Author's response to reviews

Title: Natural History of Malignant Bone Disease in Breast Cancer and the Use of Cumulative Mean Functions to Measure Skeletal Morbidity

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Author's response to reviews: see over
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Andrea Bucceri, PhD
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BMC-series Journals
BioMed Central
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RE: BMC Cancer Manuscript 1869125357241552

Dear Dr. Bucceri:

Thank you for the reviewers’ comments on the manuscript “Natural History of Malignant Bone Disease in Breast Cancer and the Use of Cumulative Mean Functions to Measure Skeletal Morbidity.” We appreciate the reviewers’ insights and are pleased that the reviewers will consider this manuscript for publication in BMC Cancer after satisfactory revision. We have revised the manuscript to address all of the reviewers’ comments and have included point-by-point responses to the suggestions. The reviewer-requested clarifications/changes are highlighted with yellow in the manuscript.

We hope that the revised manuscript is now acceptable for publication. Thank you in advance for allowing us to address the reviewers’ comments. I look forward to hearing from you.

Sincerely,

Pierre P. Major, MD
Response to Reviewer #1’s (Sue-Anne McLachlan) comments:

1. “The placebo arm of a RCT of bisphosphonate therapy has provided an opportunity to examine the skeletal morbidity and prognosis of women with bone metastases from breast cancer. A retrospective statistical analysis has been conducted to examine for factors that predict for skeletal related events and overall survival in this population. The aim of the study is well described and the methods are sound. The manuscript is clearly presented and well written. Interpretation of the data could be enhanced. There is emphasis on the statistical associations rather than the clinical significance of many of the findings. Multiple significance tests have been performed thereby increasing the probability of detecting spurious associations due to chance. For example in the reduced multivariate models a higher HP/C ratio significantly correlated with reduced survival. The relative risk was 1.042. Is this a clinically significant finding?”

   • Because this is a secondary analysis of data from a completed trial, we limited our attention to reporting associations between demographic and clinical variables and clinical endpoints; we are not reporting on concrete clinical findings. However, in our revised manuscript we have expanded the discussion regarding the clinical relevance of these associations on page 13 (lines 1-17).

   • The higher hydroxyproline/creatinine ratio (HP/C) is indeed associated with reduced survival. The relative risk for HP/C is scale dependent because it is a continuous variable. Expressing the effect in larger increments of HP/C could provide a larger relative risk value for comparison, but the p value would remain the same. Moreover, the p value demonstrates the significant association between high HP/C and survival. For an additional publication illustrating this point please refer to Hirsh V, et al. J Thorac Oncol. 2008;3:228-236. No changes have been made to the manuscript.

2. “Similarly why should diagnosis of lung mets but not liver mets be a significant risk factor for death in these women.”

   • Our results demonstrate no significant survival difference between patients diagnosed with lung and liver metastases; however, it has previously been suggested that patients with bone-only metastases survive longer compared with patients with lung metastases. Moreover, patients with metastases to the liver survive longer than patients with lung metastases but not as long as patients with bone-only metastases. For additional support of this point, please refer to Figure 5 in Elder EE, et al. Eur J Surg Oncol. 2006;32:922-927. No changes have been made to the manuscript.

3. “These results are best considered hypothesis generating. Is there scope to test these hypotheses in another independent set of patients?”

   • We have carried out numerous diagnostic checks on our models using residual analyses and testing for the assumption of proportional hazards. We therefore feel comfortable with the conclusions and associations revealed from these models. Currently there are no statistical methods available for validating models of nonfatal intermediate endpoints such as skeletal-related events (for the first one or recurrent analyses). Indeed, this is an active area of statistical research and when such methods are available we intend to test our models using databases of patients receiving zoledronic acid. Additionally, the sample size for our analysis is not large
enough to split the data into two for further analysis. No changes have been made to the manuscript in response to this comment.

• To our knowledge this is the only relevant placebo-controlled database available from which natural history data could be extracted. Dr. Kohno performed a placebo-controlled study in 228 women with bone metastases from breast cancer (J Clin Oncol. 2005;23:3314-3321); however, there were only 8 deaths in the placebo arm (7.1%), thereby rendering this study not useful for validation. Additionally, more recent trials of patients with bone metastases used active controls rather than placebo and therefore could not be used to assess the natural history of bone metastases. No changes have been made to the manuscript.

4. “A discussion of the limitations of the analysis and data is deserved.”

• Although these analyses are exploratory and descriptive, this is the largest database available from which to learn about the natural history of bone metastases from breast cancer. There are several limitations of these analyses and they are described in the manuscript on page 11 (lines 22-26) and page 12 (lines 1-6).

5. “Figure 1A should be labelled ‘Overall Survival’”.

• We have corrected Figure 1A of the manuscript.

6. “In the legend make it clear that the relative risks displayed in the forest plots (1A and 1B) are derived from the reduced multivariate models.”

• We have clarified the Figure 1 legend in the manuscript.

7. “How many patients had died at the time of the analysis? This would be useful information when considering the number of events in relation to the number of prognostic factors assessed.”

• Approximately 56% of patients with bone metastases from breast cancer experienced \( \geq 1 \) SRE, and 43% of patients were alive at follow-up completion. These findings demonstrate an important part of the natural history of bone metastases from breast cancer and have been included in the manuscript on page 8 (lines 14-15 and 20-21).
Response to Reviewer #2’s (Antonio AR Rulli) comments:

1. “This is a peculiar study since is trying to divulge information before the trial’s expiry (considered the very scarce duration of survival of the sample).”
   
   - This study is a secondary, post hoc, exploratory analysis of data from a completed trial that was published in 1996 (Hortobagyi GN, et al. *N Engl J Med*. 1996;335:1785-1791). To clarify this point, we have included the timeline of this trial in the Methods section on page 6 (lines 7-8).

2. In any case, more than on the course of the illness, the study is based on the bio-mechanic of the bone lesion location. It is taken for granted that the SREs rather affect the spine than the skull due to the different load of the body weight. It would have been correct to analyse a specific location, i.e. the femur, and evaluate the metastasization in different locations: skull, neck, diaphyses, condyles. As a matter of fact, from the conclusions one deduces that the median survival of the studied patients is similar for the several examined subgroups and suggestion that every patient with bone metastases, independently from the location, ought to be submitted to specific therapies is taken for granted.

   - The underlying biomechanics is still being developed and therefore have not been used in our analyses. As more clinically applicable measures of bone structure such as micro-MRI become available they will provide useful insight into risk factors for future studies.

3. Finally, the risk of SREs, that doubles owing to the first incident, might also be referable to the type of metastasization of the breast cancer that rather appears in “small shot” form than in single units. Just one bone metastasis location is often evident where there actually are many smaller ones that escape the clinical-instrumental investigation.

   - We appreciate the insightful comments on the manuscript and agree with the reviewer. There is evidence that bone micrometastases can go undetected for an extended period of time. To this end it is important to provide early and continuous bisphosphonate treatment to patients with bone metastases. Previous studies demonstrated that zoledronic acid treatment of bone metastases in patients with prostate or lung cancer reduced the risk of both first and subsequent SREs compared with placebo (Saad F, et al. *J Natl Cancer Inst*. 2004;96:879-882 and Hirsh V, et al. *Clin Lung Cancer*. 2004;6:170-174). These results, in combination with our natural history findings, stress that treatment should not be discontinued after an SRE develops. This has been included on page 13 (lines 1-17) of the manuscript.
Response to Editor’s comments:

1. We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns. As you can see only minor revisions are needed before the manuscript can be accepted for publication. Please modify the figure legend of Table 1 and clearly state that permission was obtained from New England Journal of Medicine to reproduce the table.

- The footnote for Table 1 includes the necessary specific permission language as received in the permission letter from The New England Journal of Medicine. We have also added “with permission” to this credit line.