Author's response to reviews

Title: Effects of Androgen Deprivation on Brain Function in Prostate Cancer Patients - A Prospective Observational Cohort Analysis

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Author's response to reviews: see over
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To:
Dr. Motoyoshi Tanaka
BMC Cancer

Re: MS: 1528196268688370
“Effects of Androgen Deprivation on Brain Function in Prostate Cancer Patients - A Prospective Observational Cohort Analysis” by Herta H Chao, Edward Uchio, Sheng Zhang, Sien Hu, Sarah R Bednarski, Xi Luo, Michal Rose, John Concato and Chiang-shan R Li

Dear Dr. Tanaka:

We thank the reviewers for their most helpful comments and suggestions. Below is an item by item reply along with the specifics of revision. Please note that the reviewers’ comments are underlined.

Reviewer 1:

1. The authors should provide information concerning 1) The grading and staging systems used for prostate cancer (table 1) and 2) The image of the control patients should be shown (figure 3).

   As suggested, we have provided these information in the revision (Table 1 and Figure 3). Please note that the staging follows the current guidelines of the 2010 American Joint Committee on Cancer that include Gleason grade scoring as part of the staging.

2. In the introduction section, the authors mentioned the deactivation in the left middle dorsolateral prefrontal cortex and premotor cortex in breast cancer patients who underwent chemotherapy. However, this study showed ADT decreases activation of medial prefrontal cortex (MPCF) and connection to dorsolateral prefrontal cortex (DLFPC). In the discussion section, the authors should refer to the difference of deactivated lesion between ADT and chemotherapy of breast cancer in women, especially in MPCF and DLFPC.

   In the Introduction we described earlier studies showing reduced activation of frontal cortices during cognitive challenges in breast cancer patients receiving chemotherapy. In the current study, we showed that prostate cancer patients undergoing ADT similarly demonstrated decreased frontal cortical activations (although the locales of the regions are not the same because of task
differences). In addition, we showed that functional connectivities of these frontal regions decreased during resting state in patients who received ADT, compared to those who did not.

Reviewer 2:

1. There is no clinical connection to the change in fMRI. What is the importance of the MRI finding if there is no measurable clinical effect?

There are a few possible, non-exclusive explanations for the lack of behavioral or clinical effects despite changes in cerebral activations after ADT. First, as discussed in the manuscript, these results rule out the role of effort or motivation in the performance of cognitive tasks (p. 9). Second, the results may suggest that changes in cerebral activity may occur before behavioral and clinical changes become overt. That is, brain imaging may be more sensitive in capturing the effects of ADT than behavioral and clinical assessments. Future studies with longer follow-up will be able to determine whether these changes predict clinical outcomes including cognitive functioning. We have listed this as a limitation of the study (p. 10).

2. The study duration is short. Is 6 months really enough to see the effects of androgen deprivation on the brain?

Many previous studies employed neuropsychological testing reported effects of ADT after a few months of treatment. Similarly, the effects of chemotherapy on cognition were observed in other forms of cancer after patients received treatment for a few months. On the other hand, we concur with the reviewer that a longer follow-up period would be essential in future studies to document whether these changes are reversible in those patients who receive ADT only for six months and whether the changes would aggravate in patients who receive ADT beyond six months. We have discussed these issues along with those raised in the previous comment in the revision (p. 10).

3. In table 1, the baseline Testosterone levels should be specified.

We did not measure baseline testosterone level for our participants. However, the post-ADT testosterone levels clearly showed that the ADT group is chemically castrated.

4. The control is not shown in Fig 3.

Figure 3 showed the differences in the post- and pre-ADT contrasts between groups. As suggested, we have included these contrasts separately for ADT and control groups.

Thank you very much for your attention to this matter. We look forward to the editorial decision.

Sincerely yours,

Herta Chao, M.D., Ph.D.