European Journal of Cancer (2012) **48**, 1176–1184

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New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: A pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials

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Available online 28 March 2012

KEYWORDS
Recurrent glioblastoma
Prognostic models
Predictive accuracy
Risk calculators

Abstract ***Background:*** Prognostic models have been developed to predict survival of patients with newly diagnosed glioblastoma (GBM). To improve predictions, models should be updated with information at the recurrence. We performed a pooled analysis of European Organization for Research and Treatment of Cancer (EORTC) trials on recurrent glioblastoma to validate existing clinical prognostic factors, identify new markers, and derive new predictions for overall survival (OS) and progression free survival (PFS).

Methods: Data from 300 patients with recurrent GBM recruited in eight phase I or II trials conducted by the EORTC Brain Tumour Group were used to evaluate patient's age, sex, World Health Organisation (WHO) performance status (PS), presence of neurological deficits, disease history, use of steroids or anti-epileptics and disease characteristics to predict PFS and OS. Prognostic calculators were developed in patients initially treated by chemoradiation with temozolomide.

Results: Poor PS and more than one target lesion had a significant negative prognostic impact for both PFS and OS. Patients with large tumours measured by the maximum diameter of the

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http://dx.doi.org/10.1016/j.ejca.2012.02.004

largest lesion ($\geqslant$42 mm) and treated with steroids at baseline had shorter OS. Tumours with predominant frontal location had better survival. Age and sex did not show independent prognostic values for PFS or OS.

Conclusions: This analysis confirms performance status but not age as a major prognostic factor for PFS and OS in recurrent GBM. Patients with multiple and large lesions have an increased risk of death. With these data prognostic calculators with confidence intervals for both medians and fixed time probabilities of survival were derived.

1. Introduction

The prognosis of patients with glioblastoma (GBM) remains dismal despite substantial therapeutic improvement provided by chemoradiation with temozolomide (TMZ) at the initial diagnosis.[1] As yet, there is still no universally accepted standard treatment at the first recurrence, many patients being treated with nitrosoureas (e.g. lomustine [CCNU]) or with bevacizumab or considered for experimental therapy within clinical trials.[2] Clinical trials of new treatments or novel approaches aiming at improving outcome after disease recurrence are urgently needed. In order to identify a real sign of activity of investigational treatments, reliable end-points for phase II trials are required. Probabilities of progression-free survival at 6 months (PFS6) and of overall survival at 1 year (OS12) are both recognised end-points for clinical trials to assess the outcome of patients with recurrent GBM.[3] The identification of accurate prognostic factors is an important issue to guide therapeutic decisions and patient management.[4] In a previous report, we reviewed the prognostic importance of clinicobiological factors for predicting survival in newly diagnosed GBM. We showed that combined and concomitant radio and TMZ chemotherapy (TMZ/Radiotherapy (RT) $\rightarrow$ TMZ), O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, extent of primary surgery, age, World Health Organization (WHO) performance status (PS), Mini-Mental State Examination (MMSE) and administration of corticosteroids at the baseline strongly impacted on patient's survival.[5] At the time of tumour progression other prognostic factors may be relevant. Patients commonly have an altered performance status, and will require more frequent corticosteroids administration. Furthermore, treatment specific molecular alterations may be selected for in the recurrent tumour, such as inactivation of mismatch repair pathway constituents in TMZ treated patients.[6] The New Approaches to Brain Tumor Therapy Central Nervous System (NABTT CNS) Consortium performed a Recursive Partitioning Analysis (RPA) for overall survival in recurrent high-grade gliomas. They identified histology, age, Karnofsky's index (KPS), tumour localisation and corticosteroids at the baseline as important prognostic factors.[7] Joint North Central Cancer Treatment Group (NCCTG) and North America Brain Tumor Coalition (NABTC) analyses found grade, age, PS, baseline steroids and time since initial diagnosis (Wu et al., 2010) as most influential factors for survival.[8]

Dempsey et al. showed that a large tumour by volumetric measurement had a detrimental effect on survival in a group of malignant gliomas. They also identified older age and male sex as risk factors for survival.[9] Age was not identified as an independent prognostic factor for survival in two previous reports.[10,11]

We have pooled the data from phase I and phase II clinical trials on recurrent GBM conducted by the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumour Group (BTG) in order to further assess prognostic factors for clinical outcome and to develop prognostic models. We have derived prognostic calculators providing estimates with confidence intervals for both medians and fixed time probabilities of survival.

2. Patients and methods

2.1. Patient selection

Between 1999 and 2010, the EORTC has conducted eight prospective multicentre phase 1 and phase 2 clinical trials investigating safety and activity of novel therapeutic agents in recurrent malignant glioma.[12–19] Agents under study in dose finding phase I trials were SCH66336 (lonafarnib) and LY317615 (enzastaurin). The phase II trials involved XR5000 (DACA, Xenova®), D19575 (glufosfamide), RFS 2000, STI571 (imatinib, Glivec®), OSI 774 (erlotinib, Tarceva®) and ZK219477 (sagopilone). Supplemental Table 1 presents a description of trial characteristics. None of the experimental agents showed clinically relevant activity. In all studies, eligibility criteria were similar. Patients were at least 18 years of age, with WHO PS 0-2 or KPS 70–100%, adequate haematological, renal and hepatic functions. Corticosteroid doses, if applicable, were to be stable or decreasing for at least 1 week. In three studies, newly diagnosed patients with multifocal disease not amenable to radiotherapy were allowed. In the two phase I trials, measurable disease was not mandatory but at least one bi-dimensional lesion was recommended. In phase II trials, prior radiotherapy had to be completed more than 3 months before registration in order to reduce the chance of treating a pseudoprogression. Three of the

trials included patients who had received prior chemotherapy for a disease recurrence or progression. In two trials patients using enzyme inducing anti epileptic drugs (EIAED) were excluded. In one trial a higher dose of the investigational drug (erlotinib) in patients under EIAED was to be prescribed.

Each trial was approved by the EORTC Protocol Review Committee as well as by the participating institutions local ethical committee and the respective national regulatory authorities. Written informed consent was obtained prior to enrolment into the trial.

In order to determine whether our pooled patient population was representative of a standard patient population, the survival of the patients in the pooled dataset was compared to the survival from the date of first disease progression of patients recruited in the EORTC 26981/22981/National Cancer Institute of Canada (NCIC) CE.3 trial who were treated with TMZ/RT → TMZ and subsequently received another line of chemotherapy after first progression.[1]

2.2. Candidate prognostic factors

Factors screened for their prognostic value were sex, age, WHO PS, time from initial surgery or biopsy, prior chemotherapy, time since last dose of chemotherapy, time since last day of irradiation, surgery for recurrent disease, use of corticoids, administration of anti-epileptic drugs, United Kingdom Medical Research Council (MRC) neurological evaluation score (available in six studies), tumour load as assessed by the number of target lesions (defined as MRI contrast enhancing lesions with the largest diameter of at least 2 cm) and tumour size measured by the maximum diameter of the largest lesion. The effect of the presence of non-targeted lesions was also evaluated. Tumour localisation could be retrieved in five trials. The effect on prognosis of any concomitant chronic disease was also assessed. Online Supplemental Table 2 lists the factors screened and the coding conventions.

2.3. Patient outcome measurements

In all trials, Macdonald's criteria were used to assess tumour response.[20] Follow-up assessments were obtained every 8 weeks until disease progression. Progression free survival was computed as the time between the date of registration or randomization and the date of progression or death, whichever occurred first. Patients alive without evidence of progression were censored at the date of the last visit. Overall survival was calculated from the date of registration or randomization until date of death for any cause. Surviving patients were censored at date of last visit.

In the EORTC/NCIC 26981/22981 trial residual survival was computed from the date of start of a new chemotherapy for recurrence after chemoradiation with TMZ until date of death. Patients alive at the date of last visit were censored.

3. Statistical considerations

Categorical data were tabulated with frequencies and percentages. Medians and ranges (minimum–maximum) were used to summarise continuous variables. The significance of the association between categorical factors was assessed by the Fisher Exact test (nominal) or the Jonckheere-Terpstra test (ordinal). Between continuous variables, significance was computed based on a specific student's statistic for testing the null hypothesis of no association. For the association between continuous and categorical (nominal) factors, the Wilcoxon rank sum test (two levels) or the Kruskall Wallis test (more than two levels) was used. In all analyses, p-values lower than 1% ($p < 0.01$) have been reported. Survival analyses were carried out in two patient populations: all GBM patients and the subset of patients who were treated for first progression after chemoradiation with TMZ. Kaplan Meier curves and logrank tests were computed stratified by category of treatment for the recurrence (an experimental agent, a cytotoxic agent, and a combination of both).

Multivariate Cox models were fit of a significant difference between the different categories of treatment, non-stratified multivariate Cox models were fitted. Factors with a p-value less than 10% in univariate analysis were considered for Cox multivariate analyses. Proportional hazards (PH) assumptions were tested with the Supremum Test and by graphical method (LLS plot). PH assumptions were considered strongly violated if the p-values were less than 1%. The stepwise forward method was used for factors selection. The model's internal validity was assessed by the bootstrap method. Factors with an importance (PI: posterior probabilities that the regression coefficients are different from zero) lower than 60% were excluded from the final models. A significance level of 5% was applied to all multivariate analyses. Model's discrimination was assessed by the Harrel's C-index corrected for optimism by the bootstrap technique.[21,22] The model's goodness of fit was assessed by the Schemper's percentage of explained variation (PEV).[23] A PEV of at least 20% is considered a minimum requirement for a model to provide sufficiently precise individual survival predictions.[24]

Prognostic calculators were developed for each final model in the population pre-treated with TMZ/RT → TMZ and the model calibration was assessed. Predictions for median PFS, OS, 6-month PFS (PFS6) and 1-year OS (OS12) were derived. SAS version 9.2 (SAS Institute Inc., Cary, NC, United States of America (USA)) was used for all statistical analyses except the computation of the C-index and calibration plots which were obtained from the R 'Design' and 'Hmisc'

Packages. The percentage of explained variation was computed using the SAS macro RELIMPCR (Comparing the importance of prognostic factors in Cox regression using SAS).[24] The reflected method was used to estimate median survival with 95% confidence interval.[25] The loglog transformation was used for the 95% confidence intervals of PFS6 and OS12.

4. Results

4.1. Patients characteristics and correlation analyses

Four hundred eleven patients were recruited in the eight trials, 300 had a local histopathological diagnosis of GBM (astrocytoma grade IV according to WHO). Central pathology review was available for 155 patients (52%), in 149 patients (96%) GBM was confirmed. Baseline characteristics are summarised in Table 1. One hundred thirty eight patients had received TMZ/RT → TMZ as first-line therapy. One hundred fifty eight patients received standard fractionated RT to the equivalent of approximately 60 Gy alone or with another chemotherapy, four were treated without previous radiotherapy. Patients who received TMZ/RT → TMZ were significantly less often under baseline steroids (57% versus 73%, $p = 0.004$). At progression, patients in this subgroup received Carmustine (BCNU) (11%) or TMZ (7%) or various other therapies (36%, including Procarbazine, Lomustine, and Vincristine (PCV), Lomustine (CCNU), Irinotecan (CPT11), Etoposide (VP16), Natulan). No patient received Bevacizumab after protocol treatment. Eight percent of the patients were re-operated at the time of progression. Supplemental Table 3 shows the results of correlation analyses.

4.2. Outcome description and prognostic factor analyses

Supplemental Table 4a & b summarises the univariate analyses of PFS and OS for each candidate prognostic factor and each category of treatment at recurrence in the two populations by presenting median PFS, 6-month PFS rate (PFS6), median OS, 1-year OS rate (OS12), hazard ratios and p-values. Table 2 displays the results of the final multivariate Cox analyses. For both PFS and OS, the results of the proportional hazards assumptions analyses can be found at http://www.eortc.be/tools/recgbmcalculator/Sensitivity.aspx. No strong PH assumption violation was observed in all analyses.

4.2.1. Progression free survival

For all GBM patients, median PFS was 1.8 months (1.7–1.9) and PFS6 was 14.7% (11.0–19.0). Patients treated with experimental agents at the recurrence had a lower PFS6 (9.6%) compared to patients who received a combined therapy of an experimental agent and TMZ (27.8%, $p = 0.003$) or BCNU (25.5%, $p = 0.003$). Among the factors screened, a higher WHO PS ($p = 0.0003$), the presence of neurological deficits ($p = 0.06$), the administration of steroids ($p = 0.08$), multiple target lesions ($p = 0.007$), larger area of the target lesions ($p = 0.09$), were negatively associated to PFS in univariate analyses stratified by the category of treatment ($p < 10\%$). The maximum diameter of the largest lesion was borderline not significant ($p = 0.11$). After stepwise selection and assessment of the model's internal validity by the bootstrap technique, two factors remained in the final prognostic model: WHO PS (code: 0/1/2, $p = 0.0002$, PI = 91%) and the number of target lesions ($p = 0.004$, PI = 84%). The C-index corrected for optimism was 0.62 and PEV was 3.4%.

It was decided to maintain it in the final model (PI = 58%) assuming a lack of power of the analysis in the subset having received TMZ/RT → TMZ as first-line therapy ($n = 138$), median PFS was 1.84 months (1.74, 2.14) and PFS6 was 18.3% (12.3, 25.1). There was no significant difference of PFS between the three categories of treatment for the recurrence ($p = 0.35$). WHO PS (code: 0, >0) ($p = 0.04$), the number of target lesions ($p = 0.02$) were the only factors selected by univariate analysis. Both variables were selected by stepwise technique. Although performance status had a PI lower than 60%, it was maintained in the final model (PI = 58%) assuming that the reason was a lack of power in this subset. Discrimination and goodness of fit of this two factors model was low (C-index = 0.56, PEV = 4.6%).

4.2.2. Overall survival

For all GBM patients, median OS was 6.2 months (5.7, 7.1), OS12 was 22.1% (17.5, 27.0). There was no significant difference of survival between the three categories of treatment ($p = 0.42$). WHO PS ($p \leqslant 0.0001$), presence of neurological deficits ($p = 0.0002$), time since initial diagnosis ($p = 0.06$), baseline administration of steroids ($p < 0.0001$), number of target lesions ($p < 0.0001$), tumour size (largest tumour diameter, $p < 0.0001$), frontal tumour location ($p = 0.02$) and prior chemotherapy with TMZ ($p = 0.096$) were the factors which passed the 10% significance criterion (see http://www.eortc.be/tools/recgbmcalculator/Curves.aspx).

Age was not related to survival outcome ($p = 0.21$) and undergoing a surgery for recurrence did not significantly impact on the survival ($p = 0.25$). After stepwise selection and assessment of factor importance by bootstrap, WHO PS ($p = 0.008$, PI = 69%), baseline steroids ($p = 0.0001$, PI = 91%), the number of target lesions ($p = 0.003$, PI = 80%), frontal location ($p = 0.02$,PI = 62%), tumour size (maximum diameter of the largest lesion, split by the median ie ⩽42 mm versus >42 mm, $p = 0.015$, PI = 70%) were retained in the final multivariate model. The C-index was 0.68 and PEV = 15.7%. The C-index was not substantially

Table 1
Characteristics of all GBM patients and of patients (non) pre-treated by TMZ/RT → TMZ.

Patient and disease characteristics	Prior administration of TMZ/RT → TMZ			*p*-value
	No ($N = 162$)	Yes ($N = 138$)	Total ($N = 300$)	
	N (%)	*N* (%)	*N* (%)	
Central review				
No	76 (46.9)	69 (50.0)	145 (48.3)	0.64
Yes	86 (53.1)	69 (50.0)	155 (51.7)	
Central diagnosis				
GBM	85 (52.5)	64 (46.4)	149 (49.7)	0.10
OA	0 (0.0)	2 (1.4)	2 (0.7)	
AA	1 (0.6)	1 (0.7)	2 (0.7)	
Other	0 (0.0)	2 (1.4)	2 (0.7)	
Missing	76 (46.9)	69 (50.0)	145 (48.3)	
Disease status				
First progression	142 (87.7)	138 (100.0)	280 (93.3)	N/A
Second progression	20 (12.3)	0 (0.0)	20 (6.7)	
Presence of measurable disease				
No	2 (1.2)	5 (3.6)	7 (2.3)	0.25
Yes	160 (98.8)	133 (96.4)	293 (97.7)	
Sex				
Male	101 (62.3)	95 (68.8)	196 (65.3)	0.27
Female	61 (37.7)	43 (31.2)	104 (34.7)	
WHO performance status				
0	44 (27.2)	40 (29.0)	84 (28.0)	0.20
1	88 (54.3)	84 (60.9)	172 (57.3)	
2	30 (18.5)	14 (10.1)	44 (14.7)	
Neurological deficit				
No	50 (30.9)	50 (36.2)	100 (33.3)	0.09
Some	47 (29.0)	54 (39.1)	101 (33.7)	
Moderate	38 (23.5)	20 (14.5)	58 (19.3)	
Major	5 (3.1)	2 (1.4)	7 (2.3)	
Missing	22 (13.6)	12 (8.7)	34 (11.3)	
Age (years)				
Median	53.5	53.5	53.5	0.72
Range	19.0–75.0	18.0–78.0	18.0–78.0	
N	162	138	300	
Associated chronic disease				
No	110 (67.9)	73 (52.9)	183 (61.0)	0.78
Yes	49 (30.2)	30 (21.7)	79 (26.3)	
Missing	3 (1.9)	35 (25.4)	38 (12.7)	
Time since initial diagnosis (weeks)				
Median	42.3	47.1	44.1	0.16
Range	2.0–319.6	6.4–393.1	2.0–393.1	
N	162	138	300	
Extent of initial surgery				
Biopsy	6 (3.7)	4 (2.9)	10 (3.3)	1.00
Resection	57 (35.2)	36 (26.1)	93 (31.0)	
Missing	99 (61.1)	98 (71.0)	197 (65.7)	
Time since initial surgery (weeks)				
Median	40.1	45.0	41.9	0.06
Range	2.0–222.4	11.7–393.1	2.0–393.1	
N	157	131	288	
Prior radiotherapy				
No	4 (2.5)	0 (0.0)	4 (1.3)	0.13
Yes	158 (97.5)	138 (100.0)	296 (98.7)	

(*continued on next page*)

Table 1 (*continued*)

Time since last dose of irradiation (weeks)				
Median	30.1	35.7	31.9	0.16
Range	4.9–308.6	13.0–221.6	4.9–308.6	
N	156	138	294	
Prior chemotherapy				
No	89 (54.9)	0 (0.0)	89 (29.7)	N/A
Yes, without temozolomide	55 (34.0)	0 (0.0)	55 (18.3)	
Yes, with temozolomide	18 (11.1)[†]	138 (100.0)	156 (52.0)	
Time since last chemo (weeks)				
Median	12.1	8.1	9.6	0.02[*]
Range	3.4–128.6	3.9–171.3	3.4–171.3	
N	73	138	211	
Surgery for recurrence				
No	145 (89.5)	118 (85.5)	263 (87.7)	0.38
Yes	17 (10.5)	20 (14.5)	37 (12.3)	
Baseline steroids				
No	44 (27.2)	60 (43.5)	104 (34.7)	0.004[**]
Yes	118 (72.8)	78 (56.5)	196 (65.3)	
Baseline anti-epileptic				
No AED	56 (34.6)	51 (37.0)	107 (35.7)	0.72
EIAED	43 (26.5)	31 (22.5)	74 (24.7)	
Non-EIAED only	63 (38.9)	56 (40.6)	119 (39.7)	
Number of target lesions				
0	2 (1.2)	5 (3.6)	7 (2.3)	0.22
1	132 (81.5)	114 (82.6)	246 (82.0)	
2	24 (14.8)	17 (12.3)	41 (13.7)	
3	3 (1.9)	2 (1.4)	5 (1.7)	
4	1 (0.6)	0 (0.0)	1 (0.3)	
Presence of non-target lesions				
No	137 (84.6)	116 (84.1)	253 (84.3)	1.00
Yes	25 (15.4)	22 (15.9)	47 (15.7)	
Frontal location				
No	50 (30.9)	75 (54.3)	125 (41.7)	1.00
Yes	27 (16.7)	42 (30.4)	69 (23.0)	
Missing	85 (52.5)	21 (15.2)	106 (35.3)	
Largest lesion area (mm^2)				
Median	1483.5	1134.0	1289.0	0.02[*]
Range	125.0–8000.0	80.0–4950.0	80.0–8000.0	
N obs	160	132	292	
Largest lesion diameter (mm)				
Median	43.0	41.5	42.0	0.07
Range	19.0–100.0	10.0–94.0	10.0–100.0	
N obs	160	132	292	

[†] Temozolomide administered at first progression after radiotherapy.
[*] $p < 0.05$.
[**] $p < 0.01$.

increased when continuous measures for tumour size were considered (C-index = 0.69). Therefore, for ease of interpretation the model with binary tumour size was considered.

In the patient group having received TMZ/RT → TMZ as first-line therapy, median OS was 7.1 months (6.2, 8.7) and OS12 was equal to 26.6% (19.5, 34.3) not significantly different from the EORTC/NCIC phase III trial patient population ($n = 125$, median OS = 8.0 months (6.5–9.3), OS12 = 28.8% (21.1–37.0), $p = 0.91$, complementary Fig. 1). Our pooled dataset was considered representative of the recurrent GBM population receiving further chemotherapy at progression. There was no significant difference in survival between the three categories of treatment at recurrence ($p = 0.29$). In this pre-treated subgroup the same factors were selected in univariate analysis except the time since initial diagnosis and the frontal location. The final model included four factors: WHO PS ($p = 0.009$ PI = 79%), baseline steroids ($p = 0.02$, PI = 71%), number of target lesions ($p < 0.0001$, PI = 99%), maximum diameter of the

Table 2
Cox multivariate models for progression free survival and overall survival.

	Final models for progression free survival				Final models for overall survival			
	GBM pretreated with TMZ/RT → TMZ (n = 138, 138 used, 136 PFS events)		All GBM (n = 300, 300 used, 298 PFS events)		GBM pretreated with TMZ/RT → TMZ (n=138, 132 used,122 deaths)		All GBM (n=300, 189 used, 176 deaths)	
	Hazard Ratio (95% CI)	*P*-value (Imp %)	Hazard Ratio (95% CI)	*P*-value (Imp %)	Hazard Ratio (95% CI)	*P*-value (Imp %)	Hazard Ratio (95% CI)	*P*-value (Imp %)
Performance Status								
0	N/A	N/A	1.42 (1.18-1.71)	0.0002 (91)	1.54 (1.11-2.13)	0.009 (79)	1.42 (1.10-1.83)	0.008 (69)
1								
2								
or								
0	1.56 (1.06-2.29)	0.02 (58)						
>0								
Neurological deficit	NI	NI	NS	NS (9)	NS	NS (11)	NS	NS (13)
No								
Some								
Moderate/major								
Prior chemotherapy	NI	NI	NI	NI	NI	NI	NS	NS (14)
No								
Yes, without temozolomide								
Yes, with temozolomide								
Baseline steroids	NI	NI	NS	NS (6)				
No					1.60 (1.09-2.36)	0.02 (71)	2.01 (1.40-2.88)	0.0001 (91)
Yes								
Number of target lesions								
0-1	2.14 (1.29-3.53)	0.003 (83)	1.6 (1.16-2.19)	0.004 (84)	3.09 (1.82-5.27)	<0.0001 (100)	1.87 (1.24-2.82)	0.003 (80)
>1								
Frontal location	NI	NI	NI	NI	NI	NI		
No							0.69 (0.50-0.95)	0.02 (62)
Yes								
Largest lesion diameter (median)	NI	NI	NI	NI				
<=42 mm					2.01 (1.37-2.94)	0.0003 (95)	1.49 (1.08-2.05)	0.015 (70)
>42 mm								
C-index corrected for optimism	0.56		0.62		0.70		0.68	

Note: Only factors selected in the univariate analysis were included. NA: Not Applicable, NI: Not Included, factors was not selected in univariate analysis for the outcome in the subset, NS: Not Selected in multivariate model. Imp: Importance.

largest lesion (binary, $p = 0.0003$, PI = 95%). The C-index was 0.70 and PEV was 19%.

4.2.3. Development of prognostic calculators

The final multivariate models for PFS and OS in recurrent GBM patients having received TMZ/RT → TMZ as first line therapy were used to compute two prognostic calculators. They are available online at http://www.eortc.be/tools/recgbmcalculator/Default.aspx. Their calibration was satisfactory (see http://www.eortc.be/tools/recgbmcalculator/Calibration.aspx).

5. Discussion

In this report, baseline characteristics and outcome data were available for 300 patients diagnosed with GBM by the local pathologist. In all pooled phase II trials, the last dose of radiotherapy had to be administered more than 3 months from the time of recruitment thus making the chance of pseudoprogression less likely.[26,27] One hundred thirty eight had received TMZ/RT → TMZ at initial diagnosis. We have shown that tumour load measured by the maximum diameter of

the largest target lesion and the number of target lesions have strong prognostic relevance for OS. In previous studies, WHO PS and baseline steroids were identified as major prognostic factors for OS. This report confirms these findings. Our patients tended to be older compared to previous report, nevertheless age did not show prognostic significance.[7] WHO PS and the number of target lesions were the two main factors selected in the PFS models. Patients with an initially large lesion and/or who were receiving steroids at baseline tended to progress more rapidly but the association was not statistically significant in this subset. The use of anti-angiogenic therapies might change the prognostic potential of some factors e.g. bevacizumab administration might reduce the detrimental effect of the need for steroids and of larger or multiple tumours, at least on PFS.

Recently, Weller et al. assessed the prognostic value of 11 molecular markers in patients treated by TMZ/RT → TMZ.[28] The only factor of prognostic significance was *MGMT* gene promoter methylation.[29] It is however not clear if the status of molecular markers remains constant over time and how eventual changes might affect the markers prognostic value.[6,30] In our study, biological material was not systematically collected or analysed for molecular prognostic factors. Potentially, more accurate models for PFS and OS could be obtained by the addition of prognostic genomic signatures or biologically relevant biomarkers assessed at initial diagnosis and at recurrence, respectively, taking into account prior therapies.[31] The model's accuracy will also be improved once biomarkers predicting the activity of new active targeted agents are identified.[32]

This study is exploratory and suffers some limitations: the heterogeneity of the treatments for recurrence, the small sample size, the lack of molecular data and the absence of validation of the prognostic models in a large independent dataset. This validation might be complicated because more and more patients will receive bevacizumab or other active treatments at different times of their disease, which may change their outcome.

In the present study we developed prognostic calculators in the patients treated at initial diagnosis with TMZ/RT → TMZ. Four factors were retained for OS: WHO PS, baseline administration of steroids, tumour size (maximum diameter of the largest lesion; split by the median $\leqslant$42 mm versus >42 mm) and initial number of target lesions (1 versus >1). All four should be used as stratification factors in randomised trials when OS is the primary end-point. When PFS is the end-point stratifying by the WHO PS and the number of target lesions may suffice. The prognostic calculators provide outcome estimates with 95% confidence intervals. Our models and calculators can help physicians by providing objective information to patients and their families about their disease prognosis, discussing with them the best therapeutic strategy or the opportunity to participate to a clinical trial taking patient's individual characteristics into account.

Conflict of interest statement

Thierry Gorlia, Mario M. Campone, Pierre Fumoleau, Eric Raymond, Roy R. Rampling, Chris C. Twelves and Denis Lacombe had no conflict of interest. The research institute directed by Christian Dittrich has received unrestricted research Grants from Novartis, Basel, Switzerland and MSD/Merck & Co. (formerly Schering-Plough), North Wales, PA, USA. Martin van den Bent provided consultancy for Roche Pharma, Basel, Switzerland, Novartis, Basel, Switzerland and Bayer HealthCare Pharma (formerly Schering AG), Berlin, Germany. Monika E. Hegi is an advisor for MDx-Health, Bruxelles, Belgium and Merck Serono, Darmstadt, Germany. Alba A. Brandes is an advisor for Roche Pharma, Basel, Switzerland and MSD/Merck & Co. (formerly Schering-Plough), North Wales, PA, USA, receives honoraria from GlaxoSmithKline, Brentford, Middlesex, United Kingdom and Roche Pharma, Basel, Switzerland. Roger Stupp received consulting fees (advisory boards) from Merck Serono, Darmstadt, Germany, MSD/Merck & Co. (formerly Schering-Plough), North Wales, PA, USA, MDx Health, Bruxelles, Belgium, Roche Pharma, Basel, Switzerland.

Acknowledgements

This publication was supported by Grants number 5U10 CA11488-29 through 2U10 CA011488-41 from the National Cancer Institute (Bethesda, Maryland, USA) and by a donation from the 'Vlaamse Liga Tegen Kanker' from Belgium through the EORTC Charitable Trust. Its content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Cancer Institute.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2012.02.004.

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