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Supratotal resection for newly diagnosed GBMs: is there a role for surgery beyond the enhancing boundaries?

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Background

- The **outcome** of newly diagnosed glioblastoma multiforme (GBM) patients is **poor**, with a median survival time of 15-18 months and 2 year overall survival rate of 25%.
- **Local progression** in the site of the primary treatment is **the main reason of failure** and it occurs in almost all patients within 1 year from the initial diagnosis
- Also in a **multimodal approach** the extent of surgical resection **(EOR)** has been diffusely recorded as conditioning survival in gliomas and recently widely investigated in GBM patients

Prognostic factors

Controversy remains regarding the optimal application of prognostic factors and the available treatment options in the clinical management of adult
patients with GBMs.

Tumour volume
Histology and grade
Patient age
Comorbidities
Post operative neurological status
The timing of surgical intervention
Completeness of resection
The use and type of adjuvant therapy

AIMS

MAXIMIZE CYTOREDUCTION → IMPROVE OUTCOME

MINIMIZE NEUROLOGICAL DEFICITS → IMPROVE QoL

Key concepts

- Extent of resection was defined as (pre-operative volume – post-operative volume/ pre-operative volume) x100%

- RTV defined as any residual post-contrast abnormality onto volumetric post-operative MRI, that was actually evident in the pre-operative study, independently from the percentage of tumor removal

Evidences

An extent of resection threshold for newly diagnosed glioblastomas

Clinical article

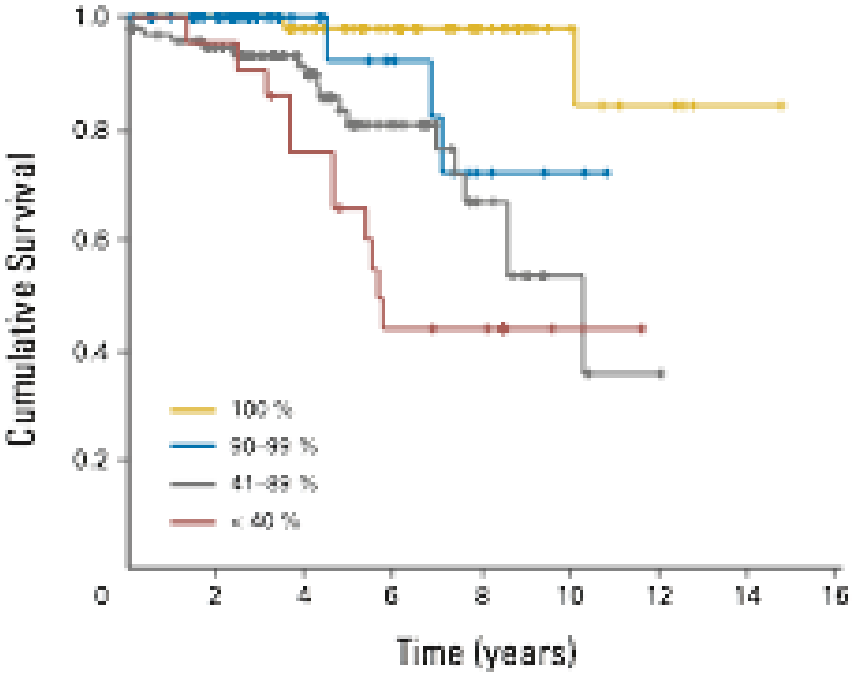
Nader Sanai, M.D.,[1] Mei-Yin Polley, Ph.D.,[2] Michael W. McDermott, M.D.,[1] Andrew T. Parsa, M.D., Ph.D.,[1] and Mitchel S. Berger, M.D.[1]

[1]Brain Tumor Research Center, and [2]Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California

JNS, 2011

The rationale: Why ?

What's the evidence?



Smith JS, Chang EF, Lamborn KR et al
J Clin Oncol (2008)

Sanai, N, Polley MY, MCDermott MW et al
J Neurosurgery (2011)

Survival advantage as little as 78%

Enhancing abnormalities

Table 1 | Selected retrospective studies on the influence of volumetric extent of glioma resection on patient survival

Study (year of publication)	Number of patients	WHO grade	Glioma histology	Association of extent of resection (EoR) with overall survival (OS)	Malignant transformation effect observed
Chaichana *et al.*[34] (2014)	259	IV	All	EoR ≥70%: median OS 14.4 months	NA
Sanai *et al.*[31] (2011)	500	IV	All	• EoR ≥78%: median OS 12.5 months • EoR ≥80%: median OS 12.8 months • EoR ≥90%: median OS 13.8 months • EoR 100%: median OS 16.0 months	NA
Pessina *et al.*[154] (2016)	136	III	All	• EoR <76%: 5-year OS 0%; 10-year OS 0% • EoR ≥76%: 5-year OS 68%; 10-year OS 42%	NA
Snyder *et al.*[155] (2014)	93	II	Oligodendroglioma	• EoR <90%: 5-year OS 87% • EoR ≥90%: 5-year OS 90%	No
Smith *et al.*[18] (2008)	216	II	All	• EoR <90%: 5-year OS 76%, 8-year OS 60% • EoR ≥90%: 5-year OS 97%, 8-year OS 91%	Yes

NA, not assessed.

Extent of tumour resection is positively associated with overall survival, although most of evidence supporting this issue is derived from retrospective studies

Different percentages and different outcomes

J Neurosurg 121:1115–1123, 2014

Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma

Clinical article

MATTHEW M. GRABOWSKI, B.S.,[1] PABLO F. RECINOS, M.D.,[1] AMY S. NOWACKI, PH.D.,[2] JASON L. SCHROEDER, M.D.,[1] LILYANA ANGELOV, M.D.,[1] GENE H. BARNETT, M.D., M.B.A.,[1] AND MICHAEL A. VOGELBAUM, M.D., PH.D.[1]

[1]Brain Tumor and Neuro-Oncology Center and Department of Neurosurgery, and [2]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio

CONCLUSIONS: contrast enhanced residual tumor volume (CE-RTV) and EOR were found to be significant predictors of survival after GBM resection. CE-RTV was the more significant predictor of survival compared with EOR, suggesting that the volume of residual contrast-enhancing tumor may be a more accurate and meaningful reflection of the pathobiology of GBM.

Ann Surg Oncol (2016) 23:3040–3046
DOI 10.1245/s10434-016-5222-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – NEURO-ONCOLOGY

Value of Surgical Resection in Patients with Newly Diagnosed Grade III Glioma Treated in a Multimodal Approach: Surgery, Chemotherapy and Radiotherapy

Federico Pessina, MD[1], Pierina Navarria, MD[2], Luca Cozzi, PhD[2], Anna Maria Ascolese, MD[2], Matteo Simonelli, MD[3], Armando Santoro, MD[3], Stefano Tomatis, MSc[2], Marco Riva, MD[1], Enrica Fava, MD[1], Marta Scorsetti, MD[2], and Lorenzo Bello, MD[1]

[1]Department of Neurosurgery, Istituto Clinico Humanitas, Milan, Italy; [2]Department of Radiotherapy, Istituto Clinico Humanitas, Milan, Italy; [3]Department of Oncology and Hematology, Istituto Clinico Humanitas, Milan, Italy

Also in grade III RTV is a factor stronger than EOR affecting PFS and OS

Importance of volumetric assessment in treatment management

It is pivotal

to categorize different amount of resection

to establish a threshold of residual volume influencing survival

to differentiate the radiological and pathological features of residual tumors able to impact

Notwithstanding complete resection of enhancing areas, 80–90 % of relapses were marginal to treatment field (*Petrecca et al, J Neuroncology, 2013*)

Gliomas high infiltration trend (LGG experience)

Swanson (*J Neurol Sci* and *BR J Cancer*, 2008)

Sterotactic biopies and in vitro cell cultures

The region outside enhancing areas is usually infiltered by tumor cells

Flair alterations

Resection of Flair abnormalities (SUPr) recently introduced in GBM

LI et al (JNS, 2016) analyzed 1229 patients

Significative impact on OS if Flair abnormalities resection ≥ 53.21% ($p<0.001$)

Patients underwent **different adjuvant treatments** (40% of patients before EORTC NCIC trial), 39% of patients previously treated

Importance of morbidity (as reported by McGirt et al, new motor or language deficits are associated with significant decreases in the median survival of patients with GBM suggesting the needs of maximal tumor resection preserving neurological integrity): **brain mapping**

Table 1. Study Demographics

Investigator	Country	Definition of GTR	Definition of SPTR	HR: Group Comparison*	HR: Multivariate Analysis†	Quality of Evidence (GRADE)‡
Aldave et al.,[12] 2013	Spain	100% of CE area	100% of CE + total resection of fluorescing tumor	Yes	Yes	3
Li et al.,[8] 2016	USA	100% of CE area	100% of CE + >0%–100% FLAIR	Yes	Yes	2
Eyüpoglu et al.,[19] 2016	Germany	100% of CE area	100% of CE + total resection of fluorescing tumor	Yes	No	3
Pessina et al.,[28] 2017	Italy	100% of CE area	100% of CE + 100% of FLAIR	Yes	Yes	3
Esquenazi et al.,[18] 2017	USA	95%–100% of CE area	>100% of CE	Yes	Yes	3
Glenn et al.,[21] 2018	USA	100% of CE area	100% of CE + >1 cm of surrounding brain tissue	Yes	Yes	4

Different definitions of completness of surgical resection and supratotal resection

J Neurooncol (2017) 135:129–139
DOI 10.1007/s11060-017-2559-9

CLINICAL STUDY

Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience

Federico Pessina[1] · Pierina Navarria[2] · Luca Cozzi[2,4] · Anna Maria Ascolese[2] · Matteo Simonelli[3] · Armando Santoro[3] · Elena Clerici[2] · Marco Rossi[1] · Marta Scorsetti[2,4] · Lorenzo Bello[1]

Our analysis

Retrospective evaluation

. Impact of different EOR entities on PFS and OS

. Comparison outcome of GTR at decreasing interval of Flair RTV with SUPr

. Threshold of FLAIR RTV

Methods

282 patients included from December 2003 to October 2015

- All patients underwent surgery plus concomitant and adjuvant chemoradiotherapy as for Stupp regimen
- The lesion and RTV were measured by three indipendent physicians on pre and post-operative MR (T1 contrast enhanced and Flair sequences)
- Surgery aimed at maximally remove tumor mass according with functional boundaries: cortical and subcortical mapping, intraoperative ultrasounds, neuronavigation

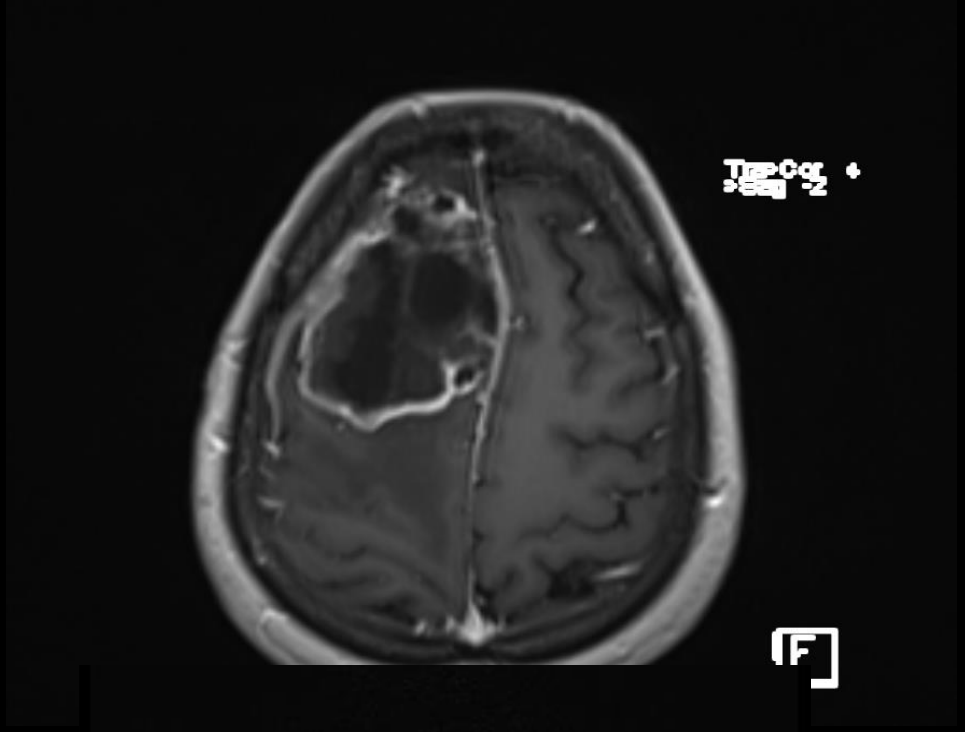
EOR

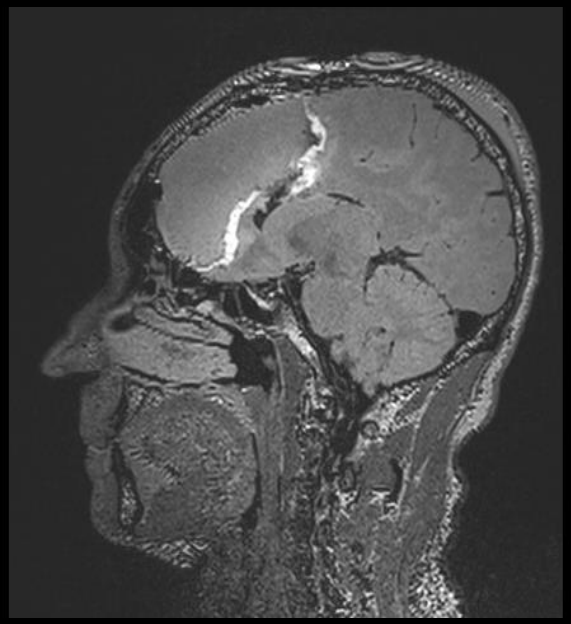
SUPr: resection of 100% of enhancing areas and Flair abnormalities

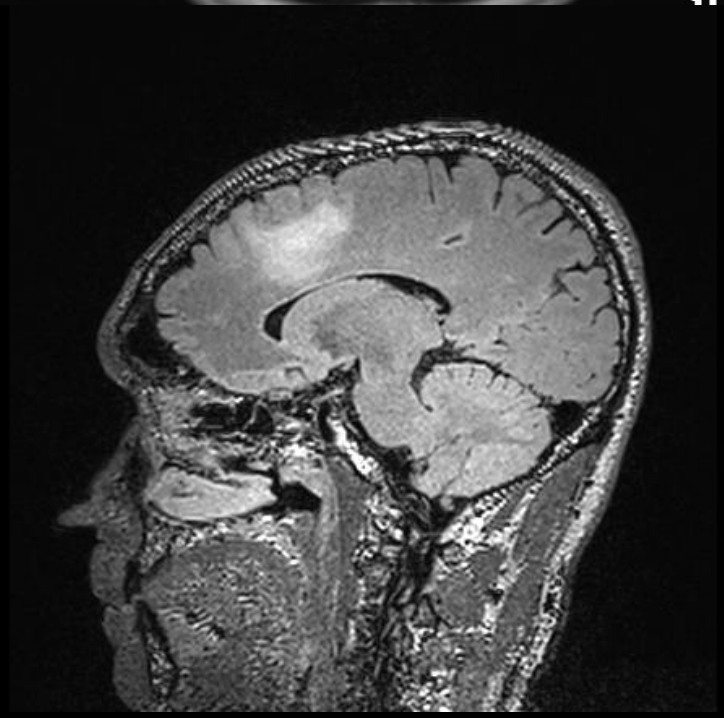
GTR: resection between 90-100% of enhancing areas with variable RTV of Flair abnormalities

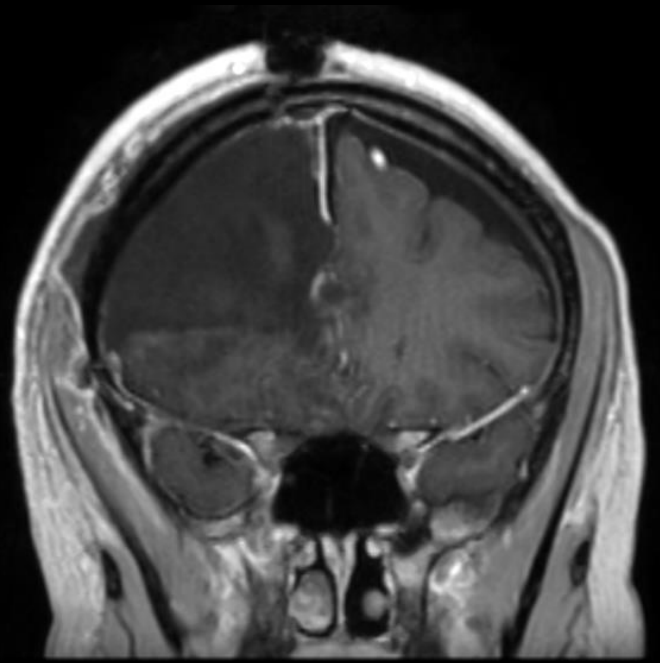
STR: resection between 10-89% of enhancing areas

B: resection < 10% of enhancing areas









Methods

RTV was defined as any residual abnormality on postoperative MRI that was evident in the preoperative study. Particularly, FLAIR MRI was used to measure not enhancing residual masses (FLAIR-RTV).

In case of GTR we dichotomized FLAIR residual volume in increments of 5% to eventually obtain a relevant RTV threshold

Lesions were classified with functional grading score (Sawaya et al)

Clinical outcome was evaluated by neurological examination on admission, at discharge and during the brain MRI performed one month after treatment and then every 3 months

Table 1 Patients, tumors characteristics and treatments performed

	N of patients	%
Total	282	100
Gender		
Female	105	37.2
Male	177	62.8
Median Age	61 yrs	(range 21-82 yrs)
Karnosky Performance Status (KPS)		
60	9	3.2
70	50	17.7
80	116	41.4
90	74	26.2
100	33	11.7
Isocitrate dehydrogenase (IDH) mutation status		
Wild type	273	96.8
Mutated	9	3.2
O-6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status		
Methylated	160	56.7
Unmethylated	122	43.3
Tumor volume(TV)		
Median preoperative total TV cm^3	59.1 cm^3	(range 9.1-399.4 cm^3)
Median preoperative FLAIR TV	19.0 cm^3	(range 1.5-337.7 cm^3)
Surgery		
Supratotal resection (SUPr)	21	7.4
Gross total resection (GTR)	60	21.3
Subtotal Resection (STR)	143	50.7
Biopsy (B)	58	20.6
Adjuvant treatment		
RT+concurrentCHT+ adjuvant CHT (TMZ)	282	100

Results

Median follow up time was

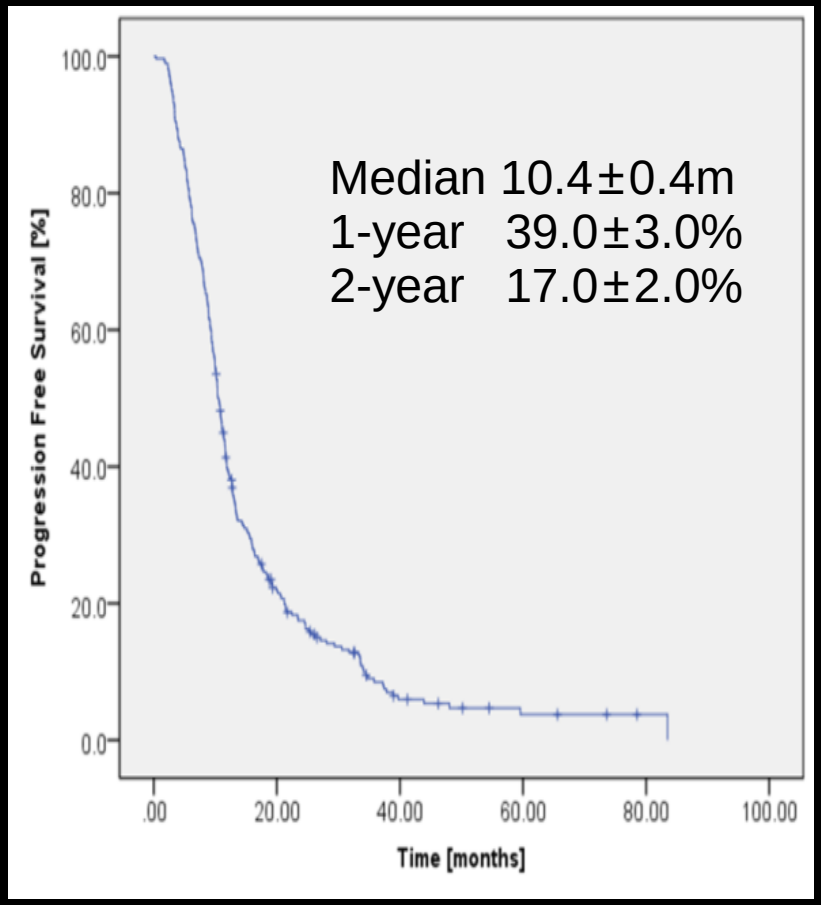
13.8 months (range 4.0-86.5 months) for the entire cohort

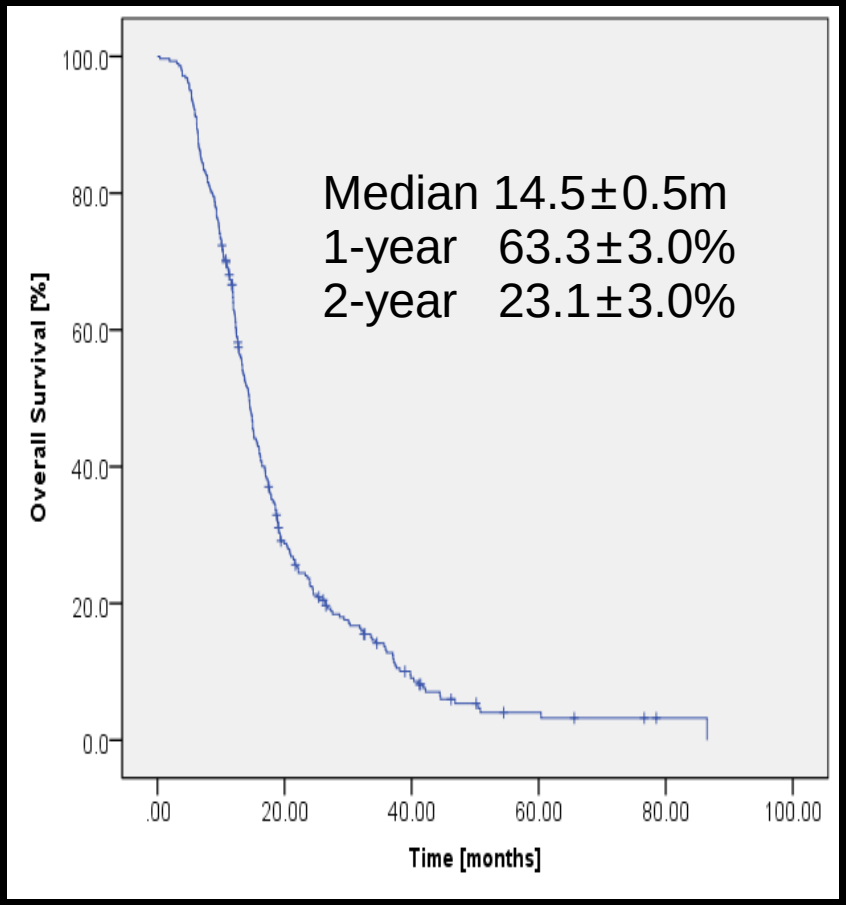
25.7 months (range 10.1-78.5 months) for the alive patients

Last observation time 254 (90.1%) patients were dead

73% of patients had local recurrence, in 6.1% of cases associated with distant

Population PFS and OS

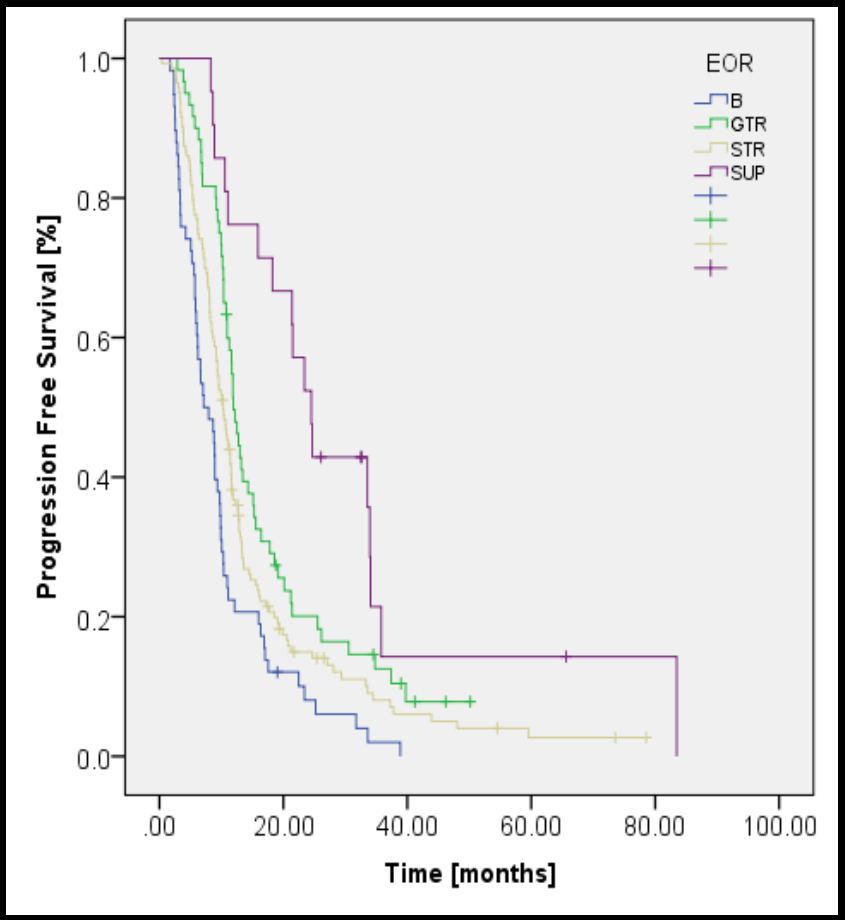




Factors recorded as conditioning progression free survival (PFS) and overall survival (OS)

Factors analyzed	median PFS mos (95%CI)	1-year PFS %	2-year PFS %	p value/analysis univ.	multiv.	median OS mos	1-year OS %	2-year OS %	p value/analysis univ.	multiv.
KPS										
60-70	6.6±0.5 (5.6-7.7)	20±5	5±3	**<0.001**	**<0.001**	9.3±0.7 (7.9-10.7)	37±6	7±3	**<0.001**	**<0.001**
80	10.6±0.5 (9.7-11.5)	39±5	24±3			13.6±0.8 (11.9-15.2)	62±4	20±4		
90-100	12.8±1.3 (10.2-15.5)	51±4	28±5			17.5±1 (15.5-19.6)	78±4	35±5		
MGMT status										
methylated	11.9±0.6 (10.8-12.9)	49±4	24±3	**<0.001**	**0.02**	16.2±0.9 (14.5-17.9)	71±4	28±4	**<0.001**	**0.02**
unmethylated	9.2±0.4 (8.4-9.9)	26±4	9±3			12.2±0.4 (11.5-12.9)	52±5	16±3		
EOR										
SUP	24.5±2.4 (19.8-29.2)	76±9	52±11	**<0.001**	**0.001**	28.6±5.2 (18.4-38.9)	90±6	71±10	**<0.001**	**0.001**
GTR	11.9±0.6 (10.7-13.1)	49±7	19±5			16.2±1.2 (13.9-18.6)	81±5	24±6		
STR	10.3±0.7 (8.9-11.6)	36±4	14±3			13.8±0.8 (12.2-15.4)	59±4	19±3		
B	7.2±1.4 (4.5-9.9)	21±6	8±4			7.2±1.4 (4.5-9.9)	40±6	10±4		
Eloquence										
Eloquent	5.7±0.3 (5.1-6.3)	25±10	0	**0.003**	0.06	9.0±1.9 (5.2-12.8)	45±11	5±5	**0.03**	NS
Near eloquent	10.4±0.4 (6.6-11.3)	39±4	19±3			14.5±0.6 (13.3-15.7)	64.3±	23±3		
Not Eloquent	11.4±1.1 (9.2-13.6)	45±6	19±5			14.9±1.9 (11.2-18.6)	66±6	27±6		
FLAIR removal										
≥45%	11.9±0.6 (10.7-13.1)	62±7	41±7	**0.001**	**0.03**	24.5±2.8 (18.9-30.1)	88±5	54±7	**<0.001**	**0.001**
<45%	19.2±3.2 (12.9-25.4)	44±9	9±5			15.7±0.8 (14.2-17.2)	79±7	12±6		

EOR


EOR
B
GTR
STR
SUP
Progression Free Survival [%]
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20.00
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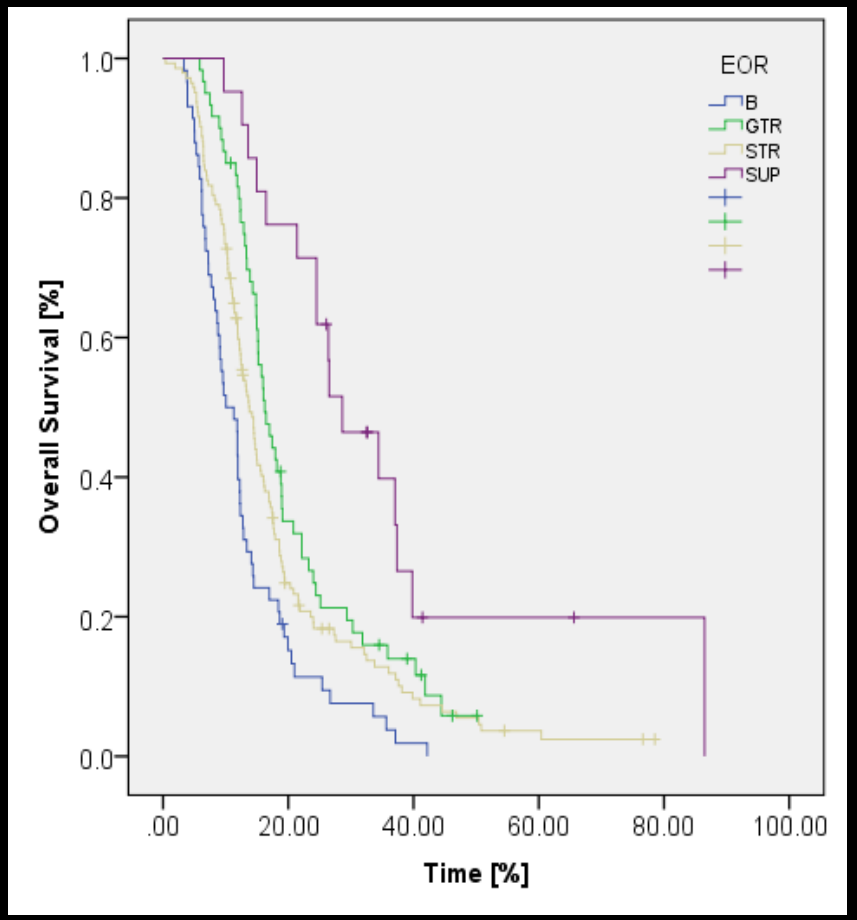
Time [months]


EOR
B
GTR
STR
SUP
Overall Survival [%]
1.0
0.8
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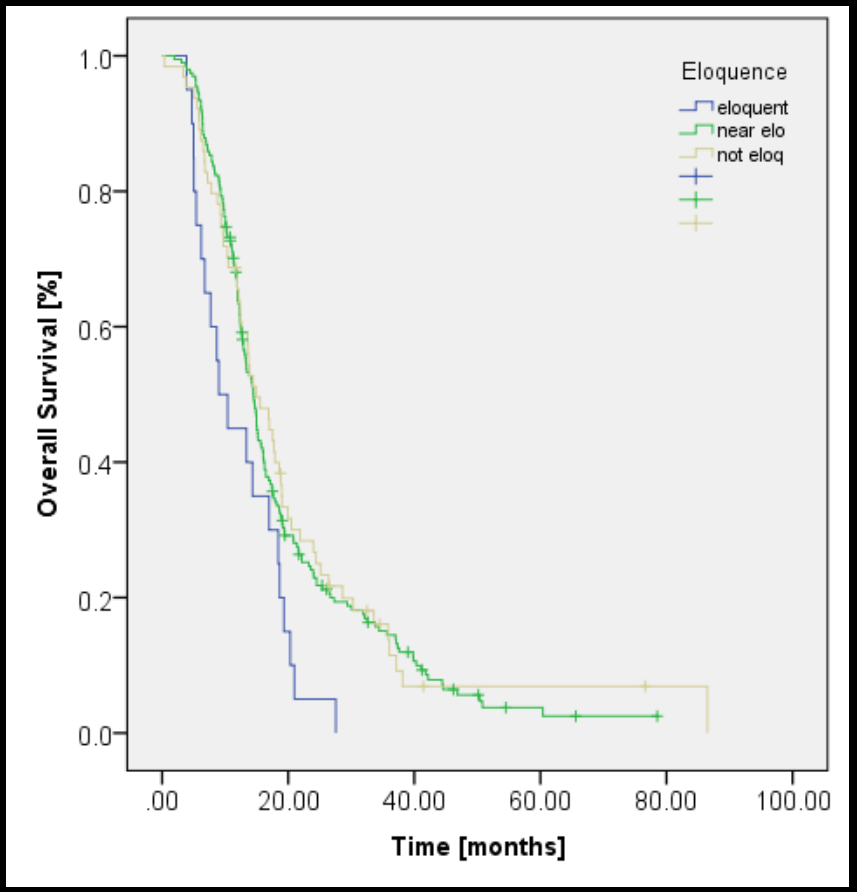
20.00
40.00
60.00
80.00
100.00
Time [%]

TFG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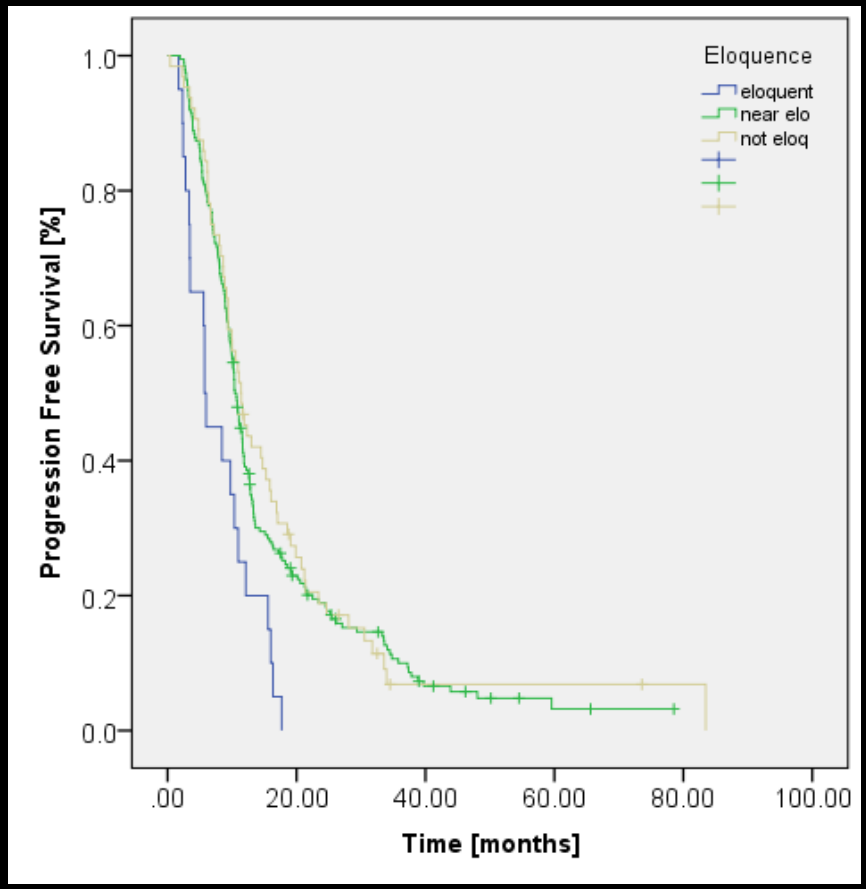
Time [months]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Progression Free Survival [%]
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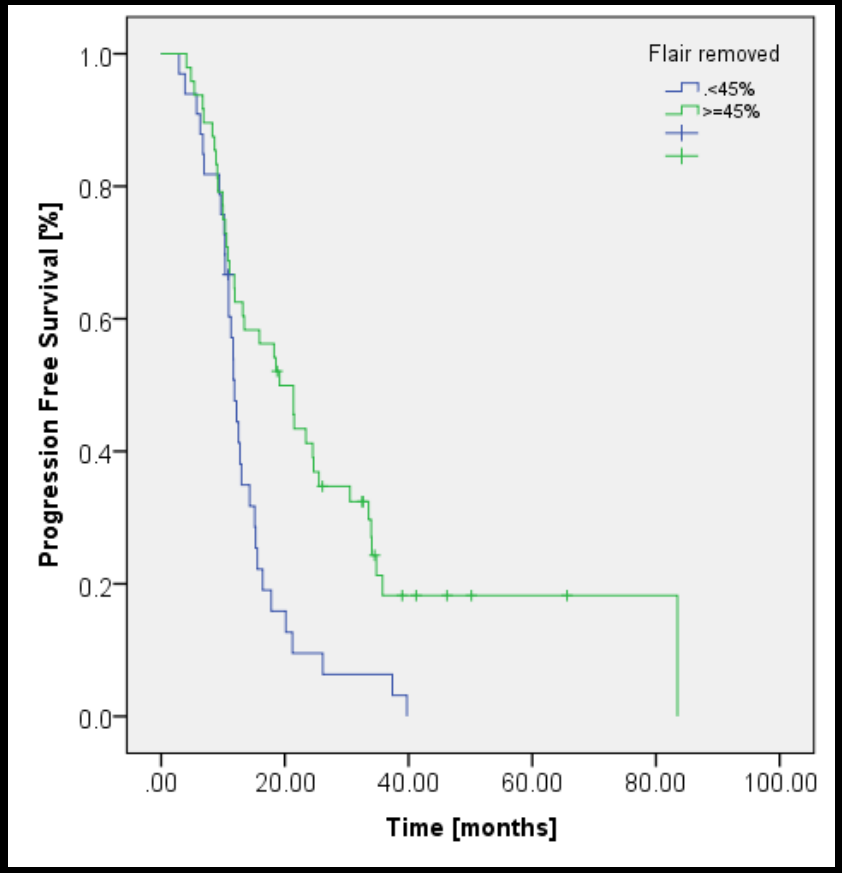
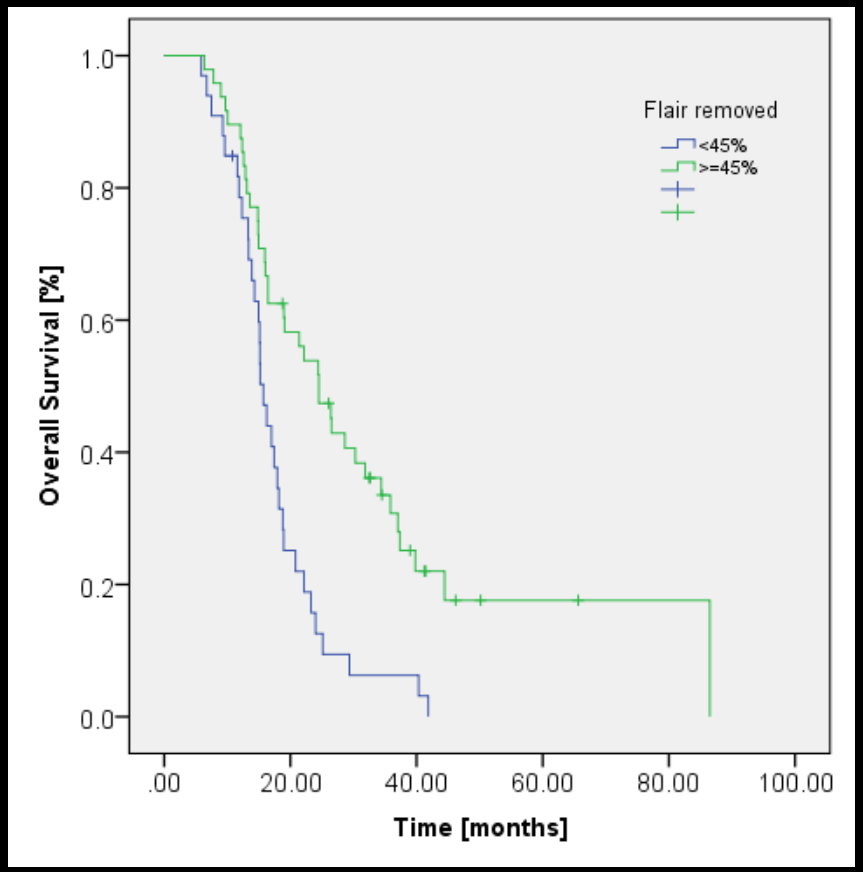
100.00
Time [months]

% of Flair abnormalities removal





Mortality and perioperative morbidity

No mortality

35 perioperative complications:

- 14 hematomas (new surgery)
- 9 pulmonary thromboembolisms
- 12 infections (2 weeks of median hospitalization)

Table 3 pre-operative neurological symptoms and post-operative clinical status in relation to the extent of resection (EOR)

	N.	Deficits												
Symptoms		haedache	dizziness	diplopia	seizures	Ideo-motor	sensitive	motor	visual	language	SUPr	GTR	STR	B
Asymptomatic	10													
Symptomatic	272													
Preoperative symptoms	272	58	14	5	99	22	15	33	8	18	6	25	23	11
Postoperative symptoms														
Stable	39	0	0	0	0	0	6	19	8	6	3	3	8	0
Improved	35	0	0	0	0	0	9	14	0	12	1	4	1	8
Worsened	0	0	0	0	0	0	0	0	0	0	1	8	8	2
Complete remission	198	58	14	5	99	22	0	0	0	0	1	10	6	1
New ND	8				6			1		1			8	

ND=neurological deficit; EOR=extent of resection; SUPr=supratotal resection; CR=complete resection;GTR=gross total resection; STR=subtotal resection; B=biopsy;

Conclusions

Our results compare favorably with previous report, confirming the strong value of EOR, particularly considering that the entire cohort of patients received the ilk adjuvant treatment

The median OS time and 2 year OS rate were 29 months and 71% for patients underwent maximal resection compared to 16 months and 24%, for patients underwent GTR of enhancing tumor and different amounts of FLAIR alterations.

The identified cut-off value of FLAIR removal influencing outcome was 45%, with a 2 years OS rate of 54% in case of FLAIR-RTV lower than 45% and 12% in case of FLAIR-RTV higher

Using this strategy no major neurological morbidities were recorded in case of GTR or SUPr.

Final remarks

Classical limitations of the retrospective studies

Precisely distinguish tumor invasion from brain edema on Flair MRI

To minimize the variables related to characteristics of tumors and treatments

The systematical employing of intraoperative neurophysiological mapping, when needed, and the ilk standardized volume calculation modality in all cases

A careful patients selection is pivotal but further analysis can give **more robust data** on this strategy

The field of Neuro-Oncology

Neuro*Surgery*

Neuro*Psychology*

Neuro*Radiology*

Neuro*Physiology*

Nuclear Medicine

Neuro*Oncology*

Basic Research

Neurological Rehab

Radiation Therapy

Current clinical management is necessarily multidisciplinary

Thank you