Author's response to reviews

Title: Age-related differences in the clinical management of women with metastatic breast cancer

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Author's response to reviews:

BMC Cancer
To The Editor

Maastricht, March 13, 2006

Re: revised manuscript MS 1766346313846398

Dear Editor,

We are grateful to the two referees for the critical reading of our manuscript. Our responses to their comments have been added to this letter and, as a result of these comments, the manuscript has been revised at several places.

Formatting changes have been made on the title page, throughout the text and in the tables, according to the checklist.

We look forward to receiving your final decision regarding our manuscript.

Yours faithfully,

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Response to the referees' comments

Manuscript Number: 1766346313846398
Authors: Klaartje Manders, Lonneke V van de Poll-Franse, Geert-Jan Creemers, Gerard Vreugdenhil,
Reply to the comments of Dr. M. Pandey:

General:

....This study suffers from the same. The authors have not reported on performance status of the women making it difficult to interpret the data whether these differences were due to age alone or were due to poor performance status of these women.

Reply:

The lack of information with respect to performance status is inherent to the retrospective design of the study and is a problem which our study has in common with most studies that have to rely on the data recorded in clinical charts. However, our attempt to retrieve data on co-morbidity, which also give a picture of the physical well-being of the patient, was much more successful, and they have been added to Table 1 of the revised manuscript. They show that elderly patients were much more likely to suffer from one or more co-morbid conditions. However, as is also recognized by the reviewer, the small number of elderly patients (n=20), did not allow multivariate analyses in which the independent effect of age and other factors could be assessed. We know from other studies that poor performance status and co-morbidity play an important role in the prognosis of elderly patients with metastatic breast cancer and limit the use of chemotherapy or immuno-modulators, which are associated with more severe side-effects compared to hormonal therapy. In our revised manuscript we have referred to a review paper by Kimmick and Muss on this subject (Reference number 14), and have added the following sentence: "As was confirmed by our findings, planning therapy is not always straightforward in older patients because they are more likely to present with co-morbid illnesses and frailty that limit therapeutic choices[14].

As is indicated in our discussion, a comprehensive geriatric assessment may be a useful tool for oncologists to predict the risk of toxicity and/or activity of systemic treatment in elderly patients with metastatic disease which patients are fit enough to undergo aggressive systemic treatment and help them to master this complex decision-making process.

Major Compulsory Revisions:

1. The authors should also report their results for single versus multiple metastases, size of the metastasis, etc.

Reply:
During the course of their disease, the large majority of the patients with metastatic disease will develop metastases at multiple sites. From Table 1 it can be deduced that the mean number of metastatic sites is larger for younger patients.

2. The data should be presented in absolute numbers. Actually more women in 50-69 group have T4 lesions than women in >70 group ... due to small denominator.

Reply:
The results of the statistical tests have been added to Table 1 and show that the age groups do not differ significantly with respect to T-stage.

3. There are some errors in data in Table 1 age 50-69 T3 1% with only 62 women in the group how one subgroup can have 1%? It is better to give absolute number rather than percentage.

Reply:
The reviewer is correct. This should be 2% (1/62=0.16). In the revised manuscript both the absolute numbers and the percentages have are given in Table 1.
Reply to the comments of Dr RJ Lelle

Major Compulsory Revisions:

1. As the authors state, all clinical charts were reviewed. Subsequently, information on co-morbidity such as cardiovascular disease, diabetes, hypertension, medication etc. is available. These data need to be included.

Reply:
Data on co-morbidity, as well as significance levels for the differences between the age groups, have been added to Table 1. These figures illustrate (as one would have expected) that the risk of having one or more co-morbid conditions is strongly related to age.

2. Page 3, 3rd paragraph, line 7: which 281 patients? Does that mean that 148 died of causes other than breast cancer? This would be a very large number. What are the characteristics of these patients?

Reply:
These 281 patients were the patients who all patients who were known to have died. This information is reported to the Eindhoven cancer registry. It is estimated that the ECR was complete for the patients from the two hospitals with respect to the occurrence of distant disease or loco-regional recurrence. Only the clinical charts of these patients were reviewed, so no information is available for the 148 who died of causes other than breast cancer, except for their mean age at the time of dying, which was 77 years.

The following information was added to the methods to clarify this issue:
"Information on date of death is obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Central Bureau for Genealogy. The latter is an institution that collects data on all deceased Dutch citizens via the municipal registries. In this way, information on patients who had moved outside the registry area was also obtained. Patients who died outside the Netherlands were wrongly considered as 'being alive'. However, the estimated proportion of these patients was less than 0.3%.

And:
"The remaining 148 patients were assumed not to have died from breast cancer. Their mean age at death was 77 years."

3. As the paper is focusing on age, more details on age distribution should be given (e.g. as figure).

Reply:
A Figure was added to the results section, showing the age distribution of the patients per 10-year age group. The following text was added to the results section:
"The mean age of the patients was 58 years (range: 21-88) at the time of diagnosis of the primary tumor and 61.5 years (range: 23-93) at the time of diagnosis of metastatic disease (Figure)."

4. The authors have chosen three age groups....How many patients belong to this age group and would it make sense to list those as a fourth group?

Reply:
As can be derived from the Figure (see point 3), there were only 5 patients who were younger than 40 years at the time of diagnosis of their primary tumor. This number is too small to determine if the treatment for this age group really differs from the older age groups.

5. Reporting of statistical testing needs to be revised: ...Statistical significance should be given instead of using vague statements such as "much more likely", etc. Table 1 should include results of statistical testing between age groups, at least for the data on metastases

Reply:
Results of statistical testing have been added to Table 1 and the statements in the results have been
brought into line with the outcome of the statistical testing. The tables are meant as a supplement to Table 2; in Table 2 all relevant comparisons with respect to age-related differences have been supported by statistical testing. Tables 3a-c give the reader insight into the type of drugs used and give an impression of the reasons for postponement of chemotherapy and dose reductions and response rates. Moreover, because of the large number of categories for the variables in Tables 3a-c, the numbers per category become very small and random variation becomes large, making statistical testing less appropriate.

Minor Essential Revisions:

Data in Table 2 would be clearer if p-values larger than or equal to 0.05 were indicated as "not significant"

Reply:
We do not agree with the view of the reviewer. Regarding the exploratory character of the study of the relationship between age and treatment of metastatic disease, we think that one should be careful to rule out small but clinically significant differences (i.e., false-negative results). By giving the exact p-value for the non-significant outcomes, the reader will be able to identify such potentially clinical significant (but statistically non-significant) differences.

In table 2 all percentages in brackets should be marked as such and not only in the first column.

Reply:
In the revised manuscript, all percentages in brackets have been marked as such.