Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

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Purpose: **To identify prognostic factors for survival in adult patients with cerebral low-grade glioma (LGG), to derive a prognostic scoring system, and to validate results using an independent data set.**

Patients and Methods: **European Organization for Research and Treatment of Cancer (EORTC) trial 22844 and EORTC trial 22845 are the largest phase III trials ever carried out in adult patients with LGG. The trials were designed to investigate the dosage and timing of postoperative radiotherapy in LGG. Cox analysis was performed on 322 patients from EORTC trial 22844 (construction set), and the results were validated on 288 patients from trial 22845 (validation set). Patients with pilocytic astrocytomas were excluded from this prognostic factor analysis.**

Results: **Multivariate analysis on the construction set showed that age ≥ 40 years, astrocytoma histology subtype, largest diameter of the tumor ≥ 6 cm, tumor crossing the midline, and presence of neurologic deficit before surgery were unfavorable prognostic factors for survival. The total number of unfavorable factors present can be used to determine the prognostic score. Presence of up to two of these factors identifies the low-risk group, whereas a higher score identifies high-risk patients. The validity of the multivariate model and of the scoring system was confirmed in the validation set.**

Conclusion: **In adult patients with LGG, older age, astrocytoma histology, presence of neurologic deficits before surgery, largest tumor diameter, and tumor crossing the midline were important prognostic factors for survival. These factors can be used to identify low-risk and high-risk patients.**

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LOW-GRADE GLIOMAS (LGGs) are in general relatively slow-growing primary brain tumors, but they have a very heterogeneous clinical behavior. Many patients present with seizures only and remain stable for a prolonged period of time, whereas others present with functional deficits or signs of increased intracranial pressure that necessitate prompt surgical treatment. The best treatment policy for these tumors is still unclear. Some physicians advocate early and extensive surgery or early radiation therapy,[1-3] whereas others tend to postpone treatment until functional deficits are present.[1-4] Several studies have attempted to identify prognostic factors in LGG.[1,5-12] Prognostic factors have various applications that could be of particular value in the heterogeneous population of LGG. This includes guidance for stratification in phase III trials and ultimately for treatment in individual patients. However, except for age, the importance of other prognostic factors for survival in LGG remains a matter of debate, and the need for validated prognostic factors has not been resolved. A number of patient and tumor characteristics, such as age at diagnosis, performance status, histology subtype, primary tumor classification (T classification), tumor site, presence of seizures at diagnosis, and extent of resection, have been proposed as prognostic factors for progression-free or overall survival. Unfortunately, in many of those retrospective studies, the small number of patients and the heterogeneity of treatments limited the analysis of prognostic factors. In addition, the existing analyses of larger data sets are based on different statistical techniques and, most importantly, have not been validated in subsequent studies. Thus there is no consensus about the relative importance of each of these factors, and the same holds for the prognostic importance of treatment-related factors like the extent of resection or the administration of radiation therapy.

The European Organization for Research and Treatment of Cancer (EORTC) conducted two large phase III trials to investigate the role of radiotherapy in LGG. EORTC trial 22844 compared postoperative irradiation with 45 Gy in 5 weeks versus 59.4 Gy in 6.6 weeks.[3] EORTC trial 22845,

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which was conducted in collaboration with the United Kingdom Medical Research Council (MRC), compared 54.0 Gy in 6 weeks postoperative radiotherapy with no immediate postoperative radiotherapy.[13] In both trials, the same set of baseline variables presumed to be of prognostic influence were recorded. These trials were carried out separately, with the different institutions choosing to participate in only one of the two trials. This provided two distinct data sets of considerable size, giving the possibility to construct a statistical model on one set and to validate its predictive ability on the other.

By means of Cox regression, we identified and validated important factors for survival that could be of value for staging patients into low- and high-risk groups.

PATIENTS AND METHODS

A total of 379 and 311 patients were randomized in EORTC trials 22844 and 22845, respectively. Local ethics committees of participating institutions approved the studies, and informed consent was obtained from each subject before screening.

The maximum allowed World Health Organization (WHO) performance status at randomization was 2. Adult patients were eligible if surgery had been carried out within 8 weeks from randomization and a local histopathologic diagnosis of low-grade cerebral astrocytoma, oligodendroglioma, or mixed oligoastrocytoma according to WHO typing (1979 edition) had been made.[14]

Patients with totally excised small grade 1 tumors; pregnancy; gross hepatic, renal, cardiovascular, or respiratory disease; other malignancies in the prior 5 years; or any other disease that was considered to limit 5-year survival were not eligible.

From this prognostic factor analysis, we excluded patients based on failure to meet the eligibility criteria (20 and three patients, as had been determined before main analysis of these studies). The main reasons for patient ineligibility were wrong histopathology, poor performance status, or excessive delay between surgery and randomization. Patients with pilocytic astrocytoma histology subtype (32 and seven patients for trials 22844 and 22845, respectively) were excluded from this prognostic factor analysis. Patients who were nonassessable because of incomplete data (five and 13 patients, respectively) were also excluded from the analysis.

The resulting data sets consist of baseline and survival data for 322 patients enrolled onto trial 22844, which was used for model construction, and 288 patients for trial 22845, which was used for validation.

The variables (and transformations) considered for the analysis consisted of patient and tumor characteristics before randomization (Table 1), such as age, sex, presence of associated chronic disease, presence of diabetes, presence of aphasia or cranial nerve abnormalities, and symptom duration (>1 or >6 months *v* shorter duration). The cut point for age at randomization (<40 or ≥ 40 years) was chosen based on the median. Neurologic signs and symptoms were also recorded after surgery but, except for WHO performance status (0 *v* >0), which was only available after surgery, these were not used because of the high correlation with the presurgical signs and symptoms. Neurologic deficit was defined as absent (Medical Research Council [MRC] neurologic scale 1 or 2, Table 2) or present (MRC grade >2).

Tumor characteristics were recorded based on the local interpretation of preoperative computed tomography scans. Predominant site and side were coded as binary factors (fronto-temporal, temporo-parietal, pario-occipital, corpus callosum, left side, right side, central). Other factors recorded were the number of lobes involved (one *v* $>$ one), tumor encroaching on ventricular system, tumor crossing the midline, tumor crossing infratentorial structures, cystic tumor, tumor attached to the dura, and largest diameter of the tumor without edematous zone (<6 *v* ≥ 6 cm).

Extent of surgical removal, which had been determined intraoperatively, was coded into a binary factor: extensive tumor excision (90% to 100%

Table 1. Summary of Patient Characteristics at Randomization for EORTC Trial 22844 (construction set) and EORTC Trial 22845 (validation set)

Factor	Construction Set (n = 322)		Validation Set (n = 288)	
	No. of Patients	%	No. of Patients	%
Age				
<40 years	173	53.7	151	52.4
≥ 40 years	149	46.3	137	47.6
Headache				
No	217	68.5	136	47.4
Yes	100	31.5	151	52.6
Epilepsy				
No	71	22.2	58	20.3
Yes	249	77.8	228	79.7
Mental disturbances				
No	250	78.1	199	69.6
Yes	70	21.9	87	30.4
Motor disturbances				
No	241	75.3	200	74.3
Yes	79	24.7	69	25.7
Neurologic deficit				
Absent	256	79.5	241	83.7
Present	66	20.5	47	16.3
Largest diameter of the tumor				
<6 cm	181	64.4	164	64.6
≥ 6 cm	100	35.6	90	35.4
Tumor crossing midline				
No	214	68.2	234	88.0
Yes	100	31.8	32	12.0
Surgery (extent of removal)				
Biopsy	117	36.6	82	28.9
$<50\%$	29	9.1	20	7.0
50%-89%	96	30	54	19.0
90%-100%	78	24.4	128	45.1
Histology subtype				
Oligo/mixed	106	32.9	109	37.8
Astrocytoma	216	67.1	179	62.2

NOTE. Missing data not shown.

Table 2. MRC Neurologic Scale

1	No neurologic deficit
2	Some neurologic deficit but function adequate for useful work
3	Neurologic deficit causing moderate functional impairment, eg, able to move limbs only with difficulty, moderate dysphasia, moderate paresis, some visual disturbances (eg, field defect)
4	Neurologic deficit causing major functional impairment, eg, inability to use limbs, gross speech or visual disturbances
5	No useful function—inability to make conscious responses

tumor excised) versus less extensive excision or biopsy. Histology subtype was grouped as oligodendroglioma/mixed versus astrocytoma.

Model Selection and Validation

Survival was calculated as the time from randomization until death regardless of cause (event) or censoring at the last follow-up. Survival was estimated using the Kaplan-Meier technique.[15] The Cox proportional hazards model was used for model selection and validation, with stratification by treatment.[16]

Model selection was based on the technique described by Collett.[17] The 10% and 1% significance levels were chosen for univariate screening and multivariate analysis, respectively. This technique essentially consists of four different steps. In the first step, univariate screening is performed and all factors that reach the desired level of significance (ie, the 10% level) based on likelihood ratio tests are selected. The second step consists of a backward elimination procedure. In a model containing all factors selected in the previous step, for each factor, the impact on model fit is assessed by measuring the difference between models with or without that particular factor, based on likelihood ratio tests. The factor that has the least impact on the model is removed and the process is repeated until all remaining factors, if removed from the model, cause an increase of the −2 log-likelihood statistic, which is significant at the 1% level. The third step consists of a forward selection procedure in which it is tested whether factors left out due to the univariate screening in the first step might enter the reduced model obtained with the second step. This allows factors that are not important at univariate level but are important in the presence of other factors to enter the model. Lastly, a final check, again based on likelihood ratio testing, is carried out to ensure that no term can be dropped and that no term that has been excluded in the preceding steps can be added to the model (fourth step).

After selection of the final model using this technique on the construction set, the model was validated by fitting it to the validation set. Lastly, descriptive statistics for the validation set were produced. Model diagnostics were carried out at each step of screening, selection, and validation.[18] Detailed univariate analysis results are only reported

Table 3. Median Survival and Hazard Ratio Based on Univariate Analysis of EORTC Trial 22844 (construction set)

Factor	O/N	Survival (years)		HR	95% CI	*P**
		Median	95% CI			
Factors significant at the 1% level						
Headache						
Absent	93/217	7.5	6.2-9.2			
Present	67/100	4.0	3.1-5.4	1.81	1.32-2.49	.0002
Epilepsy						
Absent	43/71	3.5	2.8-5.4			
Present	119/249	6.9	5.9-8.2	0.52	0.36-0.74	.0002
Epilepsy only						
Absent	120/208	4.8	4.1-5.9			
Present	41/110	8.8	7.2-NA	0.49	0.34-0.70	.0001
Mental disturbances						
Absent	117/250	7.2	5.5-8.7			
Present	44/70	4.1	3.1-6.5	1.68	1.19-2.39	.0035
Motor disturbances						
Absent	109/241	7.2	6.0-8.8			
Present	52/79	3.5	2.7-5.1	2.02	1.44-2.83	.0001
Neurologic deficits						
Absent	116/256	7.1	5.9-8.6			
Present	46/66	3.9	3.0-5.4	1.40	1.18-1.66	.0001
No. of lobes involved						
1	92/209	7.6	5.9-NA			
> 1	65/104	4.8	3.3-6.6	1.63	1.19-2.25	.0026
Ventricles involved						
No	88/194	7.4	6.2-8.8			
Yes	73/117	4.4	3.3-5.4	1.65	1.21-2.25	.0017
Tumor crossing midline						
No	92/214	7.9	7.1-NA			
Yes	70/100	3.6	3.1-5.1	2.21	1.61-3.02	.0001
Largest diameter of the tumor						
< 6 cm	80/181	8.02	6.67-NA			
≥ 6 cm	71/100	3.52	3.23-5.04	1.43	1.22-1.69	.0001
Factors not significant at the 1% level present in multivariate model						
Age						
< 40 years	86/173	6.0	5.1-8.2			
≥ 40 years	76/149	5.9	4.3-8.0	1.06	0.91-1.24	.4394
Histology subtype						
Oligo/mixed	45/106	8.2	6.5-NA			
Astrocytoma	117/216	5.0	4.2-6.3	1.57	1.11-2.21	.0110

NOTE. Missing data not shown; univariate screening was done at the 10% significance level (only those factors that were significant at the 1% level are reported in the table).

Abbreviations: O/N, observed number of deaths/number of patients within group; NA, not available; HR, hazard ratio.

*Likelihood ratio test.

for those factors that were found significant at the 1% level in univariate or multivariate analysis.

Prognostic Score

The prognostic scoring system was generated using the estimated log hazard ratios for the prognostic factors in the final model of the construction set. A simplified score was then calculated for each patient based on the total number of poor prognostic factors present. Arbitrary cut points of the prognostic score were selected to partition the population into two groups in order to identify low-risk and high-risk patients.

In a separate analysis, the possibility of constructing a four-level tumor classification (T classification) based on a reduced model consisting only of those characteristics of the primary tumor that were available from radiologic imaging and ignoring other factors was also explored.

The analysis was carried out in SAS (Version 12.0; SAS Institute, Cary, NC) and S-PLUS (2000 release 1; Statistical Sciences, Seattle, WA).

RESULTS

Summary patient characteristics for the data sets used in this analysis are reported in Table 1. The observed numbers of deaths were 162 of 322 and 123 of 288 patients, median survival was 6.0 years (95% confidence interval [CI], 5.1 to 7.5 years) and 6.8 years (95% CI, 6.3 to 8.3 years), and median follow-up was 6.6 and 5.5 years for the construction and validation sets, respectively.

In the construction set, data were missing in 1% or more of the patients for largest tumor diameter, tumor crossing the midline, and headache (with observations missing for 13%, 3%, and 2% of patients, respectively). In the validation set, data were missing in 1% or more of the patients for largest tumor diameter, tumor crossing the midline, motor disturbances, and type of surgery (with observations missing for 12%, 8%, 7%, and 1% of patients, respectively).

Univariate Analysis

Univariate analysis is summarized in Table 3 for those factors that were found significant at the 1% level or other factors that entered the final multivariate model. For example, the estimated hazard ratio for headache was 1.81, meaning that the death rate of patients presenting with headache was 1.81 times that of patients who did not present with headache. In addition to the factors reported in Table 3, the following factors were found significant at the 5% level (positive effect): tumor not crossing infratentorial structures, absence of aphasia, extensive surgery, absence of predominant involvement of the right hemisphere, and absence of cranial nerve abnormalities. Kaplan-Meier survival estimates based on the construction set are shown in Figs 1 to 5 for each of the factors retained in the final multivariate model.

Multivariate Model Selection and Validation

Model selection yielded one model with five predictors (Table 4): age, largest diameter of the tumor, tumor crossing the midline, histology type, and presence of neurologic deficits before surgery. To assess the validity of the final model, the model was fit to the construction set after including all patients who had been excluded from the analysis or after excluding all patients who had undergone biopsy only or by stratifying the analysis according to extent of surgery. These analyses supported the validity of the final model.

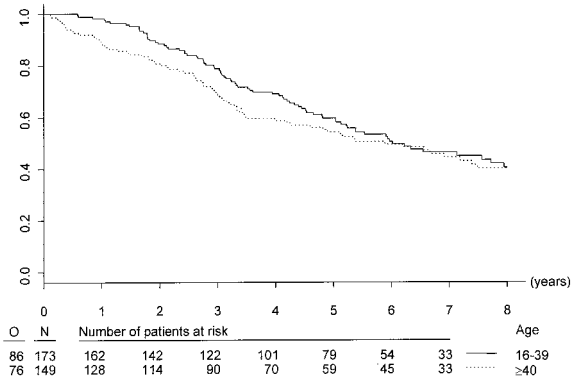

Fig 1. Age (construction set).

Exploratory analyses in the construction set revealed a positive association between presence of neurologic deficits and presence of motor disturbances, and a similar association was observed between the presence of neurologic deficits and the WHO performance status after surgery. A negative association was found between presence of epilepsy and the presence of either motor disturbances, neurologic deficits, or headache (χ^2 P = .001). Multivariate logistic regression analysis in the construction set showed an association between extensive surgery and both tumor crossing the midline (P = .014) and the largest diameter of the tumor (P = .018). The odds of undergoing extensive surgery decreased for tumors crossing the midline and for

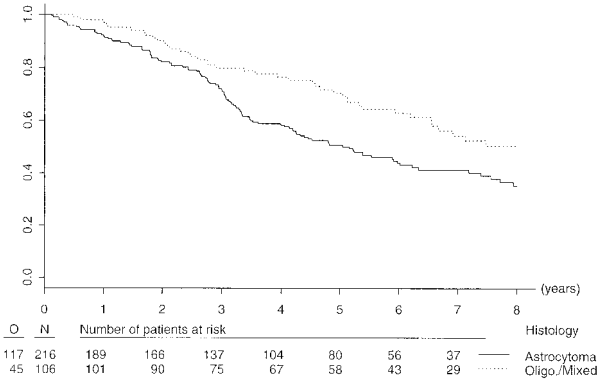

Fig 2. Histologic type (construction set).

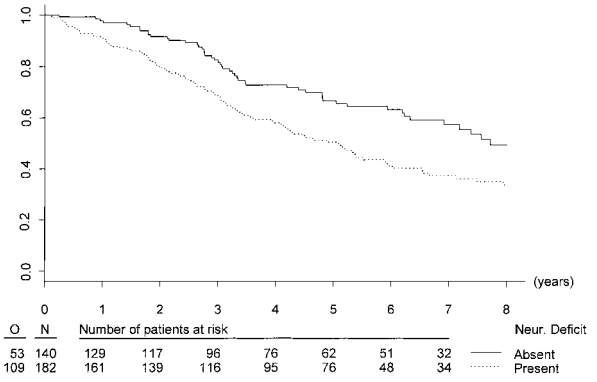

Fig 3. Neurologic deficit (construction set).

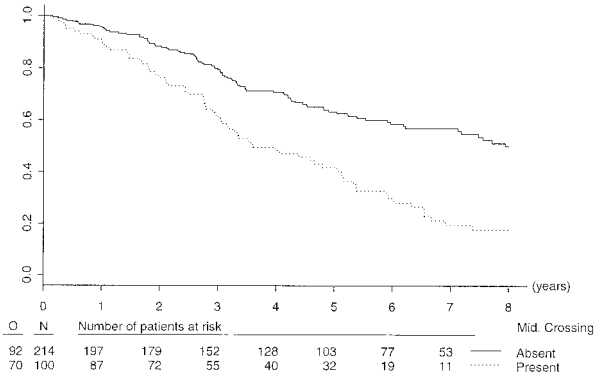

Fig 5. Tumor crossing the midline (construction set).

larger tumors. In the final model, extensive tumor excision (90% to 100% tumor excised) had a positive effect on survival in univariate analysis ($P = .034$), but this was not significant 1% level in multivariate analysis ($P = .046$).

Prognostic Score

It was possible to calculate a prognostic score based on the estimated coefficients in the construction set, ie, the logarithms of the hazard ratios reported in Table 4. However, for practical purposes, a simplification was introduced and the effect of each factor was considered to be 1 in view of the fact that the magnitude of the estimated coefficients of the final model in the construction set was similar across factors. Thus, rather than through a summation of the actual coefficients, a simplified prognostic score for each patient was calculated by counting the number of unfavorable prognostic factors present among those identified in the final multivariate model. This yielded a score between 0 (most favorable prognosis) and 5 (worst prognosis), which is shown in Table 5 and in Figs 6a and 6b. The score was further categorized to identify two distinct risk groups, namely a low-risk group (score 0 to 2) and high-risk group (score 3 to 5), which were subsequently validated in the validation set (Table 6 and Figs 7a and 7b).

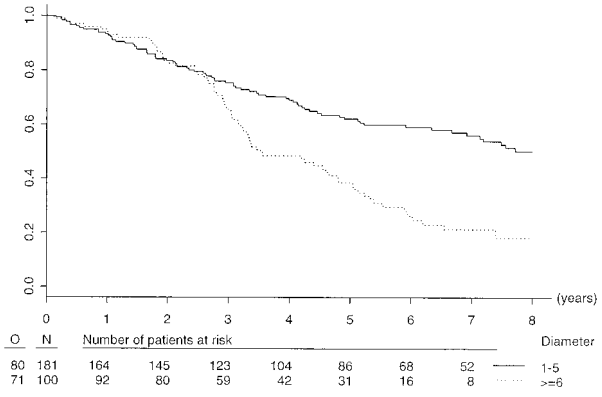

Fig 4. Largest tumor dimension (construction set).

Construction of a T classification based on a reduced model containing only radiologic characteristics of the primary tumor (ie, largest diameter of the tumor and tumor crossing the midline) was not successful and showed substantial overlapping of the survival curves for the four different groups in the construction set (data not shown).

DISCUSSION

This prognostic factor analysis is based on the largest prospective studies that have ever been carried out in adult patients with LGG. The final model selected contained age, largest diameter of the tumor, tumor crossing the midline, histology subtype, and presence of neurologic deficits before surgery. The validity of this model was subsequently confirmed in the validation set.

A major advantage of these prospective data is that after surgery, patients were treated according to a strictly defined study protocol. Although patients were selected according to the inclusion criteria of the trials, the entry criteria for the EORTC trials were designed broadly. This makes an important selection bias unlikely.

The EORTC trials provided two distinct data sets that allowed carrying out a prognostic factor analysis on one data set and subsequently validating the results on the other. Because of the data-driven nature of prognostic factor analyses, the importance of model validation cannot be overemphasized. Validation was missing from previously published prognostic factor analyses in LGG. A disadvantage of the approach chosen for this analysis is that only part of the available data is used for constructing the model, resulting in a potential loss of information. However, for the purpose of this analysis, the amount of data that was

Table 4. Prognostic Factors for Survival in Adults Patients with Cerebral LGG: Multivariate Model Construction and Validation

	Construction Set (n = 281)			Validation Set (n = 253)		
Prognostic Factor (reference level)	HR	95% CI	*P*	HR	95% CI	*P*
Age at randomization						
< 40 years	1			1		
≥ 40 years	1.26	1.06-1.48	.0077	1.43	1.17-1.74	.0005
Largest diameter of the tumor						
< 6 cm	1			1		
≥ 6 cm	1.39	1.16-1.66	.0003	1.23	1.02-1.50	.0350
Tumor crossing midline						
No	1			1		
Yes	1.37	1.15-1.63	.0005	1.43	1.11-1.84	.0051
Histology type						
Oligo/mixed	1			1		
Astrocytoma	1.30	1.08-1.56	.0050	1.46	1.18-1.82	.0006
Neurologic deficit						
Absent	1			1		
Present	1.35	1.13-1.62	.0013	1.29	1.02-1.63	.0310

NOTE. Forty-one and 35 observations were excluded from the construction and validation sets, respectively, due to missing data.

available for constructing the model was considered to be sufficient due to the considerable size of the two data sets. Furthermore, we preferred this approach because it mimics the real-life situation, in which proposed models are fitted to new series.

This analysis revealed some different findings as compared with a previous prognostic factor analysis on the construction set.[3] The differences are mainly due to the exclusion in the present analysis of patients with WHO grade 1 astrocytoma subtype and to the more mature character of the construction set at the time of this analysis, with longer follow-up and 162 versus 133 events observed.

Age is a well-established prognostic factor for survival in LGG.[5-7,9,19-21] The association between age and survival, the prognosis being worse for older patients, was confirmed in this analysis. Similarly to other series, a linear functional relationship between age and prognosis was observed.[6] A cut point at 40 years was chosen based on the median, but in clinical practice, this should not be interpreted as an absolute cutoff value.[19,21,22]

Oligodendroglioma and mixed oligoastrocytoma were grouped together because of the distinct pathologic features that separate them from astrocytoma and because approximately half of the mixed oligoastrocytomas have the oligodendroglial type of chromosomal lesions (in particular, loss of chromosome 1p and 19q).[23] In this series, patients with oligodendrogliomas or mixed oligoastrocytic tumors had a more favorable prognosis than patients with pure astrocytoma. Histology subtype was still statistically significant after excluding patients having undergone biopsy rather than tumor resection. This excluded patients in whom the assessment of histology subtype might have been less reliable. In other series, both on low- and high-grade glioma, tumors with oligodendroglial elements also had a better prognosis,[5,24-26] although some failed to observe this difference.[6,8] The small numbers of oligodendroglial tumors in the latter series may have prevented the detection of a favorable effect of histology on the prognosis. The notorious difficulties with respect to the histologic diagnosis of gliomas may also be an important cause for differences

Table 5. Median Survival by Prognostic Score Based on the Total Number of Unfavorable Prognostic Factors (construction and validation sets)

	Construction Set (n = 281)				Validation Set (n = 253)			
	Group Size		Survival (years)		Group Size		Survival (years)	
Score	No. of Patients	%	Median	95% CI	No. of Patients	%	Median	95% CI
0	18	6	9.2	8.2-NA	24	9	9.1	9.1-NA
1	69	25	8.8	7.7-NA	102	40	8.6	7.4-NA
2	113	40	5.5	4.7-8.0	69	27	6.3	5.3-7.8
3	55	20	3.6	3.2-4.8	39	15	4.4	3.0-6.4
4	20	7	1.9	1.1-4.3	16	6	3.0	1.9-NA
5	6	2	0.7	0.3-NA	3	1	2.4	0.7-NA

NOTE. Forty-one and 35 observations were excluded from the construction and validation sets, respectively, due to missing data.

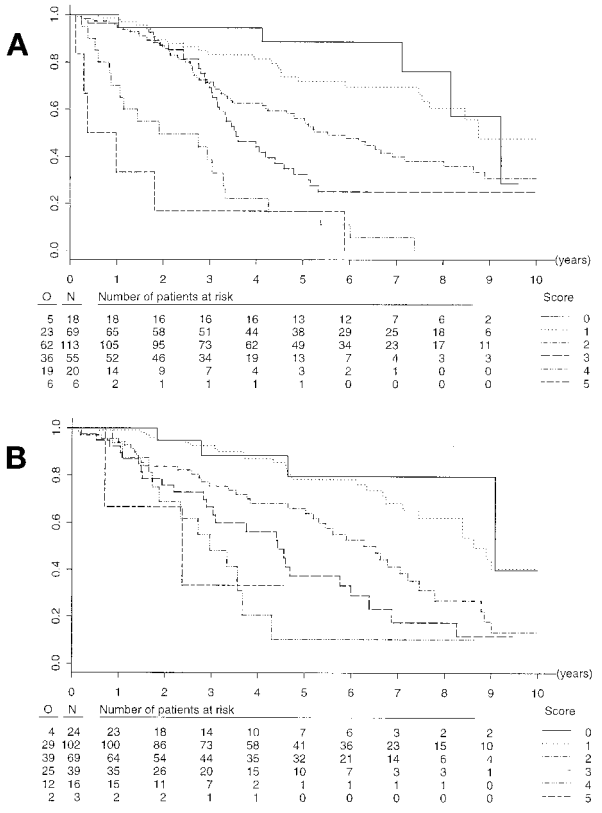

Fig 6. Prognostic score. (A) Construction set; (B) validation set.

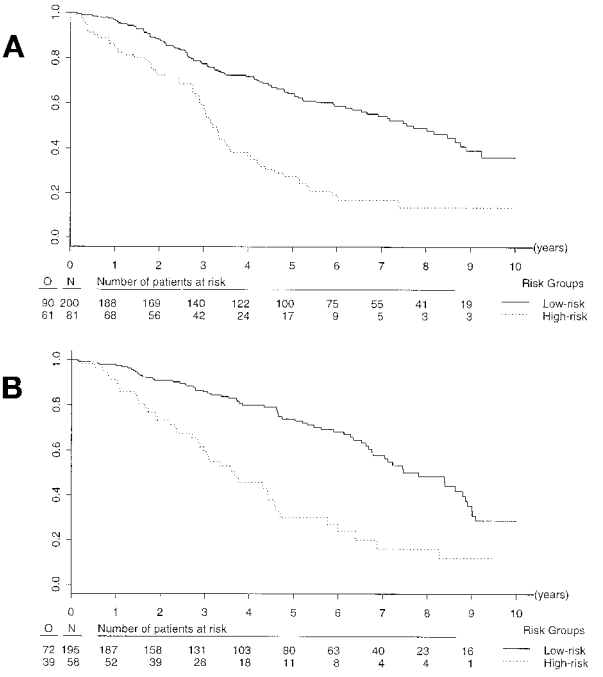

Fig 7. Risk groups. (A) Construction set; (B) validation set.

between study results.[27] Gemistocytic astrocytomas and a high MIB labeling index have also been related to a poor prognosis in LGG, but our data do not allow analysis of these histologic characteristics.[7,11,28]

Most studies on LGG found some association between prognosis and signs and symptoms at presentation. Our results confirmed that the presence of neurologic deficits is associated with worse survival.[29,6] One series observed a favorable outcome in patients presenting with seizures.[5] Others found the performance status of the patients of prognostic significance.[5,6,8,21,29] These three factors (presence of seizures, presence of neurologic deficits, and performance status) are interrelated. The present study revealed a strong negative association between the presence of seizures and the presence of other symptoms. Similarly, once mental changes or functional deficits are present, a decrease in performance status is to be expected. This association was also observed in one series in which epilepsy was only related to a better outcome if this was the only symptom present.[9] Once other symptoms were present, seizures were no longer of good prognostic significance. In the present series, in univariate analysis, the presence of epilepsy was associated with longer survival, but the presence of neurologic deficits superseded its prognostic importance in multivariate analysis. Likewise, although the presence of headache, motor disturbances before surgery, or WHO performance status more than 0 after surgery were individually associated with shorter survival, the presence of neurologic deficits superseded their prognostic importance. With the observed associations between the various

Table 6. Median Survival by Risk Group Based on the Prognostic Score (construction and validation sets)

Risk Group	Score	Construction Set (n = 281) O/N	Survival (years) Median	95% CI	HR	95% CI	Validation Set (n = 253) O/N	Survival (years) Median	95% CI	HR	95% CI
Low risk	0-2	90/200	7.72	6.55-9.25	1		72/195	7.80	6.77-8.90	1	
High risk	3-5	61/81	3.20	2.95-3.99	1.62	1.38-1.92	39/58	3.67	2.89-4.69	1.83	1.48-2.26

NOTE. Forty-one and 35 observations were excluded from the construction and validation sets, respectively, due to missing data.

symptoms, most studies reached a similar conclusion: the clinical presentation is of fundamental prognostic importance, whether expressed as the presence of seizures, the absence of deficits, or the presence of a good performance status.

In this series, largest diameter of the tumor and tumor crossing the midline were important prognostic factors. Smaller tumors or tumors not crossing the midline had better prognosis. The actual criteria for assessment of tumor crossing the midline were left to the discretion of investigators. This measure reflects both mass effect and infiltration in midline structures (corpus callosum). Kreth et al[8] found tumor volume greater than 20 mL to be of unfavorable prognostic significance, with the presence of midline shift being correlated with volume. Another study found the former T classification to be related to prognosis in univariate analysis, but this was lost in multivariate analysis.[6] Others found no association between survival and the site or the size of the tumor.[5,7,10]

Due to persistent negative results, a T-classification system for brain tumors, purely based on characteristics of the primary tumor, was dropped by the International Union Against Cancer. This analysis confirmed the limited value of such classification, and although largest diameter of the tumor and tumor crossing the midline are important prognostic factors, the role of age, histology, and neurologic status must also be taken into account to determine prognosis. Contrast enhancement, which may reflect endothelial proliferation with leaking blood vessels suggestive of a tumor with anaplastic histologic characteristics, is another radiographic feature that was found to be of prognostic significance in several series,[6,8,30-32] although other large series did not observe this relation.[5,21] This information was unfortunately not available in the present series.

In this analysis, no statistically significant impact of the extent of surgery on survival was observed in the presence of other important prognostic factors. Up until today, the role of extent of surgical removal remains one of the most controversial issues in the treatment of LGG. The theoretical goals of surgical resection in LGG are the improvement of neurologic deficits and the minimization of the risk of recurrence or of malignant transformation. Extent of resection was an important prognostic factor in several studies[1,5,11,21,29] but was of no importance in others.[7,10] A drawback of the present study is that the quantification of the amount of tumor tissue left behind was based on the intraoperative estimation of the surgeon and not on postoperative imaging. This possibly added to the overall variability of this factor, making it more difficult to detect its effect. Still, another large study that reached the opposite conclusion used the same methodology.[5]

It has been argued that the good prognosis of LGG patients having undergone an extensive resection may not be due to the resection itself but to the limited size and superficial site of the tumor (thus being accessible to more extensive surgery). Our observations seemed to support that theory, with a clear association being apparent between extent of resection and both tumor size and midline crossing of the tumor. Another series of hemispheric LGG confirmed the prognostic value of extent of resection but also noted that presurgical extension was significantly related to surgical resection: the smaller the tumor, the higher the probability of a radical resection.[11] Similarly, Berger et al[1] found both the preoperative as well as the postoperative volume to be of prognostic significance for the time to progression. It may well be that extent of surgery, as recorded in our data, is liable to an important measurement error and that its prognostic importance is further diminished by the fact that this variable may express information already expressed by tumor size and its crossing the midline. Besides, the nature of the surgical intervention itself may also contribute to variability in diagnosis. Areas of high-grade glioma within a low-grade tumor may go undetected in patients who undergo biopsy rather than tumor excision, potentially resulting in a bias toward more unrecognized high-grade tumors, with a poorer prognosis in the group of patients with less extensive resections or biopsies. The importance of the extent of surgery will remain a matter of debate until a randomized surgery trial has been carried out, although beforehand, its feasibility must be doubted.

In summary, this analysis highlighted the importance of largest tumor diameter and tumor crossing the midline, and it confirmed the importance of age, histology subtype, and presence of neurologic deficits as prognostic factors for survival in adult patients with cerebral LGG. These factors were used to derive a prognostic scoring system that can be readily calculated based on the total number of unfavorable prognostic factors present, with increasing scores corresponding to worse prognosis. Low-risk patients with two or fewer risk factors have an expected median survival of more than 7 years, but patients carrying three or more risk factors should be considered high risk and have a significantly shorter median survival time.

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