Neurosurgical Review (2019) 42:603–618
https://doi.org/10.1007/s10143-018-1014-5

REVIEW

Correlation between glioma location and preoperative seizures: a systematic review and meta-analysis

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Received: 24 February 2018 / Revised: 11 July 2018 / Accepted: 16 July 2018 / Published online: 3 August 2018

Abstract

Epilepsy is a common manifestation of glioma patients and negatively impacts on quality of life and neurocognitive function. The risk of preoperative seizures in patients with glioma is currently under discussion. We aimed to evaluate the relationship between tumor locations in the cerebrum and preoperative seizures in patients with glioma. PubMed, EMBASE, Web of Science, China Biology Medicine, and the Cochrane Library were systematically searched from inception to July 15, 2017, for original studies including reports of preoperative seizures in patients with gliomas in different brain regions. The pooled odds ratio (OR) and 95% confidence interval (CI) of the meta-analysis for preoperative seizure risk stratified by cerebrum regions were calculated. The quality of evidence was assessed per outcome, using the approach of the Grades of Recommendation, Assessment, Development and Evaluation. Overall, 4323 participants in 16 population-based studies were included in this meta-analysis. The meta-analysis indicated that gliomas in the frontal lobe (OR = 1.51, 95% CI = 1.09–2.09, $P = 0.013$) were associated with a higher risk for preoperative seizure compared to occipital lobe involved (OR = 0.53, 95% CI = 0.32–0.88, $P = 0.014$). Regarding the other three lobe involved gliomas, no difference was found between the incidence of preoperative seizures and tumor location. Current limited data suggest that frontal gliomas were associated with a higher risk of preoperative seizures, while gliomas in the occipital lobe were associated with a lower seizure risk. Further RCT studies recruiting larger sample sizes are required to validate these results and guide clinical practice.

Keywords Gliomas · Glioma-associated seizure · Tumor location · Meta-analysis

Introduction

Epileptic seizures are common clinical manifestations in patients with primary brain neoplasms [1–3]. Gliomas are thought to originate from neuroepithelial cells, account for 35.3–60.9% of brain tumors, and comprise the most frequent type of intracranial tumor [4]. Preoperative seizures, which occur in 50–90% of patients with low-grade glioma and 20–50% of patients with glioblastoma [5, 6], are important symptoms associated with gliomas, and significantly impact patients' quality of life [6]. At least 10% of patients with glioma will develop status epilepticus, which is a life-threatening condition wherein a seizure lasts longer than 5 min, or when multiple seizures occur without regaining consciousness [7]. According to relevant studies [8], factors such as tumor location, histopathological subtype, and genetic mutations have been linked to the risk of preoperative GAS. Ruda et al. [5] have reported that about 47.4% of patients with grade II tumors, 28.6% of those with grade III tumors, and 19.8% of patients with grade IV tumors according to the World Health Organization grading system might have seizures. In addition, Pei Yang et al. [9] found that EGFR amplification was an independent predictor for preoperative seizures in patients with anaplastic gliomas, which has not been previously reported.

Currently, increasing numbers of studies suggest that tumor location plays a crucial role in the occurrence of preoperative GAS. Preoperative seizure as a first symptom might prompt

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earlier clinical intervention [10]. This would in turn might enable the prolongation of survival in patients with gliomas and lead to a longer period without tumor progression. In addition, because patients with preoperative seizures have a higher risk of postoperative seizures [1], clinicians should carefully monitor patients with gliomas in different locations. Significant controversy still exists regarding the incidence of preoperative seizures in different brain regions. Some scholars [11–13] believe that gliomas involving the temporal lobe are more likely to lead to preoperative seizures, while Lee et al. [4] have proposed the idea that gliomas within the insular cortex are more likely to occur before operative seizures. In a univariate analysis [12], gliomas in the frontal lobe were shown to be associated with a higher risk of seizures, while those in the occipital lobe led to a lower risk.

Nevertheless, the incidence of preoperative GAS has not yet been systematically evaluated, and many studies have been limited by a lack of strict research methods, incomplete database indexing, and small sample size. Therefore, in order to systematically assess the above hypotheses, we carried out a meta-analysis to further explore the relationship between the occurrence of gliomas in different cerebrum regions and the risk of preoperative GAS.

Materials and methods

Search strategy

PubMed, EMBASE, Web of Science, China Biology Medicine (CBM), and the Cochrane Library were systematically searched from inception date to July 15, 2017, to identify studies which precisely described the relationship between tumor location and the incidence of preoperative seizures in glioma patients. There was no language restriction on the search. The following search terms were used: "seizure or epilepsy" and "glioma or astrocytoma or oligodendroglioma or oligoastrocytoma." All searches were carried out by the combination of medical subject heading (MeSH) terms and free words. Retrieval strategies were determined by carrying out multiple pre-retrieval. According to the references provided by the literature that had been retrieved, we supplemented our searches by manually reviewing the references of all relevant studies.

Study selection and criteria selection

Two authors (Jian Zhang and Shaopeng Peng) who were trained professionally independently screened the abstracts and titles of the searched articles, and then excluded the literatures that were not relevant to our topic. The same authors (Jian Zhang and Shaopeng Peng) independently assessed the remaining full-text articles in details on the basis of the eligibility criteria mentioned below. Any disagreements were resolved by discussion with the third author (Liang Yao). The following inclusion and exclusion criteria for study selection were formulated.

Inclusion criteria: (1) prospective or retrospective studies; (2) studies comparing preoperative seizure incidence between patients with gliomas with and without lobe involvement; (3) studies focused on preoperative seizures caused by gliomas; (4) studies on gliomas in the frontal, temporal, parietal, occipital, or insular lobes; (5) studies reporting risk point estimates as odds ratios or those in which we were able to calculate the based on the data; and (6) studies in which the 95% CI and odds ratio could be extracted or those for which the 95% CI and odds ratio could be calculated based on the presented data. When studies were repeated, the highest quality study, as assessed using the Newcastle-Ottawa Scale (NOS ≥ 6) [14], was included.

Exclusion criteria: (1) studies that did not precisely describe the population, including precise definitions of glioma causing seizure preoperatively; (2) studies that were case series, reviews, or conference abstracts; (3) studies for which raw data could not be extracted; (4) studies that reported postoperative glioma-associated seizures; (5) studies including patients with severe hepatic or renal insufficiency, or acute or chronic infectious diseases; and (6) studies with poor quality (NOS < 6), or those with insufficient information.

Quality assessment and data extraction

Two authors (Jian Zhang and Yuan Fang) independently evaluated the methodological quality of the selected studies in a standardized data-collection form; grading was performed by the NOS, which is a validated scale for nonrandomized studies in meta-analyses. In our meta-analysis, studies that received $\geq$ 6 points were considered of high quality. The following information, if available, was extracted and summarized from each selected study, such as first author, publication year, country, study design, sample size, age median, sex ratio, glioma WHO grade (according to the old WHO classification, appendix Table 8), histopathological subtype, preoperative seizure rate, and incidence of preoperative seizure with or without lobar involvement. The processes were independently conducted by two trained authors (Jian Zhang and Yuan Fang), who formally evaluated and performed two preliminary experiments so as to guarantee the consistency and accuracy of the evaluation. Inconsistent conclusions between the two authors (Jian Zhang and Yuan Fang) were resolved through negotiation or consulting with the third author (Liang Yao).

Statistical analysis

The meta-analysis was performed by STATA 12.0 software (Stata Corp, College Station, TX, USA). A random effects

model was applied, which was recommended in medical decision-making contexts, especially when events were rare. In our meta-analysis, OR and 95% CI were considered as the effect size for all included studies. Forest plots were produced to visually assess the OR and corresponding 95% CI using random effects model. Heterogeneity was evaluated by using the I^2 value, and base on Higgins' I^2 statistic, $I^2 < 25$, $I^2 = 25$–50, and $I^2 > 50\%$ were of low, moderate, and high heterogeneity, respectively. Potential causes of high heterogeneity were explored and interpreted by carrying out sensitivity analysis, which could confirm the stability and reliability of the pooled analysis. The risk of publication bias was further assessed using the Egger test and P values less than 0.05 were considered significant [15].

Assessment of evidence quality

Our meta-analysis used the approach of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) to assess the quality of evidence on this subject to ensure the reliability of meta-analysis results. The GRADE could be divided into four quality levels: (1) high quality; (2) moderate quality; (3) low quality; and (4) very low quality. We applied the methods developed by the GRADE Working Group to rate the quality of evidence, starting at high quality and downgrading for risk of bias, imprecision, inconsistency, indirectness, and publication bias. We rated the quality of the evidence for the following outcomes: frontal, temporal, parietal, occipital, and insular lobes. GRADE software was utilized to edit and analyze the evidence grades and for drafting.

Results

Identification of eligible studies

The initial search yielded 8246 potentially relevant references. After the exclusion of duplicates, 7178 references remained. Among these, 196 studies remained after excluding unrelated studies. Ultimately, we identified 16 studies [1, 4, 9, 12, 16–27] for our meta-analysis after reading full-text and excluding papers that did not meet the inclusion criteria. All 16 studies reported the incidence of preoperative seizures in association with temporal gliomas. Thirteen studies evaluated the relationship between the risk of preoperative seizures and frontal or parietal gliomas. Ten studies described the incidence of preoperative seizures in association with occipital gliomas, and seven studies focused on the relationship between the risk of preoperative seizures and insular gliomas. The flow diagram of the literature screening process and the selection of articles is presented in Fig. 1.

Study characteristics

Sixteen studies [1, 4, 9, 12, 16–27] including 4323 participants were considered in our meta-analysis. Of these studies, nine [1, 9, 16, 17, 20, 24–27] were from Asia, two [19, 22] were from Europe, and the rest [4, 12, 18, 21, 23] were from Australia (two studies [18, 21]), Canada (one study [23]), and the USA (two studies [4, 12]). The publication years of these articles ranged from 2001 to 2017, and the sample sizes ranged from 30 to 1509. There were two prospective [17, 18] and 13 retrospective studies [1, 4, 9, 12, 16, 19, 20, 22–27] in the present meta-analysis. In addition, one study [21] comprised a separate report on retrospective and prospective studies. The results of the detailed outcome indicators of each study are shown in Table 1.

Frontal lobe

Thirteen studies [1, 9, 12, 16–24, 27] indicated that frontal gliomas were associated with a risk for GAS. The total sample size reached 4065 cases. The incidence of preoperative seizures ranged from 18.4 to 92.1% and 11.1 to 87.7% in gliomas involved and non-involved frontal lobe (Table 2). A statistically significant association between frontal gliomas and the risk of preoperative seizures was observed in our meta-analysis (OR = 1.51, 95% CI = 1.09–2.09, $P = 0.013$). However, the I^2 value of 71.0% and a P value < 0.001 indicated high heterogeneity (Fig. 2).

Parietal lobe

Meta-analysis of 13 researches [1, 9, 12, 16–24, 27] with 4065 cases explored the correlation between parietal gliomas and the risk of preoperative seizures. The rate of preoperative seizures ranged from 13.6 to 100.0% in parietal gliomas (Table 2). Meta-analysis demonstrated that there was no significant difference in either group of studies (OR = 0.96, 95% CI = 0.76–1.21, $P = 0.725$). No significant heterogeneity was found among the studies ($I^2 = 0.0\%$, $P = 0.483$) (Fig. 3).

Temporal lobe

Meta-analysis of 16 studies [1, 4, 9, 12, 16–27] indicated a correlation between temporal gliomas and the risk of preoperative seizures in a total sample size of 4323 cases. We found that gliomas involving the temporal lobe were associated with a 21% risk increment of the incidence of preoperative seizures, although the differences were not statistically significant (OR = 1.16, 95% CI = 0.88–1.53, $P = 0.294$) and there was some between-study heterogeneity ($I^2 = 55.9\%$, $P = 0.003$) (Fig. 4).

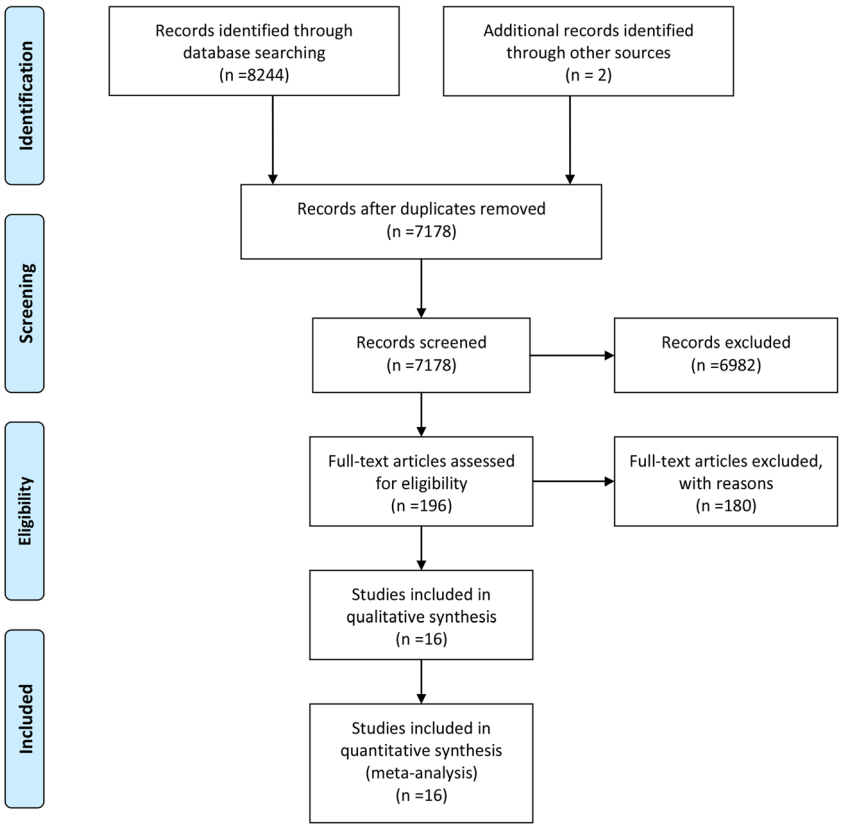


Fig. 1 The flow diagram of the literature screening process and the selection of articles

Occipital lobe

One hundred three patients with occipital gliomas and 1613 gliomas without occipital lobe were included in ten studies. Meta-analysis revealed that occipital gliomas were significantly associated with a 53% risk reduction in the incidence of preoperative seizures (OR = 0.53, 95% CI = 0.32–0.88, P = 0.014). There was no heterogeneity among the studies of occipital gliomas and the risk of preoperative seizures (I^2 = 0.0%, P = 0.65) (Fig. 5).

Insular lobe

Of the included studies, seven studies including 3167 cases assessed the relationship between risk of preoperative seizures and insular gliomas. The pooled meta-analysis suggested that there was no statistical correlation between insular gliomas and the risk of preoperative seizures (OR = 1.18, 95% CI = 0.92–1.51, P = 0.195). No significant between-study heterogeneity was found among the seven studies (I^2 = 0.0%, P = 0.930) (Fig. 6).

Subgroup analysis

To find the source of the heterogeneity, we further performed stratification analysis by ethnicity for the outcomes. There were obvious differences between East Asian and Caucasian studies for both frontal and temporal gliomas. The results indicated that frontal gliomas tended to be associated with preoperative seizure risk in East Asians (OR = 2.02, 95% CI 1.58–2.58, P = 0.329 for heterogeneity test), but not in Caucasians (OR = 1.04, 95% CI 0.64–1.60, P < 0.05 for heterogeneity test) (Table 3). However, the association between temporal gliomas and preoperative seizure risk was significant in Caucasians (OR = 1.75, 95% CI 1.34–2.27, P = 0.658 for heterogeneity test), but not in East Asians (OR = 0.78, 95% CI 0.59–1.04, P = 0.173 for heterogeneity test) (Table 3). These differences may be induced by different genetic backgrounds and environmental exposures [28]. The effect of genetic variants on glioma-associated seizure risk may be different between multiple ethnic groups.

Sensitivity analysis

In the meta-analysis, we conducted a sensitivity analysis by leave-on-out method and found that ethnicity was a significant source of heterogeneity for frontal gliomas. The result indicated that a single study [19] caused the high heterogeneity. The I^2 value decreased to 29.0% when we excluded this study. However, the exclusion did not substantially affect the results of the meta-analysis for frontal gliomas (OR = 1.72, 95% CI = 1.37–2.16, P < 0.001), which would indicate that our analyzed results are robust.

Table 1 Summary of main characteristics of included studies in the meta-analysis

References	Country	Ethnicity	Study design	Sample size	Age median(range) (years)	Gender (M/F)	Glioma pathology (WHO grades I/II/III/IV)	Histopathological subtype (AA/AO/AOA/GBM)	Quality evaluation (NOS)
Lieu et al. (2001)	Tai wan	East Asian	Retrospective	190	44	111/79	ND	117/0/0/73	7
Hwang et al. (2004)	Tai wan	East Asian	Retrospective	101	59.3	61/40	ND	44/0/0/57	6
Chang et al. (2008)	USA	Caucasian	Retrospective	332	39.3	194/138	0/332/0/0	129/95/109/0	6
Lee et al. (2010)	USA	Caucasian	Retrospective	124	18–88	61/63	ND	23/28/24/49	7
Lei et al. (2011)	China	East Asian	Retrospective	103	39.4	60/43	ND	41/35/27/0	7
Mirsattari et al. (2011)	Canada	Caucasian	Retrospective	166	42.8	91/75	0/107/59/0	0/166/0/0	7
Stockhammer et al.(2012)	Germany	Caucasian	Retrospective	79	40	ND	0/79/0/0	79/0/0/0	6
Yuen et al. (2012)a	Australia	Caucasian	Retrospective	190	45.9–57.9	105/85	ND	13/25/27/125	7
Yuen et al. (2012)b	Australia	Caucasian	Prospective	100	50.6–55.8	56/44	ND	13/10/15/64	7
You et al. (2012)	China	East Asian	Retrospective	508	38.1	306/202	ND	229/48/231/0	7
Pallud et al. (2014)	France	Caucasian	Retrospective	1509	ND	857/652	ND	327/781/0/0	7
Liubinas et al. (2014)	Australia	Caucasian	Prospective	30	35.4	15/15	0/30/0/0	11/11/8/0	6
Huang et al. (2014)	China	East Asian	Retrospective	31	25.6–26.1	14/17	ND	0/31/0/0	7
Yang et al. (2014)	China	East Asian	Retrospective	198	43	114/84	ND	56/39/103/0	7
Luchi et al. (2015)	Japan	East Asian	Retrospective	121	58	74/47	0/19/21/81	0/22/99/0	7
Wang et al. (2015)	China	East Asian	Prospective	231	15–67	135/96	ND	25/70/136/0	7
Cheng et al. (2017)	China	East Asian	Retrospective	310	39.4	197/113	35/103/54/118	234/76/0/0	7

AA anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *AOA* anaplastic oligoastrocytoma, *GBM* glioblastoma multiforme *NOS* Newcastle-Ottawa Scale, *ND* no data

Table 2 Association between cerebrum regions and preoperative GAS incidence of all eligible studies

Sources	Preoperative seizure rates (%)	Seizure type		Temporal lobe (%)		Parietal lobe (%)		Frontal lobe (%)		Occipital lobe (%)		Insular lobe (%)	
		Partial	Generalized	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
Leiu et al. (2001)	50/190 (26.3)	12/50 (24.0)	38/50 (76.0)	11/55 (20.0)	39/135 (28.9)	9/31 (29.0)	41/159 (25.8)	25/66 (37.9)	25/124 (20.2)	2/7 (28.6)	48/183 (26.2)	ND	ND
Hwang et al. (2004)	14/101 (13.9)	ND	ND	3/36 (8.3)	11/65 (16.9)	3/22 (13.6)	11/79 (13.9)	7/38 (18.4)	7/63 (11.1)	1/5 (20.0)	13/96 (13.5)	ND	ND
Chang et al. (2008)	269/332 (81.0)	165/269 (61.3)	144/269 (53.5)	95/111 (85.6)	174/221 (78.7)	43/51 (84.3)	226/281 (80.4)	156/182 (85.7)	113/150 (75.3)	ND	ND	22/28 (78.6)	247/304 (81.3)
Lee et al. (2010)	61/124 (49.2)	ND	ND	31/49 (63.3)	30/75 (40.0)	ND	ND	ND	ND	ND	ND	ND	ND
Lei et al. (2011)	71/103 (68.9)	13/71 (18.3)	58/71 (81.7)	27/44 (61.4)	44/59 (74.6)	ND	ND	ND	ND	ND	ND	ND	ND
Mirsattari et al. (2011)	150/166 (90.4)	121/150 (80.7)	97/150 (64.7)	60/62 (96.8)	90/104 (86.5)	39/44 (88.6)	111/122 (91.0)	93/101 (92.1)	57/65 (87.7)	7/8 (87.5)	143/158 (90.5)	ND	ND
Stockhammer et al. (2012)	57/79 (72.2)	19/57 (33.3)	36/57 (63.2)	24/29 (82.8)	33/50 (66.0)	9/16 (56.3)	48/63 (76.2)	33/45 (73.3)	24/34 (70.6)	1/5 (20.0)	56/74 (75.7)	48/67 (71.6)	9/12 (75.0)
Yuen et al. (2012)a	73/190 (38.4)	ND	ND	29/59 (49.2)	44/131 (33.6)	7/30 (23.3)	66/160 (41.3)	36/93 (38.7)	37/97 (38.1)	1/8 (12.5)	72/182 (39.6)	ND	ND
Yuen et al. (2012)b	43/100 (43.0)	ND	ND	17/33 (51.5)	26/67 (38.8)	4/14 (28.6)	39/86 (45.3)	22/51 (43.1)	21/49 (42.9)	0/2 (0.0)	43/98 (43.9)	ND	ND
You et al. (2012)	350/508 (68.9)	106/350 (30.3)	235/350 (67.1)	132/189 (69.8)	218/319 (68.3)	29/46 (63.0)	321/462 (69.5)	254/360 (70.6)	96/148 (64.9)	ND	ND	77/107 (72.0)	273/401 (68.1)
Pallud et al. (2014)	1356/1509 (89.9)	ND	ND	251/274 (91.6)	1105/1235 (89.5)	133/142 (93.7)	1223/1367 (89.5)	665/759 (87.6)	691/750 (92.1)	ND	ND	223/241 (92.5)	1133/1268 (89.4)
Liubinas et al. (2014)	23/30 (76.7)	ND	ND	7/8 (87.5)	16/22 (72.7)	3/3 (100.0)	20/27 (74.1)	11/16 (68.8)	12/14 (85.7)	2/2 (100.0)	21/28 (75.0)	ND	ND
Huang et al. (2014)	19/31 (61.3)	ND	ND	11/12 (91.7)	8/19 (42.1)	ND	ND	ND	ND	ND	ND	ND	ND
Yang et al. (2014)	68/198 (34.3)	26/68 (38.2)	42/68 (61.8)	24/80 (30.0)	44/118 (37.3)	10/29 (34.5)	58/169 (34.3)	48/114 (42.1)	20/84 (23.8)	3/20 (15.0)	65/178 (36.5)	8/23 (34.8)	60/175 (34.3)
Luchi et al. (2015)	31/121 (25.6)	ND	ND	7/31 (22.6)	24/90 (26.7)	3/16 (18.8)	28/105 (26.7)	19/60 (31.7)	12/61 (19.7)	1/9 (11.1)	30/112 (26.8)	ND	ND
Wang et al. (2015)	152/231 (65.8)	45/152 (29.6)	107/152 (70.4)	39/67 (58.2)	113/164 (68.9)	22/34 (64.7)	130/197 (66.0)	108/147 (73.5)	44/84 (52.4)	3/4 (75.0)	149/227 (65.6)	30/46 (65.2)	122/185 (65.9)
Cheng et al. (2017)	104/310 (33.5)	42/104 (40.4)	62/104 (59.6)	54/172 (31.4)	50/138 (36.2)	29/77 (37.7)	75/233 (32.2)	78/186 (42.0)	26/124 (21.0)	8/33 (24.2)	96/277 (34.7)	24/64 (37.5)	80/246 (32.5)

+ involvement, − non-involvement, *ND* no data

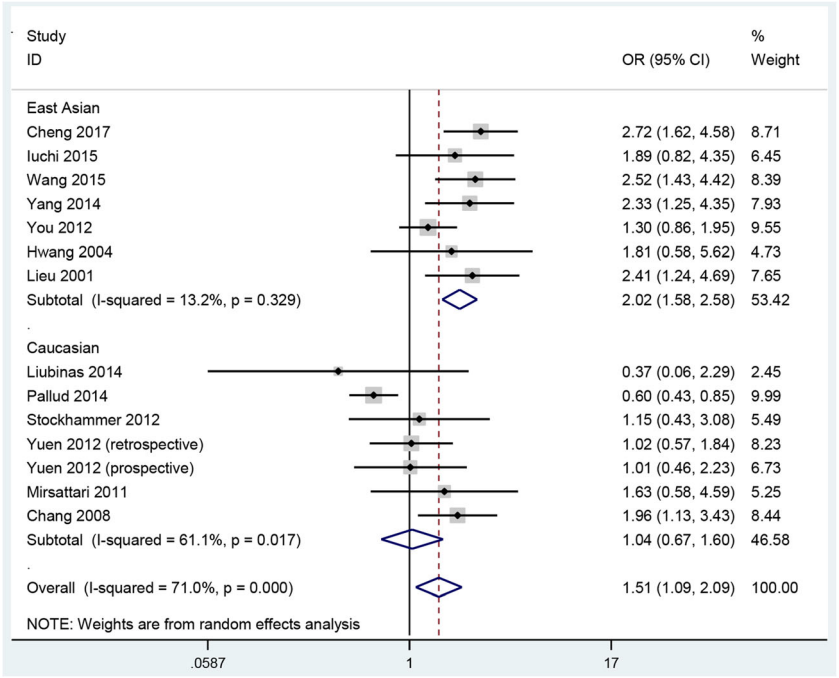


Fig. 2 Forest plot showing the relationship between gliomas involved frontal lobe and the risk of preoperative seizures

Publication bias

We conducted a Begg's test to test for publication bias in the studies on frontal gliomas and the risk of preoperative seizures (Fig. 7). The *P* value for the Begg test was 0.511, which indicated that there was no obvious risk of publication bias in the meta-analysis. Similarly, the conclusion of Egger test was consistent with the Begg's test (Table 4), suggesting low publication bias in the outcome indexes of our meta-analysis, which had provided potent support for the results of Begg's test.

Discussion

To clarify the relationship between tumor location and glioma-related epilepsy, our meta-analysis retrospectively analyzed 16 eligible studies with a total number of 4323 patients. The

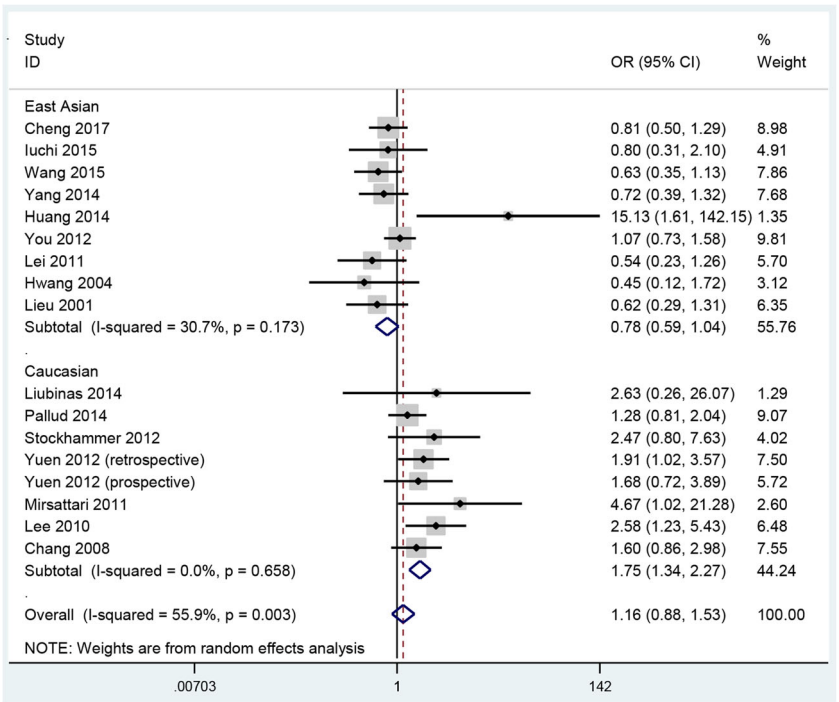


Fig. 3 Forest plot showing the relationship between gliomas involved temporal lobe and the risk of preoperative seizures

Table 3 Associations between frontal/temporal gliomas and preoperative seizure risk by races

Lobe involved	Ethnicities	Studies	OR (95% CI)	$P_{(OR)}$	P^*
Frontal	Total	13	1.51 (1.09, 2.09)	< 0.05	< 0.05
	East Asian	7	2.02 (1.58, 2.58)	< 0.05	0.329
	Caucasian	6	1.04 (0.67, 1.60)	0.089	< 0.05
Temporal	Total	16	1.16 (0.88, 1.53)	0.295	< 0.05
	East Asian	9	0.78 (0.59, 1.04)	0.088	0.173
	Caucasian	7	1.75 (1.34, 2.27)	< 0.05	0.658

meta-analysis indicated that tumor localization was a known strong predictor for glioma-associated seizures. We found the lowest incidence of preoperative seizures in patients with gliomas in the occipital lobe, while the highest rate of preoperative seizure incidence was found in patients with gliomas in the frontal lobe. Our meta-analysis did not find any significant correlations between the location of gliomas in the other three lobes and the incidence of preoperative seizure. However, epileptologists and neurosurgeons differ slightly in the diagnosis of preoperative seizures in the included studies. Epileptologists mainly based on the guidelines for diagnosis of epilepsy, while neurosurgeons are based on clinical symptoms, physical examination, and auxiliary examination, because there are no special guidelines for the diagnosis and treatment of glioma-related seizures. In addition, neurosurgeons should also consider patients' medical history and semiology of seizures for the diagnosis of glioma-associated seizures. This may be one of the factors that cause bias risk in our meta-analysis.

Gliomas are known to be the most epileptogenic brain tumors [6]. Current studies lack further investigations of how the tumor itself can cause seizures. The pathogenesis of glioma-related epilepsy appears to be different from that of idiopathic epilepsy. Two views concerning the pathogenesis of glioma-associated seizures are available at present [9]. One potential explanation is that the seizure originates in the surrounding normal tissue. To be specific, it is thought that the tumor mechanically compresses the surrounding normal tissue, which then gives rise to a mass effect. The affected tissues have decreased pH level, ischemia, and hypoxia, and become seizure foci [29, 30].

The other possibility is that the seizure originates in the tumor. Specifically, the tumor itself may excrete certain chemical actors, which can then change the peritumoral microenvironment into an epileptic focus. Liang et al. [11] found that glutamate released from glioma cells is related to the development of epileptic activity. A greater concentration of glutamate, the major excitatory amino acid neurotransmitter in the brain, has been found in brain tumor samples from patients with active epilepsy [31]. In addition, as early as 1999, Ye et al. [32] carried out the experimental study of cell lines of human astrocytomas (included STTG-1, U-138 MG, U-251 MG, U-373 MG, CH-235 MG, D-54 MG, and D-65 MG) and found that glutamate released by tumors might contribute to seizure

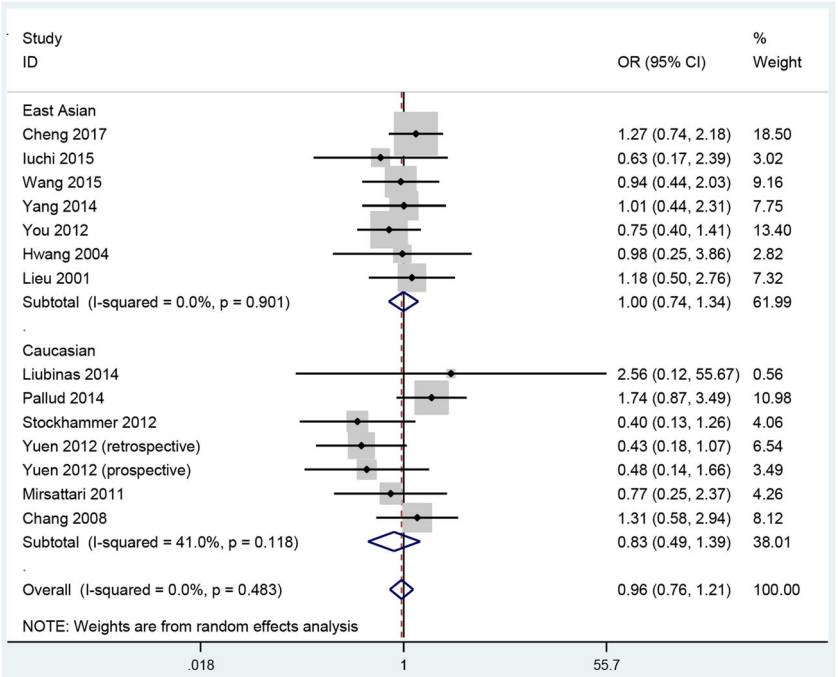
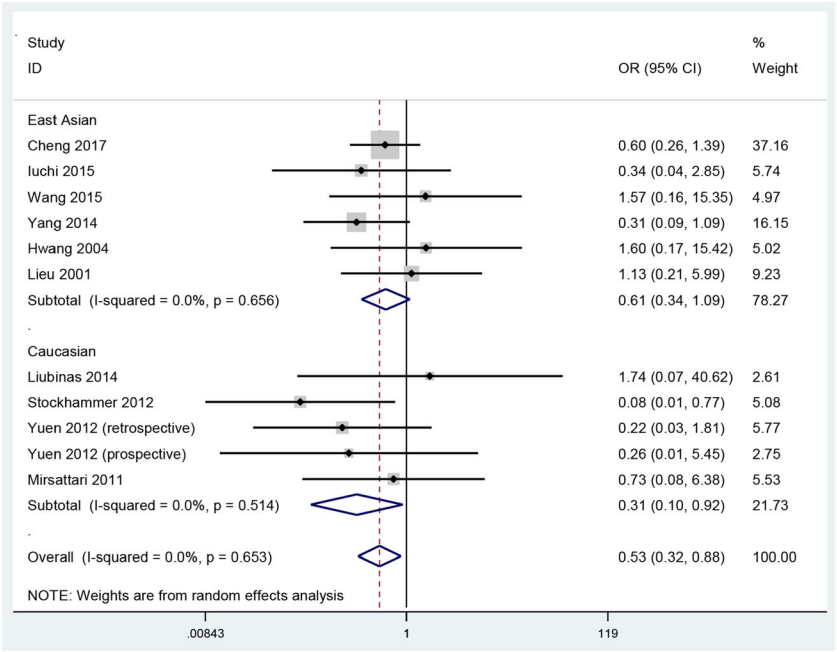


Fig. 4 Forest plot showing the relationship between gliomas involved parietal lobe and the risk of preoperative seizures



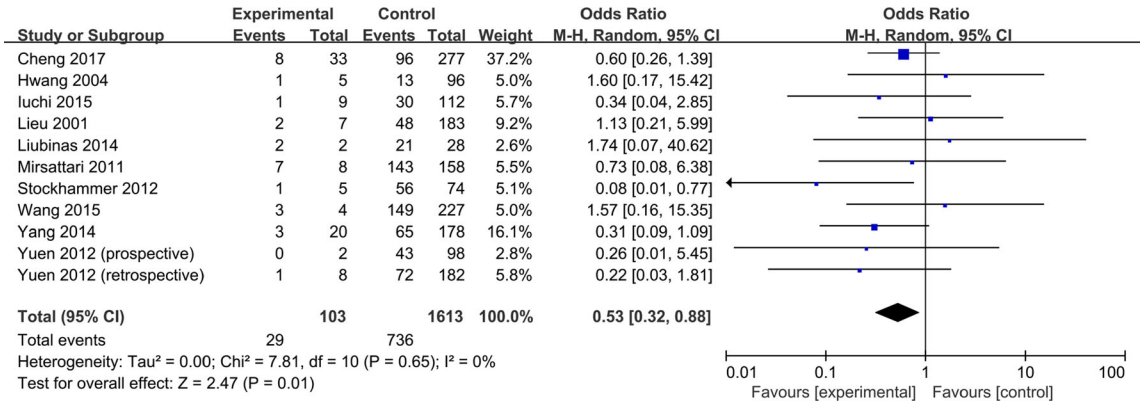


Fig. 5 Forest plot showing the relationship between gliomas involved occipital lobe and the risk of preoperative seizures

activity arising from peritumoral brain regions. These underlying effects may alter the balance between intracortical inhibitory and excitatory mechanisms, which consequently lead to epileptogenic activity [32–34].

For frontal gliomas, we found that there was significant heterogeneity among the 13 studies. Our sensitivity analysis of the meta-analysis data revealed that heterogeneity was caused by one study [19] for diffuse low-grade gliomas included and the heterogeneity of the data sources used. The pooled estimated effects were not altered when we removed this study from the analysis.

Our meta-analysis declared the highest incidence of preoperative seizures in frontal gliomas. However, the mechanism underlying frontal glioma-related seizure initiation has yet to be clarified. It is known that the frontal lobe has the greatest volume of all the cerebral lobes. This is associated with the highest probability of glioma formation in this region [13]. In addition, the frontal lobe is extensively associated with the surrounding tissues and structures, such as the thalamus, basal ganglia, and brainstem. Therefore, discharges of frontal neurons are likely to extend to the above-mentioned sites and induce epileptic seizures [13]. Frontal lobe lesions mainly involve cortical and superficial cerebral tissue and white matter fibers are seldom destroyed due to frontal lobe lesions. This contributes to the preservation of a route for the transmission of lesion discharge [13, 35]. Nevertheless, large prospective multicenter studies are required to clarify the various questions raised by this study.

In the study of occipital lobe, two studies [9, 27] have the largest sample size, and the sum of them has a large weight, which renders the final conclusion to tend to be similar with them, but not exactly the same. Therefore, the included studies were comprehensively analyzed and concluded the lowest

incidence of preoperative seizures in occipital gliomas. Until now, the mechanism underlying this observation has not been fully understood. The occipital lobe is located in the posterior cerebral hemisphere above the tentorium cerebelli. It has the smallest volume among all the cerebral lobes and has relatively low incidence of gliomas, which may be an important factor underlying our findings. Further high-quality basic experimental researches are required to explore the pathogenesis of occipital gliomas.

Compared to gliomas with frontal and occipital lobes, we did not find gliomas with temporal, insular, and parietal lobes that were associated with preoperative seizure risk. These negative findings may be due to several factors, such as differences in the study design and the different populations studied. Future research should focus on identifying regions with susceptibility to GAS in larger multicenter studies.

Uncontrolled preoperative seizures might lead to hospitalization, which is typically not a desired option for patients and might subsequently decrease their quality of life. Caregivers, who may already have a heavy burden of care, might experience additional distress when caring for patients with ongoing seizures [36]. Therefore, adequate preoperative seizure management is essential for glioma patients. Preoperative seizure control in glioma patients involving different lobes has been described, with success rates ranging from 48 to 77% [12, 13, 37–39]. Although some studies [2, 38] have reported that there is no significant association between the type of surgical resection and control of seizures, recent research [12, 37, 40–42] suggests that gross total resection is one of the strongest predictors for glioma-related seizure control. Gross total resection is defined as removal of more than 90% of the tumor. Minimizing the residual tumor volume through total resection may enable removal of the epileptogenic zone. Therefore, surgical resection of tumor lesions is one of the most important methods to control epileptic seizures.

In addition, a univariate analysis [20] indicated that chemotherapy may lead to better seizure control, which might partly be related to its effects on tumor progression. Chalifoux et al. [43] reported that radiation therapy can significantly reduce the frequency of seizures and control tumor growth. The mechanism may be related to the fact that radiotherapy can change the microenvironment of epilepsy foci and destroy the epileptic conduction pathway [43]. However, compared with chemotherapy or radiotherapy alone, concomitant chemoradiotherapy could effectively improve the tumor's progression-free survival and prolong the overall survival period [44, 45]. The European Organization of Research and Treatment for Cancer (EORTC) [46] had carried out a randomized controlled experimental study on 22,845 glioma cases and demonstrated that radiotherapy combined with chemotherapy could reduce the frequency of epileptic seizures in 50–60% glioma patients, and epilepsy disappeared in 20–40% patients. The latest research had shown [47] radiochemotherapy combined with surgical treatment is effective in reducing postoperative seizures. In conclusion, the combination of radiotherapy and chemotherapy is very effective and necessary in the treatment of glioma-associated seizures.

Currently, there are different views regarding the active use of antiepileptic drugs (AEDs) for the treatment of preoperative glioma-related epilepsy. To date, there are no data to support a preferred drug of choice. Gan You et al. [20] found that valproic acid could be used to successfully control preoperative seizures. However, due to the potential neurotoxicity of

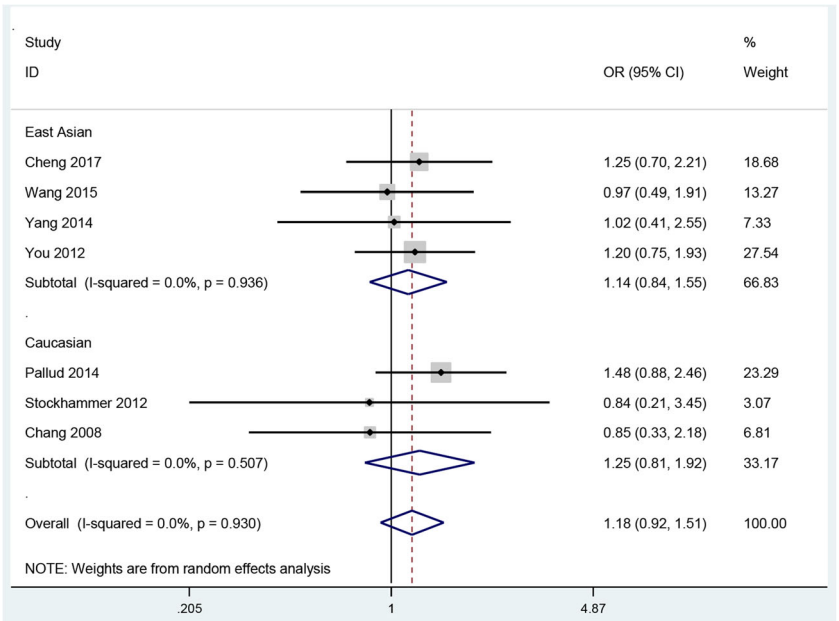


Fig. 6 Forest plot showing the relationship between gliomas involved insular lobe and the risk of preoperative seizures

Table 4 Comparison between Begg's test and Egger's test for publication bias

Outcomes	Begg's test		Egger's test	
	*Z*值	*P*值	*t*值	*P*值
Frontal	0.66	0.511	1.00	0.338
Temporal	1.28	0.202	1.36	0.195
Parietal	0.99	0.324	−1.18	0.261
Insular	1.50	0.133	−2.61	0.058
Occipital	0.62	0.533	−0.01	0.989

valproate, the clinical application of valproic acid was also reduced. Another study [48] reported that levetiracetam had minimal side effects in the central nervous system. Levetiracetam (except for patients with abnormal renal function) was considered to be the first choice for controlling partial seizures and focal epileptic seizures induced by gliomas, along with favorable tolerance. Newly developed AEDs do not undergo hepatic metabolism, such as lamotrigine, which was mainly eliminated through the acidification metabolism of glucal and could be inhibited by sodium valproate [49]. Besides, it was also effective in controlling GAS [50]. More importantly, lamotrigine and levetiracetam would not impact the cytochrome P450 enzyme system or other metabolic pathways, which were vital to glioma patients requiring chemotherapy [51, 52].

Furthermore, a study [53] had found that sulfasalazine (SAS), which is a drug approved by the Food and Drug Administration, inhibited peritumoral hyperexcitability and reduced epileptic event frequency in tumor-bearing mice. This drug had the most benefit in patients with slow-growing gliomas. Clearly, a well-designed clinical study of SAS for the treatment of patients with gliomas is warranted. Until now, there has only been limited evidence to recommend the use of certain AEDs for the treatment of GAS. Therefore, more prospective studies are required to provide better evidence to guide clinical decision-making.

The overall quality of evidence varies for different outcomes, as shown in Table 5. The quality of evidence was poor for temporal gliomas; moderate for frontal, parietal, and insular gliomas; and high for occipital gliomas. The major reasons for this poor assessment of temporal gliomas were that most of the included studies were case-control studies. In addition, some potential confounding biases also affecting the result, such as gene mutation or histopathological subtype, have been linked to the risk of glioma-related seizures. Small sample sizes resulted in wide confidence intervals for the outcomes of temporal and frontal gliomas, which decreased the quality of evidence. Future multicenter, large-scale clinical studies should be adequately powered to measure differences in clinically important outcomes.

In the current meta-analysis, several studies [18, 22] analyzed the association between seizure as the initial symptom and mutation of IDH1/2. The two above-mentioned studies demonstrated that there is significantly increased incidence of preoperative seizures in gliomas with mutations of IDH1/2 compared to those with no IDH1/2 mutations. In addition, Chen et al. [54] studied a large cohort (712 cases) WHO grade II-IV gliomas from three institutions where they found that IDH mutant tumors confer risk for preoperative seizures and D-2-hydroxyglutarate (D2HG) product of mutant isocitrate dehydrogenase 1 (IDH1mut) may increase neuronal activity by mimicking the activity of glutamate on the NMDA receptor. A recent meta-analysis [55] also demonstrated that the association between IDH1/2 mutation status and incidence of preoperative seizures is significant for low-grade gliomas (grade II) but not for high-grade gliomas (grades III and IV). Therefore, IDH1/2 mutation has an important effect on the incidence of preoperative glioma-related epilepsy. Since the included studies did not carry out correction analysis for this confounding factor, which leads to a certain bias in our meta-analysis, prospective studies are needed to provide better evidence to confirm our results.

Large-scale comprehensive reports were included in this study and the database was searched without language restriction. In addition, the requirements for the internal control group were determined in accordance with specific diagnostic criteria. This allowed us to improve the quality of the quantitative analysis. Furthermore, our meta-analysis strictly obeyed the literature inclusion and exclusion criteria and all the enrolled studies were assigned semi-quantified scores using the Newcastle-Ottawa Scale after strict quality control and data extraction. The corresponding computational models were selected in the data analysis through rigid heterogeneity testing. Finally, a sensitivity analysis was performed on the results of the meta-analysis.

Our meta-analysis has several potential limitations. First, several results, for example, those of participants with occipital gliomas, had quite small sample sizes. It seems that larger numbers of eligible studies with large samples are needed. Fortunately, our powerful analysis indicated that we were able to draw conclusions with great power using our methods. Secondly, glioma-associated seizures may also be related to gene mutations, histopathological subtype, and patient age. However, due to the lack of detailed data on these factors in several included studies, our confidence in the findings may be weakened. Furthermore, in the included studies, the types of preoperative seizures induced by gliomas are mainly simple partial seizures and secondary general seizures. It may affect reporting of preoperative seizure incidence and lead to a certain publication bias. Consequently, we believe that large-scale, high-quality research should be performed to further verify the above results.

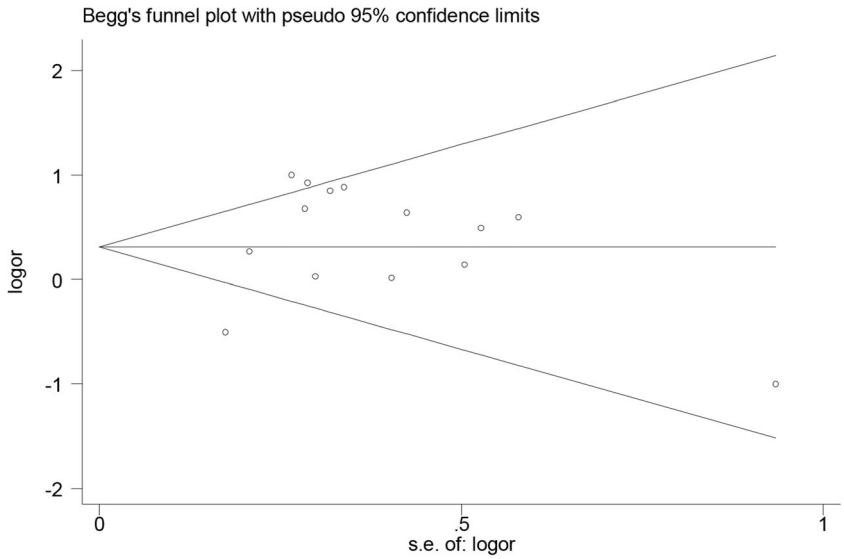


Fig. 7 Begg's funnel plot with pseudo 95% confidence limits for frontal gliomas

Conclusions

Our meta-analysis demonstrated a correlation between glioma location and preoperative seizure risk. The meta-analysis of seizure-susceptible regions furthers our understanding of the etiology of glioma-related seizure. Additionally, these findings provide new evidence that may eventually be useful for customized seizure management, although currently further evidence is needed. Future prospective studies also should take into account the complexity of AED administration in patients with preoperative GAS. This in turn may contribute to the development of more targeted preoperative seizure treatments.

Table 5 Summary of findings for the main comparisons

Glioma involved a lobe compared to non-involved for preoperative seizures

Patient or population: patients with gliomas with preoperative seizures

Settings:

Intervention: lobe involvement

Comparison: lobe non-involvement

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Lobe non-involvement	Lobe involvement				
Frontal lobe	642 per 1000	730 per 1000 (661 to 789)	OR 1.51 (1.09 to 2.09)	4065 (13 studies)	⊕⊕⊕⊖ moderate[a]	
Temporal lobe	687 per 1000	718 per 1000 (659 to 770)	OR 1.16 (0.88 to 1.53)	4323 (16 studies)	⊕⊕⊖⊖ low[a,b]	
Parietal lobe	683 per 1000	674 per 1000 (621 to 723)	OR 0.96 (0.76 to 1.21)	4065 (13 studies)	⊕⊕⊕⊖ moderate[b]	
Insular lobe	743 per 1000	773 per 1000 (726 to 813)	OR 1.18 (0.92 to 1.51)	3167 (7 studies)	⊖⊕⊕⊖ moderate[b]	
Occipital lobe	456 per 1000	308 per 1000 (212 to 425)	OR 0.53 (0.32 to 0.88)	1716 (10 studies)	⊕⊕⊕⊕ high	

*The basis for the *assumed risk* (e.g., the median control group risk across studies) is provided in footnotes. The *corresponding risk* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI)

CI, confidence interval; *OR*, odds ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate

[a] The heterogeneity was high

[b] Imprecision

Authors' contributions Jian Zhang conceived the study and drafted this manuscript. Shaopeng Peng and Liang Yao participated in literature search, study selection, and evidence quality assessment. Yuan Fang and Ruitian Tang carried out data extraction and the statistical analysis. Jianxiong Liu mainly participated in study design and critical revision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval is not applicable as this is a meta-analysis.

Informed consent For this type of study, formal consent is not required.

Appendix 1

Table 6 Search strategies

Web of Science	
#1	TS = (glioma OR astrocytoma OR oligodendroglioma OR oligoastrocytoma)
#2	TS = (seizure OR epilepsy)
#3	#2 AND #1
PubMed	
#1	Search glioma [Title/Abstract]
#2	Search "Glioma"[Mesh]
#3	Search astrocytoma [Title/Abstract]
#4	Search "Astrocytoma"[Mesh]
#5	Search oligodendroglioma [Title/Abstract]
#6	Search "Oligodendroglioma"[Mesh]
#7	Search oligoastrocytoma [Title/Abstract]
#8	Search "Oligoastrocytoma"[Mesh]
#9	Search #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	Search seizure [Title/Abstract]
#11	Search "Seizure"[Mesh]
#12	Search epilepsy [Title/Abstract]
#13	Search "Epilepsy"[Mesh]
#14	Search #10 or #11 or #12 or #13
#15	Search #9 and #14
Cochrane Library	
#1	glioma: ti,ab,kw
#2	MeSH descriptor: [Glioma] explode all trees
#3	astrocytoma: ti,ab,kw
#4	MeSH descriptor: [Astrocytoma] explode all trees
#5	oligodendroglioma: ti,ab,kw
#6	MeSH descriptor: [Oligodendroglioma] explode all trees
#7	oligoastrocytoma: ti,ab,kw
#8	MeSH descriptor: [Oligoastrocytoma] explode all trees
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	seizure: ti,ab,kw
#11	MeSH descriptor: [Seizure] explode all trees
#12	epilepsy: ti,ab,kw
#13	MeSH descriptor: [Epilepsy] explode all trees
#14	#10 or #11 or #12 or #13
#15	#9 and #14
EMBASE	
#1	'glioma': ab,ti
#2	'glioma'/exp
#3	'astrocytoma': ab,ti
#4	'astrocytoma'/exp
#5	'oligodendroglioma': ab,ti
#6	'oligodendroglioma'/exp
#7	'oligoastrocytoma': ab,ti
#8	'oligoastrocytoma'/exp
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	'seizure': ab,ti
#11	'seizure'/exp
#12	'epilepsy': ab,ti
#13	'epilepsy'/exp
#14	#10 OR #11 OR #12 OR #13
#15	#9 AND #14
CBM	
1	神经胶质瘤
2	"神经胶质瘤"[不加权:扩展]
3	星型细胞瘤
4	"星型细胞瘤"[不加权:扩展]
5	少突胶质细胞瘤
6	少突星型细胞瘤
7	(#6) OR (#5) OR (#4) OR (#3) OR (#2) OR (#1)
8	癫痫
9	"癫痫"[不加权:扩展]
10	癫痫发作
11	(#10) OR (#9) OR (#8)
12	(#11) OR (#7)

Appendix 2

Table 7 The inception date of each database

Database	Inception date to search time
PubMed	1966–2017.07
EMBASE	1974–2017.07
Cochrane Library	1992–2017.07
Web of Science	1980–2017.07
CBM	1978–2017.07

Appendix 3

Table 8 The 2007 WHO grading of tumors of the central nervous system

Tumor classification	I	II	III	IV
Astrocytic tumors				
Subependymal giant cell astrocytoma	*			
Pilocytic astrocytoma	*			
Pilomyxoid astrocytoma		*		
Diffuse astrocytoma		*		
Pleomorphic xanthoastrocytoma		*		
Anaplastic astrocytoma			*	
Glioblastoma				*
Giant cell glioblastoma				*
Gliosarcoma				*
Oligodendroglial tumors				
Oligodendroglioma		*		
Anaplastic oligodendroglioma			*	
Oligoastrocytic tumors				
Oligoastrocytoma		*		
Anaplastic oligoastrocytoma			*	
Ependymal tumors				
Subependymoma	*			
Myxopapillary ependymoma	*			
Ependymoma		*		
Anaplastic ependymoma			*	
Choroid plexus tumors				
Choroid plexus papilloma	*			
Atypical choroid plexus papilloma		*		
Choroid plexus carcinoma			*	
Other neuroepithelial tumors				
Angiocentric glioma	*			
Chordoid glioma of the third ventricle		*		
Neuronal and mixed neuronal-glial tumors				
Gangliocytoma	*			
Ganglioglioma	*			
Anaplastic ganglioglioma			*	
Desmoplastic infantile astrocytoma and ganglioglioma	*			
Dysembryoplastic neuroepithelial tumor	*			
Central neurocytoma		*		
Extraventricular neurocytoma		*		
Cerebellar liponeurocytoma		*		
Paraganglioma of the spinal cord	*			
Papillary glioneuronal tumor	*			
Rosette-forming glioneuronal tumor of the fourth ventricle	*			
Pineal tumors				
Pineocytoma	*			
Pineal parenchymal tumor of intermediate differentiation		*	*	
Pineoblastoma				*
Papillary tumor of the pineal region		*	*	
Embryonal tumors				
Medulloblastoma				*
CNS primitive neuroectodermal tumor (PNET)				*
Atypical teratoid/rhabdoid tumor				*
Tumors of the cranial and paraspinal nerves				
Schwannoma	*			
Neurofibroma	*			
Perineurioma	*	*	*	
Malignant peripheral nerve sheath tumor (MPNST)		*	*	*
Meningeal tumors				
Meningioma	*			
Atypical meningioma		*		
Anaplastic/malignant meningioma			*	
Hemangiopericytoma		*		
Anaplastic hemangiopericytoma			*	
Hemangioblastoma	*			
Tumors of the sellar region				
Craniopharyngioma	*			
Granular cell tumor of the neurohypophysis	*			
Pituicytoma	*			
Spindle cell oncocytoma of the adenohypophysis	*			

References

1. Hwang SL, Lin CL, Lee KS, Lieu AS, Kuo TH, Chang CZ, Yen CP, Lin CK, Loh JK, Huang TY, Howng SL (2004) Factors influencing seizures in adult patients with supratentorial astrocytic tumors. Acta Neurochir 146(6):589–594 discussion 594
2. Lynam LM, Lyons MK, Drazkowski JF, Sirven JI, Noe KH, Zimmerman RS, Wilkens JA (2007) Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. Clin Neurol Neurosurg 109(7):634–638
3. Michelucci R, Pasini E, Meletti S, Fallica E, Rizzi R, Florindo I, Chiari A, Monetti C, Cremonini AM, Forlivesi S, Albani F, Baruzzi A (2013) Epilepsy in primary cerebral tumors: the characteristics of epilepsy at the onset (results from the PERNO study–project of Emilia Romagna Region on Neuro-Oncology). Epilepsia 54(Suppl 7):86–91
4. Lee JW, Wen PY, Hurwitz S, Black P, Kesari S, Drappatz J, Golby AJ, Wells WM 3rd, Warfield SK, Kikinis R, Bromfield EB (2010) Morphological characteristics of brain tumors causing seizures. Arch Neurol 67(3):336–342
5. Ruda R, Trevisan E, Soffietti R (2010) Epilepsy and brain tumors. Curr Opin Oncol 22(6):611–620
6. Yang P, Liang T, Zhang C, Cai J, Zhang W, Chen B, Qiu X, Yao K, Li G, Wang H, Jiang C, You G, Jiang T (2016) Clinicopathological factors predictive of postoperative seizures in patients with gliomas. Seizure 35:93–99
7. Kerkhof M, Vecht CJ (2013) Seizure characteristics and prognostic factors of gliomas. Epilepsia 54(Suppl 9):12–17
8. Bauer R, Ortler M, Seiz-Rosenhagen M, Maier R, Anton JV, Unterberger I (2014) Treatment of epileptic seizures in brain

tumors: a critical review. Neurosurg Rev 37(3):381–388 discussion 388
9. Yang P, You G, Zhang W, Wang Y, Wang Y, Yao K, Jiang T (2014) Correlation of preoperative seizures with clinicopathological factors and prognosis in anaplastic gliomas: a report of 198 patients from China. Seizure 23(10):844–851
10. Whittle IR, Beaumont A (1995) Seizures in patients with supratentorial oligodendroglial tumours. Clinicopathological features and management considerations. Acta Neurochir 135(1–2): 19–24
11. Liang R, Fan Y, Wang X, Mao Q, Liu Y (2013) The significance of IDH1 mutations in tumor-associated seizure in 60 Chinese patients with low-grade gliomas. Sci World J 2013:403942
12. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, Berger MS (2008) Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 108(2):227–235
13. Chaichana KL, Parker SL, Olivi A, Quinones-Hinojosa A (2009) Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. J Neurosurg 111(2):282–292
14. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
15. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315(7109): 629–634
16. Iuchi T, Hasegawa Y, Kawasaki K, Sakaida T (2015) Epilepsy in patients with gliomas: incidence and control of seizures. J Clin Neurosci 22(1):87–91
17. Wang Y, Qian T, You G, Peng X, Chen C, You Y, Yao K, Wu C, Ma J, Sha Z, Wang S, Jiang T (2015) Localizing seizure-susceptible brain regions associated with low-grade gliomas using voxel-based lesion-symptom mapping. Neuro-Oncology 17(2):282–288
18. Liubinas SV, D'Abaco GM, Moffat BM, Gonzales M, Feleppa F, Nowell CJ, Gorelik A, Drummond KJ, O'Brien TJ, Kaye AH, Morokoff AP (2014) IDH1 mutation is associated with seizures and protoplasmic subtype in patients with low-grade gliomas. Epilepsia 55(9):1438–1443
19. Pallud J, Audureau E, Blonski M, Sanai N, Bauchet L, Fontaine D, Mandonnet E, Dezamis E, Psimaras D, Guyotat J, Peruzzi P, Page P, Gal B, Parraga E, Baron MH, Vlaicu M, Guillevin R, Devaux B, Duffau H, Taillandier L, Capelle L, Huberfeld G (2014) Epileptic seizures in diffuse low-grade gliomas in adults. Brain 137(Pt 2): 449–462
20. You G, Sha ZY, Yan W, Zhang W, Wang YZ, Li SW, Sang L, Wang Z, Li GL, Li SW, Song YJ, Kang CS, Jiang T (2012) Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. Neuro-Oncology 14(2):230–241
21. Yuen TI, Morokoff AP, Bjorksten A, D'Abaco G, Paradiso L, Finch S, Wong D, Reid CA, Powell KL, Drummond KJ, Rosenthal MA, Kaye AH, O'Brien TJ (2012) Glutamate is associated with a higher risk of seizures in patients with gliomas. Neurology 79(9):883–889
22. Stockhammer F, Misch M, Helms HJ, Lengler U, Prall F, von Deimling A, Hartmann C (2012) IDH1/2 mutations in WHO grade II astrocytomas associated with localization and seizure as the initial symptom. Seizure 21(3):194–197
23. Mirsattari SM, Chong JJ, Hammond RR, Megyesi JF, Macdonald DR, Lee DH, Cairncross JG (2011) Do epileptic seizures predict outcome in patients with oligodendroglioma? Epilepsy Res 94(1–2):39–44
24. Hwang SL, Lieu AS, Kuo TH, Lin CL, Chang CZ, Huang TY, Howng SL (2001) Preoperative and postoperative seizures in patients with astrocytic tumours: analysis of incidence and influencing factors. J Clin Neurosci 8(5):426–429
25. Huang C, Li H, Chen M, Si Y, Lei D (2014) Factors associated with preoperative and postoperative epileptic seizure in patients with cerebral ganglioglioma. Pak J Med Sci 30(2):245–249
26. Huang L, You G, Jiang T, Li G, Li S, Wang Z (2011) Correlation between tumor-related seizures and molecular genetic profile in 103 Chinese patients with low-grade gliomas: a preliminary study. J Neurol Sci 302(1–2):63–67
27. Huang C, Chi X-S, Hu X, Chen N, Zhou Q, Zhou D, J-m L (2017) Predictors and mechanisms of epilepsy occurrence in cerebral gliomas: what to look for in clinicopathology. Exp Mol Pathol 102(1): 115–122
28. Zhu L, Yuan H, Jiang T, Wang R, Ma H, Zhang S (2013) Association of TLR2 and TLR4 polymorphisms with risk of cancer: a meta-analysis. PLoS One 8(12):e82858
29. Schaller B (2005) Influences of brain tumor-associated pH changes and hypoxia on epileptogenesis. Acta Neurol Scand 111(2):75–83
30. Wolf HK, Roos D, Blumcke I, Pietsch T, Wiestler OD (1996) Perilesional neurochemical changes in focal epilepsies. Acta Neuropathol 91(4):376–384
31. Ricci R, Bacci A, Tugnoli V, Battaglia S, Maffei M, Agati R, Leonardi M (2007) Metabolic findings on 3T 1H-MR spectroscopy in peritumoral brain edema. AJNR Am J Neuroradiol 28(7):1287–1291
32. Ye ZC, Sontheimer H (1999) Glioma cells release excitotoxic concentrations of glutamate. Cancer Res 59(17):4383–4391
33. Bordey A, Sontheimer H (1998) Electrophysiological properties of human astrocytic tumor cells in situ: enigma of spiking glial cells. J Neurophysiol 79(5):2782–2793
34. Bordey A, Sontheimer H (1998) Properties of human glial cells associated with epileptic seizure foci. Epilepsy Res 32(1–2):286–303
35. Leone MA, Ivashynka AV, Tonini MC, Bogliun G, Montano V, Ravetti C, Gambaro P, Paladin F, Beghi E (2011) Risk factors for a first epileptic seizure symptomatic of brain tumour or brain vascular malformation. Swiss Med Wkly 141:w13155
36. Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Ruda R, Marosi C, Le Rhun E, Grant R, Oliver K, Oberg I, Bulbeck HJ, Rooney AG, Henriksson R, Pasman HRW, Oberndorfer S, Weller M, Taphoorn MJB (2017) European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. Lancet Oncol 18(6):e330–e340
37. Hildebrand J, Lecaille C, Perennes J, Delattre JY (2005) Epileptic seizures during follow-up of patients treated for primary brain tumors. Neurology 65(2):212–215
38. Rosati A, Tomassini A, Pollo B, Ambrosi C, Schwarz A, Padovani A, Bonetti B (2009) Epilepsy in cerebral glioma: timing of appearance and histological correlations. J Neuro-Oncol 93(3):395–400
39. Khan RB, Boop FA, Onar A, Sanford RA (2006) Seizures in children with low-grade tumors: outcome after tumor resection and risk factors for uncontrolled seizures. J Neurosurg 104(6 Suppl):377–382
40. Zaatreh MM, Firlik KS, Spencer DD, Spencer SS (2003) Temporal lobe tumoral epilepsy: characteristics and predictors of surgical outcome. Neurology 61(5):636–641
41. Simon M, Neuloh G, von Lehe M, Meyer B, Schramm J (2009) Insular gliomas: the case for surgical management. J Neurosurg 110(4):685–695
42. Duffau H, Capelle L, Lopes M, Bitar A, Sichez JP, van Effenterre R (2002) Medically intractable epilepsy from insular low-grade gliomas: improvement after an extended lesionectomy. Acta Neurochir 144 (6): 563–572; discussion 572-563
43. Chalifoux R, Elisevich K (1996) Effect of ionizing radiation on partial seizures attributable to malignant cerebral tumors. Stereotact Funct Neurosurg 67(3–4):169–182
44. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, Coons S, Ricci P, Bullard D, Brown PD, Stelzer K,

Brachman D, Suh JH, Schultz CJ, Bahary JP, Fisher BJ, Kim H, Murtha AD, Bell EH, Won M, Mehta MP, Curran WJ Jr (2016) Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 374(14):1344–1355

45. van den Bent MJ, Baumert B, Erridge SC, Vogelbaum MA, Nowak AK, Sanson M, Brandes AA, Clement PM, Baurain JF, Mason WP, Wheeler H, Chinot OL, Gill S, Griffin M, Brachman DG, Taal W, Ruda R, Weller M, McBain C, Reijneveld J, Enting RH, Weber DC, Lesimple T, Clenton S, Gijtenbeek A, Pascoe S, Herrlinger U, Hau P, Dhermain F, van Heuvel I, Stupp R, Aldape K, Jenkins RB, Dubbink HJ, Dinjens WNM, Wesseling P, Nuyens S, Golfinopoulos V, Gorlia T, Wick W, Kros JM (2017) Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet (London, England) 390(10103):1645–1653
46. Pace A, Vidiri A, Galie E, Carosi M, Telera S, Cianciulli AM, Canalini P, Giannarelli D, Jandolo B, Carapella CM (2003) Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann Oncol 14(12): 1722–1726
47. McCracken JA, Gonzales MF, Phal PM, Drummond KJ (2016) Angiocentric glioma transformed into anaplastic ependymoma: review of the evidence for malignant potential. J Clin Neurosci 34: 47–52
48. van Breemen MS, Rijsman RM, Taphoorn MJ, Walchenbach R, Zwinkels H, Vecht CJ (2009) Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol 256(9):1519–1526
49. Karceski S, Morrell MJ, Carpenter D (2005) Treatment of epilepsy in adults: expert opinion. Epilepsy Behav 7(Suppl 1):S1–S64 quiz S65-67
50. Brodie MJ, Sills GJ (2011) Combining antiepileptic drugs–rational polytherapy? Seizure 20(5):369–375
51. Wagner GL, Wilms EB, Van Donselaar CA, Vecht Ch J (2003) Levetiracetam: preliminary experience in patients with primary brain tumours. Seizure 12(8):585–586
52. Perry JR, Sawka C (1996) Add-on gabapentin for refractory seizures in patients with brain tumours. Can J Neurol Sci 23(2):128–131
53. Buckingham SC, Campbell SL, Haas BR, Montana V, Robel S, Ogunrinu T, Sontheimer H (2011) Glutamate release by primary brain tumors induces epileptic activity. Nat Med 17(10):1269–1274
54. Chen H, Judkins J, Thomas C, Wu M, Khoury L, Benjamin CG, Pacione D, Golfinos JG, Kumthekar P, Ghamsari F, Chen L, Lein P, Chetkovich DM, Snuderl M, Horbinski C (2017) Mutant IDH1 and seizures in patients with glioma. Neurology 88(19):1805–1813
55. Phan K, Ng W, Lu VM, McDonald KL, Fairhall J, Reddy R, Wilson P (2018) Association between IDH1 and IDH2 mutations and preoperative seizures in patients with low-grade versus high-grade glioma: a systematic review and Meta-analysis. World Neurosurg 111: e539–e545