Neurosurgical Forum LETTERS TO THE EDITOR

The T2-FLAIR–mismatch sign

TO THE EDITOR: I read with great interest the article by Goyal et al.¹ (Goyal A, Yolcu YU, Goyal A, et al. The T2-FLAIR–mismatch sign as an imaging biomarker for *IDH* and 1p/19q status in diffuse low-grade gliomas: a systematic review with a Bayesian approach to evaluation of diagnostic test performance. *Neurosurg Focus*. 2019;47(6):E13).

The authors made a good attempt at highlighting an imaging feature “T2-FLAIR–mismatch sign” described by Patel et al.² in diagnosing *IDH* mutation and 1p/19q non-codeleted gliomas (*IDH* mutant astrocytomas).

However, I was surprised by a number of inaccuracies in this manuscript that potentially seriously undermine the impact of a reputable journal such as *Neurosurgical Focus* and also have the potential to mislead future publications on this topic if not corrected. One of the most glaring mistakes is citing a wrong reference for the T2-FLAIR–mismatch sign. This sign was first published by Patel et al.² (reference 24 from the publication in question) and later validated by Broen et al.³ (reference 4 from the publication in question). When the authors described the sign in the second paragraph of the introduction, they wrongly cited the validation study as the original publication.

Another error by the authors is in the legend for Fig. 1, which mentions a WHO grade III anaplastic astrocytoma with *IDHmut-Codel*. Astrocytomas in general and also the gliomas that show T2-FLAIR–mismatch sign are *IDHmut-Noncodel* gliomas.

The *Conclusions* section of the abstract is incorrectly worded. The T2-FLAIR–mismatch sign is not an “insensitive” marker as the authors mentioned; rather, its sensitivity is low for predicting *IDHmut-Noncodel* gliomas.

I also have doubts about the methodology mentioned in Fig. 2. The authors mention 56 studies assessed for eligibility of T2-FLAIR–mismatch sign and 52 that were excluded due to various reasons. I think this is highly inaccurate due to the fact that as of 1/23/2020 the Google citation index of the original² publication is 54. So, how could they have assessed 56 studies for T2-FLAIR–mismatch sign when they actually did the study and database search, with the *Neurosurgical Focus* publication in December 2019?

The *Conclusions* section of the main text again is not worded correctly. The authors mention that the mismatch

sign is highly specific for *IDH* mutation but not 1p/19q codeletion. The original *Clinical Cancer Research* publication and validation studies showed that this sign is highly specific for *IDH* mutated and non-codeleted gliomas.

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References

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2. Patel SH, Poisson LM, Brat DJ, et al. T2-FLAIR mismatch, an imaging biomarker for *IDH* and 1p/19q status in lower-grade gliomas: a TCGA/TCIA project. *Clin Cancer Res*. 2017;23(20):6078–6085.
3. Broen MPG, Smits M, Wijnenga MMJ, et al. The T2-FLAIR mismatch sign as an imaging marker for non-enhancing *IDH*-mutant, 1p/19q-intact lower-grade glioma: a validation study. *Neuro Oncol*. 2018;20(10):1393–1399.

Disclosures

The author reports no conflict of interest.

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INCLUDE WHEN CITING

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Response

We would like to thank Dr. Jain for the comment on our article in *Neurosurgical Focus*. We have read the letter to the editor and would like to offer a response to the concerns raised. Please note point-by-point responses below to each of the comments.

First, the author mentioned the original publication that first described the T2-FLAIR–mismatch sign. We would like to clarify that the reference was not made with the intention of describing the validation study as the “original” publication in the introduction section of our manuscript. We were merely citing a reference for the sign itself; we did not intend to show who demonstrated the sign first.

Second, the MR images shown as an example in the paper do not have an incorrect legend. Our intention was

to demonstrate the sign to our readers, and the patient in question did have an *IDHmut-Codel* tumor. It is entirely possible for a patient with a positive sign to have a 1p/19q codeleted or non-codeleted tumor. We demonstrate that a positive T2-FLAIR sign is highly specific for *IDH* mutation and *IDHmut-Noncodel* molecular profile, but at the same time there are significant exceptions to this rule. We have issued an erratum amending our conclusions in both the abstract and text to reflect these findings and avoid confusion for the reader.

Third, the author raised concerns about the total number of full-text articles reviewed for potential inclusion. The data about citation index and the number of articles reviewed are irrelevant to the question. In a systematic review, all titles that are retrieved following an electronic search are screened for full-text review. In our article screening (for 860 titles/abstracts), which was performed by 2 authors separately, we determined that there were 56 titles that demanded further attention. Erring on the side of caution, there may have been a tendency toward overinclusion—with the goal in mind to not miss a potential article. It is possible that the 2 additional articles we reviewed following title and abstract screening may not actually have needed to be reviewed from the perspective of a different reviewer. This is not an error and does not bear any impact on the total number of articles included in the end or the analysis and findings of the paper.

Fourth, the conclusions mentioned in our manuscript are in alignment with the findings of the paper. For the author, the sign may have “low sensitivity” as opposed to being “insensitive.” We do not intend to argue semantics but would like to direct attention to the findings of the analysis. We found 29.9% and 33.7% sensitivity of a positive T2-FLAIR–mismatch sign to predict *IDHmut-Codel* and *IDHmut-Noncodel* molecular profile. From our perspective, this is arguably very low sensitivity. Although the sign is highly specific for *IDH* mutation and *IDHmut-Noncodel* profile, there are significant exceptions to this rule and we have added an erratum to change our concluding statement so it is less confusing to the reader. As demonstrated in our findings, it is possible for tumors with a positive sign to still be negative for the *IDHmut-Noncodel* molecular profile, either due to absence of an *IDH* mutation or due to presence of a 1p/19q codeletion.

Finally, we would like to thank the author for the interest in our article.

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