Author's response to reviews

Title: Additional Diagnostic value of Tumor markers in Cytological fluid for Diagnosis of non-small-cell lung cancer

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Author's response to reviews:

MS: 1058840592707231, Additional Diagnostic value of Tumor markers in Cytological fluid for Diagnosis of non-small-cell lung cancer

Dear Editor

We corrected our manuscript as requested by the editor and reviewers.

We additionally analyzed the diagnostic performance of NAB combined with tumor markers according to tumor stage and histological subtypes.

We hope that issues are sufficiently explained and understood.

Thank you for your grant review and comments.

Reviewer #1:

The manuscript contains valuable information about the usefulness of tumor markers in the diagnosis of lung cancer. However, some minor changes may increase the value of this manuscript

A1. The authors explain that tumor markers are present in high concentrations in cytological fluid. However, regarding CEA, significant differences are observed in serum but not in cytological fluid. Do you have an explanation for it?

: Cytological CEA was also significantly different between malignant and benign group (20.63 versus 0.31, p = 0.003). We already mentioned this in result section. However, P value was incorrect in Table 2. We corrected.

A2. Please, show the information about the stage of patients diagnosed of lung
cancer. Are there differences in accuracy between patients with initial and advanced stages?

We analyzed the diagnostic performance of NAB combined with tumor markers according to tumor stage. In subgroup analysis for stage 1 and 2, accuracy improved significantly for NAB combined with cytological CYFRA 21-1 compared with NAB alone (96.3% versus 88.1%, p = 0.021). However, the accuracy was not significantly different between NAB alone and NAB combined with cytological tumor markers in advanced stage. We added this as your suggestion.

A3. Add VAT in the list of abbreviations

We added.

A4. The histology of 66% of patients is adenocarcinoma and authors indicate that “Therefore, the value of cytological tumor markers determined in this study might be limited for cell types other than adenocarcinoma”. It may be interesting to compare results about the usefulness of tumor markers (and particularly, CYFRA 21.1) and NAB for patients with adenocarcinoma with results for patients with other type of histology.

We analyzed the diagnostic performance of NAB combined with tumor markers according to histological subtypes. In the results of subgroup analysis according to histological cell types, the sensitivity and accuracy of NAB combined with cytological CYFRA 21-1 was significantly higher than NAB alone for diagnosing adenocarcinoma. Although NAB combined with cytological CYFRA 21-1 had tendency to increase sensitivity and accuracy for diagnosing squamous cell carcinoma subtype, the sensitivity and accuracy were not significantly different between NAB alone and NAB combined with cytological CYFRA 21-1. This may be explained in that the sample size for squamous cell carcinoma subtype was small. In our study, more than half of the cases were adenocarcinomas, and only 20% were squamous cell carcinomas. We added this result as you requested.

Reviewer #2:

A1. The study by Hur et al builds on their previous study (JTO 2011, 6(8) 1330-5). They have evaluated the utility of 3 tumour markers in diagnosing NSCLC presenting as lung nodules. In the introduction section, the authors may want to mention the findings of their original study and state the reasons for undertaking the current study.

We added results of our initial study and mentioned the reasons for undertaking the current study in the introduction.

Reviewer #3:

Hur and co workers have studied additional diagnostic value of tumor markers in cytological fluid in patient with NSCLC. I think that is an interesting paper, but there is some remark to comment:

A1. Text and table 2 don’t have the same p values

This was our mistake. P value of CEA was incorrect in Table 2. We corrected.
A2. A suggestion, Creatinine values are not described, in patients with renal dysfunction may increase tumor markers in serum and to lead false positive. If patients are classified according creatinine value normal or abnormal, you could increase specificity of tumor markers in serum (see. Molina R, et al. Utility of serum tumor markers as an aid in the differential diagnosis of patients with clinical suspicion of cancer and in patients with cancer of unknown primary site. Tumour Biol. 2012;33:463-74.)

: I agree with you. However, in our study, patients with abnormal creatinine value were very small (approximately 10%). Therefore, we didn’t analyze as you suggested. We hope your understanding.

Reviewer #4:

The paper demonstrates the potential utility of tumor markers in the diagnosis of lung cancer. The authors have nicely noted the existing data on the subject. They have assembled a very respectable prospective series of patients.

: Thank you for your great review and comment.