Author's response to reviews

Title: Skeletal metastasis diagnosed without bone pain showed fewer skeletal related events and death than those with bone pain in post-operative breast cancer patients

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Author's response to reviews:

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RE: MS: 1127878436306790

Post-operative breast cancer patients diagnosed with skeletal metastasis without bone pain had fewer skeletal related events and deaths than those with bone pain. Mitsuru Koizumi, Masataka Yoshimoto, Fujio Kasumi, Takuji Iwase and Etsuro Ogata

We have changed a title a bit.

Dear Sir:

We revised the above manuscript according to the Editorial requests and Reviewers’ comments. Please find our point-by-point reply below.

We thank the Editorial Staff and Reviewers; the manuscript has been improved by their valuable advice and comments. However, we could not answer all the comments properly, because this investigation was a retrospective study and some important data were missing.

Editorial requests

1. Please also let us know if ethical approval was required for this study. If ethical approval was granted, a statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval,
with a reference number where appropriate. If no approval or ethical review was required, please let us know the circumstances under which it was waived.

2. Similarly, please let us know if informed consent was required in this study. If informed consent was obtained from patients, please note this in the manuscript. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Reply to 1 and 2

This study had been approved by Institutional Review Board. However, this study was a retrospective one so informed consent was not required.

We have included the following description at the end of Patients part of the Methods section: “Above procedures were conducted as routine clinical practice at the Cancer Institute Hospital, Tokyo, Japan”; and “This retrospective study was approved by the Institutional Review Board. Informed consent was not required as this was a retrospective study” was added at the end of Methods section. And we added the word “retrospective” in the last paragraph of Background:

“The aim of the present retrospective study was to clarify the clinical meaning of bone pain at diagnosis of skeletal metastasis by investigating the relationship of pain to SRE and survival, and comparing this with other factors.”

3. We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

Reply

We have asked for copy editing from International Science Editing.

4. Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

Reply

All changes in the revised manuscript were highlighted in red.
5. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Reply

We have changed the manuscript accordingly.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Point-by-point reply to reviewers’ comments:

Referee 1

1. The proposal that authors suggest is very well-known. If the skeletal event diagnosed with pain then we surely think that metastatic event happening in the bone is highly aggressive. Therefore the what the authors found in their study is not surprising to me.

Reply

We agree with this opinion. The comment of “If the skeletal event diagnosed with pain then we surely think that metastatic event happening in the bone is highly aggressive.” is a common view of clinicians. However, there are few publications that verify this view. This is the reason why we performed the present study.

Referee 2

Minor essential revisions:

1. The authors have to clarify if they used a validate PAIN EVALUATION METHOD

Reply

The information regarding the presence or absence of pain was reviewed in Patients Records (Cards). In the records, patients were asked about the presence of pain and the site of pain, and then the results were noted. However, pain evaluation methods and descriptions were variable (not uniform) in the records therefore, we could not evaluate pain quantitatively by a visual-analog-scale or similar methods.

We added the following description “In the inquiry card, patients were asked
about the presence or absence of pain, and sites of pain. The grade of pain (visual-analog scale) was obtained from a limited number of patients. Therefore, the focus was on the presence or absence of pain” in the pain and values of tumor markers in the diagnosis of skeletal metastasis part of the Methods section.

“Drawbacks with this retrospective study include using a database of breast cancer patients in our institute, where data collection began approximately 30 years ago. The records lacked several important pieces of information including tumor grade and HER2/neu status, and it employed the local (Japanese) pathological classification system. A second database was utilized for data analysis of skeletal metastasis in breast cancer patients. This database lacked information regarding the type of skeletal metastasis (lytic, blastic, and mixed type), and both databases lacked information regarding the pain condition of individuals. Patients’ records (cards) were checked with regard to the presence or absence of pain at diagnosis of skeletal metastasis but there was no detailed information about the pain condition of individuals. Therapy for breast cancer has changed over time with the advancement of chemotherapeutic agents and their combination, hormones and molecular targeting agents (HER2/neu). The concept of standard therapy for skeletal metastasis has changed with the advent of bisphosphonates. In Japan, bisphosphonates were first approved for use in the treatment of skeletal metastasis at the end of 2004, and actual use began in 2005. Therefore, there were limited data regarding the use of bisphosphonates in this study and this prevented analysis of the impact of bisphosphonate treatment” was added to the Discussion section.

2. The authors should include in the univariate analysis the HERE/neu status and the grading of the tumours

Reply

We agree that information regarding HER2 status is very important because it is strongly related to prognosis or aggressiveness of tumours. However, we do not have HER2 data. The histological grade by Bloom and Richardson is very helpful. We also considered that the application of histological grade by Bloom and Richardson would improve the manuscript, and asked pathologists regarding the possibility of re-revaluation. However, pathologists could not re-evaluate pathological specimens from so many patients.

We have added the following description in the Discussion section: “Drawbacks with this retrospective study include using a database of breast cancer patients in our institute, where data collection began approximately 30 years ago. The records lacked several important pieces of information including tumor grade and HER2/neu status, and it employed the local (Japanese) pathological classification system. A second database was utilized for data analysis of skeletal metastasis in breast cancer patients. This database lacked information regarding the type of skeletal metastasis (lytic, blastic, and mixed type), and both
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3. Did the authors excluded from the analysis the patients treated with analgesic for other clinical reasons (ex. visceral metastases) at the moment of bone metastases diagnosis?

Reply

Bone pain was judged by the sites of pain and nature of pain, with the information of the spread of tumors (metastatic sites; for example, liver, lymph nodes, brain etc). We omitted the use of analgesics for other clinical reasons where possible.

4. Did the authors considered the statistical interaction between number of metastases and pain at the moment of bone metastases diagnosis?

Reply

We have analyzed single and multiple numbers of bone metastasis in Tables 3 and 4.

We included this information (solitary vs multiple metastasis) as an adjusting factor in the statistical analysis in Tables 3 and 4.

Moreover, according the next comment, we have added the data; please refer to the next comment and its reply.

5. I strongly suggest to investigate the correlation between pain and SRE & survival in the separately in the following two subpopulations:

a) single bone metastasis patients at the moment of bone metastases diagnosis

b) multiple bone metastases patients at the moment of bone metastases diagnosis

Reply
We have performed the sub-analysis between the presence of pain and SRE or CSD in groups of solitary and multiple skeletal metastasis as suggested.

1. We have added the information relating to skeletal metastasis number in Table 1.

2. We have added Figure 5.

3. We have added the following descriptions:

In the Methods section:

“In addition, the number of bone metastatic lesions (solitary or multiple) at the time of diagnosis of skeletal metastasis was an important factor. The importance of this factor was reported (14) as solitary bone metastasis was a significant favorable prognostic factor compared with multiple bone lesions at initial presentation. Stratified sub-analysis was conducted of groups of individuals with a solitary bone lesion or multiple bone lesions at their initial presentation of skeletal metastasis.”

In the Results section:

“The Kaplan-Meier’s curves in patients with or without pain are presented in figure 5. Patients with a solitary bone lesion and those with multiple bone lesions were analyzed separately. This analysis was performed using SRE and CSD as events and the date of diagnosis of bone metastasis as the starting point. In patients with a solitary bone lesion, individuals with pain showed a significantly higher incidence of SRE than those without pain but showed no significant differences in terms of CSD. In patients with multiple bone lesions, individuals with pain showed a significantly higher incidence of SRE and CSD than those with no pain but CSD incidence was less than that of SRE.”

Referee 3

MAJOR COMPULSORY REVISION

1. One of the most relevant bias in the paper is in the definition of SRE. Commonly (in RCT) SRE includes fracture, hypercalcemia, radiotherapy, spinal cord compression, orthopaedic surgery. The authors included in SRE also the use of morphine for pain. Furthermore it is not clear if radiotherapy for bone was for analgesia. Because the risk of SRE increases twofold after the first SRE (Hortobagy GN J Clin Oncol 1998) (Major PP Am J Clin Oncol 2005) it is not surprising that in patients with pain the use of morphine and radiotherapy (often
used for analgesia) were more frequent than in patient without pain. Patients with these two “SREs” account for about the 66% in the pain group. The inclusion of morphine use and radiotherapy for pain in SRE classification resulted in an overestimation of the incidence of SRE in this group.

Reply

We agree with this comment. The RT and morphine use were artificial events. The inclusion of morphine use and radiotherapy for pain in SRE classification may have resulted in an overestimation of the incidence of SRE in this group.

The patients who had been treated with morphine developed other SREs afterward. We believe that morphine use is reasonable to include in SREs.

Radiotherapy was used most frequently. The data collection began in 1988. The concept of standard therapy for bone metastasis has changed during the study period; we were concerned about this point.

We performed sub-analysis;

1. First RT was not included in the analysis; revised SRE. The results were not different from the original SRE results.

2. Excluding RT from SREs, and the results were significant after excluding the RT from SREs.

We added the following description in the Discussion: “Drawbacks with this retrospective study include using a database of breast cancer patients in our institute, where data collection began approximately 30 years ago. The records lacked several important pieces of information including tumor grade and HER2/neu status, and it employed the local (Japanese) pathological classification system. A second database was utilized for data analysis of skeletal metastasis in breast cancer patients. This database lacked information regarding the type of skeletal metastasis (lytic, blastic, and mixed type), and both databases lacked information regarding the pain condition of individuals. Patients’ records (cards) were checked with regard to the presence or absence of pain at diagnosis of skeletal metastasis but there was no detailed information about the pain condition of individuals. Therapy for breast cancer has changed over time with the advancement of chemotherapeutic agents and their combination, hormones and molecular targeting agents (HER2/neu). The concept of standard therapy for skeletal metastasis has changed with the advent of bisphosphonates. In Japan, bisphosphonates were first approved for use in the treatment of skeletal metastasis at the end of 2004, and actual use began in 2005. Therefore, there were limited data regarding the use of bisphosphonates in this study and this prevented analysis of the impact of bisphosphonate treatment.
The strategy of using radiotherapy for treating skeletal metastasis changed during the study period. The inclusion of radiotherapy treatment in the SRE classification could result in an overestimation of the incidence of SRE in this study. We have also performed another analysis in which first RT was not regarded as SRE and RT at least three months apart from first RT was counted as SRE. Although the distribution of kinds of SREs has been changed, the results of statistical analyses (Cox analysis and Kaplan Meier analysis) were similar (data not shown).

2. More details should be given about the characteristics of bone metastases at the diagnosis for the patients of both groups (type: lytic, blastic or mixed, site: axial or appendicular), since both type and site in the skeleton influence the incidence of SRE and prognosis.

Reply
Thank you for this suggestion.

Data about the characteristics of bone metastases (type: lytic, blastic or mixed) at diagnosis were missing from our database. Films were missing. We could not include the type of bone metastasis in this analysis.

We have data concerning the site of bone metastasis, and some of the data have been published (Ann Oncol 2003; 1234-1240).

We have performed the analysis regarding sites; appendicular metastasis plus vs axial only. However, there was no significant difference between the two groups regarding SRE. Therefore, we did not include the data.

3. Since the use of bisphosphonates significantly influences the risk of SRE (and pain) and considered that bisphosphonates show relevant differences in their efficacy, particularly between pamidronate and zoledronate, detailed informations about the type of BP, schedule and treatment duration, need to be given. The use of bisphosphonates (as other adjuvant therapies) should be considered in Cox’ proportional hazard multivariate analysis.

Reply
This is also very good point to consider.

We also thought that the use of bisphosphonate is an important factor to
consider.

However, the use of bisphosphonate for bone metastasis was approved at the end of 2004 in Japan.

The investigation period of this study was from 1988 to 2006. Use of bisphosphonate only affected the last 2 years of the study. Therefore, we did not include the data concerning bisphosphonate use in this analysis; instead we wrote: “There was no difference in the use of bisphosphonates for patients without pain and those with pain (data not shown).” In the Discussion section.

We have added the following description in the Discussion section: “Drawbacks with this retrospective study include using a database of breast cancer patients in our institute, where data collection began approximately 30 years ago. The records lacked several important pieces of information including tumor grade and HER2/neu status, and it employed the local (Japanese) pathological classification system. A second database was utilized for data analysis of skeletal metastasis in breast cancer patients. This database lacked information regarding the type of skeletal metastasis (lytic, blastic, and mixed type), and both databases lacked information regarding the pain condition of individuals. Patients’ records (cards) were checked with regard to the presence or absence of pain at diagnosis of skeletal metastasis but there was no detailed information about the pain condition of individuals. Therapy for breast cancer has changed over time with the advancement of chemotherapeutic agents and their combination, hormones and molecular targeting agents (HER2/neu). The concept of standard therapy for skeletal metastasis has changed with the advent of bisphosphonates. In Japan, bisphosphonates were first approved for use in the treatment of skeletal metastasis at the end of 2004, and actual use began in 2005. Therefore, there were limited data regarding the use of bisphosphonates in this study and this prevented analysis of the impact of bisphosphonate treatment”

4. Taking into account the prevalence of hypovitaminosis D in Japan and the necessity for good levels of vitamin D in BPs treated patients, data on vitamin D supplementation are needed; furthermore considering the effects of vitamin D deficiency on bone turnover and consequently on the risk of SRE.

Reply

This is also a good point to consider. However, as mentioned in reply to the above question, a very limited number of patients had received bisphosphonate therapy in this study. Of course, vitamin D was supplemented with BP-treatment.

5. The two groups of patients were stratified by the presence of pain, but there were described neither the criteria of pain diagnosis or the methods or scale to
quantify it.

Reply
This is the similar to referee 2’s first inquiry.

I will copy the reply to first inquiry of referee 2.

The information regarding the presence or absence of pain was reviewed in Patients Records (Cards). In the records, patients were asked about the presence of pain and the site of pain, and then the results were logged. This referee perhaps intended us to show the results using a visual-analog-scale or similar but we do not have such data.

Therefore, we added the following description “In the inquiry card, patients were asked about the presence or absence of pain, and sites of pain. The grade of pain (visual-analog scale) was obtained from a limited number of patients. Therefore, the focus was on the presence or absence of pain” in the pain and values of tumor markers in the diagnosis of skeletal metastasis part of Methods section.

6. The intensive follow up adopted in the study after surgery, especially for what concern the frequent execution of total body scanning for detecting bone metastases is not actually suggested by the International Guidelines. Authors have to discuss this point and the obtained Ethical Committee approval and informed consensus by patients should be reported.

Reply
In Japan, the guide line was issued in 2005 and is similar to international criteria. However, there is still debate regarding this point in Japan.

This is a retrospective investigation. We have summarized the outcome of patients who had bone scans as a part of routine clinical practice; we did not intervene or influence the procedures or decision of clinical staff.

7. The limitations of the study are not be stated

Reply
We have added the flaws of this study in Discussion section.

“Drawbacks with this retrospective study include using a database of breast cancer patients in our institute, where data collection began approximately 30 years ago. The records lacked several important pieces of information including
tumor grade and HER2/neu status, and it employed the local (Japanese) pathological classification system. A second database was utilized for data analysis of skeletal metastasis in breast cancer patients. This database lacked information regarding the type of skeletal metastasis (lytic, blastic, and mixed type), and both databases lacked information regarding the pain condition of individuals. Patients’ records (cards) were checked with regard to the presence or absence of pain at diagnosis of skeletal metastasis but there was no detailed information about the pain condition of individuals. Therapy for breast cancer has changed over time with the advancement of chemotherapeutic agents and their combination, hormones and molecular targeting agents (HER2/neu). The concept of standard therapy for skeletal metastasis has changed with the advent of bisphosphonates. In Japan, bisphosphonates were first approved for use in the treatment of skeletal metastasis at the end of 2004, and actual use began in 2005. Therefore, there were limited data regarding the use of bisphosphonates in this study and this prevented analysis of the impact of bisphosphonate treatment. The strategy of using radiotherapy for treating skeletal metastasis changed during the study period. The inclusion of radiotherapy treatment in the SRE classification could result in an overestimation of the incidence of SRE in this study.”

8. Published data show that stratifying patients by pain (with or without) at the diagnosis of bone metastases there are not differences between the incidence of SRE in the two groups (Eastham J and coll (ASCO meeting 2005, abst 4561). These data should be discussed.

Reply

Eastham J and coll reported the following in an abstract at ASCO meeting 2005.

“Effect of zoledronic acid and bone pain and skeletal morbidity in patients with advanced prostate cancer”

The patients studied in the present investigation suffered from breast cancer.

Prostate cancer often develops blastic bone metastasis, and breast cancer often develops mixed types of bone metastasis. The prognosis, including SRE, is different between the two cancers. Therefore, we did not include this discussion.

9. The median time from diagnosis of bone metastases to the first SRE in both groups should be reported in the results.

Reply

We have analyzed and added the description that “The mean period from diagnosis of skeletal metastasis to development of SREs was 657 days (median
395 days) for patients without pain and 281 days (median 45 days) for patients with pain. There was a statistical difference in the period from diagnosis to development of SREs between patients with and without pain (Mann-Whitney U test p<0.0001)” in the Results section.

DISCRETIONARY REVISION

10. The discussion should try to explain the possible causes supporting the differences between the two groups (pain and no pain).

Reply

It is a very difficult question.

We have discussed the reason in the Discussion section.

“Kohno et al. reported that the SRE rate was higher among patients with pathological fractures before diagnosis than in patients with no prior fracture (12), and this could relate to the fact that the SRE rate was higher in patients with bone pain at the time of diagnosis of skeletal metastasis than in patients with no pain. Patients with skeletal metastasis but no bone pain (bone pain could be the result of micro-fractures at skeletal metastasis) should present with a lower SRE than patients with bone pain.”

MINOR ESSENTIAL REVISION

11. Bibliography should be updated

Reply

We have tried to follow this instruction. However, the majority of publications regarding bone scan were published some time ago including 2 random clinical trials from Italy.

12. Legends of tables are lacking.

Reply

We have added legends to the Tables.

Referee 4

Minor essential revisions:

1. -Further biological explanations need to be added in the discussion part regarding the relationship of pain and bone metastases as well as the
progression of disease.

Reply
This is a good point but we cannot add further reasoning at this point.

2. -Comments and biographic references regarding the psychological impact of intensive follow with bone scans and other imaging studies on quality of life and stress need to be added.

Reply
This is a very important issue. However, psychological issues are not within the remit of this study and have not been discussed.

3. -Economical issues due to additional cost of this intensive proposed follow-up need to be further discussed.

Reply
Economic issues are important but they differ in various countries.

We attempted to calculate the cost issues but they change every 2 years in Japan, and the price in Japan is quite different from other countries. The innovation of diagnosing methods will change the situation. Therefore, we did not mention cost issues in the manuscript.

Discretionary revisions:

4. -In the discussion part, the "ideal" trial to conduct could be outlined.

Reply
We suggest that the ideal trial would be:

1. Post-operative breast cancer patients at high risk of skeletal metastasis are randomly assigned for intensive and clinical follow-up with fixed adjuvant therapy.

2. When bone metastasis is diagnosed, fixed standard therapy for metastasis with bisphosphonates is added.

3. Follow-up protocol after bone metastasis and therapy should not be different between intensive and clinical groups.

4. The diagnosis criteria of bone metastasis and SRE events should be fixed.
The most important points to carry out the trial is discussion by coordinators, disease specialists and statisticians.

However, we do not think these requirements for an ideal trial should be included in the manuscript.

Regarding statistical review:

Reply

Two referees requested statistical review by specialists, while 2 referees did not request this.

The statistical analysis shown in this study was approved by a statistician.