Author's response to reviews

Title: A non-randomized comparison of gemcitabine-based chemoradiation with or without induction chemotherapy for locally advanced squamous cell carcinoma of the head and neck

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Author's response to reviews: see over
Dear Editor,

We would like to thank you and the reviewers for the extensive review of our manuscript (MS: 3886236302599073). As you will understand, we are disappointed by the decision not to accept our article for publication in BMC Cancer. However, we strongly disagree with some of the remarks made by in particular the second reviewer for reasons that will be explained below, and therefore dare to offer you a revised version of our manuscript for your consideration.

We will answer the remarks of the reviewers one by one.

Reviewer 1

1. The reviewer considered the study well performed and the manuscript well written; moreover, he considered the article of importance in its field. He stressed that the statistical calculations have to be made with caution, and we did also as exemplified by the phrasing in our discussion.

"Admittedly, the results of our analysis are to be interpreted with extreme caution as this is a non-randomized historical comparison of a relatively small number of patients treated at a single institution.... Notwithstanding the limitations of a non-randomized single-centre comparison, the results are in line with the very preliminary data of randomized comparisons, mentioned above. Nevertheless, we suggest that the outcome of the large randomized trials need to be awaited before the sequential approach of induction chemotherapy followed by chemoradiation can replace cisplatin-based chemoradiation as the new standard treatment".

In addition, we would like to underline that this is the first such comparison of cohorts where the locoregional treatment has been the same in both cohorts.

2. The reviewer mentioned that the induction chemotherapy regimen that we used over time were not the same. This is true and a result of the fact that over time chemotherapy protocols have evolved. However, the only significant benefit reported in the literature are those from adding a taxane to the PF regimen (see the articles of Hitt et al, JCO 2005, Vermorken et al, NEJM 2007, Posner et al, NEJM 2007) and all but three patients in our ST cohort received a cisplatinum-based taxane containing triplet. The remaining patients received a platinum-based triplet. If any, these patients should be considered as a disadvantageous element for the ST cohort in the comparison.

3. The reviewer suggested we include a passage where the results of the use of gemcitabine as a radiosensitizer are compared with those of studies using cisplatin as a radiosensitizer. We have done so.

Concerning the small points made by reviewer 1

4. Have some patients been operated after the application of 70 Gy?

The answer is as follows:

In the CRT cohort:
None of the patients underwent a resection of the primary tumor.
Lymph node resection was performed before the chemoradiation in one patient and a radical neck dissection was performed after chemoradiation in five patients. Four of these dissection specimens still contained tumor.

In the ST cohort:
None of the patients underwent a resection of the primary tumor.
A lymph resection was performed in 6 patients after the end of chemoradiation. Viable tumor was present in 1 resection specimen.

5. Why was the follow-up in the two cohorts so different?

The answer is simple, because these were sequential cohorts and not cohorts treated in the same time period. The ST cohort was initiated since there has been a revival of interest in the use of induction chemotherapy in our institute. Important is to mention here also that the patients were treated by the very same
team in a single institution. We initially introduced a cut off at 36 months in order to in order to correct for this difference in follow up time. In the meantime, we have contacted the patients or their relatives in order to update their status as of April 1, 2009. By updating the database, the median follow up of surviving patients in the sequential cohort has increased to 51 months. In our opinion, our current data are mature, even for the cohort with the shortest follow up. Indeed, as can be expected, the vast majority of events in this type of patients occur in the first two years after diagnosis. We propose to introduce a cut off at 60 months, which is a very meaningful follow up time in this population of patients who frequently are suffering of a lot of co-morbidities. However, our initial findings remain about as presented in our previous submission.

6. If patients with oropharynx cancer are excluded, the remaining patients are to few for a reliable statistical analysis. As we mentioned in our manuscript we performed a Cox regression analysis correcting for tumor site, T and N stage and age. Interestingly, the difference between the two cohorts even further increased when we corrected for these factors and in particular for the item “tumor site”. We initially inserted the analysis excluding the patients with oropharyngeal cancer in order to support the results of cox regression analysis which demonstrated a survival benefit when taking into account age, T and N stage and tumor site. However, considering the comments of the reviewer, we are prepared to remove the separate analysis from the manuscript.

7. Concerning the tables, please provide the p-values to show that the cohorts are comparable. So we did.

Reviewer 2

1. The sample size is small, compromising the results and the conclusion. The sample size is indeed rather small but we also clearly stressed this in our conclusions. On the other hand, it is at least remarkable to see a statistically significant difference, even with a rather low number of patients. Moreover, we refer to what was mentioned under item 1 to reviewer 1.

2. The median follow-up was different to such an extent that the cohorts could not be compared. We disagree here. The vast majority of progression events occur in the first two years after diagnosis. For the remaining we like to refer to what we mentioned under point 5 in our answer to the first reviewer.

3. The treatment in the ST cohort was extremely heterogeneous. We think it might be heterogeneous in singular components but not in efficacy; 28 of the 31 patients received a platinum-based taxane containing triple regimen, which are considered to be the most efficacious regimens for induction. The fact that 90% of our patients responded to these regimens is a proof of that. TPF is considered standard for induction nowadays. The DIP regimen might be even more efficacious (although also more toxic) (see Abstract Specenier et al, ESMO 2007, Istanbul). The remaining 3 patients received platinum-containing doublets. As we mentioned to the first reviewer: if any, these three patients should be considered as a disadvantageous element for the ST group in the comparison.

4. The populations of the two cohorts are not similar in their composition. We agree that the composition of the cohorts was not entirely the same, but except for tumour site there were no major (statistically significant) differences between the two cohorts regarding the patient characteristics. Moreover, we performed a Cox regression analysis correcting for tumor site, T and N stage and age. However, in fact the observed difference even increased when we corrected for these factors, and particularly for tumor site.
5. The second reviewer questions the choice of factors taken into account in the Cox regression analysis. However, age, T and N stage and tumor site are the classic and in fact the only validated prognostic factors for head and neck cancer. We did not include any other prognostic factors. We do not understand the statement by the second reviewer “However, the samples of these two cohorts included in this study are very small and the distribution of the events does not follow a normal distribution. Consequently the Cox regression analysis must not be used, because there is a risk of overestimate the effect”. In fact, in a survival analysis, the endpoint is survival time, which obviously is not normally distributed. Cox regression is used when the hazard can be considered to be constant, leading to an exponential distribution (and not a normal distribution) of survival time. We therefore are convinced that the use of the Cox regression analysis is appropriate.

We hope we have been able to answer the questions of the two reviewers. Because of the fact that the second reviewer misinterprets the use of the Cox analysis in this manuscript, we hope that you will reconsider the manuscript for publication in BMC Cancer, taking into account that both reviewers considered the manuscript important in its field.

With kind regards

Yours sincerely

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