Author's response to reviews

Title: Role of serum S100B and PET-CT in follow-up of patients with cutaneous melanoma B. Peric, I. Zagar, S Novakovic, J. Zgajnar, M. Hocevar Institute of Oncology Ljubljana, Slovenia

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Author's response to reviews: see over
Dear Prof Vordermark,

we would like to thank you for your help with our manuscript Role of serum S100B and PET-CT in follow-up of patients with cutaneous melanoma. We are pleased that our work was considered interesting enough for your reviewer. After careful consideration of reviewer’s comments, we included the proposed modifications and explanations which in our opinion substantially improve the quality of our manuscript.

Reviewer #1

Ad 1: (the authors did not adjust their results by potential confounding variables (age, gender, TNM stage and so on) by means of a multivariable model.)

The aim of this study was to determine clinical value of regular S100B measurements and subsequent PET-CT for patients with different AJCC stages of cutaneous melanoma. In our case, results of performed linear regression did not show any statistically meaningful influence of gender (p=0.951), age (p=0.666) or AJCC stage (p=0.747) on the value of S100B.

To our knowledge, there is only one study concerning influences on preoperative S100B values in melanoma stage III patients where only increased lymph node size was associated with elevated S100B. More than two positive nodes (p=0.5), age (p=0.6) or gender (p=0.6) showed no association with the level of tumour marker (1).

When we compared influences on the outcome of the PET-CT by the means of logistic regression, similar results were obtained. Neither gender (p=0.960), AJCC stage (p=0.950), age (p=0.636) or level of S100B (p=0.456) were associated with positive PET-CT.

Since we did not feel that results of multivariate analysis would add valuable information to our study, they were not included.

Ad 2: (the authors did not formally compare the predictive performance of S100 with that of PET (e.g., by means of a McNemar test)

Page 5, paragraph 3 it should read:
The McNemar symmetry chi square test was used to compare performance of the S100B with that of PET-CT. Sensitivity, specificity, ...

Page 7, paragraph 1 it should read:
... Metastases were actually confirmed in 94 (81.7%) out of 115 patients. The χ² value for McNemar test comparing S100B and PET-CT was 21.9 with p < 0.0001 respectively.

Ad 3: (the authors did not study the functional form of a continuous variable such as S100 and thus the cut-off they used to distinguish between positive and negative cases appears arbitrary)

In a paragraph Patients and methods, section S100B, we stated, that reference values were obtained from apparently healthy volunteers and 0.105 µg/L was determined as the upper normal value (Roche Diagnostics).

In 1998 Bonfrer published a study concerning sensitivity of the luminescence immunoassay. The 95th percentile of the group of normal individuals was established at a 0.16 µg/L and
result was compared with earlier studies, where levels of S100 were never higher then 0.20 µg/L in healthy individuals (2). More recent studies compared improved methods of S100 determination, but reference values calculated as the 95th percentile in the group of healthy individuals did not change much. Even more, only slight differences were noted between calculated cut-off levels and cut-off levels quoted by the manufacturer. It was also proposed, that a percentage of elevated S100B levels in different AJCC stages can be calculated based on the obtained reference values and the sensitivity can be estimated (2;3).

Since the aim of our study was to determine whether regular measurements of serum S100B with commercially available tests are a useful tool for discovering patients with CM metastases, we used a cut-off level proposed by the manufacturer and confirmed by our laboratory prior to the implementation of the method in every day use. We agree that value used to distinguish between negative and positive cases is arbitrary, but that only confirms observation made by us and in prior publications, that a use of uniform reference standards and perhaps methods would enable us to compare results more efficiently (3). Sensitivity and specificity of different cut-off values for our group of patients were not compared, since the group of patients with increased values of S100B was too small (N=58, 33 patients without clinical signs of the disease).

Ad 4: (the presentation of the role of S100 in the management of patients with skin melanoma is quite approximate/poor/simplistic as compared to the amount of literature already present on this subject: they should at least acknowledge that a meta-analysis (Mocellin et al, Int J Cancer 2008, 123:2370-6) has been published that supports the role of this biomarker in the management of these patients.)

Page 3, paragraph 3 it should read:
… poor prognostic factor in CM (3). Findings published by Mocellin even proved, that this serum marker influences patients survival independently of the TNM staging system (4). S100B has also been used as a valuable marker in assessing …

Page 10, paragraph 2 it should read:
… survival of patients with CM. A meta-analysis of twenty-two articles published until 2008 proved S100B as an independent prognostic factor of survival with special regard to stage I-III patients (4). In advanced disease elevated levels of S100B also demonstrate a strong correlation …
Reference List


