Author's response to reviews

Title: Radiation Therapy for Desmoplastic Medulloblastoma - A Retrospective Analysis of Outcome and Prognostic Factors

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Author's response to reviews: see over
Re.: Revision MS 1052173443333246

Dear Ms Neilan,

today we are submitting our revised original article entitled

**Outcome and Prognostic Factors of Desmoplastic Medulloblastoma treated within a Multidisciplinary Treatment Concept**

We added a statement of ethical approval according to our institutional guidelines in the methods section. Please find below a point-to-point response to the concerns raised by the referees. All corresponding changes in the manuscript were highlighted in red colour.

**Referee 1: Jaques Grill**

**Major revision:**

i. The aim of this study was to describe outcome and results within the group of desmoplastic medulloblastoma. Comparing treatment results in desmoplastic medulloblastoma with classical medulloblastoma will be addressed in a separate manuscript. Preliminary data have been published by our group and the results are now included in the discussion (Rieken, S. et al, PO047, DKK 2010).

ii. Pediatric patients were included, because just like their adult counterpart, in case of desmoplasia they are are diagnosed with typical histology-associated features such as preferential lateral tumor locations and better outcome. Pramanik et al provided a substantial description of both biochemical/histological and clinical characteristics of desmoplastic medulloblastomas in both pediatric and adult patients confirming equal distribution of those feature defining desmoplasia in both age groups (Pramanik, P. et al 2003).

iii. Figures (Fig. 5 and 6) were removed.

**Minor revision**

iv. Included in the discussion

v. We agree that no substance-specific toxicity can be identified in the present cohort. However, heterogeneity of
Chemotherapy is due to the rare incidence of desmoplasia in medulloblastoma, reflecting evolving concepts of systemic treatment regimes over the past 20 years. Patients treated with additional chemotherapy reported remarkably more frequent side effects.

Discretionary revision
vi. Results from pediatric studies were included because they provide valuable information on chemotherapy for medulloblastoma and lowering of CSI doses from 35.2 to 23.4 Gy. Both aspects may be introduced into the treatment of adult patients.

Referee 2: Christian Senft

Major compulsory revisions
i. This study was set up not to analyse the specific benefit of chemotherapy in desmoplastic medulloblastoma, but to describe outcome in general and prognostic factors in this rare tumor. Chemotherapy was administered to 14 patients (70%), of whom 7 received concomitant radiochemotherapy with additional adjuvant chemotherapy.

ii. This question will be answered in a separate manuscript. Preliminary data were published already by our group and the results of this study are now included in the discussion (Rieken, S. et al, PO047, DKK 2010).

iii. Stratification of patients according to median age (21 years) was performed, because patients older than 18 but younger than 22 years are still included in pediatric studies therefore usually being administered chemotherapy (Rutkowski, S. et al HIT 2000 protocol). An additional stratification between \( \leq 18 \) years vs. > 18 years was performed and added in the “results” section.

Minor essential revisions
iv. Title was changed.

v. Poor survival rates are epiphenomena of metastases and recurrent disease. They emphasize the need for initially aggressive multimodal treatment. Sex as a prognostic factor probably corresponds to both the small number of patients and the fact that two female patients did not complete CSI (now included in the discussion).

vi. A new table was added
vii. Statistik 6.1, now included in the “methods” section.

Discretionary revisions
viii. Sentence was rephrased
ix. References were deleted.

Referee 3: Helmut Bertalanffy
i. Description of surgery in relapsing disease was included in the results section ("Patterns of relapse").
ii. Impact of extent of resection is described in the text document and included in a new table.

Referee 4: Ira Dunkel

Major compulsory revision

i. A figure displaying event-free survival was added.
ii. Aim of this study was not to compare desmoplastic medulloblastoma with classic medulloblastoma, but to characterize outcome and results within the group of desmoplastic medulloblastoma. Comparing treatment results in desmoplastic medulloblastoma with classical medulloblastoma will be addressed in a separate manuscript. Preliminary data have been published by our group and the results are now included in the discussion.
iii. Included in the methods section
iv. Data addressing whether or not desmoplasia is a prognostic factor of better outcome have been controversial. The discussion was expanded now considering results of several clinical trials.

Minor essential revisions

v. Now included in the “methods” section: Based on surgical reports and/or in postoperative imaging
vi. Changed into progression-free survival
vii. This is true, however, heterogeneity of chemotherapy is due to the rare incidence of desmoplasiia in medulloblastoma, reflecting evolving concepts of systemic treatment over the past 20 years. Patients treated with additional chemotherapy reported remarkably more frequent side effects.
viii. Based upon whether or not regular schools were visited.
ix. Neuropathological diagnosis was desmoplastic medulloblastoma with neuronal differentiation based upon reticulin stained section and additional immune histology. The diagnosis was confirmed by an external second neuropathological review (University of Bonn, Germany). The probe was positive for expression of neurotrophin receptor p75 and MIB-1 (30%). The INI-1 status was not assessed.
x. Changed to 5-year data only
xi. Limitation was noted.
xii. We agree that WBRT cannot cure medulloblastoma, as exemplified by both patients described here who died from recurring disease supporting the need for CSI in all cases. For adequate epidemiological description of completed therapies, they should be included.
xiii. “classical” was removed.
xiv. Reference was updated

Discretionary revisions

 xv. Deleted
xvi. Changed into carboplatin
xvii. Table was deleted.

All authors have read and approved the revised manuscript. Please do not hesitate to contact us for any further questions.

Sincerely

Dr. Stephanie Combs and Dr. Stefan Rieken
For all co-authors