Reviewer's report

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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Reviewer: Sue-Anne McLachlan

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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.

Minor Essential Revisions

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? Similarly why should diagnosis of lung mets but not liver mets be a significant risk factor for death in these women. These results are best considered hypothesis generating. Is there scope to test these hypotheses in another independent set of patients?

1. A discussion of the limitations of the analysis and data is deserved.
2. Figure 1A should be labelled “Overall Survival”.
3. 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.
4. 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.

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

Quality of written English: Acceptable

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'