

Cosa è cambiato nella definizione del target per i glioblastomi e quale possibile scenario futuro

GIUSEPPE MINNITI, MD, PhD

Department of Medicine, Surgery and Neuroscience, University of Siena, Siena;
University of Pittsburgh, UPMC Hillman Cancer Center San Pietro Rome;
IRCCS Neuromed, Pozzilli (IS); Italy

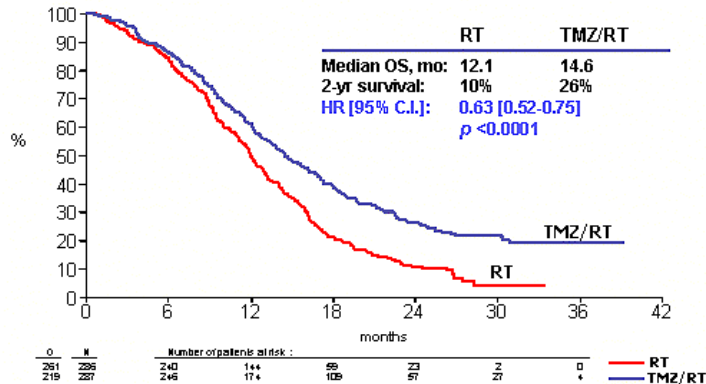
DECLARATION OF INTERESTS

- Honoraria fees from Brainlab
- Honoraria fees from Accuray

Background



Overall Survival



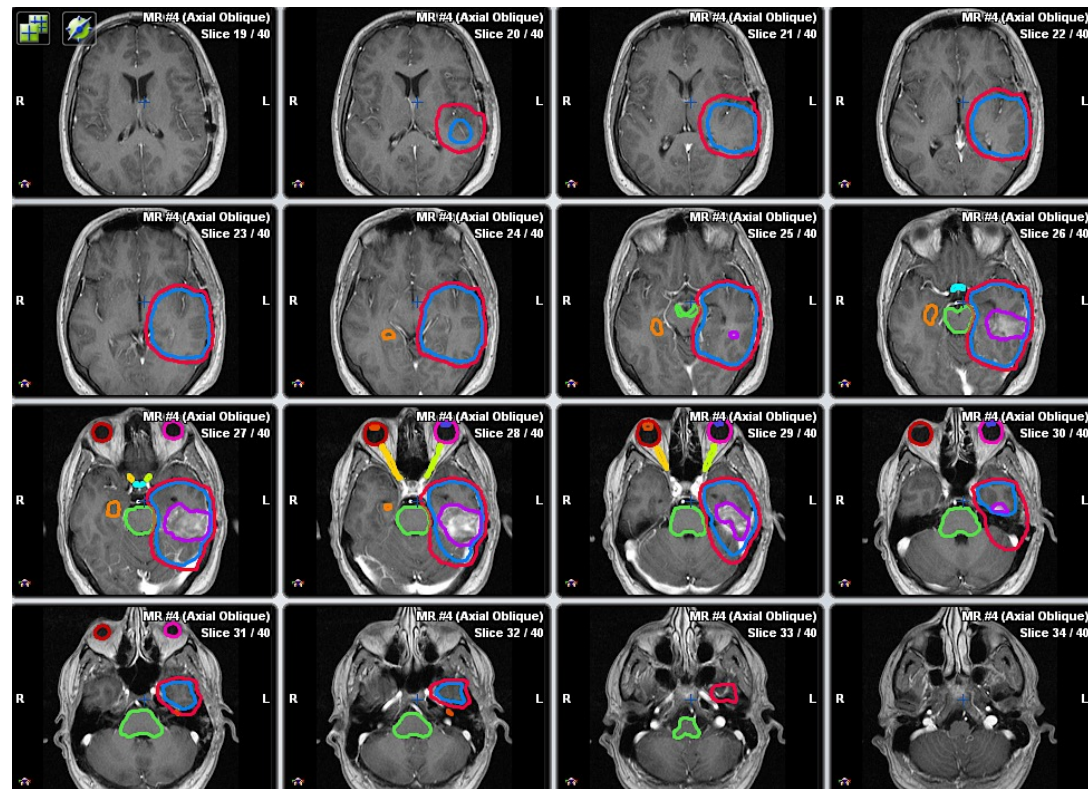
The current standard of care for newly diagnosed GBM is maximal surgical debulking, followed by adjuvant RT (60 Gy/30#) with concomitant and adjuvant TMZ chemotherapy.

ESTRO-ACROP guideline “target delineation of glioblastomas”

Maximilian Niyazi^{a,*}, Michael Brada^b, Anthony J. Chalmers^c, Stephanie E. Combs^d, Sara C. Erridge^e, Alba Fiorentino^f, Anca L. Grosu^g, Frank J. Lagerwaard^h, Giuseppe Minnitiⁱ, René-Olivier Mirimanoff^j, Umberto Ricardi^k, Susan C. Short^l, Damien C. Weber^{m,n}, Claus Belka^a

ESTRO guideline committee on GBM target delineation recommends a single clinical target volume (CTV) as defined by an expansion of 2 cm from the residual tumor and resection cavity (GTV) without inclusion of peritumoral edema.

This target approach has been used in several EORTC trials.

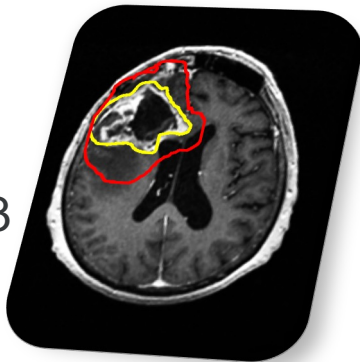


Target volume definitions utilized by cooperative groups in the United States and Europe

Cooperative Group	One or Two Phase	CTV (initial)	CTV(boost)	PTV
ABTC	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 5 mm	Cavity + T1E + 5 mm	Institution specific but generally 3-5 mm
EORTC	One-phase	Cavity + T1E + 2-3 cm	-	Institution specific but generally 5-7 mm
NCCTG/Alliance	Two-phase: 50 + 10 = 60 Gy	T2 + T1E + cavity + 20 mm to block edge	Cavity + T1E + 20 mm to block edge	PTV addressed in CTV expansions
RTOG/NRG	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 20 mm	Cavity + T1E + 20 mm	3-5 mm

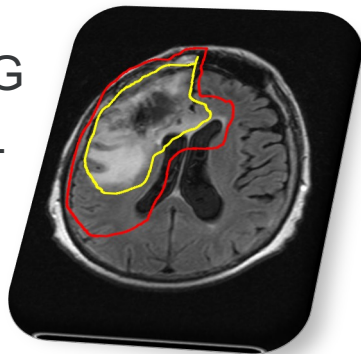
EORTC

Cavity +
T1E + 2-3
cm



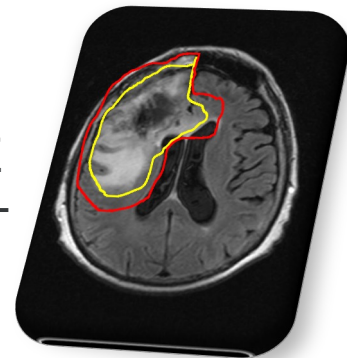
RTOG/NRG

T2 + T1E +
cavity + 20
mm



ABTC

T2 + T1E
+ cavity +
5 mm



Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide

Giuseppe Minniti^{a,b,*}, Dante Amelio^c, Maurizio Amichetti^c, Maurizio Salvati^b, Roberta Muni^a, Alessandro Bozzao^d, Gaetano Lanzetta^b, Stefania Scarpino^e, Antonella Arcella^b, Riccardo Maurizi Enrici^a

CTV according to different plan delineations.

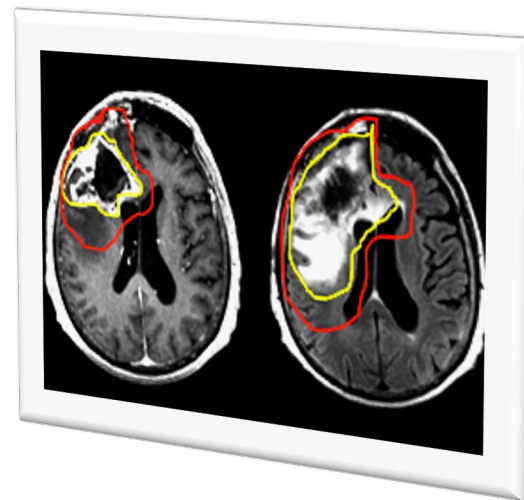
Target volumes	S'Andrea _{plans} (residual tumor/cavity plus 2 cm)		RTOG _{plans} (edema plus 2 cm)	
	CTV1	CTV1/CTV2 ^a	CTV _{RTOG}	CTV _{RTOG-boost}
Median volume (cm ³)	214.3	177.8	319.6	214.3
Dose prescribed (Gy)	50	60	46	60
Range	125.3–380	123–262.1	134.2–418	125.3–380
Standard deviation (SD)	56.2	37.3	58.6	56.2
Median coverage (range)	100% (90–100)	100% (89–100)	100% (91–100)	100% (90–100)

Percent of volume of brain irradiated according to different plans.

	S'Andrea _{plans} (residual tumor/cavity plus 2 cm)		RTOG _{plans} (edema plus 2 cm)	
Dose received (Gy)	46	60	46	60
Median volume (%)	29.8	16.7	35.4*	20.5**
Range	11.2–44	7.6–25.8	14.3–48.2	11.2–34
Standard deviation (SD)	4.3	3.5	5.1	3.7

* $P = 0.0001$ between S'Andrea_{plans} and RTOG_{plans} at a dose of 46 Gy.

** $P = 0.005$ between S'Andrea_{plans} and RTOG_{plans} at a dose of 60 Gy.



Focus CNS subgroup members

Maximilian Niyazi
Nicolaus Andratschke
Martin Bendszus
Anthony J Chalmers
Sara C Erridge
Norbert Galldiks
Frank J Lagerwaard
Pierina Navarria
Per Munck af Rosenschöld
Umberto Ricardi
Martin J van den Bent
Michael Weller
Claus Belka
Giuseppe Minniti



Passen Sie Ihre Ansicht an, indem Sie eines oder mehrere Videos auf die Bühne ziehen.

Alles klar

KLINIKUM ESTRO 2020

Participants/topics (bold: chair/co-chair)

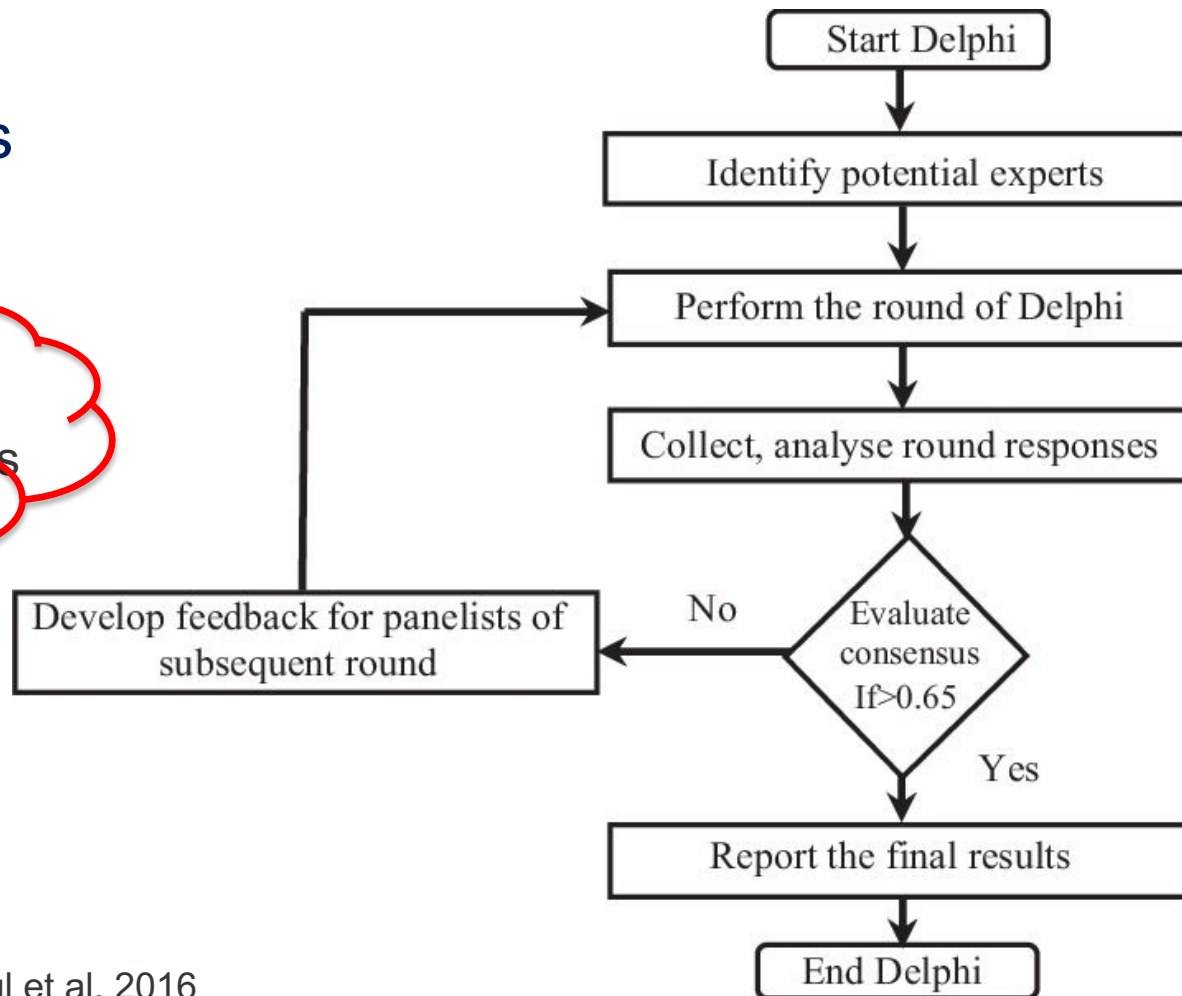
- ➔ GBM delineation/RT details: **Niyazi/Minniti**, Lagerwaard, Erridge, Munck af Rosenschöld, Navarria, Ricardi, Chalmers, Belka, Andratschke, Bendszus (**Joint with EANO**)
- ➔ Re-irradiation primary brain tumors: **Minniti/Andratschke**, Dhermain, Weber, Grosu, Niyazi, Alongi, Erridge, Lagerwaard, Baumert, Belka, Williamson (**Joint with EANO**)
- ➔ Adult lower grade gliomas: **Baumert/Dhermain**, Ricardi, Timmermann, Weber, Grosu, Niyazi, Erridge, Minniti, Izycka-Swieszewska, Lagerwaard, Navarria, Falini, De Witt Hamer, Keil (**Joint with EANO**)
- Spine SBRT: **Guckenberger/Alongi**, Andratschke, Niyazi, Minniti, Munck af Rosenschöld, Ricardi, Belka, Sahgal, Dahele, Josipovic, Verbakel, Mancosu, Cuccia, Stella
- Pediatrics/ATRT: **Timmermann/Weber**, Alapetite, Dieckmann, Giral, Kortmann, Lassen, Maduro, Ricardi, Izycka-Swieszewska (joint guideline with SIOPE)
- Brain mets: **Belka/Grosu**, Alongi, Minniti, Niyazi, Andratschke, Munck af Rosenschöld, Lagerwaard, Baumert, Navarria, Ricardi, Guckenberger, Dhermain, Williamson, Arcangeli, Steinbach, Hoyer, Slotman, Metellus

Literature search strategy

- ✓ The final literature review was conducted in April 2022 1.013 abstracts were retrieved,
- ✓ 51 studies providing data on target delineation and radiation therapy details for glioblastoma were selected for evaluation.
- ✓ Abstracts presented at the ESTRO and ASTRO conferences between 2015 and 2021 were analysed separately.

Delphi process: 2 predefined rounds (modified)

65% consensus
80% strong consensus



Delphi process: 2 predefined rounds

Q1: This guideline will mainly cover glioblastoma WHO 4, IDH wt - a small side paragraph will cover less frequently observed entities such as astrocytoma WHO 4, IDH mut (identical target volume concept) or WHO 2, IDH wt (TERT wt vs mut) pointing on lack of definitive evidence on target delineation: diffuse hemispheric (IDH3 G34-mutated) or midline (IDH K27M) glioma (WHO 4) will be excluded

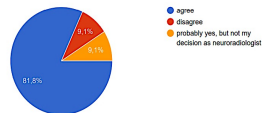
11 Antworten



Kopieren

Q2: In glioblastoma, a 1.5 cm CTV margin shall be added to the contrast enhancing GTV + resection cavity, independently of the patient's age - given a novel MRI within two weeks to therapy

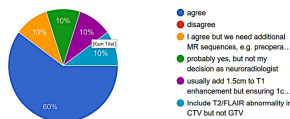
11 Antworten



Kopieren

Q3: A non-contrast enhancing tumor (part) that can be clearly distinguished from edema on T2/FLAIR images will be included in the GTV and the same margins will be used as on CE T1

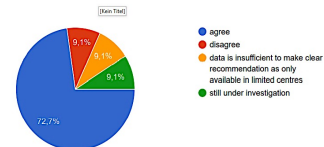
10 Antworten



Kopieren

Q4: Amino acid PET is valuable for target delineation postoperatively or before / s/p biopsy.

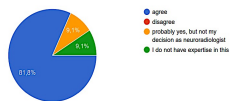
11 Antworten



Kopieren

Q4.1: In case FET PET is used for target delineation, we provide a best practice advice based on histopathological confirmatory studies: use SUVmax (TBR) of 1.6 - 1.8; to avoid decreased specificity postoperatively, earliest time point should be at least two weeks apart from surgery

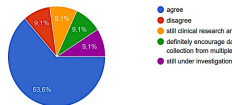
11 Antworten



Kopieren

Q4.2: if amino acid PET is used in experienced hands in addition to MRI, margin reduction to minimally 1 cm may be employed; it is encouraged to collect these cases within a prospective database and audit own results/recurrence patterns regularly.

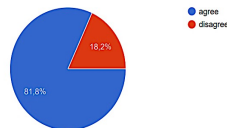
11 Antworten



Kopieren

Q5: the subventricular zone should not be included into the CTV intentionally

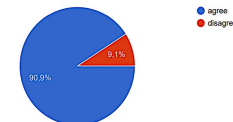
11 Antworten



Kopiere

Q6: The panel recommends the following anatomical corrections of the CTV: tentorium/falk/bone/brainstem/visual pathway including chiasm -> 0mm, ventricles -> 5mm, brainstem if midbrain involved -> 1.5 cm

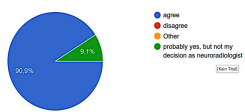
11 Antworten



Kopieren

Q7: The "brain" OAR is defined as the entire brain parenchyma excluding brainstem, visual pathway, cavernous sinuses and the GTV. Though no definite brain constraints exist, it is encouraged to use different parameters for optimization, e. g. mean brain dose, V30, V40, 45 and/or EUD (a=9).

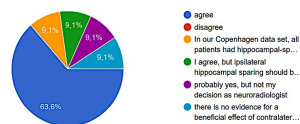
11 Antworten



Kopieren

Q8: Hippocampal sparing ipsilaterally is discouraged and may be used contralaterally if the tumor is well lateralized.

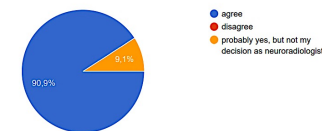
11 Antworten



Kopieren

Q9: PTV = PRV margin and PRVs may be helpful for the following organs for planning purposes: chiasm, optic nerves, brainstem

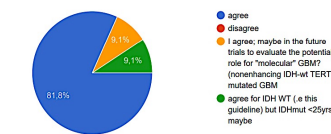
11 Antworten



Kopf

Q12: There is no role for particle therapy in glioblastoma (primary situation).

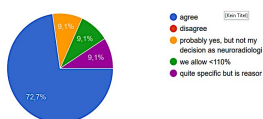
11 Antworten



Kopieren

Q11: PTV dose prescription aims at D95 greater or equal to 95% of the prescribed dose, and overdosage should be limited to D2 < 107%.

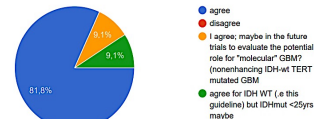
11 Antworten



Kf

Q12: There is no role for particle therapy in glioblastoma (primary situation).

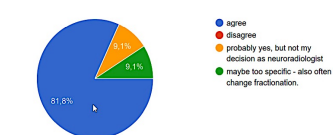
11 Antworten



Kopiere

Q13: In large uni-/multifocal lesions margins or prescription dose may be reduced according to experience and cumulative brain exposure, e.g. if V45 of the brain is $\geq 50\%$ or CTV > 350 cc

11 Antworten

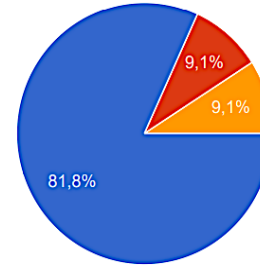


Kopieren

Delphi process: 2 predefined rounds

Q2: In glioblastoma, a 1.5 cm CTV margin shall be added to the contrast enhancing GTV + resection cavity, independently of the patient's age - given a novel MRI within two weeks to therapy

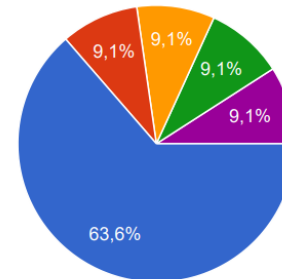
11 Antworten



- agree
- disagree
- probably yes, but not my decision as neuroradiologist

Q4.2: If amino acid PET is used in experienced hands in addition to MRI, margin reduction to minimally 1 cm may be employed; it is encouraged to collect these cases within a prospective database and audit own results/recurrence patterns regularly.

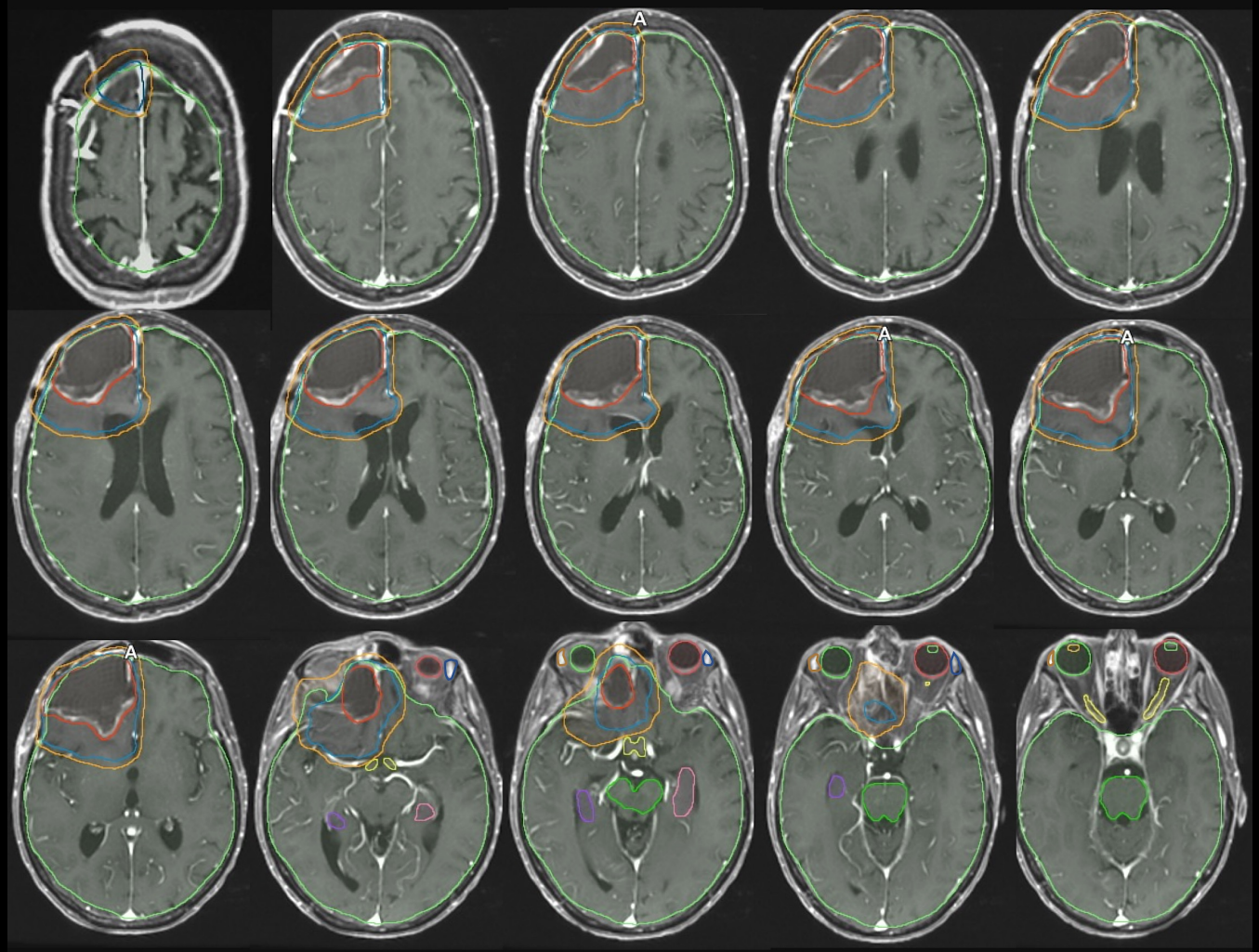
11 Antworten



- agree
- disagree
- still clinical research area
- definitely encourage data collection from multiple centres
- still under investigation

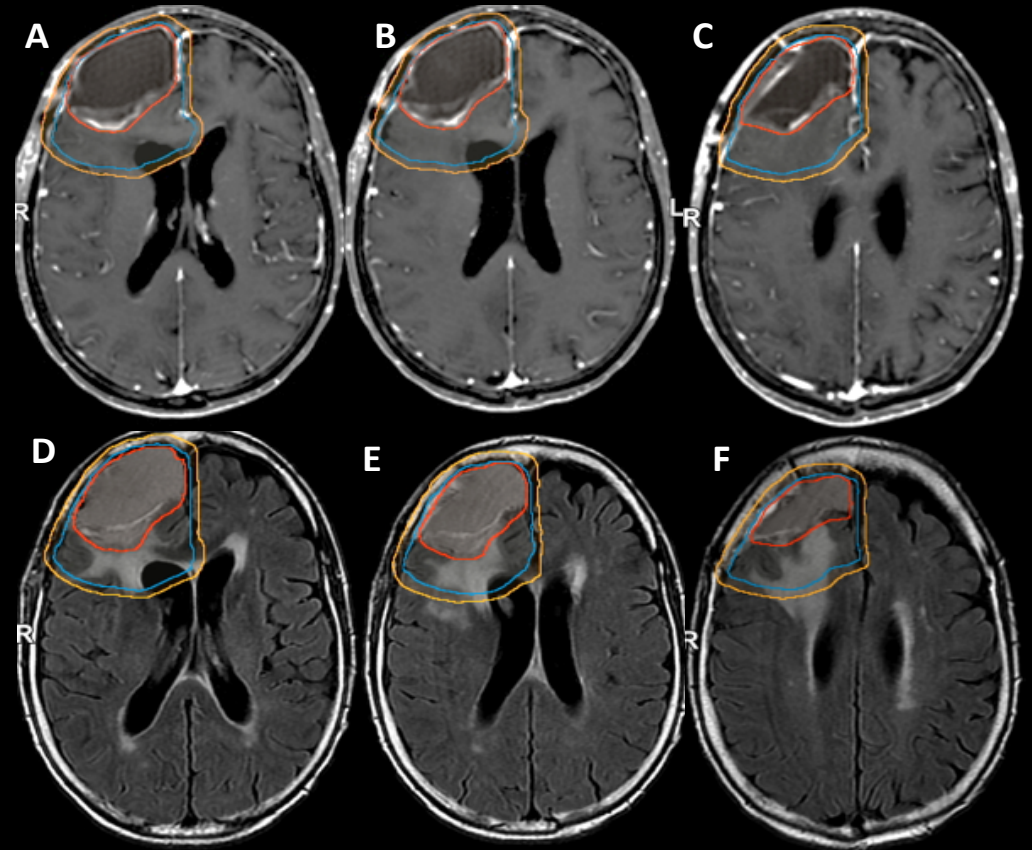
The grid contains 15 questions (Q1-Q15) with pie charts showing the distribution of responses. Each question includes a legend for the response categories. For example, Q1 (GTV margin) shows 81.8% agree, 9.1% disagree, and 9.1% probably yes. Q15 (margin reduction) shows 63.6% agree, 9.1% disagree, 9.1% still clinical research area, 9.1% definitely encourage data collection, and 9.1% still under investigation.

ESTRO-EANO
guideline on
target
delineation
and
radiotherapy
details for
glioblastoma:
an example of
postoperative
contouring of a
frontal GBM



ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma

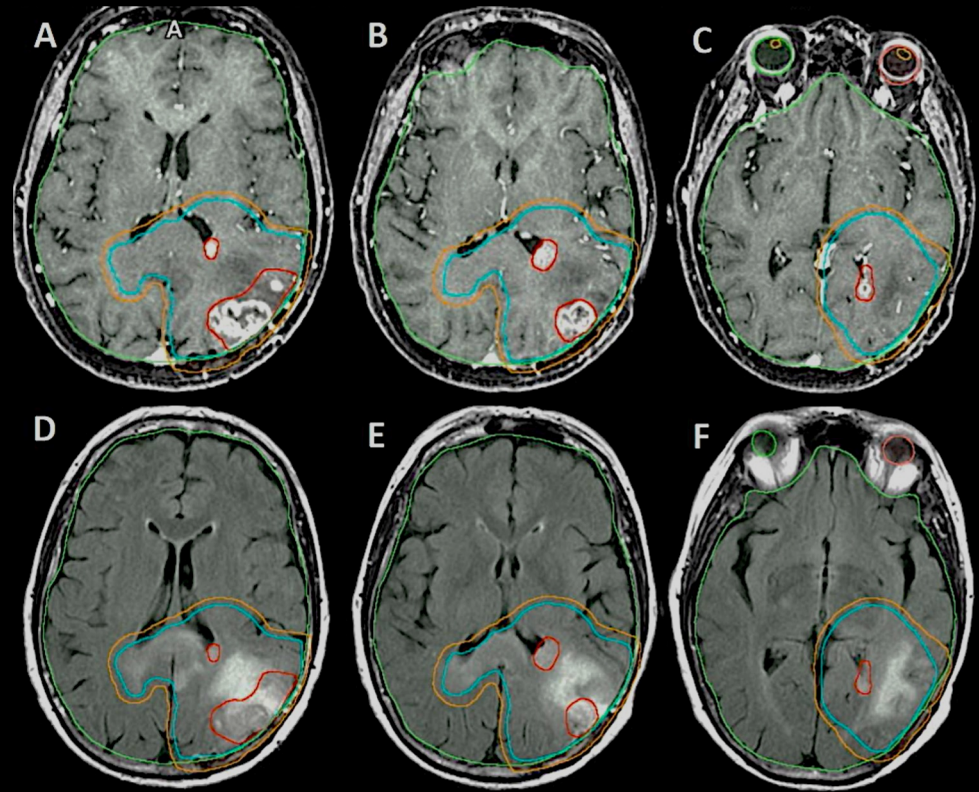
Distinguishing infiltrating non-enhancing tumour from oedema on T2/FLAIR can be challenging. The expert panel agreed that it is not necessary to include all T2/FLAIR signal abnormality where these are felt to represent oedema.



ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma

Changes that were felt to represent non-enhancing tumour they should be encompassed in the CTV.

However, based on currently available evidence, no consensus could be reached regarding the margin that should be added to the T2/FLAIR volume (0 – 15 mm).





Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original Article

ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma



Maximilian Niyazi ^{a,b,c,*}, Nicolaus Andratschke ^d, Martin Bendszus ^e, Anthony J Chalmers ^f, Sara C Erridge ^g, Norbert Galldiks ^{h,i,j}, Frank J Lagerwaard ^k, Pierina Navarria ^l, Per Munck af Rosenschöld ^m, Umberto Ricardi ⁿ, Martin J van den Bent ^o, Michael Weller ^p, Claus Belka ^{a,b,c}, Giuseppe Minniti ^{q,r}

^a Department of Radiation Oncology, University Hospital, LMU Munich; ^b German Cancer Consortium (DKTK), partner site Munich; ^c Bavarian Cancer Research Center (BZKF), Munich, Germany; ^d Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; ^e Department of Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany; ^f School of Cancer Sciences, University of Glasgow, Glasgow G61 1QH; ^g Edinburgh Centre for Neuro-Oncology, University of Edinburgh, Western General Hospital, Edinburgh EH4 1EU, UK; ^h Department of Neurology, Faculty of Medicine, University Hospital Cologne, University of Cologne, Cologne; ⁱ Institute of Neuroscience and Medicine (INM-3), Research Center Juelich, Juelich; ^j Center for Integrated Oncology (CIO), Universities of Aachen, Bonn, Cologne, and Duesseldorf, Germany; ^k Department of Radiation Oncology, Amsterdam UMC location Vrije Universiteit Amsterdam, the Netherlands; ^l Radiotherapy and Radiosurgery Department, IRCCS, Humanitas Research Hospital, Rozzano, MI, Italy; ^m Radiation Physics, Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, and Lund University, Lund, Sweden; ⁿ Department of Oncology, University of Turin, Turin, Italy; ^o Erasmus MC Cancer Institute, Rotterdam, the Netherlands; ^p Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland; ^q Dept. of Medicine, Surgery and Neuroscience, University of Siena, Siena; and ^r IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy

ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma

Maximilian Niyazi
 Nicolaus Andratschke
 Martin Bendszus
 Anthony J Chalmers
 Sara C Erridge
 Norbert Galldiks
 Frank J Lagerwaard
 Pierina Navarria
 Per Munck af Rosenschöld
 Umberto Ricardi
 Martin J van den Bent
 Michael Weller
 Claus Belka
 Giuseppe Minniti

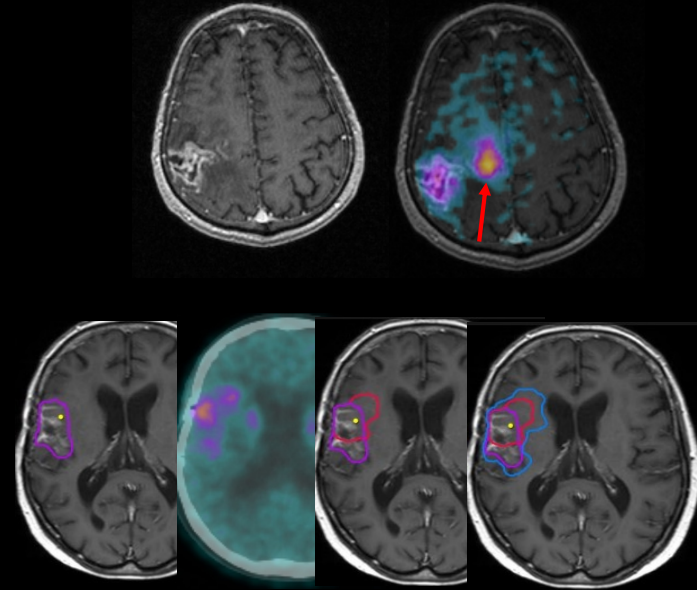
	Guideline 2016	Current guideline
GTV	Cavity + T1 CE	Cavity + T1 CE, optionally PET-based BTV or FLARI alteration clearly visualized as tumour
Role of PET	Lack of definite evidence	Amino acid PET a valuable tool for target delineation
CTV Margin	20 mm	15 mm
PTV margin	3-5 mm, audit own IGRT capabilities	At maximum 3 mm advised
Anatomical adaptations	falx/tentorium 5 mm	falx/tentorium 0 mm

The ESTRO-EANO guideline committee proposes the following pragmatic algorithm

- Immobilisation with a thermoplastic mask system; planning CT with 1–2 mm slice thickness
- Fusion with postoperative MRI (+/- novel MRI sequences) acquired within two weeks of the RT start date; postoperative MRI within 72 h after surgery can be used for assessment of extent of resection and preoperative MRI may help with interpretation of postoperative images and provide information on pre-operative tumour extent.
- GTV defined as T1 contrast-enhancing tumour (for biopsy only patients) and/or resection cavity plus residual contrast-enhancing tumour, if present
- A 15 mm margin around the GTV should be applied in three dimensions to generate the CTV, edited to take account of anatomical barriers to tumour spread
- Inclusion of T2 abnormalities (oedema) within CTV is not advised
- Non-enhancing areas may represent a component of glioblastoma, as defined in the new WHO brain tumour classification; in such cases, consideration should be given to including regions of high T2/FLAIR signal intensity within the GTV in addition to contrast enhancing tumour, and to adapting or decreasing GTV to CTV margins
- CTV to PTV margin is department-specific based on measured patient relocation accuracy and other unavoidable errors. It is determined by the accuracy of the fixation system and setup verification. In the absence of department values, 3 mm is advised and this can be reduced if regular, high precision IGRT techniques are employed.
- The standard dose in good performance adult patients is 60 Gy in 2 Gy fractions; for elderly patients a hypofractionated schedule should be regarded as current standard (using the same CTV/PTV definitions).

What's next?

- ✓ Is it possible further CTV margin reduction?
- ✓ Use of positron emission tomography (PET) with aminoacid tracers and advanced physiology-based MRI techniques, such as MR spectroscopy, diffusion MRI and perfusion MRI, for target delineation with the aim of providing additional metabolic and structural information integrating the information of conventional MRI.
- ✓ Special situations: target delineation for molecular IDH-wt gliomas, hypofractionated schedules, reirradiation



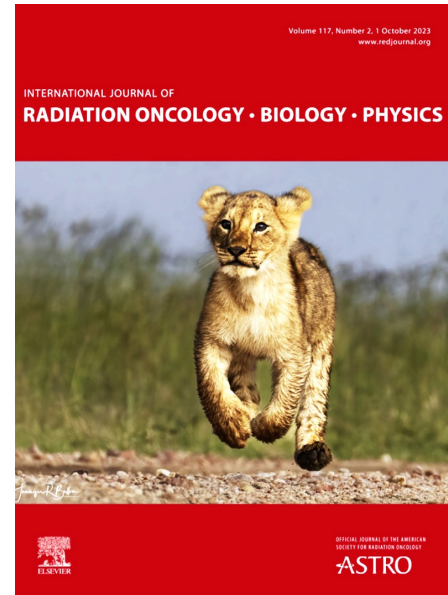
Treatment Planning Expansions in Glioblastoma: How Less Can Be More

Daniel M. Trifiletti, MD,* Michael T. Milano, MD, PhD,† Kristin J. Redmond, MD, MPH,‡ Erqi L. Pollom, MD,§
Jona A. Hattangadi-Gluth, MD,|| and Michelle M. Kim, MD¶

Minniti G, Tini P, Giraffa M, et al. Feasibility of clinical target volume reduction for glioblastoma treated with standard chemoradiation based on patterns of failure analysis. *Radiother Oncol.* 2022;181:109435.¹²

Laack NN, Pafundi D, Anderson SK, et al. Initial results of a phase 2 trial of ¹⁸F-DOPA PET-guided dose-escalated radiation therapy for glioblastoma. *Int J Radiat Oncol Biol Phys.* 2021;110:1383-1395.¹³

Mendoza MG, Azoulay M, Chang SD, et al. Patterns of progression in patients with newly diagnosed glioblastoma treated with 5-mm margins in a phase 1/2 trial of 5-fraction stereotactic radiosurgery with concurrent and adjuvant temozolomide [e-pub ahead of print]. *Pract Radiat Oncol.* doi:10.1016/j.prro.2023.01.008, accessed August 3, 2023.¹⁴

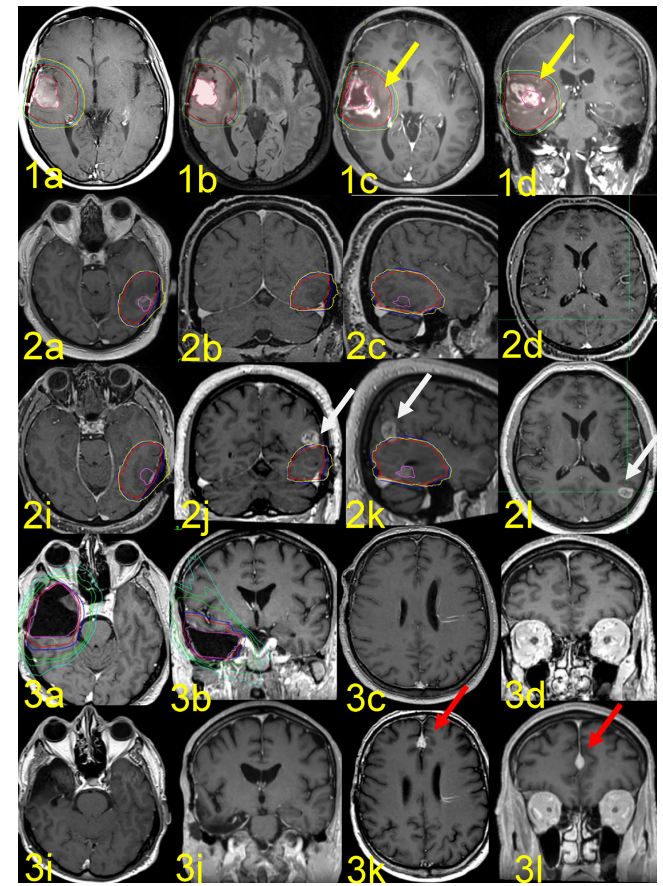


Feasibility of clinical target volume reduction for glioblastoma treated with standard chemoradiation based on patterns of failure analysis

Giuseppe Minniti ^{a,b,*}, Paolo Tini ^a, Martina Giraffa ^c, Luca Capone ^c, Giorgio Raza ^c, Ivana Russo ^d, Elisa Cinelli ^a, PierCarlo Gentile ^c, Alessandro Bozzao ^e, Sergio Paolini ^b, Vincenzo Esposito ^b

Analysis of tumor recurrences

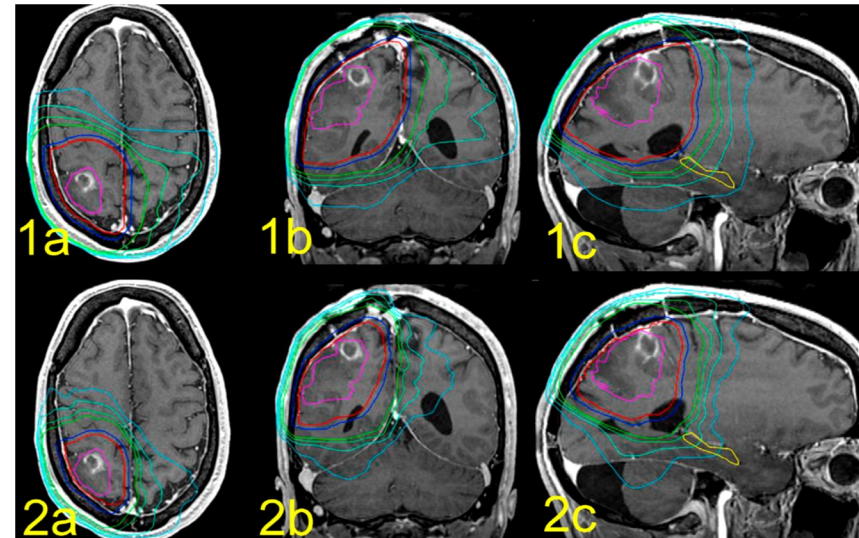
Pattern of recurrence	Original plans	Theoretical plans	P
	2-cm GTV-to-CTV margin	1-cm GTV-to-CTV margin	
In-field	180	177	0.29
Marginal	5	3	0.24
Distant	22	27	0.09



Radiotherapy and Oncology 181 (2023) 109435

There is a significant difference between standard-CTV and reduced-CTV plans in CTV volume and radiation dose to normal brain

Parameter	Original plans	Theoretical plans	p
	2-cm GTV-to-CTV margin	1-cm GTV-to-CTV margin	
CTV			< 0.0001
mean volume (SD)	248.3 (101.9)	150.7 (88.8)	
median volume	234.6	136.5	
range	56.2–449.1	43.4–336.9	
V50Gy			< 0.0001
mean (SD)	332.3 (63.0)	192.4 (40.6)	
median	307.6	178.7	
range	154.0–399.0	92.9–282.8	
V40Gy			< 0.0001
mean (SD)	454.0 (98.9)	276.8 (69.4)	
median	428.3	254.8	
range	204.9–552.0	122.5–266.0	
V30Gy			< 0.0001
mean (SD)	609.6 (142.1)	379.4 (111.2)	
median	570.5	362.7	
range	238.5–808.5	158.8–604.3	
V20Gy			< 0.0001
mean (SD)	889.4 (217.8)	548.1 (168.2)	
median	845.5	511.9	
range	297.4–988.0	205.4–897.5	



18F-DOPA PET-Guided Dose-Escalated RT for GBM

Initial Results of a Phase 2 Trial

target volumes.

Upper panel:

yellow = MTV51;

fuchsia = MTV76.

Lower panel:

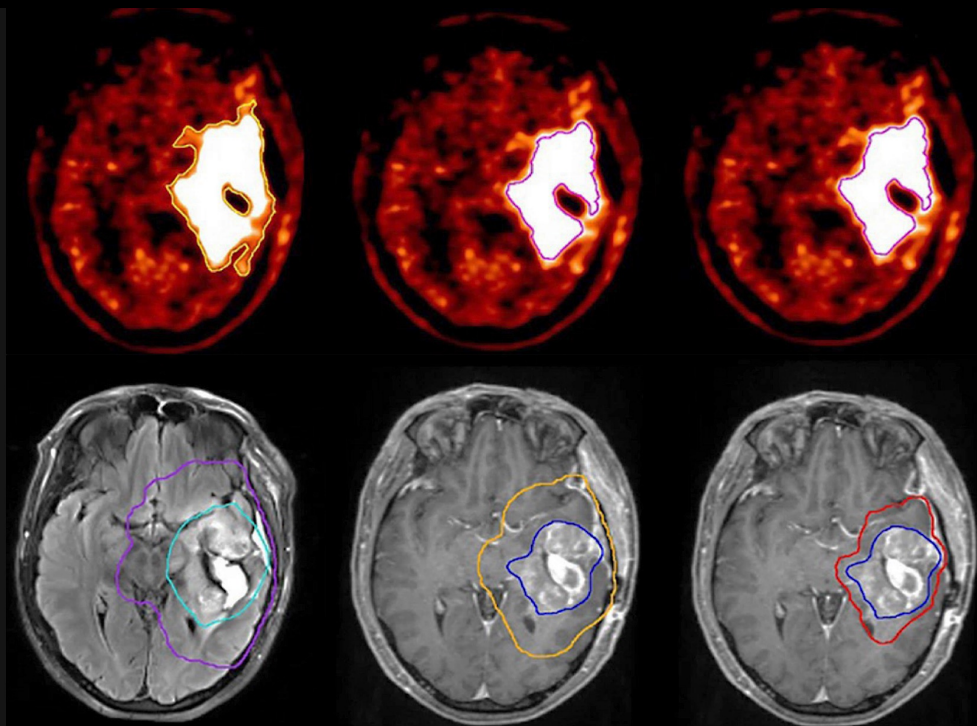
teal = GTV51_MR;

purple = PTV51;

blue = GTVMR_60;

yellow = PTV60;

red = PTV76.



Summary

More accurate and precise target delineation guidelines for glioblastoma would help to promote standardisation and uniformity of treatments;

Reduced dose to normal brain and OARs (e.g. hippocampi) with new target delineation strategies will help to reduce the incidence of ARE and improve quality of life;

Future research priorities include the use of positron emission tomography (PET) with aminoacid tracers and advanced physiology-based MRI techniques, such as MR spectroscopy, diffusion MRI and perfusion MRI to integrate conventional MRI. New approaches require validation in prospective trials before being adopted into clinical practice.



SAPIENZA
UNIVERSITÀ DI ROMA

UPMC
LIFE CHANGING
MEDICINE

NEUROIMED
LIFE CHANGING
MEDICINE

Thank you for your attention



***A special thank to our patients and their families,
and staff supporting clinical work and research
at University of Rome Sapienza, IRCCS Neuromed,
and UPMC Hillman Cancer Center San Pietro FBF, Rome, Italy***

