Author's response to reviews

Title: Prognostic Impact of Array-based Genomic Profiles in Esophageal Squamous Cell Cancer

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Re: MS: 1998581436164416

“Prognostic Impact of Array-based Genomic Profiles in Esophageal Squamous Cell Cancer”.

Dear Editor,

Thank you for thorough comments and positive criticism to the manuscript above. We have, in line with the reviewers’ suggestions, revised the manuscript and would like to clarify/comment on the following:

Reviewer K. Sasaki

Major compulsory revisions

Impact of normal cell contamination on array CGH sensitivity and validity of the data obtained from high molecular weight DNA extracted from whole tumor fresh frozen tissue samples.

The normal cell content in tumors is a well-known confounder in most studies of fresh tumor tissue, which we tried to correct for using tumors from which touch imprints showed >50% tumor cells. Tiling array sets with lower resolution than the one used herein have by Garnis et al. [1] been demonstrated to reliably identify copy-number changes in samples with 30% tumor cell content. The application of high-resolution CGH arrays improves precision as well as confidence and sensitivity in detecting genetic alterations. Also, the detection of high level amplifications and homozygous deletions identified serve as an internal quality control since these would have been difficult to detect if a very high fraction of normal cells had been present in the samples.

Interpretation of figure 1 and meaning of inter-tumor variability between genome wide profiles.

Figure 1 depicts A) a genome wide frequency plot of A) gains and losses in all tumors and B-C) in two separate tumors. The data point fluctuation in the whole tumor profile reflects overall genetic complexity with multiple gains and losses, which is supported also in other types of genetic profiling studies within esophageal cancer. It also reflects the use of high-resolution arrays, which reveals small gains/losses that would have escaped detection using lower resolution arrays or traditional CGH.

Minor revisions

- Page 3, §1, line 6: a reference has been added to the sentence referring to ESCC development
Page 8, §1, line 1: the paragraph has been rewritten stating the difference between stage I and stage II-IV tumors

Page 10, §2, line 13 and page 11, §2, line 2: typographical errors corrected

Referee L. Wang

Discretionary revisions

Description of the geographical origin of the patients.
In the Materials and Methods section, geographical origin has been clarified.

Sample size
We agree with the reviewer that given the large amount of data generated by microarrays, a larger sample set is needed to statistically validate our findings. These data should therefore preferably be tested in a larger, independent samples set, perhaps also using other means e.g. RT-PCR or FISH. Nevertheless, we believe these results hold promise for the use of genetic classifiers for prognostic purposes in esophageal cancer.

We hope you will find these revisions satisfactory, and that the manuscript may now be acceptable for publication in BMC Cancer.
On behalf of the authors, sincerely yours

Mef Nilbert and Ana Carneiro