



UNIVERSITÀ  
CATTOLICA  
del Sacro Cuore

XXIII CONGRESSO  
**AIRO2013**



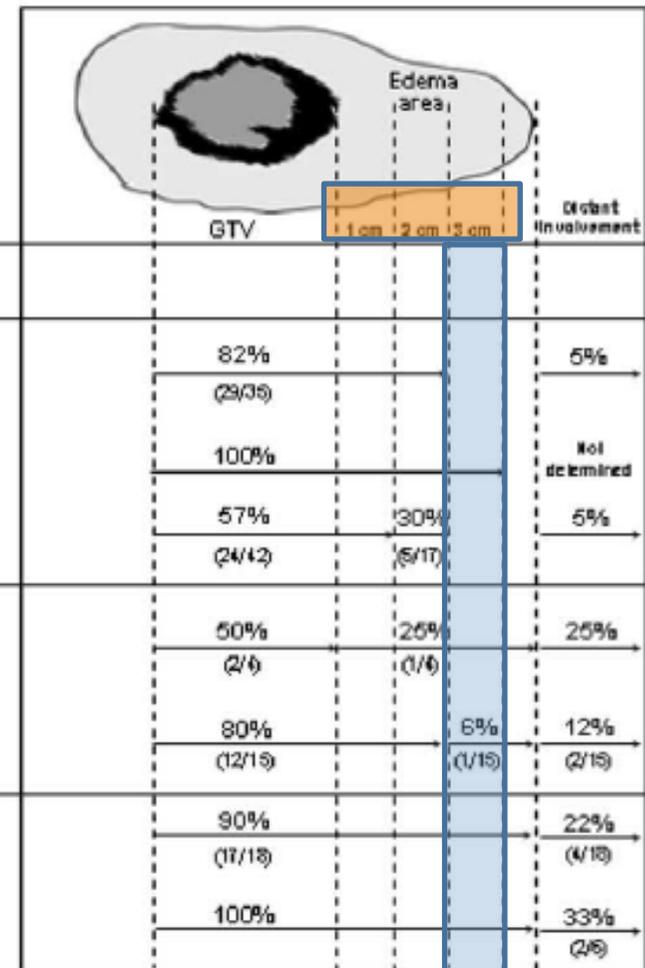
# **E' possibile escludere l'edema nella definizione del CTV nei Glioblastomi Multiformi senza aumentare il rischio di comparsa delle recidive?**

S. Chiesa, C. Mazarella, M. Ferro, G.R. D'Agostino, M. Ferro, V. Frascino, G. C. Mattiucci,  
C. Anile, C. Colosimo, A.G. Morganti, V. Valentini, M. Balducci

**Giardini Naxos-Taormina-27 Ottobre 2013**

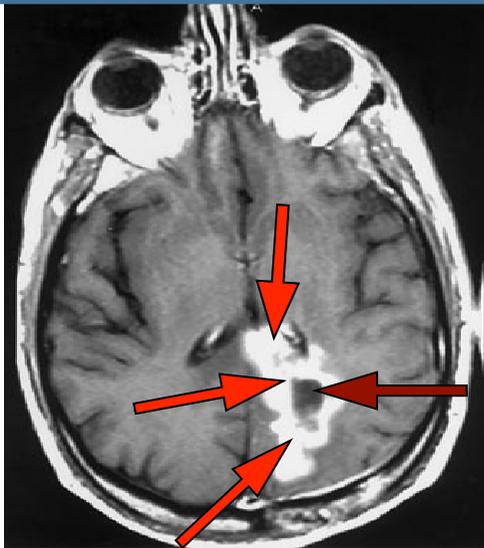
# Definizione Volumi

## GTV: Histopathological correlations with CT and MRI



Diagnostic means	No. cases / evaluable population	Ref author	1 cm	2 cm	3 cm	Direct Involvement
CT and stereotactic biopsies	35 GBM	Hochberg <sup>37</sup>	82%			5%
	15 GBM / 11 evaluable cases	Halperin <sup>40</sup>	(29/35)			
	29 (18 untreated GBM evaluable)	Greene <sup>38</sup>	100%			Not determined
CT and whole brain slices	8 (4 GBM)	Lilja <sup>41</sup>	57%	30%		5%
	15 GBM (11 untreated)	Burger <sup>39</sup>	(24/42)	(6/17)		
			50%	25%		25%
MRI and whole brain slices	26 GBM (18 postoperatives)	Watanabee <sup>43</sup>	80%	6%		12%
	18 GBM	Johnson <sup>45</sup>	(12/15)	(1/15)		(2/15)
			90%			22%
		(17/18)			(4/18)	
			100%			33%
						(2/6)

# Definizione Volumi



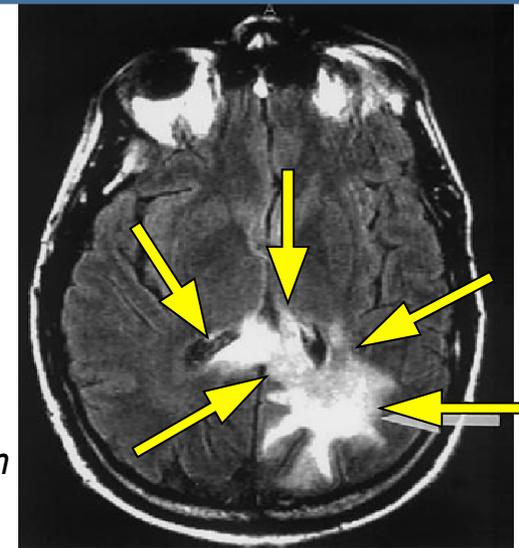
*Viable tumor cells*



*necrosis*



*Edematous brain containing tumor cells within 2-3 cm from border of necrotic center*



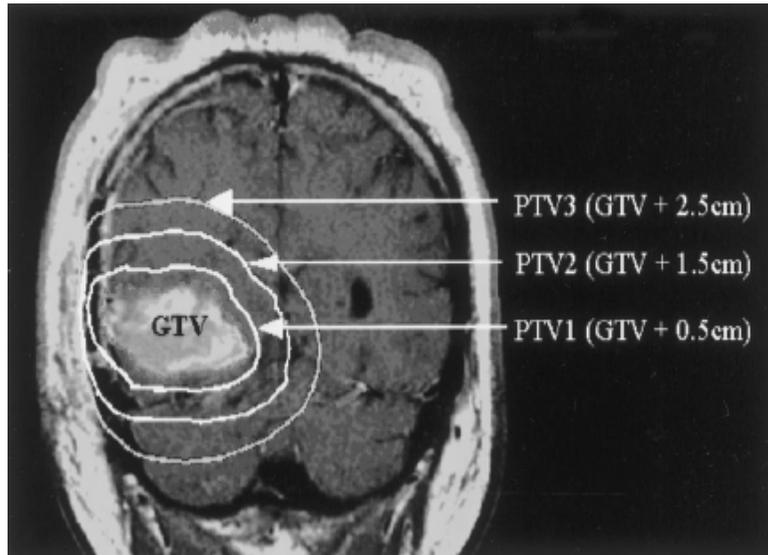
<i>Guideline</i>			
<i>RTOG (from RTOG 97-10<sup>6</sup>)</i>		<i>EORTC (from EORTC 22981/22961<sup>5</sup>)</i>	
<i>Phase 1 of 2</i>		<i>Phase 1 of 1</i>	
Treatment volume	Contrasting enhancing lesion, plus peritumoural edema, plus 2-cm margin to PTV	Treatment volume	Contrast enhancing lesion (GTV), plus 2-cm (or 3-cm) to CTV
Treatment dose	46 Gy in 2.0-Gy fractions	Treatment dose	50–60 Gy in 1.8-Gy to 2.0-Gy fractions
<i>Phase 2 of 2</i>			
Treatment volume	Contrast enhancing lesion (preoperative MR imaging), plus 2.5-cm margin to PTV		
Treatment dose	14 Gy boost in 2.0-Gy fractions		

PTV = planning target volume; GTV = gross tumour volume; CTV = clinical target volume; MR = magnetic resonance.

# Survival and Failure Patterns of High-Grade Gliomas After Three-Dimensional Conformal Radiotherapy

By June L. Chan, Susan W. Lee, Benedick A. Fraass, Daniel P. Normolle, Harry S. Greenberg, Larry R. Junck, Stephen S. Gebarski, and Howard M. Sandler

*Journal of Clinical Oncology*, Vol 20, No 6 (March 15), 2002



Recurrence

67,6% (23/36)

← 44 Gy  
← 60 Gy  
← 90 Gy

Table 5. Recurrence Location Characteristics

	Frequency	
	No. of Patients	%
Recurrence location		
Central	18/23	78
In-field	3/23	13
Marginal	2/23	9
Distant	0	
Reclassified location		
Inside	21/23	91
Marginal	2/23	9
Distant	0	

# 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<sup>a,b,\*</sup>, Dante Amelio<sup>c</sup>, Maurizio Amichetti<sup>c</sup>, Maurizio Salvati<sup>b</sup>, Roberta Muni<sup>a</sup>, Alessandro Bozzao<sup>d</sup>, Gaetano Lanzetta<sup>b</sup>, Stefania Scarpino<sup>e</sup>, Antonella Arcella<sup>b</sup>, Riccardo Maurizi Enrici<sup>a</sup>

<sup>a</sup>Department of Radiation Oncology, Sant' Andrea Hospital, University "La Sapienza", Rome, Italy; <sup>b</sup>Department of Neurosurgical Sciences, Neuromed Institute, Pozzilli (IS), Italy; <sup>c</sup>ATreP – Provincial Agency for Proton Therapy, Trento, Italy; <sup>d</sup>Department of Radiology; and <sup>e</sup>Department of Pathology, Sant' Andrea Hospital, University "La Sapienza", Rome, Italy

## Analysis of tumor recurrences in 105 patients with GBM.

Recurrence volume within radiation field	S'Andrea <sub>plans</sub>	RTOG <sub>plans</sub>
Central	79	80
In-field	6	7
Marginal	6	4
Outside	14	14

⊙ CTV1: cavo chirurgico +/- residuo + 2 cm margine

⊙ CTV2: CTV1 + 1 cm di margine

⊙ PTV2 (60 Gy) and PTV1 (50 Gy): CTVs +0,3 cm di margine

## Percent of volume of brain irradiated according to different plans.

	S'Andrea <sub>plans</sub> (residual tumor/cavity plus 2 cm)		RTOG <sub>plans</sub> (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<sub>plans</sub> and RTOG<sub>plans</sub> at a dose of 46 Gy.

\*\*  $P = 0.005$  between S'Andrea<sub>plans</sub> and RTOG<sub>plans</sub> at a dose of 60 Gy.

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

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Percent of volume of brain irradiated according to different plans.

	S'Andrea <sub>plans</sub> (residual tumor/cavity plus 2 cm)		RTOG <sub>plans</sub> (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

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\*\*  $P = 0.005$  between S'Andrea<sub>plans</sub> and RTOG<sub>plans</sub> at a dose of 60 Gy.

**Conclusions.** The use of target delineation using postoperative residual tumor and cavity plus 2-cm margin is associated with smaller volumes of normal brain irradiated without a significant increase of risk of marginal recurrences

# Obiettivo

Valutare l' **impatto** della definizione del **CTV2**, comprendente o meno l' **edema**, sul **controllo locale** e sulla **sopravvivenza** di pazienti affetti da GBM trattati con radioterapia (RT) e Temozolomide (TMZ) concomitante e sequenziale.



# Materiali e Metodi

- Diagnosi di GBM IV WHO
- CTV1: 59,4 Gy
- TMZ conc 75mg/mq + TMZ Adj

## GRUPPO A

Marzo 2008

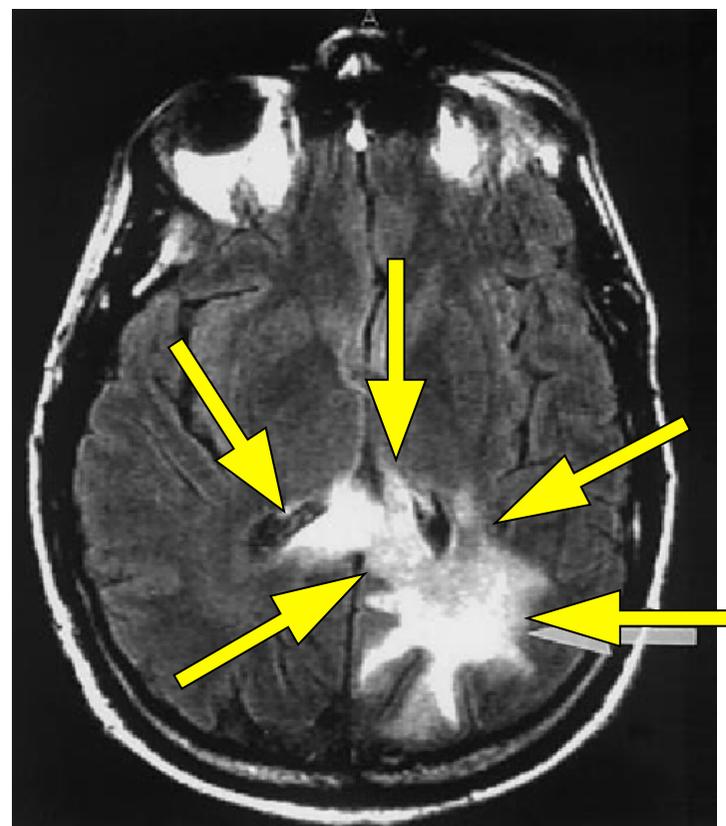
CTV2: Letto tumorale +/- residuo +  
**edema**

45 Gy

CTV1: letto tumorale +/- residuo +  
1,5 cm margine

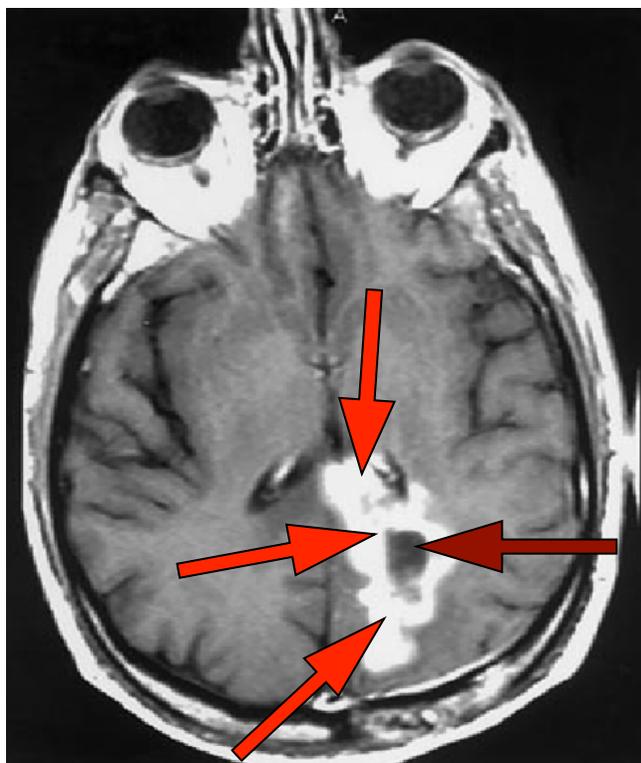
14,4 Gy

CTV1: 59,4Gy



# Materiali e Metodi

- Diagnosi di GBM IV WHO
- CTV1: 59.4 Gy
- TMZ conc 75mg/mq + TMZ Adj



## GRUPPO B

Aprile 2008 - Oggi

CTV2: Letto tumorale +/- residuo +  
2.5 cm **margin**  
46 Gy

CTV1: letto tumorale +/- residuo +  
1 cm margin  
14 Gy

CTV1: 59.4Gy



# Risultati: selezione dei pz

- Diagnosi di GBM IV WHO
- CTV1: 60 Gy
- TMZ conc 75mg/mq + TMZ Adj

261 pz

- 120 pz esclusi:
- Dose tot RT
  - Dose/fr RT
  - Altra schedula TMZ

141 pz

Gruppo A (edema): 66 pz

Gruppo B (margini): 75 pz



# Risultati

## Caratteristiche dei 141 pazienti reclutati

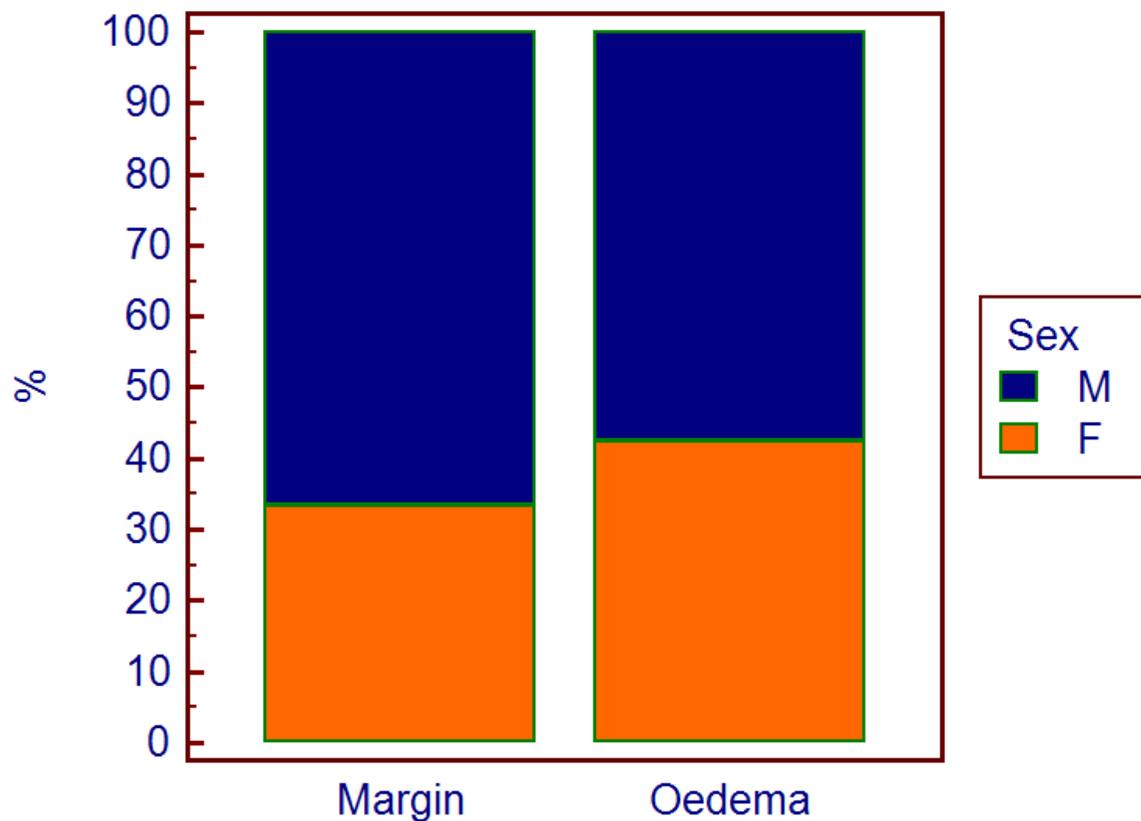
	Tot pz 141	Gruppo A (Edema) 66 pz	Gruppo B (Margini) 75 pz	p value
<b>Età</b> Mediana (aa) Range (aa)	61 21-28	63 21-80	60 21-79	<b>P=0.78</b> Test Mann Whitney



# Risultati

## Caratteristiche dei 141 pazienti reclutati

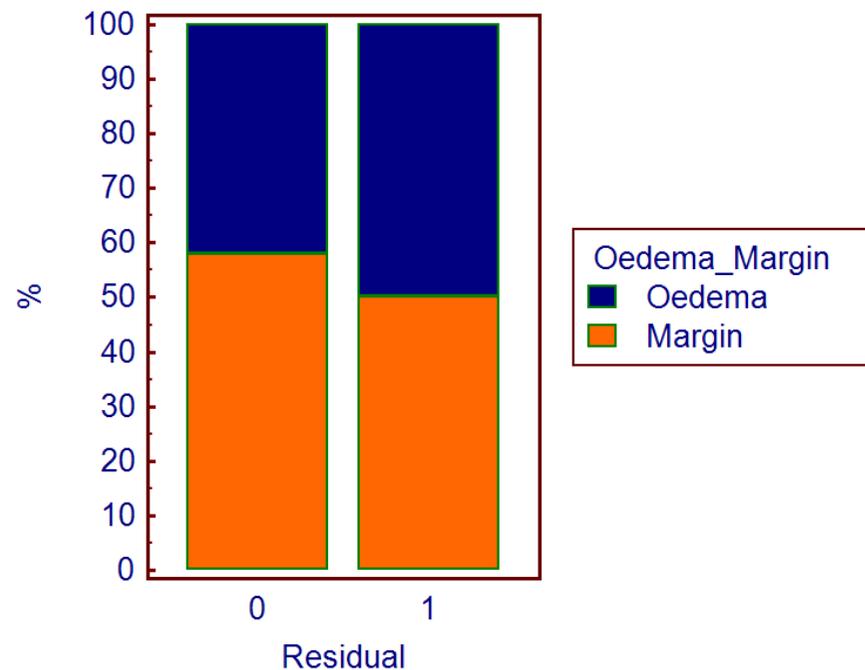
	Tot pz 141	Gruppo A (Edema) 66 pz	Gruppo B (Margini) 75 pz	p value
<b>Sesso</b>				<b>p: 0.34</b> Chi-squared test
Maschi	88 (75%)	38	50	
Femmine	53 (25%)	28	25	



# Risultati

## Caratteristiche dei 141 pazienti reclutati

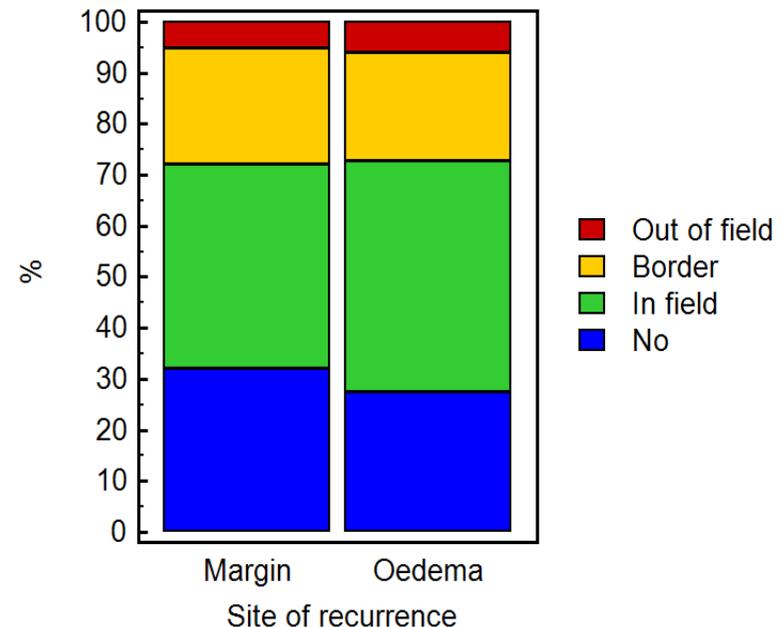
	Tot pz 141	Gruppo A (Edema) 66 pz	Gruppo B (Margini) 75 pz	p value
<b>Tipo di CH</b>				
Completa	57 (40,4%)	<u>Senza recidiva (18pz)</u> Completa: 6 (23%) Parziale: 12 (67%)	<u>Senza recidiva (24pz)</u> Completa: 12 (50%) Parziale: 12 (50%)	<b>p: 0.45</b> Chi-squared test
Parziale	84 (59,6%)	<u>Con recidiva (48 pz)</u> Completa: 18 Parziale: 30	<u>Con recidiva (51 pz)</u> Completa: 21 (41%) Parziale: 30 (59%)	



# Risultati

	Tot	Gruppo A (edema)	Gruppo B (margini)
	141 pz	66 pz	75 pz
Recidiva	99/141 (70,2%)	48/66 (73%)	51/75 (68%)
Sede recidiva	In field: 60 (61%) Marginali: 31 (31%) A distanza: 8 (8%)	In field: 30 (63%) Marginali: 14 (29%) A distanza: 4 (8%)	In field: 30 (59%) Marginali: 17 (33%) A distanza: 4 (8%)

**p=0.9**



# Risultati

	<b>Gruppo A (edema)</b>	<b>Gruppo B (margini)</b>
Dose ricevuta (Gy)	45	
Mediana Volume cc %	208.17 24.03	188.45 22.45
Range cc %	18.31-485.11 1.89-52.38	27.14-540.15 2.70-62.40
Enc sano irradiato cc Range	1356.16 1079.43-1707.66	925.71 109.25-1327.6



# Risultati

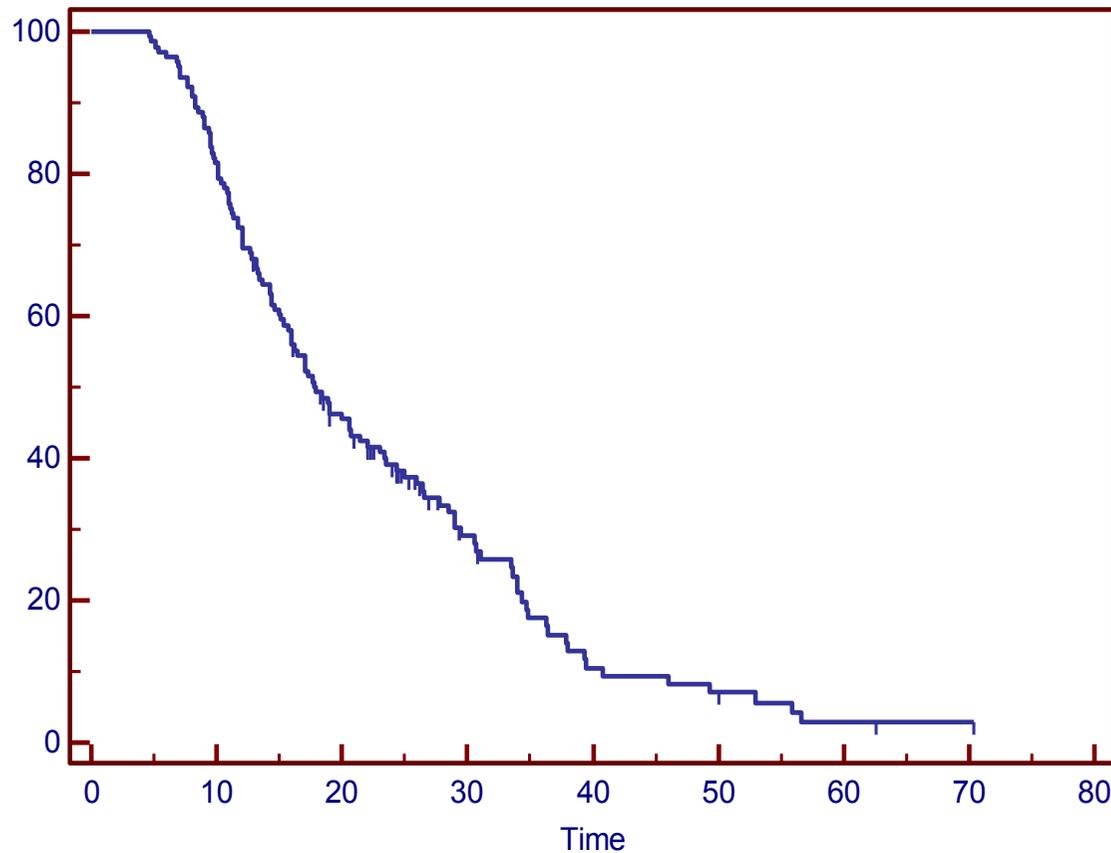
## TOSSICITA' NEUROLOGICA

	Gruppo A (edema) 66 pz	Gruppo B (marginari) 75 pz	Tot 141 pz
<b>Ipertensione endocranica</b>			
G0	56 (85%)	71 (95%)	127 (90%)
G1	7 (11%)	0	7 (5%)
G2	1 (1%)	4 (5%)	5 (4%)
G3	2 (3%)	0	2 (1%)
<b>Crisi epilettiche/ Stato funzionale</b>			
G0	58 (88%)	73 (96%)	131 (93%)
G1	3 (5%)	0	3 (2%)
G2	3 (5%)	1 (2%)	4 (3%)
G3	2 (2%)	1 (2%)	3 (2%)



# Risultati: PFS

FUP mediano: 57 mesi (range 6-116 mesi)



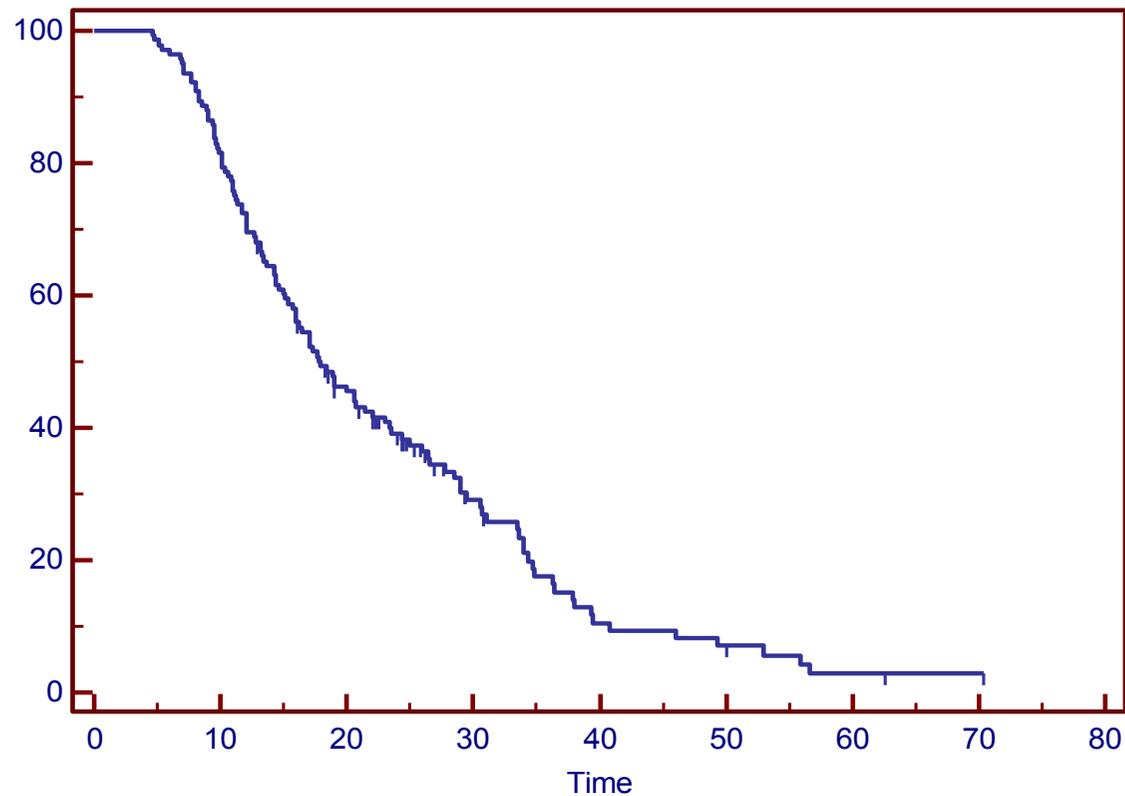
<b>Median PFS</b>	<b>13 mesi</b>
2 yrs	34%
5 yrs	0,06%

	<b>p</b>
Età	0,0402
Sede della recidiva	0,0052



# Risultati : OS

FUP mediano: 57 mesi (range 6-116 mesi)



<b>Median OS</b>	<b>17,8 mesi</b>
2 yrs	37,4%
5 yrs	0,02%

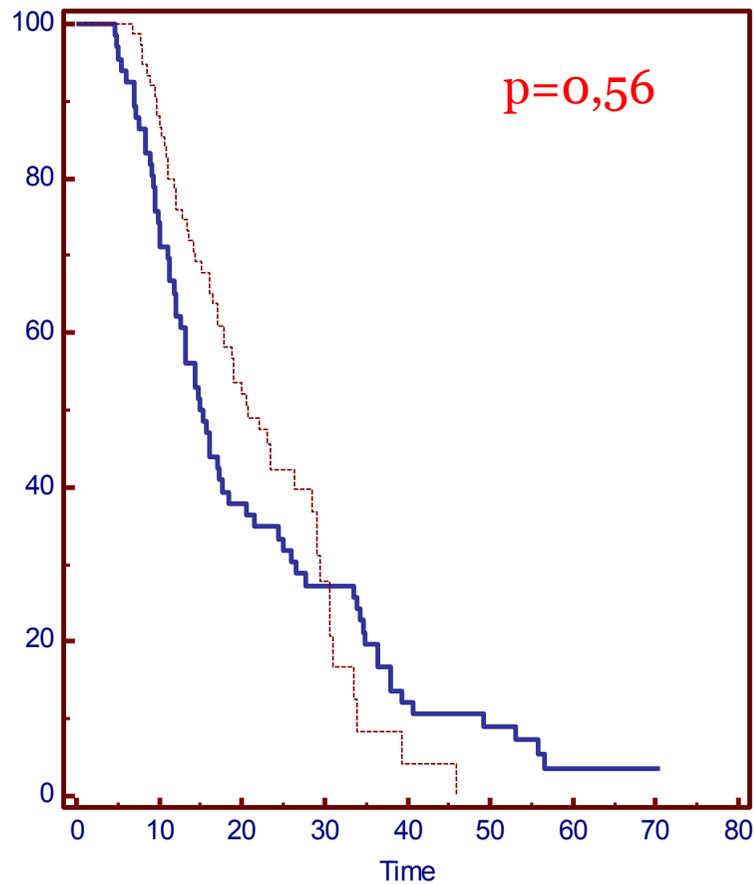
	<b>p</b>
Età	0,0004
Chirurgia	0,0081
Sede della recidiva	0,0040



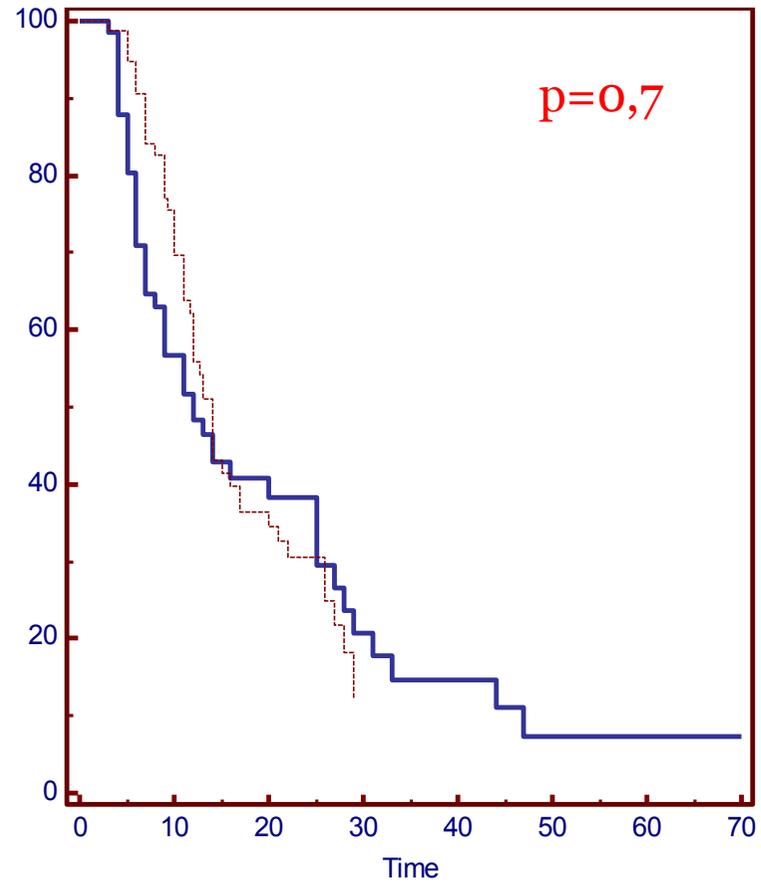
# Risultati: edema o margini

FUP mediano: 57 mesi (range 6-116 mesi)

OS



PFS



# Conclusioni

- **Recidiva locale** si conferma il pattern più frequente
- L'inclusione dell'**edema** nel CTV2 **non** sembra **influenzare** gli outcomes in modo significativo

