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


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Reply

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We greatly appreciate Dr. Stummer’s and Dr. Thomas’s interest in our study and their important comments [1]. Due to their pioneering work in the field of the application of 5-aminolevulinic acid (5-ALA) in brain tumor surgery [2–4], it is a special honor that we added “an important contribution to the field” according to the authors’ opinion.

We congratulate Jaber et al. [5] on conducting the first systematical single center study in a large patient cohort and again pioneering work in this field investigating the prognostic value of 5-ALA in World Health Organization (WHO) grade II gliomas. As stated in our manuscript [6] and the comment, we performed “the first study [. . .] in two specialized independent centers”. As also stated in our manuscript, “We were able to confirm [. . .] the findings of the recent study conducted by Jaber et al.” [5]. Therefore, the results of our current independent study conducted at two specialized centers confirm and thus highlight the importance of visible intraoperative 5-ALA fluorescence as a prognostic factor in pure WHO grade II gliomas as first shown in the single center study by Jaber et al. [5].

We also thank the authors for the effort of summarizing and comparing the results of both studies [5,6]. Indeed, the number of isocitrate dehydrogenase (IDH) wildtype low-grade gliomas (LGG) was lower in our cohort ($n = 5$) compared to the study of Jaber et al. [5]. However, the exact number of IDH wildtype LGG included in this study by Jaber et al. is not fully clear for us. According to Table 1 of your comment, 46 IDH mutated gliomas were included; i.e., 28 IDH wildtype gliomas should be expected in this cohort accordingly. Interestingly, according to the Results section, including Table 2 of the original publication of Jaber et al. [5], only 16 IDH wildtype gliomas were indicated. Nevertheless, a higher portion of IDH wildtype gliomas were analyzed in the study by Jaber et al. [5] compared to our study [6]. Due to the low number of IDH wildtype gliomas in our cohort

($n = 5$), the statistical power of a multivariate survival analysis was thus too low. Since we were not able to perform a multivariate analysis, we cannot compare our results based on univariate analysis with the findings of the multivariate analysis of Jaber et al. [5], which identified IDH mutational status and fluorescence as independent prognostic factors for survival. Ideally, future studies including multiple centers with a high number of IDH wildtype LGG would be desirable to finally clarify the precise relationship between 5-ALA fluorescence and molecular markers in LGG, such as IDH status.

We fully agree with the authors of the comment that visible intraoperative 5-ALA fluorescence is an unfavorable prognostic factor in pure LGG according to the data of both studies, and thus we also agree with the comment that early initiation of radio- and chemotherapy should be considered in these patients.

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