Epidermal Growth Factor Receptor and Labeling Index Are Independent Prognostic Factors in Glial Tumor Outcome

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ABSTRACT

The aim of this study was to perform a multivariate analysis including clinical and biological prognostic factors on glial tumor outcome. Seventy-nine patients were analyzed (48 men and 31 women; mean age on diagnosis was 62 years, range = 16–77 years): 7 had a benign glial tumor (grades 1 and 2), 21 had an anaplastic glial tumor (grade 3), and 51 had a glioblastoma (grade 4). Median follow-up was 17.9 months for patients who survived (50 patients died). Biopsies were obtained at time of diagnosis (complete tumor resection in 62 patients and stereotaxic biopsies in 17 patients). Epidermal growth factor receptor (EGFR) was measured by a binding assay, and labeling index (LI) was measured by tritiated thymidine incorporation.

EGFR varied from 4 to 73,110 fmol/mg protein (mean = 3912 fmol/mg protein; median = 374 fmol/mg protein; n = 79). LI varied between 0.1 and 16.5% (mean = 6.2%; median = 5.2%; n = 40). Log_{10} EGFR was significantly and positively correlated with patient age. LI was significantly different according to tumor histology. Univariate Cox analysis (end point was cancer death) showed that age (P = 0.027), log_{10} EGFR (P = 0.025), and LI (P = 0.0019) were significant continuous variables, the survival being shortened when the covariate increased; tumor resection (P = 0.015, relative risk = 0.45) and histology (P = 0.0009) were significant categorical factors. A multivariate Cox analysis (forward selection) including age, histology, tumor resection, log_{10} EGFR, and LI revealed that log_{10} EGFR, LI, and tumor resection were the only independent significant predictors of survival.

This multivariate approach reveals that the clinical prognostic factors of glial tumors, namely age and tumor histology, disappear, to the benefit of intrinsic characteristics of the tumor, i.e., EGFR expression and LI, suggesting that coupled EGFR and LI determination could be a useful tool for better evaluation of glial tumor outcome.

INTRODUCTION

Glial tumors represent 50% of adult CNS tumors (1). Histology of these tumors is age related, with increasingly higher grade in the fifth decade (1). The prognosis of patients with malignant glioma remains extremely poor. Different factors have been identified as having a more or less marked influence on the outcome of CNS tumors, including patient age (2), tumor characteristics like grading and histopathological parameters (3–5), Karnofsky index (6), and the feasibility of complete surgical removal (6).

EGFR belongs to the tyrosine kinase cell membrane receptor family of proteins, which have an extracellular domain that interacts with the specific ligand (EGF and transforming growth factor-α) and an intracellular part characterized by tyrosine kinase activity. Overexpression of EGFR has been shown to be related to an unfavorable prognosis in various tumors, including breast (7), bladder (8), esophagus (9), cervix (10), ovary (11), lung (12), and head and neck (13, 14). Particularly high levels of EGFR have been reported in CNS tumors (15, 16), and EGFR was found simultaneously amplified and overexpressed in a majority of malignant gliomas (17, 18). There are surprisingly few studies of CNS tumors that have thoroughly evaluated the impact of EGFR overexpression on patient survival using a multivariate approach (19, 20). Zhu et al. (20) reached the conclusion that EGFR expression is the best indicator of survival, and Jaros et al. (19) pointed out that Ki-67, an indicator of tumoral cell proliferation, is a more powerful survival predictor than EGFR. Both studies involved an immunohistochemical estimation of EGFR expression. This technical approach confers advantages in terms of tumoral specificity but categorization of results (positive versus negative) leads to information loss.

It was thus important to reevaluate the prognostic significance of EGFR by using a quantitative determination of this parameter based on a ligand binding assay. Because of a possible association between tumoral cell proliferation and EGFR expression, as suggested by the data of Jaros and colleagues (19), we analyzed the prognostic value of LI in this multivariate
study. Besides EGFR and LI, other conventional factors were taken into account, such as age, sex, histology, and applied treatment (tumor resection, chemotherapy, and radiotherapy). A total of 79 patients with various histological forms of glial tumors were analyzed.

**MATERIALS AND METHODS**

**Patients.** This study was conducted on 79 consecutive patients who developed a glial tumor between April 1985 and June 1995. Tumoral biopsies were obtained before any radiotherapy or chemotherapy treatment was given, at time of diagnosis or during surgical removal of the tumor. The tumoral samples used in this study were a part of the biopsy taken in the most representative area of the histological grade of the tumor. The average weight of samples was 380 mg (range = 60–640 mg). All tissue samples were stored frozen in liquid nitrogen until processing.

There were 48 men and 31 women. The mean age was 56 years (range = 16–77 years). Three histological groups were defined according to Daumas-Duport classification (5). Seven patients exhibited a benign glial tumor (two grade 1 oligodendrogliomas, two grade 1 astrocytomas, one grade 2 oligoastrocytoma, and two grade 2 astrocytomas). Twenty-one patients had an anaplastic glial tumor (8 grade 3 oligodendrogliomas and 13 grade 3 astrocytomas). Fifty-one patients had a glioblastoma. Initial treatment consisted of tumor resection, chemotherapy, and/or radiotherapy. When the tumor was not located in an eloquent area, as complete a tumor resection as possible was performed (62 patients); in the other situations, only stereotaxic biopsies were performed (17 patients). Radiotherapy was applied in 65 patients and consisted of cobalt or 25-MV photons (total dose = 30–60 Gy; 1.8–3 Gy per fraction). Chemotherapy was administered in 36 patients, either monotherapy with fotemustine or polychemotherapy including cisplatin, etoposide, and fotemustine (one to three cycles). Among the 62 patients undergoing tumor resection, 8 did not receive additional therapy, 26 received radiotherapy, 2 received chemotherapy, and 26 had both radiotherapy and chemotherapy. Duration of survival was calculated from the date of initial diagnosis. The end point was cancer death. Only three patients were lost to follow-up and were considered censored observations in the survival analysis. Median follow-up was 11.6 months for the whole population and 17.9 months for surviving patients. At time of study analysis, 50 patients had died.

**EGFR Determination.** EGFR was assayed according to a method described previously (21). Human recombinant 125I-labeled EGFR (specific activity = 900-1400 Ci/mmol) and unlabeled recombinant human EGFR were purchased from Amersham (Les Ulis, France). Frozen tumoral samples were weighed, homogenized in a buffer A containing 10 mm Tris-HCl, 1 mm EDTA, 0.5 mm DTT, and 10 mm sodium molybdate (pH 7.4). After centrifugation (800 × g for 10 min at 4°C), the supernatant was collected and ultracentrifuged for 1 h (105,000 × g, 4°C). The resulting pellet, containing crude cellular membranes, was resuspended in buffer B containing 10 mm Tris-HCl, 10 mm MgCl₂, 1 mm phenylmethylsulfonyl fluoride, and 0.02% NaN₃ (pH 7.4). An aliquot was taken for protein concentration measurement using the Bradford method. One hundred μl of 125I-labeled EGFR (0.16 nm final) was incubated with 100 μl of the membrane preparation and increasing concentrations of unlabeled EGFR (50 μl; 0–8 nm final concentration). An added concentration of unlabeled EGFR (160 nm) allowed determination of nonspecific binding. Labeled and unlabeled EGFR solutions were prepared in a buffer (10 mm Tris-HCl, 10 mm MgCl₂, 100 μg/ml bacitracin, and 0.02% NaN₃) containing 0.1% BSA. The reaction was stopped by the addition of 1 ml of cold buffer B, and the tubes were immediately centrifuged at 11,000 × g (15 min at 4°C). After removal of the supernatant, γ radioactivity was counted in the pellet. Specific binding was expressed as fmol of bound EGFR/mg of membrane protein after Scatchard plot analysis. For each series of EGFR assays, an internal standard (aliquot of a membrane preparation from human placenta) was used (mean = 281 fmol/mg protein; coefficient of variation = 11%; n = 11).

**LI Determination.** LI was determined by using a technique described previously (22). Briefly, biopsy fragments were incubated for 30 min in a culture medium containing tritiated thymidine. They were then fixed, embedded in paraffin, and sectioned. Slices were dipped in Ilford K2 emulsion and exposed for 21 days at 4°C. They were then developed, fixed, and stained. Cells containing five or more grains were considered labeled. On average, 1000 cells were scored per sample, and three samples per tumor were examined. LI was expressed as the number of labeled tumor cells × 100/the number of total tumor cells.

**Statistics.** Parameters analyzed as continuous variables were EGFR (log₁₀ transformed), LI, and age. Sex, tumor histology (group 1, benign glial tumors; group 2, anaplastic gliomas; and group 3, glioblastomas), tumor resection (yes/no), radiotherapy (yes/no), and chemotherapy (yes/no) were analyzed as coded variables. Comparison of log₁₀ EGFR and LI between men and women was performed by means of the Student's t test; comparison according to tumor histology was performed using ANOVA. Correlations between LI and age, between log₁₀ EGFR and age, and between LI and log₁₀ EGFR were tested through simple linear regressions. Overall survival was computed according to the Kaplan-Meier method. The influence of each predictor variable on overall survival was analyzed according to the Cox proportional hazard regression. For that purpose, tumor histology was coded with the effect of each group being compared to the reference group (benign glial tumors having the longest survival). Selection of predictor vari-
by performing successive Cox regression analyses including LI

tively. The best LI and log10 EGFR thresholds were determined

Probability for entry and removal were 0.05 and 0.10 respec-

histology was not different between these 40 patients (2 benign

material (biopsies performed at time of diagnosis were small to

drawn up on SPSS software (Chicago, IL).

log10 EGFR between 2.0 and 3.0 (by a 0.1 step). Statistics were

and third quartiles: LI between 4.0 and 6.0 (by a 0.2 step) and

the greater Wald value). Thresholds were tested within the first

threshold, 1 if greater than the threshold). Criteria were the

analysis, based on the maximum partial likelihood estimates.

was positively correlated with patient age (Table 2), and age was

poorer histological groups (Fig. 1B.

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link

 according to tumor histology and age are shown in Table 2. The

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and LI). EGFR expression and LI were not significantly differ-

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EGFR

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were independent parameters

When log10 transformation was used, the distnibu-

0.625 ± 0.432 nM) . The Scatchard analysis of

expression varied from 4 to

were demonstrated between log10 EGFR and LI, between tumor resection

median survival was 15.6 months (95% confidence interval = 8.4–22.7). In

the group of seven patients with benign glial tumor, one patient died (at 50.1 months). In the anaplastic glial tumor group (12 events) and glioblastoma group (37 events), median survival was 27.5 and 11.2 months, respectively. Univariate Cox analyses are shown in Table 3. Significant continuous variables were age, log10 EGFR, and LI, survival being shortened when the covariable increased. Significant categorical variables were tu-

result (relative risk = 0.45; 95% confidence interval = 0.23–0.85) and tumor histology. As compared to benign glial tumors, relative risks were 4.80 (95% confidence interval = 0.62–37.24) and 13.99 (95% confidence interval = 1.90–103.31) for anaplastic glial tumors and glioblastoma, re-

Because EGFR was linked to age and LI was de-

upon tumor histology, a possible interaction between

influenced by age.

The overall survival curve for the whole population is

shown in Fig. 2 (50 events, 29 censored data). Median survival
time was 15.6 months (95% confidence interval = 8.4–22.7). In

variables was done by means of forward analysis, based on the maximum partial likelihood estimates. Probability for entry and removal were 0.05 and 0.10 respectively. The best LI and log10 EGFR thresholds were determined by performing successive Cox regression analyses including LI or log10 EGFR as a categorical variable (0 if lower than the threshold, 1 if greater than the threshold). Criteria were the Wald statistics (the best threshold was defined as the one giving the greater Wald value). Thresholds were tested within the first and third quartiles: LI between 4.0 and 6.0 (by a 0.2 step) and log10 EGFR between 2.0 and 3.0 (by a 0.1 step). Statistics were drawn up on SPSS software (Chicago, IL).

RESULTS

EGFR and LI measured on glial tumors exhibited wide

variability (Table 1). Due to the limited quantity of biological

material (biopsies performed at time of diagnosis were small to

avoid unacceptable risk of damage to normal brain), LI deter-

mination was only feasible in a subgroup of 40 patients. Tumor

histology was not different between these 40 patients (2 benign
glial tumors, 14 anaplastic glial tumors, and 24 glioblastomas) and the 39 patients without LI determination (P = 0.15 by χ² test). LI varied between 0.1 and 16.5% (mean = 6.2%; median = 5.2%; Table 1). EGFR expression varied from 4 to 73,110 fmol/mg protein (mean = 3,912 fmol/mg protein; median = 374 fmol/mg protein) and showed an asymmetrical distribution. When log10 transformation was used, the distribution of EGFR fitted the Gaussian law (mean = 2.65; median = 2.57; skewness = 0.49 ± 0.27). The Scatchard analysis of EGFR revealed a single family of high-affinity binding sites (mean Kd = 0.625 ± 0.432 nm).

EGFR and LI were independent parameters (P = 0.31, r = −0.16, and n = 40, by linear regression between log10 EGFR and LI). EGFR expression and LI were not significantly different according to patient sex. Analyses of log10 EGFR and LI according to tumor histology and age are shown in Table 2. The link between EGFR expression and tumor histology was at the limit of significance (Fig. 1A, P = 0.066). LI was significantly different according to tumor histology, with higher values in poorer histological groups (Fig. 1B, P = 0.014). Log10 EGFR was positively correlated with patient age (Table 2), and age was significantly different according to tumor histology (mean = 36.6, 53.2, and 59.5 in benign tumors, anaplastic tumors, and glioblastoma, respectively; P < 0.001 by ANOVA). LI was not influenced by age.

log10 EGFR or LI as a categorical variable were performed to estimate the best EGFR and LI thresholds to be used from a clinical point of view. For LI, the best threshold was 4.6% (P = 0.0048). The median survival for patients exhibiting LIs of <4.6% was 120.4 months, whereas that of patients with LIs of >4.6% was 13.6 months; the relative risk was 3.51 (95% confidence interval = 1.47–8.4). Regarding log10 EGFR, the best threshold was 2.4, giving an EGFR value at 250 fmol/mg protein (P = 0.0093); median survival for patients exhibiting an EGFR value of <250 was 29.0 months, whereas in patients with EGFR values of >250 median survival was 12.1 months; the relative risk was 2.34 (95% confidence interval = 1.23–4.43). Fig. 3 illustrates survival curves according to LI and EGFR thresholds, respectively.

Table 2: Relationships between the main covariables analyzed

<table>
<thead>
<tr>
<th>Tumor histology</th>
<th>EGFR (fmol/mg protein)</th>
<th>LI (%)</th>
<th>Tumor resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Linear regression analysis*</td>
<td>Linear regression analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 79  r = 0.27  P = 0.017</td>
<td>n = 40  r = 0.05  P = 0.77</td>
<td></td>
</tr>
<tr>
<td>Tumor histology</td>
<td>N  Geometric Min–max mean</td>
<td>N  Geometric Min–max mean</td>
<td>N</td>
</tr>
<tr>
<td>Benign glial tumor</td>
<td>7  100  10–1,435</td>
<td>2  2.45  1.13–3.77</td>
<td>6</td>
</tr>
<tr>
<td>Anaplastic glial tumor</td>
<td>21 369 18–37,530</td>
<td>14 4.26 0.10–10.93</td>
<td>17 1</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>51 600 4–73,115</td>
<td>24 7.69 1.52–16.49</td>
<td>39 12</td>
</tr>
<tr>
<td>ANOVA: P = 0.066*</td>
<td>ANOVA: P = 0.014</td>
<td></td>
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</tr>
</tbody>
</table>

* Statistics performed on log₁₀ EGFR.

The Table 2 shows the relationships between the main covariables analyzed. The table includes the number of patients (n), the correlation coefficient (r), and the p-value (P) for the linear regression analysis of EGFR and LI, as well as the correlation coefficient and p-value for the linear regression analysis of LI and Tumor resection. The table also includes the number of patients (n) and the results of the ANOVA for the categorical analysis of EGFR, LI, and Tumor resection.

The results show that EGFR and LI were independent parameters, with a p-value of 0.31 and a correlation coefficient of -0.16. The best LI threshold was determined to be 4.6%, with a p-value of 0.066. The best log₁₀ EGFR threshold was determined to be 2.4, with a p-value of 0.0093. The table also includes the results of the ANOVA for the categorical analysis of EGFR, LI, and Tumor resection.
DISCUSSION

The aim of this study was to analyze the prognostic value of different variables related to the patient and tumor characteristics on CNS tumor outcome. Particular attention was paid to the role of EGFR and proliferation index. Among the genetic alterations involved in the progression of human glial tumors, amplification and rearrangement of EGFR are considered a key event that occurs at the transition to glioblastoma multiforme (23). Most of previous EGFR studies on CNS tumors were based on immunohistochemical analysis with various percentages of positivity ranging from 17% (24) to 74% (19). In this study, a ligand binding assay allowing a physiologically relevant determination was performed because not only the relative number of functional receptor sites but also the affinity of the ligand for its binding site were quantified. A human recombinant EGF was used in the assay to remain as close as possible to physiological conditions. The limitation of this assay is the lack of evaluation of contamination by normal tissue that could artifactually decrease the EGFR level; however, this limitation is counterbalanced by the fact that the biopsy was taken in the more representative area of the histological grade of the tumor. To our knowledge, no EGFR data quantified by a ligand binding assay have been published on a large series of patients with glial tumors. The Scatchard analyses performed on the 79 tumoral biopsies showed a single class of high affinity binding sites in all cases (mean $K_d = 0.625 \text{ nm}$). In this study, tremendous variability was observed for EGFR expression in CNS tumors (4–73,113 fmol/mg protein; coefficient of variation = 311%). This underscores the multiple genetic pathways characterizing malignant gliomas with variable levels of amplification and overexpression of EGFR (18, 23, 25). In agreement with previous reports by Zhu et al. (20) and by Agosti et al. (24), EGFR expression was not significantly linked to tumor histology, although a tendency was observed with higher EGFR levels in poorer histological groups ($P = 0.066$; Table 2). Patients were older in poorer histological groups ($P < 0.0001$), and this relationship could explain the significant positive correlation demonstrated between EGFR and age (Table 2). The phenotypic overexpression of EGFR in glial tumors can be due to EGFR gene amplification. Such amplification is frequently associated with structural rearrangement of EGFR resulting in changes in the extracellular domain (25–27). The most common mutated EGFR is an aberrant EGFR with mRNA lacking 801 bases (EGFR type III), which functions as a continuously activated tyrosine kinase (27, 28). The precise role of this EGFR mutated form is not clearly defined because it has been previously shown that its presence is related to poorer survival (29), this observation contrasting with the findings by Moscatello et al. (30) showing that altered EGFR was more frequently found in low-grade glial tumors than it was in high-grade tumors. Also, the tumoral cell heterogeneity within glial tumors as well as the variability of EGFR expression within tumoral cells make it difficult to draw conclusions. In glial tumors, the presence of functional EGFR, as investigated here, and of mutated forms still needs to be clearly delineated, as do their respective impacts on CNS outcome.

In CNS tumors, classic prognostic factors are patient age (2, 31) and tumor histology (5). Univariate analyses performed in this study confirm the significant influence of age and histology group on patient survival (Table 3). Although the aim of this study was not to investigate the efficacy of the different therapies administered, univariate analyses indicated that neither radiotherapy nor chemotherapy had a significant impact on survival. In contrast, patients in whom complete excision of the tumor was possible exhibited significantly longer survival than did patients for whom no complete surgical resection was done. This result concords with that of Kim et al. (5) and Ammirati et al. (32). The univariate analysis performed here demonstrates that EGFR was a significant predictor of overall survival (Table 3). Tumor cell kinetics have been found to have a high prognostic value for a wide variety of tumors (33). Although not determined on the whole group of patients, univariate analysis shows that LI carries a strong prognostic value (Table 3).

The main purpose of this work was to test the prognostic value of these different factors in a multifactorial approach. The multivariate analysis performed on the subgroup of 40 patients
Fig. 2  Plot of cumulative survival according to Kaplan Meier method. Survival was calculated from the date of initial diagnosis; the end point was cancer death. A total of 79 patients were analyzed (50 events observed), 29 censored observations. Median survival was 15.55 months (95% confidence interval = 8.36–22.74).

**Table 3**  Univariate and multivariate analysis of patient survival according to the Cox model

<table>
<thead>
<tr>
<th>Covariable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Wald</td>
</tr>
<tr>
<td>Age</td>
<td>79</td>
<td>4.87</td>
</tr>
<tr>
<td>Log10 EGFR</td>
<td>79</td>
<td>5.06</td>
</tr>
<tr>
<td>LI</td>
<td>40</td>
<td>9.63</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>79</td>
<td>13.93</td>
</tr>
<tr>
<td>Benign glial tumor (reference group)</td>
<td></td>
<td>4.80</td>
</tr>
<tr>
<td>Anaplastic glial tumor</td>
<td></td>
<td>13.99</td>
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<tr>
<td>Glioblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor resection (no = 0, yes = 1)</td>
<td>79</td>
<td>5.96</td>
</tr>
<tr>
<td>Radiotherapy (no = 0, yes = 1)</td>
<td>79</td>
<td>2.17</td>
</tr>
<tr>
<td>Chemotherapy (no = 0, yes = 1)</td>
<td>79</td>
<td>2.11</td>
</tr>
</tbody>
</table>

* For any covariable, the relative risk (e^β) is equal to the risk of death of a patient presenting the value x, divided by the risk of death of a patient presenting the value x, - 1, whatever the value of x. In case of categorial variable, e^β represents the relative risk of death between the two classes of the variable. When e^β > 1, the risk of death rises when the variable increases; when e^β < 1, the risk of death decreases when the variable increases.

B Stepwise multivariate analysis included age, log10 EGFR, LI, tumor histology, and tumor resection (complete resection of the tumor); age and tumor histology were not retained in the final model.

with assessable LI demonstrates that LI emerges as the stronger prognostic factor (higher Wald statistics; Table 3). However, it must be noted that the prognostic value of EGFR was not significant in a univariate approach performed on this subgroup of 40 patients (data not shown); also, EGFR values were significantly higher in this patient subgroup (geometric mean = 730 fmol/mg protein) as compared to the remaining 39 patients (geometric mean = 280 fmol/mg protein; P = 0.029). Overall, the Cox multivariate analysis leads to the conclusion that EGFR, LI, and tumor resection were independent significant prognostic factors in glial tumor outcome (Table 3). Such results would merit to be confirmed on a larger and homogeneous set of patients. Importantly, the prognostic significance of EGFR and LI were demonstrated when EGFR and LI were analyzed as continuous variables (the higher the variable, the shorter the patient survival), thus avoiding the problematic use of cutoff points. Noteworthy, classic prognostic parameters like age and tumor histology were not selected as significant parameters in a multivariate approach. In line with data from Nishizaki et al. (34), we found that LI was significantly linked to tumor histology, with the highest LI values observed in glioblastoma and the lowest observed in benign glial tumors. Because the multivariate...
Fig. 3  Plots of cumulative survival according to EGFR and LI thresholds. A, survival of patients with EGFR values of >250 fmol/mg protein (---; 47 patients, 35 events, 12 censored observations, median survival = 12.10 months) and of patients with EGFR values of <250 fmol/mg protein (- - - -; 32 patients, 15 events, 17 censored observations, median survival = 29.0 months). P = 0.0073 (log-rank test). B, survival of patients with LIs of >4.6% (---; 24 patients, 20 events, 4 censored observations, median survival = 13.58 months) and of patients with LIs of <4.6% (- - - -; 16 patients, 8 events, 8 censored observations, median survival = 120.36 months). P = 0.0027 (log-rank test).
analysis shows that LI is a stronger predictor of patient survival than tumor histology, it is quite likely that the well-known prognostic value of histology is mainly due to the proliferative potential of the malignant cell types. This prognostic significance of LI agrees with the results by Hoshino et al. (36) performed on 174 patients with brain tumors. In a subset Cox analysis, these authors showed that LI was the best predictor of survival in low-grade astrocytoma and anaplastic astrocytoma.

Importantly, this multivariate analysis shows that the clinical prognostic factors of glial tumors, namely, age and tumor histology, disappear, to the benefit of intrinsic characteristics of the tumor, namely, EGFR expression and LI. Besides their strong prognostic values, it can be noted that EGFR and LI measurements are objective determinations, contrary to histology grading, which can be dependent on the anatomopathological evaluation. At first sight, the complementarity between EGFR and LI in glioblastoma outcome and demonstrates their independence, suggesting that coupled EGFR and LI determination would be a useful tool for better evaluation of glial tumor outcome.

In conclusion, this study confirms the prognostic role of EGFR and LI in glial tumor outcome and demonstrates their independence, suggesting that coupled EGFR and LI determination would be a useful tool for better evaluation of glioblastoma multiforme.

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Epidermal growth factor receptor and labeling index are independent prognostic factors in glial tumor outcome.

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