Author's response to reviews

Title: Impact of modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer

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Author's response to reviews: see over
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To the Editor:

We would like to express our sincere thanks to the reviewers for a thorough review of our paper, for the excellent suggestions which we feel strengthened the quality of our paper, and for the opportunity to submit a revised manuscript. We are grateful for the comments and have addressed them below.

Response to Comments from Dr. Kathy Prichard:

1. **Comment**: This is a nice paper that examines in a cohort, in a single center, the impact of specifically modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer. The study has the limitations of being an observational study and of being a single institution study but is well conducted and clearly written up.

   The study is also limited to women who presented with de novo metastatic breast cancer which as the authors clearly discuss, may be a different “animal” than recurrent metastatic breast cancer. The authors do discuss the implications of this clearly as well however.

   The authors interesting results would suggest that hormonal therapy and herceptin and the having of estrogen receptor are the most influential things in how patients survive, are sobering. Also, the fact that the receipt of bisphosphonates in particular, Zoledronic acid, is as influential as the receipt of “newer” (Group B) chemotherapeutic agents is quite interesting.

   **Response**: We appreciate this favorable review of our work. As no specific suggestions were inferred, no changes were made to the manuscript on the basis of this commentary.

Response to Comments from Dr. Tjan-Heijnen:

1. **Comment**: In the methods section, paragraph statistical analysis the authors do not state what test they used to determine the p-values stated in table 2.

   **Response**: We have clarified the tables to indicate that these differences were identified using the Chi square test.

2. **Comment**: Table 2 with patient characteristics is not clear and not complete. The meaning/definition of the 2 numbers behind each variable is unknown (most likely number and percentage, but it is not clearly stated). If it is indeed number and percentages than at least some of the given numbers and percentages are incorrect. For example the presence of bone metastases. In period A, 84 patients have bone metastases, which is not 61% as now stated but 56%. In period B, 82 patients have bone metastases, which is not 61% as stated but 67%. The percentage of 61% in both groups is now stated as being equal which does not correlate with a p-value of 0.008. As stated in comment 1, it is not clear what and with which test the p-value is reported.

   **Response**: We appreciate the thorough review of this data, and our re-review of this data has resulted in modification of several reported percentages. We have more clearly stated that the Chi square test was used to estimate differences amongst the various subsets. Fortunately, re-review of our statistical analyses have shown no changes to the stated P-values. To clarify the data presented in Table 2, we have added the following to the table heading:
“Percentages reflect the proportion of patients in each subgroup relative to the total number of patients in the respective period (i.e., Period A or Period B), except for ER, PR, and HER2 status. For these variables, percentages reflect the proportion of patients in each subgroup relative to the total number of patients in the respective period for whom pathologic data is available. P-values determined using the Chi-square test.”

3. **Comment:** In the methods section it is stated that histology was classified as either inflammatory or invasive ductal but in table 2 the used terms are inflammatory versus non-inflammatory. If you add up the numbers of patients in both groups the total amount of patients is more than the total amount of included patients. Furthermore, the range of age should be given in addition to median age in years.

**Response:** We appreciate this important point, and have clarified that we classified patients as inflammatory and non-inflammatory. The distribution of patients in Table 2 has been modified to reflect this.

4. **Comment:** In both univariate and multivariate analyses several factors influencing survival of metastatic breast cancer is tested, however no information of the actual median survival times of these patients is provided. Given the patient characteristics in table 2 (high rates of palliative chemotherapy (69% in period A and 89% in period B) and low median age in both periods), the median survival of patients in both periods is essential to determine whether this chosen cohort is representative of general primary metastatic breast cancer patients.

**Response:** To address this important query, we have added to the section titled, “Univariate Analysis” the following statement:

“Patients diagnosed during period B had a slightly longer median survival as compared to patients treated during period A, although this difference was not statistically significant (3.0 years vs 2.5 years, respectively; P=0.10).”

5. **Comment:** In the paragraph on univariate analyses, the authors state that there is no difference in survival among patients receiving chemotherapy category A compared with patients receiving chemotherapy category A+B (p=0.13). However, they also state that there is a difference in survival in patients receiving HER2-directed agents compared with patients not receiving HER2-directed agents (p=0.15). With the same not-statistically significant different results these statements seem contradictory.

**Response:** We have removed the following statement, “… nonetheless, those were treated with this therapy demonstrated improved survival (HR 0.69, 95%CI 0.41-1.14; P=0.15),” and have acknowledged that the small proportion of patients with HER2 positive disease limits the potential inferences from this data.

6. **Comment:** In the paragraph on stepwise multivariate analysis, the whole first section is a description of methods and is possibly more appropriate in the method section.

**Response:** We agree that a portion of this paragraph is redundant with what is already stated in the Methods section. We have therefore removed the following text:

“As noted previously, for stepwise multivariate analysis, all variables identified on univariate analysis with a P<0.20 were included, and values with a P-value < 0.05 were retained as well as the comparison of survival in patients who received chemotherapeutic agents from Category A v [Category A and B], given the underlying a priori hypothesis of this work.”

7. **Comment:** The numbers of patients included is too low (n=274), to make any firm conclusions.
Response: We agree that all single-institution experiences are constrained by sample size. We have therefore limited the scope of our conclusions in the last paragraph, and made a call for the formation of multi-institutional collaborative databases to better account from these phenomena:

“The impact of conventional chemotherapy on survival appears to be is minimal in the context of our retrospective cohort; perhaps these findings warrant more definitive exploration through the formation of multi-institution databases. Findings from such efforts could surely supplant the existent studies which draw from limited single-institution experiences.”

8. Comment: Many missings in HER2 status and other items (table 2), which compromises any conclusion to be drawn.

Response: We agree that there are many missing datapoints in several categories, especially in the domain of HER2 status. Of course, missing datapoints for HER2 status are anticipated to some extent, due to the infrequent use of the assay during the earlier portion of the first period (period A), when HER2-directed therapies had not yet received key approvals. We have added modified the previous text to include the following statement in “Results”, acknowledging the small size of the HER2 population:

“In the current analysis, patients receiving HER2-directed agents comprised a relatively small subset (n=21), challenging inferences in this subset.”

9. Comment: Unclear: is a comparable treatment of ovarian function suppression such as surgery included in the LHRH agonist analyses, and/or was LHRH agonist continued after progression.

Response: We only captured pharmacologic methods of ovarian suppression, and have added the following statement to the “Methods” section to delineate this fact:

“Notably, with respect to ovarian suppression, only pharmacologic suppression with LHRH analogues was recorded; oophorectomy, ovarian ablation, and other surgical techniques were not captured.”

10. Comment: Multivariate analysis: bisphosphonates comes up as a significant factor. However, was the ER status included and corrected for?, as it is likely that especially in the ER positive group bisphosphonates were given because of bone metastases, where the ER positive patient group with bone metastases has the best survival as we know from other studies.

Response: Our multivariate model used a stepwise approach, with each variable examined, including ER status. Ultimately, although receipt of AI was found to be a predictor of survival, ER status was not. We may focus subsequent reports on a more detailed analysis of the population of patients receiving bisphosphonate therapy and the association with ER status.

11. Comment: In table 6 all previously published studies on the research question of interest are summarized. However, again this table is not clear. They did not clarify the used abbreviations.

Response: All abbreviations have been removed from the table.

12. Comment: Furthermore, not all information seems correct. The study by Ruiterkamp et al. did only include women with primary distant metastatic breast cancer (Citation: According to the database of the Netherlands Cancer Registry, 160,595 new patients were diagnosed with invasive breast cancer in the period 1995–2008. Of these patients, 8,031 (5.0%) had distant metastases at diagnosis (stage IV disease). from Ruiterkamp J, Ernst MF, de Munck L, et al. Improved survival of patients with primary distant metastatic breast cancer in the period of 1995-2008. A nationwide population-based study in the Netherlands. Breast Cancer Res Treat 2011;128:495-503.) and not patients with recurrent metastatic breast cancer as stated in table 6.
Response: We have removed the statement suggesting that the Ruiterkamp paper included patients with locoregional recurrence; we agree that the focus of this paper was the population of patients with distant metastasis.

13. Comment: The authors state in the discussion section, in paragraph 3 that both this study as well as the study by Andre et al. reported overall improvement in survival. As stated in comment 3, there are no survival times reported in this study and therefore this statement is not supported by any data.

Response: As stated in the response to the previous query, we have provided the following comparison of survival in the two time-based cohorts:

“Patients diagnosed during period B had a slightly longer median survival as compared to patients treated during period A, although this difference was not statistically significant (3.0 years vs 2.5 years, respectively; P=0.10).”

As indicated by the reviewer, with the inclusion of this statement, we feel that the comparison to the Andre study is reasonable.

14. Comment: The authors use the term de novo metastatic breast cancer, which could be changed into the more commonly used term of primary distant metastatic breast cancer.

Response: Although we feel that use of the term de novo metastatic breast cancer is appropriate, we acknowledge that there are other terms commonly used to describe this condition. We have therefore included the description of “primary distant metastatic breast cancer” at the same time we introduce the term “de novo metastatic breast cancer”, as follows:

“The goal of this study was to assess the impact of newer chemotherapy agents on overall survival of women with newly diagnosed de novo metastatic disease (i.e., primary distant metastatic breast cancer).”

15. Comment: In the introduction section, the authors state their research question which is well defined and clearly stated. Furthermore, they refer to other studies previously performed with the same research question (Giordano et al, reference number 4 and Chia et al, references number 5). However, this is far from a complete overview of previously published studies on this subject, as the authors also show in table 6 and state in the discussion. I suggest to refer to all six studies described in table 6 in the introduction, in the paragraph on the previous studies with similar research questions.

Response: We agree that in the context of an original research manuscript, it is challenging to offer a detailed analysis of each of the existing retrospective studies that take on the issue of survival in metastatic breast cancer. We have modified our reference list in the introduction to include all of the studies referred to in Table 6; however, we did not feel that there would be adequate “room” in the introduction or discussion to discuss each individually. As such, we offer the table to briefly summarize the key points and contrasts in these studies.

16. Comment: In the introduction, in the second paragraph ration is misspelled (should be ratio).

Response: This has been corrected.

17. Comment: In the introduction section, third paragraph the term metastatic breast cancer is mentioned for the first time. After that, the authors use the abbreviation MBC. In order to do so, the used abbreviation should be stated after the first use of the complete term (e.g. metastatic breast cancer (MBC)).

Response: This has been corrected.
18. **Comment:** In the discussion section, third paragraph the sentence "We found no advantage to the use of the newer chemotherapeutic agents and Anders found no survival advantage for women with hormone receptor-negative disease. It is not clear what the authors mean with Anders. Maybe they misspelled Andre and are they referring to the study by Andre et al. but no reference number is given.

**Response:** The reviewer is correct in this assertion; the reference (Andre et al.) is now cited correctly.

19. **Comment:** The final sentence is incorrect; the impact ...... appears to be is minimal.

**Response:** This has been corrected.

**Response to Comments from Dr. Briest:**

1. **Comment:** In the study you are presenting you performed an analysis of 274 patients treated for de novo metastatic breast cancer during a period of 20 years (1985 – 2004). The aim of the study was to associate the use of novel systemic therapies with survival of patients with breast cancer. For this reason the patients were divided into 2 groups: treatment period between 1985 and 1994 as well as 1994 and 2004.

The fact that the survival of patients with de novo metastatic breast cancer has improved over the last 20 years is without doubt. You state, that the contribution of conventional cytotoxic agents to the improvement of survival is minimal. We think, that such a small number of patients treated over such long period of time with supposedly so different regimens is not the way to prove the hypothesis. And: there are no data about radiation and surgery.

**Response:** We have taken an approach similar to other authors to address trends in survival in metastatic breast cancer, and we understand (and have delineated in our revised discussion) the limitations of our approach. We especially appreciate the reviewer’s suggestion to include radiation and surgical data in analyses like ours. Therefore, in our call to develop large, multi-institutional databases with highly granular data, we have stated the following:

“The impact of conventional chemotherapy on survival appears to be minimal in the context of our retrospective cohort; perhaps these findings warrant more definitive exploration through the formation of multi-institution databases. These multi-institutional databases should include ideally the same granularity of data as in our analysis and other, and should also capture surgical and radiation data to infer the benefits rendered from these modalities. Findings from such efforts could surely supplant the existent studies which draw from limited single-institution experiences.”

2. **Comment:** The correlation of bisphosphonates as a therapy with a better survival seems to be biased by the fact, that not all patients with bone metastasis received the appropriate therapy. For analysis only patients who got the standard treatment should be compared. If i.e. 31 patients are HER2 positive and only 19 received therapy, no effect can be awaited; the same with bone metastases.

**Response:** We feel that the finding of bisphosphonates predicting survival is quite interesting, especially given the caveat that the reviewer has cited. While it is true that not all patients with bone metastases appropriately received bisphosphonates, bisphosphonate therapy nonetheless was borne out as an independent predictor of survival on multivariate analysis. Had more patients appropriately received bisphosphonate therapy, one might wonder whether an even stronger effect size would be observed.

3. **Comment:** The paper is clearly laid out. All the key elements are present: abstract, introduction, materials and methods, statistical analysis, results, and conclusions.

The title and abstract describe the content of the article. The introduction is clear.
The authors describe the patient cohort and the results in a correct way. The discussion addresses the problems of the presented work.

The article does not seem to meet the question, which is the reason that we didn't advise it for publication.

**Response:** We appreciate these largely favorable comments from the reviewer, as we certainly put a great deal of effort into presenting our data in a logical and unbiased manner. We have revised our discussion to soften some of the inferences made from our study, as noted in the response to this reviewer's first comment. We hope that this will improve the integrity of the work and make it worthy of publication in your esteemed journal.

We greatly appreciate your excellent and detailed feedback, and hope that we have addressed your concerns in a satisfactory manner.

Sincere thanks,

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