Author's response to reviews

Title: Prognostic value of hematogenous dissemination and biological profile of the tumor in early breast cancer patients. A prospective observational study

Authors:

Montserrat Solá (msola.germanstrias@gencat.net)
Mireia Margelí (33198mmv@comb.es)
Eva Castellá (ecastella.germanstrias@gencat.net)
Juan Francisco Julián (421127jji@gmail.com)
Miquel Rull (miquelrull@gmail.com)
Josep M Gubern (jgubern@csdm.cat)
Antonio Mariscal (mariscal.germanstrias@gencat.cat)
Agustí Barnadas (ABarnadasM@santpau.cat)
Manel Fraile (mfraile.germanstrias@gencat.cat)

Version: 3 Date: 13 April 2011

Author's response to reviews: see over
Dear Natasha Mellins-Cohen,

Together with this letter, we submit the revised version of our manuscript: “Prognostic value of hematogenous dissemination and biological profile of the tumor in early breast cancer patients. A prospective observational study” (MS:1215098591482621) to be reconsidered for publication in *BMC Cancer*.

As you recommended, the manuscript has undergone numerous modifications to enhance its clarity and has been revised by a native English translator. We hope the reviewers will now find it easily comprehensible.

We have made every attempt to satisfy the requirements of the reviewers and explain our viewpoint on the issues raised, but if the Editor feels that additional adjustments are needed, we are open to further suggestions. In any case, we hope that in its present form our manuscript will be acceptable for publication and look forward to your reply.

Yours sincerely,

Montserrat Solá, MD
Comments to Reviewer 3

We would like to thank the reviewer for the helpful suggestions to improve our manuscript. The following is a point-by-point response to the comments. The changes are highlighted in red in the manuscript.

1. We agree that 22% BM positivity and 28% positive lymph nodes are good quality markers.

2. Patients were not randomized, so we described the study as a prospective observational study.

3. It is true that BM aspirates were done before the first incision and not "during" the surgical procedure (Material and Methods, 5th paragraph). This imprecision has been corrected. We tried to aspirate 10 mL from both iliac crests, as is mentioned in the same paragraph.

4. SLN were definitively evaluated by multilevel sectioning. This information has been added to the text (Material and Methods, 3rd paragraph).

5. Patients were consecutively accrued. This has been added to Material and Methods, 2nd paragraph.

6. In 2003, the American Joint Committee on Cancer (AJCC) revised the breast cancer staging system (6th edition), with particular attention to the differentiation between micrometastases (MIC) and isolated tumor cells (ITC). This revision classifies ITC (\(0.2\) mm) as node negative, pN0 (\(^-\)). ITC are defined as single tumor cells or clusters usually detected only by IHC or molecular methods, but that may be verified on H&E stain. MIC (\(0.2\) mm to 2 mm) are now classified as node positive (pN1mi). Hence, micrometastasis are considered as N1 by TNM and international consensus, and that is why all patients received some type of adjuvant therapy. We have added the reference for this document (number 16) in the Patient Follow-up section of Material and Methods.

7. The considerations mentioned above are also included in our institutional guidelines.

8. Follow-up reached 60 months in all patients, but the last follow-up was in 2009, so the total follow-up was longer in several patients (maximum to 90 months). In our institution, clinical follow-up visits are scheduled every 3 months during the first 2 years and every 6 months up to 5 years. These visits include a physical examination, in which particular attention is placed on lymph node evaluation and identification of metastasis. Chest X-ray and mammography are performed once a year.

9. Use of the combination of dye and radiotracer was only performed during the validation phase of the SLN detection technique (Fraile M. Ann Oncol. 2000 Jun;11(6):701-5).

10. Internal mammary nodes are harvested on a routine basis in our institution.

11. The AATRM trial (048/13/2000) is a multicenter, randomized, controlled trial conducted in our hospital. Its interim results have been published (reference 16) and they are also published online (www.gencat.cat/salut/depsan/units/aatrm/pdf/merec00es.pdf). In our study, 4 patients presented with sentinel node micrometastasis. These 4 were also included in the
AATRM trial and they did not undergo lymphadenectomy. None of them had a cancer-related death or disease relapse. Additional follow-up information has been included in RESULTS, paragraph 7.

12. Table 2 has been modified according to the reviewer’s comments. In the 5th paragraph of RESULTS of the first version, we wanted to emphasize the coinciding positive status of both nodes and bone marrow biopsies. Thus, 17% would refer to 5 of 29 patients with positive lymph node involvement. Nevertheless, we have adopted the recommendation of the reviewer to avoid confusion in the results.

13. Cancer-related deaths occurred in 4 patients, and 4 other patients presented disease relapse, consisting of local progression (2 patients) or distant disease recurrence (2 patients). This information appears in paragraph 7 of RESULTS.

14. Because of the small number of events and no differences in risk, we decided not to include survival curves.

15. As reviewer suggested, we agree that comments on the results of Langer’s study should be included (Discussion, 8th paragraph).

16. We have also added comments on the ACOSOG-Z10 study.

17-19. We have changed the figures in the CONCLUSION paragraph, corrected the typing errors mentioned, and eliminated some figures, as the reviewer suggested.

Comments to reviewer 1.

We are grateful to the reviewer for the comprehensive evaluation of our paper and the valuable suggestions for improving the presentation and to enhance comprehension.

Major revisions

1. In response to the reviewer’s comment, we have added this information to the FOLLOW-UP paragraph: Tumor markers were assessed every 6 months. Chest radiography and mammography were performed once a year. Bone scintigraphy, abdominal ultrasound study, or computed tomography (CT) scanning was done in cases of suspected relapse.

2a. Because this was not an objective of our study, we have only described the overall results of internal mammary drainage: 0 positive in 20 biopsied patients (Table 1). Nonetheless, if the reviewer and Editor consider this information necessary, we can reexamine our database to extract these results.

2b. As the reviewer suggested, we have changed the term SLN in the sentence mentioned, as well as the percentages, as follows:

Of the 23 patients with positive bone marrow aspirates, lymph node involvement was negative in 18 patients and was positive in 5 patients, 1 of whom showed micrometastasis. Thus, only 5 patients (4.8%) tested positive to both lymph node and bone marrow involvement, with no overall correlation between the two routes of metastatic spread (chi-square=0.232; \( P=0.63 \)) (Table 2).

We agree that the change improves the clarity of the sentence.
In keeping with the reviewer’s comments, we have also changed Table 2 and the related paragraph to better reflect the results.

We have expanded the abbreviations in a footnote to the table:

Abbreviations: LNi, lymph node involvement; BMi, bone marrow involvement; ns, nonsignificant

2c. The percentages of patients receiving treatment have been clarified as follows:

According to the established hospital protocols, patients received adjuvant chemotherapy (71%) and hormonal therapy (29%); within this total, 12% were given a sequential combination of both treatments.

As can be seen in the text, 4 patients died and 4 patients presented disease relapse. In Table 4 the results should be read in relation to lymph node involvement (LNi) or bone marrow involvement (BMi). We have changed the design of this table to make it easier to read.

Minor revisions

1. As was mentioned above, on the tables we have changed the abbreviations (LNi, lymph node involvement; BMi, bone marrow involvement) to avoid confusion.

Currently the presence of disseminated tumor cells (DTC) in bone marrow is the criterion for assessing initial hematogenous metastatic spread in patients with breast carcinoma. It is mainly determined by assessing bone marrow (BM) specimens by IHC techniques. In this context, we have used the terms DTC and BM to express the two related concepts: DTC in bone marrow when referring to its incidence, BM when related to its determination.

2. Table 4 has been changed to follow the scheme of Table 3.

3. We agree with the reviewer that ‘incidence’ fits better than ‘prevalence’, as patients are examined at the time of the diagnosis.

Comments to reviewer 2

We thank the reviewer for reading the paper and the general comments made.

We have had the paper revised by a native English speaker with experience in medical texts to correct language errors. The aims have been rewritten in a more clear-cut and less descriptive manner. We believe that the changes suggested by the other two reviewers have also contributed to improving the presentation of the study. If the reviewer should wish to further analyze the paper, we will be pleased to respond to any specific comments or suggestions offered.