HIGH GRADE GLIOMAS

Focus RT

GRADING OF ASTROCYTIC TUMORS (WHO 2007)

Commonest – 1/3 of primary brain tumors

Astrocytic Tumours	I	II	III	IV
SEGA	*			
Pilocytic astrocytoma	*			
Pilomyxoid astrocytoma		*		
Diffuse astrocytoma		*		
PXA		*		
Anaplastic astrocytoma			*	
GBM				*
Giant cellGBM				*
Gliosarcoma				*

Malignant glioma

- Grade III and IV – Malignant gliomas
- Glioblastomas approximately 60 to 70%
- Anaplastic astrocytomas for 10 to 15%,
- Anaplastic oligodendrogliomas and Anaplastic oligoastrocytomas for 10%;

Incidenza:

- Importanza della **sede** nel determinare la prognosi
- pattern di diffusione: **diffusione attraverso gli spazi subaracnoidei**

Sintomatologia Ingravescente

edema and mass effect,

- Epilessia (focale o generalizzata)
- Deficit neurologici focali
- Ipertensione endocranica
- Idrocefalo

Esami strumentali di diagnosi.

L'indagine strumentale di primo livello, eseguita spesso in urgenza per la comparsa di sintomi neurologici acuti, è la TC senza ed, eventualmente, con mezzo di contrasto iodato, che consente di indirizzare il successivo iter terapeutico.

La **RM** con e senza mezzo di contrasto (gadolinio) è considerata l'esame strumentale di elezione sia per la diagnosi di presumibile natura che per l'indirizzo della chirurgia [livello di evidenza Ia] [9].

La RMN standard include varie sequenze:

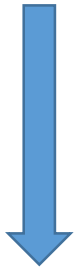
- **T1** pesate senza gadolinio per la valutazione di eventuali emorragie intratumorali;
- **T1 con gadolinio** per evidenziare aree di alterazione della barriera ematoencefalica in corrispondenza delle quali è presente captazione di mdc, tipica delle lesioni neoplastiche ad alto grado in generale e del glioblastoma in particolare;
- **T2** pesate (FLAIR) per la valutazione della porzione di tumore che non capta il contrasto e dell'edema intratumorale. [livello di evidenza Ia].
- Le **sequenze funzionali**, attualmente considerate standard, sono quelle con valutazione della diffusione (**DWI**), con restrizione della diffusione in aree di alta cellularità o in aree di ischemia, e quelle con valutazione della perfusione (**CBV**) (cioè del volume sanguigno all'interno del tumore) con un netto aumento della perfusione nelle lesioni gliali maligne ad alto grado.
- **L'analisi spettroscopica in RM (MRS)** produce uno spettro tale da correlare i picchi della colina (Cho) con quelli di N-acetylaspartato (NAA): l'aumento della Cho e la riduzione di NAA, che condizionano quindi un aumento del rapporto Cho/NAA, possono indicare la presenza di tumore [livello di evidenza Ia].

L'uso combinato delle diverse metodiche contribuisce ad una definizione accurata della natura della malattia, alla guida del trattamento in termini di potenzialità chirurgiche e alla valutazione della risposta al trattamento.

- Contrast enhancement
- Restrizione Diffusione
- Perfusione (rCBV)
- Spettroscopia (colina, a- chetoglutarato)

Prognosi

- Età ,Performance status ,Localizzazione Parametri RMN Attività proliferativa , Alterazioni genetiche.
- ***ESTENSIONE RESEZIONE***
- WHO grado III sopravvivenza 2-3 anni
- WHO grado IV sopravvivenza determinata dalla efficacia delle terapie disponibili: Glioblastoma : < 1 anno .



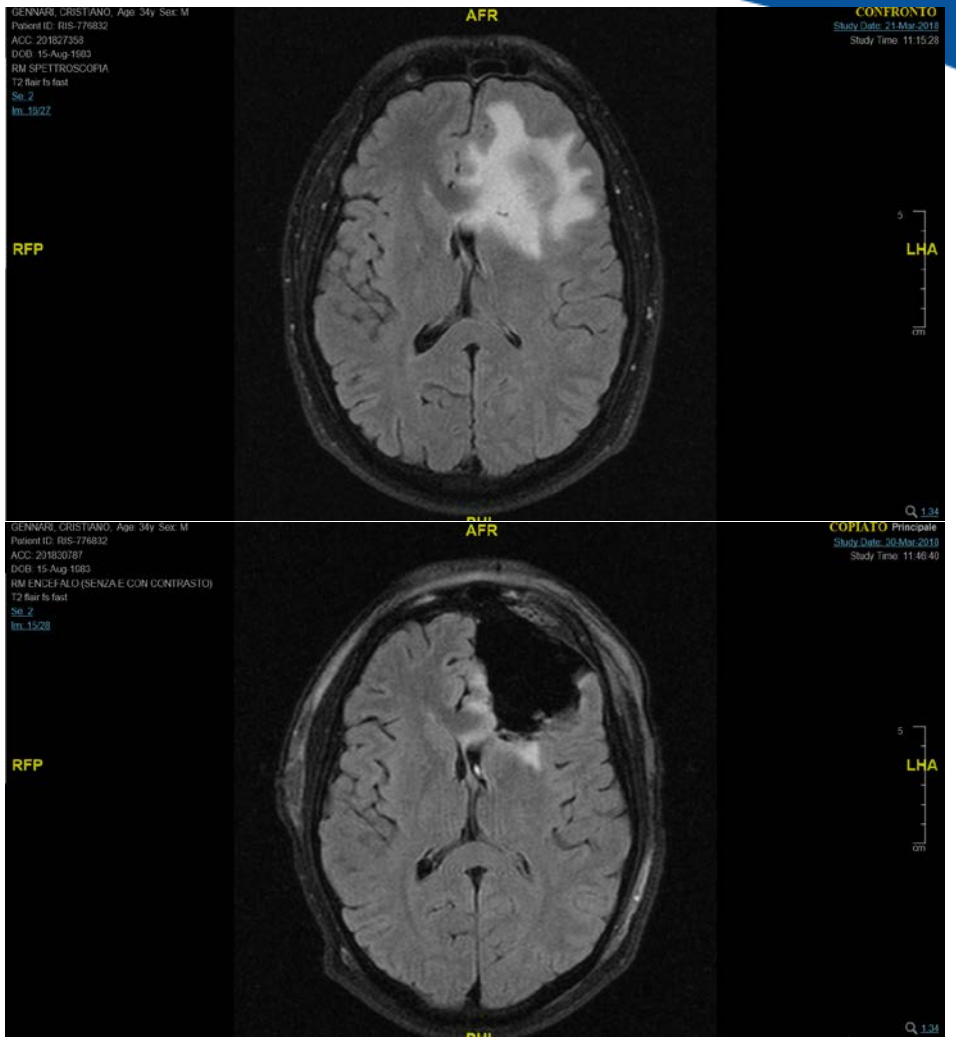
(5-year survival rates between 1%–19%, depending on age),

Treatment Overview

Surgery

The goals of surgery are to obtain a diagnosis, alleviate symptoms related to increased intracranial pressure or compression by tumor, increase survival, and decrease the need for corticosteroids. A meta-analysis including six studies with 1618 patients with glioblastoma showed that GTR is associated with superior OS and PFS, compared to incomplete resection and biopsy.[127] Unfortunately, the infiltrative nature of high-grade astrocytomas frequently renders GTR difficult. On the other hand, GTR is often possible for oligodendrogliomas, because most occur in the frontal lobes, and the tumors are frequently well demarcated.

Unfortunately, nearly all high-grade gliomas recur. At recurrence, reoperation may improve the outcome for select patients.[128] According to an analysis by Park et al,[129] tumor involvement in specific critical brain areas, poor KPS score, and large tumor volume were associated with unfavorable re-resection outcomes.



For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era.

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Lo stato di metilazione del promotore MGMT valutato sul tumore primitivo è considerato un fattore prognostico positivo e predittivo di maggiore responsività al trattamento combinato [5]. Vi sono, inoltre, altri fattori biologici e molecolari utili, soprattutto, nel predire la prognosi dei pazienti affetti da neoplasia gliale ad alto grado quali la mutazione/amplificazione di EGFR, la mutazione di p53 e la mutazione di IDH1 e IDH2.
L'amplificazione di EGFR è spesso associata a sue alterazioni strutturali quali, nel 20-50% dei casi, la variante III (EGFR vIII). L'associazione della mutazione di p53 e dell'amplificazione di EGFR

identificano delle sottoclassi specifiche di glioblastoma (glioblastomi secondari cioè esito di trasformazione da un glioma a basso grado) caratterizzati da una prognosi migliore rispetto ai GBM primitivi (caratterizzati da mutezione *de novo* di EGFR) (fig.1). [6]
Anche la mutazione di IDH, presente in una percentuale minore di glioblastomi, sembra essere associata ai glioblastomi secondari e quindi sembra essere associata con una migliore prognosi.[7]
Nessuno dei dati riportati ha peraltro ancora un rilievo, nella pratica clinica e nella scelta del trattamento adiuvante.
Il crescente ricorso alla valutazione dei fattori biologici, genetici nell'inquadramento diagnostico anche di queste neoplasie, sta rendendo necessaria la creazione di nuove classificazioni da associare a quella semplicemente morfologica utilizzata nella WHO. [8]

Molecular-Based Recursive Partitioning Analysis (RPA) Model for Glioblastoma in the Temozolomide Era: A Correlative Analysis Based Upon NRG Oncology RTOG 0525

Abstract

Importance—The need for a more refined, molecularly-based classification model for glioblastoma (GBM) in the temozolomide era.

Objective—Refine the existing clinically-based recursive partitioning analysis (RPA) model by incorporating molecular variables.

Design, Setting, and Participants—NRG Oncology RTOG 0525 specimens (n=452) were analyzed for protein biomarkers representing key pathways in GBM by a quantitative molecular microscopy-based approach with semi-quantitative immunohistochemical validation. Prognostic significance of each protein was examined by single-marker and multi-marker Cox-regression analyses. In order to reclassify the prognostic risk groups, significant protein biomarkers upon single-marker analysis were incorporated into a RPA model consisting of the same clinical variables (age, KPS, extent of resection, and neurologic function) as the existing RTOG RPA. The new RPA model (NRG-GBM-RPA) was confirmed using traditional immunohistochemistry in an independent dataset (n=176).

Main Outcomes and Measures—Overall survival (OS)

Results—MGMT (HR=1.81, 95% CI(1.37, 2.39), p<0.001), survivin (HR=1.36, 95% CI(1.04, 1.76), p=0.02), c-Met (HR=1.53, 95% CI(1.06,2.23), p=0.02), pmTOR (HR=0.76, 95% CI(0.60,0.97), p=0.03), and Ki-67 (HR=1.40, 95% CI(1.10, 1.78), p=0.007), were found to be significant upon single-marker multivariate analysis of OS. To refine the existing RPA, significant protein biomarkers together with clinical variables (age, performance status, extent of resection, and neurological function) were incorporated into a new model. Higher MGMT protein was significantly associated with decreased *MGMT* promoter methylation and vice-versa. Further, MGMT protein expression had greater prognostic value for OS compared to *MGMT* promoter methylation. The refined NRG-GBM-RPA consisting of MGMT protein, c-Met protein, and age revealed greater separation of OS prognostic classes compared to the existing clinically-based RPA model and *MGMT* promoter methylation in NRG Oncology RTOG 0525. The prognostic significance of the NRG-GBM-RPA was subsequently confirmed in an independent dataset (N=176).

Conclusions and Relevance—The new NRG-GBM-RPA model significantly enhances outcome stratification over both the current RTOG RPA model and *MGMT* promoter methylation, respectively, for GBM patients treated with radiation and temozolomide and was biologically validated in an independent dataset. The revised RPA has the potential to significantly contribute to improving the accurate assessment of prognostic groups in GBM patients treated with radiation and temozolomide and also influence clinical decision making.

Tab 1. Classi RPA sec Curran

Classe RPA	Definizione	Sopravvivenza media (mesi)
III	Età <50, Glioblastoma multiforme and KPS 90–100.	18
IV	Età <50, Glioblastoma, KPS <90. Età >50, Glioblastoma, resezione chirurgica, e buona funzione neurologica	11
V	Età >=50, KPS 70–100, glioblastoma, o resezione chirurgica e deficit neurologici che impediscono di lavorare o solo biopsia seguita da RT con dosi di almeno 54 Gy. Età >=50, KPS <70, stato mentale normale.	9
VI	Age >=50, KPS <70, stato mentale anormale. Age >=50, KPS 70–100, glioblastoma, solo biopsia seguita da RT con dose minore di 54.4 Gy.	5

Tab 2. Classi RPA rielaborate sec Li

Classe RPA	Definizione	Sopravvivenza media (mesi)
I I	Età <50, Glioblastoma multiforme and KPS 90–100.	18
IV	Età <50, Glioblastoma, KPS <90. Età >50, Glioblastoma, resezione chirurgica, e buona funzione neurologica	11
V (V+VI)	Età >=50, KPS 70–100, glioblastoma, o resezione chirurgica e deficit neurologici che impediscono di lavorare o solo biopsia seguita da RT con dosi di almeno 54 Gy. Età >=50, KPS <70, stato mentale normale.	7

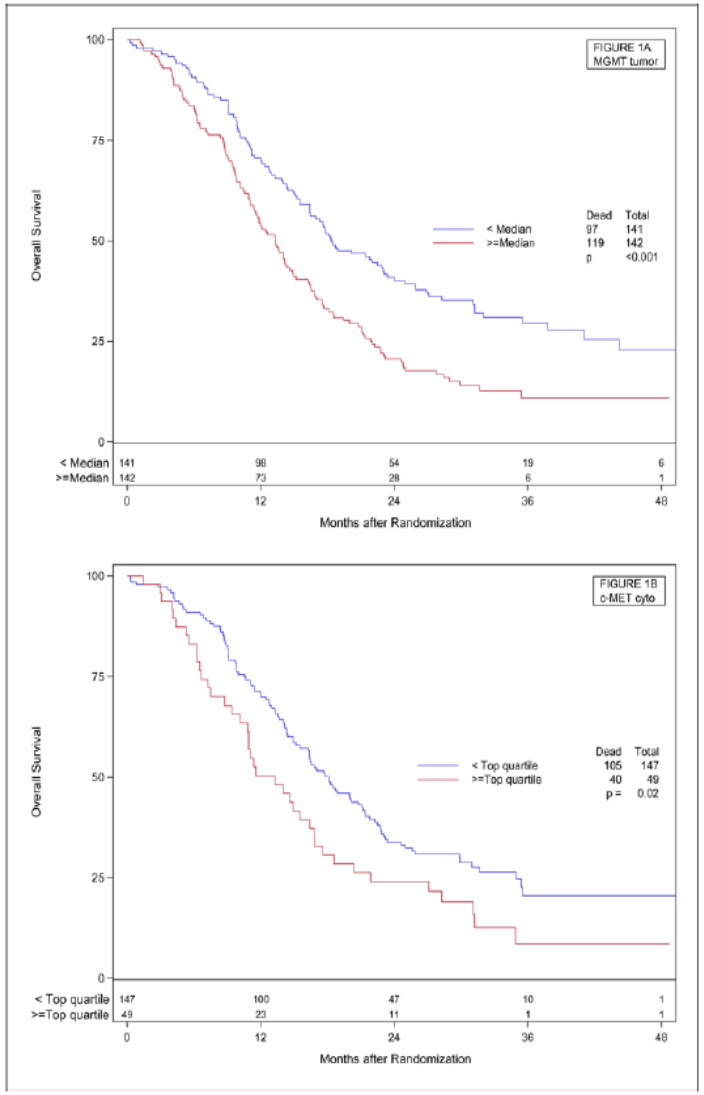
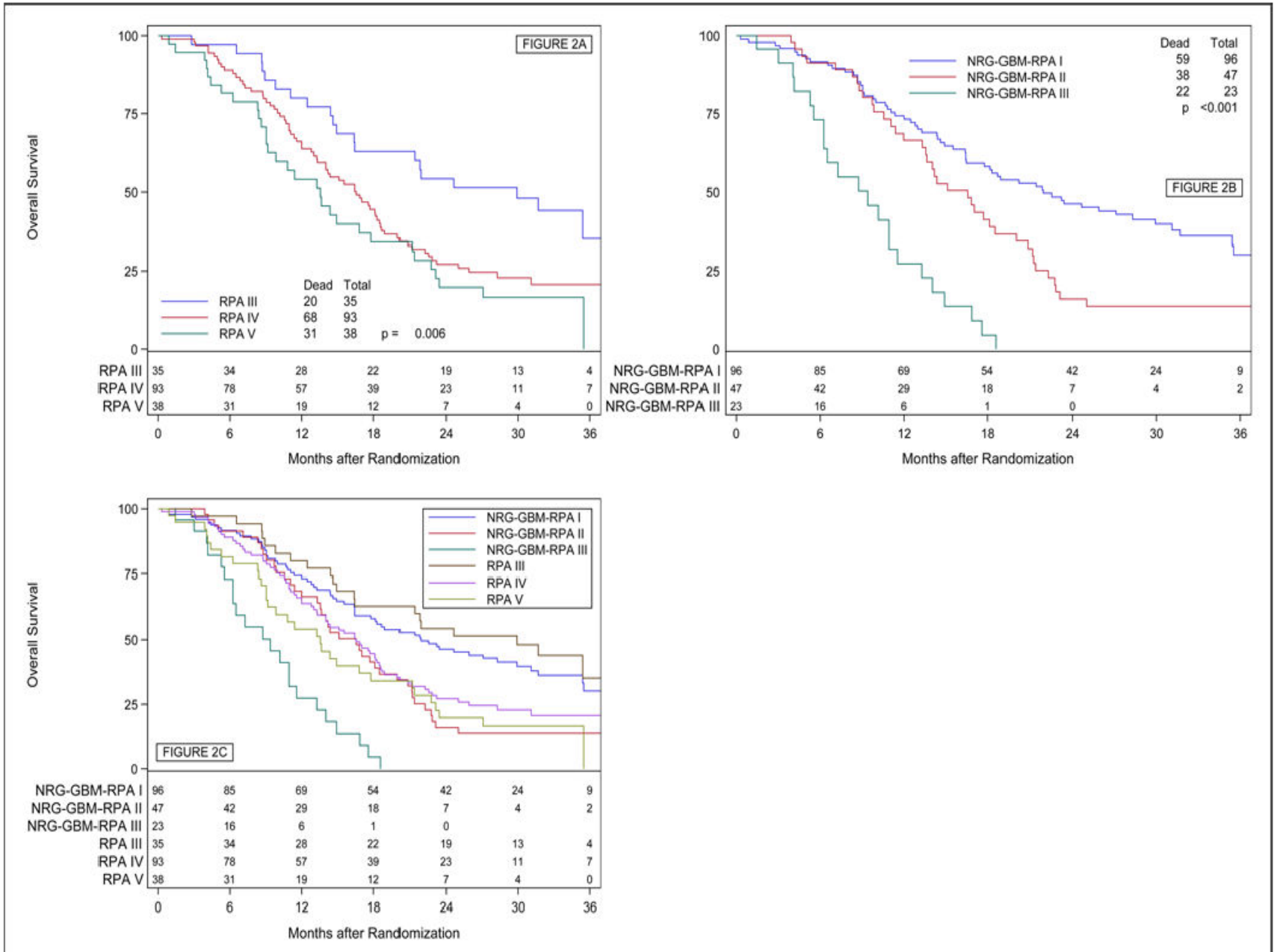


Figure 1. MGMT and c-Met correlate with OS in randomized NRG Oncology RTOG 0525 study participants

High MGMT tumor protein staining when split by the median significantly associate with decreased OS (A). High levels of c-Met cytoplasmic protein staining when split by the top quartile significantly associate with decreased OS (B).



An independently validated nomogram for individualized estimation of survival among patients with newly diagnosed glioblastoma: NRG Oncology RTOG 0525 and 0825

Abstract

Background. Glioblastoma (GBM) is the most common primary malignant brain tumor. Nomograms are often used for individualized estimation of prognosis. This study aimed to build and independently validate a nomogram to estimate individualized survival probabilities for patients with newly diagnosed GBM, using data from 2 independent NRG Oncology Radiation Therapy Oncology Group (RTOG) clinical trials.

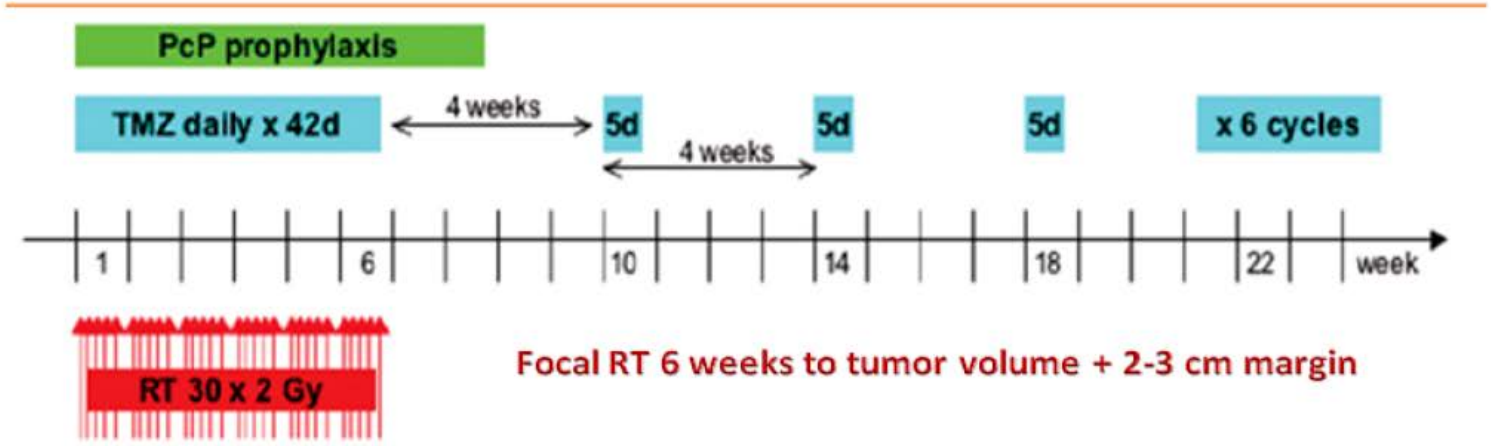
Methods. This analysis included information on 799 (RTOG 0525) and 555 (RTOG 0825) eligible and randomized patients with newly diagnosed GBM and contained the following variables: age at diagnosis, race, gender, Karnofsky performance status (KPS), extent of resection, O^6-methylguanine-DNA methyltransferase (*MGMT*) methylation status, and survival (in months). Survival was assessed using Cox proportional hazards regression, random survival forests, and recursive partitioning analysis, with adjustment for known prognostic factors. The models were developed using the 0525 data and were independently validated using the 0825 data. Models were internally validated using 10-fold cross-validation, and individually predicted 6-, 12-, and 24-month survival probabilities were generated to measure the predictive accuracy and calibration against the actual survival status.

Results. A final nomogram was built using the Cox proportional hazards model. Factors that increased the probability of shorter survival included greater age at diagnosis, male gender, lower KPS, not having total resection, and unmethylated *MGMT* status.

Conclusions. A nomogram that assesses individualized survival probabilities (6-, 12-, and 24-mo) for patients with newly diagnosed GBM could be useful to health care providers for counseling patients regarding treatment decisions and optimizing therapeutic approaches. Free software for implementing this nomogram is provided: http://cancer4.case.edu/rCalculator/rCalculator.html.

Current Therapies- STUPP Regimen

, 573 patients from 85 institutions in 15 countries were randomly assigned to receive radiotherapy (286 patients) or radiotherapy plus temozolomide (287 patients).



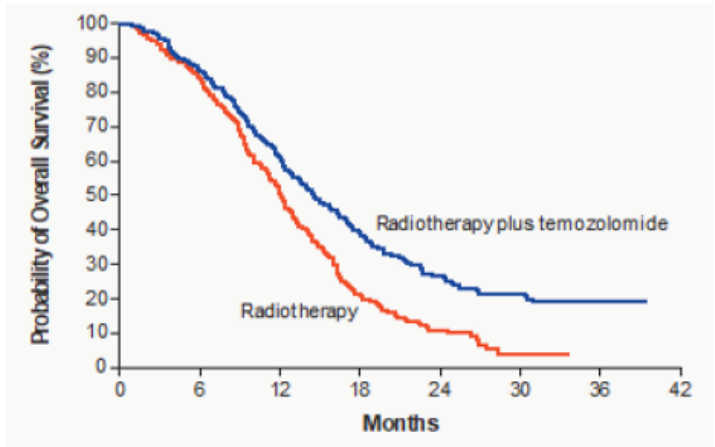
Diapositiva5.png

Stupp, Roger, et al. N Engl J Med 2005; 352:987-996

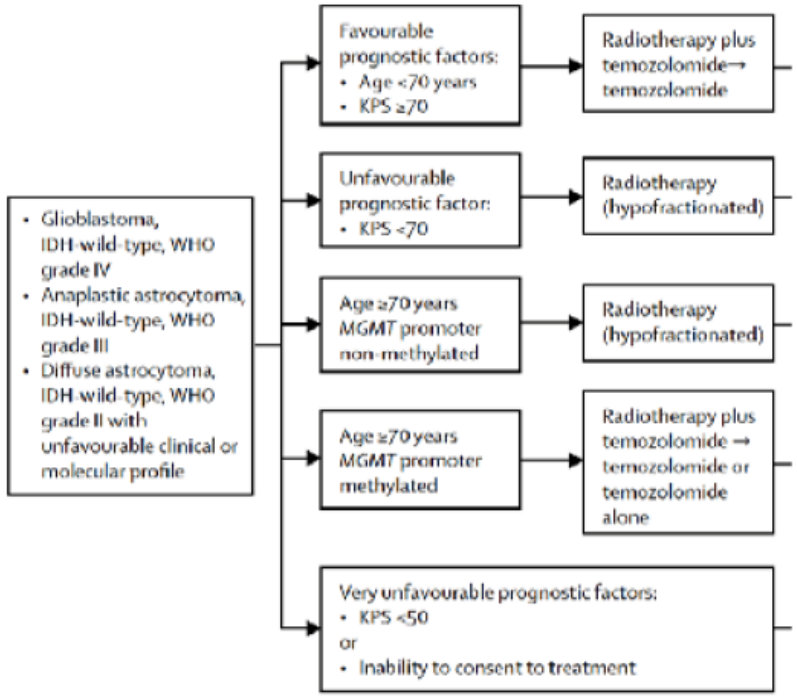
The (long standing) standard of care for GBM

original article

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

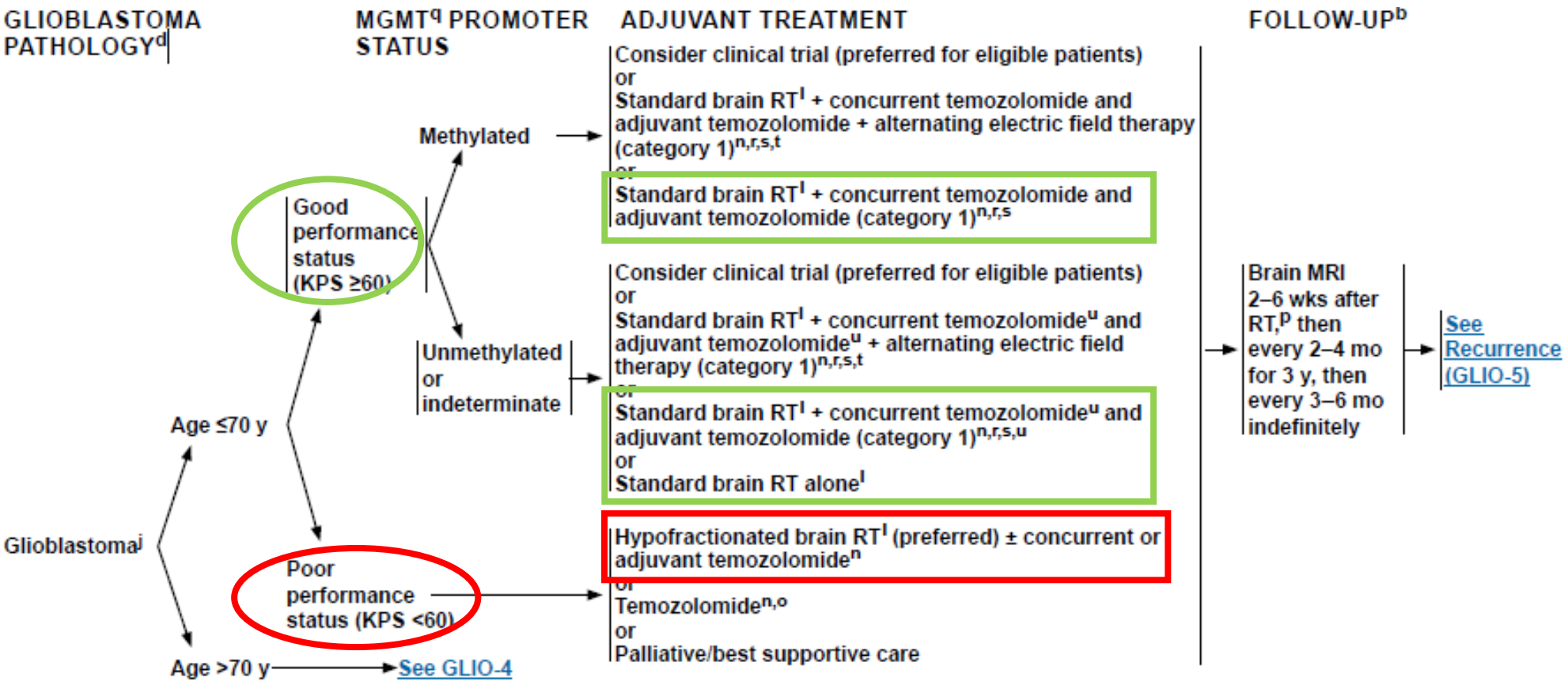


Stupp et al. New Eng J Med. **2005**

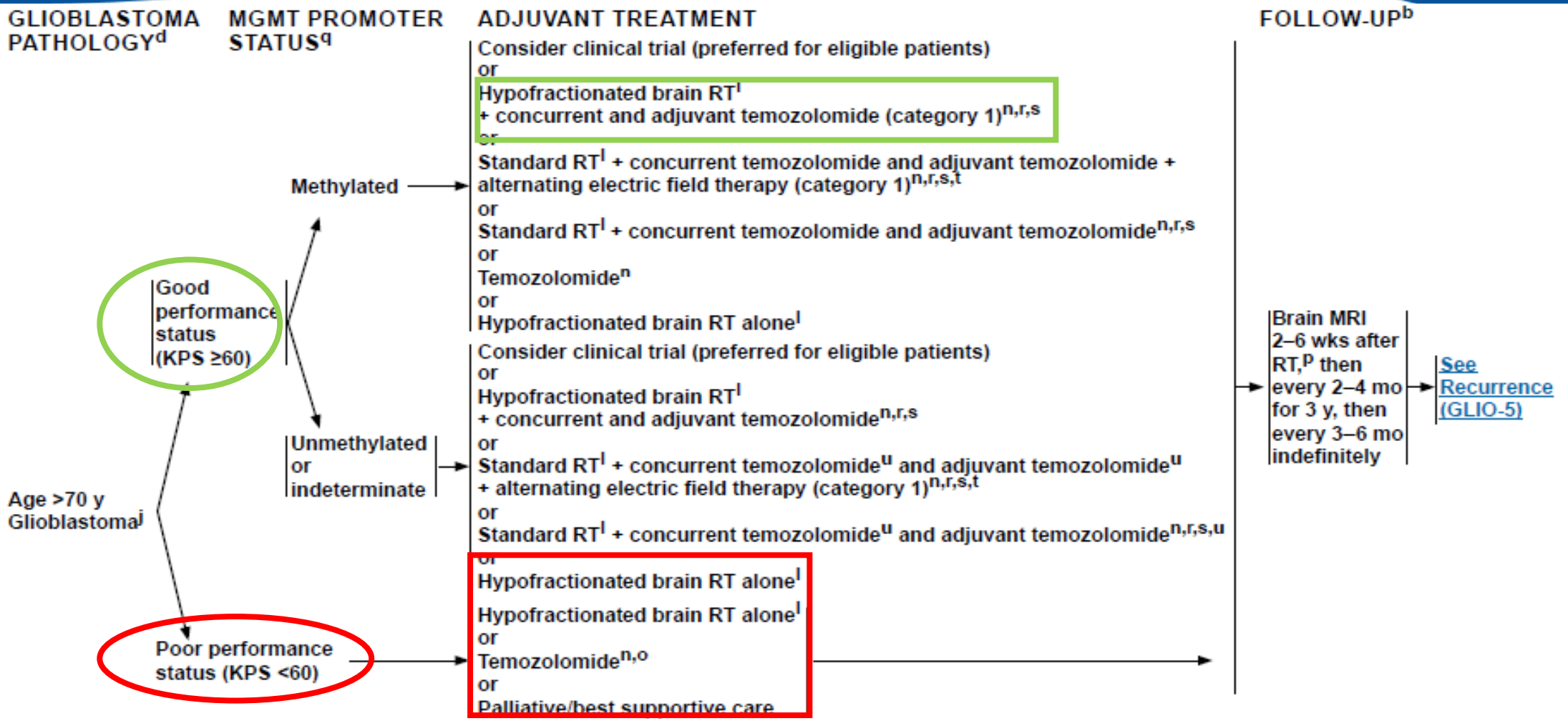


Weller et al. Lancet Oncol. **2017**

median survival benefit : 2.5 months;
median survival **14.6 months** with radiotherapy plus TMZ and
12.1 months with radiotherapy alone.
37% percent relative reduction in the risk of death



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q]MGMT= O6-methylguanine-DNA methyltransferase.
[r]Combination of agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.



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PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

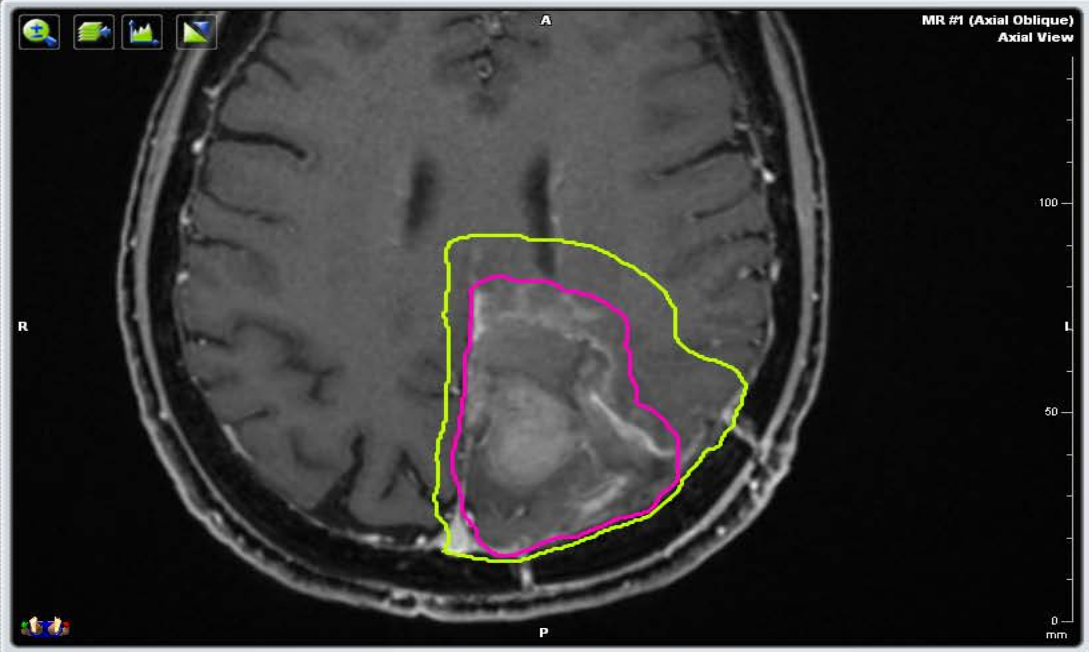
Anaplastic Gliomas/Glioblastoma High-Grade (Grades III/IV)

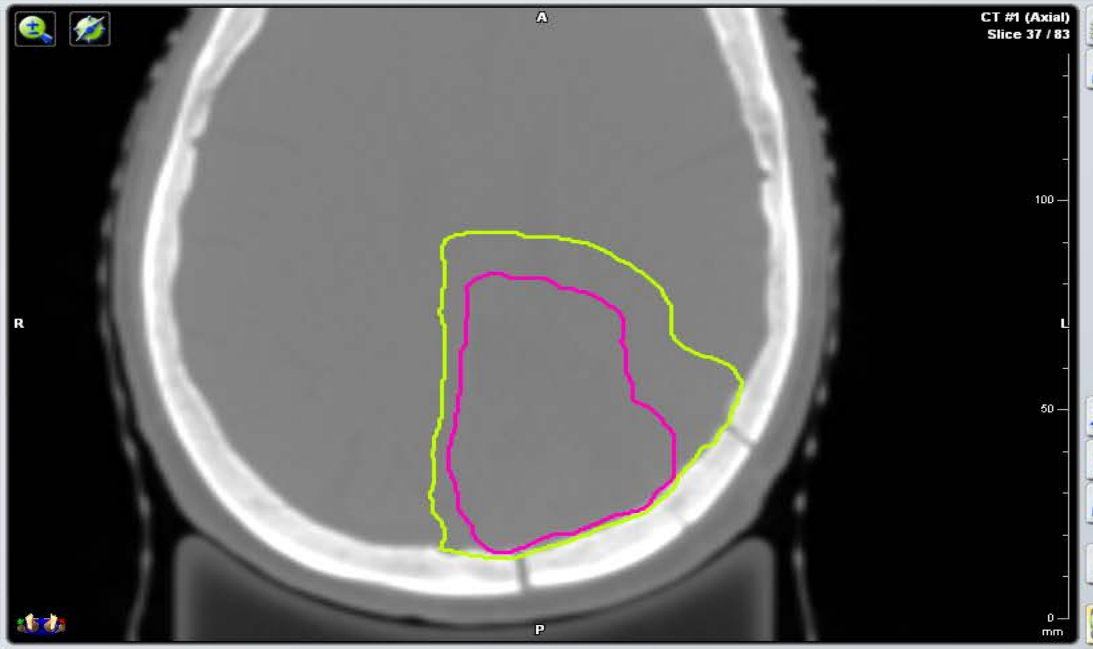
Simulation and Treatment Planning

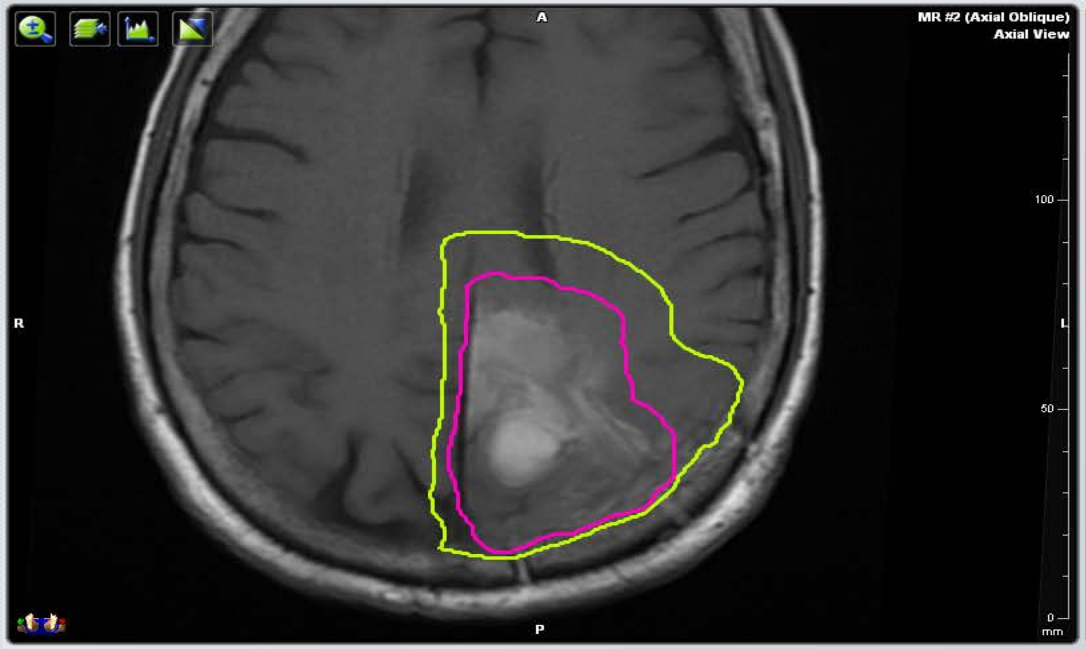
- Tumor volumes are best defined using pre- and postoperative MRI imaging using enhanced T1 with/without FLAIR/T2 sequences to define GTV. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1–2 cm (CTV) for grade III, and up to 2–2.5 cm (CTV) for grade IV. Although trials in glioblastoma have historically used CTV expansion in the range of 2 cm, smaller CTV expansions are supported in the literature and can be appropriate. A planning target volume (PTV) of margin of 3–5 mm is typically added to the CTV to account for daily setup errors and image registration. Daily image guidance is required if smaller PTV margins are used (3 mm or less). When edema as assessed by T2/FLAIR is included in the initial phase of treatment, fields are usually reduced for the last phase of the treatment (boost). The boost target volume will typically encompass only the gross residual tumor and the resection cavity. A range of acceptable clinical target volume margins exists. Both strategies appear to produce similar outcomes.[4]

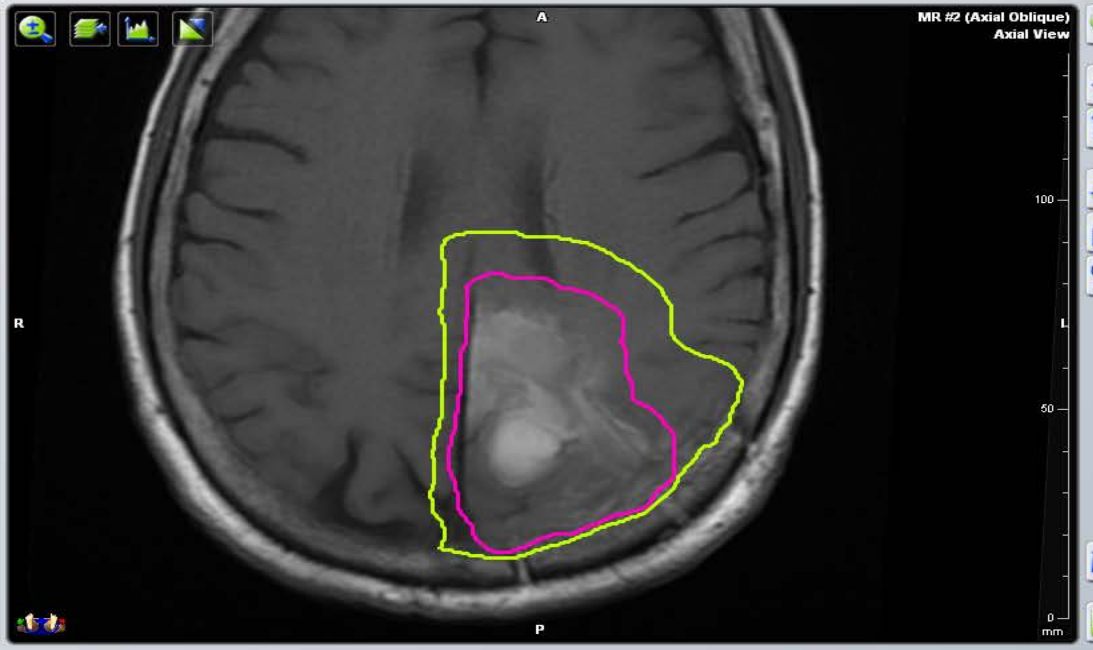
RT Dosing Information

- The recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions.
- A slightly lower dose, such as 54–55.8 Gy in 1.8 Gy or 57 Gy in 1.9 Gy fractions, can be applied when the tumor volume is very large (gliomatosis), there is brainstem/spinal cord involvement, or for grade III astrocytoma.
- If a boost volume is used, the initial phase of the RT plan will receive 46 Gy in 2 Gy fractions or 45–50.4 Gy in 1.8 Gy fractions. The boost plan will typically then receive 14 Gy in 2 Gy fractions or 9–14.4 Gy in 1.8 Gy fractions.[4]
- In poorly performing patients or elderly patients, a hypofractionated accelerated course should be considered with the goal of completing the treatment in 2–4 weeks. Typical fractionation schedules are 34 Gy/10 fx, 40.05 Gy/15 fx, or 50 Gy/20 fx.[5,6] Alternatively, a shorter fractionation schedule of 25 Gy/5 fx may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable.[7]









Navigator

target GBM def

Object Creation

Verification

Go to...

Next

Object

Brainstem
Chiasm
CTV 1 cm + edema
cavo chirurgico
Eye, Left
Eye, Right
Lens, Left

New...

Remove

Auto Segmentation...

Brush Size

Contours

Outlining

Brush

Eraser

SmartBrush

Draw Sphere

SmartShaper...

Auto Fill

Interpolation

Advanced Manipulation...

4-D Morphing...

Undo

Redo

Overview

Slices

Multiple Sets

Plan Content

BRAINLAB
iPlan RT Image 4.1

BETTINELLI^FIORELLA

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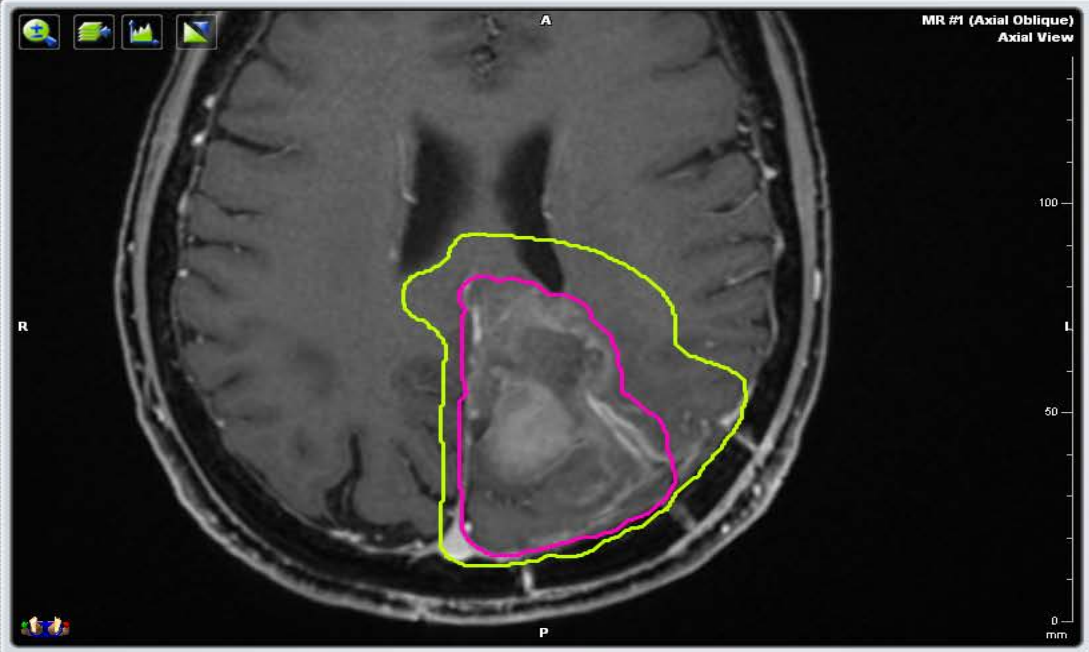

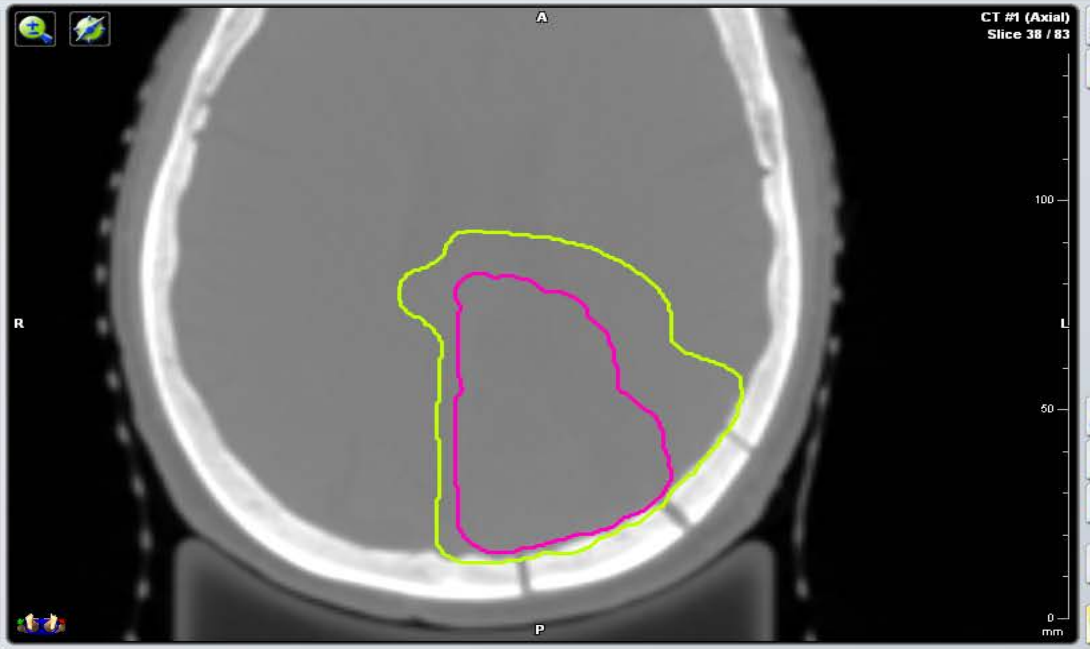

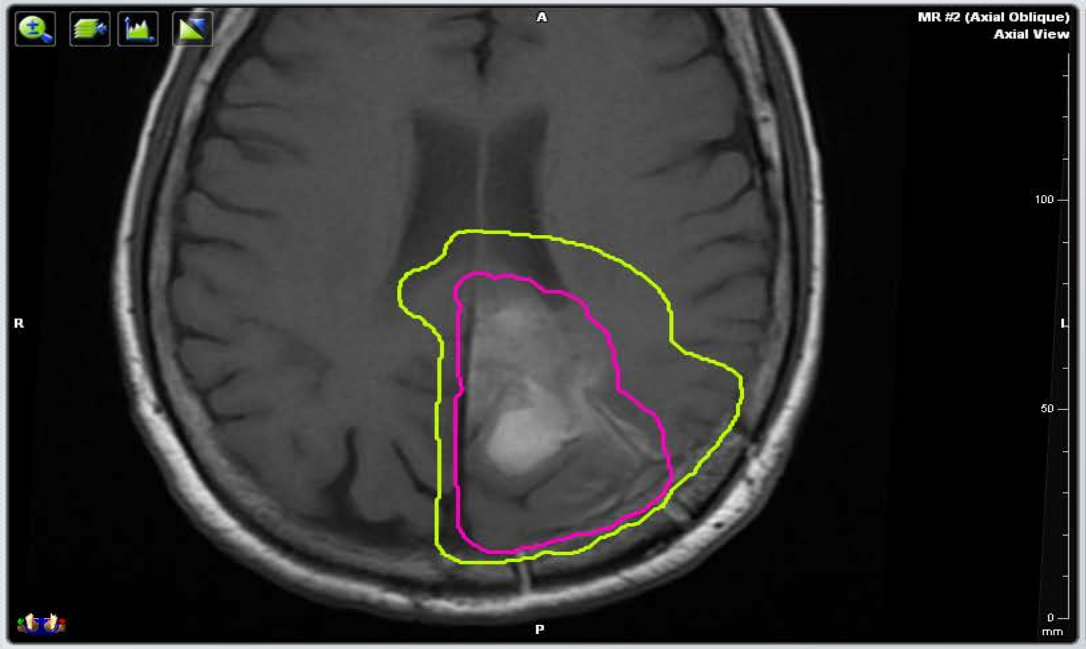

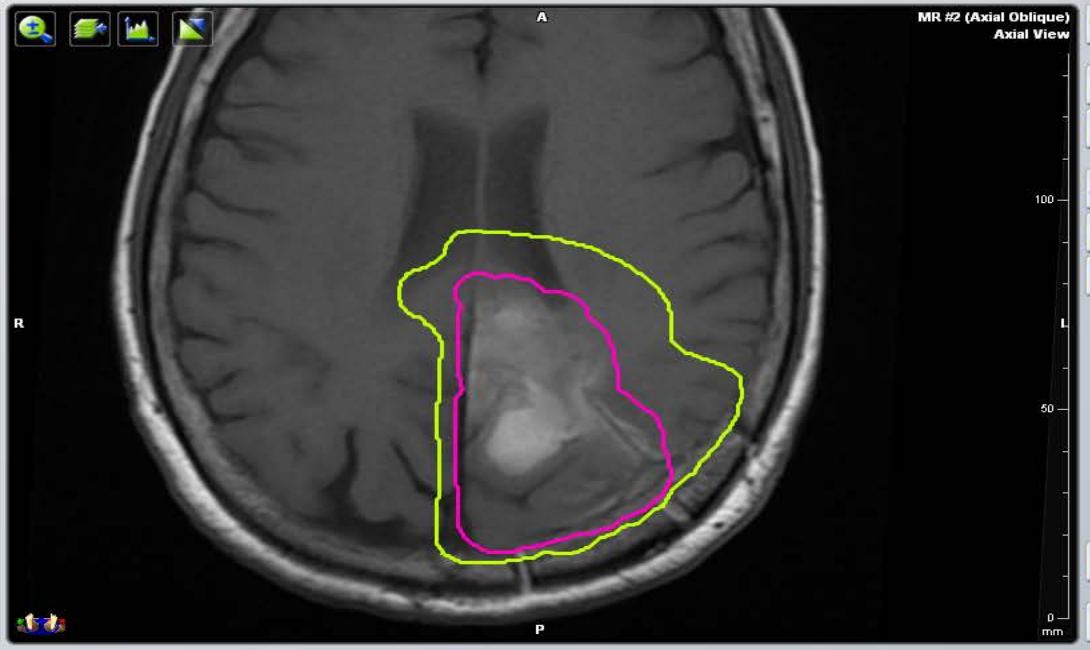

Navigator

target GBM def

Object Creation

Verification

Go to...

Next

Object

Brainstem
Chiasm
CTV 1 cm + edema
cavo chirurgico
Eye, Left
Eye, Right
Lens, Left

New...

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Brush Size

Contours

Outlining

Brush

Eraser

SmartBrush

Draw Sphere

SmartShaper...

Auto Fill

Interpolation

Advanced Manipulation...

4-D Morphing...

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Overview

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Multiple Sets

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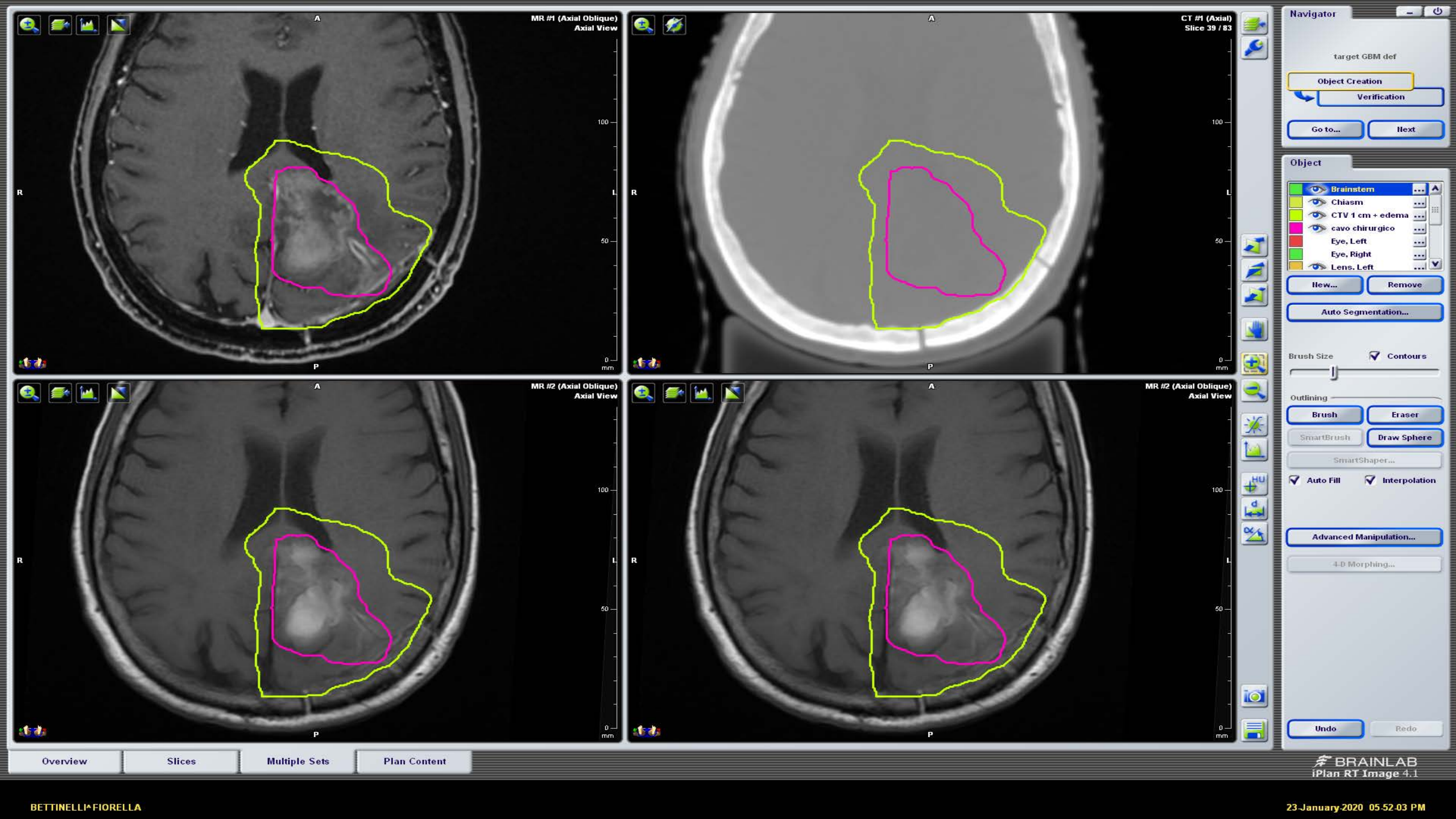
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Axial View
CT #1 (Axial)
Slice 39 / 83
MR #2 (Axial Oblique)
Axial View
MR #2 (Axial Oblique)
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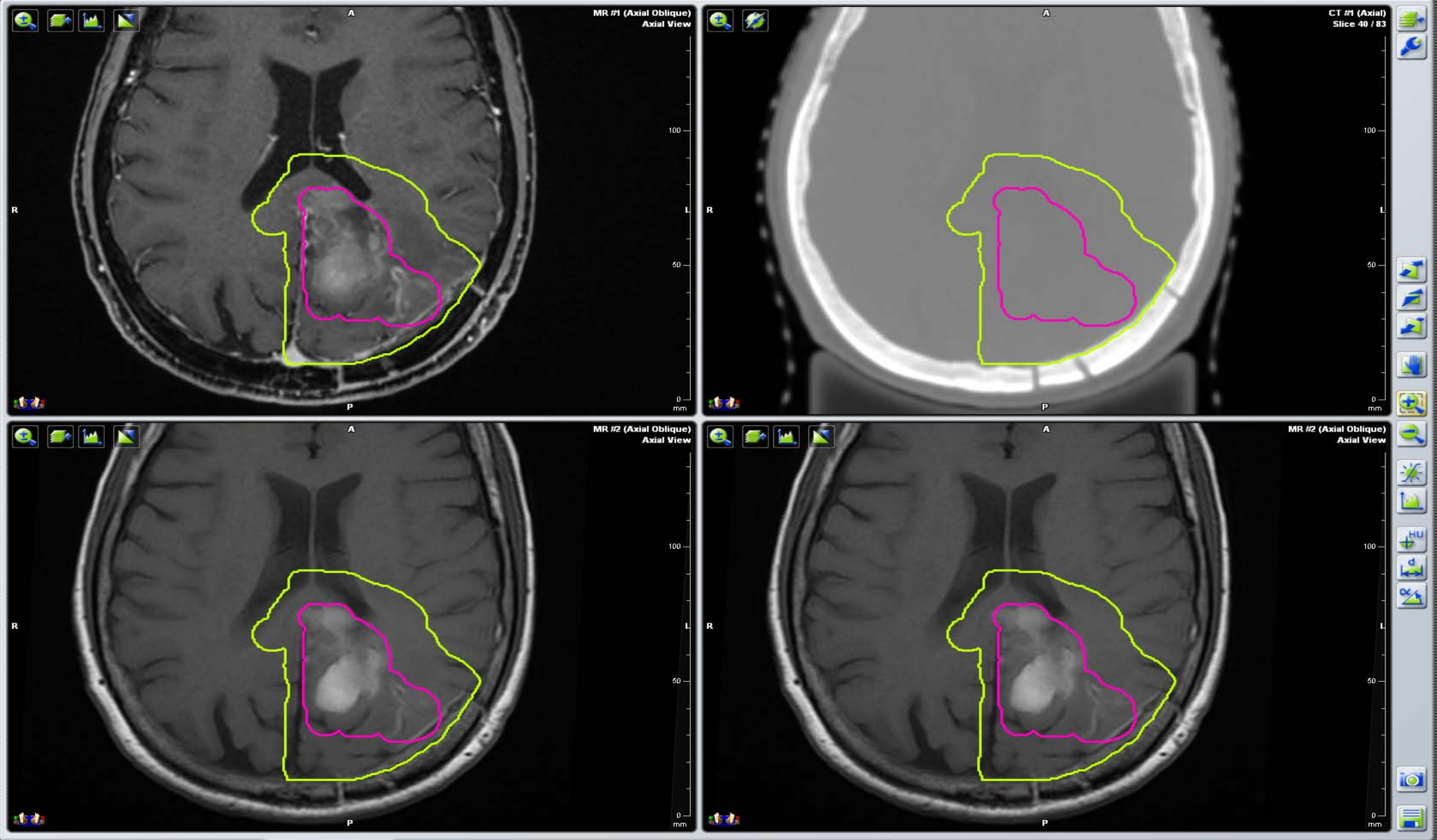

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CTV 1 cm + edema
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4-D Morphing...

Undo

Redo

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Slices

Multiple Sets

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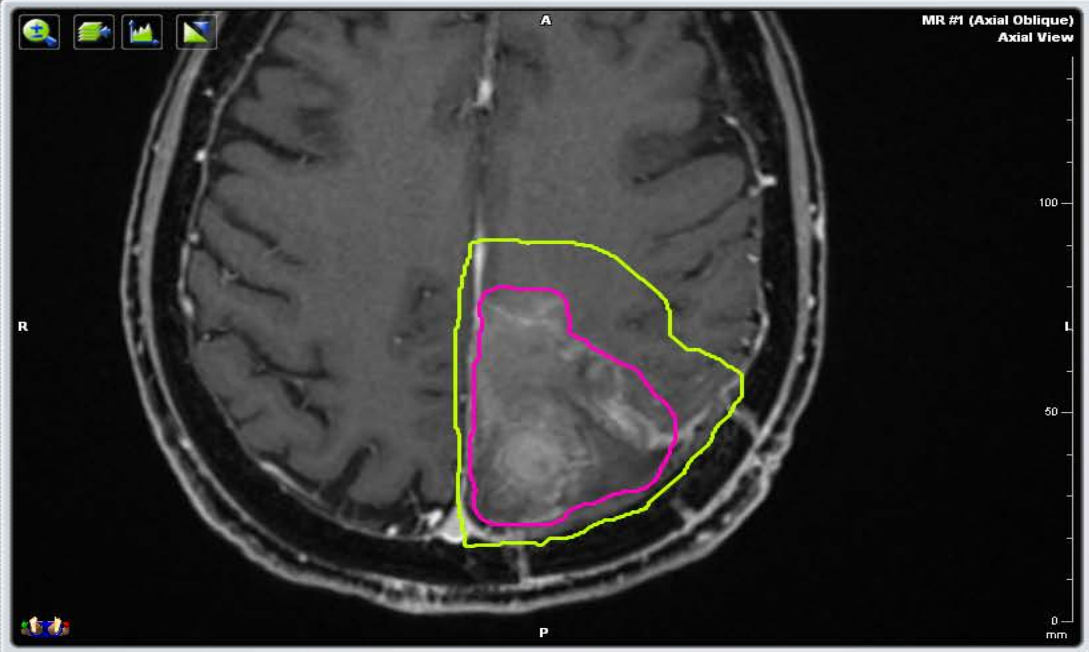

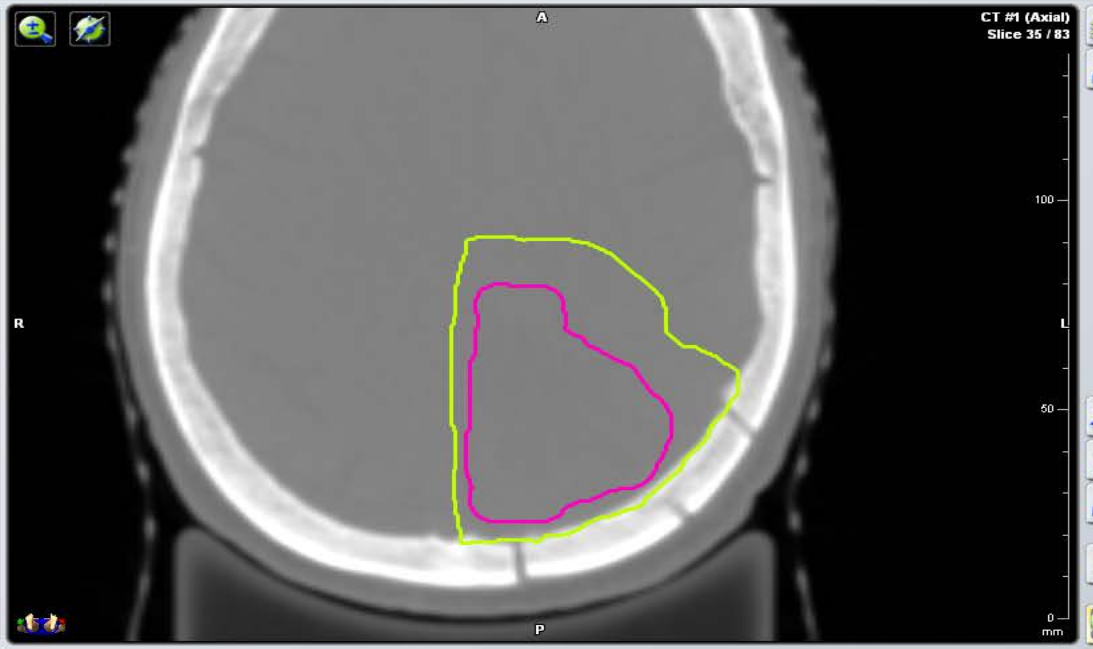

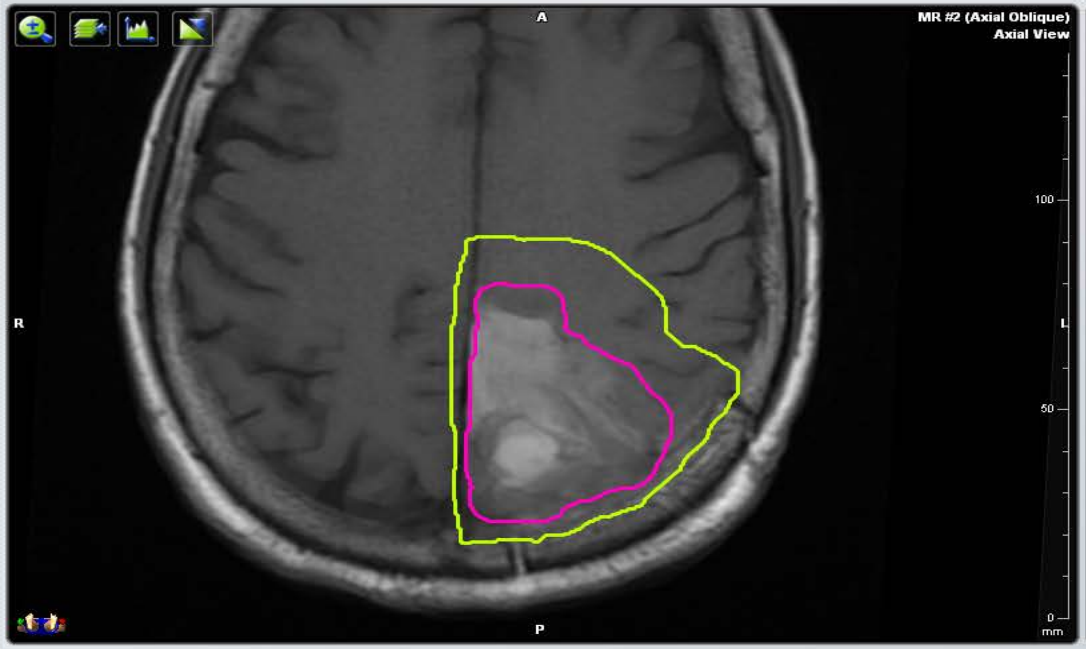

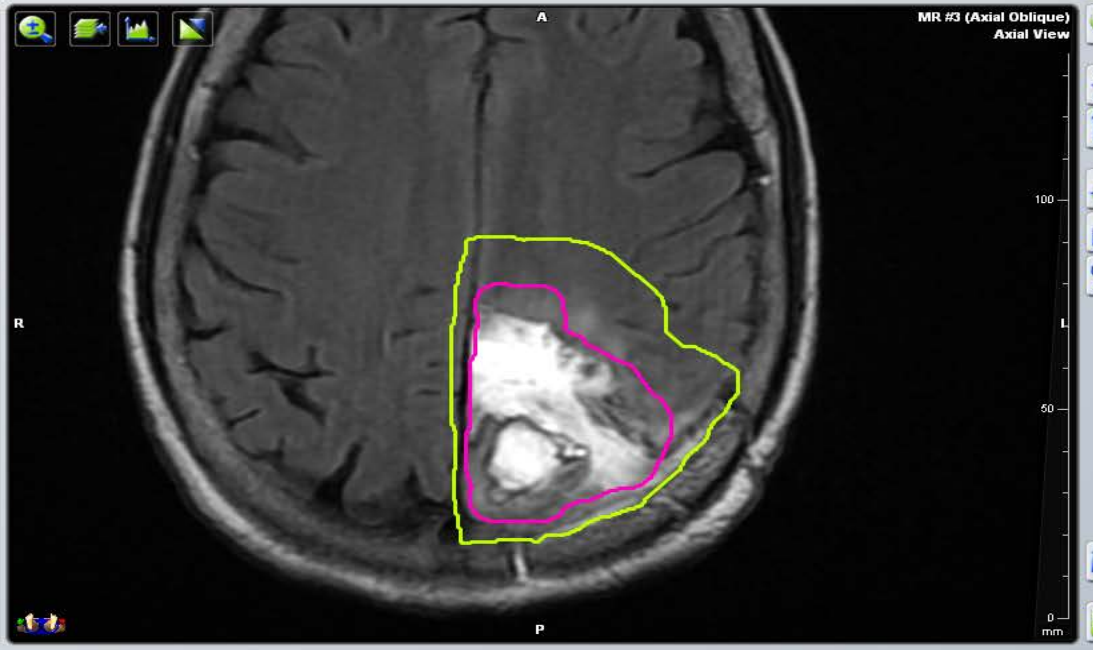

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iPlan RT Image 4.1

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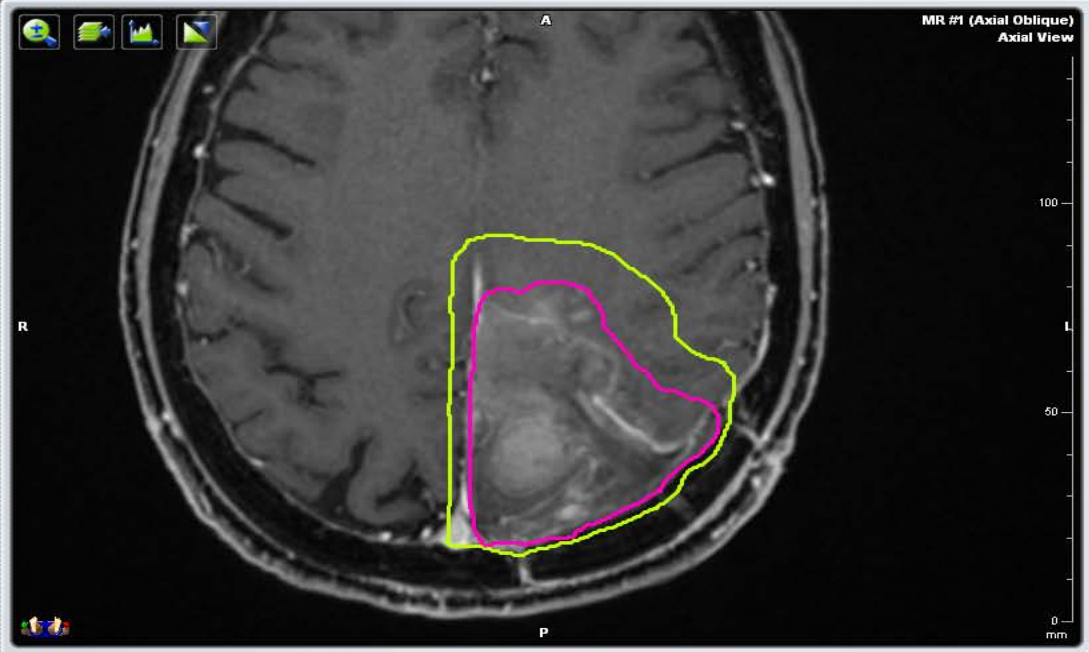

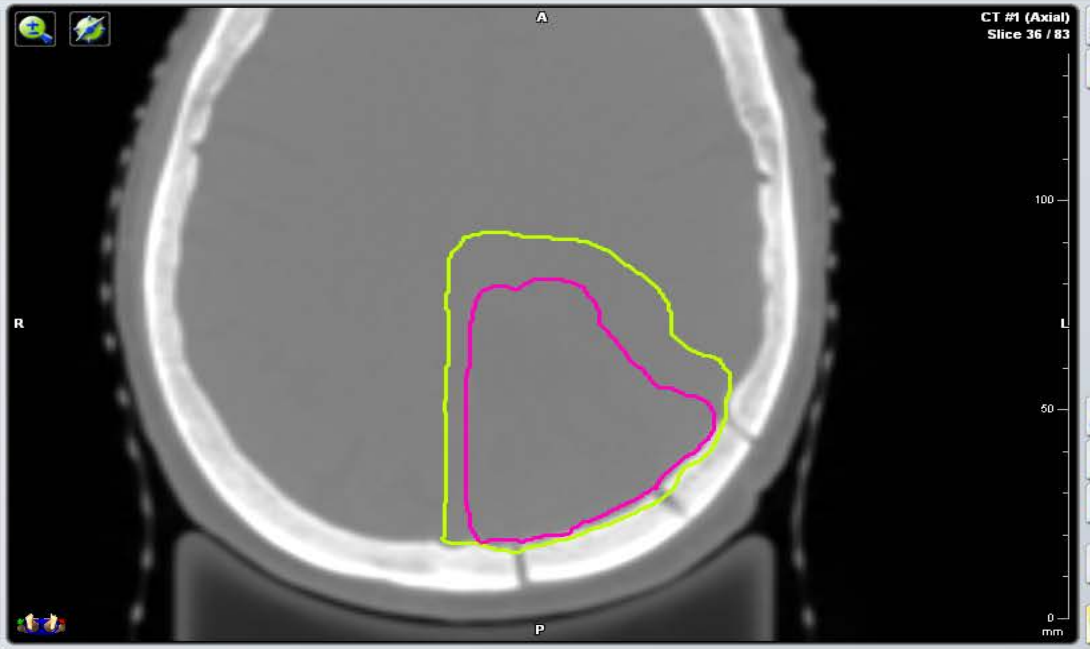

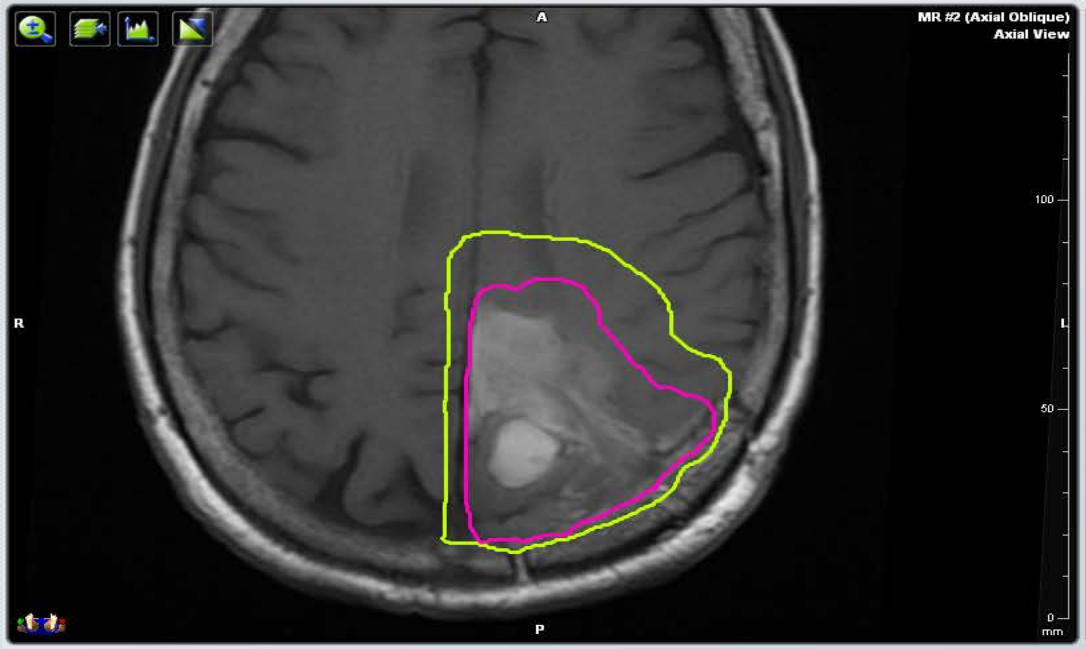

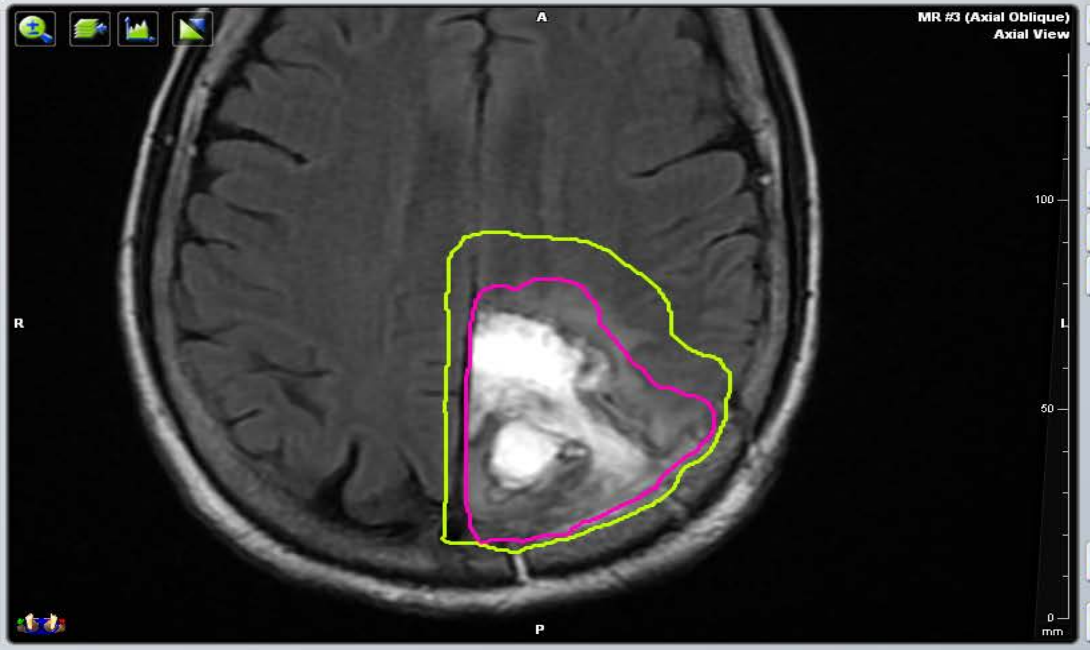

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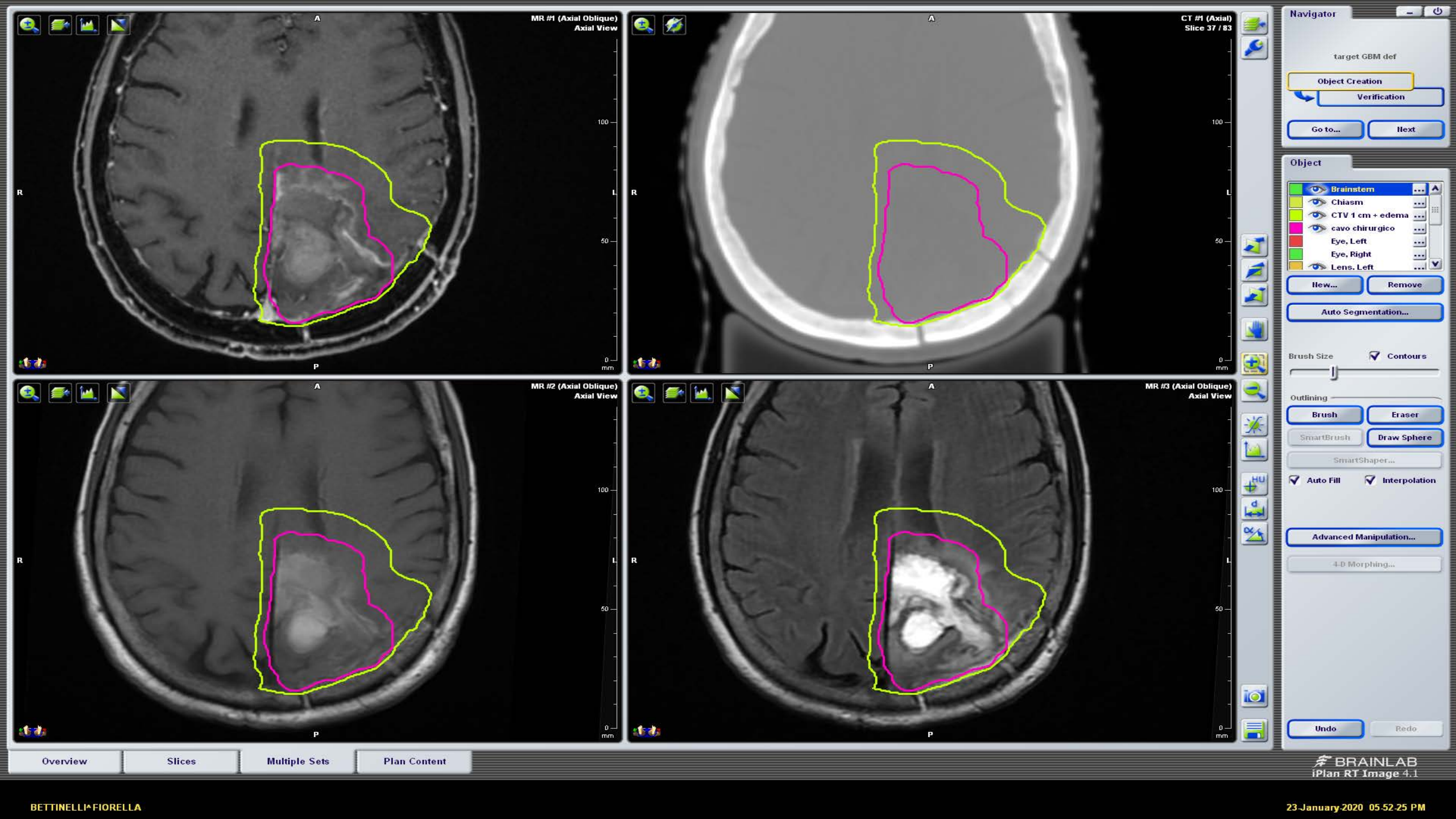
MR #1 (Axial Oblique)
Axial View
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Slice 37 / 83
MR #2 (Axial Oblique)
Axial View
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Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice

Silvia Scoccianti [a,*], Beatrice Detti [a], Davide Gadda [b], Daniela Greto [a], Ilaria Furfaro [a], Fiammetta Meacci [a], Gabriele Simontacchi [a], Lucia Di Brina [a], Pierluigi Bonomo [a], Irene Giacomelli [a], Icro Meattini [a], Monica Mangoni [a], Sabrina Cappelli [a], Sara Cassani [a], Cinzia Talamonti [c], Lorenzo Bordi [d], Lorenzo Livi [a]

[a] *Radiation Oncology;* [b] *Neuroradiology Unit;* [c] *Medical Physics; and* [d] *Neurosurgery, Azienda Universitaria Ospedaliera Careggi, Florence, Italy*

Table 1
Dose constraints and recommendations for intracranial organs at risk when conventional fractionation is used.

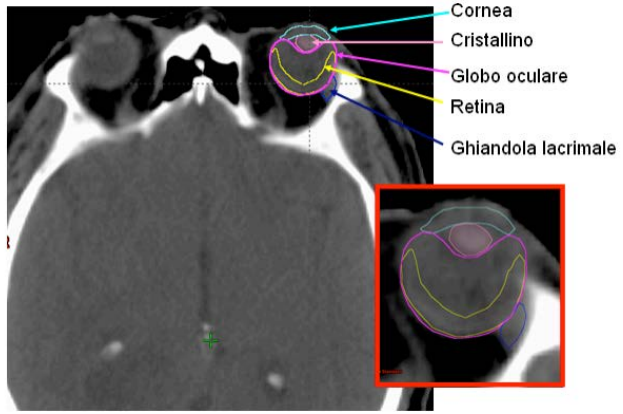
OAR	Constraints for adults		Constraints for children (if different from the ones reported for adult patients)
	Primary criteria	Secondary criteria	
Optic chiasma	D_{max} < 54 [10,11] D_{max} < 55 [12]	D_{max} < 60 [10]	
Cochlea	D_{mean} ⩽ 45 Gy [13,14] D_{mean} < 50 Gy [10]		D_{mean} < 35 Gy [16]
Hippocampus	Hippocampus D_{max} ⩽ 6 Gy and $V_{3\ Gy}$ ⩽ 20% Hippocampal avoidance volume D_{max} < 25.2 Gy and $V_{20\ Gy}$ ⩽ 20% [21,22] D_{max} < 12 Gy [23] $V_{7.2\ Gy}$ < 40% [25] D_{mean} < 30 Gy [24]		
Brainstem	D_{max} < 54 Gy [10,29]	D_{max} < 60 Gy [10] $D_{59\ Gy}$ < 10 cc [29]	
Pituitary gland	D_{max} < 50 Gy [34] D_{max} < 60 [10]		D_{mean} < 25 or 30 Gy [32] D_{max} < 42 Gy [35]
Retina	D_{max} < 45 Gy [10, Yamazaki] D_{max} < 50 Gy [Shaffer]		
Lacrimal gland	$V_{30\ Gy}$ < 50% [Sreeraman] D_{max} < 40 Gy [Jeganathan]		
Lens	D_{max} < 6 Gy [Piroth] D_{max} < 10 Gy [10, Yamazaki]		

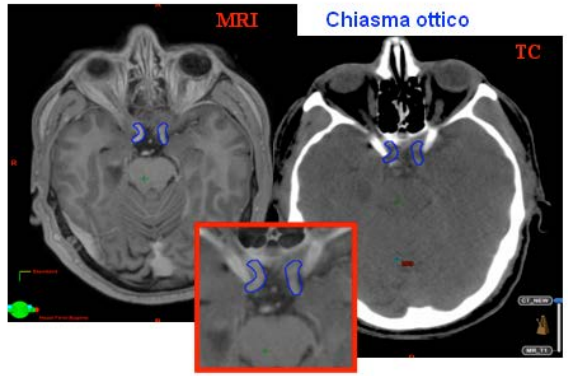
Tab. 1: Dosi di tolleranza da Emami et al.:

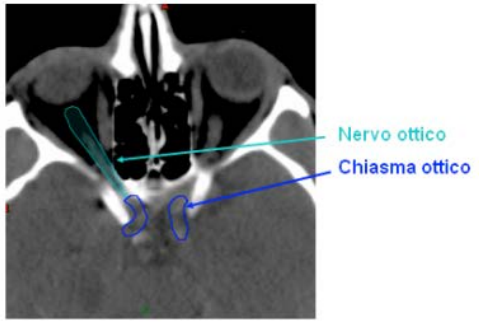
Organo	TD 5/5 (Gy)-Volume						TD 50/5 (Gy)-Volume						End-point
	1/3		2/3		3/3		1/3		2/3		3/3		
	clin	calc	clin	Calc	clin	calc	clin	calc	clin	calc	clin	calc	
Cristallino	-	10	-	10	10	10	-	18	-	18	18	18	Cataratta
Nervo ottico	-	50	-	50	50	50	-	65	-	65	65	65	Cecità
Chiasma	-	50	-	50	50	50	-	65	-	65	65	65	Cecità
Retina	-	45	-	45	45	45	-	65	-	65	65	65	Cecità

Tab. 2: Dosi di normale tolleranza tissutale con il 95% "confidence interval" (Gy) (dati combinati da Emami ed altri ricercatori):

Organo	TD 5/5 (1/3) +/- 95%CI	TD 5/5 (2/3) +/- 95%CI	TD 5/5 (3/3) +/- 95%CI	TD 50/5 (1/3) +/- 95%CI	TD 50/5 (2/3) +/- 95%CI	TD 50/5 (3/3) +/- 95%CI
Cristallino (cataratta)	6.762 (4.29-9.23)	6.762 (4.294-9.229)	6.762 (4.294-9.229)	6.762 (4.294-9.229)	16.86 (14.39-19.32)	16.86 (14.39-19.32)
Nervo ottico (cecità)	49.34 (46.06-52.62)	49.34 (46.06-52.62)	49.34 (46.06-52.62)	67.02 (63.74-70.31)	67.02 (63.74-70.31)	67.02 (63.74-70.31)
Chiasma ottico (cecità)	49.54 (37.54-61.54)	49.54 (37.54-61.54)	49.54 (37.54-61.54)	84.57 (72.57-96.57)	84.57 (72.57-96.57)	84.57 (72.57-96.57)
Retina (cecità)	44.67 (43.04-46.29)	44.67 (43.04-46.29)	44.67 (43.04-46.29)	61.58 (59.95-63.20)	61.58 (59.95-63.20)	61.58 (59.95-63.20)





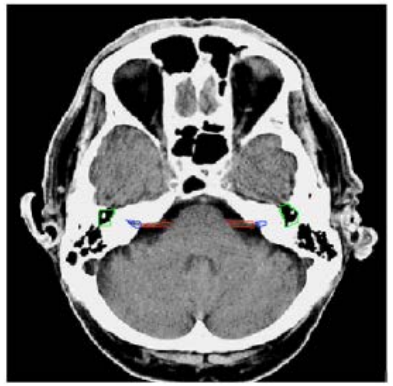


Tab. 1: Dosi di tolleranza di Emami et al. (1991)

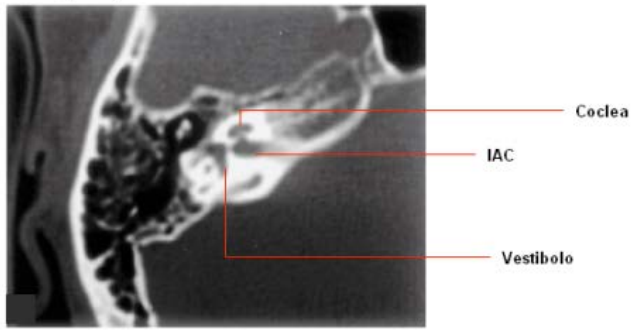
Organo	TD $_{5/5}$ (Gy) Volume						TD $_{50/5}$ (Gy) Volume						End point
	1/3		2/3		3/3		1/3		2/3		3/3		
	Clin	Calc	Clin	Calc	Clin	Calc	Clin	Calc	Clin	Calc	Clin	calc	
Orecchio E/M	30	30	30	30	30	30	40	40	40	40	40	40	Otite sierosa acuta
Orecchio E/M	55	55	55	55	55	55	65	65	65	65	65	65	Otite sierosa cronica
Orecchio E/M	79	78	70	72	70	68	90	89	80	83	80	79	Necrosi cartilaginea
Orecchio Int	-	50	-	50	-	50	-	65	-	65	-	65	Vertigini-sordità

Tab. 2: Dosi di normale tolleranza tissutale con il 95% "confidence interval" (Gy) (dati combinati da Emami ed altri ricercatori):

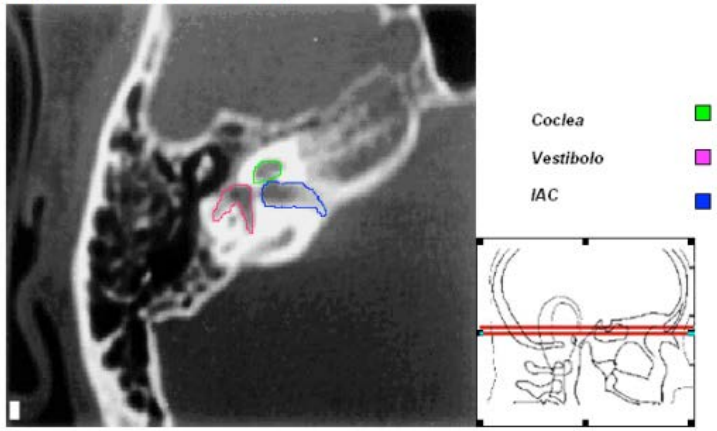
Organo	TD $_{5/5}$ (1/3) +/- 95%CI	TD $_{5/5}$ (2/3) +/- 95%CI	TD $_{5/5}$ (3/3) +/- 95%CI	TD $_{50/5}$ (1/3) +/- 95%CI	TD $_{50/5}$ (2/3) +/- 95%CI	TD $_{50/5}$ (3/3) +/- 95%CI
Orecchio E/M (otite sierosa acuta)	29.99 (29.99-30)	29.99 (29.99-30)	29.99 (29.99-30)	39.99 (39.99-40)	39.99 (39.99-40)	39.99 (39.99-40)
Orecchio E/M (otite sierosa cronica)	57.30 (54.74-60.87)	56.41 (53.85-58.98)	55.90 (53.33-58.46)	68.66 (66.06-71.22)	67.77 (65.21-70.33)	67.25 (64.69-69.81)
Orecchio E/M (necrosi cart.)	Dati non disponibili					
Orecchio Int	Dati non disponibili					



La slice successiva in dettaglio mostra l'apparato cocleovestibolare contenuto nel labirinto osseo, che avviluppa la coclea costituendone il limiti anteriore e laterale. Il limite posteriore è costituito dallo IAC mentre quello postero laterale dal vestibolo.



Di seguito il dettaglio in contouring



ACUTE TOXICITIES
(up to 6 weeks)

- Consequence of a transient peritumoral edema
- Transient worsening of pretreatment deficits
- General symptoms: Fatigue,headache, drowsiness
- Mild dermatitis in irradiated areas
- Alopecia within the irradiated areas
- Otitis externa, serous otitis media
- Hematologic toxicity
- **Usually respond to a short-term increase of corticosteroids**

SUBACUTE TOXICITIES
(6-week to 6-month)

- Attributed to changes in capillary permeability and transient demyelination.
- Headache, somnolence, fatigability, and deterioration of pre-existing deficits.
- Usually respond to steroids
- Phenomenon of "pseudoprogression"

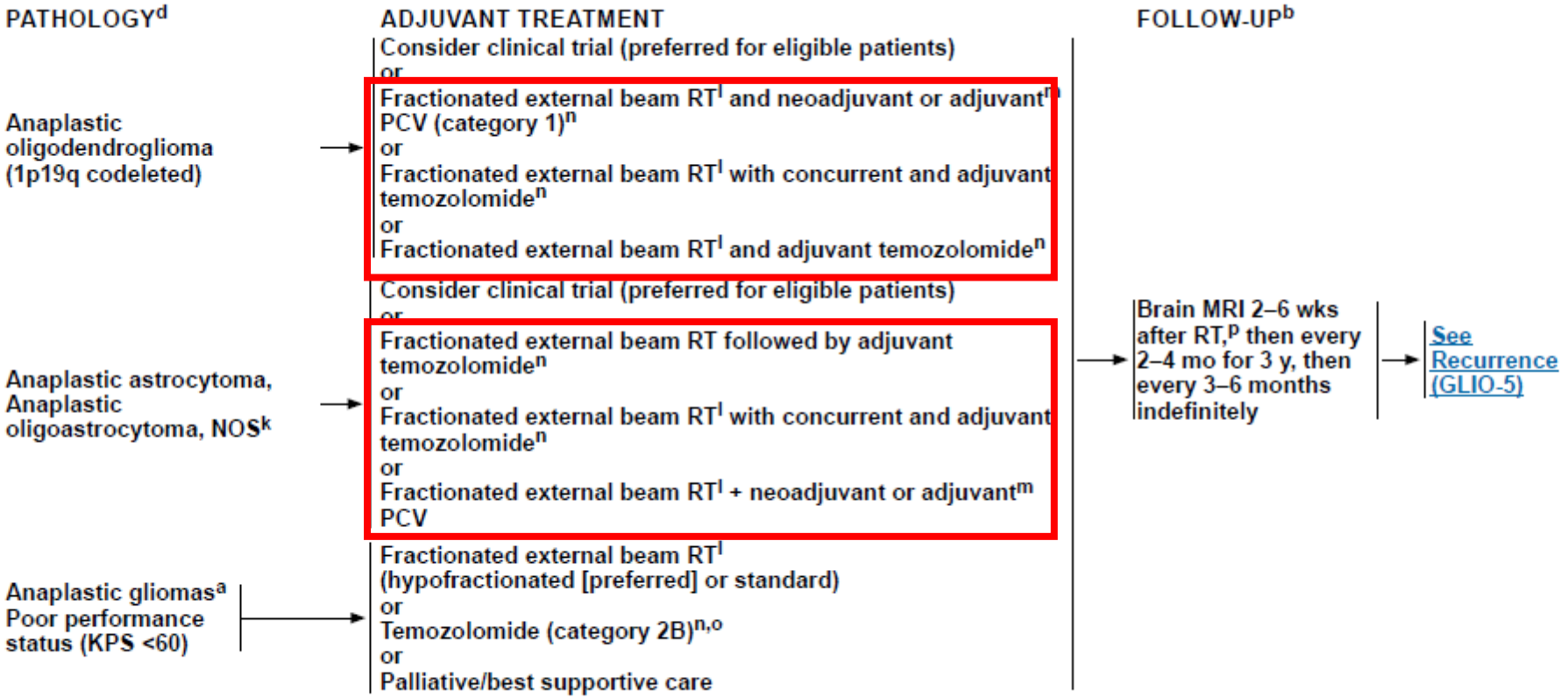
Main challenge is to distinguish clinical and imaging findings vs from tumor recurrence

LATE SEQUELAE
(6 months to many years following)

- Due to white matter damage, demyelination, and **radiation necrosis 12m-15m tipically**
- Usually irreversible and progressive
- high-tone hearing loss and vestibular damages
- Retinopathy or cataract visual acuity, visual field changes, or blindness at doses >54 to 60 Gy
- Hormone insufficiency with doses as low as 20 Gy
- Neuropsychological changes and neurocognitive impairment

ASTROCITOMI, OLIGODENDROGLIOMI e OLIGOASTROCITOMI ANAPLASTICI

ANAPLASTIC GLIOMAS (SEE GLIO-3/GLIO-4 FOR GLIOBLASTOMA)



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[k]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m]The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ANAPLASTIC GLIOMAS

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment **Anaplastic oligodendroglioma (1p19q co-deleted) (KPS ≥60)**	• RT with adjuvant PCV (category 1)[e,14] • RT with neoadjuvant PCV (category 1)[e,15]	• RT with concurrent and adjuvant TMZ[16] • RT with adjuvant TMZ[17,18]	• None
Adjuvant Treatment **Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[f] (KPS ≥60)**	• RT with concurrent and adjuvant TMZ[19,20] • RT followed by adjuvant TMZ (12 cycles)[20]	• RT with adjuvant PCV[e,21,22] • RT with neoadjuvant PCV[e]	• None
Adjuvant Treatment **Anaplastic gliomas (KPS <60)**	• None	• TMZ[g] (category 2B)[23]	• None

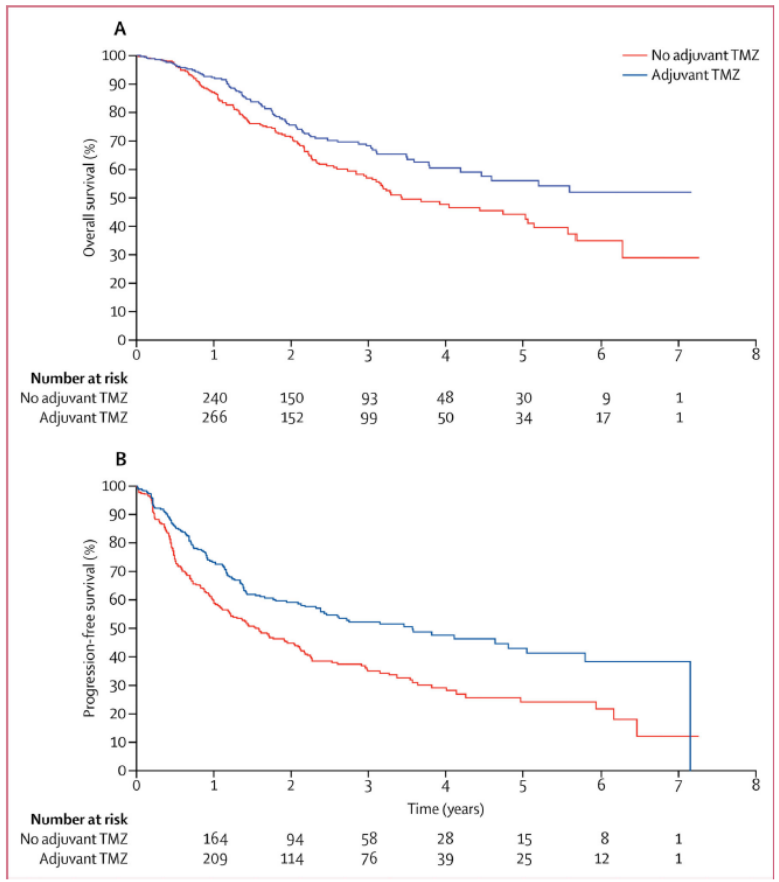


Figure 2. Survival in patients treated with or without adjuvant temozolomide
(A) Overall survival. (B) Progression-free survival. TMZ=temozolomide.

Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

Background—The role of temozolomide chemotherapy in newly diagnosed 1p/19q non-co-deleted anaplastic gliomas, which are associated with lower sensitivity to chemotherapy and worse prognosis than 1p/19q co-deleted tumours, is unclear. We assessed the use of radiotherapy with concurrent and adjuvant temozolomide in adults with non-co-deleted anaplastic gliomas.

Methods—This was a phase 3, randomised, open-label study with a 2 × 2 factorial design. Eligible patients were aged 18 years or older and had newly diagnosed non-co-deleted anaplastic glioma with WHO performance status scores of 0–2. The randomisation schedule was generated with the electronic EORTC web-based ORTA system. Patients were assigned in equal numbers (1:1:1:1), using the minimisation technique, to receive radiotherapy (59·4 Gy in 33 fractions of 1·8 Gy) alone or with adjuvant temozolomide (12 4-week cycles of 150–200 mg/m^2 temozolomide given on days 1–5); or to receive radiotherapy with concurrent temozolomide 75 mg/m^2 per day, with or without adjuvant temozolomide. The primary endpoint was overall survival adjusted for performance status score, age, 1p loss of heterozygosity, presence of oligodendroglial elements, and *MGMT* promoter methylation status, analysed by intention to treat. We did a planned interim analysis after 219 (41%) deaths had occurred to test the null hypothesis of no efficacy (threshold for rejection p<0·0084). This trial is registered with ClinicalTrials.gov, number NCT00626990.

Findings—At the time of the interim analysis, 745 (99%) of the planned 748 patients had been enrolled. The hazard ratio for overall survival with use of adjuvant temozolomide was 0·65 (99·145% CI 0·45–0·93). Overall survival at 5 years was 55·9% (95% CI 47·2–63·8) with and 44·1% (36·3–51·6) without adjuvant temozolomide. Grade 3–4 adverse events were seen in 8–12% of 549 patients assigned temozolomide, and were mainly haematological and reversible.

Interpretation—Adjuvant temozolomide chemotherapy was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma. Further analysis of the role of concurrent temozolomide treatment and molecular factors is needed.

Funding—Schering Plough and MSD.

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Neuro-Oncology

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Phase III randomized study of radiation and temozolomide versus radiation and nitrosourea therapy for anaplastic astrocytoma: results of NRG Oncology RTOG 9813

Abstract

Background. The primary objective of this study was to compare the overall survival (OS) of patients with anaplastic astrocytoma (AA) treated with radiotherapy (RT) and either temozolomide (TMZ) or a nitrosourea (NU). Secondary endpoints were time to tumor progression (TTP), toxicity, and the effect of *IDH1* mutation status on clinical outcome.
Methods. Eligible patients with centrally reviewed, histologically confirmed, newly diagnosed AA were randomized to receive either RT+TMZ ($n = 97$) or RT+NU ($n = 99$). The study closed early because the target accrual rate was not met.
Results. Median follow-up time for patients still alive was 10.1 years (1.9–12.6 y); 66% of the patients died. Median survival time was 3.9 years in the RT/TMZ arm (95% CI, 3.0–7.0) and 3.8 years in the RT/NU arm (95% CI, 2.2–7.0), corresponding to a hazard ratio (HR) of 0.94 ($P = .36$; 95% CI, 0.67–1.32). The differences in progression-free survival (PFS) and TTP between the 2 arms were not statistically significant. Patients in the RT+NU arm experienced more grade ≥3 toxicity (75.8% vs 47.9%, $P < .001$), mainly related to myelosuppression. Of the 196 patients, 111 were tested for *IDH1-R132H* status (60 RT+TMZ and 51 RT+NU). Fifty-four patients were *IDH* negative and 49 were IDH positive with a better OS in *IDH*-positive patients (median survival time 7.9 vs 2.8 y; $P = .004$, HR = 0.50; 95% CI, 0.31–0.81).
Conclusions. RT+TMZ did not appear to significantly improve OS or TTP for AA compared with RT+ NU. RT+TMZ was better tolerated. *IDH1-R132H* mutation was associated with longer survival.

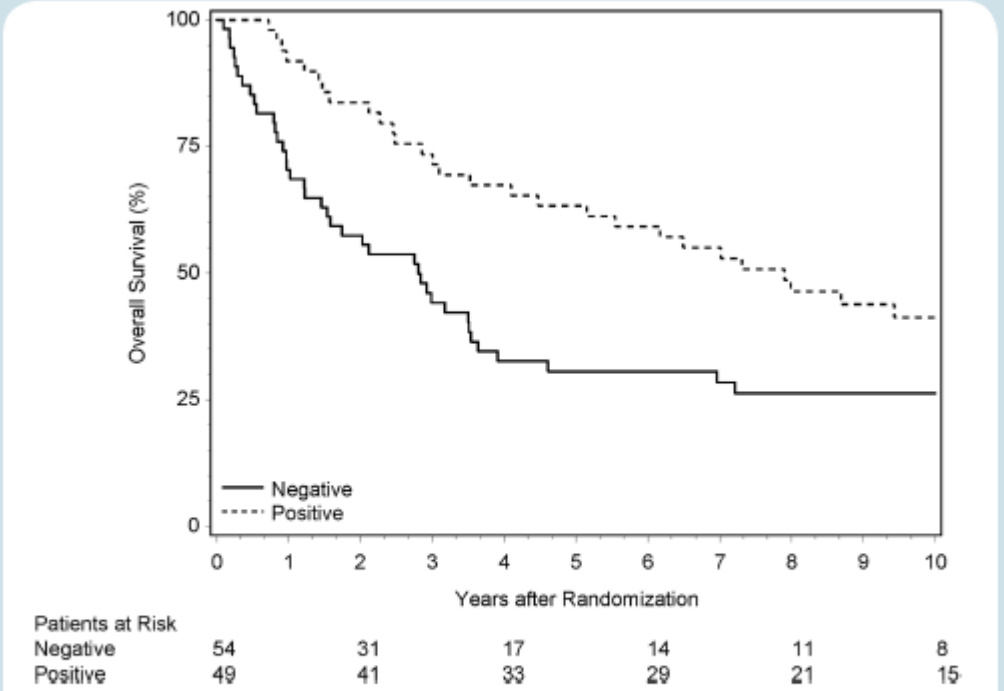

Fig. 3 Overall survival by *IDH1-R132H* mutation status

SAPIENZA UNIVERSITÀ DI ROMA

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan

See accompanying editorial on page 299 and article on page 337

A B S T R A C T

Purpose
Anaplastic oligodendroglioma are chemotherapy-sensitive tumors. We now present the long-term follow-up findings of a randomized phase III study on the addition of six cycles of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy (RT).

Patients and Methods
Adult patients with newly diagnosed anaplastic oligodendroglial tumors were randomly assigned to either 59.4 Gy of RT or the same RT followed by six cycles of adjuvant PCV. An exploratory analysis of the correlation between 1p/19q status and survival was part of the study. Retrospectively, the methylation status of the methyl-guanine methyl transferase gene promoter and the mutational status of the isocitrate dehydrogenase (*IDH*) gene were determined. The primary end points were overall survival (OS) and progression-free survival based on intent-to-treat analysis.

Results
A total of 368 patients were enrolled. With a median follow-up of 140 months, OS in the RT/PCV arm was significantly longer (42.3 *v* 30.6 months in the RT arm, hazard ratio [HR], 0.75; 95% CI, 0.60 to 0.95). In the 80 patients with a 1p/19q codeletion, OS was increased, with a trend toward more benefit from adjuvant PCV (OS not reached in the RT/PCV group *v* 112 months in the RT group; HR, 0.56; 95% CI, 0.31 to 1.03). *IDH* mutational status was also of prognostic significance.

Conclusion
The addition of six cycles of PCV after 59.4 Gy of RT increases both OS and PFS in anaplastic oligodendroglial tumors. 1p/19q-codeleted tumors derive more benefit from adjuvant PCV compared with non–1p/19q-deleted tumors.

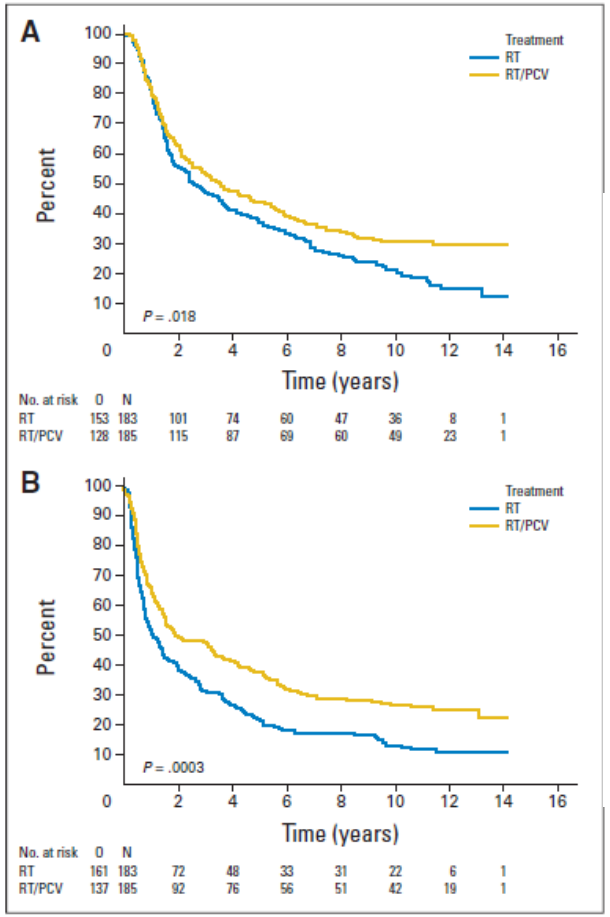

Fig 2. (A) Overall survival and (B) progression-free survival in both treatment arms in the intent-to-treat population. N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

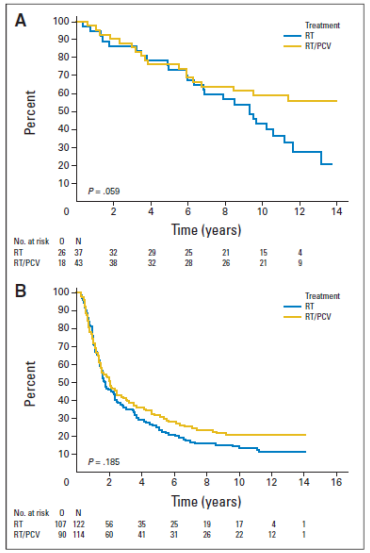

Fig 3. Overall survival in both treatment arms for (A) the patients with 1p/19q-codeleted tumors (n = 80) and (B) the patients with non–1p/19q-codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

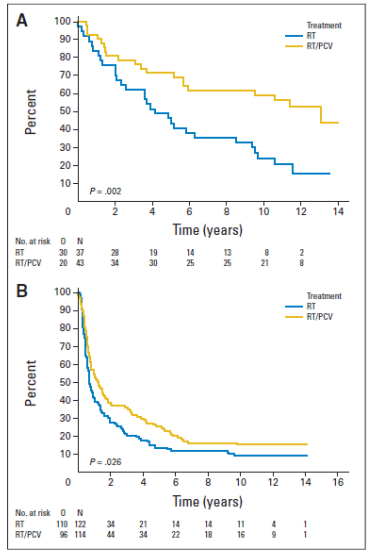

Fig 4. Progression-free survival in both treatment arms for (A) patients with 1p/19q-codeleted tumors (n = 80) and (B) patients with non–1p/19q-codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

MGMT-STP27 Methylation Status as Predictive Marker for Response to PCV in Anaplastic Oligodendrogliomas and Oligoastrocytomas. A Report from EORTC Study 26951

Abstract

Purpose: The long-term follow-up results from the EORTC-26951 trial showed that the addition of procarbazine, CCNU, and vincristine (PCV) after radiotherapy increases survival in anaplastic oligodendrogliomas/oligoastrocytomas (AOD/AOA). However, some patients appeared to benefit more from PCV treatment than others.

Experimental Design: We conducted genome-wide methylation profiling of 115 samples included in the EORTC-26951 trial and extracted the CpG island hypermethylated phenotype (CIMP) and *MGMT* promoter methylation (*MGMT*-STP27) status.

Results: We first show that methylation profiling can be conducted on archival tissues with a performance that is similar to snap-frozen tissue samples. We then conducted methylation profiling on EORTC-26951 clinical trial samples. Univariate analysis indicated that CIMP+ or *MGMT*-STP27 methylated tumors had an improved survival compared with CIMP− and/or *MGMT*-STP27 unmethylated tumors [median overall survival (OS), 1.05 vs. 6.46 years and 1.06 vs. 3.8 years, both $P < 0.0001$ for CIMP and *MGMT*-STP27 status, respectively]. Multivariable analysis indicates that CIMP and MGMT-STP27 are significant prognostic factors for survival in presence of age, sex, performance score, and review diagnosis in the model. CIMP+ and *MGMT*-STP27 methylated tumors showed a clear benefit from adjuvant PCV chemotherapy: the median OS of CIMP+ samples in the RT and RT-PCV arms was 3.27 and 9.51 years, respectively ($P = 0.0033$); for *MGMT*-STP27 methylated samples, it was 1.98 and 8.65 years. There was no such benefit for CIMP- or for *MGMT*-STP27 unmethylated tumors. *MGMT*-STP27 status remained significant in an interaction test ($P = 0.003$). Statistical analysis of microarray (SAM) identified 259 novel CpGs associated with treatment response.

Conclusions: *MGMT*-STP27 may be used to guide treatment decisions in this tumor type. *Clin Cancer Res; 19(19); 5513–22. ©2013 AACR.*

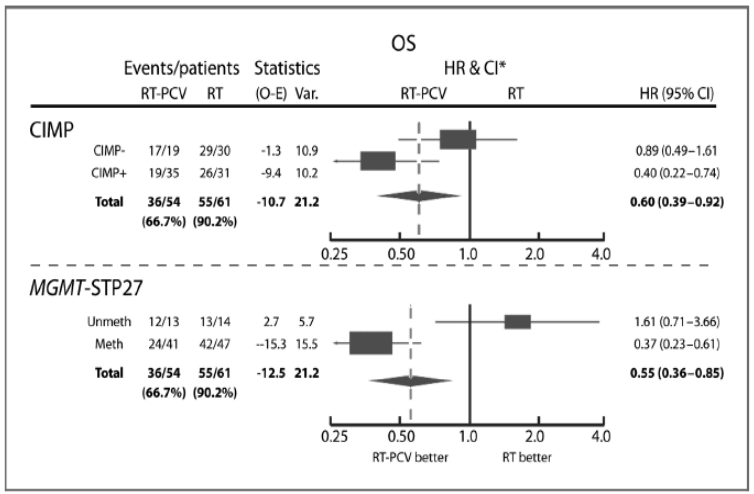

Figure 4. Forest plots of relative risk of CIMP and *MGMT*-STP27 in the RT and RT-PCV treatment arms. The interaction test for CIMP status of borderline significance, $P = 0.07$, χ^2 3.37, degrees of freedom (df) = 1. For *MGMT*-STP27, the interaction test was significant $P = 0.003$, χ^2 8.93, df = 1.

RECURRENCE

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Anaplastic Gliomas[a]/Glioblastoma

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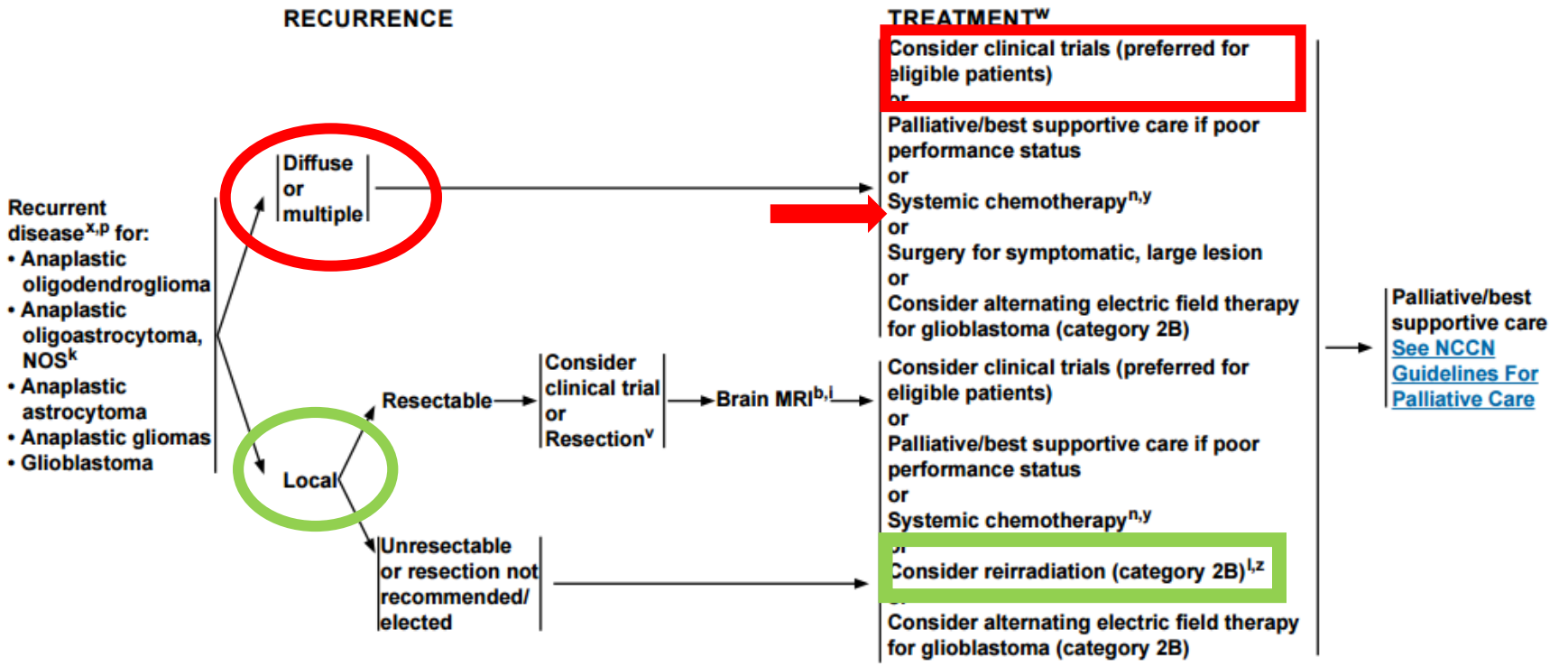

[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[i]Postoperative brain MRI within 48 hours after surgery.
[k]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[v]Consider carmustine (BCNU) wafer implant during resection. Treatment with carmustine wafer may impact enrollment in clinical trials.
[w]The efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.
[x]Consider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.
[y]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[z]Especially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

GLIOBLASTOMA

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant or Concurrent Treatment	• RT with concurrent and adjuvant TMZ[42, 43]	• None	• RT with concurrent or adjuvant TMZ (for patients age 70 or younger and KPS <60)[44] • TMZ (for patients with MGMT promoter-methylated tumors and KPS <60 or age >70 years and KPS ≥60)[42,45]
Recurrence Therapy[h,l]	• Bevacizumab[i,k, 46-49] • Temozolomide[9,25,50,51] • Lomustine or carmustine[52-55] • PCV[56,57]	• Bevacizumab + chemotherapy[j] (carmustine or lomustine,[58,59] TMZ,[60,61] carboplatin [category 2B][62,63])	• If failure or intolerance to the preferred or other recommended regimens ‣ Etoposide (category 2B)[37] ‣ Platinum-based regimens[d] (category 3)[62,63]

ANAPLASTIC GLIOMAS

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment **Anaplastic oligodendroglioma (1p19q co-deleted) (KPS ≥60)**	• RT with adjuvant PCV (category 1)[e,14] • RT with neoadjuvant PCV (category 1)[e,15]	• RT with concurrent and adjuvant TMZ[16] • RT with adjuvant TMZ[17,18]	• None
Adjuvant Treatment **Anaplastic astrocytoma/anaplastic oligoastrocytoma, NOS[f] (KPS ≥60)**	• RT with concurrent and adjuvant TMZ[19,20] • RT followed by adjuvant TMZ (12 cycles)[20]	• RT with adjuvant PCV[e,21,22] • RT with neoadjuvant PCV[e]	• None
Adjuvant Treatment **Anaplastic gliomas (KPS <60)**	• None	• TMZ[g] (category 2B)[23]	• None
Recurrence Therapy[h]	• TMZ[8,9,24,25] • Lomustine or carmustine[26] • PCV[27] • Bevacizumab[i, 28-30]	• Bevacizumab + chemotherapy[j] (carmustine or lomustine,[31,32] TMZ,[33,34] carboplatin [category 2B][35,36])	• If failure or intolerance to the preferred or other recommended regimens ▸ Etoposide[37,38] (category 2B) ▸ Platinum-based regimens[d,39-41] (category 3)

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Anaplastic Gliomas[a]/Glioblastoma

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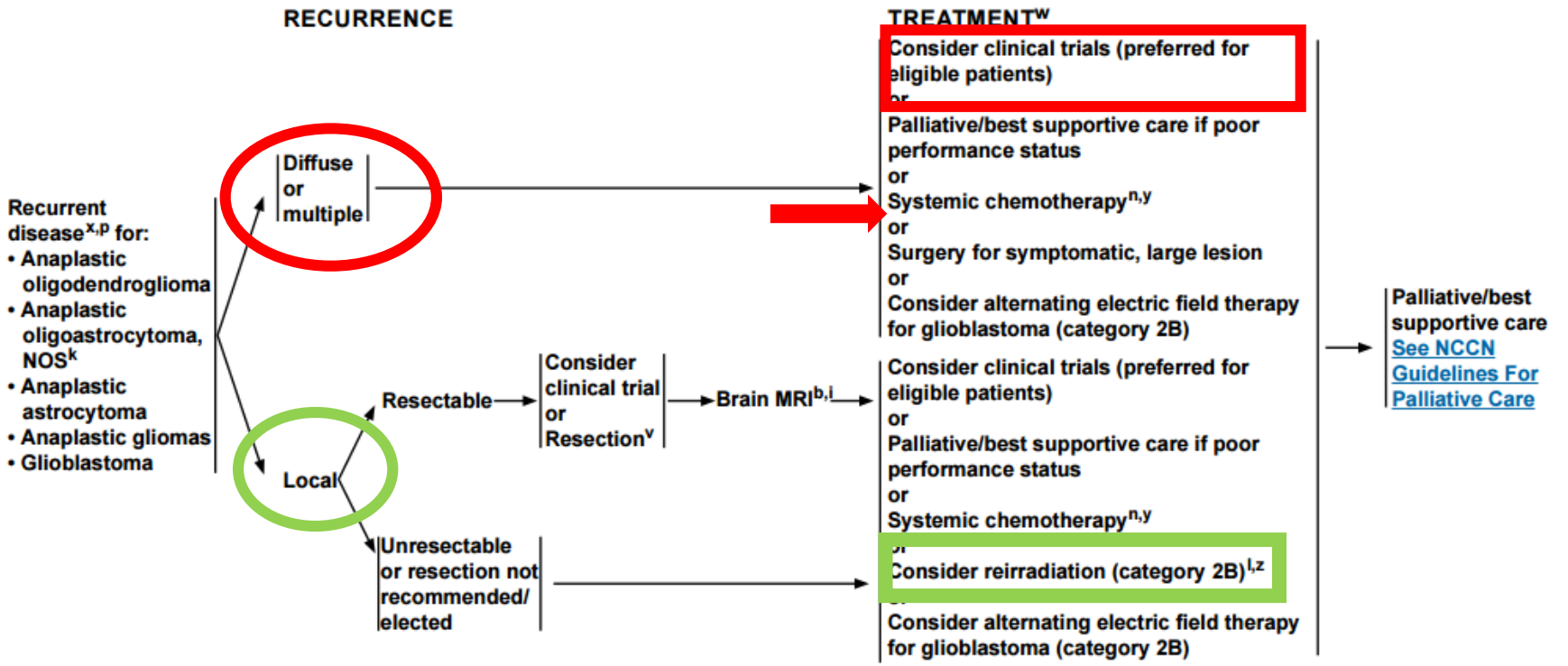

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

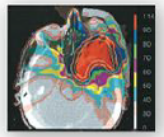
Repeat radiotherapy using one of several different methods (including radiosurgery, brachytherapy, GliaSite balloon brachytherapy, and even repeat external beam radiotherapy) may be considered for carefully selected patients. Hypofractionated re-irradiation with bevacizumab has shown promising results in small single institutional reports, with surprisingly limited toxicity, attributed to "vascular stabilization and protection" resulting from bevacizumab, and more investigations of this approach are being considered.[155] The hypofractionated approach with TMZ and bevacizumab has been extended to the newly diagnosed setting, and at the Society of Neuro-oncology 2011 meeting, investigators from MSKCC reported median survival in excess of 21 months in a small cohort of unmethylated MGMT GBM patients.[156] A prospective randomized trial of hypofractionated re-irradiation with bevacizumab has completed accrual, and results are pending.

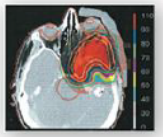
Recurrence	Resectable and/or symptomatic: surgery. Consider adjuvant chemo or RT
	Unresectable, localized: Chemo and/or highly conformal RT (30–35 Gy/ 10 fx, 25 Gy/5 fx) or SRS
	Diffuse recurrence: chemo + best supportive care

Proton Therapy

Dosimetrical or Clinical Advantage?

Intensity-Modulated (Photon) RT





Intensity-Modulated Proton RT

Protons allow medium to low-dose sparing of healthy tissues

Tumors with good control/prognosis

Delivery of a **standard dose**

Less risk of

both early and late side effects

Better Quality of Life

Tumors with worse control/prognosis

Delivery of **higher dose**

Same risk of

both early and late side effects

Better Tumor Control

Carbon ion radiotherapy boost in the treatment of glioblastoma: a randomized phase I/III clinical trial.

Kong L[1], Gao J[2], Hu J[2], Lu R[2], Yang J[2], Qiu X[2], Hu W[2], Lu JJ[3].

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Abstract

BACKGROUND: Glioblastoma (GBM) is a highly virulent tumor of the central nervous system, with a median survival < 15 months. Clearly, an improvement in treatment outcomes is needed. However, the emergence of these malignancies within the delicate brain parenchyma and their infiltrative growth pattern severely limit the use of aggressive local therapies. The particle therapy represents a new promising therapeutic approach to circumvent these prohibitive conditions with improved treatment efficacy.

METHODS AND DESIGN: Patients with newly diagnosed malignant gliomas will have their tumor tissue samples submitted for the analysis of the status of O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. In Phase I, the patients will undergo an induction carbon ion radiotherapy (CIRT) boost followed by 60 GyE of proton irradiation with concurrent temozolomide (TMZ) at 75 mg/m^2. To determine the maximal dose of safe induction boost, the tolerance, and acute toxicity rates in a dose-escalation manner from 9 to 18 GyE in three fractions will be used. In Phase III, GBM-only patients will be randomized to receive either 60 GyE (2 GyE per fraction) of proton irradiation with concurrent TMZ (control arm) or a CIRT boost (dose determined in Phase I of this trial) followed by 60 GyE of proton irradiation with concurrent TMZ. The primary endpoints are overall survival (OS) and toxicity rates (acute and long-term). Secondary endpoints are progression-free survival (PFS), and tumor response (based upon assessment with C-methionine/fluoro-ethyl-tyrosine positron emission tomography [MET/FET PET] or magnetic resonance imaging [MRI] and detection of serologic immune markers). We hypothesize that the induction CIRT boost will result in a greater initial tumor-killing ability and prime the tumor microenvironment for enhanced immunologic tumor clearance, resulting in an expected 33% improvement in OS rates.

DISCUSSION: The prognosis of GBM remains grim. The mechanism underpinning the poor prognosis of this malignancy is its chronic state of tumor hypoxia, which promotes both immunosuppression/immunologic evasion and radio-resistance. The unique physical and biological properties of CIRT are expected to overcome these microenvironmental limitations to confer an improved tumor-killing ability and anti-tumor immune response, which could result in an improvement in OS with minimal toxicity. Trial registration number This trial has been registered with the China Clinical Trials Registry, and was allocated the number ChiCTR-OID-17013702.

KEYWORDS: Anaplastic astrocytoma; Carbon ion radiotherapy; Glioblastoma; O-6-methylguanine-DNA methyltransferase; Overall survival; Progression-free survival; Proton radiotherapy; Serologic immune response; Temozolomide; Toxicity

GRAZIE PER L'ATTENZIONE