Original article

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Relationship between tumour location and preoperative seizure incidence in patients with gliomas: a systematic review and meta-analysis

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ABSTRACT – *Aim*. The aim of this meta-analysis was to assess the relationship between tumour location and preoperative seizure incidence in patients with gliomas.

Methods. Systematic computerised searches of PubMed and the Web of Knowledge were performed. The meta-analysis of pooled odds ratio (OR) and 95% confidence interval (CI) for preoperative seizure risk, stratified by tumour location, were calculated.

Results. Eleven studies with 2,047 patients were included for meta-analysis. For gliomas with or without frontal lobe involvement, the preoperative seizure incidence ranged from 31.7% (19/60) to 85.7% (156/182) and 19.7% (12/61) to 85.7% (12/14), respectively; the pooled OR was 1.560 (95% CI: 1.266-1.923; Z: 4.17; p=0.000). For gliomas with or without temporal lobe involvement, seizure incidence was 22.6% (7/31) to 91.7% (11/12) and 26.7% (24/90) to 78.7% (174/221), respectively; the pooled OR was 1.070 (95% CI: 0.794-1.443; Z: 0.45; p=0.656). For gliomas with or without parietal lobe involvement, seizure incidence was 18.1% (3/16) to 100.0% (3/3) and 26.7% (28/105) to 80.4% (226/281), respectively; the pooled OR was 0.770 (95% CI: 0.570-1.040; Z: 1.71; p=0.088). For gliomas with or without occipital lobe involvement, seizure incidence was 0.0% (0/2) to 100.0% (2/2) and 26.8% (30/112) to 75.7% (56/74), respectively; the pooled OR was 0.336 (95% CI: 0.164-0.686; Z: 2.99; p=0.003). For gliomas with or without insula lobe involvement, seizure incidence was 34.8% (8/23) to 72.0% (77/107) and 34.3% (60/175) to 81.3% (247/304), respectively; the pooled OR was 1.058 (95% CI: 0.765-1.463; Z: 0.34; p=0.732). No significant publication bias was found.

Conclusion. Our meta-analysis indicates that frontal lobe gliomas are related to a higher preoperative seizure incidence, while occipital lobe gliomas are related to a lower incidence.

Key words: glioma, preoperative seizure, tumor location, meta-analysis

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Seizure is a common symptom of many types of brain tumours (Rossetti and Stupp, 2010; Maschio and Dinapoli, 2012). In particular, gliomas are associated with the highest risk of preoperative seizure, with an incidence of 30-100% (Kerkhof and Vecht, 2013). Seizures in glioma patients significantly contribute to patient morbidity. A history of epileptic seizures at diagnosis was reported to be associated with increased malignant progression-free survival and overall survival (Pallud *et al.,* 2014). Seizures in patients with gliomas are also disruptive and impact on quality of life; autonomy, the capacity to operate motor vehicles, and employment opportunities (Maurice and Mason, 2014).

Some studies have investigated the factors predisposing to tumour-associated seizures. The frequency of seizures differs widely according to histopathological type. Glioneuronal tumours, such as gangliogliomas and disembryoplastic neuroepithelial tumours, are typically associated with a chronic pharmacoresistant epilepsy in up to 90-100% of patients (Prayson, 2010). The frequency of seizures decreases significantly in high-grade gliomas, with an incidence of 31% (Riva *et al*., 2006). Young age is another risk factor for preoperative seizures in patients with gliomas; seizures are much less frequent in patients ≥60 years compared with younger patients (47% vs. 85%, respectively) (Kaloshi *et al.,* 2009). Gene mutations in patients with tumour-associated seizures have also been detected, and isocitrate dehydrogenase (IDH) mutation is reported to be associated with seizures in patients with gliomas (OR 22.563; p=0.0019) (Stockhammer *et al.,* 2012; Zhong *et al.,* 2015).

Tumour location was also recognized as a factor for tumour-associated seizures in patients with gliomas. Kerkhof and Vecht (2013) found that tumour location in the temporal and insular cortex was associated with a higher risk of developing epilepsy in both neuroglial tumours and low-grade gliomas; focal seizures with or without alteration of consciousness and/or secondary generalization were common, focal seizures with altered consciousness were present in 50-70% of neuroglial tumours, and secondary generalized seizures were present in 70% of low-grade gliomas. Rudà *et al*. (2012) reported that tumours involving the frontal, temporal, and parietal lobes were more commonly associated with seizures, relative to occipital lesions; infratentorial tumours rarely cause seizures and intractable epilepsy is particularly frequent in tumours that involve the mesiotemporal and insular (paralimbic) structures. Pallud *et al*. (2014) reported that insular location (p=0.003) and tumour location close to functional areas (p=0.038) were independent predictors of uncontrolled epileptic seizures at diagnosis, and parietal (p=0.029) and insular (p=0.002) locations were independent predictors of uncontrolled epileptic seizures after oncological treatment. Some of these results, however, are controversial, and the sample sizes of these studies were small. Moreover, the literature for tumour location and tumour-associated seizures have not been reviewed systematically.

The aim of this meta-analysis was to assess the relationship between tumour location and preoperative seizure incidence in patents with gliomas.

Methods

Database and literature search

We searched PubMed and the Web of Knowledge from their inception to 15 May 2015. The search terms included: "seizure", "epilepsy", "glioma", "astrocytoma", "oligodendroglioma", "oligoastrocytoma", "isocitrate dehydrogenase", and "tumor location". The search detail in PubMed was (seizure* [title/abstract] OR "seizure" [MeSH Terms] OR epilepsy [title/abstract] OR "epilepsy" [MeSH Terms]) AND (glioma* [title/abstract] OR "glioma" [MeSH Terms] OR astrocytoma [title/abstract] OR oligodendroglioma [title/abstract] OR oligoastrocytoma [title/abstract]) AND location (Text Word). In the Web of Knowledge Databases advanced search, the search detail was used as follows: (TS=seizure* OR TS=epilepsy) AND (TS=glioma OR TS=astrocytoma OR TS=oligodendroglioma OR TS=oligoastrocytoma) AND TS=location. We supplemented our searches by manually reviewing the references of all relevant studies.

Study selection

The following inclusion criteria were fulfilled:

– a report of patients with glioma causing seizure preoperatively were selected;

– an observational study design, which included cohorts, case-control studies, and cross-sectional survey;

– a comparison of preoperative seizure incidence between lobar involvement and non-involvement;

– the assessed lobes included the frontal, temporal, parietal, occipital, and insula lobes;

– odds ratio (OR) of preoperative seizure incidence was provided, or could be calculated from the data presented in the article.

We excluded animal experiments and biological research. We also excluded case reports, case series, and reviews.

Data extraction

We used a standardized data collection form to extract the following information: first author, publication

year, study location, study design, year of enrolment, number of patients, age, sex ratio, glioma WHO grade, tumour type, preoperative seizure rate, number of patients with or without seizure and with or without lobar involvement. Data extraction was carried out independently by two reviewers and disagreements were resolved by discussion between the two.

Qualitative assessment

The quality of studies was assessed according to the Newcastle-Ottawa Scale (NOS) (Wells *et al.,* 2015). The NOS contains eight items, categorized into three dimensions including Selection (four items), Comparability (one item), and Exposure (three items). A high quality study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. The NOS ranges between zero up to nine stars.

Statistical analysis

Statistical heterogeneity was explored by $\chi 2$ and inconsistency (I^2) statistics; $p<0.05$ for $\chi 2$ or I^2 value of 50% or more represented substantial heterogeneity (Higgins and Thompson, 2002). In the absence of significant heterogeneity, studies were pooled using a fixed-effect model. If heterogeneity was observed, a random-effects model was used. Overall effects were determined using the Z test. Publication bias was evaluated using Egger's regression test and Begg's adjusted rank correlation test. Funnel plots were also generated. Two-sided $p<0.050$ was considered statistically significant. Meta-analysis was performed with Stata software, version 12.0 (Stata Corp, College Station, Texas).

Results

Eligible studies

Eleven studies (Chang *et al.,* 2008; Lee *et al.,* 2010; Huang *et al.,* 2011; Stockhammer *et al.,* 2012; You *et al.,* 2012; Yuen *et al.,* 2012; Huang *et al.,* 2014; Liubinas *et al.,* 2014; Yang *et al.,* 2014; Iuchi *et al.,* 2015; Wang *et al.,* 2015) with 2,047 patients were included for meta-analysis. The detailed steps of our literature search are shown in *figure 1*. Of the 11 studies, five were conducted in China, three in Australia, two in the USA, and the other two conducted in Japan and Germany. Three studies were prospective cohorts, and the other eight were retrospective case control studies. The tumour stages included WHO grade I to grade IV. The preoperative seizure rate was reported from 24.8% to 81.0%. The quality rating of the included studies ranged from six to eight stars on the scale of nine. *Table 1* shows the main characteristics of the 20 included studies.

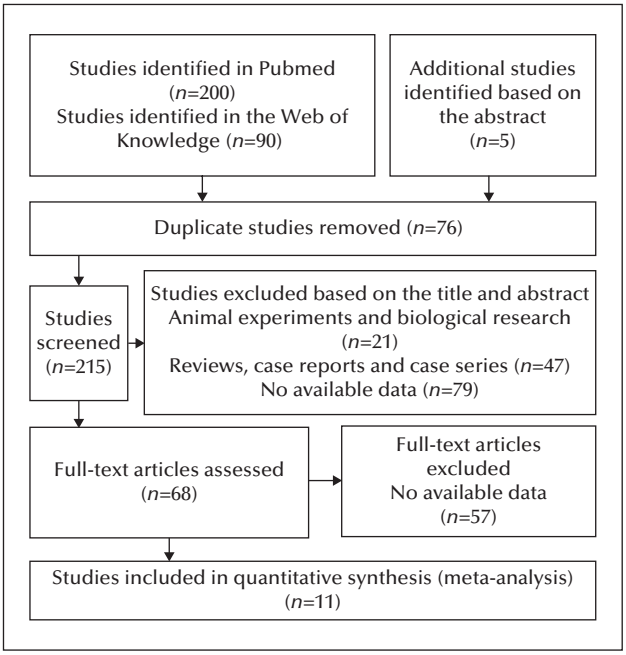

Figure 1. Flow diagram showing study selection.

Relationship between tumour location and preoperative seizure incidence

The preoperative seizure incidence in glioma patients with or without frontal lobe involvement was assessed in eight studies with nine cohorts. The incidence ranged from 31.7% to 85.7% (mean: 64.3%; 95%CI: 61.4%-67.2%) for frontal lobe gliomas, compared to 19.7% to 85.7% (mean: 52.3%; 95%CI: 48.6%-56.0%) for gliomas without frontal lobe involvement. No significant heterogeneity was found between the studies (I^2=37.9%; p=0.116). The pooled OR was 1.560 (95% CI: 1.266-1.923; Z=4.17; p=0.000) according to the fix-effects model (*figure 2A*). The Begg's test (z=0.94, p=0.348), the Egger's test (t=0.87, p=0.411), and the funnel plot (*figure 2B*) suggested there was no significant publication bias.

The preoperative seizure incidence in glioma patients with or without temporal lobe involvement was assessed in all 11 studies with 12 cohorts. The incidence ranged from 22.6% to 91.7% (mean: 59.5%; 95% CI: 55.9%-63.0%) for temporal lobe gliomas, compared to 26.7% to 78.7% (mean: 59.4%; 95% CI: 56.7%-62.2%) for gliomas without temporal lobe involvement. Significant heterogeneity was found between the studies (I^2=46.8%; p=0.037). The pooled OR was 1.070 (95% CI: 0.794-1.443; Z=0.45, p=0.656) according to the random-effects model (*figure 3A*). The Begg's test

Table 1. Basic characteristics of all included studies.

Study	Country	Study design	Enrolment years	Patient number	Patient age (year)	Gender (M/F)	Tumour type (AA/AO/ AOA/GBM)	Preope-rative seizure rate	NOS
Iuchi *et al.*, 2015	Japan	Retrospective	2006-2012	121	Mean: 58	74/47	0/22/99/0	24.8%	7
Wang *et al.*, 2015	China	Prospective	2006-2011	231	15-67	135/96	25/70/136/0	65.8%	8
Yang *et al.*, 2014	China	Retrospective	2006-2012	198	Median: 43 (18-74)	114/84	56/39/103/0	34.3%	7
Huang *et al.*, 2014	China	Retrospective	2003-2011	31	Mean: 25.6-26.1	14/17	0/31/0/0	61.3%	7
Liubinas *et al.*, 2014	Australia	Prospective	2010-2012	30	Mean 35.4 (17-70)	15/15	11/11/8/0	76.7%	7
You *et al.*, 2012	China	Retrospective	2005-2009	508	38.1 (16 -72)	306/202	229/48/231/0	68.9%	7
Yuen *et al.*, 2012	Australia	Retrospective	1996-2006	190	Mean: 45.9-57.9	105/85	13/25/27/125	38.4%	7
Yuen *et al.*, 2012	Australia	Prospective	2007-2009	100	Mean: 50.6-55.8	56/44	13/10/15/64	43.0%	7
Stockhammer *et al.*, 2012	Germany	Retrospective	NR	79	40 (13-72)	NR	79/0/0/0	72.2%	6
Huang *et al.*, 2011	China	Retrospective	2006-2008	103	Mean: 39.4 (17-65)	60/43	41/35/27/0	68.9%	6
Lee *et al.*, 2010	USA	Retrospective	2005-2007	124	18-88	61/63	23/28/24/49	49.2%	7
Chang *et al.*, 2008	USA	Retrospective	1997-2003	332	39.3 (16–95)	194/138	129/95/109/0	81.0%	7

AA: anaplastic astrocytoma; AO: anaplastic oligodendroglioma; AOA: anaplastic oligoastrocytoma; GBM: glioblastoma multiforme; NOS: Newcastle-Ottawa Scale; NR: not reported.

(z=0.89; p=0.373), the Egger's test (t=1.19, p=0.260), and the funnel plot (*figure 3B*) suggested there was no significant publication bias.

The preoperative seizure incidence in glioma patients with or without parietal lobe involvement was assessed in eight studies with nine cohorts. The incidence ranged from 18.1% to 100.0% (mean: 54.4%; 95%CI: 47.8%-60.8%) for parietal lobe gliomas, compared to 26.7% to 80.0% (mean: 60.4%; 95% CI: 57.9%-62.8%) for gliomas without parietal lobe involvement. No significant heterogeneity was found between the studies (I^2=0.0%; p=0.609). The pooled OR was 0.770 (95% CI: 0.570-1.040; Z=1.71; p=0.088) according to the fix-effects model (*figure 4A*). The Begg's test (z=0.10; p=1.000), the Egger's test (t=0.27; p=0.795), and the funnel plot (*figure 4B*) suggested there was no significant publication bias.

The preoperative seizure incidence in glioma patients with or without occipital lobe involvement was assessed in seven studies with eight cohorts. The incidence ranged from 0.0% to 100.0% (mean: 22.0%; 95% CI: 11.5%-36.0%) for occipital lobe gliomas, compared to 26.8% to 75.7% (mean: 48.5%; 95% CI: 45.2%-51.8%) for gliomas without occipital lobe involvement. No significant heterogeneity was found between the studies (I^2=0.0%; p=0.601). The pooled OR was 0.336 (95% CI: 0.164-0.686; Z=2.99; p=0.003) according to the fix-effects model (*figure 5A*). The Begg's test (z=0.60; p=0.548), the Egger's test (t=0.54; p=0.612), and the funnel plot (*figure 5B*) suggested there was no significant publication bias.

The preoperative seizure incidence in glioma patients with or without insula lobe involvement was assessed in five studies with five cohorts. The incidence ranged from 34.8% to 72.0% (mean: 68.2%; 95% CI: 62.4%-73.8%) for insula lobe gliomas, compared to 34.3% to 81.3% (mean: 66.0%; 95% CI: 63.1%-68.8%) for gliomas without insula lobe involvement.

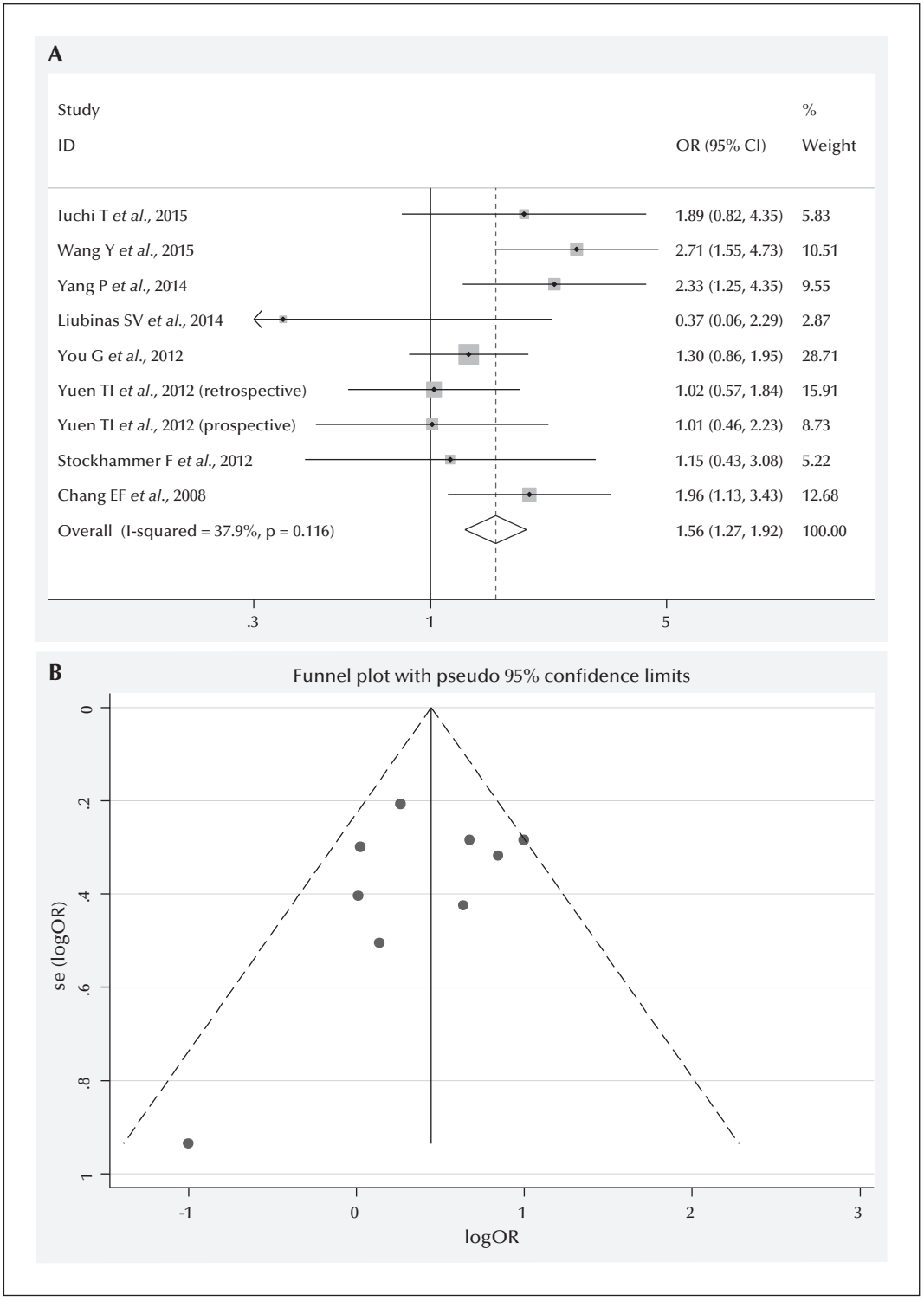

Figure 2. Frontal lobe gliomas and preoperative seizure incidence. (A) Forest plot demonstrating a higher preoperative seizure incidence for frontal lobe gliomas compared to gliomas without frontal lobe involvement; (B) funnel plot suggested no publication bias.

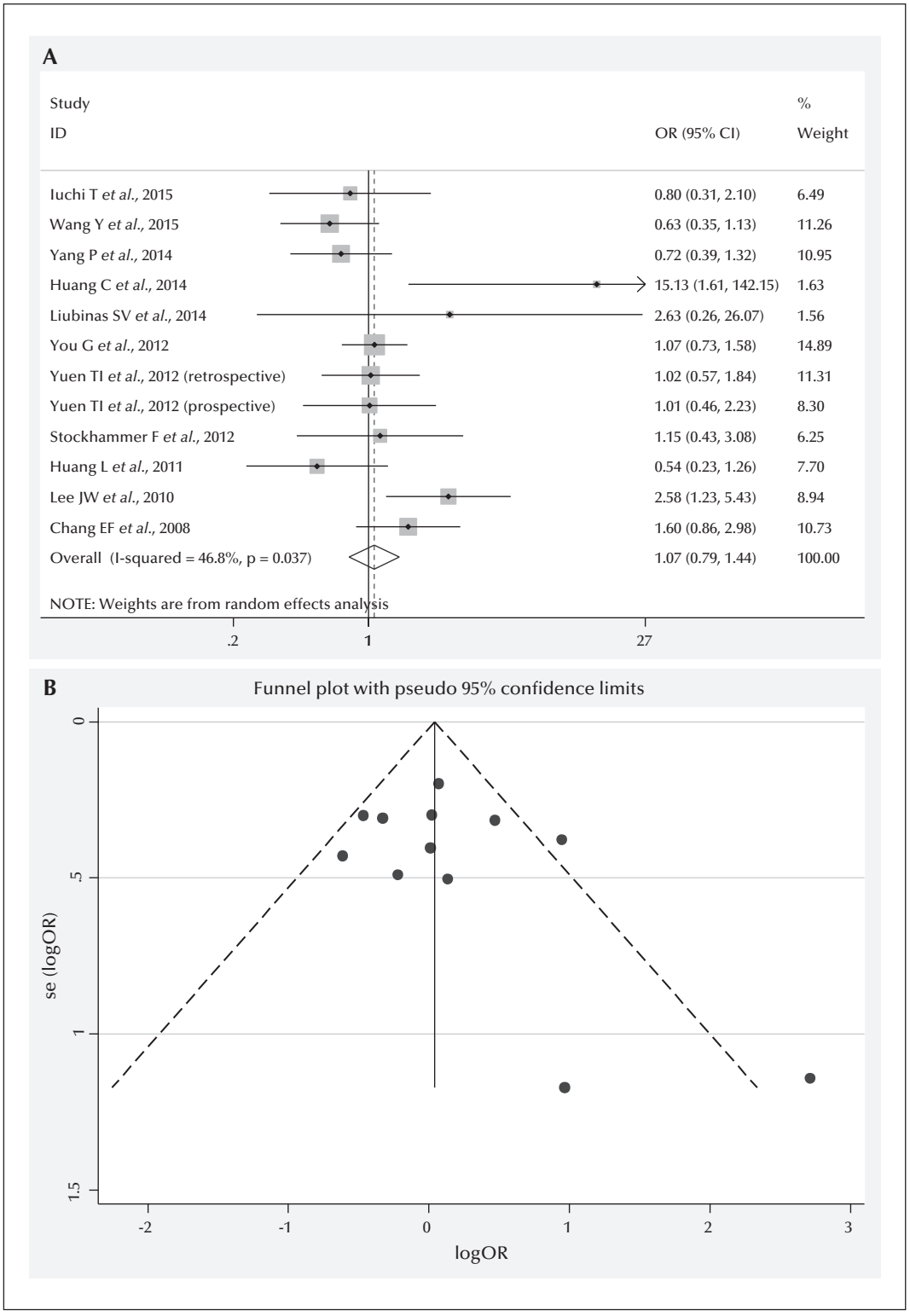

Figure 3. Temporal lobe gliomas and preoperative seizure incidence. (A) Forest plot demonstrating no significant difference in preoperative seizure incidence between gliomas with and without temporal lobe involvement; (B) funnel plot suggested no publication bias.

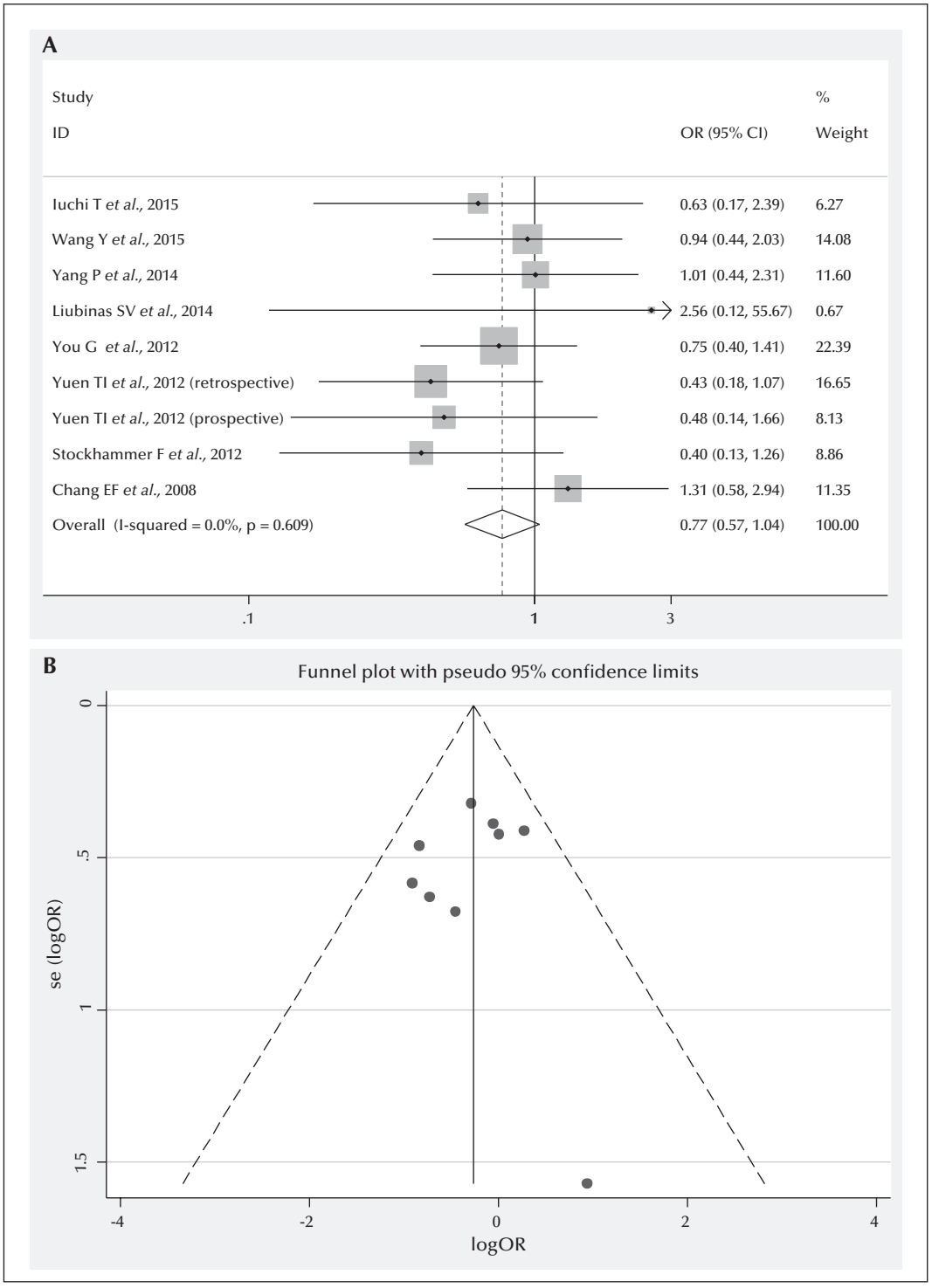

Figure 4. Parietal lobe gliomas and preoperative seizure incidence. (A) Forest plot demonstrating no significant difference in preoperative seizure incidence between gliomas with and without parietal lobe involvement; (B) funnel plot suggested no publication bias.

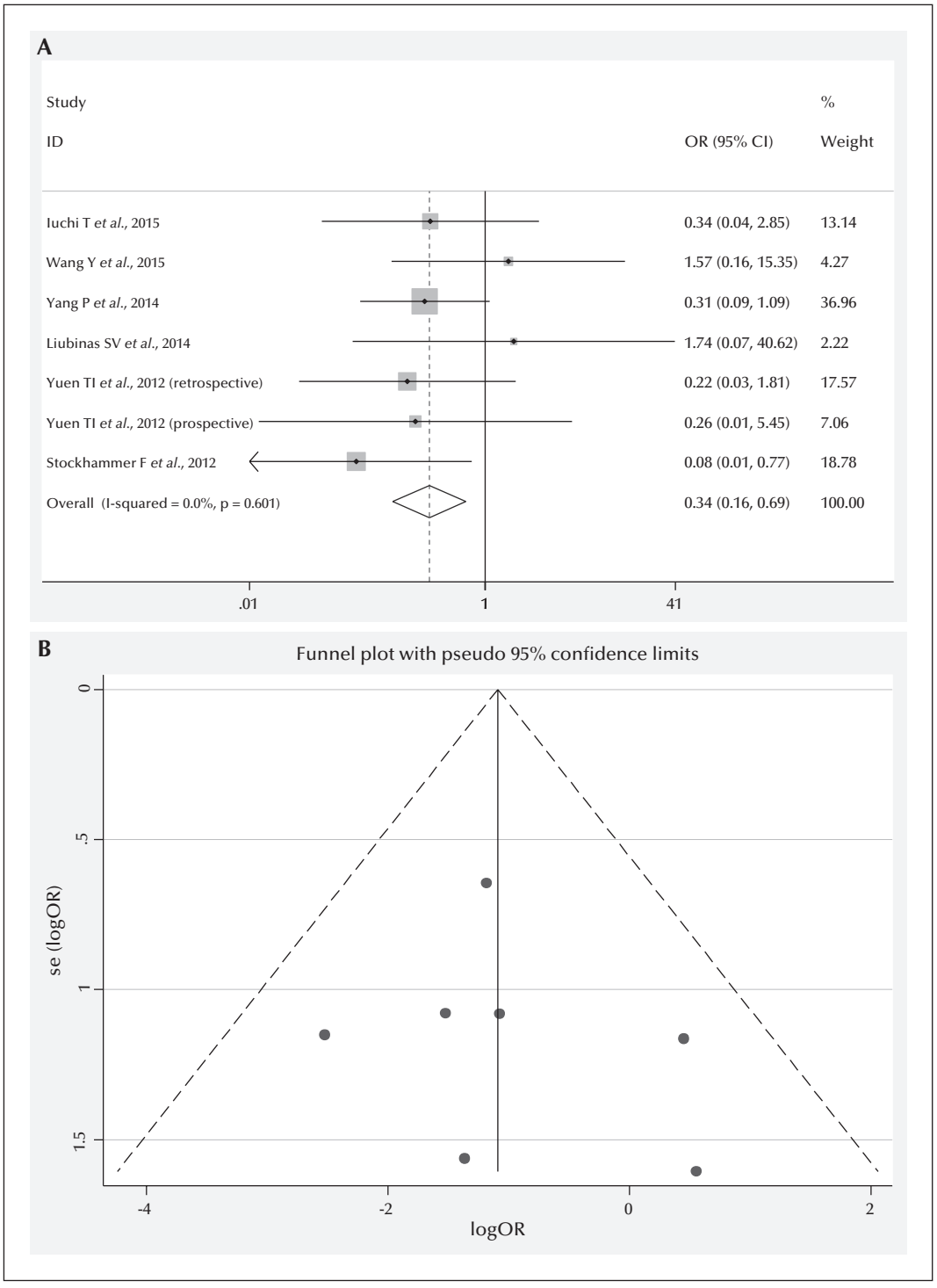

Figure 5. Occipital lobe gliomas and preoperative seizure incidence. (A) Forest plot demonstrating a lower preoperative seizure incidence for occipital lobe gliomas compared to gliomas without occipital lobe involvement; (B) funnel plot suggested no publication bias.

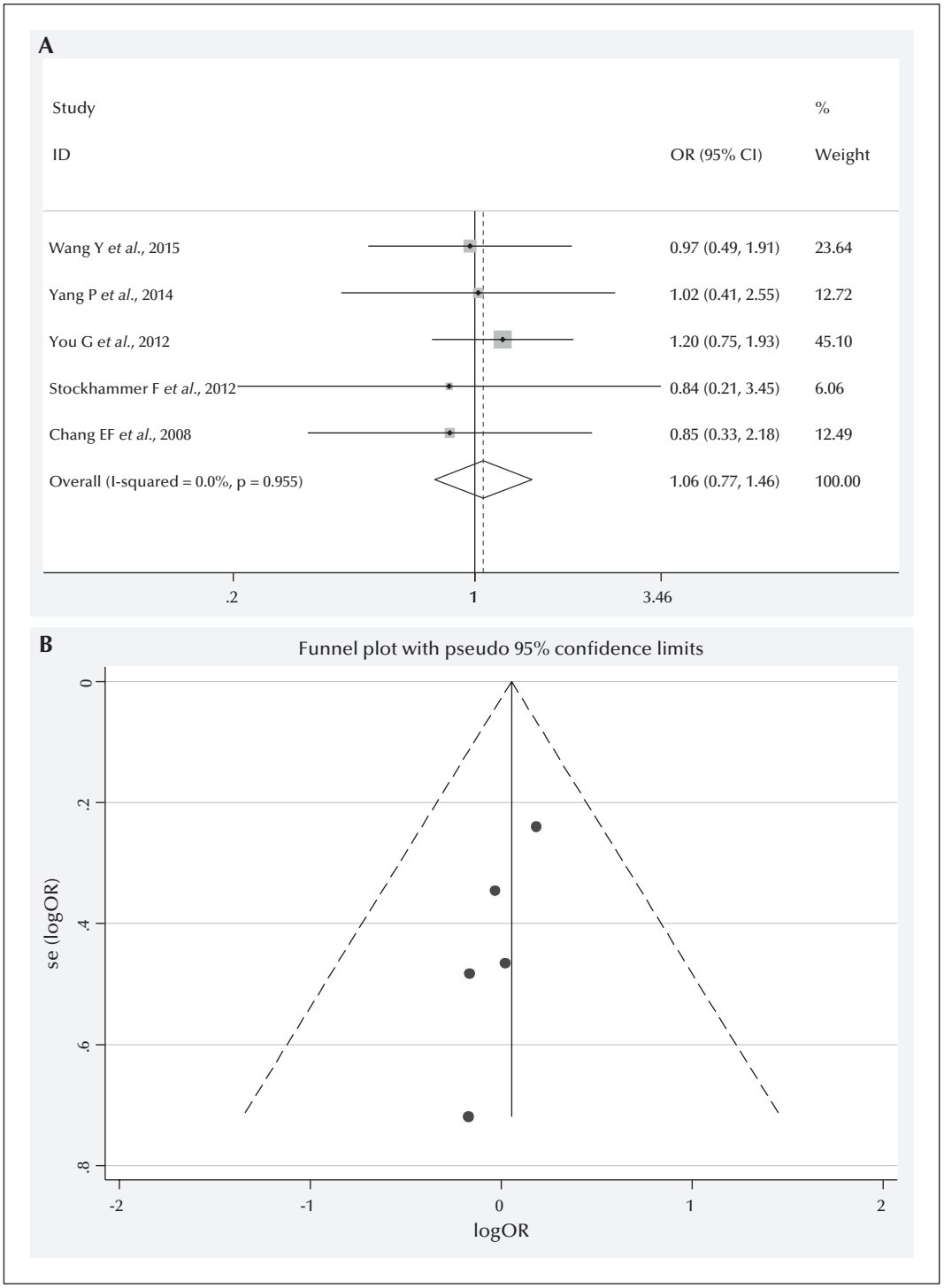

Figure 6. Insula lobe gliomas and preoperative seizure incidence. (A) Forest plot demonstrating no significant difference in preoperative seizure incidence between gliomas with and without insula lobe involvement; (B) funnel plot suggested no publication bias.

Table 2. Preoperative seizure incidence in patients with gliomas, relative to tumour location.

Study	Frontal lobe		Temporal lobe		Parietal lobe		Occipital lobe		Insula lobe	
	Involved	Not involved	Involved	Not involved	Involved	Not involved	Involved	Not involved	Involved	Not involved
Iuchi *et al.*, 2015	31.7% (19/60)	19.7% (12/61)	22.6% (7/31)	26.7% (24/90)	18.8% (3/16)	26.7% (28/105)	11.1% (1/9)	26.8% (30/112)	NR	NR
Wang *et al.*, 2015	73.5% (108/147)	50.6% (44/87)	58.2% (39/67)	68.9% (113/164)	64.7% (22/34)	66.0% (130/197)	75.0% (3/4)	65.6% (149/227)	65.2% (30/46)	65.9% (122/185)
Yang *et al.*, 2014	42.1% (48/114)	23.8% (20/84)	30.0% (24/80)	37.3% (44/118)	34.5% (10/29)	34.3% (58/169)	15.0% (3/20)	36.5% (65/178)	34.8% (8/23)	34.3% (60/175)
Huang *et al.*, 2014	NR	NR	91.7% (11/12)	42.1% (8/19)	NR	NR	NR	NR	NR	NR
Liubinas *et al.*, 2014	68.8% (11/16)	85.7% (12/14)	87.5% (7/8)	72.7% (16/22)	100.0% (3/3)	74.1% (20/27)	100.0% (2/2)	75.0% (21/28)	NR	NR
You *et al.*, 2012	70.6% (254/360)	64.9% (96/148)	69.8% (132/189)	68.3% (218/319)	63.0% (29/46)	69.5% (321/462)	NR	NR	72.0% (77/107)	68.1% (273/401)
Yuen *et al.*, 2012 (retrospective)	38.7% (36/93)	38.1% (37/97)	49.2% (29/59)	31.2% (44/141)	23.3% (7/30)	41.3% (66/160)	12.5% (1/8)	39.6% (72/182)	NR	NR
Yuen *et al.*, 2012 (prospective)	43.1% (22/51)	42.9% (21/49)	51.5% (17/33)	38.8% (26/67)	28.6% (4/14)	45.3% (39/86)	0.0% (0/2)	43.9% (43/98)	NR	NR
Stockhammer *et al.*, 2012	73.3% (33/45)	70.6% (24/34)	82.8% (24/29)	66.0% (33/50)	56.3% (9/16)	76.2% (48/63)	20.0% (1/5)	75.7% (56/74)	71.6% (48/67)	75.0% (9/12)
Huang *et al.*, 2011	NR	NR	61.4% (27/44)	74.6% (44/59)	NR	NR	NR	NR	NR	NR
Lee *et al.*, 2010	NR	NR	63.3% (31/49)	40.0% (30/75)	NR	NR	NR	NR	NR	NR
Chang *et al.*, 2008	85.7% (156/182)	75.3% (113/150)	85.6% (95/111)	78.7% (174/221)	84.3% (43/51)	80.4% (226/281)	NR	NR	78.6% (22/28)	81.3% (247/304)

NR: not reported

No significant heterogeneity was found between the studies (I^2=0.0%; p=0.955). The pooled OR was 1.058 (95% CI: 0.765-1.463; Z=0.34; p=0.732) according to the fix-effects model (*figure 6A*). The Begg's test (z=1.22; p=0.221), the Egger's test (t=2.92; p=0.061), and the funnel plot (*figure 6B*) suggested there was no significant publication bias. Data is summarised in *table 2*.

Figure 7 shows the relationship between tumour location and preoperative seizure incidence in patients with gliomas. The results show that, relative to other lobes, frontal lobe gliomas were associated with a higher preoperative seizure incidence and occipital lobe gliomas were associated with a lower preoperative seizure incidence, while no difference in preoperative seizure incidence was identified for gliomas with or without temporal, parietal, or insula lobe involvement.

Discussion

Based on our study, we have identified that frontal lobe gliomas were associated with higher preoperative seizure incidence, with a pooled OR of 1.560 (95% CI: 1.266-1.923), while occipital lobe gliomas were associated with lower preoperative seizure incidence, with a pooled OR of 0.336 (95% CI: 0.164-0.686), relative to the other lobes investigated. Although tumour location appears to be related to preoperative seizure incidence in patents with gliomas, the mechanism is still not understood.

Glutamate is the main excitatory neurotransmitter in the central nervous system, and a change in glutamate release is documented in gliomas (de Groot and Sontheimer, 2011). Musazzi *et al.* (2015) reported that behavioural stress induces functional and structural

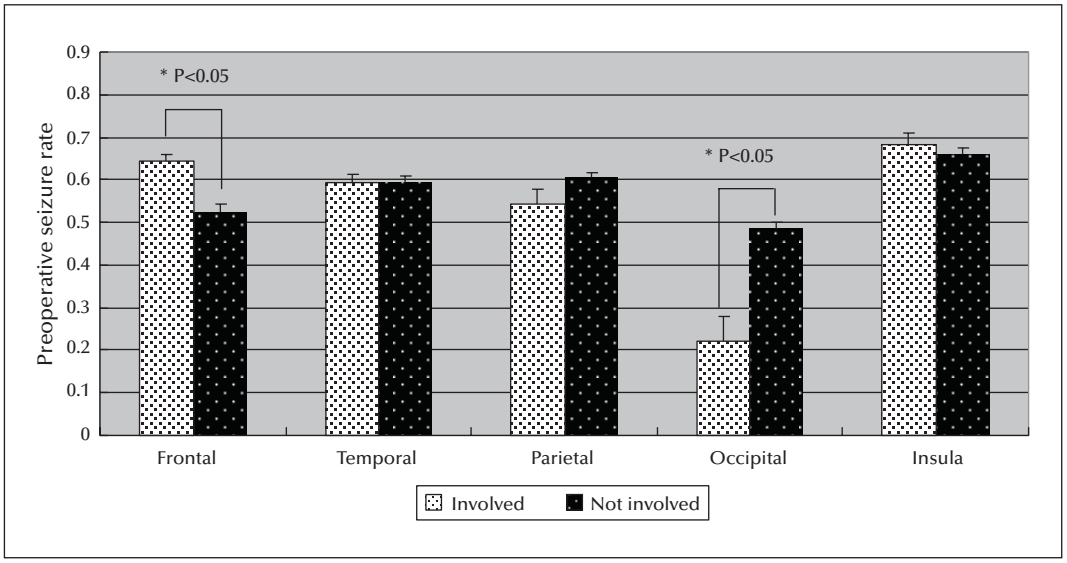

Figure 7. Tumour location and preoperative seizure incidence in patients with gliomas.

remodelling of glutamate synapses in prefrontal and frontal cortex. Jamal *et al*. (2015) also found that aldehyde dehydrogenase 2 deficiency increases resting-state glutamate and expression of the GluN1 subunit of N-methyl-D-aspartate receptor in the frontal cortex of mice. Change in glutamate concentration often occurs in the occipital lobe. This may be a possible mechanism.

A previous meta-analysis showed no statistical benefit of seizure prophylaxis with antiepileptic drugs in patients with brain tumours (Sirven *et al*., 2004). However, in our study, we found higher preoperative seizure incidence associated with frontal lobe gliomas. Treatment for frontal lobe gliomas may therefore be an appropriate option for seizure prophylaxis, however, future studies are needed to confirm our hypothesis.

There are some limitations in this meta-analysis. First, most of the included studies were retrospective case control studies. This therefore may have led to bias. Second, the included studies did not provide sufficient information for subgroup analysis by patient age, type of seizure, tumour histopathological subtype (astrocytomas, oligodendrogliomas or oligoastrocytomas), or gene status. These limitations should be considered when evaluating the conclusions.

Our meta-analysis indicates that frontal lobe gliomas are related to higher preoperative seizure incidence, while occipital lobe gliomas are related to lower incidence. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) In patients with glioma, the involvement of which lobe is associated with the highest preoperative seizure incidence?

(2) In patients with glioma, the involvement of which lobe is associated with the lowest preoperative seizure incidence?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".