Author's response to reviews

Title: Expression of Follicle-Stimulating Hormone receptor by the vascular endothelium in tumor metastases

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ANOTHER RESPONSE TO THE REVIEWERS’ QUESTIONS AND COMMENTS

REVIEWER 1

Comment (C): The study has been exclusively performed on metastatic lesions without considering the primary tumors, so that it is impossible to draw any meaningful consideration. For instance, we don’t know if exist any concordance in the positive as well as negative cases between metastasis and primary tumor.

Answer (A): No large sections were available from primary tumors from the same patients from which metastases have been analyzed, with the exception of five breast cancer cases.
The results for the latter pairs of primary tumors and metastases have been introduced in the revised text.

C: No data are given about the intensity of the immunostain (weak, moderate, strong?). Was the degree of intensity homogenous?
A: No significant differences in the staining intensity were noticed among the cancer types and location of metastases. This was introduced in the revised text.

C: The discussion of the results has to be improved. The paper appears to be mainly a mere description of the obtained data.
A: The discussions have been extended.

C: The reported cases include exclusively malignant epithelial lesions, namely carcinoma. What about metastasis of sarcoma? Adding some cases of sarcoma metastasis would be very interesting for the discussion.
A: Sarcoma cases have been added.

C: Needs some language corrections before being published.
A: Corrections were made.

REVIEWER 2 - NA

REVIEWER 3
C: In the Results paragraph (Metastases contain FSH-R-positive vessels subparagraph), the authors report the expression of the receptor in the deeper area of primary tumors. Did they analyze primary tumors too?
A: The sentence refers to localized cancers analyzed in our previous publication. In the revised text we introduced data from five primary breast tumors and corresponding metastases.
C: The authors should be use accordingly the term 'primary tumors', that should be confusing in this context.

A: The use of the term “primary tumors’ was restricted to the proper situations.

C: In addition I believe that it could be interesting if the authors provided some informations about the comparison of FSH-R expression in both primary and metastatic tumors, also if it is possible in a smaller series of cases, even if in a series of a single tumor, in order to define if this expression could be observed in the primary tumors. Moreover the series could be matched with a series of prognostically no metastatic tumors of the same series. Alternatively since the authors have analyzed a very wide series of primary tumors with FSH-R (N Engl J Med. 2010 Oct 21;363(17):1621-30), the comparison should be provided in the discussion paragraph, if a series of primary tumors in the previous series correspond to a series of metastasis of this paper.

A: Comparisons between metastases and parent primary tumors were introduced in the revised text.

C: the authors should provide methodological assessment of the expression of FSH-R in the vessels of the tumors front when they analyzed breast metastasis in a TMA.

A: As mentioned in the text, the presence of FSHR-positive vessels in the tumor, at the limit between the tumor and the normal tissue, was equal to that in the interior, up to 7 mm inside the tumor, the maximum depth available. The data suggest that FSHR expression is equal throughout the lesion. For this reason, all TMA samples of breast cancer to pleura are equally representative independently of their location (at the periphery or in the interior of the tumor). This was explained in the revised text.

C: Minor point: Comments about epyleptogen brain should be removed.

A: The comments were removed.