

# Relationship between tumour location and preoperative seizure incidence depends on glioma grade of malignancy

## To the Editor,

We enjoyed reading the recent paper by Su *et al.* (2014), published in the previous edition of *Epileptic Disorders*, entitled "Relationship between tumour location and preoperative seizure incidence in patients with gliomas: a systematic review and meta-analysis". The authors are to be congratulated for this informative meta-analysis, which confirms the notion that tumour location has an impact on the incidence of epileptic seizures in patients with gliomas.

First, before performing their meta-analysis to assess the risk of epileptic seizures in relation to glioma location using a lobar-based approach, the authors reported in the introduction that glioma-related seizure incidence varies relative to the World Health Organisation (WHO) grade of malignancy (from 60-100% for grade II, 50-60% for grade III, and 25-50% for grade IV gliomas) (Pallud *et al.*, 2010), as well as to mutation of the gene encoding isocitrate dehydrogenase. However, we question why the authors did not stratify their analysis according to the WHO grade of malignancy (available in all included studies) or isocitrate dehydrogenase mutation status (if available in the included studies). This should be done to ensure that these confounders did not impact the results, as both the WHO grade of malignancy and isocitrate dehydrogenase mutation status vary with tumour location (Duffau and Capelle, 2004; Metellus *et al.*, 2010; Sonoda *et al.*, 2015). For example, glioblastomas are reported more frequently in the parieto-temporo-occipital junction which may account for a lower seizure incidence in occipital lobe gliomas (odds ratio [OR]: 0.336) and parietal lobe gliomas (OR: 0.770), and low-grade gliomas are reported more frequently in frontal and insular lobes which may account for a higher seizure incidence in frontal lobe gliomas (OR: 1.560), as observed in this meta-analysis (Duffau and Capelle, 2004; Su *et al.*, 2015). This is a main limitation of this important study and the authors are encouraged to pursue their analyses using this complimentary approach.

Second, a recent report from our group in which the required inclusion criteria were fulfilled (published in English, observational study of 1,509 adults patients harbouring a WHO grade II glioma, available preoperative seizure status, available seizure status

by lobe involvement, and available OR of preoperative seizure incidence by lobe involvement) was not incorporated into this meta-analysis (Pallud *et al.*, 2014). This report represents the largest series ever published regarding epileptic seizures in patients with WHO grade II gliomas, forming about 75% of the patients studied in the present meta-analysis. These previous results appear to be contradictory to those of Su *et al.* (2015), possibly due to inclusion criteria restricted to WHO grade II gliomas, thus avoiding a "glioma grade" bias effect, which is possible. To help the readers get a better idea of the contribution of the above discussed parameters, we strongly encourage the authors to add the results of our previous study to the present meta-analysis together with a glioma grade stratification, in order to refine and strengthen their conclusions.

Last, it is not clear how many studies were finally included in the meta-analysis as 11 studies are presented in the tables whereas 20 studies were eligible according to the results.

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## Reply

### An updated meta-analysis of the relationship between tumour location and preoperative seizure incidence in patients with gliomas

In response to our report entitled "Relationship between tumour location and preoperative seizure incidence in patients with gliomas: a systematic review and meta-analysis" (Su *et al.*, 2015), J. Pallud, A. Roux, and M. Zanella note that a recent publication in *Brain* (Pallud *et al.*, 2014), in which the required inclusion criteria were fulfilled, was absent from our meta-analysis. We have reassessed this most informative report and found that it fulfils our inclusion criteria for meta-analysis. We have therefore added this report to our study and updated our meta-analysis accordingly.

Having combined this report, 12 studies with 3,556 patients were included for meta-analysis. Frontal involvement and preoperative seizure incidence was assessed in nine studies with 10 cohorts. The incidence ranged from 31.7-87.6% (mean: 74.0%; 95% CI: 71.9-76.0%) for the group with frontal involvement, compared to 19.7-92.1% (mean: 72.6%; 95% CI: 70.2-74.9%) in the group without frontal involvement. Significant heterogeneity was found between the studies ( $I^2=73.8\%$ ;  $p=0.000$ ). The pooled OR was 1.33 (95% CI: 0.91-1.95) according to the random-effects model (figure 1A). The funnel plot (figure 1B) suggested that there was no significant publication bias.

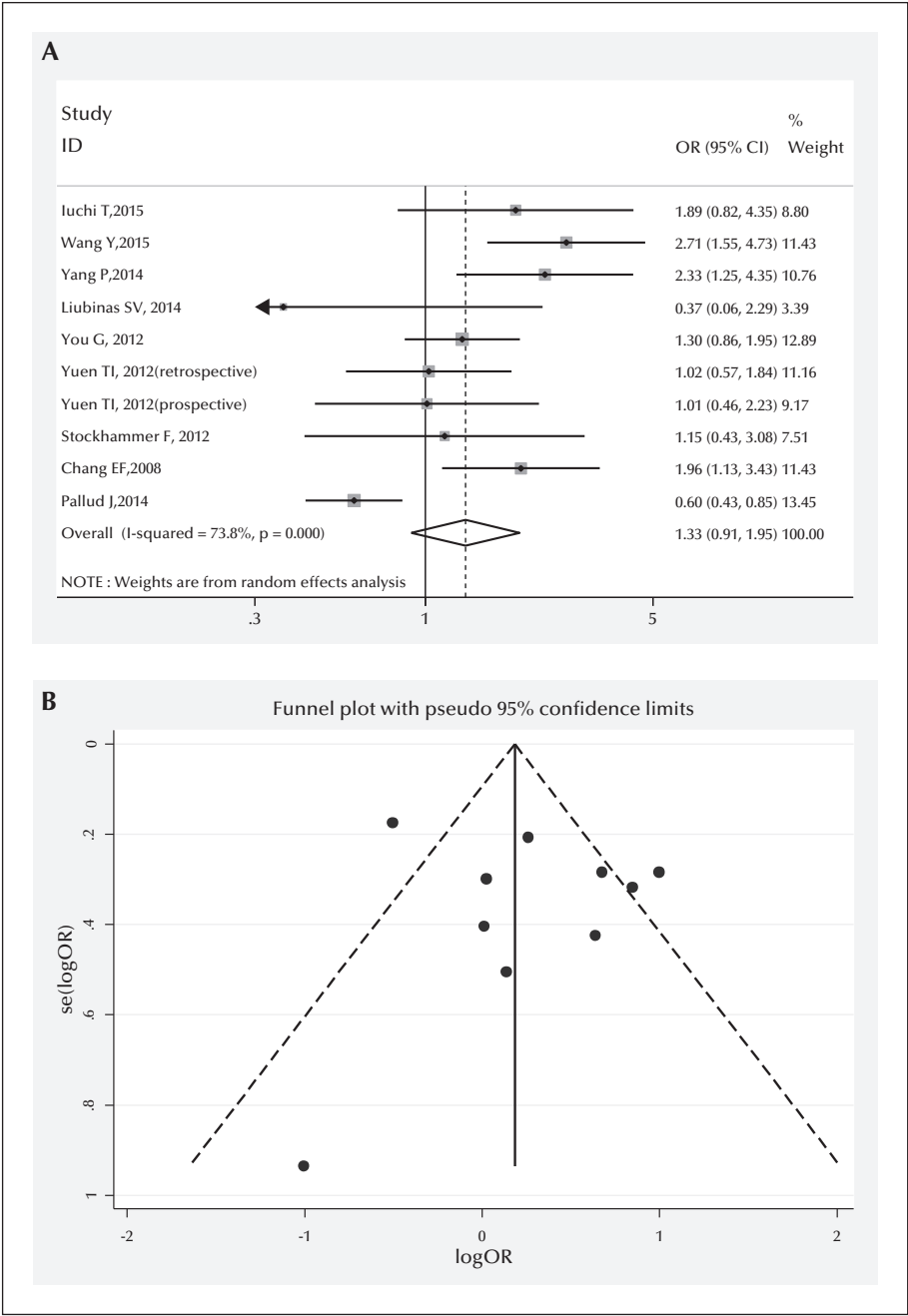
Temporal involvement and preoperative seizure incidence was assessed in all 12 studies with 13 cohorts. The incidence ranged from 22.6-91.7% (mean: 67.8%; 95% CI: 64.9-70.0%) in the group with temporal involvement, compared to 26.7-89.5% (mean: 74.3%; 95% CI: 72.5-76.0%) in the group without temporal involvement. Significant heterogeneity was found between the studies ( $I^2=43.7\%$ ;  $p=0.046$ ). The pooled OR was 1.09 (95% CI: 0.84-1.42) according to the random-effects model (supplementary figure 1A). The funnel plot (supplementary figure 1B) suggested that there was no significant publication bias. Parietal involvement and preoperative seizure incidence was assessed in nine studies with 10 cohorts. The incidence ranged from 18.1-100.0% (mean: 69.0%; 95% CI: 64.1-73.6%) in the group with parietal involvement, compared to 26.7-89.5% (mean: 74.0%; 95% CI: 72.4-75.6%)

in the group without parietal involvement. No significant heterogeneity was found between the studies ( $I^2=16.5\%$ ;  $p=0.291$ ). The pooled OR was 0.90 (95% CI: 0.69-1.18) according to the fix-effects model (supplementary figure 2A). The funnel plot (supplementary figure 2B) suggested that there was no significant publication bias. No data were updated for preoperative seizure incidence in the occipital group; the pooled OR remained at 0.336 (95% CI: 0.164-0.686). Insula involvement and preoperative seizure incidence was assessed in six studies. The incidence ranged from 34.8-92.5% (mean: 79.7%; 95% CI: 75.9-83.1%) in the group with insula involvement, compared to 34.3-89.4% (mean: 78.6%; 95% CI: 76.9-80.3%) in the group without insula involvement. No significant heterogeneity was found between the studies ( $I^2=0.0\%$ ;  $p=0.870$ ). The pooled OR was 1.17 (95% CI: 0.89-1.54) according to the fix-effects model (supplementary figure 3A). The funnel plot (supplementary figure 3B) suggested that there was no significant publication bias. According to these results, we conclude that glioma involvement in the occipital group relates to a lower preoperative seizure incidence. Since the preoperative seizure incidence of included studies was highly variable, these results should be confirmed in prospective studies.

J. Pallud, A. Roux, and M. Zanella also note that we did not stratify our meta-analysis according to either the WHO grade of malignancy or isocitrate dehydrogenase mutation status. We are grateful to J. Pallud and colleagues for this insightful remark. Stratified analysis or subgroup analysis could be performed to identify whether these confounders impact the results and might also be used to identify the source of heterogeneity which was significant between the studies in our meta-analysis. However, we could not conduct the stratified analysis according to the WHO grade of malignancy; even if the WHO grade of malignancy was available in all included studies, we still could not have collected enough information to conduct the stratified meta-analysis. Data on isocitrate dehydrogenase mutation status was similarly insufficient. This is a limitation of our meta-analysis which was mentioned in the report.

Third, J. Pallud and colleagues note that although 11 studies were presented in the tables, 20 studies were eligible according to the results. This is an error in the report; 12 studies were in fact eligible. We apologise for this misunderstanding.

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**Figure 1.** Relationship between frontal lobe involvement and preoperative seizure incidence. (A) Forest plot showing that parietal lobe involvement was not related to preoperative seizure; (B) funnel plot suggesting no publication bias.

**Supplementary data.**  
Supplementary figures are available on the [www.epilepticdisorders.com](http://www.epilepticdisorders.com) website.

**References**

Su X, Chen HL, Wang ZY, Lan Q. Relationship between tumour location and preoperative seizure incidence

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