Author’s response to reviews

Title: The combination of CTCs and CEA can help guide the management of patients with SPNs suspected of being lung cancer

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Version: 1 Date: 01 Jan 2020

Author’s response to reviews:

Dear editor and reviewers,

We collectively apologize for all these mistakes and have made amendments accordingly. Changes are highlighted in yellow.

Reply to Tetsuhiko Asao, M.D., Ph.D. (Reviewer 1)

This manuscript reports the utility of the combination of circulating tumor cells (CTCs) and carcinoembryonic antigen (CEA) for the diagnosis of solitary pulmonary nodules (SPNs). The authors detect CTCs using the i-FISH method, which needs further explanation. With the cutoff value of 6 CTC units, the sensitivity was 67.1% and the specificity was 56.5% in the diagnosis of lung cancer in patients with SPNs. After combining CTC counts and CEA levels, the area under the curve (AUC) was 0.827. As the authors noted, the validation of the detecting method (lack of healthy control) is a major limitation of the study. In this study, median CTC counts were 5.5 in benign nodules which mean there is a considerable amount of false detection in patients with benign nodules. There are some issues that I would like to have your comments.
Major comment

1. Please provide the details of i-FISH method and provide the references to the previous studies. The validity of the method is essential because the detection of CTCs is largely depending on the methods.

Response : We thank the reviewer for all these important suggestions, which we of course complied with. We added more details of the methods and references.


2. Please provide the sensitivity and specificity of CTC+CEA in Table3.

Response : We thank the reviewer for this proposal and we have now included data showing that the sensitivity and specificity of CTC+CEA in table3.


Minor comments

1. Table2: Interquartile range is lacking.

Response : We apologize for this mistake and have made amendments accordingly.

Changes : table2 lines 5-17 page24.

Reply to Helmut Popper, M.D. (Reviewer 2)

Dr. Zheng and colleagues present a manuscript on circulating tumor cells as an aid in evaluating solitary pulmonary nodules. Although this is a retrospective study it provides new and interesting data. A limitation of the study is the small size of nodules with benign lesions (46 versus 85 carcinoma patients). There are some minor points missing:

1. CTCs were detected via gene copy numbers in 8 chromosomes - this should be explained in the method section

Response : We really thank the reviewer for this suggestion and we added many details for the detection methods for CEP8.

2. How was the median number of CTCs established? Again retrospectively?

Response: We thank the reviewer for these comments. We detected the CTCs number before surgery in patients with SPNs who were suspected of lung cancers. After surgery and diagnosis, we analyzed the CTCs' median number in those patients. This is retrospective.

3. There was a site-specific difference in CTCs - upper lobe; in the manuscript, the location of the carcinomas was not mentioned; were there a higher number of upper lobe carcinomas?

Response: We thank the Reviewer for this important suggestion, which we of course have followed. We also agree the reviewer’s opinions about lung cancer are inclined to upper lobe and upper lobe carcinomas have a higher incidence. In our manuscript, the CTC levels of patients with nodules in the upper lobe of the lung were higher than those in patients with nodules in other lobes (p=0.011). So, we added the description of these data in the results section.

Changes: results section, line 4-5, page10.

Once again, we would like to thank the editor and the reviewers for their efforts, encouraging comments and constructive criticism.

Sincerely yours,

Hui Xiao (on behalf of the authors)