Author’s response to reviews

Title: Prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma: a retrospective cohort study

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Version: 2 Date: 6 March 2014

Author’s response to reviews: see over
Reviewer 1’s comments and our responses:

Title: Prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma: a retrospective cohort study

Version: 1 Date: 10 February 2014

Reviewer: yasushi nakai

Reviewer's report:

Minor essential revisions

1. Various tumors are included in this report. So patient backgrounds are very heterogenous. The most important factor for OS and RFS will be malignant potential of primary tumor. So malignant potential of primary tumor should be discussed. (T stage or Grade of primary tumor).

Answer 1) Thank you for your good comment.

As reviewer pointed, malignant potential could affect the prognosis, but the number of each tumor type was not sufficient to assess the prognostic value. In addition, T stages are all T4 because they have adrenal metastasis, although tumor grades could be various.

In addition, previous reports also didn’t describe the T stage and grade of the primary tumors.

10. Vazquez BJ, Richards ML, Lohse CM, Thompson GB, Farley DR, Grant CS, Huebner M, Moreno J: Adrenalectomy improves outcomes of selected patients with metastatic carcinoma. World J Surg. 2012, 36: 1400-1405. ) However, I think we should describe it as limitation in discussion section according to reviewer’s comment. We will add the limitation in the Discussion section (page 12, line 18-22) as follows;

In addition, heterogenous tumors are included and malignant potential of primary
tumor will be the important factor for OS and RFS. However, the number of each tumor type was not sufficient to assess the prognostic value. Larger cohort study also is needed to find out the prognostic value of the malignant potential of primary tumor

Q2, Is this population enough for multivariate analysis?

Answer 2) Thank you for your good comments. The small population is our most drawbacks because the adrenal metastatectomy is rarely performed. Muth et al also reported the prognostic factors for survival with 30 patients undergoing adrenalectomy for metastasis. We consulted biostatisticians (Kyung-Sook Yang, Dept. of Biostatistics,) about data analysis. Theoretically, if the sample size is greater than the variables, the multivariate analysis is possible. So, 4 variables needs greater than 4 samples (≥5 samples). However, generally one variable roughly needs 10 samples for multivariate analysis. In our multivariate analysis of variables affecting RFS and OS, 4 variables and 3 variables were included respectively. Therefore 4 variables needs roughly about 40 samples. Conclusively, 32 patients were relatively small for 4 variables, but 32 patients were not insufficient for multivariate analysis. However, this small number of patients is major drawback in our study. So, we add this limitation in Discussion section (page 12, line 15) as follows;

Our study has a number of limitations. The study was hampered by selection bias, and several variables are inter-related because of the retrospective study design. Furthermore, the number of patients was relatively small for multivariate analysis.

3, Operative method is not significant factor in univariate analysis. Why is operative method
included in multivariate analysis?

Answer3) We are very sorry for our carelessness. As you pointed out, operation method should haven’t included in multivariate analysis. We were ridiculously confused with RFS and we consulted once again to biostastitician about it. According to the reviewer’s comment, we performed the multivariate analysis only with intent to treat, synchronous metastasis and GPS which were significant factor in univariate analysis. As a result, only synchronous metastasis and GPS were significant factor in multivariate analysis. So, we revised the results in Table 3 as follow and we also revised manuscript in our discussion about laparoscopic method in Discussion section (page 10 line 17 to page 11 line 13). We are sorry for it again;

<table>
<thead>
<tr>
<th>Table 3. Univariate and multivariate analysis of variables affecting OS</th>
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<tbody>
<tr>
<td><strong>OS (univariate analysis)</strong></td>
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<tr>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Age (&gt; 63.5 years)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<td>Male</td>
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<td>Operative method</td>
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<tr>
<td>Open</td>
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<td>Laparoscopy</td>
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<td>Intent to treat</td>
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<td>Palliative</td>
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<tr>
<td>Cure</td>
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<tr>
<td>Synchronous metastasis</td>
</tr>
<tr>
<td>Site of metastasis</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Adrenal + other site</td>
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<tr>
<td>Site of primary tumor</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Liver</td>
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<tr>
<td>Stomach</td>
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<td>Kidney</td>
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</table>
In our study, the independent negative prognostic factors for overall survival (OS) were synchronous metastasis, and GPS. Synchronous metastasis was also an independent prognostic factor in our study. With regard to synchronous metastasis, it was explained theoretically that patients with a tumor presenting as a synchronous metastasis growing faster or more aggressively and patients with metachronous disease could be regarded as having more indolent tumors [16]. With regard to the laparoscopic and open approach, the laparoscopic method could be a feasible option even in aggressive tumor because we believe that our study include the more aggressive tumor [17,18]. As mentioned before, synchronous tumor and short disease-free interval are related to more aggressive tumor, and overall survival could reflect the tumor aggressiveness [9,10,16]. Tanvetyan et al. reported that the median overall survival was shorter (~12 months) for patients with synchronous tumor [8]. In our study, there were 19 synchronous patients (59.4%), and the disease-free interval was 8.8 months. The median overall survival was only 10.5 months. Muth et al. reported nine patients (30%) with synchronous disease, a median DFI of 26 months, and a median survival of 23 months [9]. Howell et al. described 11 synchronous patients (19%), a DFI > 12 months for 39 patients (81%), and an overall median survival of 30 months [16]. Howell et al. preferred open surgery in patients with multi-focal disease and in patients with more aggressive tumor. In our study, more aggressive patients were included, and the

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<tbody>
<tr>
<td>Lung</td>
<td>1.41 (0.34-5.75)</td>
<td>0.626</td>
<td></td>
</tr>
<tr>
<td>Previous metastasectomy</td>
<td>No</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.04 (0-67.8)</td>
<td>0.397</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>≤1.0</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>5.74 (1.24-26.5)</td>
<td>0.025</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>≥3.5</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3.5</td>
<td>1.96 (0.68-5.61)</td>
<td>0.2</td>
</tr>
<tr>
<td>GPS</td>
<td>0</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.28 (0.60-17.8)</td>
<td>0.168</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.33 (1.09-26.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td>0-1</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.81 (0.49-6.62)</td>
<td>0.368</td>
</tr>
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</table>
laparoscopic approach could be used in those patients in line with results in previous studies. However, additional studies are needed to clarify this point.

4. Did a statistician check this report?
[Answer 4] Thank you for your good comments. According to your comment, our institutional statistician reviewed our data.

5. Why isn’t the factor (interval) included in univariate analysis table?
Answer 5) The interval: primary diagnosis to adrenalectomy in multivariate analysis is the same variable with “synchronous metastasis” in univariate analysis. So, it it better to change as the same word. As reviewer pointed, we changed the word in Table 2 and 3.

6. In this report CRP is a stronger predictor than GPS. So the part about GPS is too long. By your result CRP is a good predictor for adrenalectomy. So discussion about CRP is needed more.
[Answer] As recommendation by reviewer, CRP was a stronger predictor in univariate analysis, though our purpose of this study was to evaluate the prognostic value of GPS. According to your comment, we inserted the following sentence in the Discussion section (page 11, line 19-23): “The association with elevated CRP levels and a dismal prognosis might reflect the prognostic value of tumor produced interleukin-6, an inducer of CRP production in the liver. Presurgical CRP did correlate significantly with shorter PFS and OS in univariate analysis as like other study”
7, the paragraph about laparoscopic is not enough to explain the difference between laparoscopic and open.

[Answer]

According to your comment “number 3”, we obtained the different results with regard to the operation method. So, we revised manuscript according to the different result. As recommendation by reviewer, we inserted the following sentence in the Discussion section(page 10 line 17 to page 11 line 13):

In our study, the independent negative prognostic factors for overall survival (OS) were synchronous metastasis, and GPS. Synchronous metastasis was also an independent prognostic factor in our study. With regard to synchronous metastasis, it was explained theoretically that patients with a tumor presenting as a synchronous metastasis growing faster or more aggressively and patients with metachronous disease could be regarded as having more indolent tumors [16]. With regard to the laparoscopic and open approach, the laparoscopic method could be a feasible option even in aggressive tumor because we believe that our study include the more aggressive tumor [17,18]. As mentioned before, synchronous tumor and short disease-free interval are related to more aggressive tumor, and overall survival could reflect the tumor aggressiveness [9,10,16]. Tanvetyanon et al. reported that the median overall survival was shorter (~12 months) for patients with synchronous tumor [8]. In our study, there were 19 synchronous patients (59.4%), and the disease-free interval was 8.8 months. The median overall survival was only 10.5 months. Muth et al. reported nine patients (30%) with synchronous disease, a median DFI of 26 months, and a median survival of 23 months [9]. Howell et al. described 11 synchronous patients (19%), a DFI > 12 months for 39 patients (81%), and an overall median survival of 30 months [16]. Howell et al. preferred open surgery in patients with multi-focal disease and in patients with
more aggressive tumor. In our study, more aggressive patients were included, and the laparoscopic approach could be used in those patients in line with results in previous studies. However, additional studies are needed to clarify this point.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer 2’s comments and our responses:

Title: Prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma: a retrospective cohort study

Version: 1 Date: 13 February 2014

Reviewer: Satoshi Anai

Reviewer’s report:

Major Compulsory Revisions

Nevertheless the primary site, generally speaking, adrenal metastasis is regarded as poor prognosis for patients. However, if adrenal metastasis is considered to be operative, surgeon decides to perform ADx for these patients in practical clinic. To date, prognostic factors and surgical indications for ADx have not been clearly defined. Authors have sought the predictors for PFS and OS after metastatic ADx.

As authors mentioned in this manuscript, the number of patients was relatively small in this study. Maybe due to this, there were some discrepancies in the results. Hazard ratio (HR) of both adrenal metastasis was lower than that of single metastasis. Moreover, HR of the
presence of previous metastasectomy was lower than no history of previous metastasectomy. I am not sure these data from this small cohort can provide the significant predictive marker. If possible, larger cohort should be objected to this study and the reasons for these discrepancies should be clarified.

[Answer] We agreed with reviewer’s comments. As mentioned in the documents, the major drawback of our study was small sample size. Since the adrenal metastasis was rare disease, several studies also had a small sample size. [Ref. 9. Eur J Surg Oncol. 2010, 36: 699-704. 11. Surg Endosc. 2013, 27: 992-999]. Therefore, small sample size led to a discrepant results in HR of several variables. As you mentioned, we obtained unexpected results in variables such as HR of the presence of previous metastasectomy and both adrenal metastasis. We think that it probably resulted from that the previous metastatectomy was performed in only two patients in contrast with 30 patients had no previous metastatectomy and only five patients had single metastasis. Nevertheless the small sample size, our study may provide prognostic value of inflammation based prognostic score [GPS] who had undergone adrenalectomy due to adrenal metastasis.

According to the comment, I will add a statement to the revised manuscript in the Discussion section (page 12, line 15-22) as follows;

“Furthermore, the number of patients was relatively small, maybe due to this, there were some discrepancies in the results. Hazard ratio (HR) of both adrenal metastasis was lower than that of single metastasis. Moreover, HR of the presence of previous metastasectomy was lower than no history of previous metastasectomy. Larger cohort should be needed to elucidate these discrepancies.”
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'

Reviewer3’s comments and our responses:
Title: Prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma: a retrospective cohort study

Version: 1 Date: 18 February 2014

Reviewer: Won Tae Kim

Reviewer's report:

Major revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

[Answer] The English in this document has been checked by at least two professional editors, both native speakers of English.

Statistical review: Yes, and I have assessed the statistics in my report.

This article is the study about prognostic factors for recurrence-free and overall survival after adrenalectomy for metastatic carcinoma. This article is well described relatively. However, the results of this study were not clear. So, I have a few comments about this study.

In your results, the variables were different between univariate analysis and multivariate analysis. Of course, the variables could be different between two analyses. But, in your multivariate analysis, the selection criteria of these variables (Only 3 variables: operative
method, Interval, and GPS) were not clear. These variables were not significant in univariate analysis. So, it is better to analyze the same variables in both univariate and multivariate analysis.

[Answer] The reviewer may be pointing out a positive or negative confounder, which artificially increases or decreases the observed association between a studied factor and an outcome. To reduce the confounder effect, we consulted biostatisticians about data analysis. They recommended that “we test associations of potential confounders with the outcome of interest and include them in our model using a significance level that is higher than the one we set to define a co-factor”. Therefore, we set it at p<0.25 for univariate analysis and then set it at p<0.05 for retaining a factor in our final (multivariate) model (Ref. Ann Intern Med. 2004 Jun 1; 140(11): 857-66). Furthermore, as mentioned in the Method section, we used stepwise forward procedure for multivariate analysis instead of “enter” method. The biostatisticians recommended that we use this method because of the small sample size. This method provided the final independent factors for the outcomes.

In addition, we inserted the following sentence in the Method (statistics) section: “Among the factors, those with p<0.25 were selected (on univariate analysis for RFS and OS) and included in the multivariate regression analysis using Cox proportional hazards regression model, which was performed to achieve adjusted hazard ratio (HR) to determine prognostic factors for recurrence free and progression free survival.”

And you showed the Interval: primary diagnosis to adrenalectomy in multivariate analysis. Is it same variables with metachronous metastasis in univariate analysis? Then, it is better to change same word.

[Answer] As recommendation by reviewer, we changed the word “Interval: primary diagnosis to adrenalectomy” to “synchronous metastasis” and revised the table contents.
Please divide two tables according to RFS and OS with univariate analysis and multivariate analysis. It means that in one table only RFS included with univariate and multivariate analysis simultaneously and in another table only OS included.

[Answer] As recommendation by reviewer, we divide two tables according to RFS and OS with univariate analysis and multivariate analysis.