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Validation of EORTC Prognostic Factors for Adults with Low-Grade Glioma: a Report Utilizing Intergroup 86-72-51¹

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Abstract

Purpose—A prognostic index for survival was constructed and validated from patient data from two EORTC radiation trials for low-grade glioma (LGG). We sought to independently validate this prognostic index with a separate prospectively collected dataset (Intergroup 86-72-51).

Methods and Materials—203 patients were treated on an NCCTG-led trial that randomized patients with supratentorial LGG to 50.4 or 64.8 Gy. Risk factors from the EORTC prognostic index were analyzed for prognostic value: histology, tumor size, neurological deficit, age, and tumor crossing midline. A high risk group was defined as the presence of >2 risk factors. In addition, Mini Mental Status Exam score (MMSE), extent of surgical resection, and 1p19q status were also analyzed for prognostic value.

Results—In univariate analysis the following were statistically significant ($p < 0.05$) detrimental factors for both progression free (PFS) and overall survival (OS): astrocytoma histology, tumor size, and less than total resection. MMSE > 26 was a favorable prognostic factor. Multivariate analysis showed that tumor size and MMSE were significant predictors of OS, while tumor size, astrocytoma histology, and MMSE were significant predictors of PFS.

Analyzing by the EORTC risk groups, the low risk group had significantly better median OS (10.8 vs. 3.9 yrs: $p < .0001$) and PFS (6.2 vs. 1.9 yrs: $p < .0001$) than the high risk group.

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1p19q status was available in 66 patients. Co-deletion of 1p19q was a favorable prognostic factor for OS versus one or no deletion (median OS 12.6 versus 7.2 yrs, $p=0.03$).

Conclusions—Although the low risk groups by EORTC criteria had a superior PFS and OS to the high risk group, this is primarily due to the influence of histology and tumor size. Co-deletion of 1p19q is a prognostic factor. Future studies are needed to develop a more refined prognostic system that combines clinical prognostic features with more robust molecular and genetic data.

Keywords

Radiotherapy; Low-Grade Glioma; Prognostic Factors

Low-grade gliomas (LGGs) present a therapeutic dilemma to physicians due the heterogeneity of their clinical behavior. Prognostic indices have been put forth in the past from retrospective analyses. However, retrospective studies are limited because of heterogeneity of treatment, evaluation, and management center preferences.^{1, 2} The European Organization for Research and Treatment of Cancer conducted two large phase III trials to investigate the dose (EORTC 22844) and the timing (EORTC 22845) of radiotherapy in LGG³⁻⁵. A prognostic index was constructed utilizing the prospectively collected data on EORTC trial 22844 and then validated with patients from EORTC trial 22845⁶. Five adverse prognostic factors were identified: age ≥ 40 , tumor diameter ≥ 6 cm, tumor crossing midline, astrocytoma histology, and pre-operative neurological deficit. Presence of three or more risk factors identified a high risk group with a worse median survival. The purpose of the current study is to validate the EORTC prognostic factors for adults with low-grade glioma with a separate data set of LGG patients treated on a North American Intergroup trial (86-72-51)⁷.

Patients and Methods

Intergroup 86-72-51 randomized 203 patients to postoperative radiation with 50.4 Gy in 28 fractions or 64.8 Gy in 36 fractions. The trial was open from 1986 to 1994. Eligible patients were 18 years of age or older with histologic proof of a supratentorial low-grade astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. Central pathology review was performed for all patients at Mayo Clinic by a dedicated neuropathologist⁷. A CT or MRI scan was obtained along with a Neurologic Function Score (NFS-Table 1) and Mini Mental Status Examination (MMSE) at baseline (upon study entry), every 4 months for 2 years after completion of radiation, every 6 months for 3 years, then yearly until year 15.

The variables considered for this analysis were the five factors from the EORTC prognostic index: histology (oligodendroglioma/mixed vs. astrocytoma), preoperative tumor dimension without surrounding edema ($<$ vs. ≥ 6 cm), age ($<$ vs. ≥ 40 years), tumor mass crossing midline or involvement of midline structure (no vs. yes), neurological deficit (absent vs. present) as defined by NFS ≥ 3 . A score of NFS ≥ 3 was chosen as the cutoff for neurological deficit as it is most similar to the cutoff on the MRC Neurological Functional Score used by the EORTC.

Information regarding histology, neurological deficit, age, and MMSE were gathered from data entered at the time of randomization (Table 2). Extent of resection was estimated intraoperatively by the neurosurgeon. Tumor size and midline involvement were gathered retrospectively from patient charts and preoperative imaging. Only patients with tumors greater than 5 cm were retrospectively reviewed as size greater than 5 cm was a stratification factor for enrollment in the Intergroup trial.

Statistics

The five EORTC prognostic factors were analyzed independently for overall (OS) and progression free survival (PFS). PFS and OS were also analyzed for a low risk group (≤ 2 EORTC prognostic factors) and a high risk group. MMSE and extent of surgical resections also were analyzed independently as prognostic factor for PFS and OS. Time to event distributions were calculated from date of randomization and estimated using Kaplan-Meier curves and compared using log rank tests.

As tumor dimension and histology were found to be predictors of PFS and OS on univariate analysis, a separate analysis was performed defining a high risk group as having astrocytoma histology and size ≥ 6 cm, a low risk as having neither risk factor, and an intermediate risk group as having one risk factor.

The influence of deletion of chromosomes 1p and 19q was analyzed in the 66 patients in whom this information was available. The details of the 1p19q analyses have been previously reported⁸. 1p19q status was unknown in 137 patients. 27 pts had 1p19q co-deletions. PFS and OS for these 27 were compared to 39 patients who had either one or neither deletions.

Exploratory multivariate analyses (MVA) utilizing CART (regression tree) and Cox models were performed to identify prognostic factors for time to progression and survival^{9, 10}. CART modeling was performed using data from all 203 patients and the independent variables listed in table 3. Deletion status was not included in MVA, since only 66 pts had deletion status data available.

The results of the analyses using CART models and univariate log-rank tests were used to select smaller subsets of baseline variables for Cox modeling because results may prove unstable if too many baseline variables are used^{9, 10}. Furthermore, because Cox model methods exclude patients with missing values and 20 patients were missing an NFS or MMSE score at baseline, we assumed the missing values to be normal, based on the facts that 59% of patients with an abnormal NFS (3-4) had a normal MMSE score and 83% of patients with an abnormal MMSE had a normal NFS (0-2).

Results

Analysis Based on Five EORTC Criteria

By the time of this analysis, of the 203 patients enrolled on Intergroup 86-72-51, 157 had evidence of progression while 133 had died, with a median follow-up time of 7.7 years (range 0.1 to 18.7 years). Univariate analysis of the five EORTC prognostic factors found astrocytoma histology (HR=1.82; CI: 1.21-2.73; $p=0.004$) and tumor ≥ 6 cm (HR=1.96; CI: 1.39-2.77; $p=0.0001$) to be statistically significant predictors of a worse overall survival. Both these prognostic factors, astrocytoma histology (HR=1.80; CI: 1.23-2.65; $p=0.003$) and tumor ≥ 6 cm (HR=1.93; CI: 1.40-2.65; $p<0.0001$), were also negative prognostic factors for PFS. The remaining three EORTC prognostic factors of age ≥ 40 , tumor crossing midline, and neurological deficit were not independent prognostic factor for OS (Table 3) or PFS (Table 4).

Analyzing by risk groups defined by the EORTC prognostic factors, the low risk ($n=156$ patients) group (≤ 2 risk factors) had significantly better median OS (10.8 vs. 3.9 yrs: $p<0.0001$) and PFS (6.2 vs. 1.9 yrs: $p<0.0001$) than the high risk group ($n=35$ patients). Median OS and PFS for each prognostic score 0-5 are outlined in Table 5 and Figure 1 illustrates Kaplan-Meier survival curves for each prognostic score.

Analysis Based Solely on Tumor Size and Histology

As astrocytoma histology and size ≥ 6 cm were statistically significant on univariate analysis, we analyzed the PFS and OS of patients having neither (i.e. low risk), one (i.e. intermediate risk), or both risk (i.e. high risk) factors utilizing a definition of risk based solely on size and histology (Table 6). With this definition of risk, the high risk group had a median OS of 3.5 years and PFS of 2.1 years. Patients in the intermediate risk group had median OS of 6.4 years and PFS of 3.9 years. The low risk group had a median OS of 12.6 years and PFS of 9.5 years.

OS and PFS was statistically significant comparing the low risk group vs. the intermediate and high risk groups (Figures 2 and 3). On pair wise comparisons between the low risk group and the intermediate risk group the differences were statistically significant ($p < .0001$) for both OS and PFS, but not when comparing the intermediate and high risk groups ($p = 0.1312$ for OS, $p = 0.0712$ for PFS).

Analysis Based on 1p19q Deletion Status

1p19q deletion status influence on OS and PFS was analyzed in the 66 patients for whom it was known. OS was higher with co-deletion of 1p19q vs. one or no deletions: 12.6 yrs versus 7.2 yrs ($p = 0.03$) (Figure 4). PFS for patients with co-deletion was 8.1 yrs versus 3.3 years without co-deletion ($p = 0.09$). There were no statistically significant differences in OS or PFS for patients with any deletion versus no deletion.

Cox Model Analyses for OS And PFS

The results of the Cox modeling are summarized in Tables 3 and 4 for OS and PFS. On multivariate analysis, tumor size ≥ 6 cm and MMSE score ≤ 26 were found to be statistically significant for a worse OS ($p = 0.006$ and 0.001 , respectively) with a trend for astrocytoma histology ($p = 0.08$). On multivariate analysis tumor size ≥ 6 cm, astrocytoma histology, and MMSE score ≤ 26 were found to be statistically significant for a worse PFS ($p = 0.0006$, 0.03 , and 0.0005 , respectively) with a trend for less than a gross total resection ($p = 0.06$).

Discussion

Low-grade gliomas prognostic factors have been put forth in the past. Retrospective studies have identified many prognostic factors including extent of resection, histology, size, performance status, and tumor crossing the midline^{1, 2, 11-14}. Investigators from the EORTC published a prognostic index derived from two large prospective trials evaluating the role of radiation in the treating low-grade gliomas⁶. In addition, this EORTC prognostic index was separately confirmed using information from a SEER database (although the investigators were unable to assess neurologic function)¹⁵.

For the current study (i.e. the Intergroup trial 86-72-51), two of the five EORTC prognostic variables, astrocytoma histology and size ≥ 6 cm were statistically significant for PFS and OS on univariate analysis. Baseline MMSE was the only other variable predictive of both PFS and OS; prior analyses have also found baseline neurocognitive function (i.e. MMSE) to be a strong predictor of outcome¹⁶. It is possible that unrecognized aggressiveness and invasion in subsets of low-grade gliomas, manifesting as neurocognitive deficits, could account for the poorer outcomes of patients with worse baseline MMSE scores.

The three EORTC prognostic factors of age ≥ 40 , tumor crossing midline, and neurological deficit were not independent prognostic factors in the current analyses. While the MMSE was predictive, the neurologic function score was not, possibly because the neurologic function score is less sensitive to milder neurologic changes than the MMSE, is more reliant

on observer grading, and focuses more on physical function. In addition the number of patients with neurologic deficit in the Intergroup trial (8.8%) was considerably less compared to the EORTC trials (18.5%), and these small numbers may explain why neurological deficit was not found to be an independent prognostic factor in the Intergroup trial. An explanation for the lack of predictive value for midline tumor involvement may be the common use of preoperative MRI in the Intergroup trial as compared to the more frequent use of CT in the EORTC trials. It is possible the patients having a preoperative MRI had midline involvement apparent sooner (i.e. less advanced disease) than would be apparent on CT alone and therefore weakening the predictive value of midline involvement. Age may have not been prognostic factor since it was analyzed as a categorical (possibly introducing a more “artificial” cut-off) variable instead of a continuous variable since age was a stronger predictor of outcome when analyzed as a continuous variable in the original analyses of the Intergroup study⁷. It is also important to recognize that unlike the EORTC trials (i.e. EORTC 22845), all patients in the Intergroup trial received “immediate” post-operative radiotherapy. It is possible that radiotherapy may have altered the natural history of LGG, with a resulting impact on the determination of significant prognostic factors.

Our analyses of OS and PFS of patients enrolled on the Intergroup trial using the EORTC prognostic indicators produced a high and low risk group with significantly different OS and PFS much like in the EORTC database. Patients in the EORTC trials with three or more adverse prognostic indicators (“high-risk”) had a median OS of 3.2 to 3.67 years, while the high-risk group in the Intergroup had a very similar median OS of 3.9 years. The median OS in the EORTC trials for patients fulfilling the EORTC criteria of low risk was 7.72 to 7.80 years, and in the Intergroup trial, these patients had a median OS of 10.8 years. While the results are similar between the two databases, in the Intergroup study most of the difference between the high and low risk groups was primarily due to histology and tumor size. Analyzing solely by size and histology, 3 stratified groups were identified, high risk for patients with large (≥ 6 cm) astrocytomas, an intermediate risk group with only one of these adverse factors, and a low risk group for those patients with small non-astrocytomas (median overall survival 3.5 years, 6.4 years, and 12.6 years respectively).

In the current study, 1p19q LOH (loss of heterozygosity) was a prognostic factor for those patients analyzed. Co-deletion of 1p19q LOH as a predictor of a more favorable prognosis for low-grade gliomas is well documented^{17, 18}, however 1p19q status was not analyzed as a prognostic factor for any of the previously reviewed studies focusing on prognostic indices for LGG patients. When analyzed, 1p19q LOH has been shown to be a prognostic factor and to be strongly correlated with histologic type. Jenkins and colleagues reported on 1p 19q deletion for North Central Cancer Treatment Group (NCCTG) patients enrolled on 2 prospective LGG trials⁸. Of 91 patients evaluated from these two trials, 57% of oligodendrogliomas had 1p19q codeletion, compared to 32% of oligoastrocytomas and no astrocytomas. Five year OS was superior for patients with 1p19q co-deletions (95 % vs. 59%, $p=0.004$). Similarly, Mariani and associates assessed chromosomal status and found 1p19q deletion was an independent non-treatment related favorable prognostic factor for overall survival¹⁹. Ongoing trials are prospectively evaluating 1p19 status and should further delineate chromosomal deletion status as a prognostic factor for low-grade gliomas.

In conclusion, although the low risk group as defined by the EORTC criteria had a superior PFS and OS to the high risk group, this difference was primarily due to the influence of histology and tumor size. In addition, co-deletion of 1p19q was found to be a prognostic factor for increased OS. It is anticipated the prognostic value of other molecular markers (e.g. IDH1, MGMT) will be elucidated with further study²⁰. Future studies are needed to develop a more refined prognostic system of LGG that combines clinical prognostic features with robust molecular and genetic data.

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Figure 1.
Overall Survival (in years) by Prognostic Score

Figure 2.
Kaplan-Meier Curves and Comparison for Overall Survival for Risk Groups Defined Solely
by Size and Histology

Figure 3.
Kaplan-Meier Curves and Comparison for Progression-Free Survival for Risk Groups Defined Solely by Size and Histology

Figure 4.
Overall Survival for 66 Patients with 1p19q Deletion Status Available

Table 1

Neurologic Function Score and Definitions

Score	Definition
0	No neurologic symptoms, fully active at home and work without assistance
1	Minor neurologic symptoms, fully active at home and work without assistance
2	Moderate neurologic symptoms, fully active at home and work but requires assistance
3	Moderate neurologic symptoms, less than fully active at home and work and requires assistance
4	Severe neurologic symptoms, totally inactive and unable to work, requires complete assistance at home or in an institution

Table 2**Patient Characteristics**

Characteristic	Summary
Age, yrs	
N	203
mean $\pm$ SD	40.5 $\pm$ 11.8
median (min, max)	40 (18, 73)
Age by group, N (%)	
< 40 yrs	100 (49.3%)
$\geq$ 40 yrs	103 (50.7%)
Gender	
Female	86 (42.4%)
Male	117 (57.6%)
MMSE scores	
N	187
means $\pm$ SD	27.9 $\pm$ 3.7
median (min, max)	29 (2, 30)
Missing	16
MMSE scores by group, N (%)	
$\leq$ 26	35 (18.7%)
> 26	152 (81.3%)
Neuro deficit, N (%)	
Absent	176 (91.2%)
Present	17 (8.8%)
Missing	10
Tumor largest dimension, N (%)	
< 6 cm	110 (54.7%)
$\geq$ 6 cm	91 (45.3%)
Missing	2
Tumor crossing midline, N (%)	
No	144 (71.3%)
Yes	58 (28.7%)
Missing	1
Extent of surgical resection, N (%)	
Biopsy	97 (47.8%)
Subtotal	76 (37.4%)
Gross total	30 (14.8%)
Histology, N (%)	
Oligo/Mixed	162 (79.8%)
Astro	41 (20.2%)
1p19q deletion status, N (%)	
1p19q co-deleted	27 (41.0%)

Characteristic	Summary
One/neither deletion	39 (59.0%)
Missing	137

N, number; SD, standard deviation; MMSE, Mini-Mental State Examination; Neuro, neurological; Oligo, oligodendroglioma; Astro, astrocytoma

Table 3

Association of Prognostic Variables with Overall Survival (in years)

Variable	Univariate				Multivariate		
	MEDIAN OS (95% CI)	P-VAL *	HR (95% CI)	P-VAL **	HR (95% CI)	P-VAL **	P-VAL **
Age group		0.17		0.17			0.19
< 40	10.1 (8.1, 11.6)		1.00		1.00		
≥ 40	7.1 (4.5, 10.9)		1.27 (0.90, 1.78)		1.29 (0.88, 1.88)		
Histology group		0.003		0.004			0.08
oligo/mixed	10.2 (8.1, 11.7)		1.00		1.00		
Astro	5.5 (2.2, 7.5)		1.82 (1.21, 2.73)		1.50 (0.95, 2.38)		
Tumor dimension		0.0001		0.0001			0.006
< 6 cm	11.6 (10.1, 13.6)		1.00		1.00		
≥ 6 cm	6.0 (4.5, 8.1)		1.96 (1.39, 2.77)		1.69 (1.16, 2.47)		
Tumor crossing midline		0.76		0.76			0.81
No	8.6 (7.2, 11.1)		1.00		1.00		
Yes	8.4 (4.5, 11.5)		1.06 (0.73, 1.55)		0.95 (0.63, 1.44)		
Neuro deficit		0.10		0.10			0.58
No	9.4 (7.2, 11.1)		1.00		1.00		
Yes	6.2 (1.7, 9.2)		1.59 (0.91, 2.79)		1.19 (0.64, 2.19)		
MMSE group		<.0001		<.0001			0.001
≤ 26	4.0 (2.9, 5.0)		1.00		1.00		
> 26	10.8 (8.3, 12.0)		0.42 (0.28, 0.64)		0.48 (0.31, 0.75)		
Extent of Surgical Resection		0.01		0.01			0.10
Total	13.6 (10.1, NR ^{***})		1.00		1.00		
Subtotal/Bx	7.5 (6.2, 9.9)		2.14 (1.18, 3.87)		1.79 (0.91, 3.16)		

* log-rank p-value comparing Kaplan-Meier curves

** chi-square p-value

*** Value Not Reached

Oligo, oligodendroglioma; Astro, astrocytoma; Neuro, neurological; MMSE, Mini-Mental State Examination; Bx, biopsy

Table 4

Association of Prognostic Variables with Progression-Free Survival (in years)

Univariate		Multivariate				
Variable	MEDIAN PFS (95% CI)	P-VAL *	HR (95% CI)	P-VAL **	HR (95% CI)	P-VAL **
Age group		0.39		0.39		0.85
< 40	5.4 (4.3, 7.8)		1.00		1.00	
≥ 40	4.4 (3.2, 6.9)		1.15 (0.84, 1.57)		0.97 (0.68, 1.37)	
Histology group		0.002		0.003		0.03
oligo/mixed	5.7 (4.6, 7.6)		1.00		1.00	
Astro	2.5 (1.2, 4.6)		1.80 (1.23, 2.65)		1.62 (1.06, 2.48)	
Tumor dimension		<.0001		<.0001		0.0006
< 6 cm	7.8 (5.7, 10.1)		1.00		1.00	
≥ 6 cm	3.4 (2.7, 4.3)		1.93 (1.40, 2.65)		1.85 (1.30, 2.63)	
Tumor crossing midline		0.88		0.88		0.22
No	5.2 (4.2, 6.4)		1.00		1.00	
Yes	5.0 (3.9, 9.7)		0.97 (0.68, 1.39)		0.78 (0.52, 1.16)	
Neuro deficit		0.07		0.07		0.72
No	5.5 (4.4, 6.7)		1.00		1.00	
Yes	1.9 (1.1, 4.1)		1.65 (0.96, 2.82)		1.12 (0.61, 2.04)	
MMSE group		<.0001		<.0001		0.0005
≤ 26	1.8 (1.2, 3.0)		1.00		1.00	
> 26	6.3 (5.1, 8.1)		0.44 (0.29, 0.66)		0.46 (0.30, 0.71)	
Extent of Surgical Resection		0.003		0.004		0.06
Total	10.0 (8.0, 12.2)		1.00		1.00	
Subtotal/Bx	4.6 (3.8, 5.7)		2.18 (1.28, 3.72)		1.72 (0.98, 3.00)	

* log-rank p-value comparing Kaplan-Meier curves

** chi-square p-value

Oligo, oligodendroglioma; Astro, astrocytoma; Neuro, neurological; MMSE, Mini-Mental State Examination; Bx, biopsy

Table 5

Association of Prognostic Score with OS and PFS (in years)

Score	N (%)	median OS (95% CI)	P-VAL [*]	median PFS (95% CI)	P-VAL [*]
0	32 (16.8%)	11.1 (8.2, 13.0)	<.0001	7.3 (4.3, 9.8)	<.0001
1	67 (35.1%)	10.8 (7.5, 13.7)		6.4 (4.6, 7.8)	
2	57 (29.8%)	10.2 (6.8, 13.0)		5.4 (3.8, 8.6)	
3	30 (15.7%)	4.0 (3.1, 6.2)		1.9 (1.1, 3.9)	
4	4 (2.1%)	2.0 (0.3, 6.6)		1.4 (0.1, 6.1)	
5	1 (0.5%)	1.2		1.2	
Missing	12				

^{*} log-rank p-value comparing Kaplan-Meier curves

Table 6**Risk Groups Based on Tumor Size and Histology**

Risk Group	Tumor size	Histology	N (%)
Low	< 6 cm	Oligo/mixed	88 (43.8%)
Intermediate	≥ 6 cm	Oligo/mixed	73 (36.3%)
Intermediate	< 6 cm	Astro	22 (10.9%)
High	≥ 6 cm	Astro	18 (9.0%)

N, number; Oligo, oligodendroglioma; Astro, astrocytoma