Author’s response to reviews

Title: Identification of prognostic factors and surgical indications for metastatic gastric cancer.

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Author’s response to reviews: see over
Dear Editor,

Enclosed please find our revised manuscript entitled “Identification of prognostic factors and surgical indications for metastatic gastric cancer” by Y. Mohri et al., which we would like to submit for consideration for publication in “BMC Cancer”.

This study represents a detailed analysis of the prognostic factors and the adequacy evaluation of our indication for gastrectomy with or without metastatectomy in patients with metastatic gastric cancer. We identified surgical intervention (gaatrectomy with or without metastatectomy), performance status ≤2, Nutrophil to lymphocyte ratio (NLR) <3.1, and carbohydrate antigen 19-9 level ≤37 U/mL as predictors of longer survival in patients with metastatic gastric cancer. Furthermore, NLR and CA19-9 are also independent prognostic factors in patients who underwent surgical intervention.

We revised the original manuscript according to the reviewer’s comment as below.

Response to reviewer’s comments

1. Response to reviewer (RF)

Major Critiques
Overall, this manuscript lacks adequate data analysis and breakdown to prove that surgery is an appropriate treatment for patients’ with metastatic gastric cancer. The authors retrospectively reviewed 123 metastatic gastric cancer cases. In table 1, they compare the whole group to the gastrectomy group. The whole group should be further broken down to patients who did not have surgery. It is necessary to have statistical analysis performed comparing these group variables and the p-values as they may have statistically significant differences. Additionally, more information pertaining to treatment needs to be provided, such as number of patients per group that received neoadjuvant and/or adjuvant chemotherapy. Also, how did the patients present for surgery: bleeding, perforation, or obstruction?
Were they symptomatic? It is unclear if there was a selection bias.

**We have performed statistical analysis to compare factors associated with patient, tumor, and laboratory between resection group and non-resection group. We revised the “Table 1” and demonstrated statistical differences between two groups.**

We also demonstrated the number of patients who received chemotherapy prior to surgery, or after surgery in resection group at Table 1. We described the policy of surgical approach in the method section. There were 34 patients who received gastrectomy without metastatectomy for symptom palliation (i.e., obstruction, bleeding, or perforation). Details were described in result section.

Most importantly, it is unclear why only 28% of the surgical patients had preoperative chemotherapy. Palliative chemotherapy is the mainstay of treatment for metastatic gastric cancer. It needs to be clearer as to which patients underwent chemotherapy. The author needs to elaborate and explain why so few patients received chemotherapy prior to surgery.

As mentioned above, we have described the surgical strategy for metastatic gastric cancer patients. There were 31 patients who were evaluated as initially complete resectable disease. They were received initially surgical approach and received chemotherapy after surgery. On the other hand, 23 patients of 63 patients, who were evaluated as initially complete unresectable disease, received gastrectomy with or without metastatectomy after chemotherapy. Details were demonstrated in the result section.

A larger prospective trial would be needed to further evaluate surgery as a treatment in metastatic gastric cancer.

**Minor Critiques**

1. Figures 1-5 are Kaplan Meier survival curves, and each of these needs a legend. Also, the x-axis of each should include number of patients at risk. The legend should include the n and the p-value.

**Legends of figure were demonstrated at page 22. We added the number of**
patients at each of time points in each figure.

2. Table 1 should not be supplemental.

**Table 1 was changed from supplemental file to regular file.**

3. The univariate analyses (tables 2 and 5) should not be supplemental.

**Table 2 and 5 were changed from supplemental file to regular file.**

4. In table 4, the postoperative complication data is not necessary.

**We deleted the table 4.**
2. Response to reviewer (SM)

Major

1. The authors do a reasonable job at emphasizing the importance of patient selection in this series. This needs to be highlighted a bit more directly stating that the manuscript is not advocating for a surgical approach for patients with metastatic gastric cancer routinely.

In our study, 34 patients had received palliative gastrectomy and 28 patients had received gastrectomy with metastatectomy to achieve complete resection. As reviewer’s comments, our manuscript is not advocating for surgical approach for patients with metastatic gastric cancer routinely. We revised the sentences of conclusion as follows: Elevated NLR, CA19-9 and PS are pretreatment predictors of poor prognosis for metastatic gastric cancer. Although gastrectomy with or without metastatectomy in patients with metastatic gastric cancer is safe and may prolong survival, surgical approach should be considered carefully and should be attempted in selected patients who do not have those risk factors affecting survival.

2. Was HER2 status known or reported? If amplified, were any of the patients treated with herceptin?

In our study, HER2 status was not known,

3. The median time from diagnosis to surgery was reported to be 1.9 months. This seems terribly short for this patient population. Why didn't patients get a longer course of chemotherapy prior to resection? This message cannot be advocated to operate this soon after diagnosis. These are highly selected.

We described the policy of surgical approach and evaluation of chemotherapy response in the method section. When patients initially received chemotherapy, the assessment for chemotherapy for chemotherapy response was performed at first one month, and every three months after starting chemotherapy. Unfortunately, 5 patients received gastrectomy without metastatectomy for symptom palliation. The median time from the
diagnosis to surgery of these patients was 0.6 months. However, the median time of remaining 18 patients was 3.8 months. We revised the sentences of result section.

4. On the KM curves for survival, the number of patients represented by the curve at each of the time points needs to be included. The authors report that 75% of patients have died. Given patients who are lost to follow up are censored, which in this case very likely may have died, the tail end of the curve likely represents very few patients....again emphasizing the highly selective nature of this approach.

We added the number of patients at each of time points in each figure.

5. Was intraperitoneal chemotherapy used for any of the patients?

No, intraperitoneal chemotherapy was not used in our study.
List of revised point

Page 2, Abstract, Conclusions
Although gastrectomy with or without metastatectomy in patients with metastatic gastric cancer is safe and may prolong survival, surgical approach should be considered carefully and should be attempted in selected patients who do not have those risk factors affecting survival.

Page 4, line 11
The Medical Ethics Committee of Mie University Graduate School of Medicine approved this retrospective study. The study protocol confirmed to the ethical guidelines of the 1975 Declaration of Helsinki. It was exempted to obtain informed consent from the patients in consideration of the aim and methods of this study.

Page 5, line 9
When the baseline CT showed resectable extent of tumor burden in regard to the technical aspects of surgery, surgical approach was selected as initial therapy.

Page 5, line 13
However, if the tumor burden was beyond that expected according to the baseline CT findings, and the complete resection was not feasible, resection of primary tumor followed by chemotherapy was performed.

Page 6, line 5
CT for the assessment for treatment response was undertaken after first one month and every three month interval from starting date of chemotherapy. Patients were re-discussed to have complete resectable disease at each evaluation.

Page 6, line 20
The chi-square test was performed to compare factors associated with patients, tumor, laboratory, and treatment between resection and non-resection group.

Page 7, line 9
Table 1 shows the frequency distributions of various clinicopathological factors in the whole group (n = 123) the resection group (gastrectomy with or without metastatectomy) (n = 83) and the non-resection group (n=40), including patient, primary tumor, metastatic tumor, laboratory, surgery, and chemotherapy factors.
Difference between non-resection and resection group are summarized in Table 1. The groups differed significantly with respect to performance status, adjacent organ invasion, and distal lymph node metastasis. Non-resection group had worse performance status, and had more frequency of the presence of adjacent organ invasion and distal lymph node metastasis.

Sixty patients received initial surgery for the primary and metastatic sites. In those patients, 29 patients received gastrectomy without metastatectomy for symptom palliation (i.e., obstruction, or bleeding). The remaining 31 patients, who did not have obvious symptoms caused by gastric cancer, attempt to perform initially complete surgical resection. Consequently, 15 patients of the 31 patients (48%) received gastrectomy with metastatectomy as planned and 16 patients received gastrectomy without metastatectomy due to extensive tumor burden.

The results of this study demonstrate that gastrectomy with or without metastatectomy prolongs survival in a highly selected group of patients, who have metastatic disease at the time of presentation with gastric cancer, compared with patients who do not undergo surgical intervention.

However, metastatic gastric cancer encompasses a heterogenous patient population in which both palliative and curative treatment strategies may be used.

Although there were only 28 patients who received successfully gastrectomy with metastatectomy, 13 patients of 63 patients, who were initially beyond resectable tumor burden, were converted to gastrectomy with metastatectomy.

Thank you very much in advance for your kind consideration.

Sincerely yours,

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