PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Survival in breast cancer patients with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval
AUTHORS	Cetin, Karynsa; Christiansen, Christian; Svaerke, Claus; Jacobsen, Jacob; Toft Sørensen, Henrik

VERSION 1 - REVIEW

REVIEWER	Christian Schindlbeck Department of Obstetrics and Gynecology, Klinikum Traunstein, Academic teaching hospital of the University of Munich, Traunstein, Germany
REVIEW RETURNED	02-Feb-2015

GENERAL COMMENTS	The manuscript in general is well written. However, some questions have to be addressed: 1: med. FU was 1.12 years (0.24-2.73), median bone metastasis free interval (BMFI) after primary diagnosis was 1.85 years (0.16-3.78), only 15 % had a BMFI >5 years. The median FU time and median BMFI are very short, and the 1-year survival rate of all patients was only 52 %. Looking at time cohorts, outcome of patients diagnosed between 2002 and 2006 was similar to the patients diagnosed between 1997 and 2001, despite advances in adjuvant systemic therapy. This should be discussed, as modern chemo-or hormonal treatment potentially prolongs recurrence free survival. 2. Kaplan-Meier curves for Overall Survival in dependence of BMFI would be helpful to illustrate the findings 3. In patients with BMFI < 1 year, the 5 year OS was significantly higher compared to those with a longer BMFI. An explanation could be that in these cases BM were diagnosed in an asymptomatic state by routine staging procedures performed at primary diagnosis, thus offering early and specific therapy. There is an ongoing discussion about the usefulness of routine staging procedures in asymptomatic patients. Results of this study would support application of standard staging examinations. This should be mentioned in the discussion

REVIEWER	Joon Jeong Gangnam Severance Hospital, Yonsei University
REVIEW RETURNED	12-Feb-2015

GENERAL COMMENTS	The authors tried to identify prognostic factors in breast cancer patients with bone metastasis using national cancer registry. In a large number of patients over 2,000, they showed that the stage and

	BMFI are good prognostic marker. However, with respect to BMFI, it is unusual finding that survival was highest in women with a BMFI < 1years and even better than in women with BMFI ≥ 5 years. Metastasis-free interval (MFI) is a well-established prognostic marker and short MFI is poor prognostic marker. A prognostic significance of MFI is reproducible in several studies. Of course, there is evidence that the patients with de novo bone metastasis showed a better outcome than the patients with distant relapse in skeletal system. However, it lacks evidence that women with de novo bone metastasis showed a better treatment outcome than women with late bone relapse. Furthermore, in de novo bone metastasis, exact BMFI is unknown, not 0 or less than 1yr. So, it is more reasonable to exclude de novo bone metastasis cases when analyze BMFI as a prognostic factor. It may be associated with missing data on PR, HER2, treatment information, and information of visceral metastasis, as the authors recognized it in limitations. Particularly, the absence of adjustment with visceral metastasis or concurrent multiple metastases may result in the conclusion on BMFI and act as a confounding finding in utilization of BMFI as a prognostic factor. Although the authors tried to overcome this huddle with the adjustment of a CCI score, it seems that a CCI score dose not fully reflect the status of multiple metastasis.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. "med. FU was 1.12 years (0.24-2.73), median bone metastasis free interval (BMFI) after primary diagnosis was 1.85 years (0.16-3.78), only 15 % had a BMFI >5 years. The median FU time and median BMFI are very short, and the 1-year survival rate of all patients was only 52 %. Looking at time cohorts, outcome of patients diagnosed between 2002 and 2006 was similar to the patients diagnosed between 1997 and 2001, despite advances in adjuvant systemic therapy. This should be discussed, as modern chemo-or hormonal treatment potentially prolongs recurrence free survival."

Our study cohort included women who were diagnosed with breast cancer and either presented with or were subsequently diagnosed with bone metastasis. Importantly, we did not examine outcomes among women diagnosed with breast cancer by time period of diagnosis. Therefore, we believe the reviewer may be referring to data presented in Tables 1 and 2 in the manuscript, and we are confident that some further explanation can satisfy the concerns raised.

Table 1 describes the cohort of women with breast cancer and bone metastases overall and by stage of disease at breast cancer diagnosis according to various demographic and clinical characteristics, and Table 2 describes the cohort of women with breast cancer and bone metastases overall and by length of bone metastasis-free interval (BMFI) according to various demographic and clinical characteristics. One of these characteristics is time period of breast cancer diagnosis. In looking at the distributions of stage of disease at initial breast cancer diagnosis (from Table 1) and length of BMFI (from Table 2) within each time period of breast cancer diagnosis, it appears as though breast cancer patients diagnosed in later years are more likely to present with metastatic disease and demonstrate a shorter time to bone metastasis.

However, this pattern is only a result of the study timeframe and the nature of the patients included in our study. We included all patients who were diagnosed with breast cancer in 1997-2011 who also had a simultaneous or subsequent diagnosis of bone metastasis during the same time period. This means that patients diagnosed with breast cancer in earlier years had more time to develop bone metastases and be included in our study than patients diagnosed with breast cancer in later years.

For example, women diagnosed with breast cancer in 1997 to 2001 had 10 to 14 years (1998-2011) for their development of bone metastasis, whereas women diagnosed with breast cancer in 2007 to 2011 had <1 to 4 years (2008-2011) for their development of bone metastasis. Because of this, it makes sense that among our cohort of breast cancer patients with bone metastases, there is greater representation of metastatic disease at breast cancer diagnosis and shorter lengths of BMFI in women diagnosed with breast cancer in more recent years. (For women who present with localized breast cancer, for example, the median time to bone metastasis is longer.) Had women diagnosed with breast cancer in more recent years been followed longer, more would have developed bone metastases and been included in our study. And these patients would have been distributed more evenly across stage of disease at breast cancer diagnosis and length of BMFI, as seen in patients diagnosed with breast cancer in 1997-2001.

This is why we controlled for time period of diagnosis in our Cox proportional hazards regression analyses to assess whether the risk of death in breast cancer patients with bone metastases varied by stage at the time of breast cancer diagnosis and by length of BMFI.

If the editor agrees that this is a potential point of confusion for readers, we have added an abbreviated version of the above explanation in the third paragraph of the results section.

2. "Kaplan-Meier curves for Overall Survival in dependence of BMFI would be helpful to illustrate the findings"

We considered including these figures in the manuscript (KM curves stratified on BMFI and KM curves stratified on stage of disease at breast cancer diagnosis), but we were also mindful that we already have 5 data tables. And we feel each of these tables presents important information. Table 3 in the manuscript very concisely presents the data in the KM figures we would have included. However, if the editor feels the figures should be included, we are happy to include them.

3. "In patients with BMFI < 1 year, the 5 year OS was significantly higher compared to those with a longer BMFI. An explanation could be that in these cases BM were diagnosed in an asymptomatic state by routine staging procedures performed at primary diagnosis, thus offering early and specific therapy. There is an ongoing discussion about the usefulness of routine staging procedures in asymptomatic patients. Results of this study would support application of standard staging examinations. This should be mentioned in the discussion"

We appreciate the reviewer's perspectives on this, and we agree with the reviewer's proposed explanation. In the discussion we state: "It is possible that the prolonged survival we observed among patients with a BMFI of <1 year at least partly results from occurrence of BM that are asymptomatic or less severe than those diagnosed later. This hypothesis is supported by our finding that the proportion of patients presenting with at least one SRE at the time of BM diagnosis was lowest in those with a BMFI of <1 year." As the reviewer points out, it could be that identifying asymptomatic patients with bone metastasis allows for early and specific therapy, which leads to better outcomes. This could argue for routine staging examinations in asymptomatic patients. However, we are hesitant to draw this kind of conclusion, because our data do not directly provide evidence that early detection and treatment of bone metastasis leads to better outcomes. Importantly, this is pointed out by the second reviewer: "However, it lacks evidence that women with de novo bone metastasis showed a better treatment outcome than women with late bone relapse."

Therefore, we feel we strike the right balance in offering reasons for our observation without reaching too far with our conclusions.

Reviewer #2:

1. "The authors tried to identify prognostic factors in breast cancer patients with bone metastasis using national cancer registry. In a large number of patients over 2,000, they showed that the stage and BMFI are good prognostic marker. However, with respect to BMFI, it is unusual finding that survival was highest in women with a BMFI < 1years and even better than in women with BMFI ≥ 5 years. Metastasis-free interval (MFI) is a well-established prognostic marker and short MFI is poor prognostic marker. A prognostic significance of MFI is reproducible in several studies. Of course, there is evidence that the patients with de novo bone metastasis showed a better outcome than the patients with distant relapse in skeletal system. However, it lacks evidence that women with de novo bone metastasis showed a better treatment outcome than women with late bone relapse. Furthermore, in de novo bone metastasis, exact BMFI is unknown, not 0 or less than 1yr. So, it is more reasonable to exclude de novo bone metastasis cases when analyze BMFI as a prognostic factor. It may be associated with missing data on PR, HER2, treatment information, and information of visceral metastasis, as the authors recognized it in limitations. Particularly, the absence of adjustment with visceral metastasis or concurrent multiple metastases may result in the conclusion on BMFI and act as a confounding finding in utilization of BMFI as a prognostic factor. Although the authors tried to overcome this huddle with the adjustment of a CCI score, it seems that a CCI score dose not fully reflect the status of multiple metastasis."

We sincerely appreciate this thoughtful review. Several important comments/suggestions were made.

First, the reviewer is correct that we used the Danish Cancer Registry to identify women diagnosed with breast cancer in Denmark. However, importantly, we also relied on data from the Civil Registration System, the Danish National Registry of Patients, and the Danish National Pathology Registry. The success of our project hinged on access to this entire network of data of population-based and medical databases.

With respect to our finding that survival appeared to be highest in breast cancer patients who had the shortest length of BMFI (0 to <1 year), we agree with the reviewer that on the surface this seems counterintuitive. It was an unexpected finding. In the discussion, we offer explanations for this observation, including the one described by the reviewer. Specifically, we state: “It is possible that the prolonged survival we observed among patients with a BMFI of <1 year at least partly results from occurrence of BM that are asymptomatic or less severe than those diagnosed later. This hypothesis is supported by our finding that the proportion of patients presenting with at least one SRE at the time of BM diagnosis was lowest in those with a BMFI of <1 year.” We also discuss the possibility that breast cancer patients who present with bone metastasis at the time of breast cancer diagnosis may have an indolent, chronic disease course with prolonged survival, particularly when the metastatic breast cancer remains confined to the skeletal system.[1-3] Additionally, after giving this more thought based on this reviewer’s comment, it could also be that better survival in patients with a BMFI 0 to <1 year reflects lead-time bias based on the fact that there is likely intensive follow-up during the first year after a diagnosis of breast, which could uncover asymptomatic bone metastasis. We have added this statement to the relevant paragraph in the discussion.

Importantly, we do not believe that including these patients (those with BMFI 0 to <1 year) detracts from the finding that among the rest of the patients diagnosed with bone metastases in our study cohort (i.e., those with a BMFI ≥1 year), longer BMFI was associated with decreased mortality risk, because we analyze these patients separately. Additionally, by including these patients, we feel we contribute something unique to the literature on this. As we explained in our manuscript, the majority of other studies examining the relation between length of the metastasis-free interval and survival in metastatic breast cancer patients have excluded women who presented with distant metastases at breast cancer diagnosis. We did uncover one relatively small study that was similar to ours in its inclusion of women with metastatic bone lesions at the time of breast cancer diagnosis as well as

women who developed bone metastasis later in their disease course.[4] They found that women with a longer BMFI (≥24 months) or a BMFI of zero (bone metastasis at time of breast cancer diagnosis) demonstrated longer survival compared with those who had a shorter BMFI (<24 months), but this association was not statistically significant. The nature of the relationship between length of BMFI and survival was consistent with that observed in our larger population-based study.

Lastly, the reviewer suggests that perhaps because we did not fully describe the co-occurrence of multiple metastases or visceral metastases, the presence of these may have confounded the relationship we observed between length of BMFI and survival in these patients (presumably particularly for those with a BMFI of 0 to <1 year since was an unexpected finding). To be clear, we did control for the presence of other metastases prior to or at the time of bone metastasis diagnosis to the best of our ability (it was a simple yes/no descriptor). But we did not identify the site or number of these other metastases, and we do not know the validity of coding for metastases to other distant sites in the Danish National Registry of Patients. This is a limitation we were willing to tolerate, because although this additional clinical data would have certainly informed our analyses, we do not believe that it would have changed the directional nature of the relationship between length of BMFI and survival.

1. Leone BA, Romero A, Rabinovich MG, et al. Stage IV breast cancer: clinical course and survival of patients with osseous versus extraosseous metastases at initial diagnosis. The GOCS (Grupo Oncologico Cooperativo del Sur) experience. Am J Clin Oncol 1988;11:618-622.
2. Sherry MM, Greco FA, Johnson DH, et al. Metastatic breast cancer confined to the skeletal system. An indolent disease. Am J Med 1986;81:381-386.
3. Sherry MM, Greco FA, Johnson DH, et al. Breast cancer with skeletal metastases at initial diagnosis. Distinctive clinical characteristics and favorable prognosis. Cancer 1986;58:178-182.
4. Yamashita K, Koyama H, Inaji H. Prognostic significance of bone metastasis from breast cancer. Clin Orthop Relat Res 1995;March(312):89-94.

VERSION 2 – REVIEW

REVIEWER	Christian Schindlbeck Department of Obstetrics and Gynecology, Klinikum Traunstein, Traunstein, Germany
REVIEW RETURNED	03-Mar-2015

GENERAL COMMENTS	None of the comments of reviewer #1 to the original version have been addressed in the revised manuscript 1. Looking at time cohorts, outcome of patients diagnosed between 2002 and 2006 was similar to that of the patients diagnosed between 1997 and 2001, despite advances in adjuvant therapy. This should be discussed. 2. In patients with BMFI < 1 year, the 5 year OS was significantly higher compared to those with a longer BMFI. An explanation could be that in these cases BM were diagnosed in an asymptomatic state by routine staging procedures performed at primary diagnosis, thus offering early and specific therapy. There is an ongoing discussion about the usefulness of routine imaging procedures in asymptomatic patients. Results of this study would support application of standard istaging procedures. This must be discussed.

REVIEWER	Joon Jeong Department of Surgery, Gangnam Severance Hospital, Yonsei University, Seoul, Korea
REVIEW RETURNED	12-Mar-2015

GENERAL COMMENTS	I have no comments.

VERSION 2 – AUTHOR RESPONSE

None of the comments of reviewer #1 to the original version have been addressed in the revised manuscript

1) Looking at time cohorts, outcome of patients diagnosed between 2002 and 2006 was similar to that of the patients diagnosed between 1997 and 2001, despite advances in adjuvant therapy. This should be discussed.

As explained in our initial response to this comment, we did not stratify any outcomes by calendar year of diagnosis and in fact controlled for time period of diagnosis in our Cox proportional hazards regression analyses to assess whether the risk of death in breast cancer patients with bone metastases varied by stage at the time of breast cancer diagnosis and by length of BMFI. However, we recognize the reviewer's point that data presented in Tables 1 and 2 may suggest that outcomes are similar over time despite advances in therapy. This pattern arises based on the study timeframe and the nature of the patients included for study, and we agree with the reviewer that this is an important point to highlight for readers. We added the following explanation to the third paragraph under RESULTS – Patient characteristics, on page 10:

"Just over one third (36%) of our study cohort were diagnosed with breast cancer in the earliest time period (1997-2001); 42% were diagnosed in 2002-2006; and 22% were diagnosed in 2007-2011. There was greater representation of metastatic disease at breast cancer diagnosis and shorter lengths of BMFI in women diagnosed with breast cancer in more recent years. Importantly, this simply reflects the fact that these women had less time to develop BM and be included in our study compared with women diagnosed with breast cancer in earlier years. For example, women diagnosed with breast cancer in 1997 to 2001 had 10 to 14 years (1998-2011) for their development of BM, whereas women diagnosed with breast cancer in 2007 to 2011 had <1 to 4 years (2008-2011) for their development of BM. Had women diagnosed with breast cancer in more recent years been followed longer, more would have developed BM and been included in our study. And these patients would have been distributed more evenly across stage of disease at breast cancer diagnosis and length of BMFI, as seen in patients diagnosed with breast cancer in 1997-2001."

2) In patients with BMFI < 1 year, the 5 year OS was significantly higher compared to those with a longer BMFI. An explanation could be that in these cases BM were diagnosed in an asymptomatic state by routine staging procedures performed at primary diagnosis, thus offering early and specific therapy. There is an ongoing discussion about the usefulness of routine imaging procedures in asymptomatic patients. Results of this study would support application of standard istaging procedures. This must be discussed.

We agree that this is one possible explanation. We have modified the fifth paragraph of the DISCUSSION on page 21 to clearly articulate this possibility:

"It is possible that the prolonged survival we observed among patients with a BMFI of <1 year at least partly results from occurrence of BM that are asymptomatic or less severe than those diagnosed later. There is likely intensive follow-up during the first year after a diagnosis of breast cancer, which could uncover these types of BM. Consequently, longer survival time observed in these patients could simply reflect lead-time bias. This hypothesis is supported by our finding that the proportion of patients presenting with at least one SRE at the time of BM diagnosis was lowest in those with a BMFI of <1 year. Alternatively, detection of bone metastases in asymptomatic patients could allow for early and targeted therapy, leading to better outcomes."