Author's response to reviews

Title: Fractal dimension of chromatin is an independent prognostic factor for survival in melanoma

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Author's response to reviews:

Dear Editor, dear Madam, dear Sir,

first of all I would like to thank for the critical and constructive comments, which certainly helped to improve our manuscript.

In the following we will reply in detail to all comments

I- Editorial comments:
1. We cited the documentation of the Ethics Committee
2. The grammar and style of text were revised
3. Funding was listed

II –Reviewers comments:
1. Reviewer's report
Reviewer: Lampros P Goutzanis
Minor Compulsory Revisions.
1. Page 2, Methods: You state that you examined 71 primary cutaneous and metastatic melanoma specimens. However on page 5 (Study subjects) you say that you selected patients with superficial spreading cutaneous melanoma. It is not clear to me how many of the melanomas were primary and how many metastatic. Do you feel this needs clarification;

Reply: All melanomas in THIS study were primary tumors. We corrected our error.

2. Page 9, line 4 and 5. It would seem to me that the inclusion of "60 patients"
makes the sentence unclear.

Reply: We corrected the phrase.

3. Page 1. Would suggest "reliable" instead of "robust"

Reply: We changed to reliable.

4. Page 2, Results, line 3: Would suggest "were significantly the worst prognostic factor"

Reply: The style of this phrase was revised

5. Page 7 and 8: Would suggest replacing "according to" with "in accordance with" wherever mentioned.

Reply: The style of this phrase was revised

Quality of written English: Needs some language corrections before being
Published –

Reply: The text was revised by a company.

2. Reviewer's report
Version: 1 Date: 2 February 2010
Reviewer: Jane L Messina

Reviewer's report:
-Major Compulsory Revisions
I disagree with the statement in the abstract and introduction that routine
clinicopathologic factors are not useful in determining an individual's prognosis.
Multiple studies have demonstrated their usefulness in uni- and multivariate
models, and they are currently used in the clinical setting as the most accurate
predictors of prognosis. We could certainly improve on the current factors, but
the wording dismisses their importance entirely and should be altered.

Reply: We have to confess that the above mentioned phrases in our first
manuscript sound a little bit apodictic and thus may be subjected to criticism.

Therefore we changed to:

Malignant melanoma is a highly aggressive neoplasia of the skin with a constant
and rapidly increasing incidence in the last decades [1] Prognostic factors are
currently based on clinical data and morphologic examination (including variables
such as tumor thickness, mitotic rate, etc.) [1-3], which are reliable and
reproducible. Other prognostic markers, however, which are not yet used in daily
practice, might add important information and thus improve prognosis, treatment,
and survival. Therefore a search for new prognostic factors is desirable.

Results section: Clark level of the study group was reported to range from 2 to 6, but there is no Clark level 6.
Reply: We are grateful for the detection of this horrible typing error

Results section: Mitotic rate was reported as number of mitoses/10 high power fields, but the standard method of reporting mitotic rate for melanoma is number of mitoses/sq mm. To be in line with other publications on the prognostic value of mitotic rate, the reporting of mitotic rate should be in the standard method.
Reply: We changed to mitoses per square mm.

- Minor Essential Revisions
In the introduction, the meaning of the phrase "were significant at worse prognostic factor in univariate Cox regressions" is unclear. Please revise. In the background, the statement "malignant melanoma is the most lethal tumor of skin" can be disputed, since many believe the Merkel cell carcinoma is the most lethal tumor of skin. Please revise.
Reply: We changed this phrase in the introduction

The statement "As event we defined death related directly or indirectly to malignant melanoma. Patients who expired without metastatization entered the study as censored cases." should be corrected for grammatical errors. I would suggest "Melanoma specific survival was calculated, and patient death not related to melanoma was censored."
Reply: We changed these phrases

- Discretionary Revisions
The concept of fractal dimension is somewhat difficult for a non-mathematician to understand. The paper would benefit if a more thorough explanation of the biologic phenomenon that lead to increased FD is provided.
Reply: This comment stimulated us to re-write the discussion. We tried to explain in a more detailed way the fractal concept and the nuclear architecture. Furthermore we included some very new papers from the last 3 months which are relevant.

again many thanks for the stimulating comments
sincerely yours
V Bedin and K Metze for all authors