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Malignant Progression of Diffuse Low-grade Gliomas: A Systematic Review and Meta-analysis on Incidence and Related Factors

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Abstract

Malignant progression of diffuse low-grade glioma (LGG) is a critical event affecting patient survival; however, the incidence and related factors have been inconsistent in literature. According to the PRISMA guidelines, we systematically reviewed articles from 2009, meta-analyzed the incidence of malignant progression, and clarified factors related to the transformation. Forty-one articles were included in this study (n = 7,122; n, number of patients). We identified two definitions of malignant progression: histologically proven (Htrans) and clinically defined (Ctrans). The malignant progression rate curves of Htrans and Ctrans were almost in parallel when constructed from the results of meta-regression by the mean follow-up time. The true transformation rate was supposed to lie between the two curves, approximately 40% at the 10-year mean follow-up. Risk of malignant progression was evaluated using hazard ratio (HR). Pooled HRs were significantly higher in tumors with a larger pre- and postoperative tumor volume, lower degree of resection, and notable preoperative contrast enhancement on magnetic resonance imaging than in others. Oligodendroglial histology and IDH mutation (IDHm) with 1p/19q codeletion (Codel) also significantly reduced the HRs. Using Kaplan-Meier curves from eight studies with molecular data, we extracted data and calculated the 10-year malignant progression-free survival (10yMPFS). The 10yMPFS in patients with IDHm without Codel was 30.4% (95% confidence interval [95% CI]: 22.2-39.0) in Htrans and 38.3% (95% CI: 32.3-44.3) in Ctrans, and that with IDHm with Codel was 71.7% (95% CI: 61.7-79.5) in Htrans and 62.5% (95% CI: 55.9-68.5) in Ctrans. The effect of adjuvant radiotherapy or chemotherapy could not be determined.

Keywords: low-grade glioma, diffuse astrocytoma, oligodendroglioma, malignant transformation

Introduction

The incidence rate of diffuse low-grade gliomas (LGGs) is estimated to be approximately 0.8 cases per 100,000 population.[1] LGGs histologically consist of diffuse astrocytomas and oligodendrogliomas. However, the histomorphological diagnosis of astrocytomas, oligodendrogliomas, and mixed gliomas has not been always distinct. The recent advent of molecular diagnoses, including IDH mutation (IDHm) and 1p/19q codeletion (Codel), has resulted in the development of a clearer classification system of LGGs. The 2016 WHO classification employed molecular markers in the diagnosis of LGG.[1] Although IDH wild-type (IDHw) LGG may be a heterogeneous group, the new classification (2021) defines IDHw diffuse glioma with specific molecular features as glioblastoma.[2]

LGGs are slowly growing tumors and often lack symptoms, except for seizures. The frequency of incidental cases is increasing with the spread of imaging studies, despite the low prevalence of incidental LGGs (0.064% of imaging studies).[3] Although the "wait and see" approach was often selected historically, long-term follow-up has revealed that the majority of these lesions cause malignant transformation (malignant progression from low-grade malignancy), which results in death.[4,5] Some of the researchers advocated an early diagnosis and a preventive surgical

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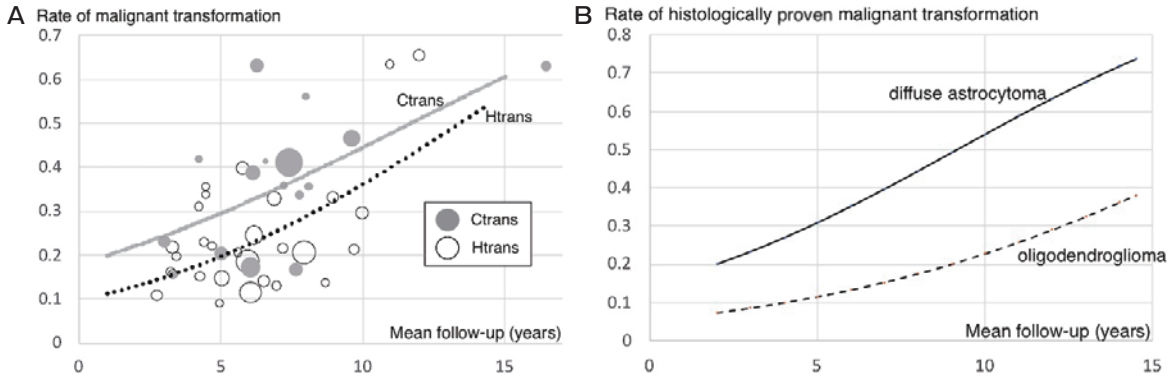

Fig. 1 A. Almost parallel regression lines of malignant transformation in Ctrans and Htrans. Size of circle = number of cases. B. The rate of malignant transformation by Htrans in diffuse astrocytomas is higher than in oligodendrogliomas. Ctrans, clinically defined malignant transformation; Htrans, histologically proved malignant transformation. (Curves are made from back transformation of logit transformed values in Table 1.)

treatment to improve the outcomes of LGGs, suggesting the relevance of a tailored screening policy.[6] Early maximal safe resection while preserving the eloquent brain areas is currently considered to be a better treatment option.[7]

Patients with malignant transformed glioma exhibited a much worse overall survival (OS) than those who still had low-grade histology at recurrence.[8] The median OS in patients with malignant transformed glioma was reported to be approximately 2 years after transformation.[9-11] Malignant transformation of diffuse LGG is a critical event influencing the patient survival, but the incidence and time-course are inconsistently reported in the literature with the 10-year malignant progression-free survival (MPFS) rates ranging from 22.4%[12] to 60.6%[5]. Although the cause of this variation is unclear, previous studies often lacked molecular data and demonstrated heterogeneity in a rate of malignant transformation (MaligR) due to differences among studies in the criteria for malignant transformation, histological diagnosis, and treatment strategies.

We reviewed articles systematically and conducted their meta-analysis.

Materials and Methods

Literature search and data extraction

A literature search was conducted independently by two of the authors. The PRISMA search flow diagram is outlined in Supplementary Figure 1. We searched for relevant English articles using the keywords "low-grade glioma," "astrocytoma," or "oligodendroglioma" and "malignant or anaplastic transformation" in PubMed, Scoups, and Google Scholar and published in 2009 or later, when the first article on IDH mutation in gliomas was published. Studies including ≥50 LGG cases were selected, as were those with ≥ 40 diffuse astrocytomas or oligodendrogliomas. Pediatric cases, spinal tumors, and studies limited to a specific location were excluded. The exact search strategy is described in Supplementary Figure 1. The search was performed on April 24, 2021. Two articles were added after a manual search on August 5, 2021.

From each study, we collected data on the age, sex, mean follow-up time (MFTime), the number of subjects, and malignant transformations. When only the median follow-up data were available, the mean was calculated using the following equation obtained from eight studies that described both the mean and median values (R^2 = 0.99): mean = 1.14 × median. The astrocytoma rate (AstroR) and pure oligodendroglioma rate (OligR) were calculated as total numbers of diffuse astrocytomas or oligodendrogliomas, respectively, divided by the total number of cases; mixed gliomas were not included. Treatment-related factors, including the extent of removal, and number of adjuvant radiotherapy and chemotherapy sessions were also recorded. The rate of gross total removal (GTRate) was calculated, defined as resection of ≥90% of the volume. Data on molecular tests, results of IDHm, and Codel were extracted whenever available.

We found two definitions of malignant transformation described in the literature. One was histologically proven (Htrans), which exhibited anaplastic transformation compatible with higher-grade glioma, and the other was clinically defined (Ctrans). Ctrans included cases that showed new progressive contrast enhancement on magnetic resonance imaging (MRI) in addition to histologically confirmed cases.

We used hazard ratio (HR) to determine the effect of malignant transformation in the meta-analysis. The HRs for age, sex, Karnofsky performance status score (KPS), pre- and postoperative volume, extent of resection, adjuvant radiotherapy and chemotherapy, and molecular markers were prospectively collected. The HRs for contrast enhancement on MRI and eloquent location were added later.

Hazard ratios in univariate and multivariate analyses were separately extracted and meta-analyzed. In the retrieved articles, the age, KPS, and size of tumor were ana-

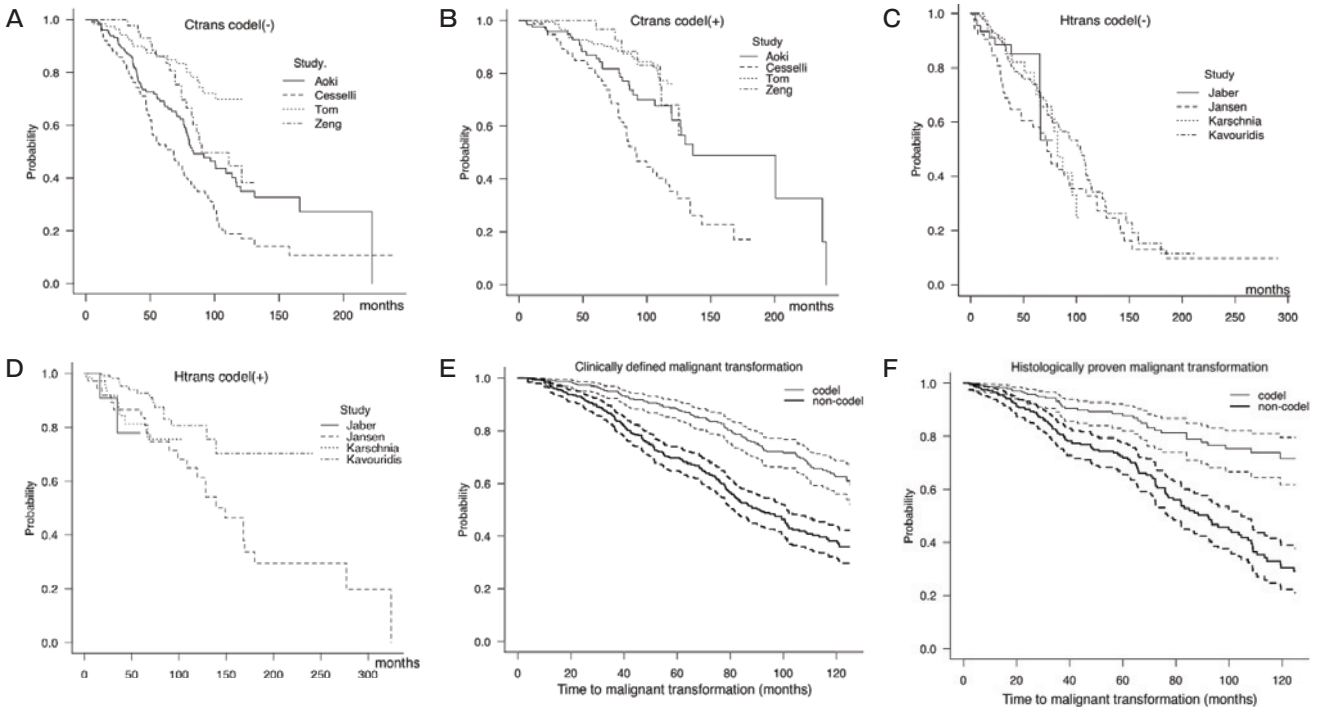

Fig. 2. Kaplan–Meier curves from extracted data. A. IDHm without Codel tumors in four studies with Ctrans. B. IDHm with Codel tumors in four studies with Ctrans. C. IDHm without Codel tumors in four studies with Htrans. D. IDHm with Codel tumors in four studies with Htrans. Synthesized Kaplan–Meier curves in Ctrans (E) and Htrans (F). Thick line, non-Codel tumors; thin line, Codel tumors; dotted line, 95% confidence interval.
IDHm, IDH mutant; Codel, 1p/19q codeletion; Ctrans, clinically defined malignant transformation; Htrans, histologically proved malignant transformation.

lyzed in different manners: categorized or continuous values (the approach most often used was adopted). When the HRs were not available, we calculated the missing values using log-rank tests or Kaplan-Meier curves according to the method of Tienarry et al.[13] We used WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) to extract data from Kaplan-Meier curves. In one study, we compared the data extracted from the Kaplan-Meier curve with those provided in the supplementary table 1.[14] Curves obtained from the extracted data and actual data were very similar (Supplementary Figure 2). The calculated 10yMPFS in the extracted data was 62.1% (95% confidence interval [95% CI]: 48.3-73.3), whereas that in the actual data was 62.2% (95% CI: 48.4-73.4) in the actual data.

This review did not involve direct studies on humans, so informed consent was not required.

Risk of bias

We used the JBI critical appraisal checklist for case series (https://jbi.global/critical-appraisal-tools). Publication bias was evaluated using a funnel plot when ≥10 studies were incorporated. A linear regression analysis was used in the test for funnel plot asymmetry.

Statistical analyses

We used the packages of EZR, Meta, and Metafor in the R software program (v4.03) (https://www.r-project.org/) to perform the statistical analyses. A single-arm meta-analysis was employed to calculate percentages using a generalized linear mixed model. The results of HR for malignant transformation in each factor were combined using the inverse-variance method with the random-effect method (DerSimonian and Laird method).

The reviewed studies were tested for heterogeneity (I^2 statistic). Meta-regression analyses were performed to identify factors related to heterogeneity, typically combined with the mean follow-up time, as this duration was a strong factor influencing transformation. Analyses were performed using the rma.glmm function in the Meta software package. Two-sided P values < 0.05 were considered to indicate statistical significance.

Results

We initially retrieved 144 articles after removing duplicates (Supplementary Figure 1). After a full-text assessment, we excluded articles that did not describe the total population size or number with malignant transformation or the follow-up period. Data from the same institute were

Table 1 Summary of the data

	Htrans	Ctrans
Total population	4261 (28 studies) *	3714 (18 studies) *
Males/females	2384/1806 (27 studies)	1971/1516 (17 studies)
Median age	Mean**: 41.9 (9 studies)	Mean**: 42.7 (4 studies)
	Median***: 38.5 (16 studies)	Median***: 38.0 (13 studies)
Malignant transformation	975	1320
Median mean follow-up (years)	5.83 [4.38–7.38]	6.45 [5.25–7.74]
Median rate of total removal	0.412 [0.309–0.49] (25 studies)	0.361 [0.135–0.457] (17 studies)
Median rate of adjuvant radiotherapy	0.314 [0.237–0.510] (25 studies)	0.312 [0.278–0.818] (17 studies)
Median rate of adjuvant chemotherapy	0.167 [0.08–0.333] (22 studies)	0.216 [0.042–0.298] (16 studies)
Median rate of astrocytoma	0.493 [0.424–0.647] (28 studies)	0.661 [0.532–0.744] (16 studies)
Median rate of oligodendroglioma	0.353 [0.241–0.456] (28 studies)	0.320 [0.184–0.421] (16 studies)
Study number	28*	18*

Htrans, histologically proven malignant transformation; Ctrans, clinically defined malignant transformation: *, including five studies (912 patients) with information for both Htrans and Ctrans; **, median of the mean age values; ***, median of the median age values.

Table 2 Results of a meta-regression analysis of malignant transformation

Histologically proved transformation (N = 28)				
	Meta-regression			
Variables	Estimate	95% CI	Intercept	95% CI
m follow-up	0.167, P = 0.0003	0.085 to 0.251	−2.24	−2.80 to −1.68
	Multi-variate meta-regression			
Oligo-rate	−0.991, P = 0.018	−1.814 to −0.168	−1.857	−2.47 to −1.25
m follow-up	0.163, P < 0.001	0.087 to 0.240		
Astro-rate	1.341, P = 0.0014	0.519 to 2.163	−3.106	−3.84 to −2.38
m follow-up	0.193, P < 0.0001	0.115 to 0.270		
Clinically defined transformation (N = 18)				
	Meta-regression			
Variables	Estimate	95% CI	Intercept	95% CI
m follow-up	0.130, P = 0.006	0.0368 to 0.221	−1.52	−2.21 to −0.84

Estimate and intercept = logit transformed value; m follow-up, mean follow-up years; oligo-rate, percentage of pure oligodendrogliomas; Astro-rate, percentage of diffuse astrocytoma.

excluded. However, we sometimes included studies from the same institute with a small amount of overlapping data or with data from different analyses. One extra study in 2008 was included because it was found to have more cases with necessary data than the searched article from the same institute. We ultimately selected 23 articles with data on Htrans,[4,15-36] 13 with data on Ctrans,[4,5,9,10,12,14,36-42], and 5 with both.[11,43-46] One study included information from two institutes,[40] so we analyzed the data, separately (summarized data are in Table 1, and all data are in Supplementary Table 1). Additional five studies were adopted only for analyses of the HR in forest plots.[47-51]

Risk of bias

Studies were either retrospective case series or observational studies. The JBI tool comprises 10 items that evaluate the risk of bias (Supplementary Table 2). The studies were classified as having a low risk of bias when ≥8 of the 10 questions were answered "yes," a moderate risk of bias when 6-7 of the 10 questions were answered "yes," and a

Table 3 Pooled hazard ratios in factors related to malignant transformation

Factors	Univariate analysis			Multivariate analysis		
	Pooled HR	95% CI (P value)	References	Pooled HR	95% CI (P value)	References
Age (Cont)	1.0006	0.997–1.015 (0.217)	5, 12, 23, 27, 29, 30, 38, 44, 46, 51	1.020*	1.00–1.04 (0.011)	27, 37
Gender (Female = 1)	1.156	0.998–1.339 (0.054)	5, 11, 12, 20, 27, 30, 38, 44, 46, 47	2.076*	1.355–3.178 (0.0008)	11, 45, 47
KPS (Cont)	0.975	0.937–1.015 (0.223)	12, 30, 38, 46	0.954*	0.921–0.988 (0.008)	12
CE on MRI (no = 1)	1.63*	1.34–1.98 (<0.0001)	20, 23, 27, 37, 47, 49	1.73*	1.23–2.45 (0.002)	27, 45, 47, 49
Eloquent location	1.89*	1.17–3.06 (0.01)	20, 27, 30, 46	1.51	0.83–2.74 (0.17)	27
Preoperative vol. (Cont)	1.005*	1.001–1.010 (0.011)	27, 30, 38, 44, 50	3.34* log	1.91–5.85 (0.0053)	12, 46
Postoperative vol. (Cont)	1.009*	1.002–1.015 (0.012)	27, 30, 38	1.013*	1.004–1.021 (0.0038)	12, 27
Degree of resection (non-total = 1)	0.36*	0.20–0.651 (0.0007)	5, 11, 20, 37, 44, 47, 51	0.272*	0.118–0.626 (0.004)	4, 20, 37, 45, 47
Radiotherapy (no = 1)	1.832*	1.183–2.837 (0.007)	12, 27, 30, 37, 38, 46, 48	1.391	0.874–2.214 (0.16)	27, 37
Chemotherapy (no =1)	1.809*	1.24–2.64 (0.002)	12, 27, 38, 46, 48	NA		
IDH mutation (IDH mut = 1)	1.586*	1.057–2.379 (0.026)	5, 11, 12, 23, 29, 38, 47, 51	3.352*	2.133–5.267 (<0.0001)	11, 12, 38, 47
Codel (Codel = 1)	2.079*	1.378–3.139 (0.0005)	11, 12, 27, 38, 47	2.782*	1.731–4.47 (<0.0001)	4, 11, 12, 49

CE, contrast enhancement; Cont, continuous value; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status scale; log, log-transformed volume; NA, not available; Codel, 1p/19q codeletion; *, statistically significant.

high risk of bias when ≤5 questions were answered "yes." Most of the studies had a low risk of bias. One study with a moderate risk that lacked some data of the total population was used only for percentage calculation and not for meta-regression analyses.

Rate of malignant transformation

We separately calculated the MaligR in Htrans and Ctrans. The pooled Ctrans rate was 34.6% (95% CI: 27.9-42.0, I^2 = 94.4%), whereas the pooled Htrans rate was 23.2% (95% CI: 18.9-28.0, I^2 = 89.8%) (forest plots in Supplementary Figure 3). Although high heterogeneities (I^2) were observed, no publication bias was detected by funnel plots (Supplementary Figure 3).

Meta-regression analyses showed the significant contribution of MFTime to the heterogeneity of Ctrans (P = 0.008) and Htrans rates (P = 0.003) (Table 2). The regression lines in the Htras and Ctrans rates indicated an almost parallel increase against MFTime (Fig. 1A). The pooled MaligR in recurrent cases was 46.5% (95% CI: 38.5-54.8) and 66.3% (95% CI: 57.7-74.0) for Htrans and Ctrans, respectively.

Multivariate meta-regression was performed only for the Htrans rate, as there were too few studies and covariates for the Ctrans rate. OligR and AstroR in each study were significantly related to MaligR when the MFTime was incorporated (Table 1). The Htrans rate in diffuse astrocytomas was much higher than that in oligodendrogliomas (Fig. 1B). Other factors, including GTRate (P = 0.18), the radiotherapy rate (P = 0.26), and the chemotherapy rate (P = 0.79), did not contribute to the heterogeneity in Htrans rates.

Factors related to malignant transformation

Pooled HRs in factors of malignant transformation were calculated without distinction of Htrans and Ctrans because they both increased in parallel with MFTime (Fig. 1 A).

We summarized the results in Table 3 (forest plots in Supplementary Figure 4). Crucial factors for malignant transformation were molecular markers (both IDHm and Codel), pre- and postoperative volume, and the extent of removal. These factors reached significance in pooled HRs in both univariate and multivariate analyses. Contrast enhancement on MRI also significantly affected malignant transformation. The age, gender, and KPS were possible factors, indicating a tendency in the pooled HRs of univariate analyses but only indicating significance in a few multivariate analyses. Tumors treated with adjuvant radiotherapy and chemotherapy exhibited an increased MaligR in the pooled results of univariate analyses but did not in that of multivariate analyses.

We investigated collinearity among GTRate, OligoR, AstroR, chemotherapy rate, and radiotherapy rate in each study. No significant correlations were found among them, except for between OligoR and AstroR (P < 0.0005).

MaligR in molecularly defined LGG

Because the molecular subtypes are crucial in the transformation of LGG, we determined the rates in tumors of IDHm with and without Codel. The extracted data from Kaplan-Meier curves from four studies with Htrans[4,23,26,27]

and four studies with Ctrans[11,12,14,52] are presented in Fig. 2 A-D. The synthesized curves from the extracted Kaplan-Meier curves indicated that the 10-year MPFS for IDHm without Codel was 30.4% (n = 307; 95% CI: 22.2-39.0) with Htrans and 38.3% (n = 458; 95% CI: 32.3-44.3) with Ctrans, and that for IDHm with Codel was 71.7% (n = 272; 95% CI: 61.7-79.5) with Htrans and 62.5% (n = 400; 95% CI: 55.9-68.5) with Ctrans (Figs. 2E and 2F).

Two studies included only patients without adjuvant therapy after surgery: GTRate of 41.1% in the study by Cesselli et al.[12] and 52.7% in that by Jansen et al.[3] In other studies, patients underwent adjuvant radiotherapy or chemotherapy in >40% of cases, with GTRate ranging from 10% to 70%. Patients with Ctrans in Cesselli et al.[12] had a significantly shorter MPFS than cases in other studies regarding both IDHm non-Codel (Fig. 2A, post-hoc test, P = 0.017) and IDHm Codel cases (Fig. 2B, post-hoc test, P = 0.026).

We performed an analysis to determine the difference in the 10yMPFS by meta-regression. The study by Jaber et al. was excluded because of the short follow-up period. "No adjuvant therapy" was the only factor associated with a poor outcome in patients with Codel tumors (meta-regression, P = 0.003), even combined with GTRate and diagnosis (Htrans or Ctrans) (multivariate meta-regression, P < 0.0005). There were no significant factors associated with tumors with IDHm without Codel.

Discussion

This is the first meta-analysis of malignant transformation in LGGs. We demonstrated that MaligR in both Htrans and Ctrans were increased almost linearly for >10 years after diagnosis. The rates were significantly affected by the pre- and postoperative tumor volumes, extent of resection, and both histological and molecular diagnoses. Diffuse astrocytomas and tumors with IDHm without Codel exhibited much higher MaligR than oligodendrogliomas or tumors with IDHm with Codel.

The rate of malignant transformation

Previous studies reported diverse MaligR and related factors during various follow-up periods. We first meta-analyzed these data. The major problem in the analyses was that there was no universal definition of malignant transformation. The majority of studies defined histologically proven progression as malignant changes, but recent studies often added clinical features, especially contrast enhancement on MRI, for the diagnosis. The former definition missed cases of malignant change that were not surgically treated at recurrence. However, the definition including new contrast enhancement on MRI sometimes overdiagnosed malignant transformation.[8] Our study demonstrated that the rates obtained through the two methods increased almost in parallel, so we suspect that the true value lies between them, being approximately 40% at MFTime of 10 years (Fig. 1A).

The MaligR value was higher in astrocytomas than in oligodendrogliomas (Fig. 1B). However, the histological diagnosis system has been changing over the past 5 years, and molecular diagnoses have become more important. We determined 10-year MPFS in IDHm non-Codel tumor to be 30.4% with Htrans and 38.3% with Ctrans, and that in IDHm Codel to be 71.7% with Htrans and 62.5% with Ctrans. We did not examine MaligR in IDHw LGG as this tumor type might include heterogeneous specimens.

Factors relating malignant transformation

Patient age is an important prognostic factor for OS in LGG.[9,12,27] This may be influenced by various confounding factors; for example, elderly patients may undergo less aggressive therapy or have serious comorbidities. Recent molecular studies have reported that IDHw astrocytomas, which are biologically more aggressive, arise more in older patients than IDHm astrocytomas.[12] Our study revealed a nonsignificant relationship between an older age and the incidence of MaligR in univariate analyses, but pooled results of two multivariate analyses indicated a significant relationship.[27,37] A similar result was observed in sex difference. In a multivariate analysis, only factors that showed significance or borderline significance in univariate analyses were included in the analyses. As a result, the pooled HR of multivariate analyses might have been skewed, as nonsignificant factors were not included. Both older age and male sex were possible factors associated with malignant transformation, but accumulation of further data is necessary.

Our study demonstrated that preoperative contrast enhancement on MRI was a strong predictor of early malignant progression in both univariate and multivariate analyses. Snyder et al. found that contrast enhancement on preoperative imaging was identified in 16% of LGGs.[31] They noted that the preoperative presence of a contrast-enhancing tumor, which indicated no high-grade tumors by pathological examination, was predictive of MPFS (p < 0.0001). Narag et al.[8] reported that the postoperative appearance of new enhancement was associated with an inferior median OS, even in patients without malignant degeneration. Thus, even though new enhancement does not always indicate malignant changes, it may indicate that tumors are likely to be aggressive.

The pre- and postoperative volume and extent of resection were found to be significantly related to MaligR. As these three factors are related to one another,[31,38] it was difficult to determine which was the most crucial. However, these relationships would be modified if the molecular diagnoses were incorporated into the analyses. Patel et al.[44] reported that in an age-adjusted Cox regression model stratified by IDH mutation status, a greater extent of resection was only associated with prolonged MPFS in IDHw

patients (P < 0.001) but not in IDHm patients (P = 0.83). The preoperative tumor volume had a statistically significant prognostic value for MPFS in the IDHm cohort (P = 0.01) but not in the IDHw cohort (P = 0.23). Tom et al.[11] reported a significant relationship between MPFS and the degree of resection (P = 0.002) and tumor size (P < 0.001) in a univariate analysis. However, only the tumor size was significant in a multivariate analysis, combined with molecular classification and other factors. Thus, the initial tumor size appears to be a significant factor for MPFS, but further studies will be necessary to determine the role of resection of molecularly defined tumors.

The role of adjuvant radiotherapy or chemotherapy in malignant transformation was not distinct in the present study. Although pooled results from univariate analyses indicated a significant negative impact of both treatments, such findings were not demonstrated in multivariate analyses. This was likely due to selection bias, as patients with high-risk tumors were selected for adjuvant radiochemotherapy. However, the present study suggested that no adjuvant therapy was a factor associated with the transformation in Codel tumors (Fig. 2). Although the result was statistically significant, we had not initially planned to perform such an analysis. Because of the limited number of studies included, further investigation will be warranted.

Recent studies have warned that temozolomide treatment of LGG induces hypermutation, which may drive malignant progression.[53,54] Tom et al.[11] reported adjuvant temozolomide monotherapy as the only modifiable risk factor for malignant transformation among adult LGG cases. Aihara et al.[55] indicated that malignancies are rarely promoted by additionally acquired mutations or genomic aberrations at recurrence of oligodendrogliomas. Such molecular characteristics may account for the clinically benign nature of oligodendroglioma compared with other diffuse gliomas. Aoki et al.[14] proposed a mathematical model for malignant transformation of LGG. This model revealed that prompt adjuvant chemoradiotherapy prolonged MPFS in small IDHm LGGs, whereas the best treatment differed according to genetic alterations for large IDHm LGGs. These previous findings suggest that the natural history and complex treatment effects, either negatively or positively, influence the malignant transformation of LGG.

Limitations

Several limitations associated with the present study warrant mention. First, the accumulated data were obtained from retrospective studies with a moderate quality, which might have caused some bias. Second, we attempted to establish two definitions of malignant transformation. This might have been inappropriate in some cases, as the histological diagnosis rate for recurrences might differ among institutes, and some institutes employed various MRI sequences or positron emission tomography for the clinical diagnosis of malignant transformation. Furthermore, histological and radiological diagnosis of malignant transformation may be difficult after radiochemotherapy, whereas the diagnostic criteria may shift to molecular basis in future. However, the heterogeneity of the MaligR may be largely explained by MFTime and histological diagnosis. The rate of Htrans and Ctrans increased almost in parallel against MFTime. Third, the method of data extraction may be a limitation. Because of several data being missing, we calculated HRs using the method established by Tienarry et al.[13] or obtained the values from Kaplan-Meier curves. The calculated data might have had a small range of error.

Conclusion

We evaluated MaligR in diffuse LGGs by a systematic review and meta-analysis. We established two definitions of malignant transformation: Htrans and Ctrans. The MaligR-MFTime curves of Htrans and C trans were almost parallel. True MaligR was suspected to lie between the curves, at approximately 40% at the 10-year follow-up. This rate was affected by the pre- and postoperative tumor volumes and extent of resection. An astrocytic histology and a molecular diagnosis of non-Codel were also strong factors affecting the transformation. The effect of adjuvant therapies could not be clarified.

Supplementary Material

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest in association with the present study.

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