Author's response to reviews

Title: Clinical management of women with metastatic breast cancer: a descriptive study according to age group.

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Author's response to reviews: see over
Maastricht, May 1, 2006

Re: manuscript MS 1766346313846398, second revision

Dear Editor,

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

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

Yours faithfully,

Adri C. Voogd, assistant professor of clinical epidemiology

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Reply to the comments of Dr M. Pandey:

**General**

…. Based on this information the authors should now conclude that their data is not robust enough to say for sure that the differences in the treatment observed are true differences due to age (as high prevalence of comorbid conditions are confounders and small sample size for patients above 70 is a limitation). The authors can further provide a cross tab of treatment received and co-morbid conditions in the following format to clear the picture. …..

Reply:

We agree with the referee that the number of patients per age group is too small to perform a robust analysis of the relationship between age, co-morbidity and treatment and that it may be too premature to conclude that the differences in treatment can be attributed to age. For that reason we have changed the title of our manuscript, in a way that it no longer suggest that it was our aim to disentangle the effect of age and co-morbidity (i.e., “Clinical management of women with metastatic breast cancer: a descriptive study according to age group.”)

Moreover, we have added the following sentence to our conclusion to underscore the complexity of the matter: “*However, more research is needed to understand the age-related differences in the treatment of metastatic breast cancer, and especially how comorbid illnesses and frailty limit therapeutic choices.*”

Still, we think that the straightforward presentation of the information on co-morbidity in Table 1, is a good illustration of the potential confounding effect of this factor. Numbers become too small to make a further subdivision within each age group according to co-morbidity and treatment, as is illustrated by the next Table. Although, one quick view might lead to the conclusion that age is a more important factor than co-morbidity regarding the decision for radiotherapy, chemotherapy and hormonal treatment, statistical testing becomes a tricky business because of the limited power of the tests.
Table. Proportion of patients receiving radiotherapy, chemotherapy or hormonal treatment, according to age group and co-morbidity.

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Hormonal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-49</td>
<td>50-69</td>
<td>70+</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% (1/1)</td>
<td>74% (17/23)</td>
<td>50% (6/12)</td>
</tr>
<tr>
<td><strong>Lung Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% (5/5)</td>
<td>63% (5/8)</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>-</td>
<td>80% (4/5)</td>
<td>43% (3/7)</td>
</tr>
<tr>
<td><strong>1 comorbid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>condition</td>
<td>100% (9/9)</td>
<td>71% (24/34)</td>
<td>56% (9/16)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>72% (18/25)</td>
<td>68% (19/28)</td>
<td>0% (0/4)</td>
</tr>
</tbody>
</table>

**Major Compulsory Revisions:**

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

Reply:
Contrary to the interpretation of the referee, the number of subsequent metastases is higher in younger patients (see Table 1). In our discussion the differences between older and younger patients regarding their metastatic pattern have been addressed in several ways (see page 9 and 10, where the role of co-morbidity, frailty, differences in metastatic pattern and age-related differences in survival following the diagnosis of metastatic disease have been discussed). Thus, we have tried to avoid giving the impression that age is the only explanatory factor for the differences in treatment between the age groups. Moreover, in the conclusion of the abstract we state that “Part of this difference could be explained by their shorter survival time following the diagnosis of metastatic disease and their lower risk of developing brain and bone metastases.” And in the conclusion of our paper we have added the following sentence: “However, more research is needed to understand the age-related differences in the treatment of metastatic breast cancer, and especially how comorbid illnesses and frailty limit therapeutic choices.”

2. … what statistical test were applied? Wouldn’t it be better to club T3, T4 and Tx…

Reply:
We used Fisher’s exact test to compare the frequency distributions with respect to tumor size between the three different age groups. A note is given at the bottom of Table 1 and Table 2, explaining the statistical tests used and their underlying assumptions. This information, and the assumptions underlying the tests, has also been added to the Methods section of the revised manuscript (“The frequency distributions of the different variables between the three age groups were compared by means of the likelihood ratio
Chi-square test or, when expected counts were less than five, Fisher’s Exact test. The Kruskal Wallis test was used to make comparisons between the three age groups with respect to continuous variables. The interval from the diagnosis of the primary tumor until diagnosis of metastatic disease and the interval from the diagnosis of metastatic disease until death of the three age groups were compared by using the logrank-test.

One argument against combining these categories is that T3 and T4 tumors are rather different clinical entities. By using Fisher’s exact test, we which argues against clubbing these

3. .. the percentage should be 70.

Reply:
This error has been corrected.

4. What statistical tests have been applied to calculate individual p-values for site of metastases (until death)…

Reply:
We used Fisher’s Exact test or the Chi-square test, depending on proportion of cells with expected counts less than 5. See also our reply to Comment 2.

5. 148 patients assumed not to have died of breast cancer? On what basis the assumption was made? Were these patients disease-free prior to death? It should be noted that this number is higher than the number of patients presented in the present manuscript.

Reply:
In the method of our paper we have given the following information:
“All patients with a history of breast cancer who died after December 31, 1999 and who had been treated at the Catharina Hospital in Eindhoven or at the Máxima Medical Center in Veldhoven were selected for the study. These hospitals are both non-academic, teaching hospitals. According to the data of the ECR, 133 of these 281 patients had developed distant metastases, including 11 patients with metastatic disease at the time of diagnosis of the primary tumor. The remaining 148 patient were assumed not to have died from breast cancer. Their mean age at death was 77 years.”
Thus, the assumption that 148 patients did not die of breast cancer was based on the information provided by the cancer registry. We do not claim that this information is 100% complete and therefore we have given the mean age at death, which was 77 years and which illustrates that it is very likely that the large majority of these 148 patients did not die from breast cancer.

6. page 6 statistical analysis…
7. … see earlier comments on statistical tests.

Reply:
See our reply to Comment 2.

a-d

Reply:
See our reply to the general comment of the referee and our reply to Comment 1, to illustrate how we have tried to discuss all possible explanations for the age-related differences in management of metastatic breast cancer, including the age-related difference in co-morbidity, metastatic pattern and survival time following the diagnosis of metastatic disease.

e. Would the authors like to comment on receptor positivity and choice of hormone treatment? Were women who were receptor negative still given hormone treatment?

Reply:
Unfortunately, we had no information on steroid receptor at our disposal. Therefore, we feel that a further discussion of this subject does not contribute to the interpretation of our results.

9. …it is not possible to conclude that that there are true age-related differences. I feel that the authors should conclude that age is a surrogate for other factors that influence choice of treatment in these patients. The word age-related should also be deleted form the title.

Reply:
See our reply to the general comment of the referee and our reply to Comment 1, to illustrate how we have tried to discuss all possible explanations for the age-related differences in management of metastatic breast cancer, including the age-related difference in co-morbidity, metastatic pattern and survival time following the diagnosis of metastatic disease. The title of the paper has been changed to avoid the impression that the age-related differences can be explained by age alone.