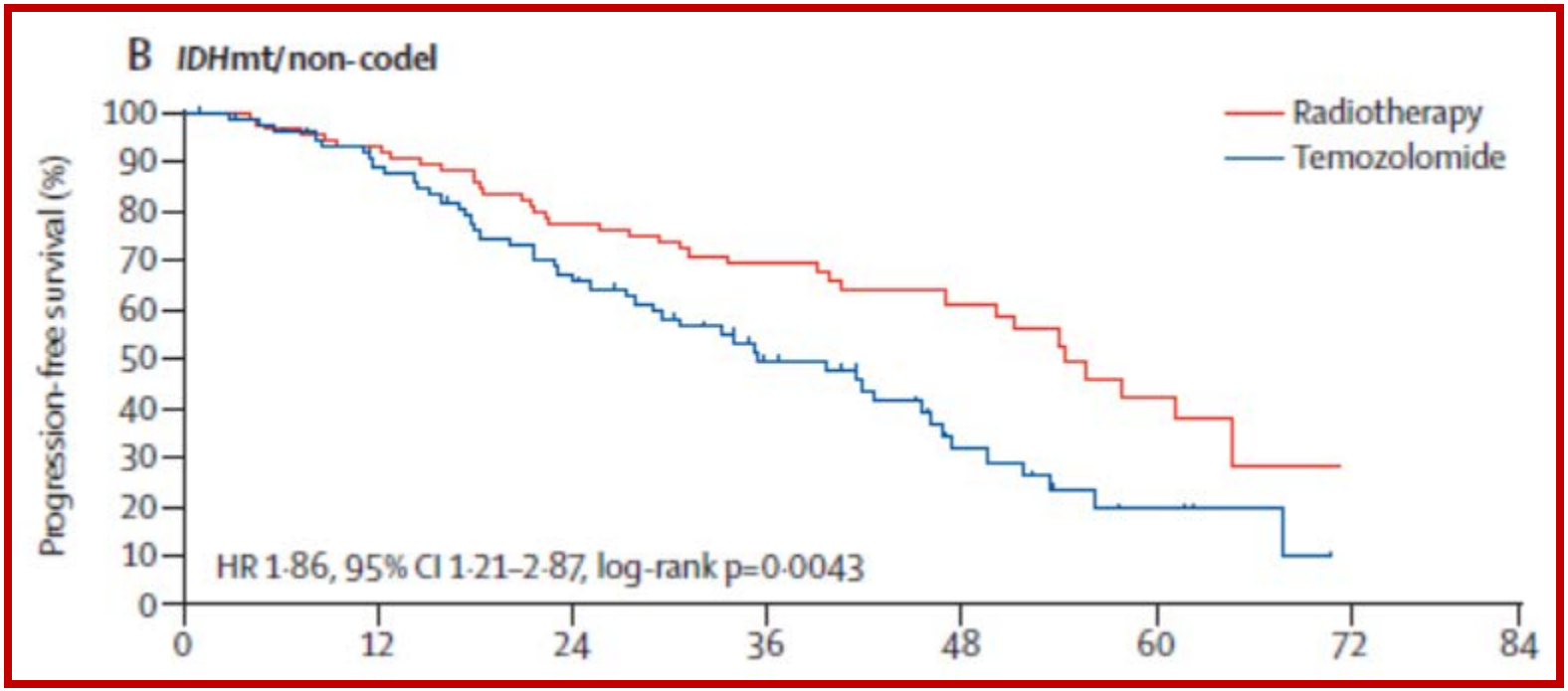
EORTC 22033-26033 - Secondary Endpoint: Molecular markers and outcome



Pts with **IDHmt/non-codel tumors** had **a longer PFS when treated with RT than with TMZ** (median PFS 55 vs 36 months, **p= 0.0043**)

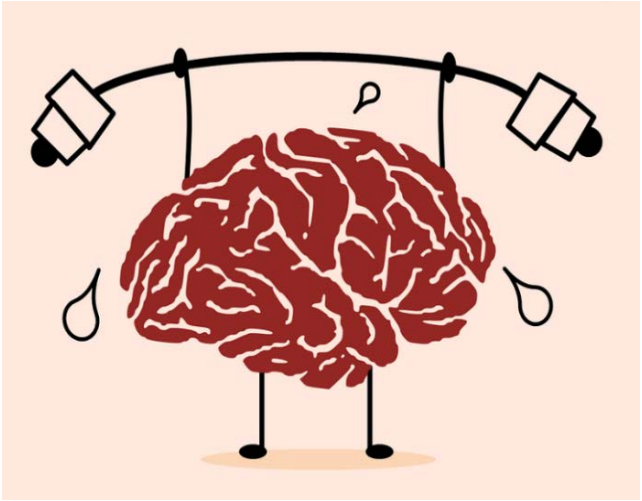
Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Jaap C Reijneveld, Martin J B Taphoorn, Corneel Coens, Jacoline E C Bromberg, Warren P Mason, Khê Hoang-Xuan, Gail Ryan, Mohamed Ben Hassel, Roelien H Enting, Alba A Brandes, Antje Wick, Olivier Chinot, Michele Reni, Guy Kantor, Brian Thiessen, Martin Klein, Eugenie Verger, Christian Borchers, Peter Hau, Michael Back, Anja Smits, Vassilis Golfinopoulos, Thierry Gorlia, Andrew Bottomley, Roger Stupp, Brigitta G Baumert

Global health

Social functioning

Communication deficit



Visual disorder

Motor dysfunction

Drowsiness

Interpretation The effect of temozolomide chemotherapy or radiotherapy on HRQOL or global cognitive functioning did not differ in patients with low-grade glioma. These results do not support the choice of temozolomide alone over radiotherapy alone in patients with high-risk low-grade glioma.

Clinical Investigation

Phase 2 Study of Temozolomide-Based Chemoradiation Therapy for High-Risk Low-Grade Gliomas: Preliminary Results of Radiation Therapy Oncology Group 0424

Barbara J. Fisher, MD,* Chen Hu, PhD,† David R. Macdonald, MD,* Glenn J. Lesser, MD,‡ Stephen W. Coons, MD,§ David G. Brachman, MD,|| Samuel Ryu, MD,¶ Maria Werner-Wasik, MD,# Jean-Paul Bahary, MD,** Junfeng Liu, PhD,†† Arnab Chakravarti, MD,‡‡ and Minesh Mehta, MD§§

International Journal of Radiation Oncology biology • physics
www.redjournal.org

There is emerging evidence that addition of chemo-therapy to radiation therapy has survival benefits for patients with low-grade gliomas (LGGs). The 3-year overall survival rate of 73.1% for eligible high-risk LGG patients treated with radiation and concurrent and adjuvant temozolomide in Radiation Therapy Oncology Group 0424 is significantly higher than the a priori specified historical controls treated with radiation alone ($P<.001$) with acceptable toxicity.

3 ys OS rate

73% present study

54% historical controls

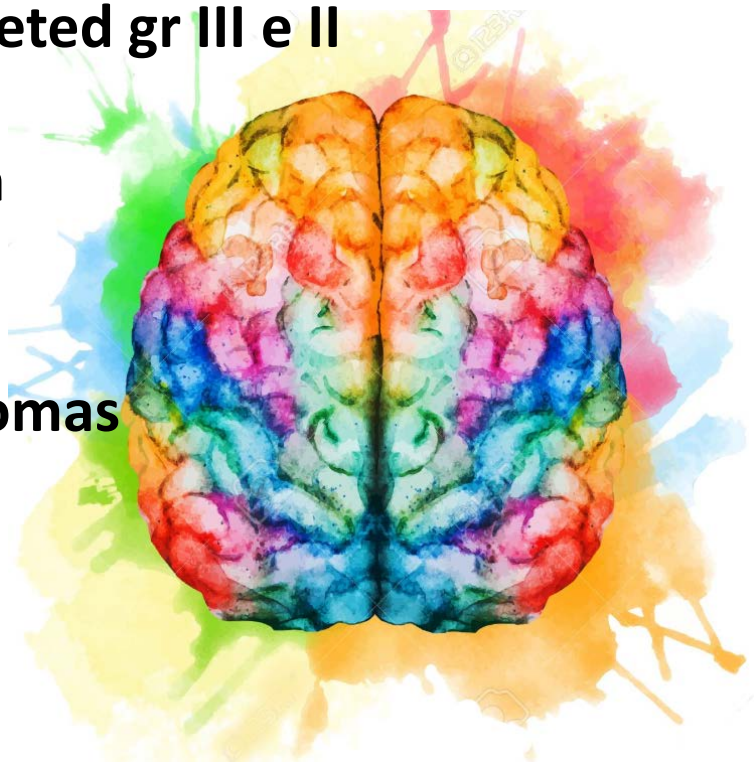
PLANNED/ONGOING TRIALS WITH MOLECULAR INCLUSION CRITERIA

NEW CODEL phase III trial (RTOG/EORTC)

RT+PCV vs RT+TMZ in 1p/19q codeleted gr III e II

Primary endopoint: PFS and OS

Secondary endpoint: neurocognition



POLO phase III trial (ANOCEF)

PCV vs RT+PCV in IDH1 mut gr II gliomas

Primary endpoint: neurocognition

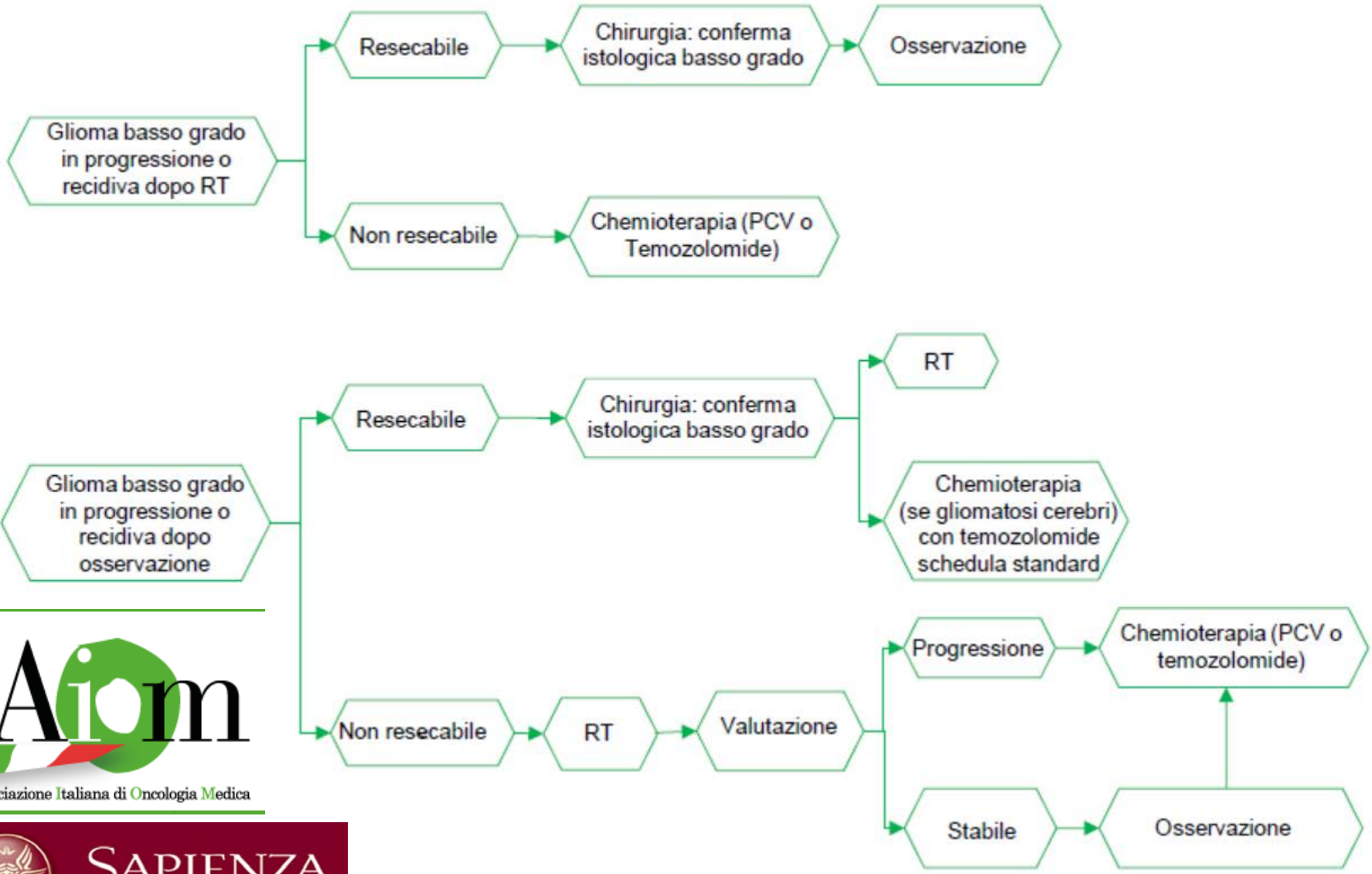
Secondary endpoint: PFS and OS

European Association for Neuro-Oncology (EANO) guideline

	First-line treatment*	Salvage therapies†‡	Comments and references
Diffuse astrocytic and oligodendroglial tumours			
Diffuse astrocytoma, IDH-mutant	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab§)	RTOG 9802 trial[15] and extrapolation from WHO grade III tumours[16]
Gemistocytic astrocytoma, IDH-mutant	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab§)	--
Diffuse astrocytoma, IDH-wild-type	Watch-and-wait (remains controversial), radiotherapy, radiotherapy followed by PCV, or temozolomide and radiotherapy followed by temozolomide (according to *MGMT* status [remains controversial])	Temozolomide, or nitrosourea (or temozolomide rechallenge) or bevacizumab§	Extrapolation from IDH-wild-type glioblastoma[17]
Diffuse astrocytoma, not otherwise specified	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab§)	--
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Watch-and-wait or radiotherapy followed by PCV	Temozolomide or bevacizumab§	Extrapolation from WHO grade III tumours[22,23] and RTOG 9802 trial[15]
Oligodendroglioma, not otherwise specified	Watch-and-wait or radiotherapy followed by PCV	Temozolomide or bevacizumab§	Extrapolation from WHO grade III tumours[22,23] and RTOG 9802
Other astrocytic tumours			
Pilocytic astrocytoma Pilomyxoid astrocytoma	Surgery only	Surgery followed by radiotherapy	--
Subependymal giant cell astrocytoma	Surgery only	Surgery	--
Pleomorphic xanthoastrocytoma	Surgery only	Surgery	--

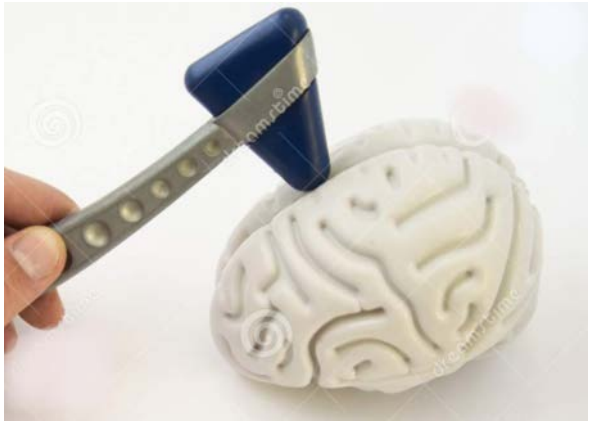
Lancet Oncology, 2017

RECIDIVA/PROGRESSIONE di LGG

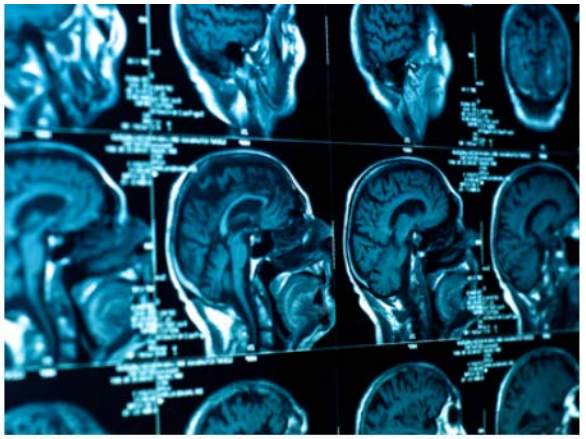


FOLLOW UP

- Follow up clinico-strumentale
- Esami bioumorali con dosaggio dell'antiepilettico



	RM cerebrale gadolinio
CHT	3 mesi
1st year	4 mesi
> 1st year	6 mesi



- Le modalità di trattamento e le sequenze ottimali in pz affetti da LGG risultano controverse
- Ad oggi il principale fattore prognostico risulta essere l'assetto molecolare del tumore, predittivo dell'aggressività e della risposta ai trattamenti
- RT postoperatoria aumenta significativamente PFS e il controllo delle crisi epilettiche
- L'obiettivo è bilanciare un effetto favorevole sulla PFS rispetto alla tossicità a lungo termine in una popolazione di giovani pazienti

Grazie per l'attenzione!