

## ANSWERING REVIEWERS

December 17, 2012

Dear Editor,

- 5 Please find enclosed the edited manuscript in Word format (file name: 6586-review.doc).

Title: Prognostic factor of stage IB gastric cancer

- 10 Author: Toru Aoyama, Takaki Yoshikawa, Hirohito Fujikawa, Tsutomu Hayashi, Takashi Ogata, Haruhiko Cho, Takanobu Yamada, Shinichi Hasegawa, Kazuhito Tsuchida, Norio Yukawa, Takashi Oshima, Mari Oba, Satoshi Morita, Yasushi Rino, and Munetaka Masuda

- 15 Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6586

- 20 The manuscript has been improved according to the suggestions of reviewers:

### Reviewers 1

- 25 This is a nicely written paper addressing prognostic factors of staged IB gastric cancer after radical surgery. I only have a few minor suggestions.

### Comments 1

Grammar checking is still needed.

### Answer to comments 1

- 30 We are very sorry. We asked native English speaker to check our manuscript one more time.

### Comments 2

- 35 Between lines 83 and 88, regarding patient follow up, was endoscopic examination required and how frequently was it done?

### **Answer to comments 2**

As pointed out, we added the frequency of the endoscopic examination. The following sentence was added in the methods section; the  
40 patients who received distal gastrectomy underwent an endoscopic examination every year for five years after the surgery (Page 6, Line 106 to Page 6, Line 107).

### **Comments 3**

45 Three patients were excluded from the study because of post-operative adjuvant chemotherapy (Figure 1). Adding this explanation in line 107 is suggested.

### **Answer to comments 3**

50 As pointed out, the following comment was added in the results section; three patients were excluded from the study because they received postoperative adjuvant chemotherapy (Page 7, Line 126 to Page 8, Line 127).

### **Comments 4**

55 Line 114, the authors mentioned “50% patients died from recurrence”. It is not clear what 50% stands for.

### **Answer to comments 4**

As pointed out, it was not clear what 50% stands for. In this study, 10  
60 patients died between January 2000 and December 2011. Among 10 patients, 5 patients died from the recurrence during the study period. However, our description was confused for the readers. Therefore, we revised the sentence in the result section as follows; five patients died from recurrence during the study period (Page 8, Line 134).

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### **Comments 5**

References or explanation are needed for the statement in line 137, “S-1 is more effective especially for relatively early disease”.

### **Answer to comments 5**

70 As pointed out, we added the following sentences; according to the subset analysis of the ACTS-GC, S-1 was much more effective against Stage

II than Stage IIIA or Stage IIIB cancers. Considering that S-1 was more effective, especially for relatively early disease, adjuvant S-1 could be option for these patients (Page 10, Line 163 to Page 10, Line 166).

#### **Comments 6**

If possible, please add a paragraph to discuss the reasons or mechanisms why patients with tumors located at the upper third of the stomach had a poorer survival.

#### **Answer to comments 6**

Some authors have reported the significance of the tumor location in terms of the prognosis of gastric cancer. For example, Piso et al. evaluated 532 patients with gastric cancer, and reported that the long-term survival was worse in patients with proximal disease than in those with distal tumors. The proximal stomach is a predominant site for the undifferentiated type tumors, which have a tendency to have a poorer prognosis than differentiated type tumors. Anatomically, the lymphatic drainage is complex, and tumors located in this region can metastasize to almost all lymph nodes except #5. Curative surgery for proximal tumors is D2 total gastrectomy with splenectomy, which is more invasive than that for distal cancer. Although the precise mechanism is unclear, multiple factors, including those described above, could explain why the patients with proximal tumors had a poorer survival (Page 10, Line 166 to Page 10, Line 176).

## **Reviewers 2**

110 First of all I would like to commend the authors for presenting a  
nicely written, short, concise and well-structured manuscript. Clearly, there  
is still an open question what are the risk factors for the early recurrence of  
gastric cancer (even when it presents as a limited disease) as these patients  
might require additional treatment modalities besides the surgery, including  
115 but not limited to the adjuvant chemotherapy, intraperitoneal chemotherapy  
(EPIC, HIPEC), biological therapy, etc. There is a need for a systematic  
review of the available in the recent literature data on the prognostic factors  
associated with the early recurrences of early gastric cancer, and the  
research team has successfully contributed to this field by adding just  
120 another important paper. Overall, little criticism could be expressed  
regarding this study. The aim and goals of the study, methodology and  
results sections are comprehensive and clear. There is little or no repetition  
of the information presented in the text and tables.

## **Comments 1**

125 This paper is similar by its structure and aims to that of Takashi  
Yokoyama et al. published in Gastric Cancer (2011) 14:372-377, but provides  
data on different risk factors (i.e. tumors located at the upper third of the  
stomach was the sole independent prognosticator in patients with stage IB  
130 gastric cancer, whereas the previous study demonstrated that the  
histologically undifferentiated adenocarcinoma is the only risk factor). I  
believe, this study should be cited and included in the discussion section in  
order to make this paper even more comprehensive

## **Answer to comments 1**

135 As pointed out, we cited and included Yokoyama's report in the  
discussion section in order to make this paper clear. The following comments  
were added in the discussion section; Yokoyama et al. previously  
demonstrated that undifferentiated-type adenocarcinoma was the only risk  
140 factor for the recurrence of stage IB gastric cancer. However, there were  
some differences in the present study and Yokoyama's study. First, the  
evaluation of the staging was different. We classified the stage by the third  
English edition of the Japanese Classification of Gastric Carcinoma, while  
the previous study used the second English edition of the Japanese

145 Classification of Gastric Carcinoma. The previous study included T3N0 and  
T1N2 cancers, which are now classified as stage IIA. Ahn analyzed the  
stage-specific survival using the third English edition of the Japanese  
Classification of Gastric Carcinoma, and reported that the five-year survival  
150 was 88.9% for stage IB (90.2% in T1N1 and 87.6% in T2N0, respectively) and  
83.1% for stage IIA (84.0% in T1N2 and 82.1% in T3N0, respectively). Thus,  
the survival was worse in the latter cases than in the former. Second, the  
previous study included the patients who received adjuvant chemotherapy in  
the analysis. Adjuvant chemotherapy could have affected the survival. (Page  
10, Line 177 to Page 11, Line 190).

155 **Comments 2**

English language requires minor polishing.

**Answer to comments 2**

160 We are very sorry. We asked native English speaker to check our  
manuscript one more time.

### **Reviewers 3**

This study examined the prognostic factors of stage IB gastric cancer according to the third English edition of Japanese classification of gastric carcinoma, and the authors concluded that tumors located at the upper third of the stomach was the sole independent prognosticator in patients with stage IB gastric cancer. However, there are important things to be considered. Even though the authors stated that the results of this study were somewhat different from those of the previous studies due to difference edition of classification, the fact that tumors located at the upper third of the stomach was the sole independent prognosticator could be an incidental finding. Therefore, to clarify the results of this study, more numbers of patients with stage IB, including multi-center study, will be needed.

### **Answer to reviewer 3**

As pointed out, this was a retrospective single-center study with a small sample size. The number of the patients may be too small to lead definite conclusion. The only way to draw definite conclusion is to collect recent data from many hospitals. However, without our data, no one knows which parameters should be included in the future study. Therefore, we believed that our study had some clinical impact. Considering these, we revised the abstract and discussion as follows; In conclusion, our data may suggest that the tumor location is associated with the survival in patients with stage IB gastric cancer. Because our study was a retrospective single-center study with a small sample size, a prospective multi-center study is necessary to confirm whether the patients with stage IB gastric tumors located in the upper third of the stomach have a poorer survival than those with tumors in other locations (Page 2, Line 33 to Page 3, Line 38) (Page 11, Line 195 to Page 11, Line 198) (Page 12, Line 203 to Page 12, Line 208).

#### **Reviewers 4**

This Article studied 103 stage IB gastric ca and found that tumor location was the independent prognostic indicator. The paper is well written but there are some areas may be improved. 1.The main focus is to study the prognostic factor of stage IB. However, you spend a lot of space to compare the difference between T1N1M0 and T2N0M0. You need to mention it in result and discuss it. 2.In line 13, 14, what is the meaning of five (50%)? Do you forget to tell 10 patients had recurrence? 3.The English of this manuscript requires an extensive editing. 4.You need to add the follow up data at Fig 1.

#### **Comments 1**

The main focus is to study the prognostic factor of stage IB. However, you spend a lot of space to compare the difference between T1N1M0 and T2N0M0. You need to mention it in result and discuss it.

#### **Answer to comments 1**

As pointed out, the present study identified the unfavorable subset of patients with Stage IB gastric cancer. We reported that the patients with stage T1N1 and T2N0 cancer had similar outcomes. Therefore, we grouped the patients with T1N1 and T2N0 disease together. Then, the further prognostic analyses were focused on the patients with stage T1N1 and T2N0 cancer. These are added in the result section and discussion section (Page 8, Line 139 to Page 8, Line 141) (Page 9, Line 154 to Page 9, Line 158).

#### **Comments 2**

In line 13, 14, what is the meaning of five (50%)? Do you forget to tell 10 patients had recurrence?

#### **Answer to comments 2**

As pointed out, it was not clear what 50% stands for. In this study, 10 patients died between January 2000 and December 2011. Among 10 patients, 5 patients died from the recurrence during the study period. However, our description was confused for the readers. Therefore, we revised the sentence in the result section as follows; five patients died from the recurrence during the study period (Page 8, Line 134).

### **Comments 3**

255           The English of this manuscript requires an extensive editing.

### **Answer to comments 3**

          We are very sorry. We asked native English speaker to check our manuscript one more time.

260

### **Comments 4**

          You need to add the follow up data at Fig 1.

### **Answer to comments 4**

265           As pointed out, we add the follow up data at Fig 1.