A model for survival from glioblastoma multiforme in a cohort of consecutive non-selected patients from a single institution

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Background

- Despite survival benefits in Glioblastoma Multiforme (GBM) patients treated with combined Radiotherapy (RT) and Temozolomide (TMZ), nearly all patients experience relapse and under 10% survive 5 years after diagnosis
- Individualized therapy could be a way to increase the survival of GBM patients, however this requires the identification of prognostic parameters.
- Although a number of clinical and molecular parameters have been correlated to the survival of GBM patients receiving RT/TMZ, no predictive parameters have yet been implemented into clinical routine

Aim

To develop a prognostic tool able to calculate the survival of GBM patients treated with radiation/TMZ therapy

Patients and methods

Patients:

- 225 consecutive patients with newly diagnosed GBM (WHO grade IV) recruited from 2005 to 2010 who were not selected other than having ECOG PS 0–2. Patient demographics are shown in table 1.

Primary treatment:

- Patients underwent surgery prior to additional therapy.
- They received 6 weeks of concomitant RT (60 Gy to the planning target volume in 30 fractions with 5 fractions/week)/TMZ (75 mg/m2/day) therapy.
- Four weeks after completion the therapy, patients were given up to 6 courses of adjuvant TMZ therapy (TMZ for 5 days followed by 23 days without therapy). The dose of the initial course was 150 mg/m2/day, while the remaining courses was 200 mg/m2/day

Treatment at relapse:

- Patients who maintained ECOG PS 0–2 were initially considered for secondary surgery removing as much tumor as possible
- Most patients were additionally considered for second-line therapy with bevacizumab (BEV, 10 mg/kg)/ Irinotecan (IRI) therapy, given every 2 weeks

Evaluation:

- **Clinical:** Contrast and non-contrast MRI scans were made at diagnosis and repeated after 2, 5, and 6 courses of adjuvant TMZ. Patients' neurological and clinical performance, together with corticosteroid treatment, was recorded at these time points. All patients were thereafter followed every 3 months until death or study cut-off date using the same procedures
- **IHC:** Were made using antibodies against p53, EGFR and MGMT. Reactions were semiquantitatively evaluated according to the number of cells stained: <10%, 10–25%, 26–50%, and >50%. For statistical analysis, expression evaluated as <10% was considered negative, while ≥10% was considered positive.

Statistical analysis:

- Univariate and multivariate analyses of response data were performed using logistic regression analysis modeling the probability of best MacDonald response. Univariate and multivariate analyses of OS and TTP for the chosen explanatory variables were performed using the Cox proportional hazards regression model.
- Estimates of survival probabilities for OS and TTP were performed by the Kaplan-Meier method.
- Analysis of time-dependent variables were performed using the landmark method as well as the time-dependent Cox regression model.
- P values < .05 were considered significant.
- Calculations have been performed using IBM SPSS Statistics (v19) and SAS (v9.2)

Patient demographics, therapy and response

Table 1

Age (years), median (range)		59.2 (22.6–75.4)
Gender, *n* (%)	Female	80 (35.6)
	Male	145 (64.4)
ECOG performance status, *n* (%)	0	132 (58.7)
	1	66 (29.3)
	2	19 (8.4)
	Missing	8 (3.6)
Multifocal Disease, *n* (%)	Yes	26 (11.6)
	No	198 (88)
	Missing	1 (0.4)
Extent of tumor resection, *n* (%)	Biopsy	29 (12.9)
	Partial resection	104 (46.2)
	Gross total resection	89 (39.6)
	Missing	3 (1.3)
Corticosteroid therapy at initiation of RT/TMZ, *n* (%)	Yes	165 (73.3)
	No	57 (25.3)
	Missing	3 (1.3)
No. of TMZ cycles following initial RT/TMZ, *n* (%)	Median	3
	0	36 (16.0)
	1	13 (5.8)
	2	54 (24.0)
	3	12 (5.3)
	4	10 (4.4)
	5	23 (10.2)
	6	75 (33.3)
	Missing	2 (0.9)
Reoperation, *n* (%)	Yes	74 (33.0)
	No	151 (67.0)
Second-line TMZ therapy, *n* (%)	Yes	12 (5.3)
	No	213 (94.7)
Second-line BEV/IRI therapy	Yes	85 (37.8)
	No	132(58.7)
	Missing	8 (3.6)
Follow-up duration (months), median (range)		60 (23–92)
Best clinical response, *n* (%)	CR	6 (2.7)
	PR	17 (7.5)
	SD	93 (41.3)
	PD	94 (41.8)
	Missing	15 (6.7)

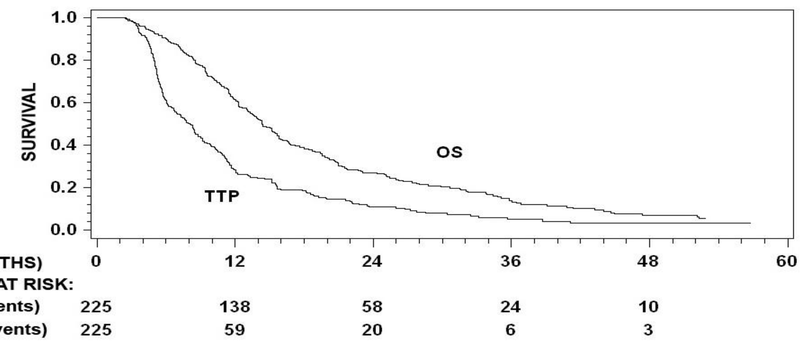
Abbrevations: CR, complete response; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease; TMZ, temozolomide

Results

- Median overall survival (OS) and time to progression (TTP) were 14.3 and 8.0 months, respectively (figure 1)
- Second-line therapy indicated that reoperation and/or BEV/IRI therapy increased patient survival compared with untreated patients and that BEV/IRI was more effective than reoperation alone (table 2)
- Patient age, Performance status (PS) and use of corticosteroid therapy were significantly correlated with patient survival and disease progression on univariate analysis (table 3)
- p53, EGFR, and MGMT expression, tumor size or multifocality, or extent of primary operation were not significant on OS, TTP or best response in univariate analysis (table 3)
- A model based on patient age, PS and corticosteroids use, able to calculate the survival probability at different time-points from diagnosis for an individual patient was estimated (figure 2)
- The predictive value of the model is at present validated in an independent dataset (n=67) (figure 3)

TTP and OS for the patient population

Figure 1:



Curves are based on data from all 225 examined patients. Numbers for patients at risk at selected times are shown in addition to the total number of events (deaths for OS and progression for TTP).

Effect of second-line treatment

Table 2

Treatment	OS (HR) (95%CI)
Reoperation	
vs. no therapy	0.39 (0.25-0.60)
vs. Reoperation and BEV/IRI	1.96 (1.20-3.23)
BEV/IRI	
vs. no therapy	0.23 (0.15-0.34)
vs. Reoperation and BEV/IRI	1.15 (0.73-2.17)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival, BEV, bevacizumab; IRI, irinotecan

Univariate analysis of correlation of molecular markers with survival, disease progression, and response

Table 3

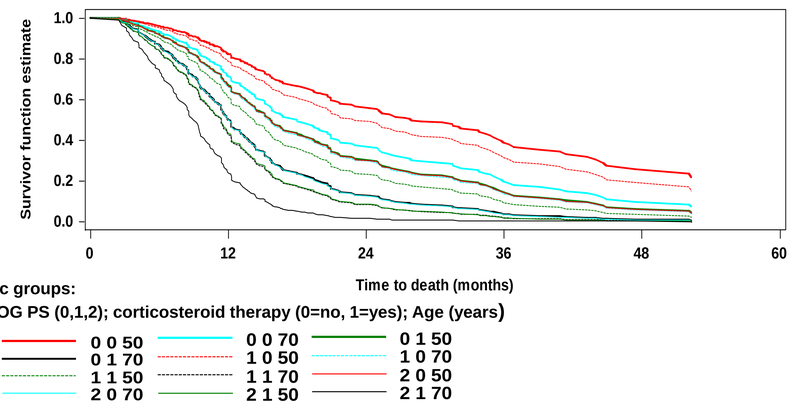
Covariate	OS (HR) [95% CI]	TTP (HR) [95% CI]	Best Response (OR) [95% CI]
Operation			
Gross total *vs.* biopsy	0.76 (0.49–1.17)	0.74 (0.48–1.16)	4.00 (0.49–32)
Partial *vs.* biopsy	0.98 (0.64–1.50) *P* = .22	0.86 (0.56–1.32) *P* = .37	2.13 (0.25–17) *P* = .24
Age (per 10-year increase)	1.36 (1.17–1.58) ***P* < .0001**	1.17 (1.01–1.36) ***P* = .034**	0.66 (0.44–0.99) ***P* = .045**
Gender (female *vs.* male)	1.11 (0.83–1.47) *P* = .47	1.07 (0.8–1.44) *P* = .64	1.68 (0.70–4.02) *P* = .24
Multifocal *vs.* single lesion	1.23 (0.80–1.88) *P* = .34	1.26 (0.82–1.93) *P* = .29	NA
Tumor size (2-fold increase)	1.00 (0.88–1.14) *P* = .97	0.98 (0.87–1.11) *P* = .74	1.39 (0.89–2.16) *P* = .15
Corticosteroid therapy (yes *vs.* no)	2.13 (1.49–2.86) ***P* < .0001**	1.41 (1.02–1.92) ***P* = .036**	0.57 (0.23–1.39) *P* = .22

Covariate	OS (HR) [95% CI]	TTP (HR) [95% CI]	Best Response (OR) [95% CI]
ECOG performance status			
1 *vs.* 0	1.42 (1.04–1.94)	1.33 (0.97–1.84)	0.22(0.05–0.97)
2 *vs.* 0	2.31 (1.40–3.82) ***P* = .0015**	1.70 (1.03–2.80) ***P* = .046**	0.71(0.15–3.35) *P* = .13
EGFR			
Positive (*n* = 145)	1.05 (0.77-1.43)	0.82 (0.61-1.12)	1.06 (0.22-1.91)
Negative (*n* = 54)	*P* = .75	*P* = .21	*P* = .43
Missing (*n* = 26)			
P53			
Positive (*n* = 105)	0.76 (0.55-1.05)	0.92 (0.66-1.27)	2.64 (0.99-7.1)
Negative (*n* = 97)	*P* = 0.10	*P* = .60	*P* = .053
Missing (*n* = 23)			
MGMT			
Positive (*n* = 65)	0.97 (0.64-1.48)	0.90 (0.59-1.36)	1.78 (0.52-6.13)
Negative (*n* = 98)	*P* = 0.89	*P* = 0.61	*P* = .36
Missing (*n* = 62)			

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; OS, overall survival; TTP, time to disease progression.

Estimated survival probabilities of newly diagnosed GBM patients

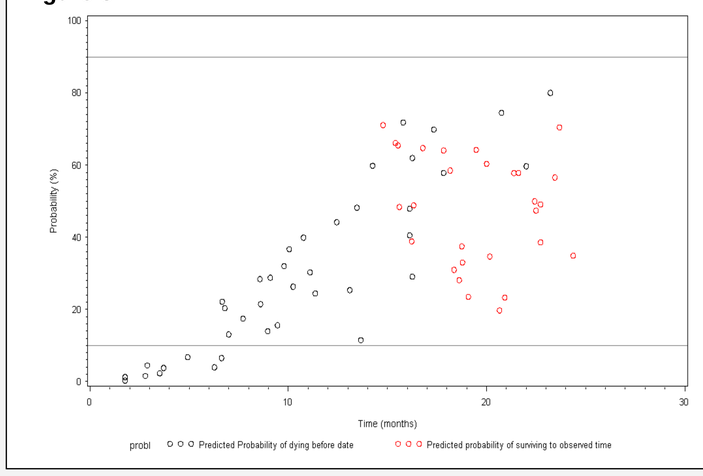
Figure 2:



Curves show predicted survival chances following diagnosis for newly diagnosed GBM patients being exact 50 and 70 years old with varying PS and corticosteroid status. The overall concordance index (C-index) for the model was 0.82 (95% CI, 0.71–0.92).

Results of applying the linear predictor to the validation cohort (n=67)

Figure 3:



Conclusion

The survival of RT/TMZ-treated GBM patients can be predicted based on patient age, PS and corticosteroid therapy status