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Treatment of Recurrent Glioblastoma (GB) after Radiotherapy (RT) and Temozolomide (TMZ): A retrospective analysis of the GLIOCAT study*

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Background

- **There is no standard treatment in recurrent GB** and overall survival (OS) ranges from 3 to 9 months.
- Standards of care for patients with recurrent GB are not well defined. Clinical decision making is influenced by previous treatment, age, Karnofsky performance score (KPS), and patterns of progression.
- **Possible treatments after recurrence are**: Nitrosourea (NU); Temozolomide (TMZ) rechallenge; Bevacizumab (BVZ); Second surgery; Re-irradiation or Experimental therapy. [Weller et al. *Lancet Oncol* 2017]

Objective

- **The aim** of this study was to identify clinical or biological factors that guide the best therapeutic strategy in recurrent GB.

Methods

• Between 2005 to 2014, data from 432 patients (pts) diagnosed of GB from 6 University Hospitals from Catalonia were collected into the GLIOCAT study database*.
• **All pts were treated uniformly by the "Stupp regimen"** (Radiotherapy plus concomitant Temozolomide followed by maintenance Temozolomide).
• They were followed by MRI every 3 months
• We identified **397 pts** who had recurrent GB**: 250 pts received 1 or more active treatment and 147 pts did not.**
• We analysed clinical and molecular characteristics, treatments received, OS and progression-free survival (PFS).

Results

Analysis of prognostic factors with respect to treated and untreated patients:

		Treated: 250	Not Treated: 147	Total: 397	P-value X [2]
Gender	Male	151	86	237	0.71
	Female	99	61	160	
Age	Median	58	67	397	< 0.001*
Mini-Mental	< 27	36	29	65	0.003
	≥ 27	87	26	113	
KPS	≥ 70	200	89	289	< 0.001
	< 70	16	23	39	
MGMT	Methylated	95	55	150	0.25
	Unmethylated	122	54	176	
Type of initial surgery	Complete	33	8	41	<0.001
	Partial or not MRI <72hours	180	96	276	
	Biopsy	23	34	57	
IDH	(+)	8	1	9	0.13
	(-)	151	83	234	
6 cycles of maintenance TMZ	Yes	130	127	257	<0.001
	No	120	20	140	

* U Mann-Whitney

Pts not treated al recurrence were older, had worse KPS (p<0.001), worse Mini-Mental (MM) (p=0.003), more biopsies than complete resection and did not complete the 6 cycles of adjuvant TMZ (p<0.001)

- **Median lines of treatment after recurrence: 1 (0-5)**

- **Treatment at First recurrence**:

	n	%
Systemic alone	189	47,6
Surgery alone	30	7.6
Surgery + CT	19	4,8
Surgery + RT + CT	2	0.5
Radiotherapy alone	6	1,6
Unknown	4	1
Palliative Care	147	37,0
Total	397	100,0

CT: Chemotherapy; RT: Radiotherapy

Type systemic treatment	N (%)
Bevacizumab ± Irinotecan	90 (48)
Temozolomide	27 (14)
Nitrosourea or Procarbazine schedules	27 (14)
Clinical Trial	42 (22)
Total	186 (98)

- **Treatment In Second recurrence:**

	n	%
Systemic alone	112	48.7
Surgery + CT	1	0.4
Surgery + RT + CT	1	0.4
Surgery	6	2.6
Radiotherapy	4	1.7
Unknown	4	1.7
Palliative Care	102	44,3
Total	230	100,0

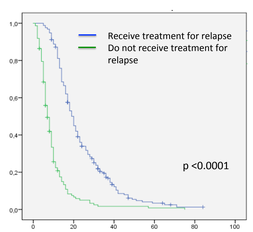
Type systemic treatment	N (%)
Bevacizumab ± Irinotecan	42 (33)
Temozolomide	19 (15)
Nitrosourea or Procarbazine	31 (24)
Clinical Trial	11 (9)
Tamoxifen	4 (3.5)
Platin schedules	3 (2.5)
Total	111 (99)

- **Treatment in third recurrence:**

	n	%
Systemic alone	40	36.5
Surgery alone	1	1
Radiotherapy	1	1
Unknown	3	3
Palliative Care	65	59
Total	110	100

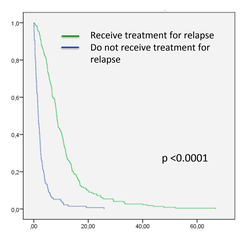
Type systemic treatment	N (%)
NU or Procarbazine schedules	17
Bevacizumab ± Irinotecan	12
Clinical Trial	7
Carboplatin	2
Tamoxifen	2
Total	40 (100)

Overall Survival from diagnoses



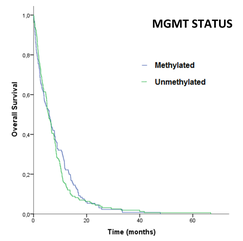
	Mean (CI 95%)	Median (CI 95%)
Treated	23.8m (21.8-25.7)	20 (18.5-21.4)
Not Treated	9.6m (8-11.3)	7 (5.8-8.1)
Overall	18.8 (17.2-20.3)	14 12.6-15.3)

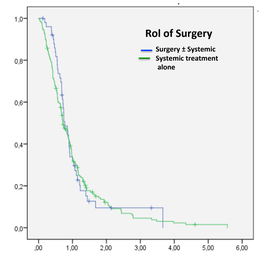
Overall Survival from 1st recurrence:

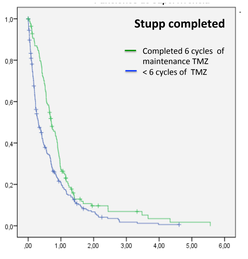


	n	Mean (CI 95%)	Median (CI 95%)
Treated	135	10.7m (9.4-11.9)	8.4m(7.8-8.9)
Not Treated	222	2.5m (2-3.1)	1.6 m(1.3-2)
Overall	357	7.6 (6.6-8.5)	5(4.3-5.8)

Overall Survival from 1st recurrence:







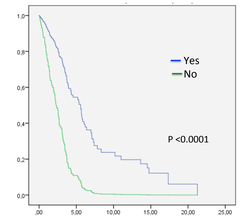
STATUS MGMT	n	Mean (CI 95%)	Median (CI 95%)
Methylated	131	7.8 m (6.5-9.2)	5.9 (4.1-7.6)
Non methyl.	158	7.6 m (6.3-8.9)	5.5 (4.3-6.7)
Total	289	7.7 m (6,7-8.6)	5.7 (4.7-6.6)

In univariate analysis for OS: MGMT status, to have completed or not the 6 maintenance TMZ cycles, Second Surgery, treatment with BCZ or not, and TMZ or NU in first recurrence did not show any statistical significance.

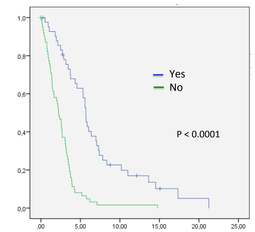
Multivariate analysis of OS:

		n	Sig.	Exp(B)	CI 95,0% Inferior	CI 95,0% Superior
Treated	YES	116		1		
	NO	50	0,000	5,033	3,289	7,702
KPS ≥ 70	YES	140		1		
	NO	26	0,117	1,439	0,913	2,268
Age	≥ 65y	61		1		
	< 65 y	105	0,615	1,103	0,753	1,616
MGMT	Methylated	144		1,023	0.801	1.306
	Not Met	165	0.855	1		
Minimental	< 27	62		1		
	>= 27	104	0,805	1,044	0,743	1,466
Complete 6 cycles of maintenance TMZ	YES	112	0.49	1	0.842	1.431
	NO	197		1.097		
Type of initial surgery	Complete Resection (MRI < 72h)	24	0,005			
	Partial R. or not MRI<72h	112	0,726	1,089	0,676	1,753
	Biopsy	30	0,009	2,202	1,219	3,978

Received treatment on 2nd recurrence



Received treatment on 3th recurrence



Median PFS in successive lines:

mPFS	Overall	BVZ	TMZ	NU-PCZ	Trial
1st to 2nd Recurrence	3.8 m	5.05 m	4.5 m	2.4 m	3.1 m
2nd to 3th Recurrence	2.8 m	3.9 m	2.5 m	2.6 m	2.3 m

Conclusions

- **Pts who received treatment at recurrence offered a better OS in multivariate analysis.**
- **MGMT methylation is not a predictor of better OS in recurrence.**
- **Pts undergoing second surgery did not present better OS than those who only received systemic T.**
- **Pts treated with Bevacizumab had longer PFS but not longer OS.**

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