Author's response to reviews

Title: In vivo measurement of tumor estradiol and Vascular Endothelial Growth Factor in breast cancer patients

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Author's response to reviews: see over
Dear Iratxe Puebla,

I would like to thank the editors and the reviewers for their comments and suggestions regarding our manuscript. We have taken all of the issues raised into consideration and as a result of the comments incorporated new data into this re-submission.

We feel that the manuscript is considerably stronger now and hope that the new submission will be acceptable for publication.

I include a point-by-point discussion of the issues raised by the 2 reviewers and have indicated where the new data and comments have been included.

Yours sincerely,

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Reviewer 1

**Major compulsory revisions**
The statement of differences in local estradiol levels in normal and cancerous breast tissue as a whole group has been deleted. We have omitted a sentence in the abstract, which may be interpreted as patients had higher levels of estradiol in cancerous tissue. On page 8 a sentence on line 13-15 has been rewritten so that the interpretation of the lack of significant is clear.

Regarding the statistics, Shapiro-Wilks’ W test for normality has been used. 4 out of 6 groups exhibited a normal distribution of the data. When non-normally distributed data were analyzed the non-parametric Wilcoxon signed rank test was used for group comparisons. When the data was normally distributed, correlations were calculated as previously using Pearson’s coefficient. This has been added in the materials and methods section under Statistical analysis. The results are now given in median and 25th-75th percentiles as appropriate using non-parametric tests. As a result Table 2 has been deleted and the significant correlation that was found has now been added in a new Figure 3. The statistics and data presentation have been changed accordingly in the results section. The main results of the study have not changed when using this statistical approach.

Where no correlation was found we have now stated that the small sample size may affect the results, page 11 line 14.

**Minor essential revisions**
The subject description is now referred to Table 1 in the methods section.

If the editor approves, we do believe that the immunohistochemistry should be included in the paper for the comprehension of the study.

The significant correlation is now presented as a new Figure 3 and Table 2 has been omitted.

Reviewer 2

**Major compulsory revisions**
The question of recovery is a very insightful remark, which exemplifies the pitfall of microdialysis. However, we do not believe that our results merely reflects changes of the in vivo recovery and to clarify the difficulties with this technique a new section under the materials and methods section, starting page 5 line 22 and ending line 17 on page 6 had to be included. Two new references have been added.

A new section in the discussion sections has also been added on page 12 lines 1-9.

The ranges of plasma values have been added in the results section on page 8.

**Discretionary revisions**
I do agree but this is a clinical material, which is formalin fixed and we do not have access to fresh frozen tissues from patients.