Author's response to reviews

Title: A non-randomised, single-centre comparison of induction chemotherapy followed by radiochemotherapy versus concomitant chemotherapy with hyperfractionated radio-therapy in inoperable head and neck carcinomas

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Author's response to reviews: see over
Title: A non-randomised, single-centre comparison of induction chemotherapy followed by radiochemotherapy versus concomitant chemotherapy with hyperfractionated radio-therapy in inoperable head and neck carcinomas.
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Covering letter with a point-by-point description of the changes made.

Reviewer 1

Major Compulsory Revisions

1. Predictors of outcome: Predictors of overall survival have been included (page 10, para 1, line 5 ff).

2. Discussion has been changed in order to put emphasis on the adverse effects of induction chemotherapy such as accelerated repopulation of surviving clonogens (page 10, para 5, line 3) and increased toxicity of induction chemotherapy, leading to subsequent treatment interruptions and poorer local control (page 10, para 5, line 5 ff).

3. The context of clinical studies has been stressed (page 12, para 1, line 1 ff). A review about clinical studies (Adelstein, ref 18) has been added which confirms that, in a significant proportion, neither significant downstaging nor substantial impact on the distant metastasis rate occurs after administration of induction chemotherapy.

4. Conclusion (page 12, para 3, line 1 ff) has been rewritten to make it more balanced and more respecting the character of a retrospective study.

Minor Essential Revisions

1. In Abstract (page 3, para 3, line 2 ff) p values for multiple comparisons have been added.

2. The term "overlapping" has been replaced by the word concurrent consistently throughout the text.

3. In treatment records (page 5, para 5, line 8 ff) — the statement about dose of 40 Gy being the tolerance dose for the spinal cord using standard fractionation has been be rephrased.

4. Fractionation has been specified when providing dose range for various lymph node areas in concern (page 6, para 1, line 10 ff).

5. Median follow up for all patients has been provided (page 6, para 3, line 3 ff).

6. In patients' characteristics p values have been provided for comparisons (page 7, para 2, line 3 ff).

7. Stages have been revised and changed in table 1, page 18, but staging according UICC, 5th ed. has not been replaced [by staging according 6th ed.] to ease comparisons with other studies.
8. The percentage of patients experiencing treatment interruptions have also been accompanied with p value (page 8, para 2, line 4).

**Discretionary Revisions**

1. Only one term for concurrent/simultaneous radiochemotherapy consistently has been used. The terms simultaneously has been replaced by the term concurrent.

2. Acute toxicity has been mentioned in the Abstract (page 3, para 3, line 5).

3. The reference of Fu et al [2] has been replaced by the reference by Adelstein 1990 thus to providing the data of original studies in this field.

4. In treatment records the misunderstandable sentence on the dose reduction of chemotherapy during RT has been rephrased to better conform the presumed meaning (page 5, para 5, line 5).

The quality of written English has been improved by language corrections making use of a copy-editing service.

**Reviewer 2**

1. A historical bias might be supposed in large multicentre trials over long time periods. However, here a time period of 8 years is considered at one institution supervised by the same doctors. The authors assure that constant diagnostic, medical and technical procedures were applied during that time (as supplemented on p. 5, para 5, line 6f for the radiotherapy technique). There was in addition a time overlap, where both schemes were applied in parallel.

2. Clearly, the two regimens differed not simply in terms of sequencing of chemotherapy and radiation. The differences in the study design lead to different treatment parameters in the groups concerning radiation dose, treatment time etc. Therefore, as mentioned in discussion (page 10, para 4, line 4 f) it might be difficult to estimate the influence of a single parameter on treatment outcome. One of other relevant differences is the chemotherapy regimen (cisplatin based versus non-cisplatin based). However, the use of more aggressive drugs (cisplatin) and high doses in the SEQ protocol does even further support the message of our study, i.e. simultaneous RCT (CON protocol) is more effective than a sequential scheme (with one concurrent cycle in addition).

3. The facts, that the sequential treatment was hampered by a reduced chemotherapy dose (38% of the patients receiving 2 courses or less), low radiotherapy dose, more pauses and longer treatment time favours in addition the concomitant approach (as mentioned in discussion page11, para 1, line 3) and could as well adversely affect a patient’s tolerance to subsequent radiation therapy. All these points contribute to the assessment of both regimens have been critically analysed in the discussion (page 10-12). All in all, the differences in the regimens can explain the clinical results. These results refer to different endpoints such as effectivity, tolerance, toxicity, and success to administer the full dosage or necessity to make reductions, respectively. In our opinion, we have performed a balanced comparison between therapeutic strategies in the discussion, and the conclusions are justified in the light of the presented data.

The quality of written English has been improved by language corrections making use of a copy-editing service.
Discretionary Revisions

Patients and methods section (former page 4): Time to the first interdisciplinary examination was 4-6 weeks. The actual time needed to perform the first follow-up CT as basis for evaluation was in the order of 6 - 8 weeks (page 5, para 3, line 1).

Major Compulsory Revisions

Patients and methods section (former page 5): The radiotherapy energies used in the CON protocol were the same as in the SEQ protocol, because patients of both study groups were treated in a distinct division of Charité, equipped with both a telecobalt unit and a linear accelerator (page 5, para 5, line 6 ff). It could be estimated, that the percentage of patients treated with telecobalt was even slightly higher in the CON arm compared to the SEQ arm.

Results section:
The “response” and “local control and survival” sessions have been rewritten in order to afford a better understanding of numbers (e.g. see page 8, para 4, line 4 ff).
The percentages and crude numbers of relapsing and surviving patients have been calculated from the total number of eligible patients (SEQ: 72, CON: 52) (page 9, para 2, line 1 and table 3). There were three eligible patients with incomplete follow-up in the SEQ group non-evaluable (as mentioned in page 7, para 3, line 5 ff) For the crude numbers of locally relapsing patients we refer to table 3, and also the crude numbers of patient in “local control and survival” (page 9, para 2, line 3 ff) have been added. The sentence on (former) page 10, line 4 and following have been re-written in order to make the statement more clear (page 8, para 4, line 4 f).

Discussion: The sentence on (former) page 12 line 20 and following have been re-written for clarity (page 11, para 2, line1 ff).

Conclusion: The concluding remarks have been modified (page 12, para 3, line 1 ff).

The quality of written English has been improved by language corrections making use of a copy-editing service.