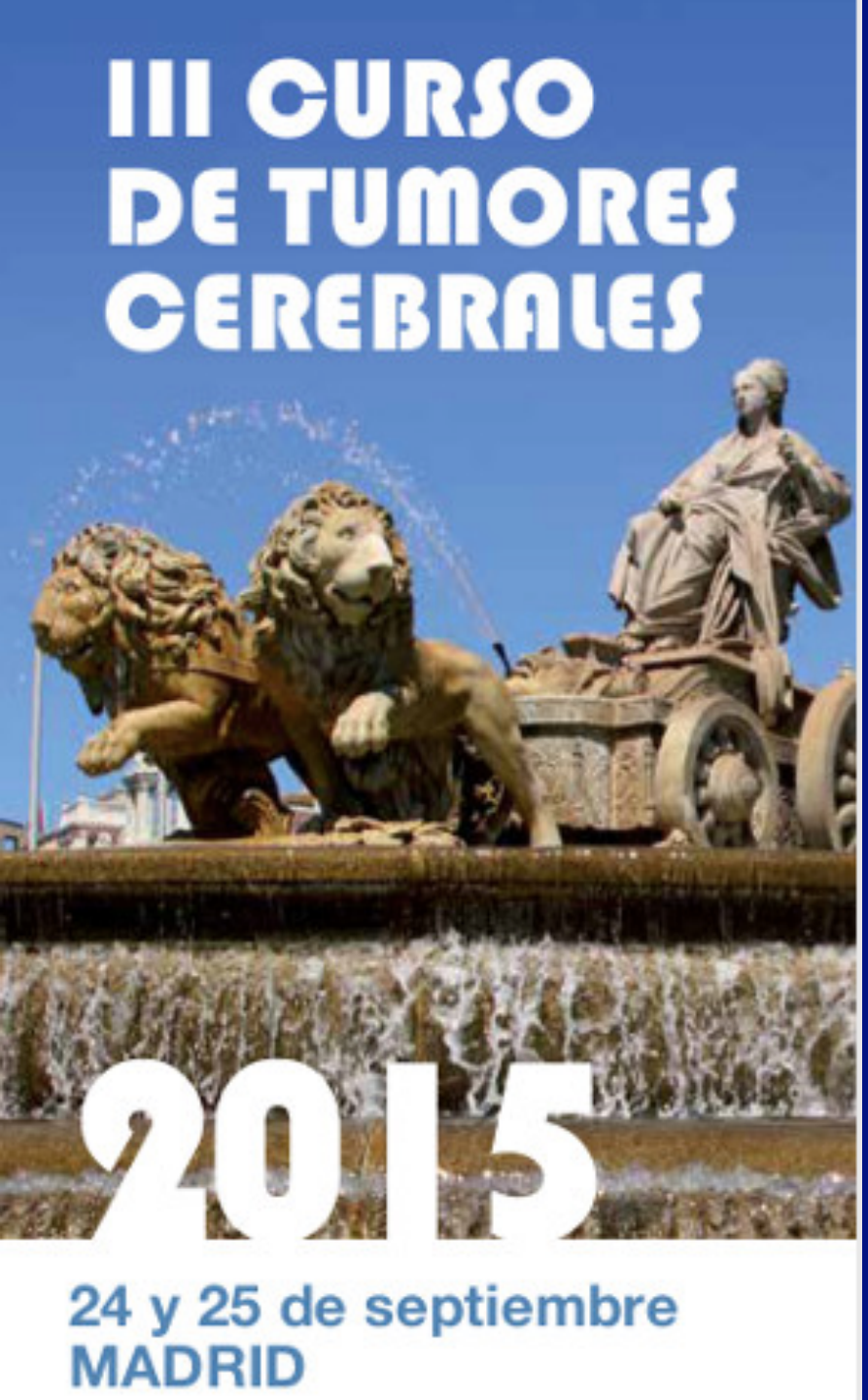
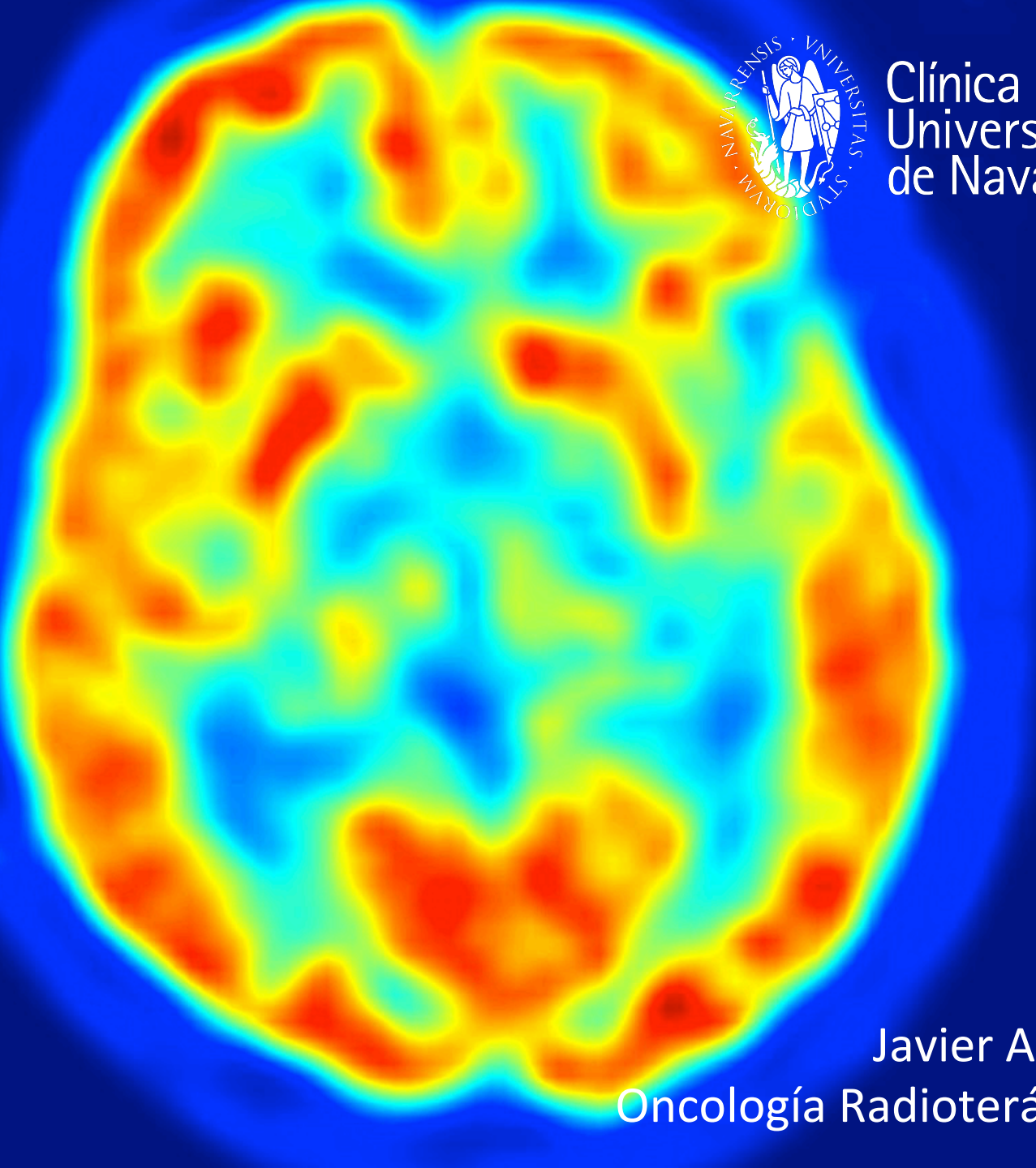


PET como herramienta de planificación en gliomas



Clínica Universidad de Navarra

Javier Aristu
Oncología Radioterápica

40 años de tratamiento del GAG

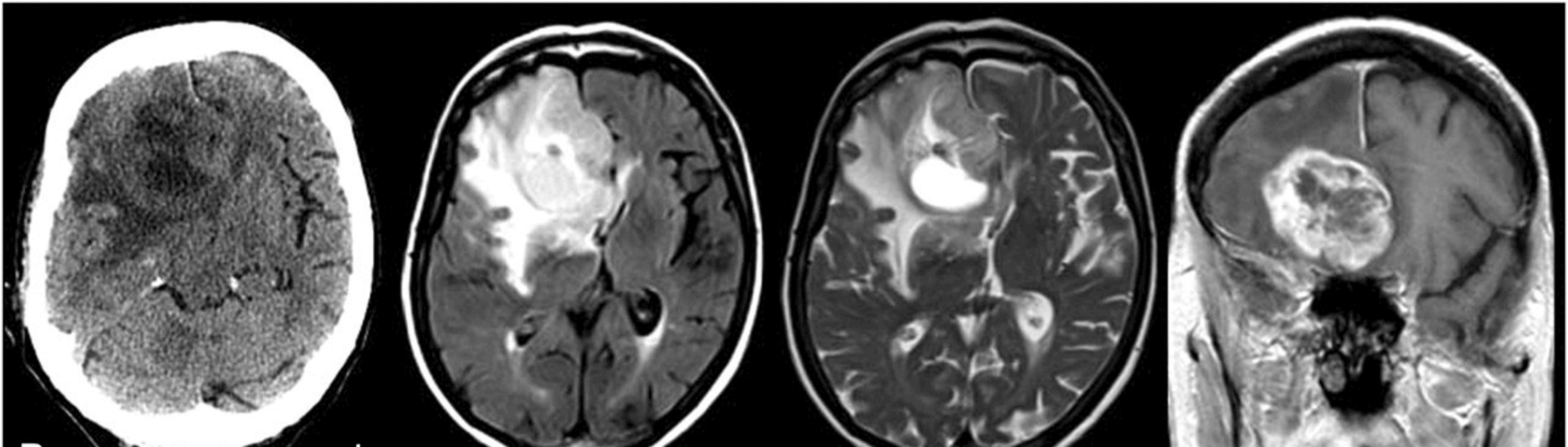
	RTOG/ECOG (1978-1990)*				EORTC 26981 (2005, 2009)**	
	Cirugía	50 Gy	55 Gy	60 Gy	60 Gy	60 Gy + TMZ
Median OS (m)	**3.5**	**6.5**	**8.5**	**10**	**12.1**	**14.6**
	Cirugía	+RT				+QT

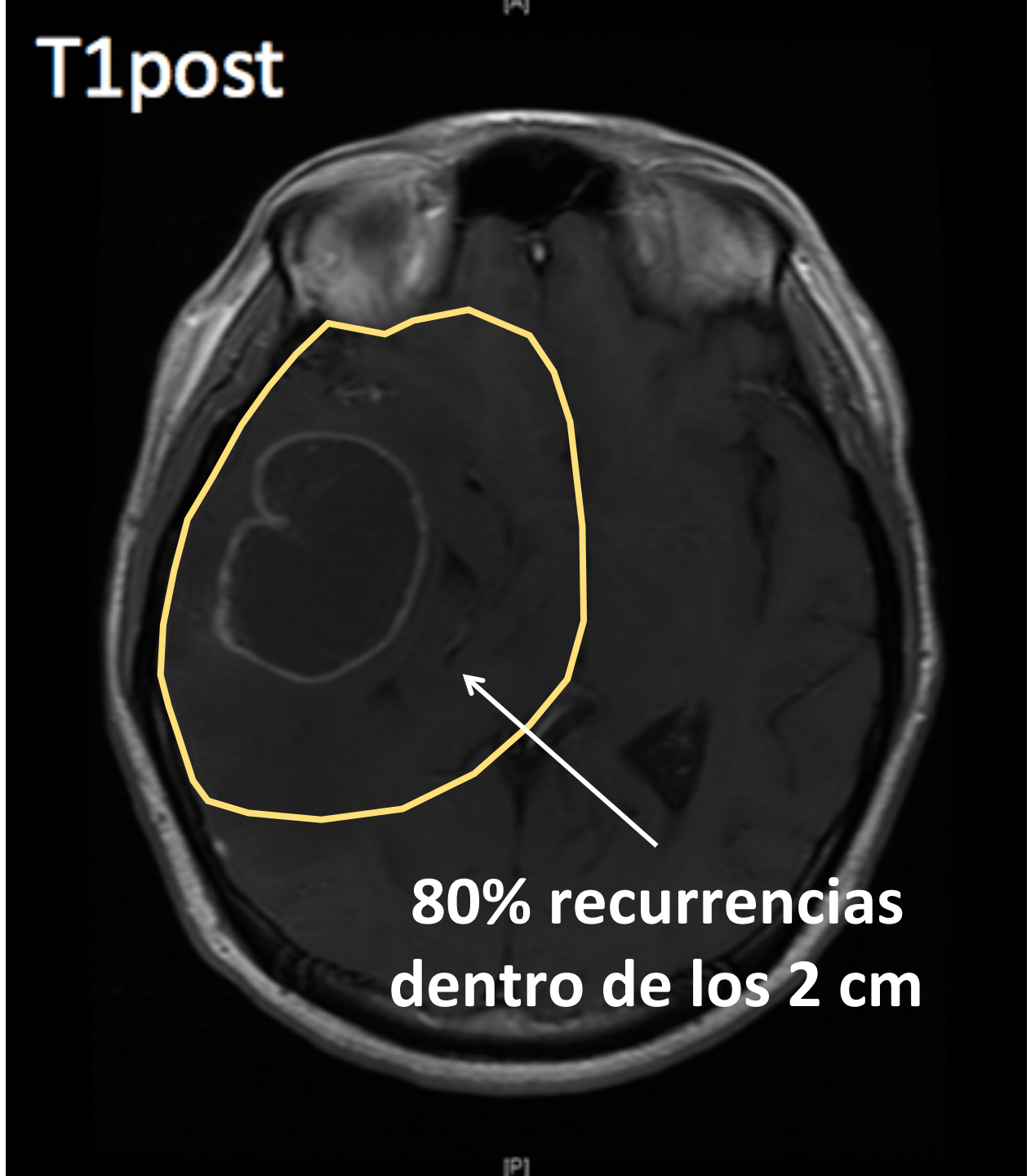
*Walker, 1978, 1979, Leibel & Sheline 1990
** Stupp NEJM 2005, Lancet 2009

¿Volumen holocraneal vs volumen parcial?

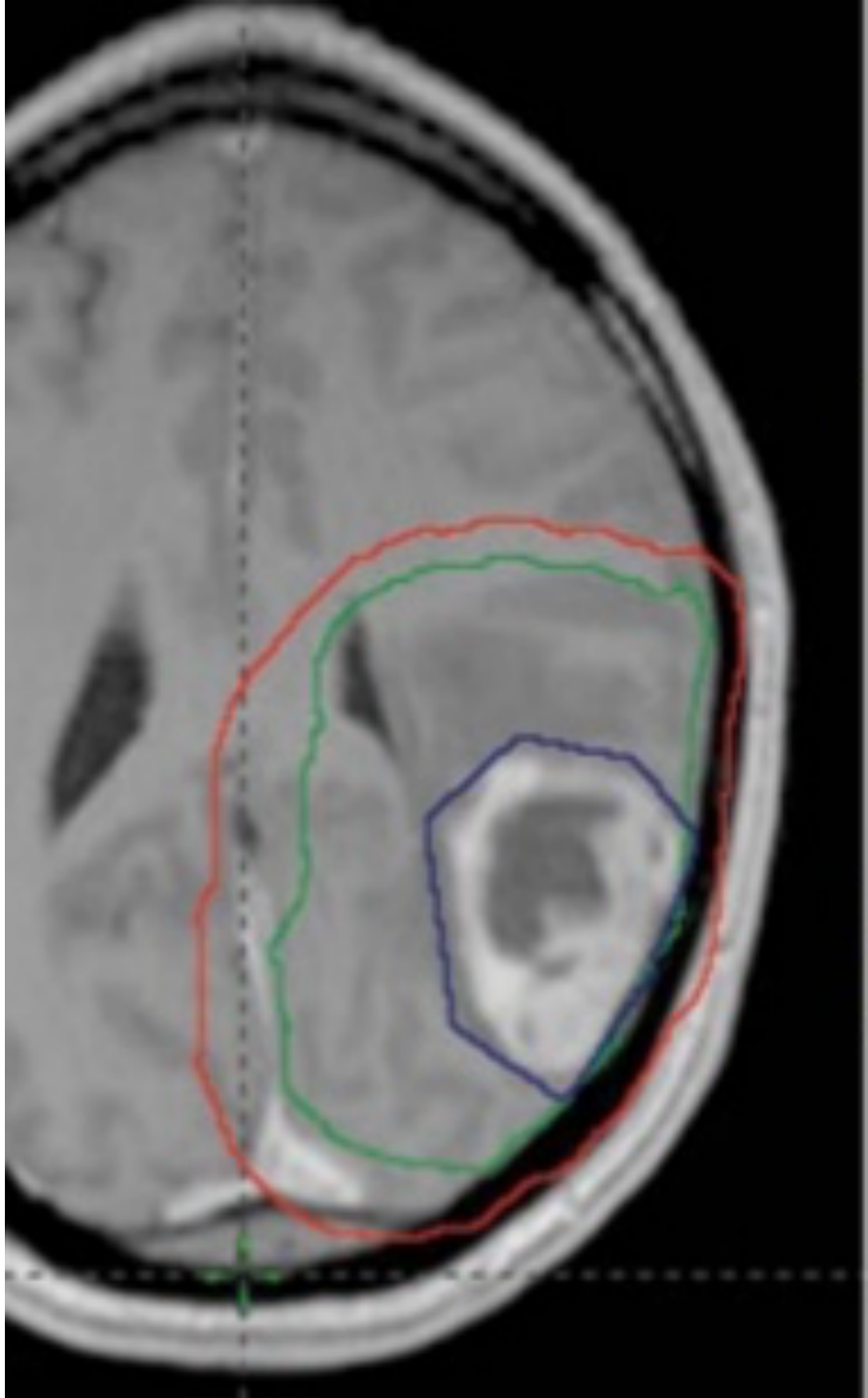
Volumen parcial

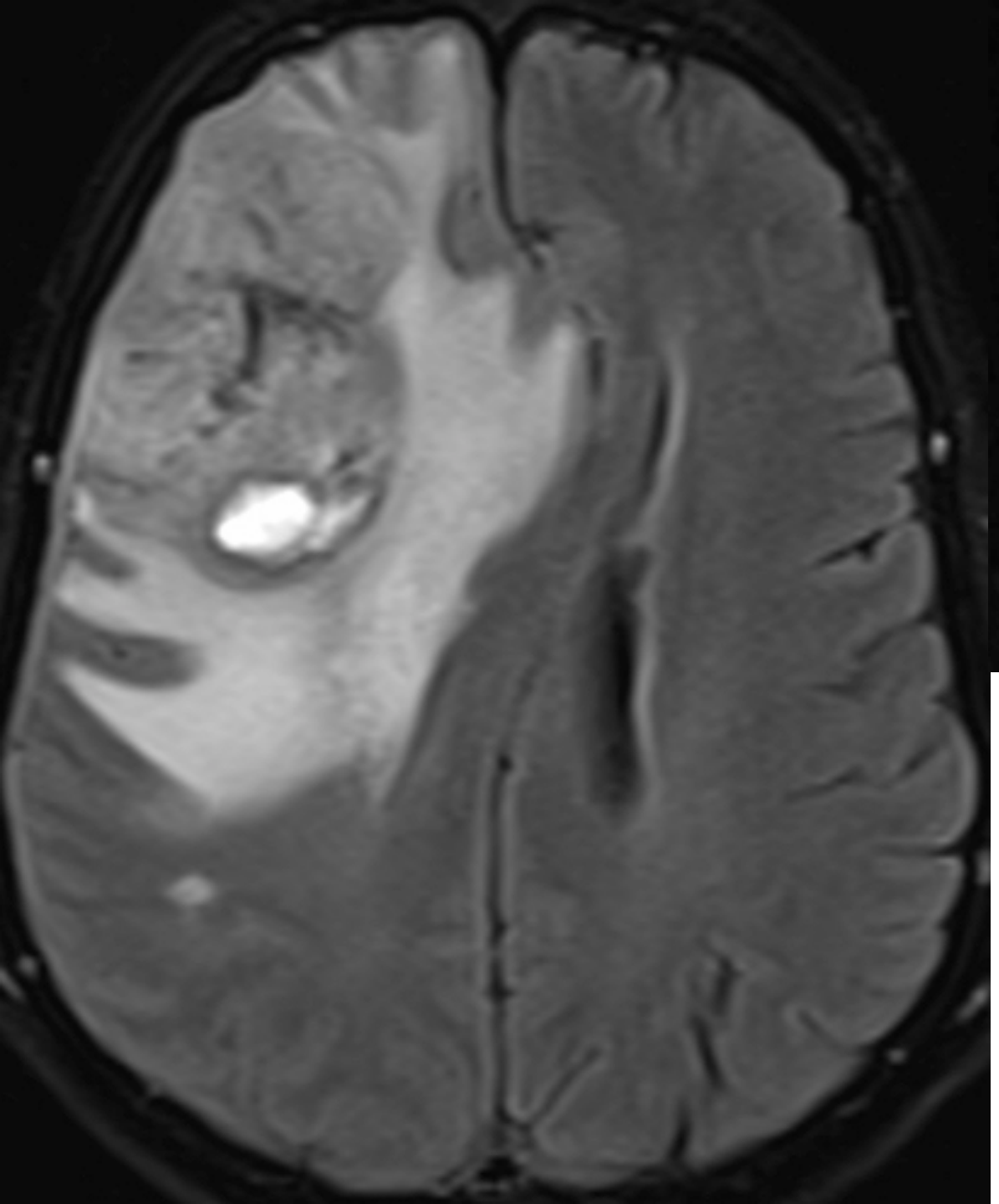
¿Qué volumen parcial cerebral?

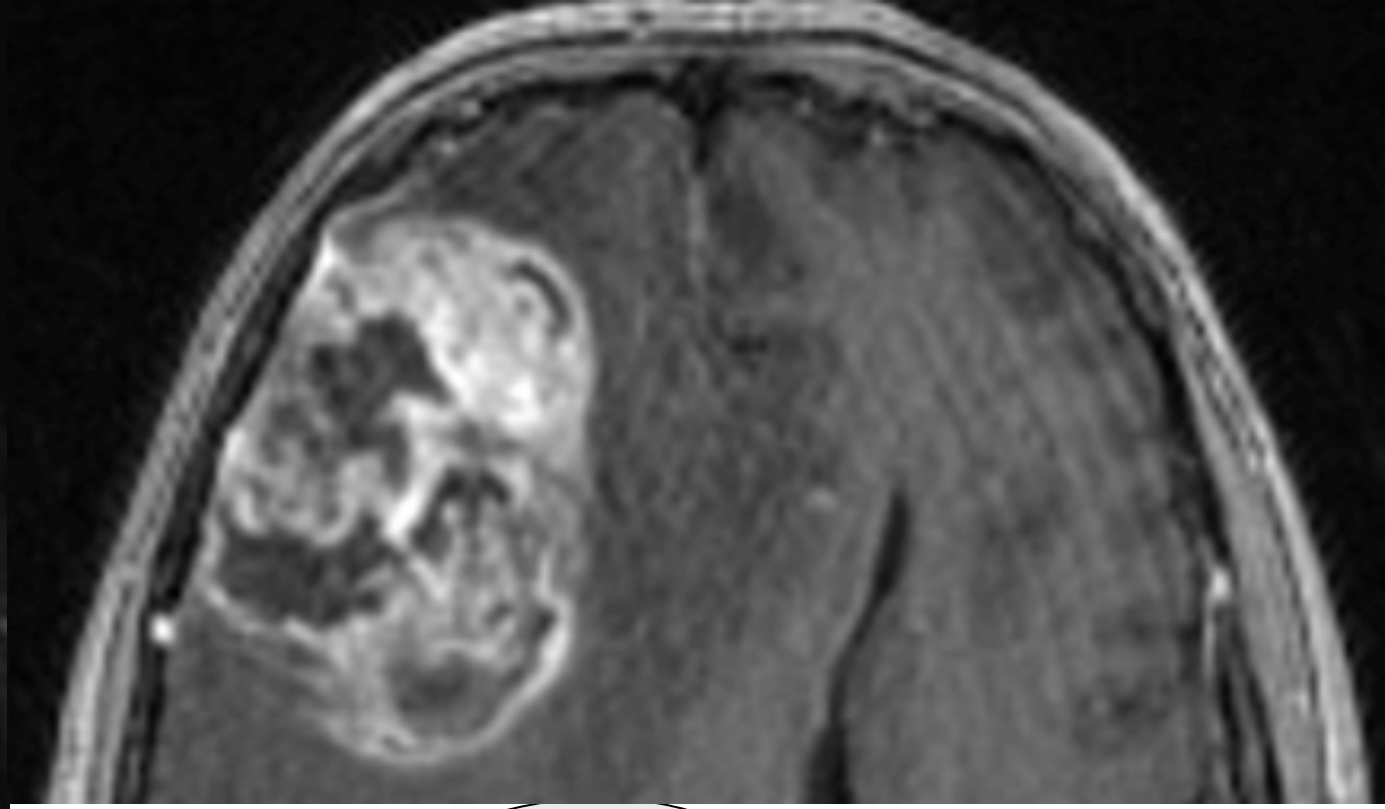


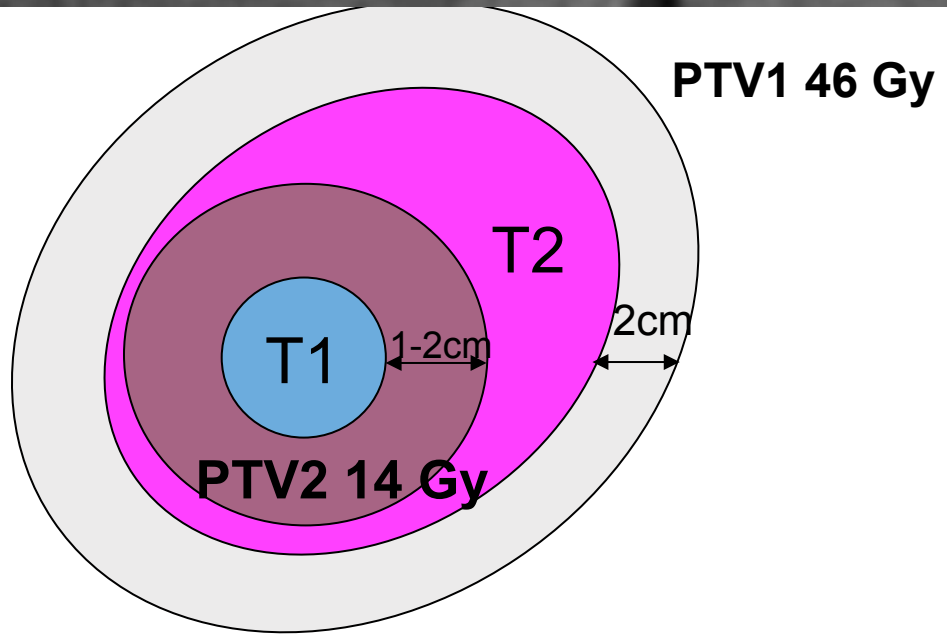

T1post
80% recurrencias
dentro de los 2 cm

RT Dose	Vol. Definition	Source of data
46 Gy	GTV1: T2 FLAIR CTV1: T2 + 2-2.5cm **PTV1: CTV1+0.3-0.5cm**	**RTOG**
14 Gy	GTV2: T1 CTV2: T1 + 2cm **PTV2: CTV2 + 0.3-0.5cm**	
60 Gy	GTV: T1 CTV: T1 + 2-3 cm **PTV: CTV + 0.5cm**	**EORTC**
50 Gy	GTV1: T2 FLAIR PTV1: T2 + 2 cm	**NCCTG**
10 Gy	GTV2: T1 PTV2T1 + 2 cm	
46 Gy	GTV1: T2 FLAIR CTV1: T2 + 1cm **PTV1: CTV1+0.5cm**	**Adult Brain Tumor Consortium (ABTC)**
14 Gy	GTV2: T1 CTV2: T1 + 1cm **PTV2: CTV2 + 0.5cm**	








PTV1 46 Gy
T2
2cm
T1
1-2cm
PTV2 14 Gy

Adult Brain Tumor Consortium guidelines (ABTC)

Table 1 ABTC guidelines for target definition

Target volume	Definition
GTV1	T1 enhancing and non-enhancing tumor volume (T2 or FLAIR)
GTV2	T1 enhancing tumor volume
CTV1;2	GTV plus a margin of 5 mm
PTV1;2	CTV plus a margin of 3–5 mm

Note: GTV volume is based on postoperative day 0–1 MRI. GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, planning target volume; ABTC, Adult Brain Tumors Consortium.

In-field: >80% of the T1-enhancing tumor volume was covered by the 95% isodose line
Marginal: >20 but ≤80% of the tumor volume was within the 95% isodose line
Distant: <20% of the tumor volume was located within the 95% isodose line

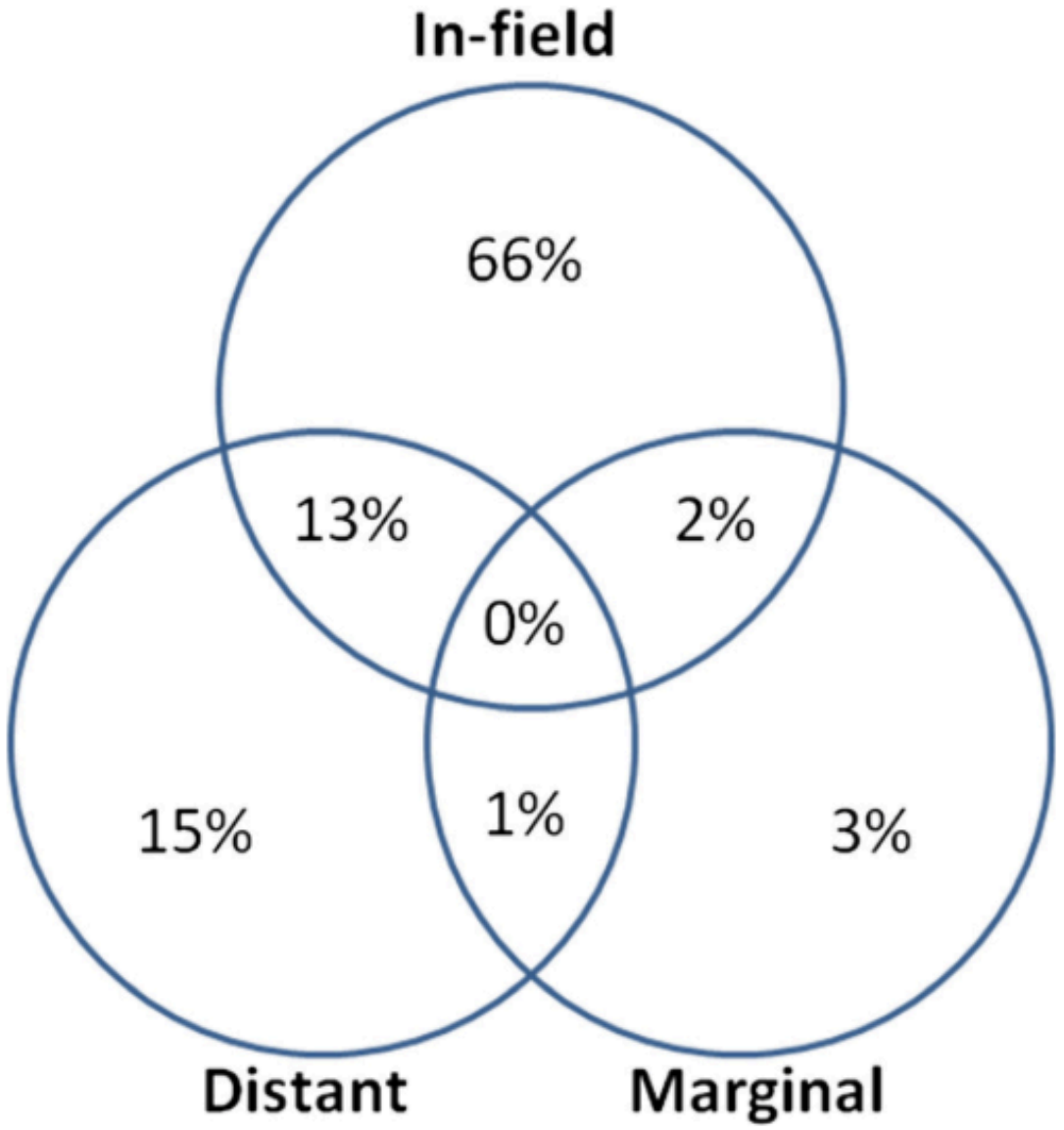


Figure 1 Patterns of Failure.

Gebhardt BJ. Radiat Oncol 2014

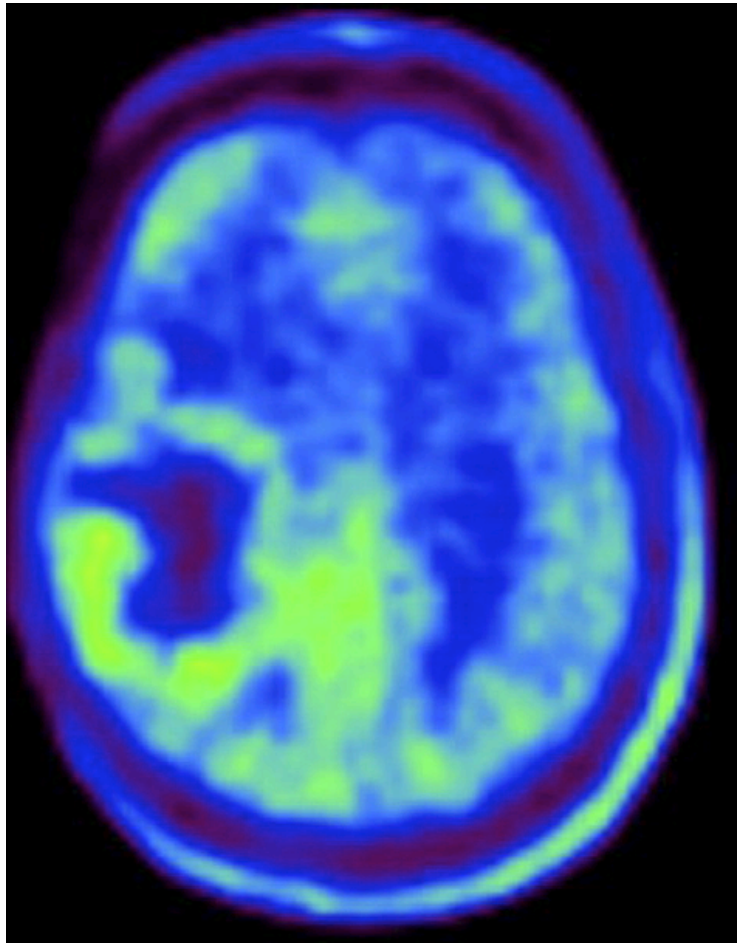
RT: 80-90% de las recurrencias son dentro de las dosis altas de RT (60 Gy) **independientemente de los márgenes**

¿Dosis de RT insuficientes?

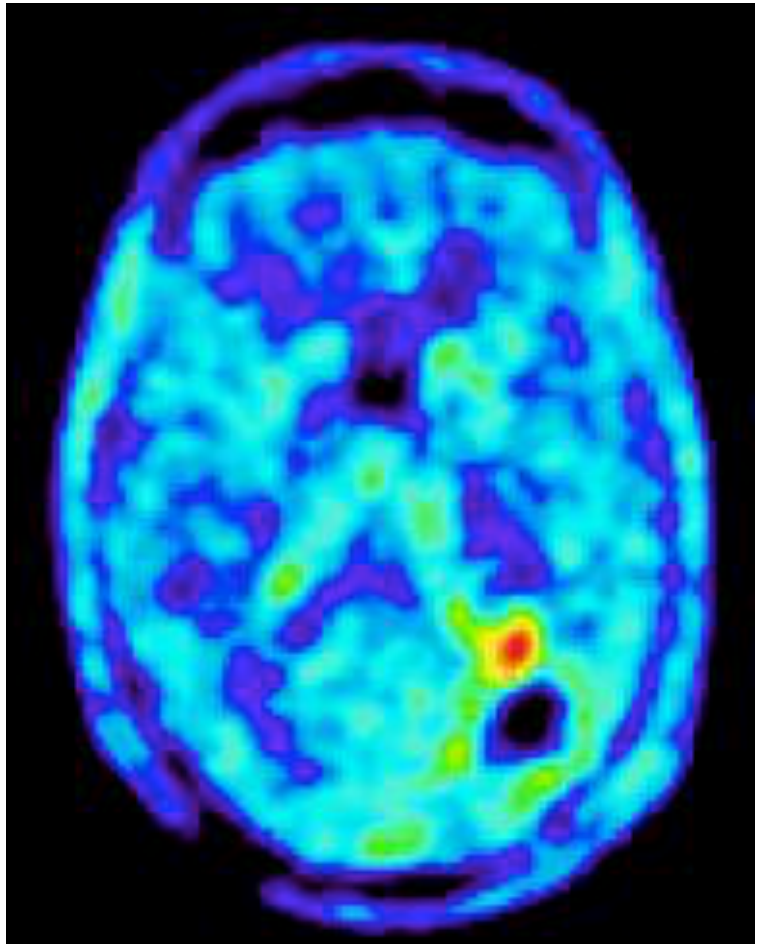
RT/TMZ: Pacientes con MGMT-met tienen más recurrencias marginales y distales

¿Delimitación de los volúmenes target?

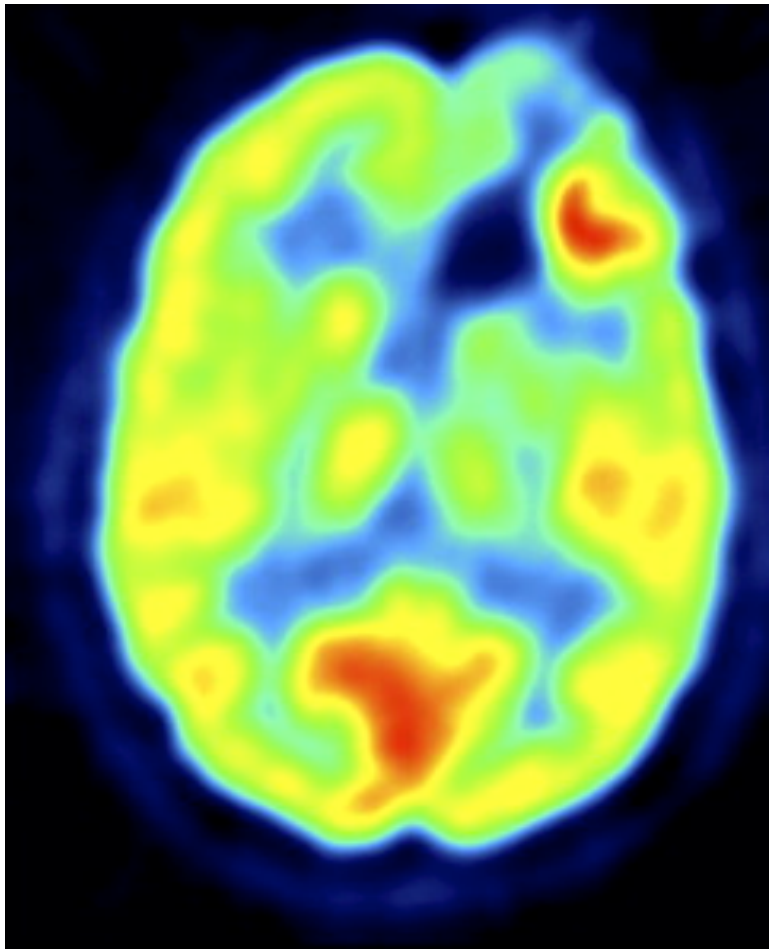
11C-methionine (MET)



18F-fluoroethyl-L-tyrosine (FET)



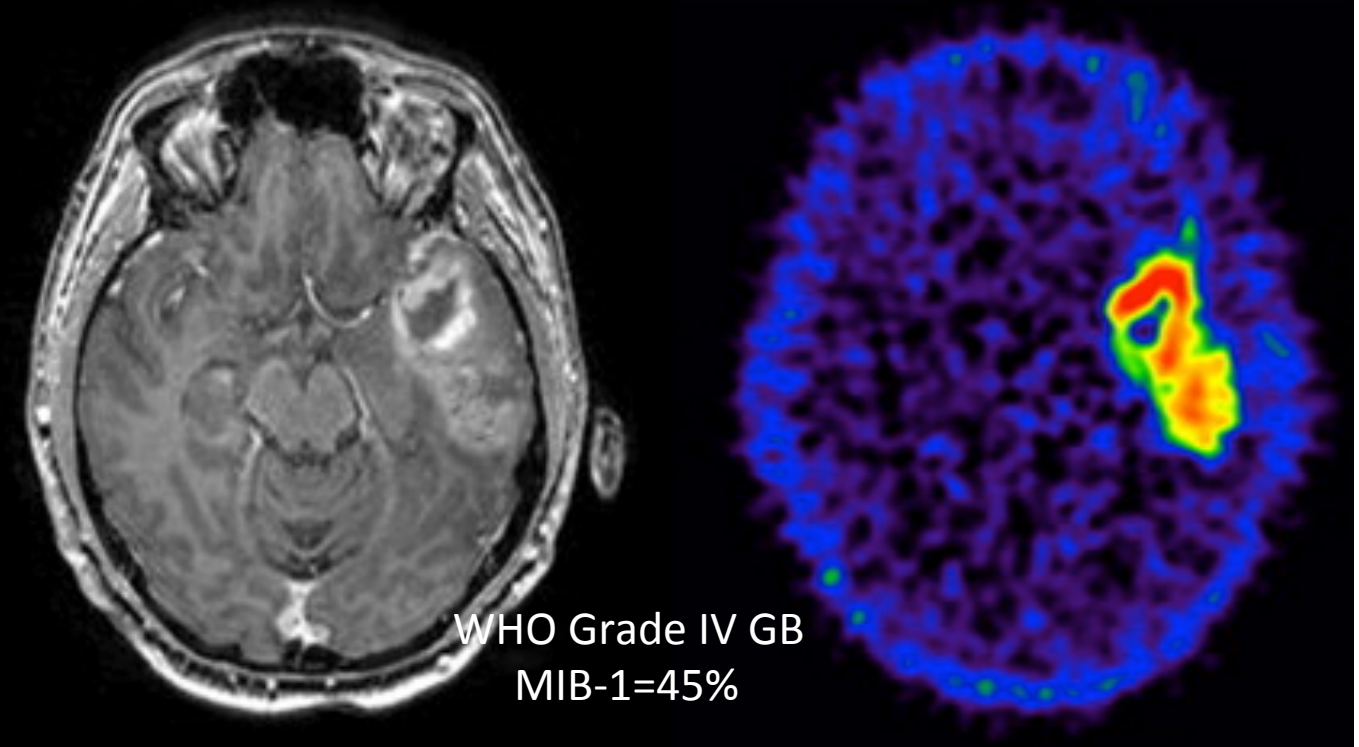
18F-fluorodeoxyglucose (FDG)

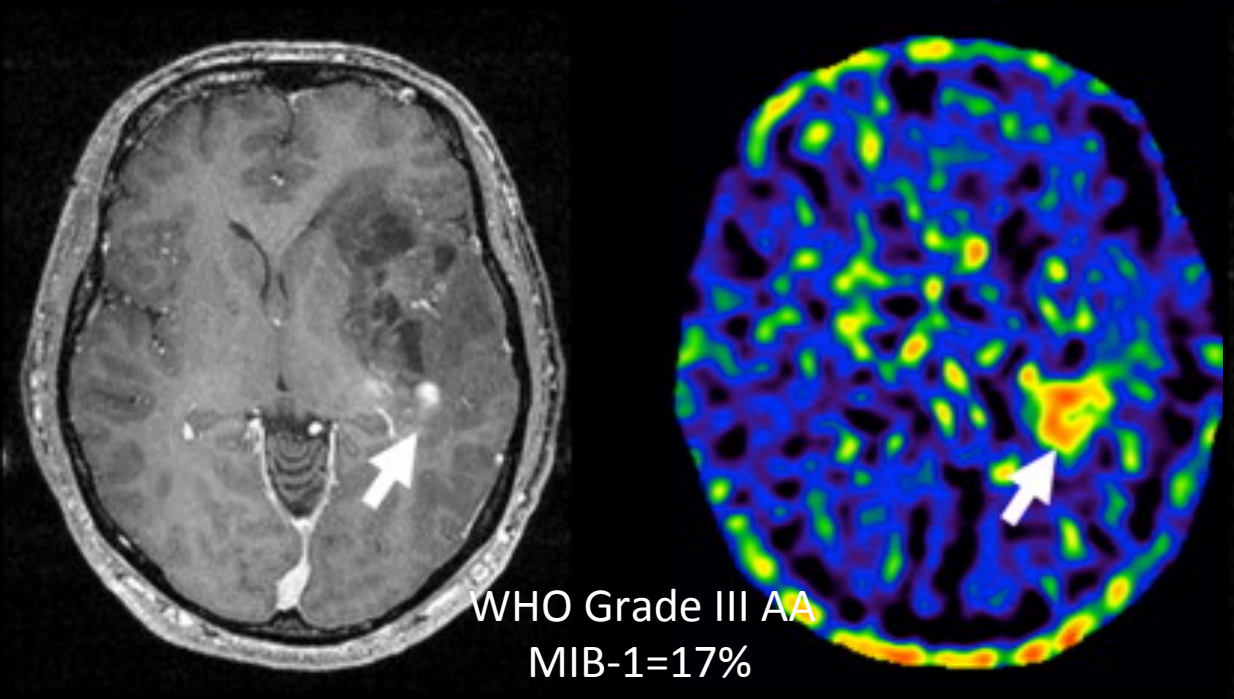


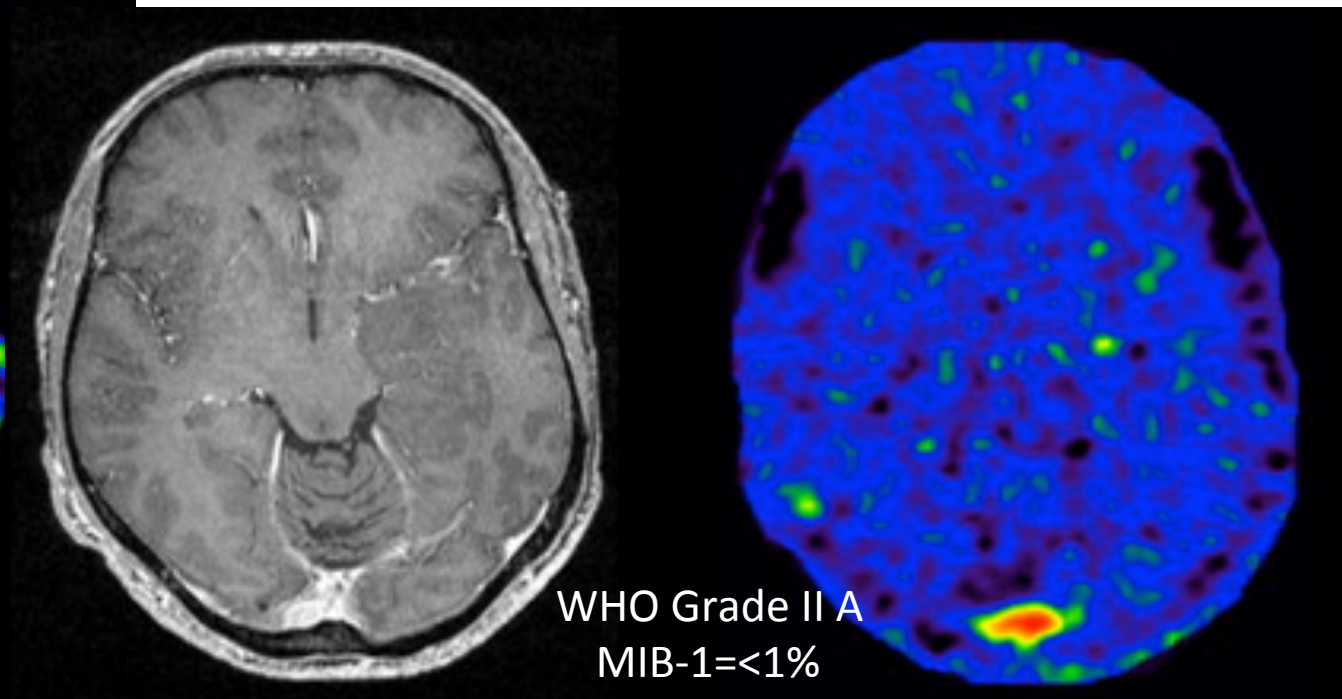
18F-fluorothymidine (FLT)

- Actively taken up into dividing cells (It is associated well with tissue markers of proliferation)
- Excellent contrast-to-background ratio
- However, FLT could underestimate the extent of the tumors in half of the cases studies (biopsy)

Price SJ. Clinical Radiology 2009







RT planning for malignant glioma after surgical resection

39 patientes / T1 vs T2 vs MET-PET

Tumor volume

MET vs T1-MR **19 cc** vs **11 cc**

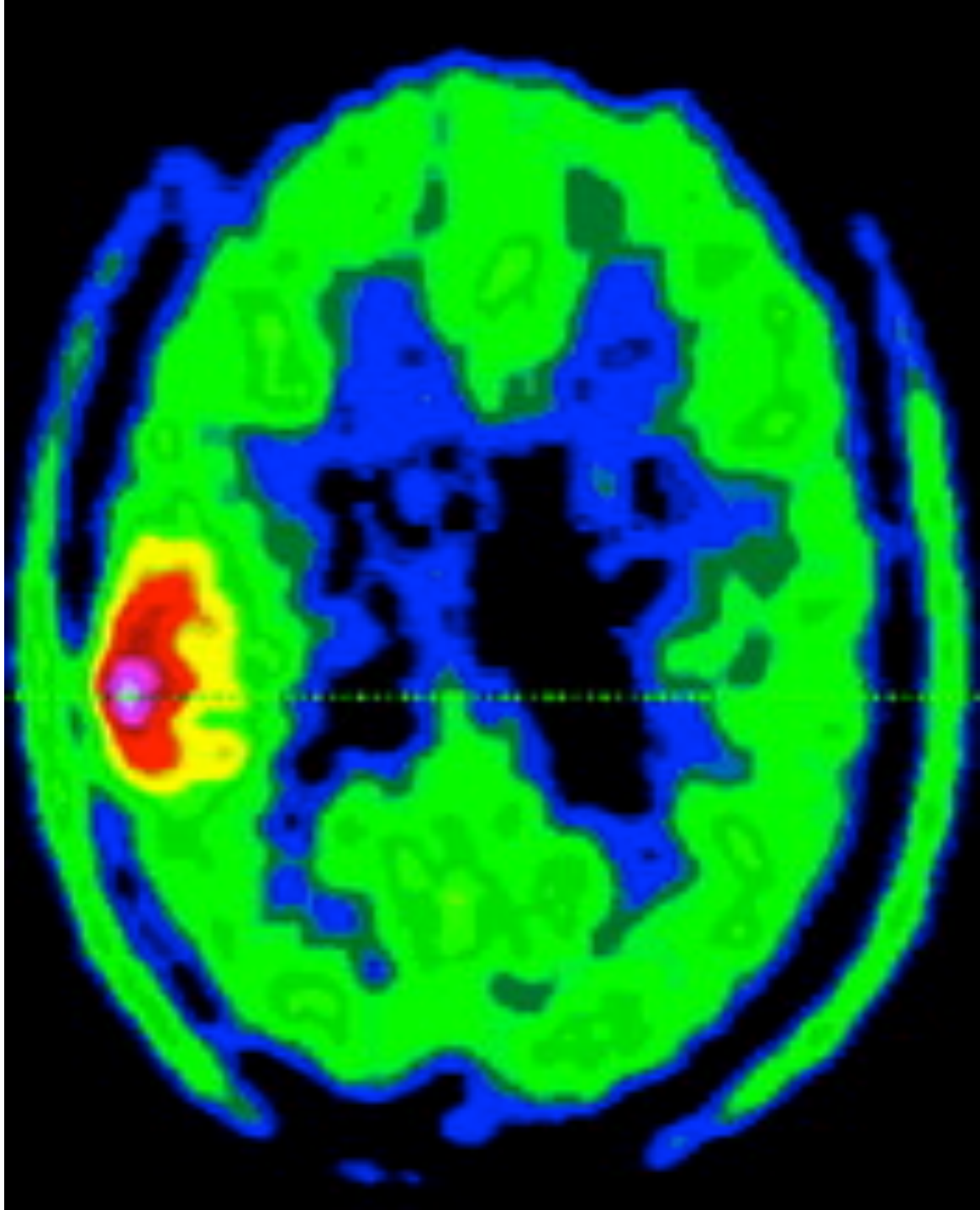
MET vs T2-MR **23 cc** vs **42 cc**

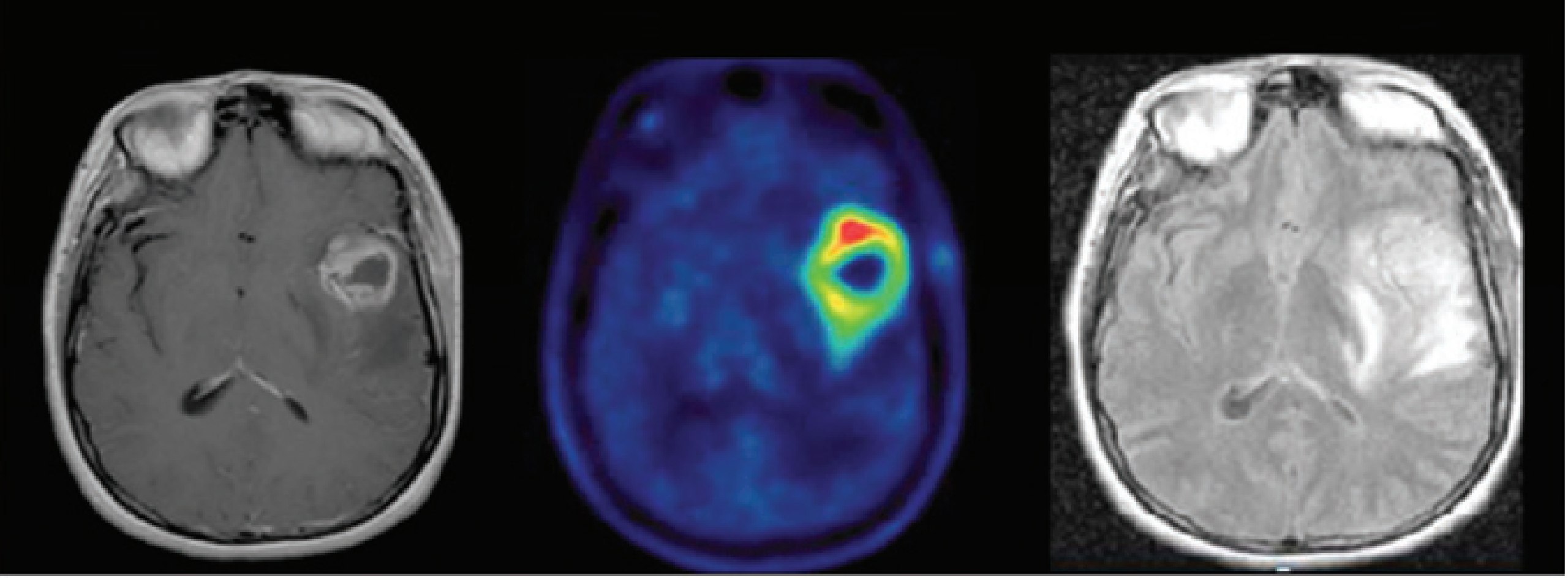
Areas of MET uptake extend beyond T2 in most cases

High MET uptake was visible **0.8 to 3 cm** beyond the T1 contrast enhancement in **69%** of cases

Grosu AL et al. Inl J Radiat Oncol Biol Phys 2005

Tsien CI. Clin Cancer Res 2012



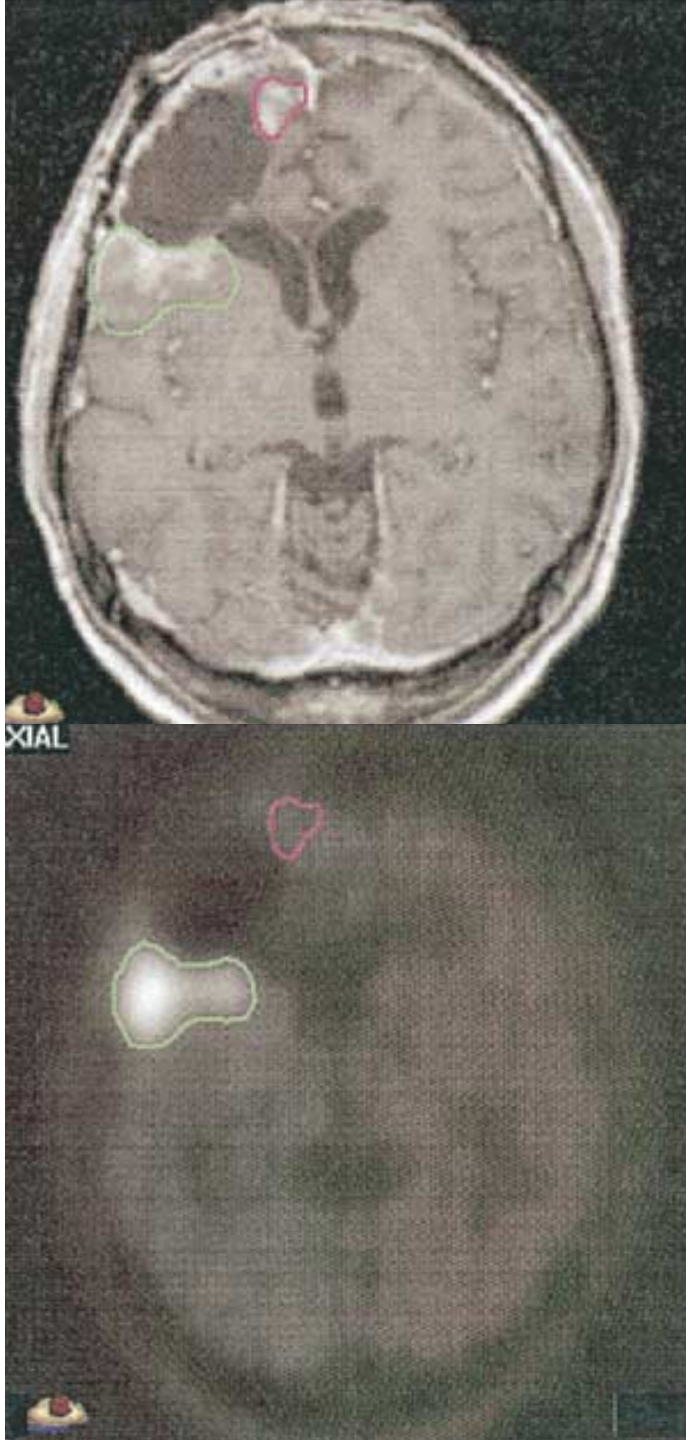


MR T1 Post-Gd | **^{11}C MET-PET** | **MR FLAIR**

^{11}C MET-PET (middle) clearly shows areas of increased metabolic uptake extending beyond the contrast-enhancing lesion on MRI (left) but not beyond MR FLAIR (right). MR FLAIR volume also includes surrounding peritumoral edema

MET exhibits a **very short half-life**

Tsien CI. Clin Cancer Res 2012

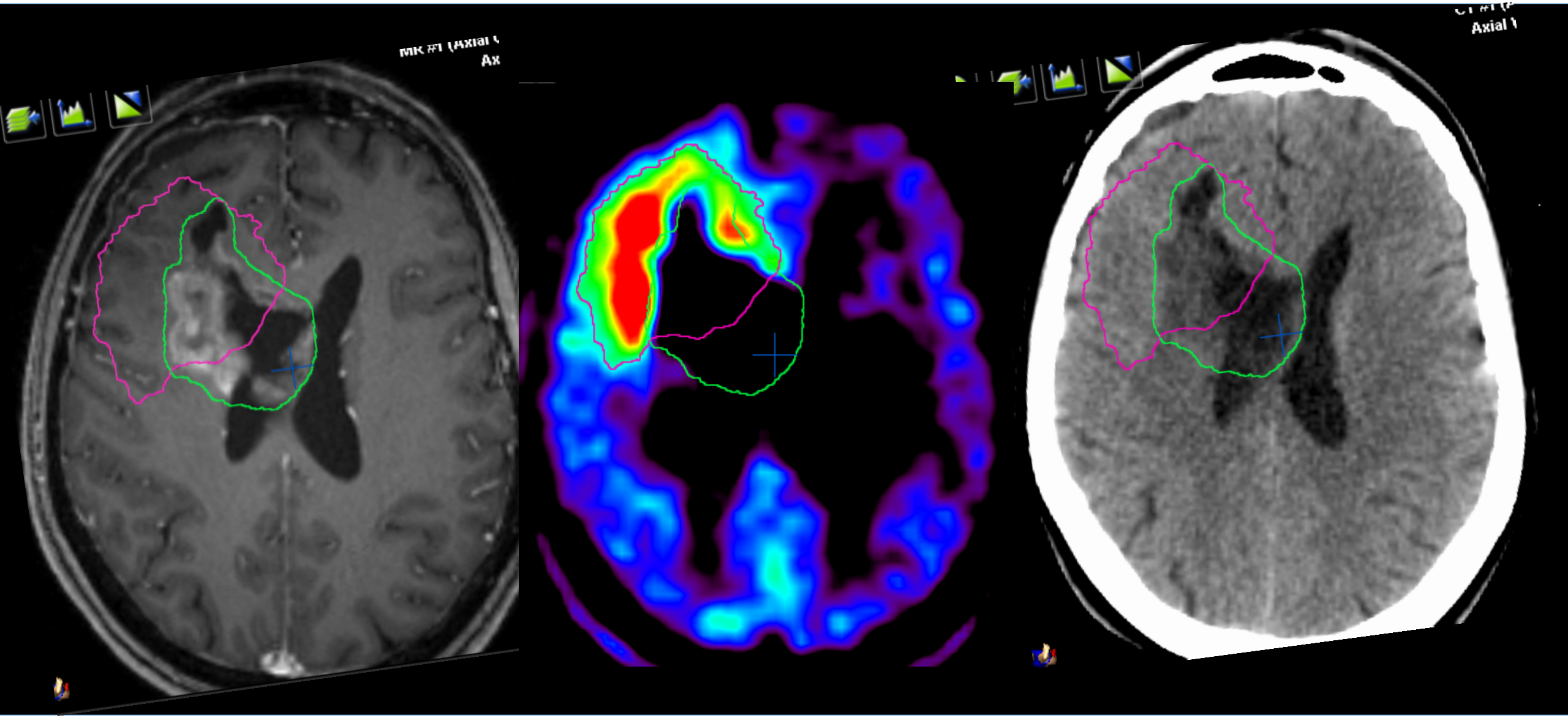


RT planning for malignant glioma after surgical resection

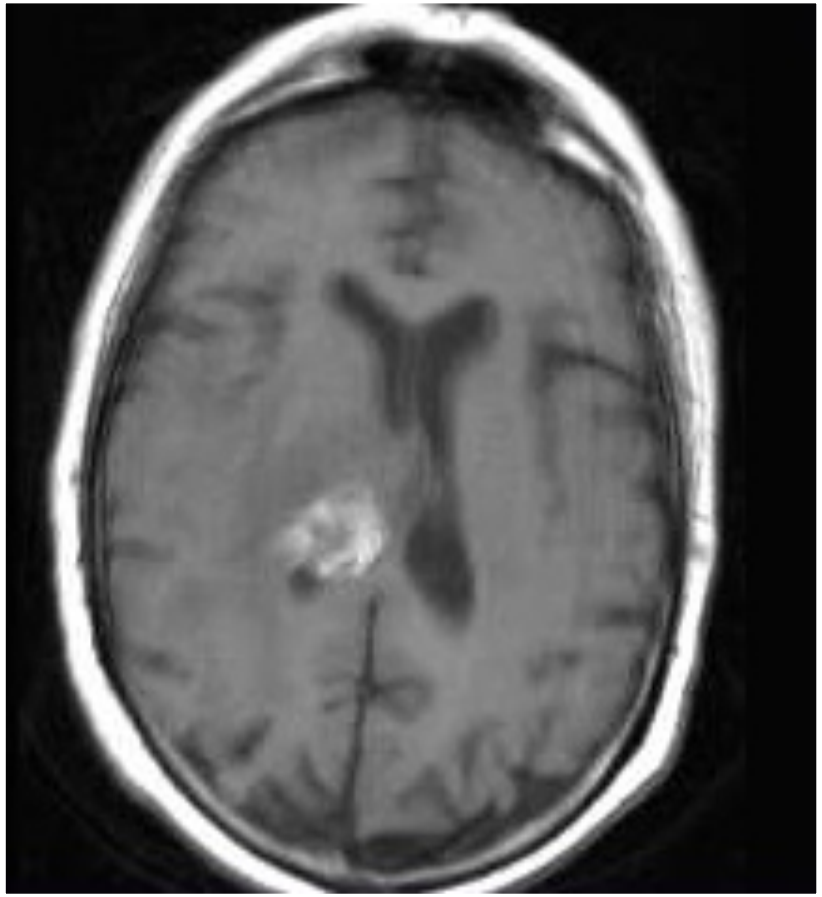
The **size and location** of residual MET uptake **differs considerably** from abnormalities found on postoperative MRI. Because postoperative changes cannot be differentiated from residual tumor by MRI, MET-PET, with a greater specificity for tumor tissue, **can help to outline the gross tumor volume** with greater accuracy

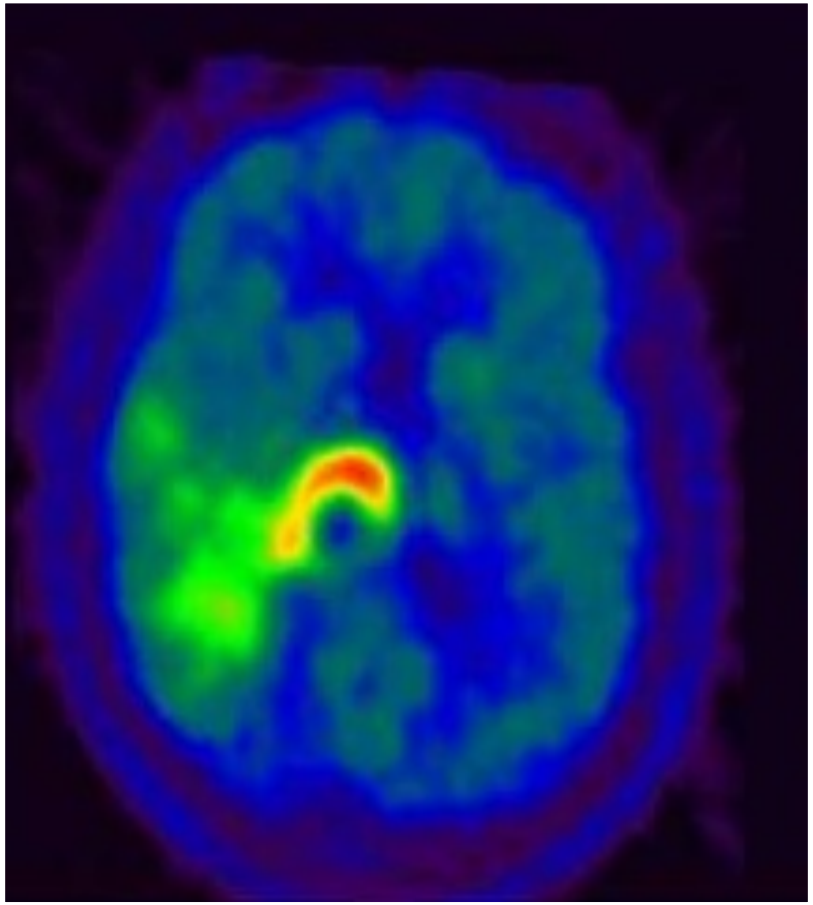
Grosu AL et al. Inl J Radiat Oncol Biol Phys 2005

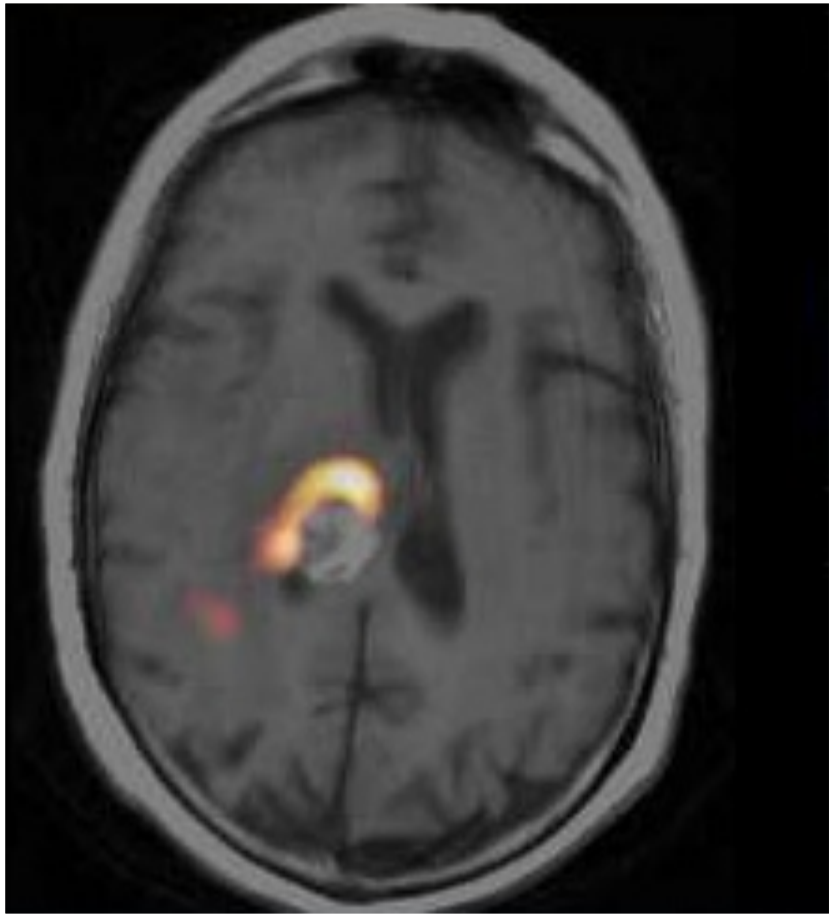
Discrepancias RM T1-Gadolinio y PET ^{11}C-Metionina



Discrepancias RM T1-Gadolinio y PET ^{11}C-Metionina







Accuracy of amino acid PET for brain tumour delineation in comparison with histologic evaluation.

Author	*N*[a]	Technique	Sensitivity[b] (%)	Specificity[b] (%)
Braun	32	MET-PET	87 (26/30)	75 (3/4)
Pirotte	32	MET-PET	100 (61/61)	100 (9/9)
Kracht	30	MET-PET	87 (87/100)	89 (16/18)
Pauleit	31	FET-PET	93[c]	94[c]
		MRI[d]	96	53

[a] Number of patients.

[b] Based on analysed lesions or biopsies.

[c] Total of 52 samples, 26 positive for tumour tissue. Sensitivity and specificity were calculated from fitted receiver operator characteristic (ROC) curve.

[d] Combined analysis of non-enhanced T1-weighted sequences, Gd-enhanced sequences and FLAIR sequences [13].

Grosu AL et al. Rad Oncol 2010

OPEN ACCESS Freely available online

PLOS | ONE

A Tri-Modality Image Fusion Method for Target Delineation of Brain Tumors in Radiotherapy

Lu Guo[1], Shuming Shen[1], Eleanor Harris[2], Zheng Wang[3], Wei Jiang[3], Yu Guo[1], Yuanming Feng[1,2]*

1 Department of Biomedical Engineering, Tianjin University, Tianjin, China, **2** Department of Radiation Oncology, East Carolina University, Greenville, North Carolina, United States of America, **3** Department of Radiation Oncology, Tianjin Huanhu Hospital, Tianjin, China

Table 4. Intra-observer comparison of GTV volumes obtained with dual-modality image fusion (MRI/CT) and tri-modality (MRI/CT/PET) image fusion.

Observer	Patient	GTV with Dual-modality		GTV with Tri-modality	
		Mean ± SD (cm^3)	COV	Mean ± SD (cm^3)	COV
Observer 1	**Patient 1**	21.52±1.48	0.07	17.15±0.68	0.04
	Patient 2	14.05±0.34	0.02	12.44±0.16	0.01
	Patient 3	2.64±0.29	0.11	1.87±0.02	0.01
Observer 2	**Patient 1**	22.52±1.00	0.04	19.76±0.31	0.02
	Patient 2	16.46±0.51	0.03	14.08±0.13	0.01
	Patient 3	2.79±0.12	0.04	1.94±0.02	0.01
Observer 3	**Patient 1**	20.28±0.96	0.05	17.55±0.47	0.03
	Patient 2	14.63±0.60	0.04	13.40±0.17	0.01
	Patient 3	1.99±0.16	0.08	1.66±0.02	0.01

GTV = gross tumor volume; COV = coefficient of variation; SD = standard deviation.

doi:10.1371/journal.pone.0112187.t004

Published November 6, 2014

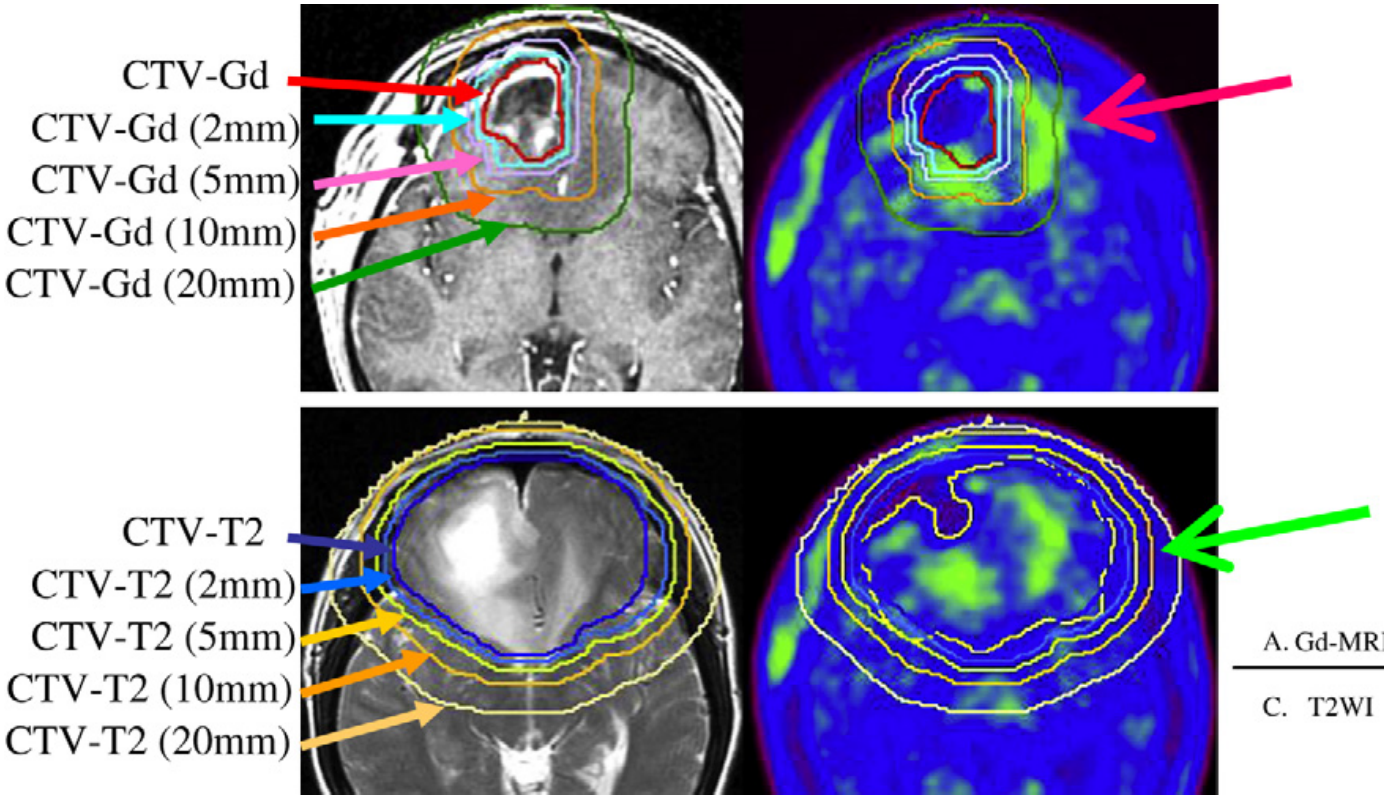
Smaller inter- and intra-observer variation in GTV definition for the brain tumors can be achieved, which improves the consistency and accuracy for target delineation in individualized radiotherapy.

2014

CT, MRI, and 18F-fluorodeoxyglucose positron emission tomography (**18F-FDG PET ??**)

IMPACT OF MET-PET-TAC FOR TARGET DEFINITION OF GLIOBLASTOMA MULTIFORME IN RADIATION THERAPY PLANNING

To define the **optimal margins** for T1Gd-MRI and T2-MRI for delineating target volumes in planning ra- diation therapy for postoperative patients with newly diagnosed glioblastoma multiforme (GBM) by comparison 11CMET-PET findings



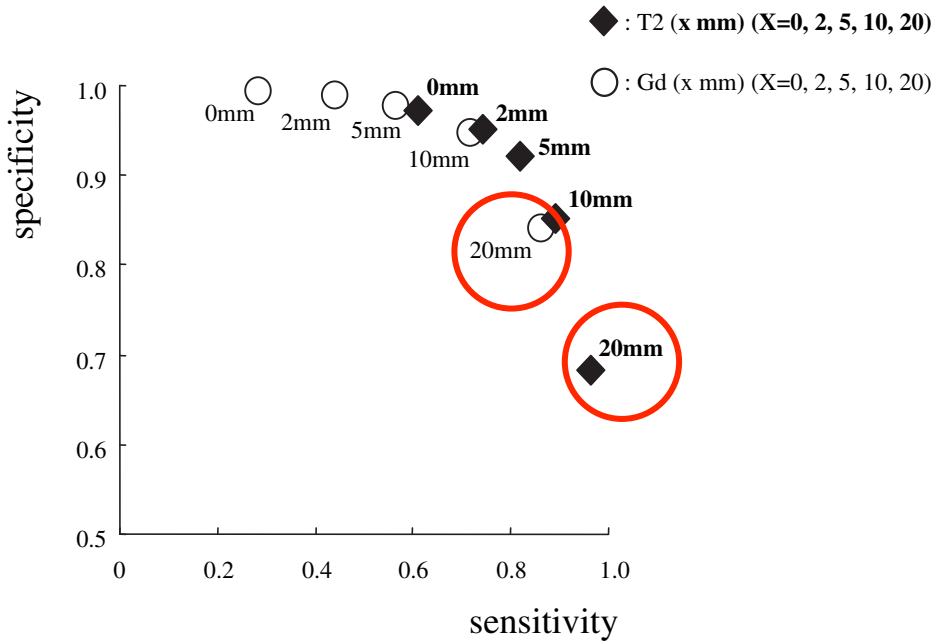


Fig. 2. Scatter plot of T_2-weighted MRI (x mm) (where $x = 0, 2, 5, 10, 20$ mm) and Gd (x mm) ($x = 0, 2, 5, 10, 20$ mm) with respect to sensitivity and specificity, respectively.

Matsuo M. IJROBP 2012

	Sensitivity	Specificity	Comments
CTV-Gad + 2cm	86%	84%	<u>CTV-T2 + 2cm</u> 1. To optimize tumor control and to prevent local failure. 2. If dose escalation, the dose of radiation to the normal tissue increases (low specificity)
CTV-T2 + 2cm	96%	68%	

It is necessary to use a margin of at least 2 cm in T2-MRI for the initial target planning of radiation therapy ???

In postoperative patients with GBM, the CTV-Gd and CTV-T2 margins differed considerably from that of CTV- [11C]MET-PET

Matsuo M. IJROBP 2012

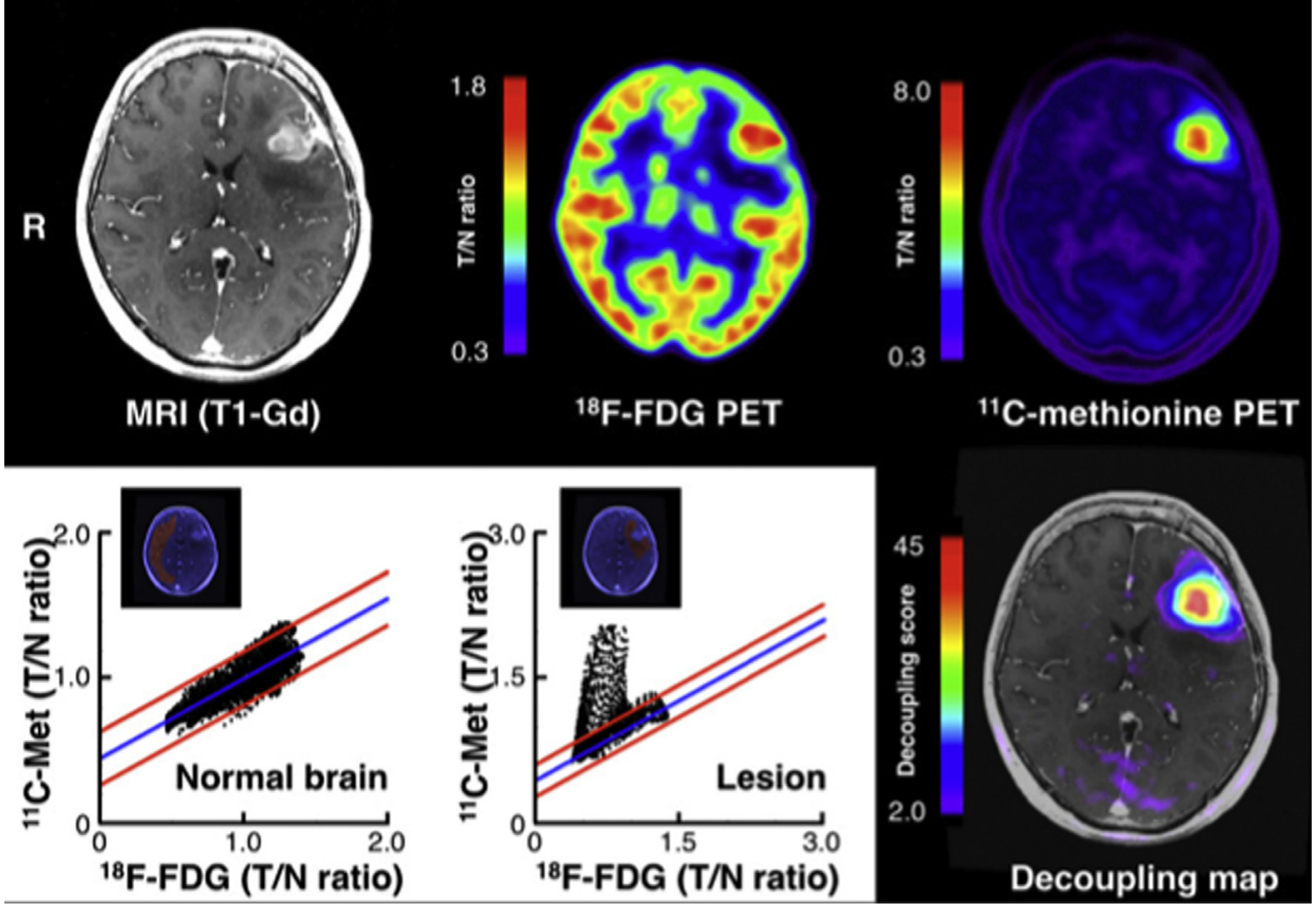
Método de análisis de imagen

Matched 18F-FDG and MET-PET para calcular el **decoupling score**

Detecta una densidad tumoral >1000/mm2

S/E: 93.5/87.5%

(MET exclusivo S/E: 87.0 and 87.5%)



Glioblastoma showing identification of voxels with a mismatch between methyl-11C-L-methionine (MET) and FDG uptake and the consequent identification of tumour extent on the decoupling map (bottom right). Kinoshita M J Nucl Med 2012

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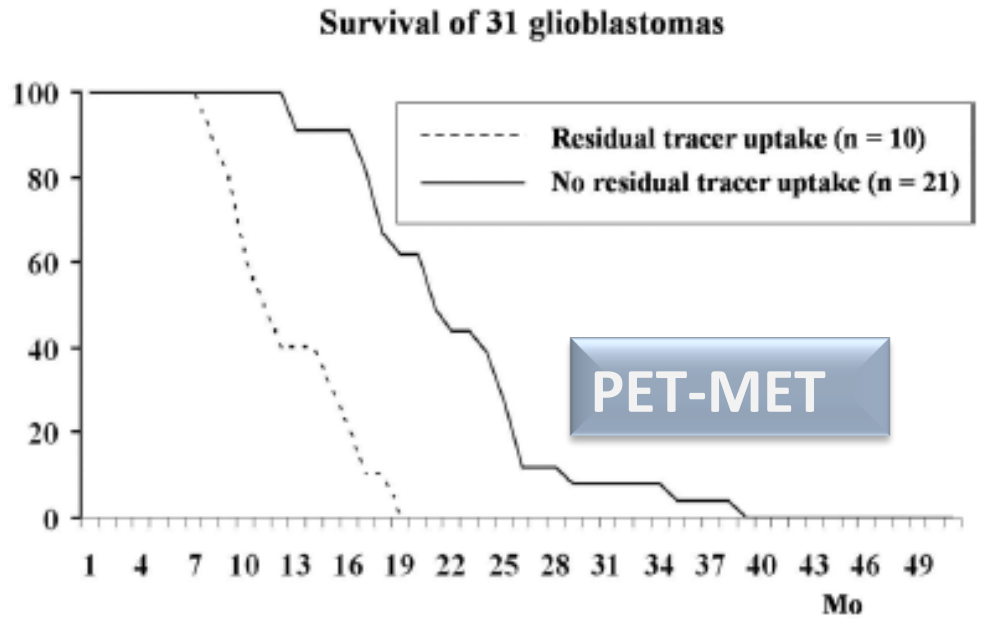
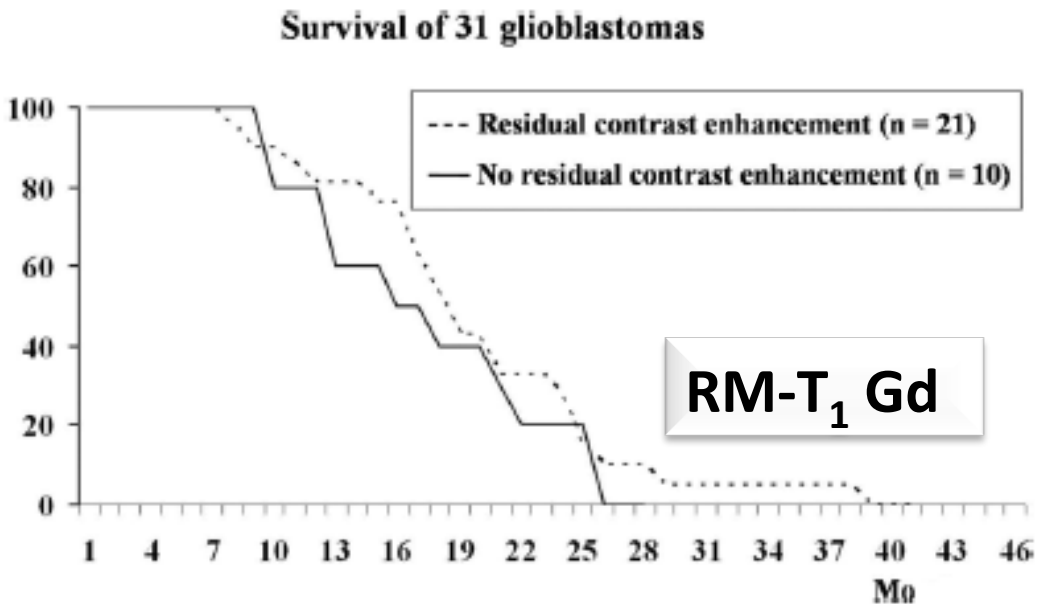
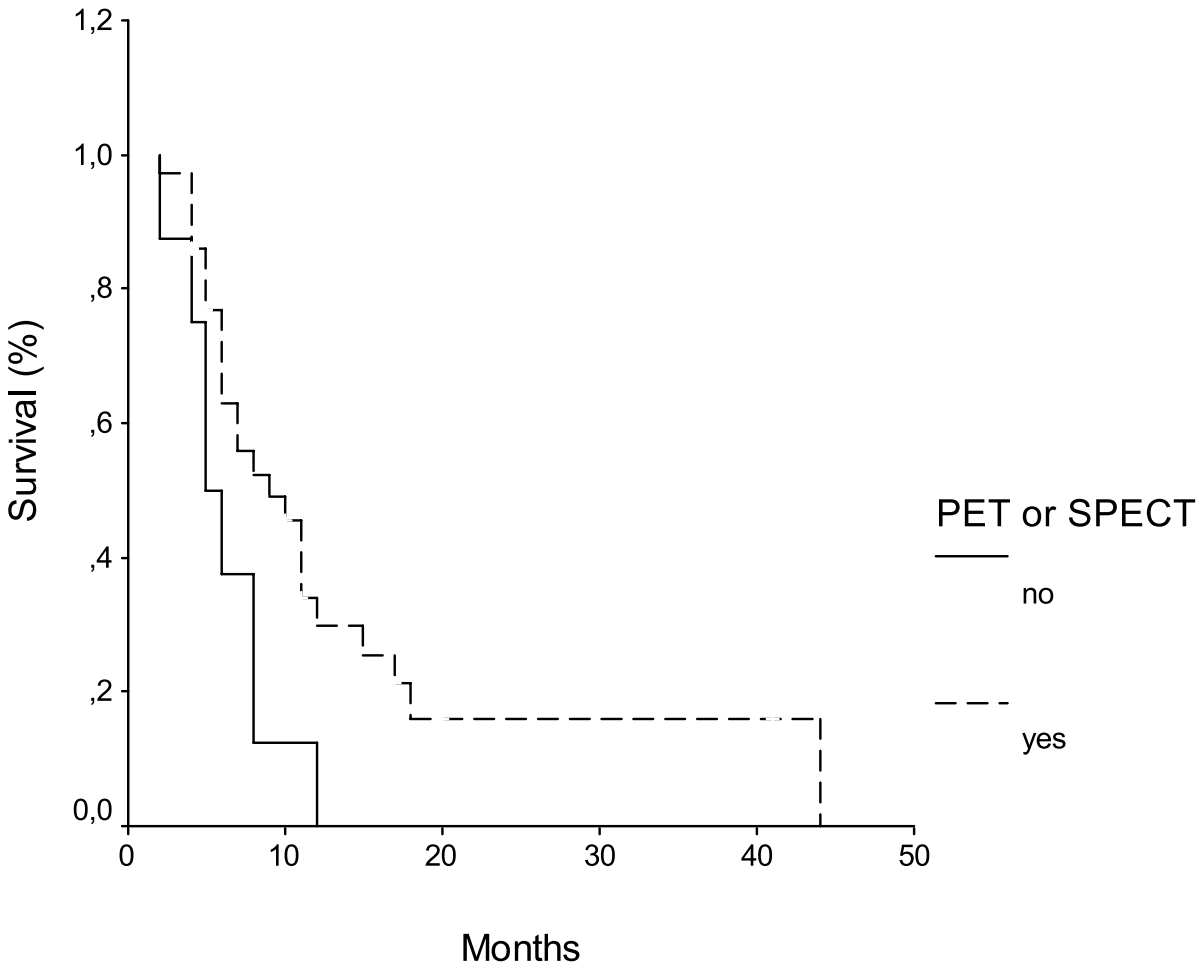
Positron Emission Tomography-guided Volumetric Resection of Supratentorial High-grade Gliomas: A Survival Analysis in 66 Consecutive Patients





Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy

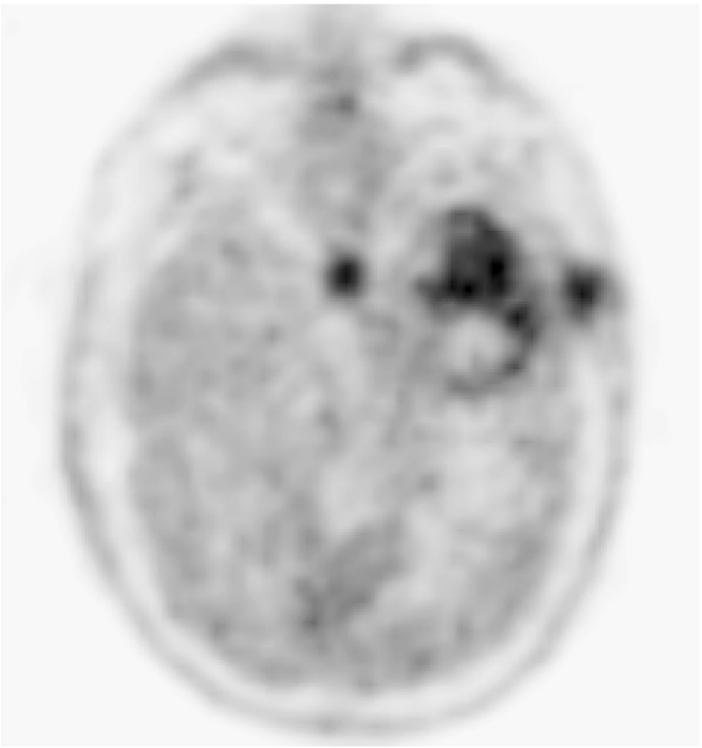
Treatment planning based on PET imaging compared with the standard MRI used for planning resulted in a **significant increase in median survival** (9 vs 5 months).

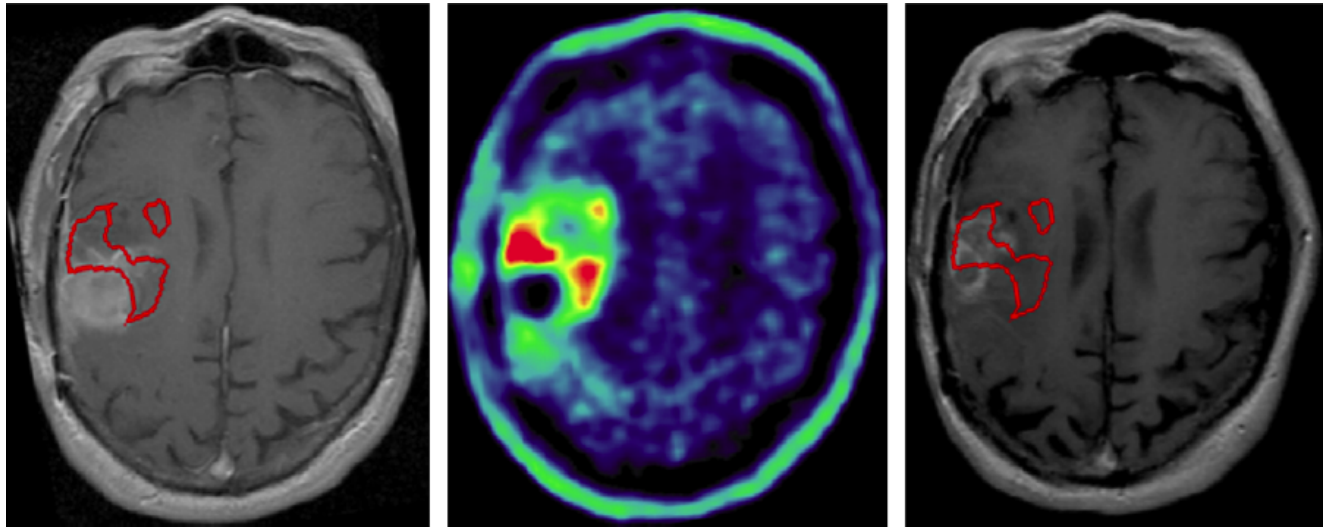


Grosu AL et al. Inl J Radiat Oncol Biol Phys 2005

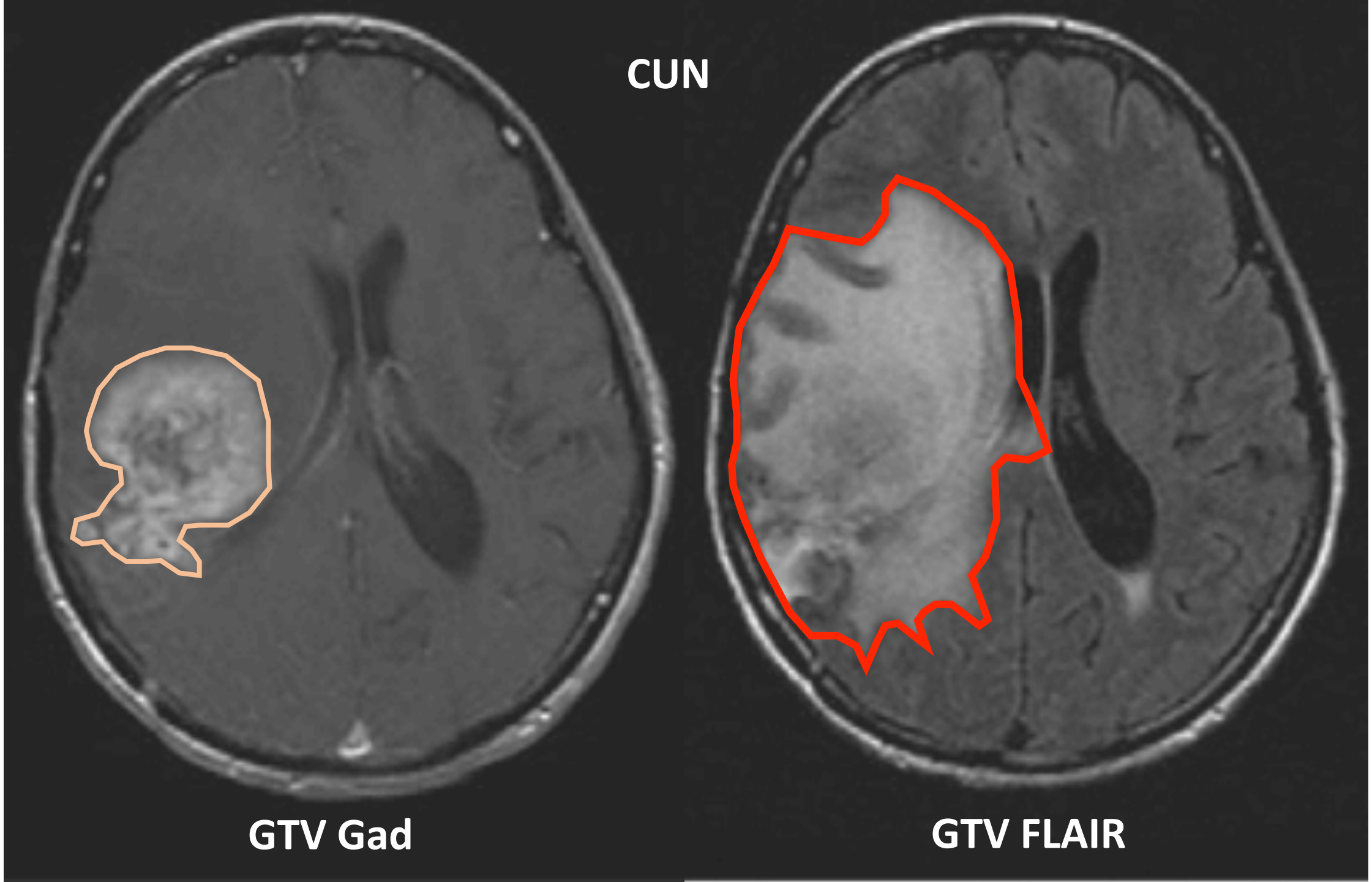
Association of ^{11}C-Methionine PET Uptake with Site of Failure After Concurrent Temozolomide and Radiation for Primary Glioblastoma Multiforme

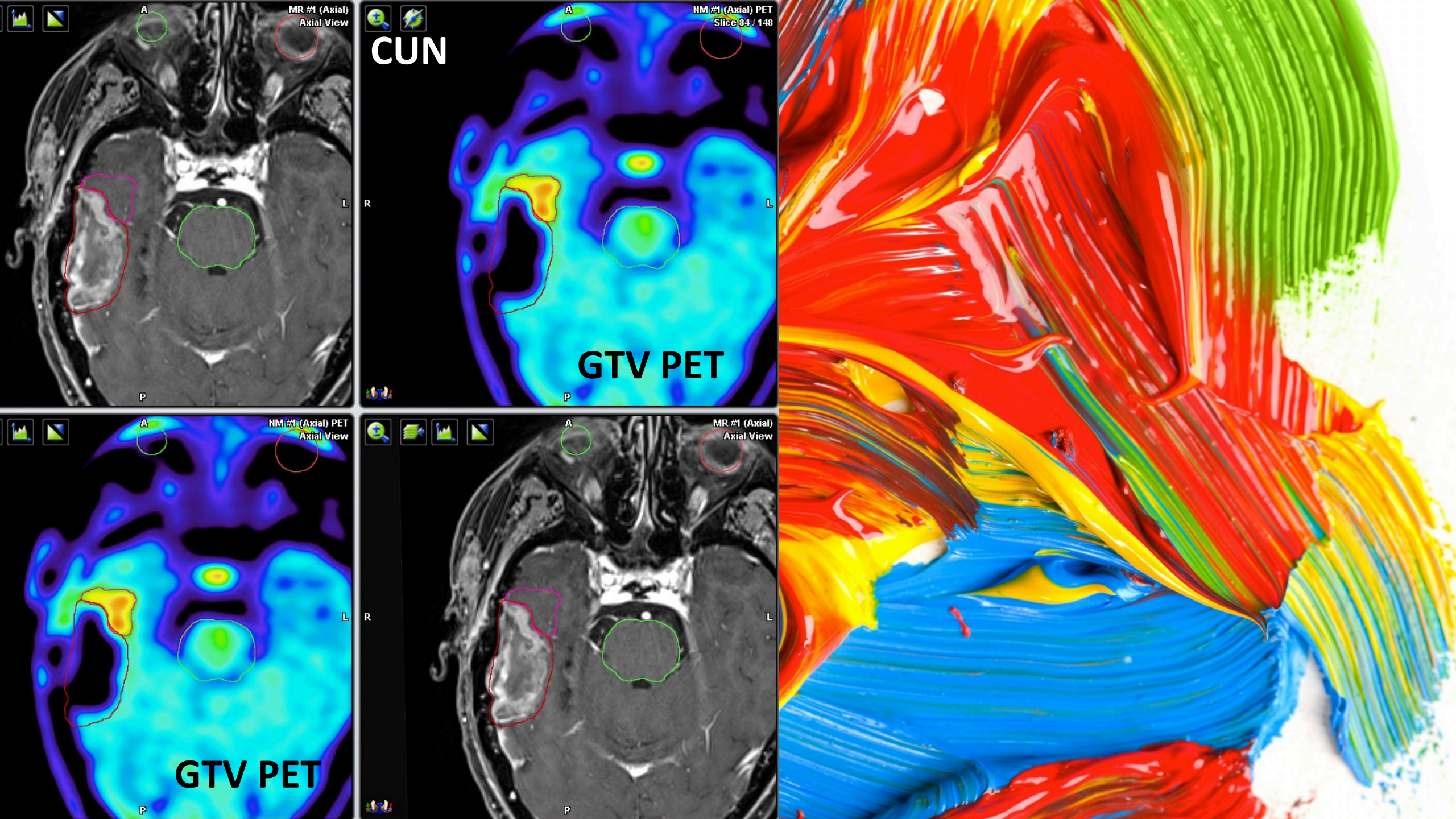
- 26 pts dose escalation study w MR-GTV (Michigan)
- 19 MET-PET +
- 5/19 PET-GTV outside the high dose region
  - 5/5 non-central recurrence
- 14/19 covered by PET-GTV
  - 2/14 non-central recurrence

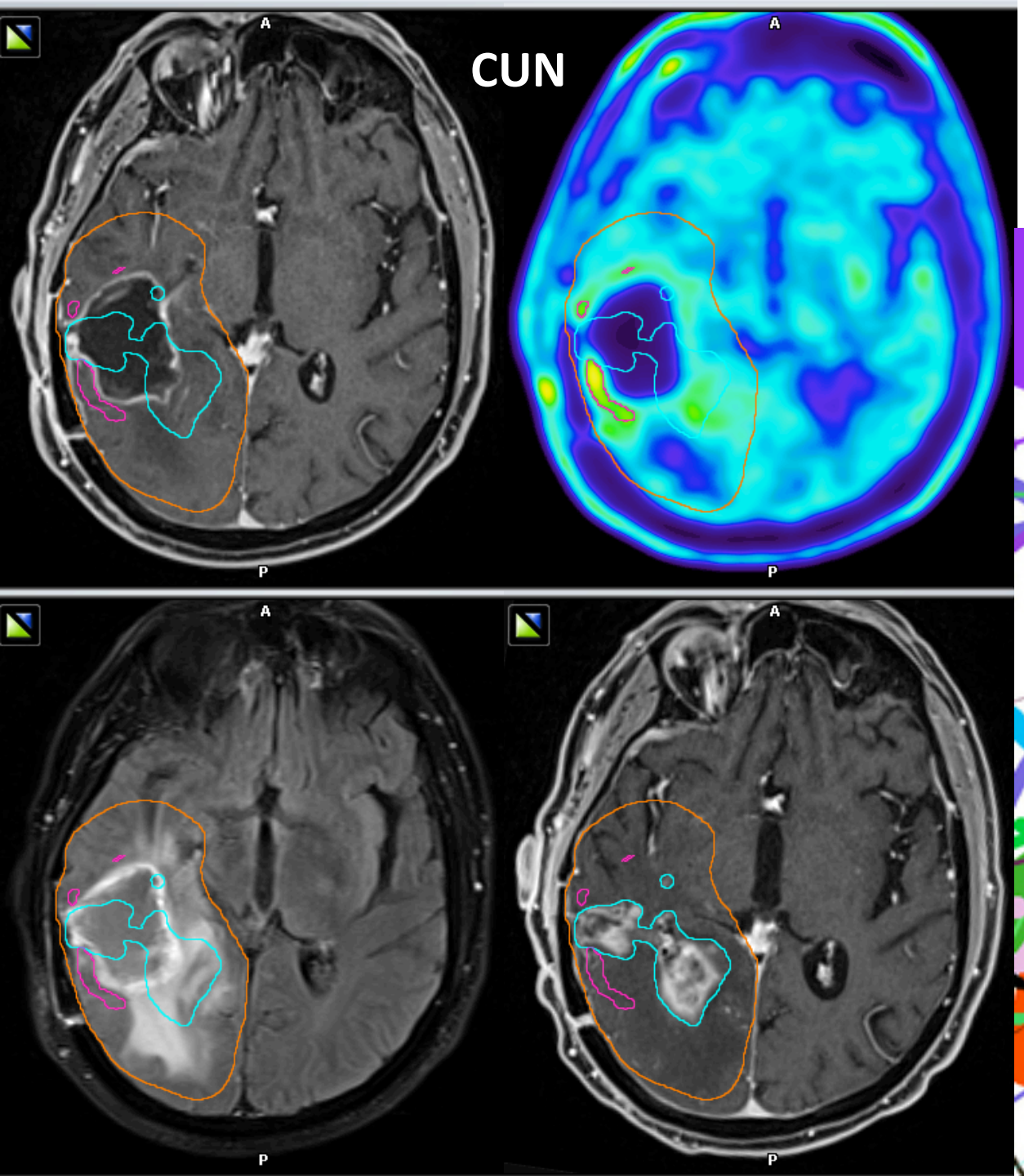




Lee IH, IJROBP 2009

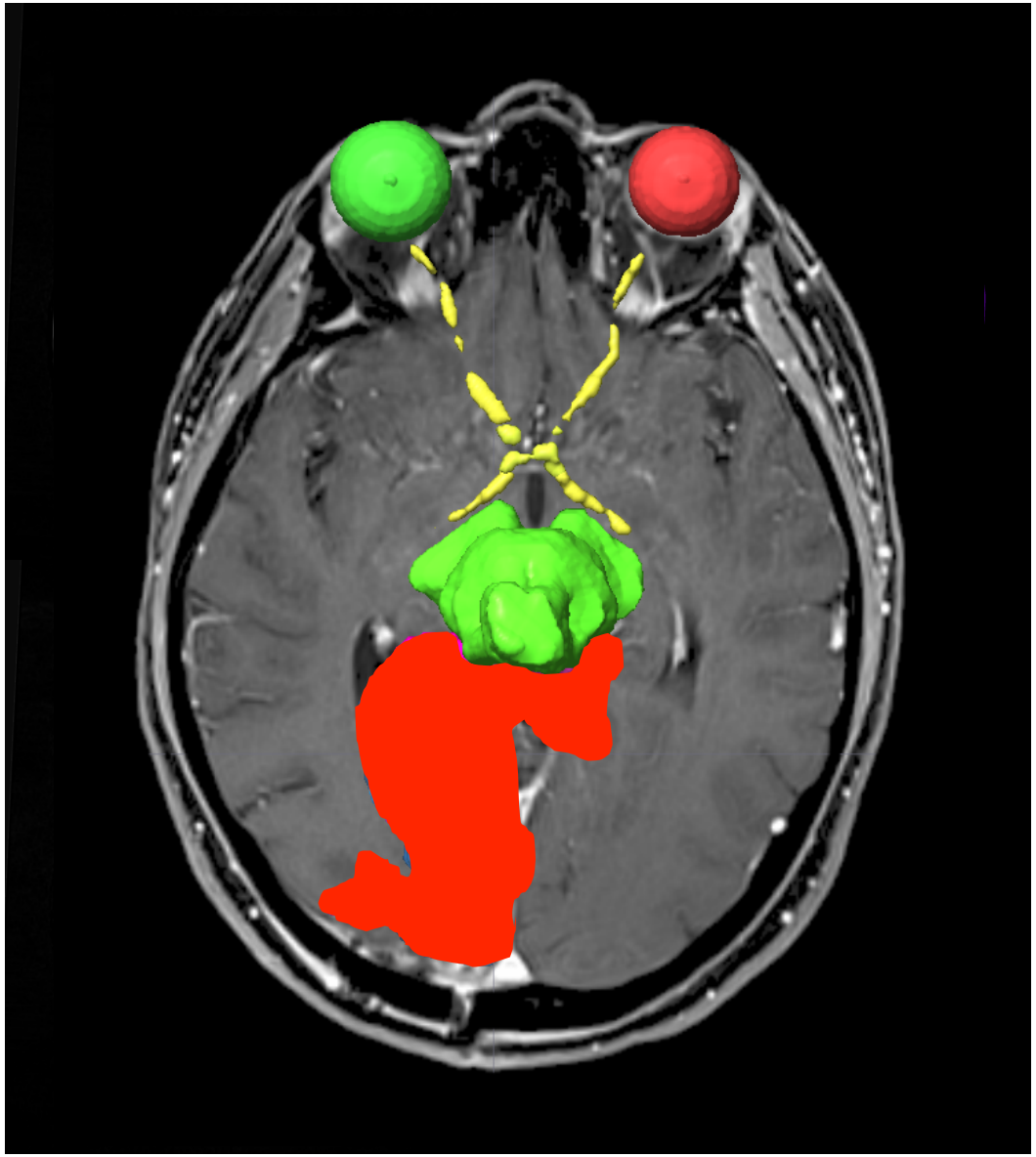

CUN
GTV Gad
GTV FLAIR


MR #1 (Axial)
Axial View
A
L
P
NM #1 (Axial) PET
Slice 84 / 148
CUN
R
GTV PET
NM #1 (Axial) PET
Axial View
GTV PET
MR #1 (Axial)
Axial View



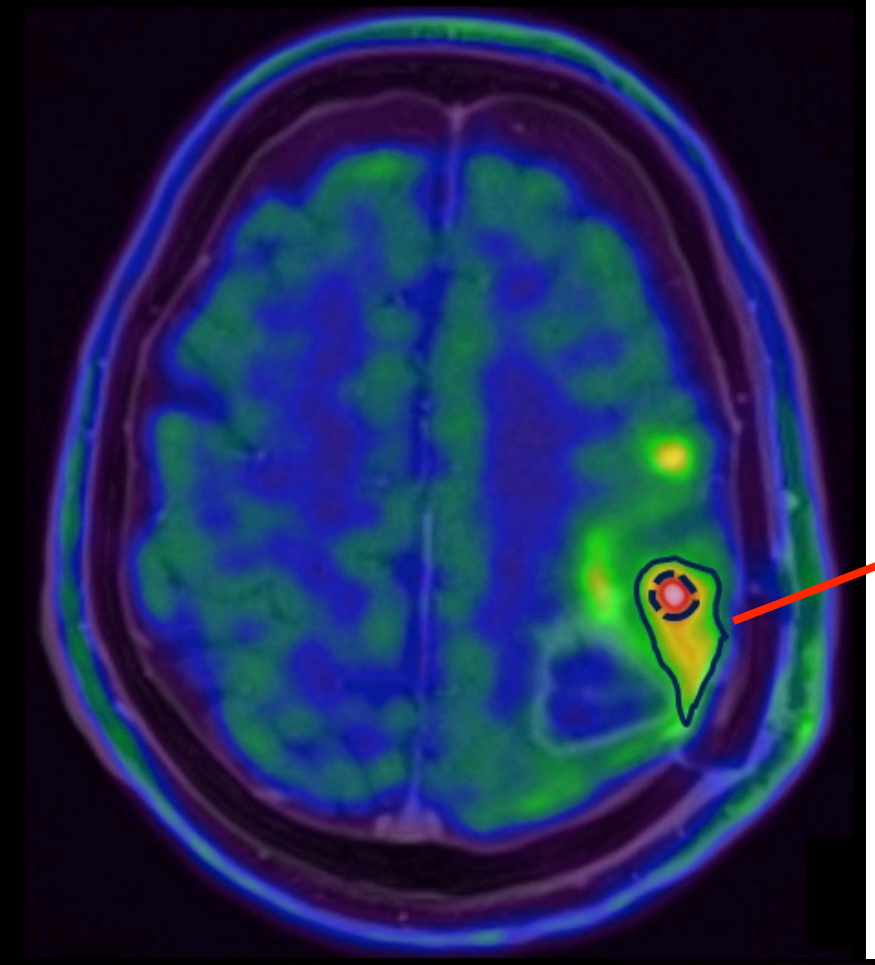
Recurrencia en relación con los volúmenes target iniciales y PET-MET de planificación

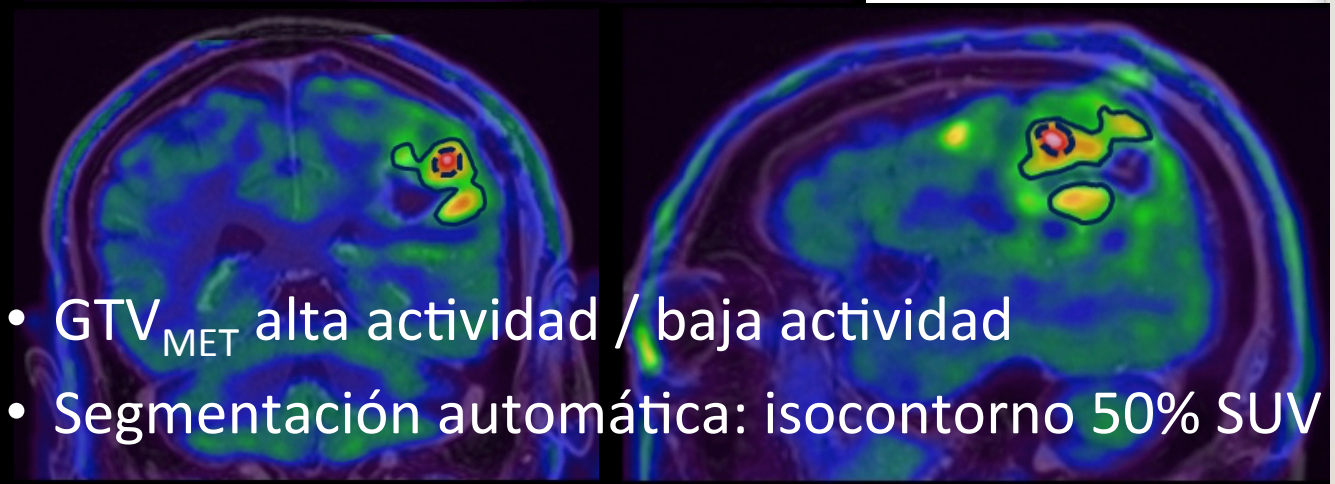
GTV_{Gd}



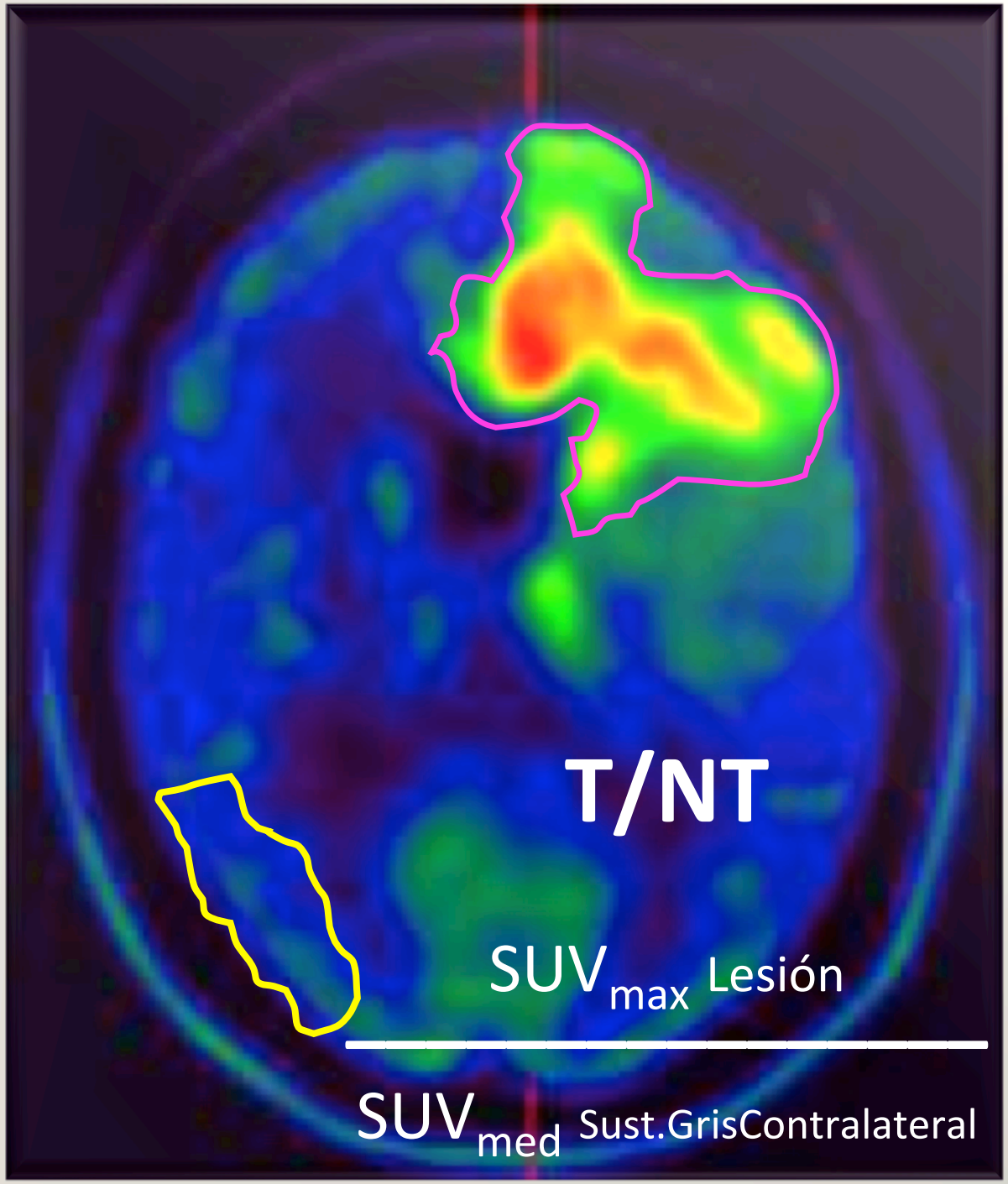
GTV_{MET}

GTV_{Total}





- GTV_{MET} alta actividad / baja actividad
- Segmentación automática: isocontorno 50% SUV



Análisis de la imagen

T/NT	**2,30**	**1,10-10,10**

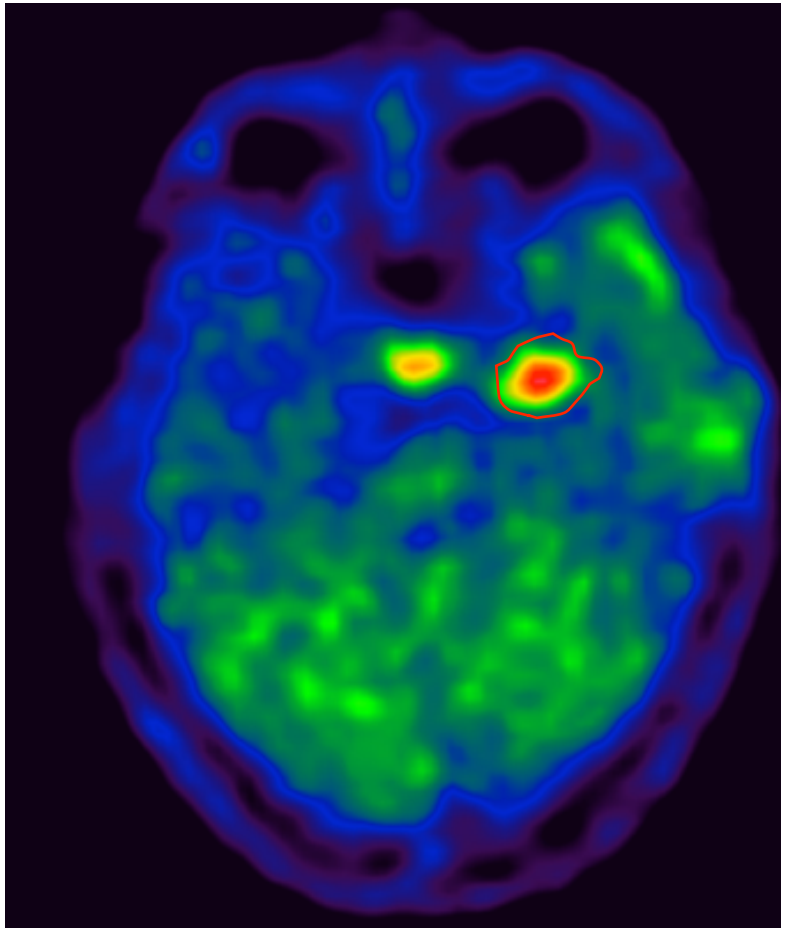
Vol. planificación	Mediana	Rango
GTV_{MET} (cc)	9,10	0,19-93,50
GTV_{Gd} (cc)	40,06	1,02-387,50
GTVTotal (cc)	45,45	1,98-403,76
GTV_{MET}–GTV_{Gd} (cc)	3,12	0,84-8,48

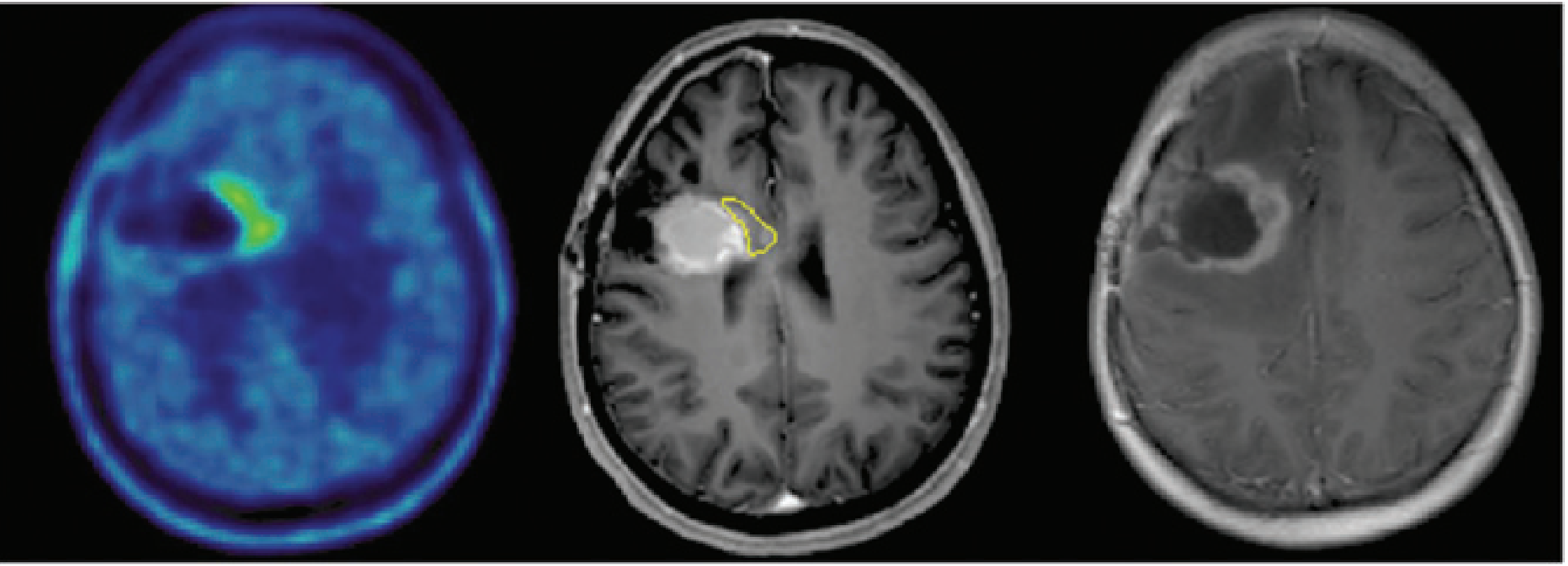
Volumen PET (cc)	Grosu 2005	Weber 2008	Niyazi 2011
Mediana	**13**	**8**	**2,5**

Análisis del volumen de recidiva tumoral

La localización de la recidiva coincidió con el área de máxima actividad del GTV_{MET} en **33/46** patients (71,1%)

(p=0,02)





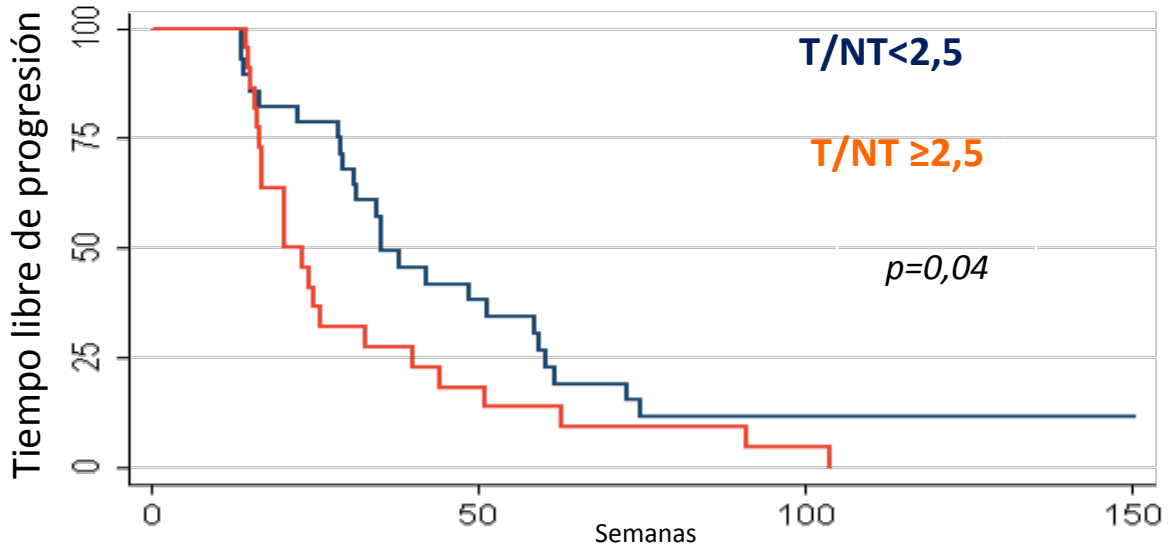
^{11}C MET-PET Pre-Tx **MR T1 Post-Gd Pre-Tx** **MR T1 Post-Gd at recurrence**

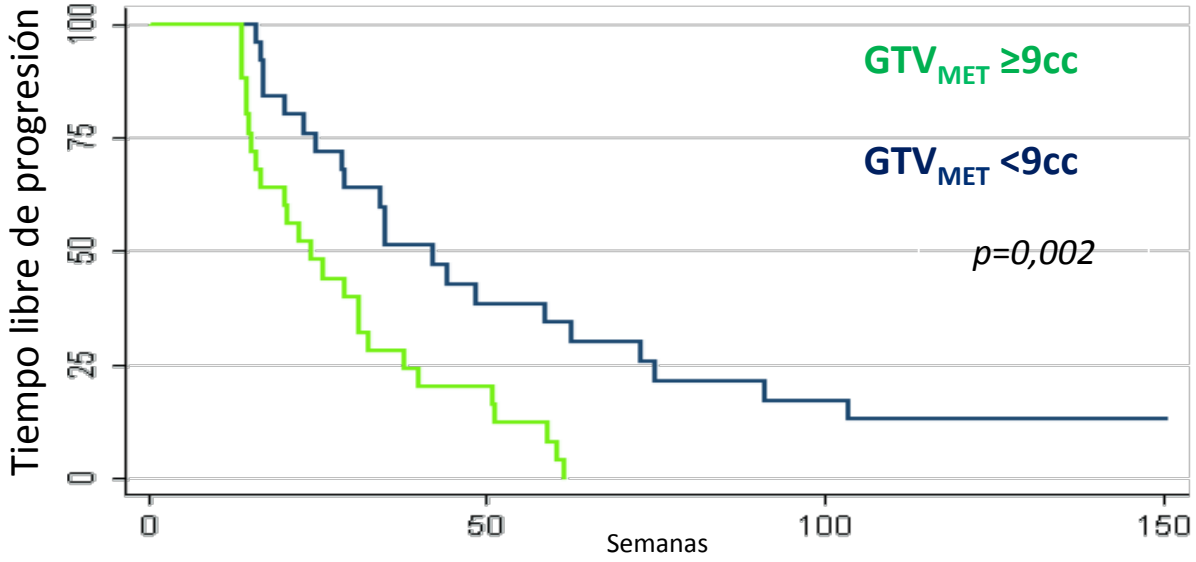
Overlap between the area of initial increased PET uptake (yellow) and eventual area of recurrence

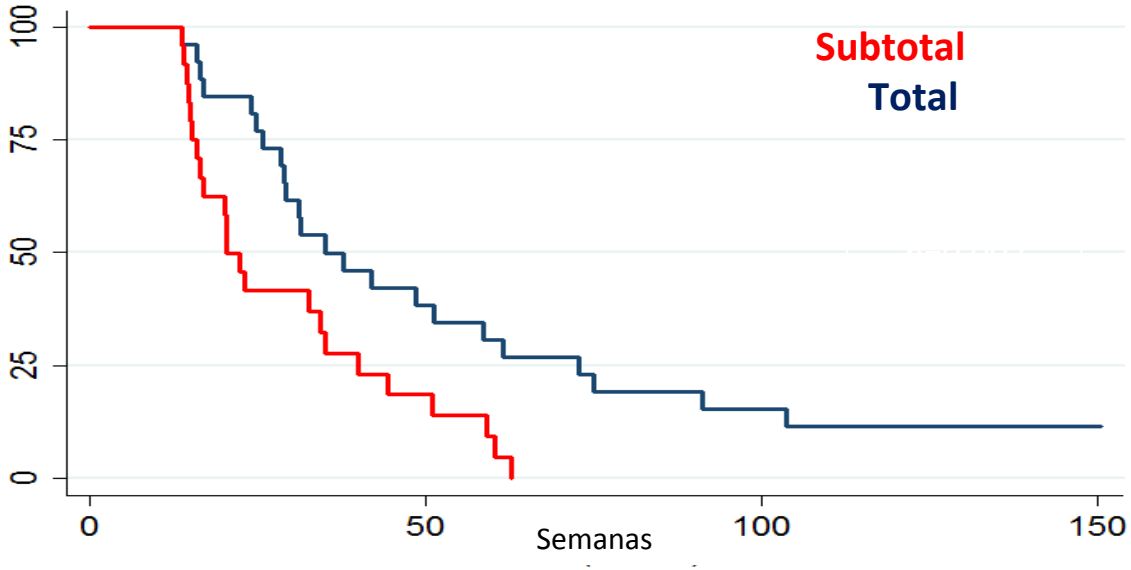
Tsien CI. Clin Cancer Res 2012

Tiempo Libre de Progresión

	A. Univariable		A. Multivariable Ajustado	
Variables	**HR (95% CI)**	**Valor p**	**HR ajustado (IC 95%)**	**Valor p**
GTV_{MET}	1.01 (1.10-1.50)	**0.048**	1.01 (0.99-1.03)	0.121
GTV_{MET} ≥9/<9cc	0.38 (0.20-0.71)	**0.003**	0.53 (0.25-1.13)	0.100
GTV_{Gd}	1.00 (0.99-1.00)	0.8	0.99 (0.99-1.00)	0.179
GTV_{Gd} ≥40/<40cc	0.84 (0.47-1.51)	0.56	0.89 (0.74-1.68)	0.731
T/NT	1.30 (1.10-1.50)	**0.003**	1.28 (1.04-1.58)	**0.016**


Tiempo libre de progresión
100
75
50
25
0
T/NT<2,5
T/NT ≥2,5
p=0,04
0
50
100
150
Semanas

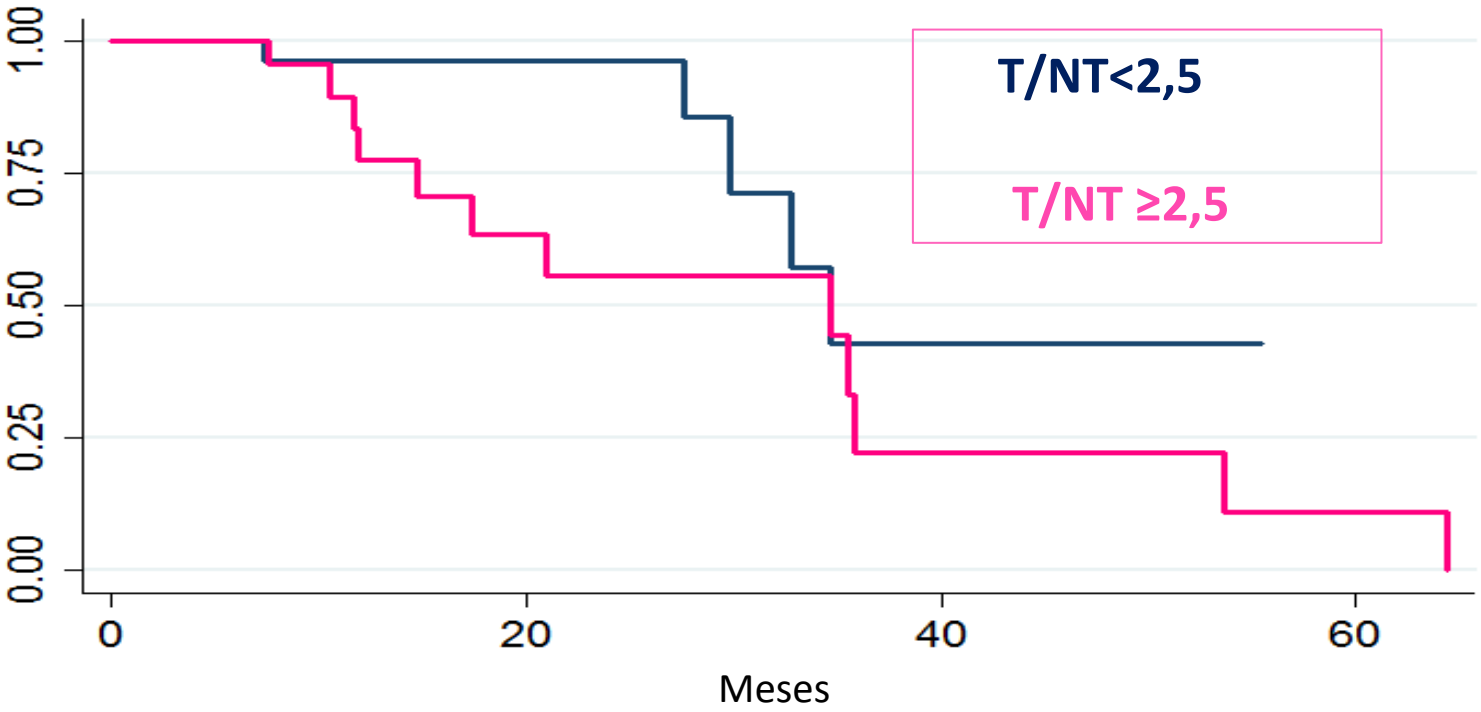

Tiempo libre de progresión
100
75
50
25
0
GTV$_{MET}$ ≥9cc
GTV$_{MET}$ <9cc
p=0,002
0
50
100
150
Semanas


100
75
50
25
0
Subtotal
Total
0
50
100
150
Semanas

Supervivencia Global

	A. Univariable		A. Multivariable Ajustado	
Variables	**HR (95% CI)**	**Valor p**	**HR ajustado (IC 95%)**	**Valor p**
GTV_{MET}	1.00 (0.99-1.01)	0.7	1.00 (0.98-1.02)	0.3
GTV_{MET} ≥9/<9cc	0.90 (0.45-1.80)	0.7	1.27 (0.53-3.05)	0.6
GTV_{Gd}	1.00 (0.99-1.01)	0.8	1.00 (0.99-1.01)	0.5
GTV_{Gd} ≥40/<40cc	1.40 (0.67-2.80)	0.4	0.48 (0.21-1.00)	0.086
T/NT	1.00 (0.74-1.40)	0.9	1.05 (0.77-1.45)	0.7

Índice T/NT y Supervivencia Global

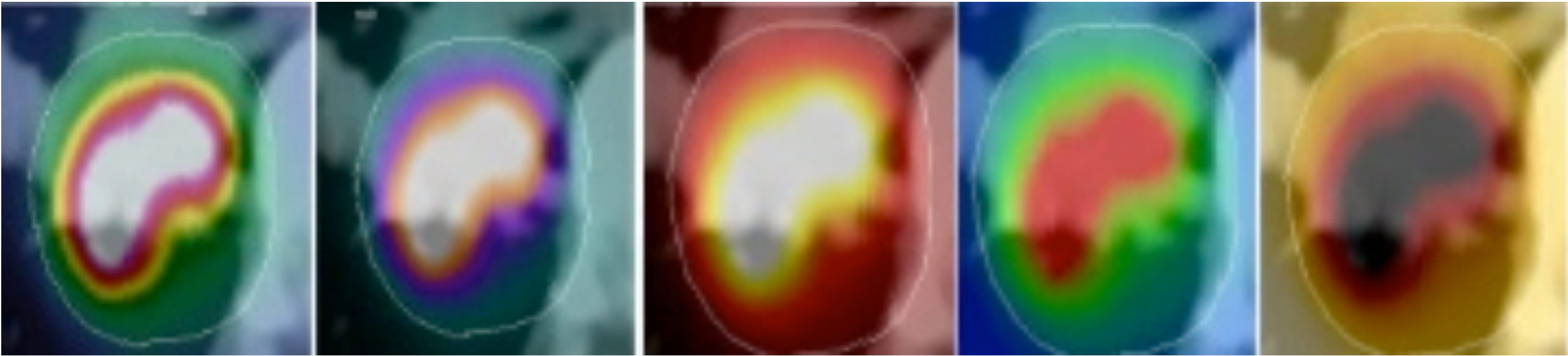


	SG <14m	SG ≥14m
T/NT <2,5	6	22
T/NT ≥2,5	13	9

Dose painting por contornos

Ling et al. en 2000
Prescripción de una dosis alta y homogénea en una parte del GTV definido por una imagen funcional

Ling CC, et al. Int J Radiat Oncol Biol Phys 2000

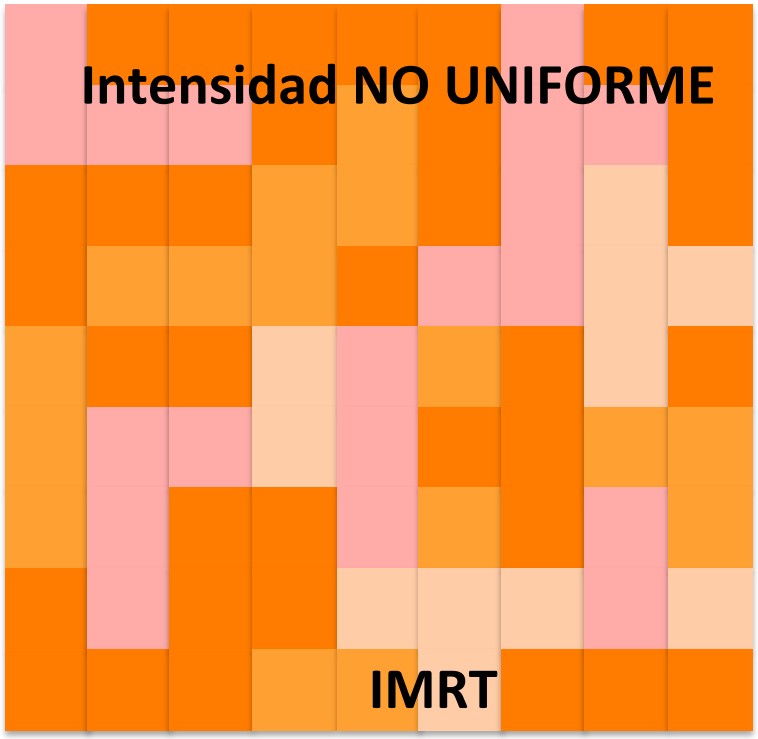


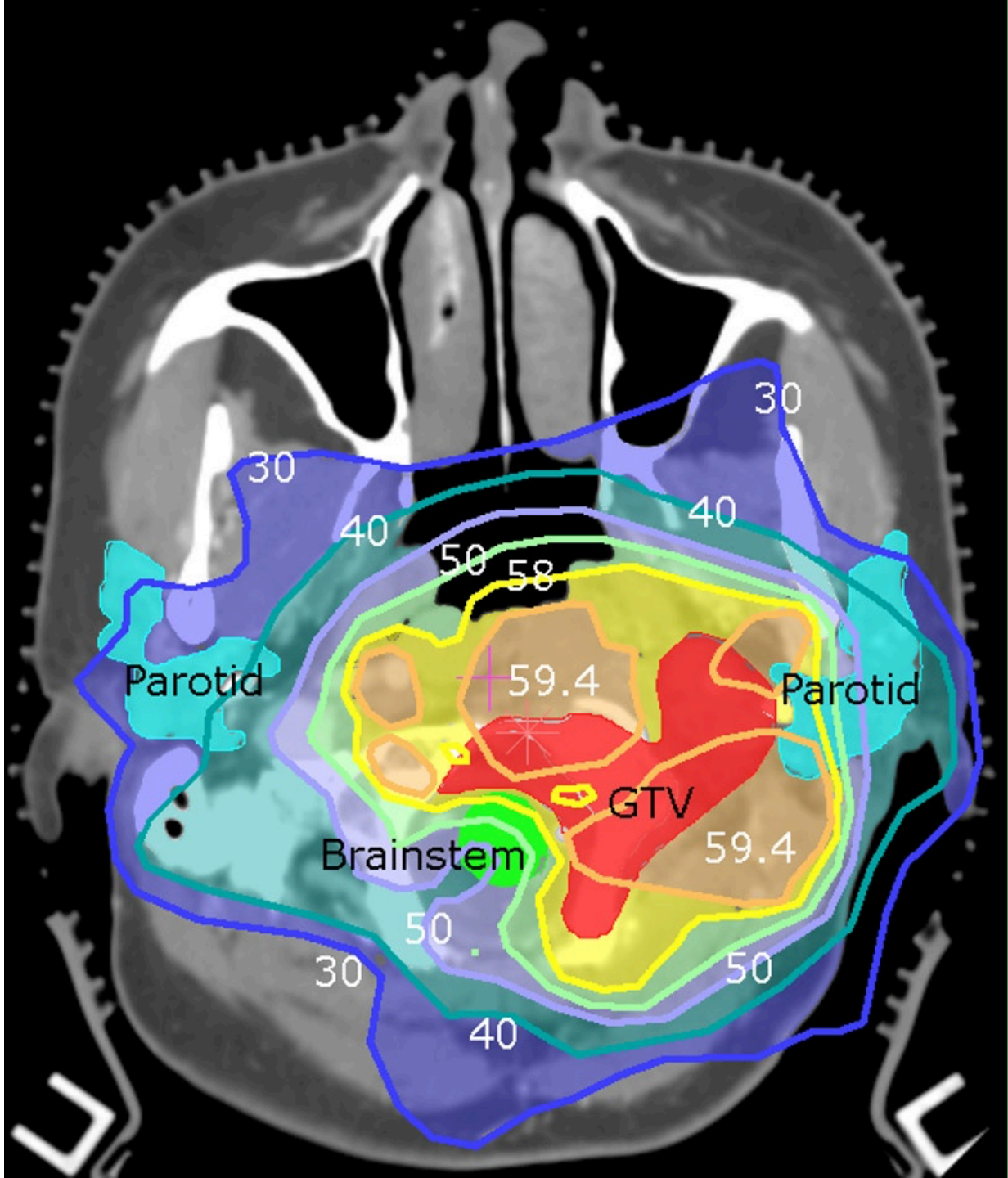
Radioterapia de intensidad modulada

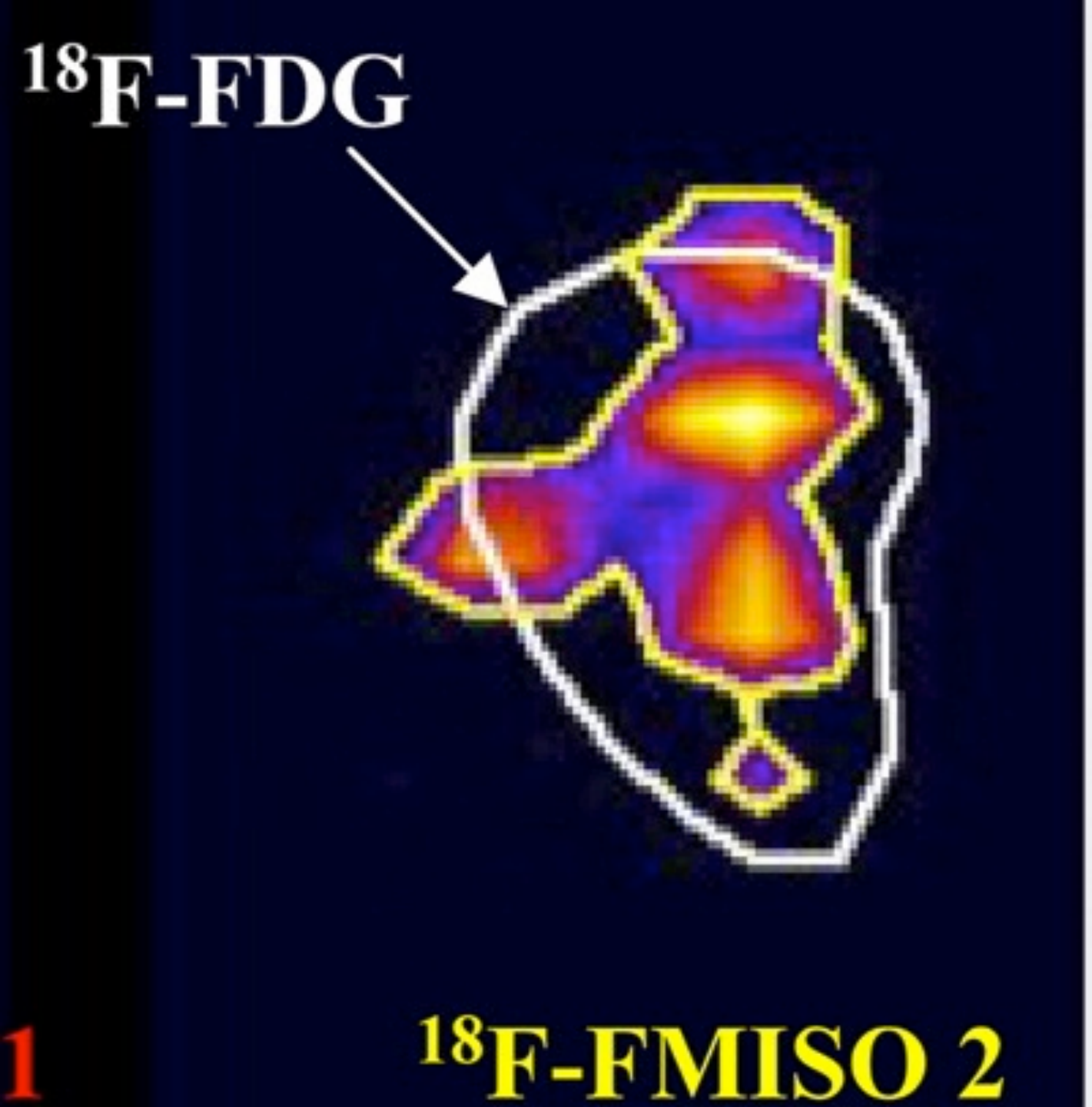
IMRT

La IMRT se basa en una distribución de dosis no homogénea

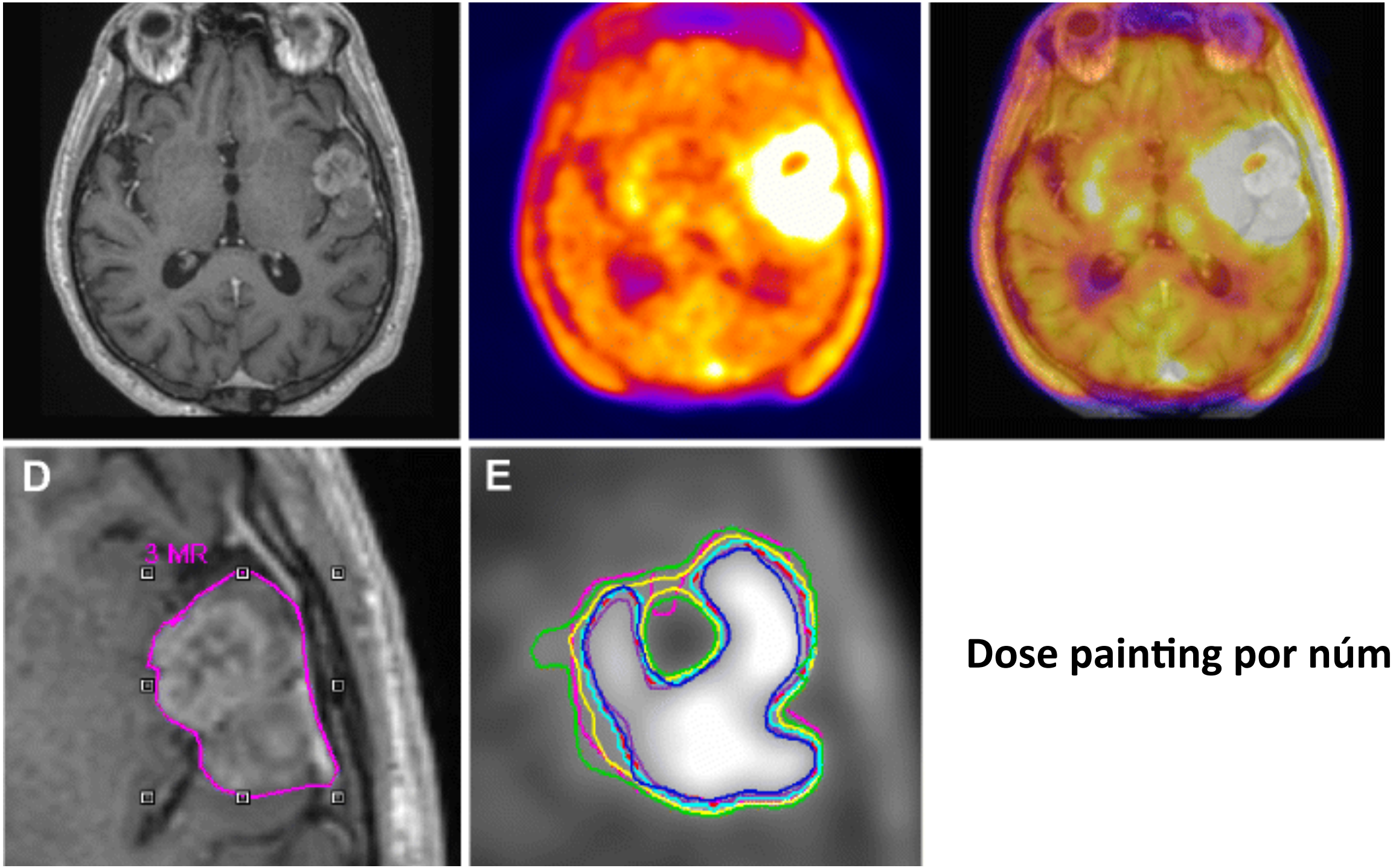
Preservación de tejido sano de altas de dosis de RT





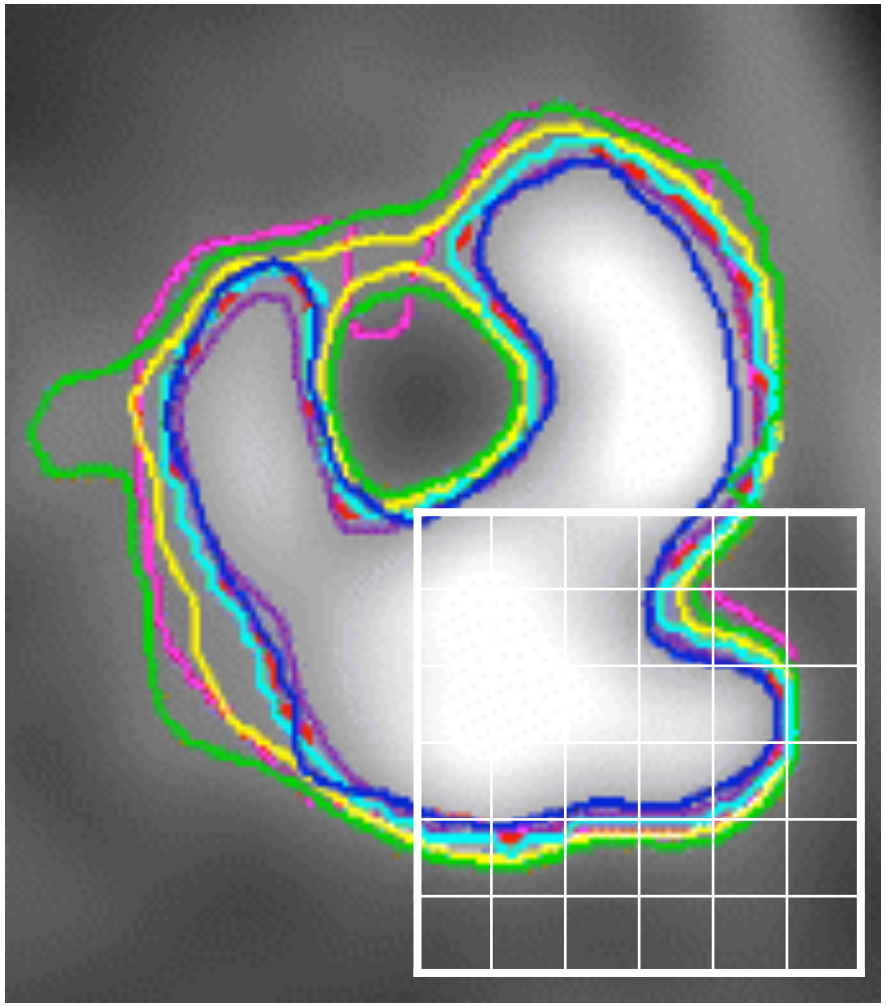


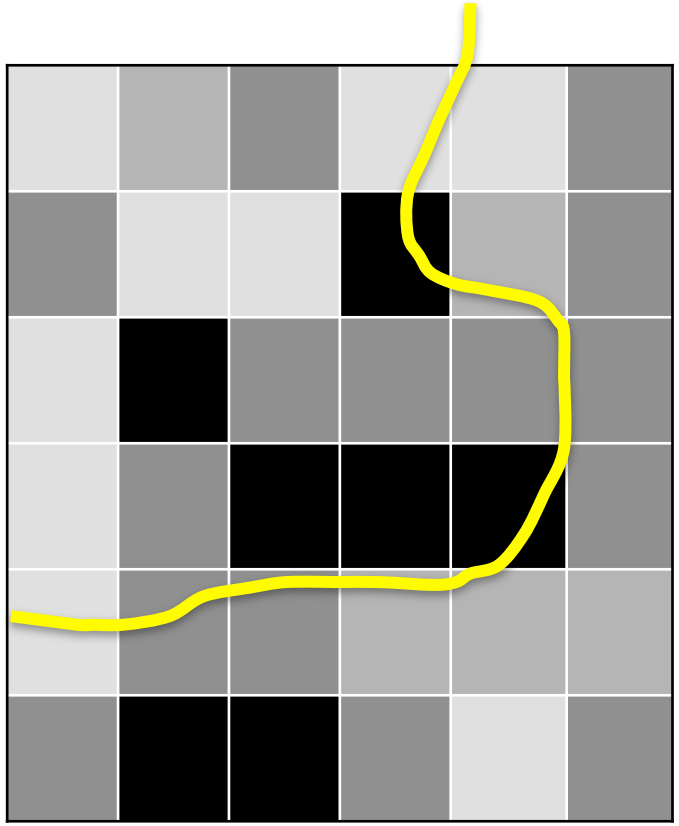
Biological target volume (BTV)
A subvolume of the GTV that is more radioresistant than the rest of the GTV either due to hypoxia, fast proliferation, high density of cancer stem cells, or other biological properties.



Dose painting por números

Procedimiento





Dosis homogénea

70	70	70	70	70	70
70	70	70	70	70	70
70	70	70	70	70	70
70	70	70	70	70	70
70	70	70	70	70	70
70	70	70	70	70	70

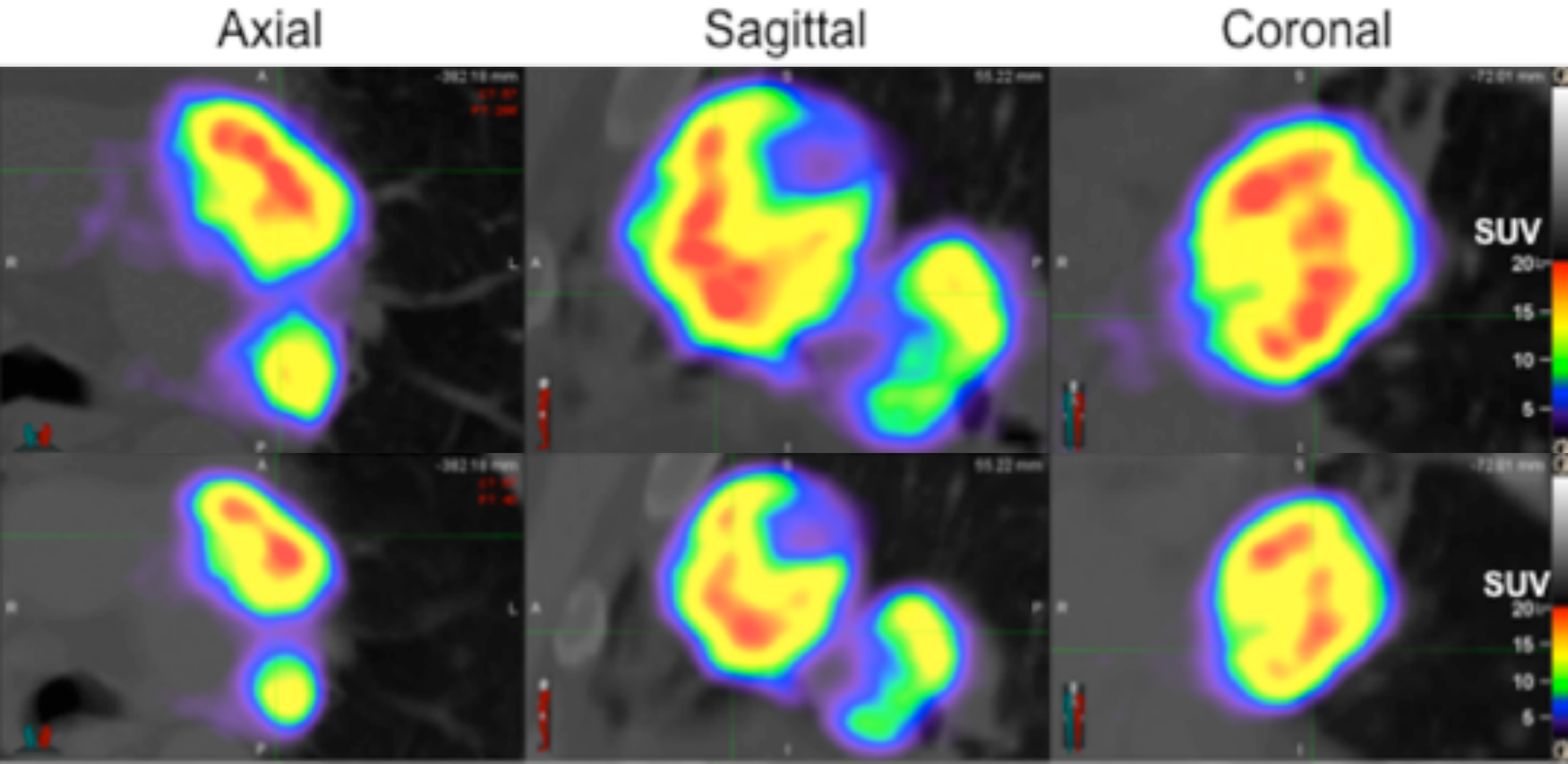
Dose painting por contornos

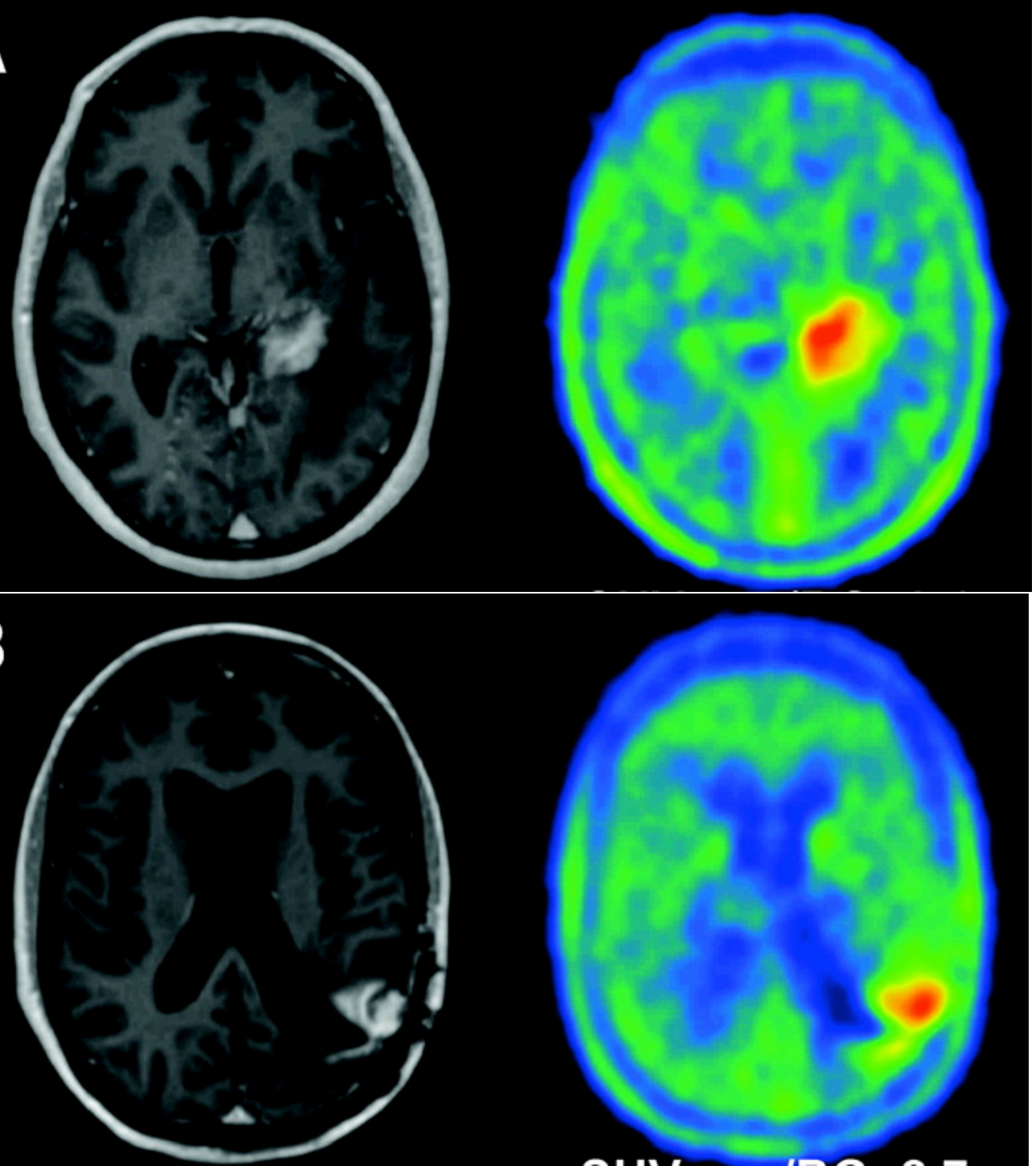
70	70	70	70	70	70
70	70	70	70	70	70
70	80	80	80	80	70
70	80	80	80	80	70
70	80	80	70	70	70
70	80	80	70	70	70

Dose painting por números

70	75	80	70	70	80
80	70	70	80	75	70
70	85	80	80	80	70
70	80	85	85	85	70
70	80	85	70	75	75
80	85	85	70	70	80

Adaptive radiation therapy

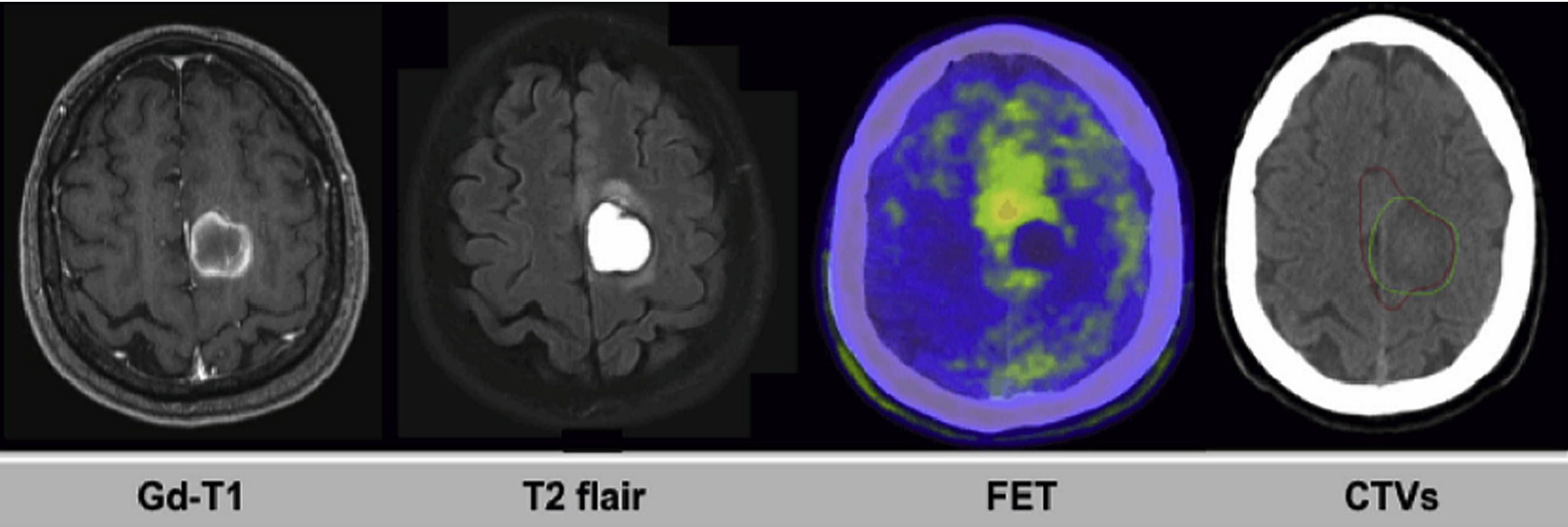




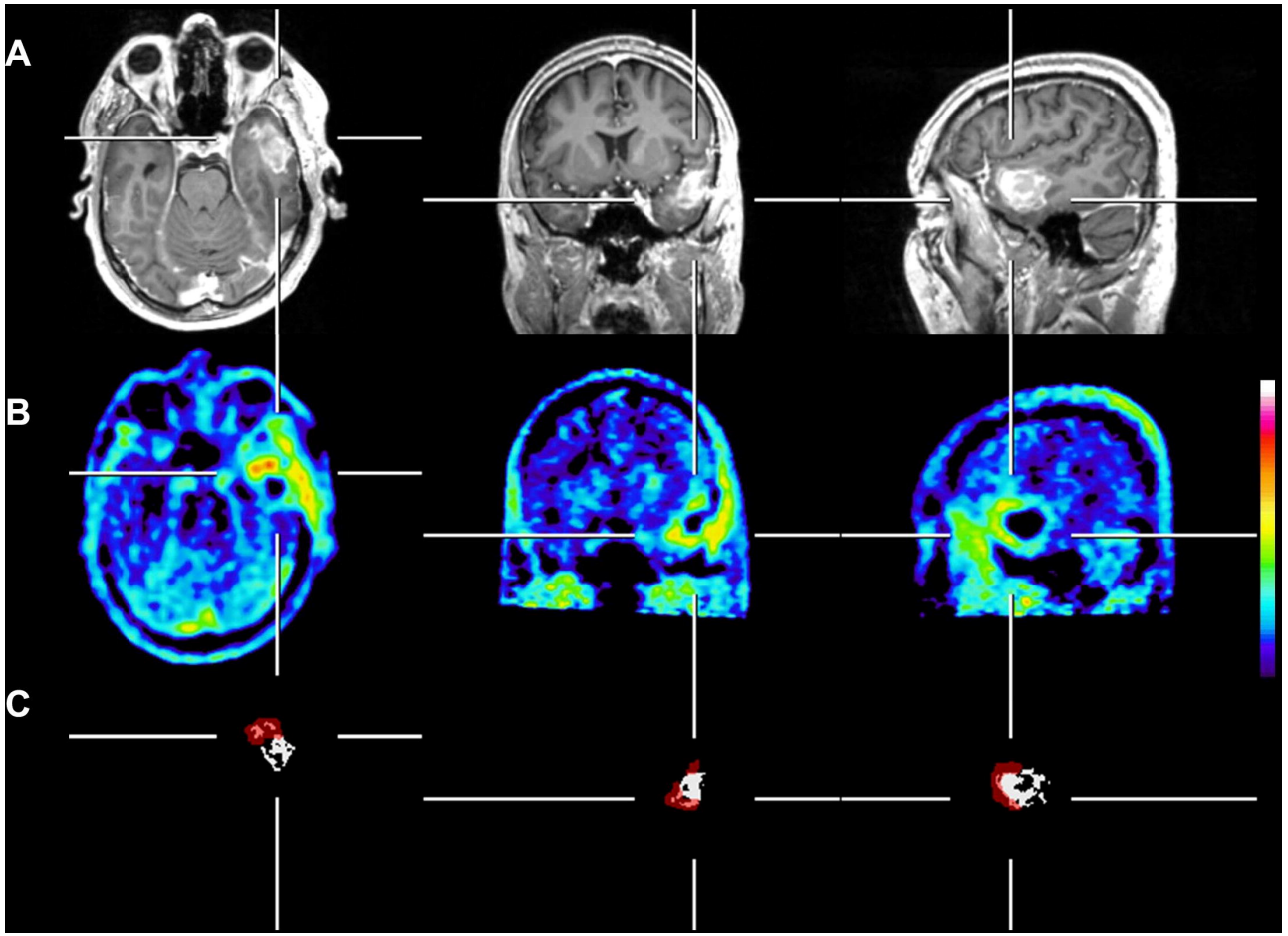
FET-PET
(18F-fluoroethyltyrosine)

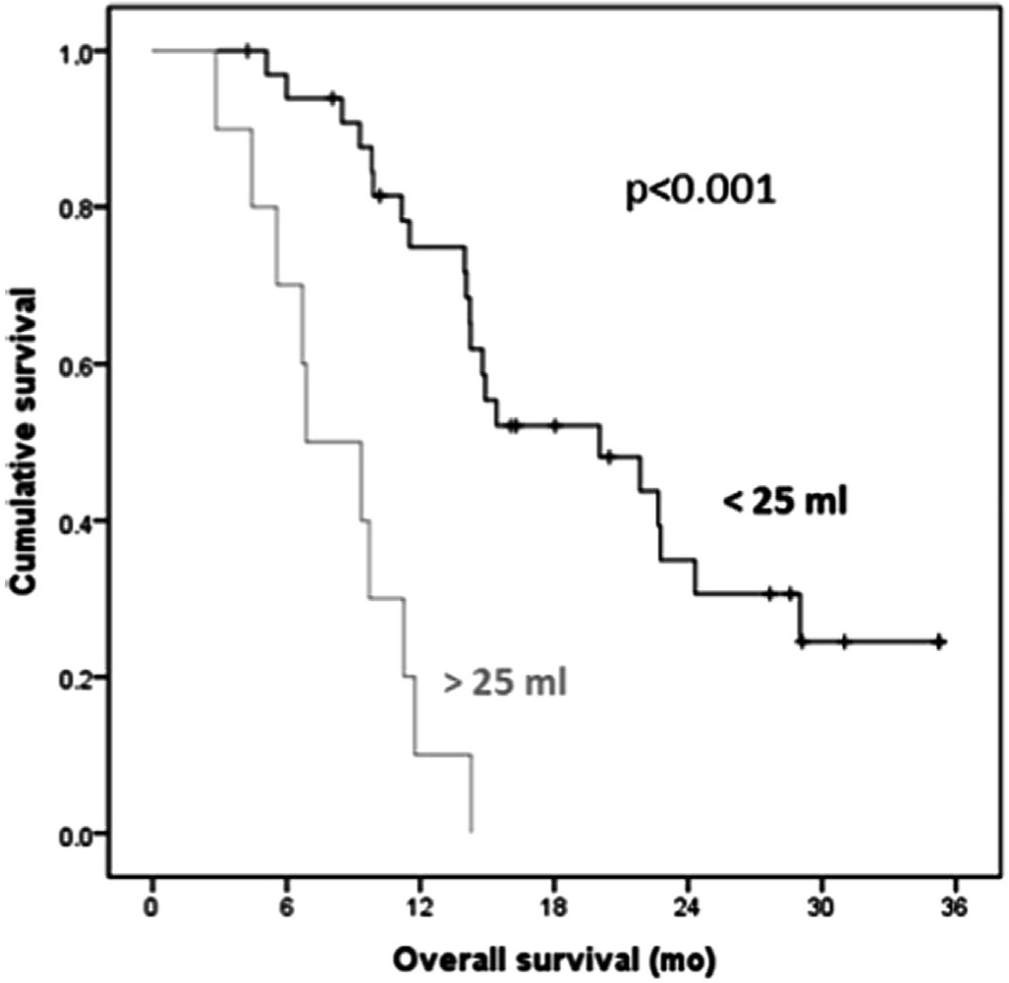
- 18F mayor vida media
- RM vs FET-PET ha mostrado diferencias entre los volúmenes en relación con la extensión tumoral
- Correlación histológica: **S** del 93% y una **E** 94%
- Puede predecir la respuesta al tratamiento

Pauleit. Brain 2005
Piroth. Radiother Oncol 2012
Galldiks N. J Nucl Med2012
Rieken. Radiother Oncol 2013



Prognostic impact of postoperative, pre-irradiation 18F-fluoroethyl-l-tyrosine uptake in glioblastoma patients treated with radiochemotherapy





Indicador de tumor residual postcirugía con valor pronóstico en **OS** y **DFS**

Piroth. Radiother Oncol 2011

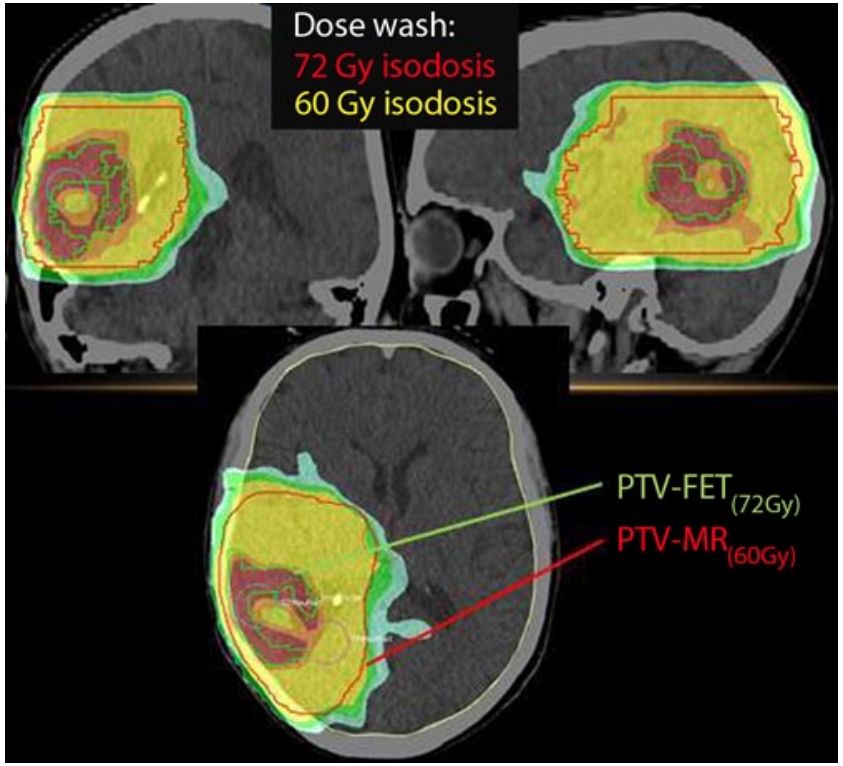


Fig. 1 ◀ Radiation treatment plan with PTV-FET$_{(72\ Gy)}$ (*green line*), PTV-MR$_{(60\ Gy)}$ (*red line*), 72 Gy isodosis (*yellow area*), and 60 Gy isodosis (*dark red*) as dose wash image

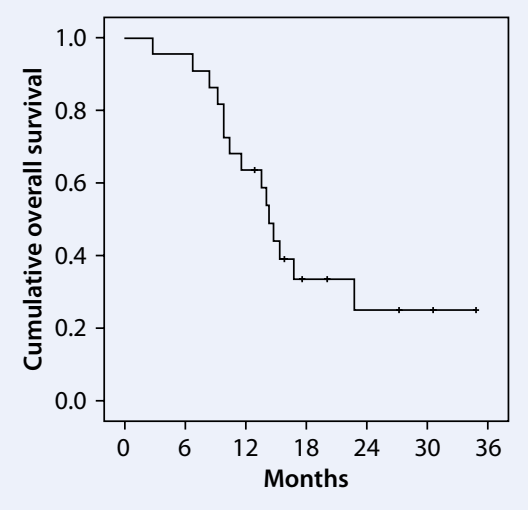


Fig. 2 ▲ Kaplan–Meier curve of overall survival

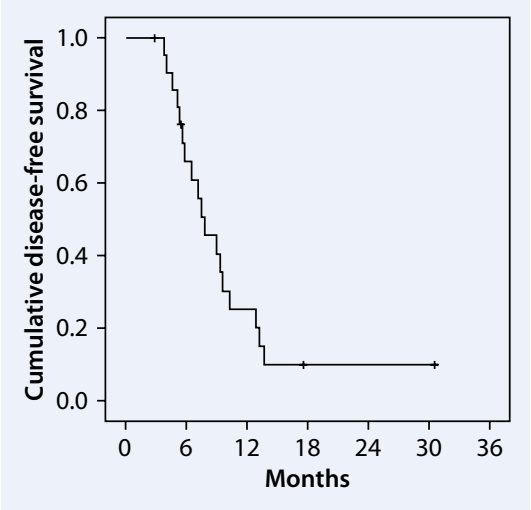


Fig. 3 ▲ Kaplan–Meier curve of disease-free survival

Incremento de dosis (72 Gy) basado en FET-PET no mejora OS pero tampoco aumenta toxicidad

Piroth. Strahlenther Onkol 2012

Conclusiones

1. El GTV MET-PET en la mayoría de los casos está incluido en el GTV T2-FLAIR y por lo tanto no modifica el CTV aunque no siempre es así
2. El PET-MET identifica áreas adicionales de alto riesgo silentes en T1-Gad que pueden ser subsidiarias de dosis más altas de irradiación (BTV)
3. El índice T/NT se asocia con la topografía de la recurrencia y la SLP
4. La introducción de nuevas técnicas de imagen como el PET-MET deben ser evaluadas de forma prospectiva para estudiar su impacto en el control local de la enfermedad.