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Seizures at presentation are correlated with better survival outcomes in adult diffuse glioma: A systematic review and meta-analysis

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ABSTRACT

Purpose: Seizures are the most common presenting sign of patients with diffuse glioma. In the current study, we performed a meta-analysis to determine the correlation of seizures at presentation to survival outcomes in adult diffuse glioma, and the possible mechanisms were also discussed.
Methods: A comprehensive literature search was performed in PUBMED, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials. The pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) were used to estimate effects. Heterogeneity among studies and publication bias were also evaluated.
Results: 11 studies with 2088 patients were finally included for the current meta-analysis. Seizure-free preoperatively was significantly associated with a poor overall survival in patients with diffuse glioma, the pooled HR was 1.73 (95% CI 1.43–2.08, Z = 5.71, $p < 0.001$). Subgroup analysis was also performed by tumor grade, the same association was identified in both low-grade glioma (pooled HR 2.49, 95% CI 1.47–4.20, Z = 3.40, $p < 0.001$) and glioblastoma (pooled HR 1.46, 95% CI 1.27–1.68, Z = 5.24, $p < 0.001$). A significant correlation of seizure-free with a poor progression-free survival was also identified (pooled HR 1.42, 95% CI 1.06–1.92, Z = 2.33, $p = 0.02$), although only 3 studies comprising 368 patients were included.
Conclusion: The current study determined that seizures at presentation were an independent predictor of better survival outcomes in adult diffuse glioma. It is the first study which provides a comprehensive standardized assessment of the association between seizures at presentation with long-term survival outcomes in patients with diffuse glioma.

1. Introduction

Epileptic seizures are the most common clinical manifestation of primary brain tumors, and the incidence of tumor-related seizures varies from 30 to 100% according to tumor type [1]. In most cases, seizures may occur as an initial symptom and lead to the diagnosis of the tumor [1]. Among those tumors that can lead to epileptic seizures, glioma, accounting for over 80% of primary malignant brain tumors, is one of the most common types (the other one is glioneuronal tumor) [2,3]. Glioma can be divided into 4 grades (from grade I to grade IV) based on pathological evaluation according to the World Health Organization (WHO) classification of tumors of the central nervous system [4,5]. As WHO grade I gliomas (such as pilocytic astrocytomas) are stable and can be cured by surgery, few attentions have been paid to them. By contrast, the association between seizures and diffuse gliomas deserves more concerns.

According the 2016 WHO classification, the diffuse glioma refers to the WHO grade II and grade III astrocytic tumors, oligodendrogliomas (also includes grade II and grade III oligoastrocytomas diagnosed according to the 2007 WHO classification) and the grade IV glioblastomas (GBM) [5]. Low-grade gliomas (LGG, WHO grade II) are considered to be associated with a higher

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seizure incidence, seizures can be observed in 65–90% of LGG patients either as the initial symptom or as a symptom occurs during tumor progression [6,7]. As for patients with high-grade glioma (HGG, WHO grade III and grade IV), this proportion is 30–62% [1,8]. Seizures carry both heavy financial and emotional burden on glioma patients, and significantly decrease their life quality: firstly, the effect of conventional treatment is not satisfied, despite combining antitumor therapies (such as surgical resection) with antiepileptic drugs, refractory epilepsy still exists in 20–30% of patients with glioma-related seizures [6,9,10]; secondly, epileptic seizures are arbitrary and unpredictable, a recent Mayo Clinic study shows that the unpredictable nature of seizures makes the patients loss their independent living ability, and results in great mental pressure to them [11]; thirdly, patients generally consider that seizures are closely related to the progression or recurrence of their tumors, which also adds to their anxiety [11].

Interestingly, according to our clinical experience, to glioma patients, although epileptic seizures mean a decreased life quality, they are often correlated with better survival outcomes. Several previous studies also reported the prognostic value of preoperative seizures in either LGG or HGG patients [12,13]. However, after a cursory review, we found that the studies investigating the association between seizure history and survival in glioma were much less than we anticipated, and the results were not so consistent. For instance, two recent studies showed that seizures at presentation were not an independent prognostic factor of survival in glioma patients [14,15]. This made us realized that it was necessary to perform a comprehensive review of the literature on this issue and give a definite conclusion on it. In the current study, we performed a meta-analysis to determine the correlation of seizures at presentation to survival outcomes in adult diffuse glioma, and the possible mechanisms were also discussed.

2. Methods

2.1. Search strategy and selection criteria

The current systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines [16]. We searched PUBMED, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies published from their inception to December 18, 2017. The search strategy was a combination of the following key words: “seizure” or “epilepsy” or “convuls*”, “glioma” or “astrocytoma” or “oligodendroglioma” or “oligoastrocytoma*” or “glioblastoma”, “survival” or “follow-up” or “prognos*” or “predict*” and “cohort” or “longitudinal” or “case-control” or “cross-sectional”. The search results were imported into Endnote X7 software (Thomson Reuters, New York, NY, USA) and duplicates were removed. Subsequently, titles and abstracts of remaining retrieved articles were further screened, studies would be excluded if they met any of the following criteria: 1) review articles, guidelines, or classifications; 2) case reports or small case series (cases <5); 3) meeting abstracts or abstract-only studies; 4) studies in children only; 5) studies only referred to other brain tumors (including WHO grade I glioma); 6) in vitro and animal experiment studies; 7) studies which investigated the prognosis of the seizures but not the survival of patients; 8) other irrelevant studies.

Next, potentially relevant full-text articles were obtained and re-screened. Studies which fulfilled the following inclusion criteria would be finally included in the current meta-analysis: 1) articles published in English; 2) reports of patients with preoperative glioma-related seizures; 3) data for progression-free survival (PFS) and/or overall survival (OS) were provided; 4) univariate and multivariate Cox Regression analysis were calculated and seizures at presentation was one of the initial enrolled factors; 5) multivariate-adjusted hazard ratio (HR) and corresponding 95% confidence interval (CI) were provided, or could be calculated. Reports from the same medical unit were examined carefully, if the results were reported by the same investigators and obtained on the same cohort, only the largest series would be included in the analysis.

2.2. Data extraction and management

The systematic literature search was conducted by a separate investigator, then two investigators screened the retrieved records and extracted data from all eligible studies independently. A standardized data collection form was used to record data from the eligible studies. Any possible conflicts would be resolved by group discussion with a third investigator.

2.3. Quality assessment

The 9-star Newcastle-Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) was applied to evaluate the methodologic quality of each eligible study. The overall quality of evidence was assessed by GRADE profiler software (version 3.6.1, McMaster University, Hamilton, Ontario, Canada) according to the grades of recommendation assessment, development and evaluation (GRADE) system [17,18]. The overall quality of literature was rated as high, moderate, low, or very low considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.4. Statistical analysis

Analyses were undertaken using Review Manager software (RevMan, version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and Stata software (version 14.0, Stata corporation, College station, Texas, USA). The HR and corresponding 95% CI were used as the primary measure to assess the correlation of preoperative seizures to survival in diffuse glioma. The significance was measured by the Z-test and p-value, a two-tailed p-value <0.05 was accepted as statistical significance criterion. Cochran's Q test, I^2 statistic and H statistic were performed to evaluate the between-study heterogeneity. In the presence of significant heterogeneity ($I^2 > 50\%$; p-value of Cochran's Q test <0.10 and $I^2 > 25\%$; $H > 1.5$ or $1.5 \geq H \geq 1.2$ and the corresponding 95% CI does not include 1), data would be pooled using a random-effects model, and Galbraith plot should be carried out, otherwise, a fixed-effect model would be used. Moreover, sensitivity analysis should also be performed if the heterogeneity was significant.

A funnel plot was generated to evaluate the publication bias. Furthermore, Egger's linear regression test and Begg's adjusted-rank correlation test were also performed to assess the publication bias, a two-tailed p-value <0.05 was considered statistically significant. If publication bias was suspected, the trim and fill method would be used to estimate the effects of the “missing” (unpublished) studies.

3. Results

3.1. Results of literature search

Fig. 1 shows the flowchart of our study. 493 publications from PUBMED, 279 from EMBASE, 168 from Web of Science and 94 from CENTRAL were identified through a comprehensive literature search. After the removal of 232 duplicate records, titles and