

## **Response letter**

Thank you for your kind comments.

We have made revision according to reviewer's comments.

Revised parts of manuscript are presented here as red color highlighted, because the locked version of editing couldn't changed to red color texts.

## **Reviewer #1**

1. Reviewer commented as 'because this is a report of a single case, it is not easy to have a conclusion. i have no further comment for the authors.'

→ Thank you for the kind compliment.

## **Reviewer #2**

1. Reviewer commented as 'The authors should present macroscopic resected stomach and metastatic tumor of the bone.'

→ We thank the reviewer for this comment. We have presented the macroscopic resected stomach and metastatic tumor of bone on the Figure 2. (Figure 2, page 18)

2. Reviewer also commented as 'Were cancer cells detected in bone marrow and/or peripheral blood?'

→ We thank the reviewer for this comment. Bone marrow was also obtained from lumbar spine during surgery, and cancer cells were not detected in bone marrow. To one's regret, we didn't studied the peripheral blood for the detection of cancer cells. We have added the results of bone marrow biopsy on the part of case report. (Case report section, line 29, page 7) Added text is 'Bone marrow was also obtained from the patient's lumbar spine during surgery, and no cancer cells were detected in the bone marrow aspirate.'

## **Reviewer #3**

1. Reviewer commented as 'The authors have not yet mentioned the potential risk of and the potential origins for "Gastric Remnant Cancer".'

→ We thank the reviewer for this comment. We have added the potential risk and potential origin of gastric remnant cancer on the part of discussion. (Discussion section, line 15 page 8)

Added text is 'In this study, we report a case of RGC with synchronous isolated bone metastasis. The average interval between initial distal gastrectomy and the second surgery for RGC is reported to be 22.0-34.6 years for benign disease and 6.8-18.8 years for gastric cancer<sup>[6]</sup>. As possible important factors for the pathogenesis for RGC, *H. pylori* infection, duodenogastric reflux and denervation of gastric mucosa have been considered. Also, Billroth-II (B-II) reconstruction is known to be more prevalent in developing RGC than Billroth-I (B-I) reconstruction; the possible reason is continuous bathing by duodenogastric reflux, as well as mucosal inflammation and regeneration<sup>[6,7]</sup>. In the case described herein, *H. pylori* infection was not identified. But, the previous B-II reconstruction and persistent duodenogastric reflux could have been the possible cause of RGC in this patient.'

2. Reviewer also commented as 'What was the patient's *H. pylori* status?'

→ We thank the reviewer for this comment. The patient's *H. pylori* status was negative. We have added this finding on the part of case report. (Case report section, line 12, page 7).

Added text is 'Serum fasting gastrin level was within normal range, and Giemsa staining did not demonstrate *Helicobacter pylori* (*H. pylori*) infection in the gastric biopsy specimen.'

3. Reviewer also commented as 'Was a fasting serum gastrin obtained? (e.g. did the authors consider origins for this poorly differentiated tumor?).'

→ We thank the reviewer for this comment. The patient's initial serum gastrin level was within normal range. (86 pg/mL, normal range: 25-111 pg/mL ) We have added

this finding on the part of case report. (Case report section, line 12, page 7)

Added text is 'Serum fasting gastrin level was within normal range, and Giemsa staining did not demonstrate *Helicobacter pylori* (*H. pylori*) infection in the gastric biopsy specimen.'

4. Reviewer also commented as 'The description of the surgical procedure needs to be more complete if other investigators are to reproduce this finding (i.e. was an esophagojejunostomy produced).

→ We thank the reviewer for this comment. The patient underwent completion total gastrectomy with Roux-en-Y esophagojejunostomy. We have added this finding on the part of case report. (Case report section, line 16, page 7)

Added text is 'The patient underwent total gastrectomy with Roux-en-Y esophagojejunostomy and lumbar vertebrae metastasectomy.'

5. Reviewer also commented minor issues as 'Page 2, Informed consent statement: patient not "patients".'

→ As you have commented, we have changed 'patients' to 'patient' on informed consent statement, Page 2. (Title pages, Informed consent statement, page 2)

6. Reviewer also commented as '2) Abstract, line 1: metastasis is a rare event; not "is rare event".'

→ We have changed 'metastasis is rare event' to 'metastasis is a rare event' according to your comment. (Abstract section, line 1, page 4)

10. Reviewer also commented as '3) Discussion, line 17: "survival gain"; authors please define or elaborate on this gain.'

→ As you have suggested, we have added elaborated survival gain and additional comments (Discussion section, line 14, page 9). Changed part of text is 'Some studies have reported survival gain in gastric cancer patients with synchronous distant metastasis who underwent resectable gastric surgery, with or

without metastasectomy<sup>[9-11]</sup>. Meta-analysis revealed that palliative gastrectomy is associated with a significant improvement in overall survival (hazard ratio: 0.62), as compared to that of patients without palliative gastrectomy<sup>[9]</sup>. Kim *et al*<sup>[11]</sup> studied the effect of gastrectomy and metastasectomy in patients with gastric cancer with distant metastases, who had previously received chemotherapy. They reported that the survival rate of patients who underwent gastrectomy plus metastasectomy was higher than that of patients who underwent debulking gastrectomy only, as well as that of patients who were administered chemotherapy only (median overall survival and 3-year survival rates reported as 28.0 mo, 15.5 mo and 9.0 mo and 42.8%, 8.1% and 3.5%, respectively). Meta-analysis also showed the survival improvement in metastatic gastric cancer patients who underwent visceral metastasectomy including liver, peritoneum and distant node. The mean increased difference in survival conferred by metastasectomy averaged between 9.3 mo and 15.7 mo<sup>[12]</sup>.

However, the above studies were retrospective and selection bias cannot be ruled out. Evidence to support surgical intervention in these patients is not conclusive. There is a need for prospective randomized controlled studies to evaluate the value of resectable surgery on patients with gastric cancer with distant metastasis.'

Also, we have changed the part of reference owing to the qualities of detailed meta-analysis datas. (Reference section, line 2, page 15, Reference 9)

11. Reviewer also commented as '4) In Discussion: please mention for the non-specialists that vimentin immunostaining is a test for Neurofilament immunoreactivity that has been identified in most neuroendocrine tumors.'

→ We thank the reviewer for this comment. We have added your comment on the part of case report. (Case report section, line 22, page 7).

Changed part of text is 'Immunohistochemistry showed that the tumor cells exhibited diffuse immunoreactivity for cytokeratin AE1/AE3, but were negative for synaptophysin and vimentin, a test for neurofilament immunoreactivity that has been identified in most neuroendocrine tumors.'

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