Author's response to reviews

Title: Androgen receptor expression in breast cancer: relationship with clinico-pathological characteristics of tumors, prognosis and metalloproteases with their inhibitors expression

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised version of our manuscript entitled "Androgen receptor expression in breast cancer: relationship with clinico-pathological characteristics of tumors, with prognosis and with metalloproteases and their inhibitors expressions", (Reference: MS: 1789308046175860).

Following the editorial’s commentaries, we included a discussion of how our data differs from previously published work (In Discussion section: page 16, last paragraph, and page 17, first paragraph), and a statistical explanation of how we have used the dichotomization in our manuscript (In results section: page 12, second paragraph). We also added a section on competing interest in the revised version of the manuscript, between conclusions and Authors’ contributions. Likewise, the manuscript was revised by a native English speaker.

In addition, we have revised the paper in response to all of the reviewer’s commentaries, according to which it has been modified. Next, I would be pleased to answer to all the specific remarks suggested by the reviewer:

Reviewer’s report:

1. Following the Referee’s suggestion, we altered the phrase “associated with dead for tumoral progression”, also in the Result section (page 13, first paragraph, in the revised version of the manuscript).

2. The term of “early” breast cancer was deleted in the three places in the revised version of the manuscript (In background of Abstract section, page 2, first paragraph; in background/Introduction section: page 5, last paragraph; and in the Discussion section, page 16, second paragraph).

3. Following the Referee’s recommendation, we discuss the discrepancies of our results with those of the previously published literature (In the Discussion section of the revised version of the manuscript: page 16, last paragraph, and page 17, first paragraph). Nevertheless, an error for us was made with regard to the work of Aggof et al (reference nº16). These authors found a significant association (p=0.049) between AR expression and relapse-free survival in patients with ER-negative tumors (n=57) in the univariate analysis, but none between the AR status and overall survival, such as it was reported in our original version of the manuscript. Therefore we now describe the
correct association in the revised version of the manuscript. In addition, we added that the association reported by these authors did not achieve significance in the multivariate analysis. On the other hand, there are possible explanations for the discrepancies with our results regarding to differences in the patient’s populations. Thus, although we have a similar number of patients with ER-negative tumors (n=59), it is of note that our study included a higher number of events (disease-relapse) (61%) than in the study of Aggof et al. (33%), because our population was selected stratifying on the basis of distant metastasis occurrence. Likewise, in our work we employed different criteria of patient’s selection, such as ductal as histological type, or distant metastasis as only type of tumoral recurrence, and only T1 or T2 tumors. All of these aspects are now described in the revised version of the manuscript (In Discussion section, page 16, last paragraph, and page 17, first paragraph). In our paper we also described the results of the paper of Schippinger et al. (reference nº25), who found the AR tumoral expression was not associated with longer survival in patients with metastatic breast cancer and in the multivariate analysis. Nevertheless, such as it is showed in the revised version of the manuscript, this patient’s population differs clinically of the patient’s population of non-metastatic breast cancer included in our study.

4. It is of note that the staining for AR is nuclear, therefore there is not of background such as in the case of cytoplasmatic staining. Nevertheless, we provide the number of cases with score values less to 10 point, which were only 5 (3 with score of 5, and 2 with score of 8), such as it is reported in the revised version of the manuscript (page 11, paragraph 2). On the other hand, We described in the Results section of the revised version of the manuscript a more explanation for statistical process for selecting the more optimal cut-off of AR score values: “We initially investigated the possible association between each immunostaining score value for AR, as cut-off points, and relapse-free survival. We found that none of these cut-off points were significantly associated with relapse-free survival in our patient’s population (data not shown). However, our results demonstrated that when patients were dichotomized in two different groups with regard to the more optimal cut-off point of score values for AR (score=0 v.s. score>0), patients with positive-AR tumors have a significantly longer survival than patients with AR-negative tumors (\(p=0.01\))...” (In Results section: page 12, second paragraph). In addition, we modified the Figure 3, now including separately the number of cases negatives (with score= “0”) (page 35 of the revised version of the manuscript).

5. Following the referee’s recommendation, the manuscript was revised by a native English speaker.

Finally, we would like to acknowledge the opinion of the expert who reviewed our manuscript.

Yours sincerely,
Dr. Francisco J. Vizoso