Reviewer's report

Title: Prognostic significance of the cumulative dose of cisplatin during concurrent chemoradiotherapy for patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy

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Reviewer: Volker Rudat

Reviewer's report:

The authors report about a study of 491 nasopharyngeal cancer patients treated with concomitant radiochemotherapy using IMRT and cisplatin. Goal of the study was to assess the outcome of patients who received a cumulative dose of <=100, 100-200, or >200 mg/m² cisplatin. On univariate analysis, patients of the low-dose cisplatin group had a significantly worse overall survival and DMFS than patients of the other groups. A similar observation was made for low-risk patients (EBV DNA level <4000 copies/ml). High-risk patients exhibited no association between the cumulative cisplatin dose groups and the overall survival or DMFS. On multivariate analysis, the cumulative cisplatin dose group had a significant impact on the overall survival but not on DMFS, DFS or LRFS. In low-risk patients, the cumulative cisplatin dose group had a significant impact on the overall survival but not on DMFS. In high-risk patients no association between the cumulative cisplatin dose group and the overall survival or DMFS was observed. The authors conclude that "the cumulative dose of cisplatin is a useful prognostic factor for NPC patients who receive IMRT".

Major Compulsory Revisions

A prognostic factor is a clinical or biologic characteristic that is objectively measurable and that provides information on the likely outcome of the cancer disease in an untreated individual. In contrast, a predictive factor is a clinical or biologic characteristic that provides information on the likely benefit from treatment [for reference see: Antoine Italiano, Prognostic or Predictive? It's Time to Get Back to Definitions!, JCO Dec 10, 2011:4718-4719]. According to this definition, the cumulative cisplatin dose is neither a prognostic nor a predictive factor. In my opinion the authors basically show that suboptimal treatment leads to suboptimal treatment outcome. Unfortunately the authors did not provide any information why and in how many patients the prescribed dose could not be applied as well as no information about the criteria used to select the patients for the different used chemotherapy protocols. A possible bias can't be excluded, and for this reason it is difficult to draw reliable conclusions concerning the optimal cumulative cisplatin dose or chemotherapy protocol. These limitations should be clearly stated in the manuscript.

The authors performed a large number of statistical tests. No correction for multiple testing was used. There is an increased probability of type 1 errors. The
authors should clearly state that the corresponding results should only be used to generate hypotheses. To reduce the number of statistical tests, the authors for example could consider to perform a multivariate Cox regression analysis stratified by the risk status of the patients (EBV DNA <4000 versus >= 4000).

The authors did not state clearly the design of the study: was it a prospective study or a retrospective analysis of patient data?

Minor Essential Revisions
There are plenty unclear or imprecise statements in the manuscript, and the manuscript should be revised by an experienced writer.

Examples:
Page 4 line 14: please state the year the overall survival is referred to.
Page 5 line 2: I do not agree that the cumulative dose is a prognostic factor.
Page 6 line 17: what is a "conformal analysis"?
Page 8 line 9: "stage IV disease": does it include M1? Or do you mean IVa and IVb?
Page 8 line 10: "PTV of the involved cervical lymph nodes" not "PTV of the GTV for the involved cervical lymph nodes"
Page 9 line 18: "or" instead of "and" 30-40 mg/m2...
Page 12 line 5: which "two groups" do you mean?
Page 12 line 20: I do not understand the sentence: "For other prognostic factors...."
Page 12 line 22: what "ratios" you are referring to?
Page 12 line 7: please state the year the overall survival is referred to.
Page 13 line 3: what do you exactly mean by "DMFS values"?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests