Author's response to reviews

Title: Retrospective analysis of 104 histologically proven adult brainstem gliomas: clinical symptoms, therapeutic approaches and prognostic factors

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Version: 2
Date: 8 December 2013

Author's response to reviews: see over
Submission of the revised manuscript MS: 4028292891016609
Retrospective analysis of 104 histologically proven adult brainstem gliomas: clinical symptoms, therapeutic approaches and prognostic factors

Dear Doctor Dr Steinmann,

thank you very much for the possibility to submit a revision of our manuscript “Retrospective analysis of 104 histologically proven adult brainstem gliomas: clinical symptoms, therapeutic approaches and prognostic factors.”

The study was approved by the local ethic committees of the participating centres and I have incorporated this in the manuscript on page 4, line 17-18.

With best regards

Thomas Reithmeier
Response for Maximilian Ruge

Thank you very much for your important remarks. We integrated them into the revised manuscript and below you will find our point-to-point answers to your concerns.

Major:

1.) The authors state that 104 patients with brainstem gliomas were included. How many suspected brainstem gliomas on preoperative imaging showed a different histology on stereotactic biopsy (e.g. metastasis, lymphoma, inflammatory diseases etc.). This information would be important.

As the inclusion criteria was histopathological diagnosis of a glioma we do not have the information how many suspected gliomas on preoperative imaging showed a different histology on stereotactic biopsy. Therefore we have provided the information how often another diagnoses than a glioma was diagnosed by preoperative imaging, how often a glioma was diagnosed and described the main radiological differential diagnoses (page 7, line 8-12).

2.) In the Method section the authors state that “the tumor was defined as a brain stem glioma when more than 50% of the tumor involved the brainstem and a histological diagnosis of a glioma was available”. This inclusion criteria is odd and deserves clarification. Brainstem involvement of >50% is usually applied for "diffuse brainstem gliomas", whereas tumors involving <50% of the brainstem are usually defined as "focal brainstem gliomas" [1,2].


We specified the definition of brainstem gliomas in the „patient and data collection“ section on page 4, line 10-12 according to the definition of Donaldson. Our broader definition of brainstem gliomas included diffuse as well as focal brainstem gliomas. A further subdivision within our patient population was not performed within this study.

3.) Although the authors mention a meta-analysis on 293 brainstem biopsies by Samadani et al. they essentially missed to discuss a very recently published meta-analysis on 1480 brainstem biopsies by Kickingeder et al. [1].


We incorporated and discussed the data of Kickingeder in the discussion section on page 14, line 1-4.
4.) The authors refer to a study by Kesari et al reporting complications 29% following stereotactic biopsy. This was a limited series of 14 patients, furthermore Kesari et al. did no report whether these were transient or permanent complications. Mentioning the complication rate from such a small series, which were probably transient in most cases is not beneficial. The authors should instead mention the complication rate derived from 1480 patients in the meta-analysis by Kickingederer et al. (7.8% overall morbidity, 1.7% permanent morbidity). Please revise.

We agree with the reviewer that mentioning data from such a small series is irrelevant. Instead we discussed the complications rates mentioned in large series of brainstem tumors and especially in the meta-analysis of Kickingederer on page 14, line 1-4.

5.) The authors state that "A higher rate of complication in operative procedures of brainstem gliomas compared to supratentorial gliomas is established, e.g., Kesari and colleagues reported a complication rate of 40% after resection and of 29% after stereotactic biopsy of brain stem gliomas". However, a crude difference in the morbidity mortality following stereotactic biopsy of supratentorial vs. infratentorial lesions is yet not fully established. Overall morbidity and mortality rates for stereotactic brain biopsy in general are reported as approximately 4.9% and 0.7% (mean value from published series with at least 100 patients) [1]. These rates are fairly comparable to those reported for brainstem lesions reported by Kickingederer et al. in their meta-analysis (7.8% overall morbidity, 0.9% mortality) [2]. Please revise.


We considered the data from Kongham and from Kickingederer and incorporated them in the discussion about the comparison of morbidity between brainstem biopsy and general brain biopsy on page 14, line 1-4.

6.) The authors state that 104 patients were included over a period of 10 years. Were the patients recruited from a single center or derive these data from a multi-center-approach? If so, please state which centers were involved and how many patients were recruited from an individual center.

We included the recruiting centres as well as the number of patients enrolled by each centre on page (page 4, line 5-6).

7.) The authors mention stereotactic brachytherapy (SBT) as an alternative treatment approach and refer to a study by Mundinger et al. They state that 89 patients received SBT, however this is not correct. Although all 89 patients underwent
stereotactic biopsy, only 55 patients received SBT (29 with iodine-125, 26 with iridium-192 in Mundinger's series. Please revise. Furthermore, the authors missed to discuss a recently published study by Ruge et al on SBT for focal brainstem gliomas [1]


We clarified this point by a detailed description of the study results of Mundinger and incorporated and discussed the publication of Ruge (page 16, line 17-25)

8.) Surgical complications: please provide information whether these were transient or permanent complications. Exact data about a longer follow-up period were not available. Therefore we described the postoperative morbidity and additionally subdivided morbidity in severe and other complications (page 7, line 25 – page 8, line 4).

9.) The authors state that "the risk of postoperative hemorrhage is likely to be higher in malignant gliomas and may explain the differences in morbidity". However postop. hemorrhage infrequently causes permanent neurological deficits according to the meta-analysis by Kickingeder et al. Please discuss.

We extensively discussed the issue of association between postoperative hemorrhage and tumor pathology according to the actual literature on page 13, line 13-24.

**Minor:**

1.) Please provide information regarding follow-up period for each WHO-grade.

The follow-up period for WHO grade I was 58.8 months, for WHO grade II was 38.1 months and for WHO grade III was 41.1 months. 4 of 14 patients with WHO grade IV tumors survived (range 6.0 – 18.9 months).