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Quantifying the prognostic significance in glioblastoma of seizure history at initial presentation: A systematic review and meta-analysis☆

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ABSTRACT

The role of prognostic factors in the management of glioblastoma (GBM) is very important given the stasis in improving its clinical outcomes. Patients who initially present with a positive seizure history at diagnosis have anecdotally experienced superior survival outcomes. The aim of this review was to perform a systematic review and meta-analysis to quantify the potential prognostic significance of positive seizure history in GBM patients. A search strategy was performed using the PRISMA guidelines for article identification, screening, eligibility and inclusion. Relevant articles were identified from six electronic databases from their inception to August 2017. These articles were screened against established criteria for inclusion into this study. Meta-analysis was conducted by pooling results with multivariate-adjusted hazard ratios (HRs). After screening, 6 relevant studies were included for analysis. There was a total cohort of 1836 GBM patients, of which 488 (27%) had a positive seizure history at initial presentation. There was a significant association found between positive seizure history in GBM patients and less mortality events, with an overall HR of 0.71 (95%CI = 0.63–0.81, $p < 0.00001$, $I^2 = 4\%$). Positive seizure history at initial presentation of GBM can be associated with improved prognosis. However, there are a number of variables that need to be considered further, including genetic profiling, lead time bias, and anti-epileptic drug (AED) therapy. This review represents the highest level of evidence to date, and its result will be validated by future, prospective study of larger cohorts.

1. Introduction

Glioblastoma (GBM) is a malignant glioma cancer with a dismal prognosis. While there has been limited success in improving survival since the establishment of the Stupp protocol (surgery followed by radiation and temozolomide (TMZ)) over a decade ago, modest gains have been achieved in identifying favourable clinical prognostic factors [1]. These include younger age, greater functional performance, greater resection margins and radiochemotherapy treatment after surgery [2–4].

It has been hypothesised for a number of years that the presence of a seizure history at GBM initial presentation conveys a more favourable prognosis [5]. Seizures at initial presentation of GBM are not uncommon, with approximately 25–30% of patients presenting with a positive history [6–8]. A number of epileptogenic mechanisms in GBM have been proposed, and centre around an imbalance between inhibitory and excitatory neural networks [9]. Contributing factors involve increased glutamate neurotransmission which induces greater excitability [10], increased Na-K-Cl (NKCC) and K-CL (KCC2) voltage-gated ion cotransporter expression which reduces GABAergic inhibition [11], local oedema which disrupts cationic balance of the neuronal membrane potential [12], and upregulation of proinflammatory cytokines which facilitates greater epileptogenic activity [13].

In case of lower grade glioma, it has been established that patients presenting with seizure history have more favourable oncological and survival outcomes [14]. Until recently, there has been a paucity of analysis for the prognostic potential of seizure history at initial GBM presentation in affecting survival, which may be attributed to the relatively rarer and malignant nature of this glioma type. The aim of this study is to provide a systematic review and meta-analysis of all published data evaluating the potential prognostic significance of positive seizure history at initial GBM presentation in terms of survival.

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2. Methods

2.1. Search strategy

The strategy was designed in the PICO format − Do glioblastoma patients (Population) that present with a history of at least one seizure at initial presentation (Indicator) compared to those without such a history (Comparator) differ in survival (Outcome)? The present review was conducted according to PRISMA guidelines and recommendations [15]. Electronic searches were performed using Ovid Embase, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to August 2017. The literature involving all comparative studies were searched by using the MeSH terms enquiry "seizure OR epilepsy" AND "glioblastoma OR GBM". The reference list of all retrieved articles were reviewed for further identification of potentially relevant studies. All identified articles were then systematically assessed against the inclusion and exclusion criteria.

2.2. Selection criteria

The inclusion criteria used to screen all identified articles were: 1) confirmed histological diagnosis of GBM, treated with conventional Stupp protocol based therapy; 2) confirmed seizure history at initial presentation of GBM diagnosis; 3) actuarial survival outcomes for cohort with seizure history and without; 4) patients over the age of 18 years only. Seizure history was defined as at least one described epileptic event before presentation. The exclusion criteria used were: 1) outcomes where GBM specific outcomes could not be discerned; 2) postoperative seizure activity; 3) other significant neurological comorbidities such as tuberous sclerosis and multiple sclerosis; 4) pregnancy; and 5) palliative treatment only. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, and when studies reported multiple time courses of the same treated cohort, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results.

2.3. Data extraction and critical appraisal

All data were extracted from article texts, tables and figures with any estimates made based on the presented data and figures. Two investigators (V.M.L. and T.R.J.) independently reviewed each included article with any discrepancy resolved by discussion to reach consensus. The primary outcome data was the hazard ratio (HR) relating positive seizure history to survival of GBM patients. Multivariate-adjusted HR was used in all studies when possible. All attempts were made to contact study authors for any clarification of data if needed. Because quality scoring is controversial in meta-analyses of observational studies, two reviewers independently appraised each article included in our analysis according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria [16].

2.4. Meta-analysis

The hazard ratio (HR) was used as the summary statistic for each outcome measure. Each outcome was presented as a forest plot; the weighted HR, the 95% Confidence Interval (CI) and the relative weightings were represented by the middle of the square, the horizontal line, and the relative size of the square respectively. In the present study, a random-effect (RE) model was tested to take into account the possible clinical diversity and methodological variation between studies. χ^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. I^2 can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom.

Cohort size bias was assessed with individual leave-one-out analyses. Publication bias was assessed through the generation of funnel plots for all outcomes and assessed for asymmetry. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively, and quantitatively, any outlying study was removed and effect on overall trend direction and significance was reassessed for any significant change. All P values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.3.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

3. Results

3.1. Literature search

The search strategy identified a total of 662 studies (Fig. 1). After removal of 133 duplicate studies, inclusion and exclusion criteria were applied to titles and abstracts of the 529 articles. This yielded 30 studies that underwent full-text analysis. Six studies [17–22] were included in this current review for quantitative analysis. All studies included were retrospective and observational in nature. Study design and cohort characteristics are summarized in Table 1.

3.2. Demographics

The included studies describe a total of 1836 GBM patients, with 488 (27%) reporting seizure activity at presentation. The cohort involved a greater proportion of male patients overall, as well in the subgroups with and without positive seizure history, ranging from 52 to 68% when reported. The reported average age range of patients was typically over 55 years, where those presenting with a positive seizure history younger than those with a negative seizure history (57–59 years versus 61–65 years, respectively). Where reported, prophylactic antiepileptic drug (AED) therapy was commonly prescribed in patients with positive seizure history (86–90%), and rarely in those with negative seizure history. The most common agent used was levetiracetam (Table 2).

3.3. Pre-treatment seizure activity effect on mortality

All six included studies reported similar trends in multivariate HRs of seizure history at GBM presentation in relation to mortality events (Table 2). The HRs ranged between 0.52-0.80, with four studies [17,19,21,23] detecting significant associations. Overall, the presence of positive seizure history in GBM patients at presentation was significantly associated with less mortality events than those with negative seizure history, where HR = 0.71, 95%CI = 0.63–0.81, $p < 0.00001$ with $I^2 = 4\%$ (Fig. 2).

3.4. Study bias assessment

The assessment of bias risk by the MOOSE criteria of each included study is presented in Table 3, with no obvious heterogeneous bias risk implicated. Individual leave-one-out analyses did not demonstrate evidence of cohort size bias (Supplementary 1). Generated funnel plot did not indicate evidence of publication bias (Supplementary 2).

4. Discussion

This study adhered strictly to PRISMA guidelines and found that