Author’s response to reviews

Title: CA15-3 is a useful serum tumor marker for diagnostic integration of hybrid positron emission tomography with integrated computed tomography during follow-up of breast cancer patients

Authors:

Mariarosaria Incoronato (mincoronato@sdn-napoli.it)
Peppino Mirabelli (pmirabelli@sdn-napoli.it)
Onofrio Catalano (onofriocatalano@yahoo.it)
Marco Aiello (marcoaiello1978@gmail.com)
Chiara Parente (caparente@sdn-napoli.it)
Andrea Soricelli (soricelli@uniparthenope.it)
Emanuele Nicolai (e.nicolai@sdn-napoli.it)

Version: 2 Date: 26 March 2014

Author’s response to reviews:

Naples, March 26, 2013

Dear Editor,

We are pleased to resubmit for publication the revised version of MS#1832484726102888 “CA15-3 is a useful serum tumor marker for diagnostic integration of hybrid Positron Emission Tomography with integrated Computed Tomography during follow-up of breast cancer patients”. We appreciate the constructive criticisms of the Reviewer, Prof. M. Gion, and we have addressed each of these concerns as listed below.

EDITORIAL REQUEST:

1). Requesting name of ethics committee:

Please update your ethics statement to include the name of the ethics committee that approved your study.

Response from Authors: As reported in the Materials and Methods section, informed consent for PETCT examination was obtained from all patients. Because this is a retrospective study and all procedures had already been performed for clinical purposes, our Institutional Review Board (Ethics Committee of IRCCS Fondazione SDN) did not require further patient approval or informed consent for the review of patient files or images.

MAJOR COMPULSORY REVISIONS

Reviewer:

The study, as it is presented, seems similar to other investigations previously published on tumor markers in breast cancer follow-up. In addition, the study presents - in my opinion - a selection bias due to the fact that the Authors enrolled only cases in which PETCT was available. The sensitivity and specificity
values of cancer markers should be examined in a consecutive patient series in which the outcome is definitely known, irrespectively of the availability of PETCT.

Response from Authors:
According to the reviewer’s suggestions, in the revised manuscript, we selected only those patients for whom the outcome was definitely known based on prolonged clinical follow-up. Therefore, we excluded all cases in which only PETCT information was available. We then re-calculated the specificity and sensitivity percentage both for CA15-3 and PETCT as described in the “Results and Discussion” section. Thanks to reviewer’s suggestions we were able to better describe the value of CA15-3 in predicting a positive PETCT result as described below.

Reviewer:
Nevertheless, the paper reports some interesting findings concerning the lead time of CA15-3 with reference to PETCT. Therefore I do suggest to the Authors to rewrite the manuscript in a shorter version (i.e., in short communication stile) focusing only on the findings concerning the value of CA15-3 in anticipating a positive PETCT result.

Response from Authors:
We have rewritten the manuscript according to these suggestions. In particular, the manuscript was shortened, and the Results and Discussion were combined into a single section. Moreover, we focused our study on the value of CA15-3 in predicting a positive PETCT result as follows:

(A) Serial CA15-3 measurements were retrieved from our internal archives at 0-3, 3-6, and 6-9 months before PETCT. These data are plotted in Figure 1 and show the progressive increase in serum CA15-3 levels in relapsing BC patients with positive PETCT. The ROC curve analysis of CA15-3 for each time point showed that the AUC value was the same at 0–3 and 3–6 months before PETCT. These data showed the ability of CA15-3 to predict a positive PETCT result with a lead time of 3-6 months.

(B) We selected BC patients during the course of the therapeutic regimen (chemotherapy or hormonal therapy) with negative PETCT and positive CA15-3 serum levels. After a median time of 158 days, all patients relapsed, whereas patients receiving anticancer medications but who were negative for CA15-3 and PETCT were free from disease for up to 1 year of follow-up.

Reviewer:
The assessment of CA125 should be omitted. In fact, CA125 is not recommended in breast cancer and its use is therefore not appropriate. I think that a scientific investigation should not consider a marker that is inappropriately used, even if the study is retrospective.

Response from Authors:
We appreciate the constructive criticism from the reviewer and have removed all data about CA125 from our study.

Reviewer:
Statistical analysis (and other points in the manuscript). The Authors say that increased CA15-3 has ‘prognostic’ significance since it predict a shorter time to relapse. This is certainly true from a generic point of view. However, the information that CA15-3 provides, is an earlier detection of the relapse in comparison to PETCT; that is, an anticipation with reference to imaging techniques. The authors should emphasize the predictive role of (and the anticipation provided by) CA15-3. In addition the analysis of serial CA15-3 values – if available - would add interest to the study (see for an example: Mariani L et al. Serial determination of CEA and CA 15.3 in breast cancer follow-up: An assessment of their diagnostic accuracy for the detection of tumour recurrences Biomarkers, 2009; 14: 130–136)

Response from Authors:
According to the reviewer’s suggestions, we retrieved serial CA15-3 measurements at 0–3, 3–6, and 6–9 months from our internal archives before performing PETCT examination. Also, as described before, we emphasized the value of CA15-3 in predicting positive PETCT results from a progressive increase in serum levels of CA15-3. Moreover, we showed the ability of CA15-3 to predict the positive metabolic imaging of the disease, especially in patients during therapeutic treatment.

MINOR ESSENTIAL REVISIONS
Reviewer:
Introduction, lines 6-7. The sentence ‘so diagnostic tools for … are needed’ should be omitted or mitigated: why are the tools needed, when the usefulness of the follow-up is itself still under debate?
Response from Authors:
We are grateful to the reviewer for this important clarification. We removed the sentence indicated by the reviewer and revised the manuscript regarding the concept of clinical follow-up.

Reviewer:
Discussion, pg 11 lines 2-8. ‘.. are frequently required by clinical oncologists as….’. It is difficult to believe that the request of cancer biomarker in patients with breast cancer is motivated by the knowledge of the biochemistry of the markers. I suggest to omit the paragraph.
Response from Authors:
We removed the paragraph about the biochemical role of cancer biomarkers.

Reviewer:
Discussion, pg 11 lines 12-14. ‘clinicians have the tendency to add in lots of extra tumor markers for monitoring BC patients …. ’. May be that this ordering modality occurs in some institutions or in some Countries, but certainly it cannot be presented as a general behavior of ‘clinicians’, as the authors seem to state. Please, omit or amend this sentence
Response from Authors:
According to the reviewer’s suggestion, we omitted the sentence about extra tumor markers being frequently requested by clinicians.

Reviewer:
Conclusions, lines 1-2. The statement ‘there is a general consensus …. As well as early detection of disease relapse’ is not entirely true. There is no consensus on the usefulness of follow-up in breast cancer. The sentence should be omitted or changed.
Response from Authors:
According to the reviewer’s suggestion, we omitted this sentence.

DISCRETIONARY REVISIONS

Reviewer:
Introduction, lines 1-2. The sentence ‘as stated by …’ is not necessary – the citation of the reference is sufficient.
Response from Authors:
According to the reviewer’s suggestion, we removed the sentence “as stated by..”

Results, pg 8 lines 9-10. ‘Interestingly, the highest serum levels of CA15-3 … and hepatic involvement’. I would omit ‘Interestingly’ since this pattern is well know.
Response from Authors:
According to the reviewer’s suggestion, we rewrote the sentence and removed “interestingly”.

Statistical review:
Reviewer: Yes, but I do not feel adequately qualified to assess the statistics.
Response from Authors:
Statistical data analysis was revised by a statistician (Dr C. Parente, co-author).

Quality of written English
Reviewer: Needs some language corrections before being published
Response from Authors:
The quality of the written English has been extensively revised by a proofreading service for scientific papers (Bioscience writers).

With my warmest regards,

Mariarosaria Incoronato

Dr. Mariarosaria Incoronato, PhD
IRCCS Fondazione SDN
Via E. Gianturco, 113
80143- Naples
Italy