Author's response to reviews

Title: Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer

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Author's response to reviews: see over
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Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer

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To the associate editor

*Journal of Cardiothoracic Surgery*

**Object:** MS: 8969990049098453

Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer

Thank you for consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to the reviewer’s comments.
Reviewer #1 (Dr Thomas Muley)

Version: 1 Date: 11 March 2013

Major Compulsory Revisions

1. **Statistical analysis:** What means “counts were compared using the chi-square test” when analyzing survival data? It is not usual to use chi-square test for comparing groups in survival analyses.

   **Answer:**

   As shown in table 1, we used the chi-square test to compare the various clinicopathological parameters with the CEA groups, not to analyze survivals.

   We corrected “the log-rank test” to “the chi-square test” in the table 1 annotation.

2. The five year survival rate in HN group is given as 85.9%. As can be seen in the graph (Fig.1), a 5-year survival rate is not defined in this group. At best they might give a ~4 year survival rate for this group. In addition, I have some doubt that the statistical differences are really significant. Especially the HN group is overlapping with both other groups.

   **Answer:**

   I agree to adopt 4-year survival when analyzing survival in the HN group. It is true that there is some overlapping between the survival curves of HN group and HH group, but we did obtain a significant difference ($p = 0.049$). As the reviewer recommended below, we excluded patients who received adjuvant chemotherapy in the revised manuscript. Then, the difference did not reach statistical significance ($p = 0.062$). We revised our survival data and figure 1 accordingly:

   “Five-year OS rates in the NN and HH groups were 95.5% and 59.3%, respectively. Four-year OS rate in the HN group was 85.5%.” (Page 2, lines 15-16), (Page 9, lines 5-6)

   “A significant difference in OS was observed between the HN and NN groups ($p = 0.043$). A trend toward a decreased survival was observed for the HH group compared to the HN group, but was not statistically significant ($p = 0.062$).” (Page 9, lines 6-8)

   “A significant difference in overall survival was observed between the HN group and NN group ($p = 0.043$). There was a marginally significant difference in overall survival between the HH group and HN group ($p = 0.062$).” (Figure legends)

3. Some of the patients already received adjuvant chemotherapy. These patients might produce a bias in the survival analysis. What is the effect on survival data when these patients are left
out?

4. When looking for a rational to apply adjuvant chemotherapy, it is hard to understand, why the later patients have been included. It might be more powerful to use only chemotherapy naïve patients.

Answer:

Adjuvant chemotherapy with UFT was unevenly delivered across the CEA groups, adding a substantial bias to the survival analysis in the present study. In the revised manuscript, we excluded 29 patients who had received adjuvant chemotherapy to seek for the candidates for adjuvant chemotherapy appropriately. We revised our inclusion criteria as follows: “(3) those who were anticancer treatment-naïve in both the neoadjuvant setting and adjuvant setting.” (Page 5 line 12)

The effects on survival rate are already mentioned above (answer 2). In univariate analysis, the same 7 factors (age, ECOG PS, serum CEA levels, tumor diameter, VPI, ALI, and differentiation grade) still remained significant prognosticators for OS. In multivariate analysis, the same 3 factors (tumor diameter of more than 30 mm, presence of VPI, and the HH group) still remained independent unfavorable prognosticators for OS. The each figure of patient number, p-value, HR, and 95% CI are corrected accordingly.

In addition, we newly found that high preoperative CEA levels significantly correlated with presence of visceral pleural invasion after excluding the 29 patients. We added “presence of visceral pleural invasion (VPI)” on page 2 lines 14-15 and page 9 line 3.

5. Only a small number of patients died at all. Therefore, it would be interesting to look at recurrence-free (disease-free) survival as an earlier and probably better end point. Since the authors claim a strict follow-up of their patients, they should have these data available! In addition, RFS is not influenced by a recurrence treatment as it is the case for overall survival.

Answer:

It is true that our study had limited observed events (n = 22, 8.4%). In this regard, RFS may be a better end point. However, even if end point was set as RFS instead of OS, we still had limited observed events (n = 26, 9.9%). In the present study, we consider that OS be more informative and appropriate end point than RFS for the following 2 reasons:

(i) We found that the HH group might be a good candidate for adjuvant therapy. We think of OS as more generally accepted end point than RFS when discussing the candidates for adjuvant therapy.

(ii) Until now, there have been no reports reviewing the prognostic values of perioperative change of serum CEA levels. We believe that our results can strengthen the study review
shown in table 4.

To address limitation, we modified the sentence. “there was a small sample size of the HH group (n = 21) and observed events, making it statistically difficult to interpret results.” (Page 13 line 16)

**Minor Essential Revisions**

1. **The authors might include further aspect which might help to differ their study from the studies listed in table 4. For example by analyzing the preoperative level of CEA in regard to prognosis. Since the authors have available preoperative CYFRA 21-1 data, they might also combine preoperative CEA + CYFRA 21-1 as tumor marker index (TMI) and look for the prognostic value of this parameter (see Lung Cancer (2008) 60, 408—415).**

**Answer:**

Very recently, we have already reported the clinical significance of the preoperative CEA levels with larger sample size (n = 467).

**Risk factors for both recurrence and survival in patients with pathological stage I non-small cell lung cancer; Eur J Cardiothorac Surg [Epub ahead of print]**

Yoshiki Kozu, Tomohiro Maniwa, Shoji Takahashi, Mitsuhiro Isaka, Yasuhisa Ohde, Takashi Nakajima

http://ejcts.oxfordjournals.org/cgi/reprint/ezt192?ijkey=mHCr5pFeCb7XFWV&keytype=ref

As have been reported earlier by Muley et al., the TMI seems to be a useful and validated prognosticator. In the present study, we could not find any prognostic values in preoperative CYFRA 21-1 levels. This may be because of the limited number of patients with preoperative high CYFRA 21-1 levels (n = 12). Consequently, there was no significant correlation of TMI with OS in the present study (p = 0.78). We would like to include this parameter in the future study with solid data of CYFRA 21-1.

2. **Is it possible to elaborate a treatment algorithm based on the prognostic factors found in multivariate analysis? (tumor diameter, VPI, Serum CEA)**

**Answer:**

We attempted to establish a new treatment algorithm based on pathological stage and postoperative CEA levels. Unfortunately, we could not show definitive conclusion because of a small sample size of the HH group in the p-stage IA patients (n = 9). Alternatively, we provided the OS curves according to the number of independent unfavorable prognostic factors (Fig. 2). We added the following paragraph (page 10 lines 2-6) and figure legend.
OS curves according to the number of unfavorable prognostic factors

Figure 2 shows OS curves according to the number of independent unfavorable prognostic factors (tumor diameter of more than 30 mm, presence of VPI, and the HH group) on the basis of the results of multivariate analyses. Five-year OS rate was 58.0% for those harboring 2 or more unfavorable prognostic factors (n = 25).

Figure 2.
Overall survival curves according to the number of independent unfavorable prognostic factors (tumor diameter of more than 30 mm, presence of VPI, and the HH group) on the basis of the results of multivariate analyses.
Five-year overall survival rate was 58.0% for those harboring 2 or more unfavorable prognostic factors (n = 25).

Discretionary Revisions

Results: In the first paragraph some descriptive data might be merged to the patients and methods section.

Answer:
The first paragraph of the Results section was moved to the Methods section. Also, we deleted the information on the adjuvant chemotherapy.
Reviewer #2 (Dr Han-Shui Hsu)

Version: 1 Date: 14 March 2013

Comments

The authors reported in this manuscript that a high postoperative CEA level was associated with poor prognosis in patients with stage I non-small cell lung cancer. The paper was nicely written, however, the issue the authors want to address has been discussed by several groups previously. 292 patients were enrolled in the study. The results obtained were similar to other studies and no new information provided.

Answer:

As was pointed out by the reviewer, there have been several reports describing the prognostic value of the postoperative CEA levels in NSCLC patients. We believe that our manuscript is valuable and worth publication for the following reasons:

(i) We found that high postoperative CEA levels could be the independent prognostic factor as well as pathological stage, which is the most widely-used prognosticator in lung cancer. This suggests that high postoperative CEA levels might be considered as an independent factor affecting survival beyond the current TNM staging system, if generalized to other pathological stages.

(ii) Until now, there have been no reports reviewing the prognostic values of perioperative change of serum CEA levels. We think that our results can strengthen the study review shown in table 4.

(iii) Actually, the previous reports had serious limitations: including those who underwent incomplete resection [4] or those with malignancies from other organs [11, 15]. Since we precluded these patients, we consider that our results reflected true prognostic value and be trustworthy.

Other minor revisions

1. In table 1, the surgical procedures were merged into 2 categories, adding the table annotation b.

2. In table 4, we corrected “2W” to “Within 2W”. We also added the table annotation b.

3. To clarify the full name of the Chairman of the Ethics Committee who approved this study, the following sentence is added. “Mitsuru Takahashi, the Chairman of the Ethics Committee,
approved this study.”

4. We made image correction in figure 1.

We appreciate your comments and hope that our manuscript is suitable for publication in *Journal of Cardiothoracic Surgery*. Thank you again for your time.

Yours Sincerely,

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