

## **Authors' answers to the reviewers' comments (Manuscript No.57726)**

Thank you very much for your constructive comments on our manuscript. Your comments were very reasonable and we agreed with them.

Our detailed responses are listed below.

### **Reviewer1:**

The way is useful way for advanced cancer. From Our experiences, we find more complications in patients with Neoadjuvant chemoradiotherapy after surgery. We need more information about the 5 patients.

→ Thank you for your very valid comment. We too were concerned about the possibility of complications after CRT followed by surgery. To prepare for possible postoperative complications, such as anastomotic leakage, pancreatic fistula, and malnutrition, each patient received an indwelling enteral tube, and enteral nutrition was started from postoperative day (POD) 1 (page 5, line 20). Fortunately, there were no serious complications and few instances of the need to use the enteral tube, except in case 4. This has been mentioned on page 9, line 22 of the revised manuscript by adding the below phrase.

Since anorexia continued for two months, he needed some support of enteral nutrition in the interim.

Science Editor:

(1) The authors did not provide original pictures. Please provide the original figure

documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

➔ According to your suggestion, we have added the original pictures as Figures 1 and 2 in the revised manuscript, in PowerPoint file format.

(2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

➔ We have added the PubMed numbers and DOI citation numbers to the reference list, as recommended.

(3) Please provide the tables in a editable format, not in an image format.

➔ We have reformatted Tables 2 and 3 as editable word files.

(4) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements.

➔ Thank you for the advice. Accordingly, the "**Case Presentation**" section was divided into "**Patients and therapeutic strategy**", "**Chief complaints and history of present /past illness**", "**Personal and family history**", "**Physical examination upon**

**admission”, “Laboratory examinations”, and “Imaging examinations”** according to the Guideline for Manuscript Presentation, and sections titled **“Final diagnosis”, “Treatment”, and “Outcomes and follow-up”** were added. Furthermore, data on the lymph node size, CEA level, postoperative condition, and postoperative period were added as below.

#### *Chief complaints and history of present/past illness*

**Case 1:** Anemia was noticed in an 80-year-old male with Alzheimer’s disease, diabetes mellitus, and hypertension. The patient’s past medical history was unremarkable.

**Case 2:** A 77-year-old male with chronic obstructive pulmonary disease (COPD) and dementia presented with epigastralgia. The patient’s past medical history was unremarkable.

**Case 3:** Anemia was identified in a 71-year-old female with a history of total hysterectomy for uterine cancer 26 years previously.

**Case 4:** A 67-year-old male presented with epigastralgia. The patient’s past medical history was unremarkable.

**Case 5:** A 73-year-old female with diabetes mellitus and hypertension presented with epigastralgia. The patient’s past medical history was unremarkable.

#### *Personal and family history*

In all five cases, their family history was unremarkable.

### ***Physical examination upon admission***

Cases 1 and 3 had no special physical signs and did not have any abdominal symptoms. Cases 2, 4, and 5 had mild epigastralgia, but did not have any other upper abdominal symptoms, including tenderness. The Eastern Cooperative Oncology Group–Performance Status (ECOG-PS) of cases 1 and 2 was 1, and those of the others was 0.

### ***Laboratory examinations***

Serum carcinoembryonic antigen (CEA) levels were 140.4 ng/ml in case 1, 37.2 ng/ml in case 2, 11.6 ng/ml in case 3, and 29.9 ng/ml in case 5. In case 4, CEA levels were less than the normal range (2.6 ng/ml).

### ***Imaging examinations***

**Case 1:** Gastroscopic examination indicated a diagnosis of two advanced gastric cancers (types 2 and 3 in the lower and upper thirds of the stomach, respectively). MDCT showed enlargement of lymph node No. 6 to 3.02 cm in diameter. Furthermore, colonofiberscopic examination identified early transverse colon cancer and MDCT imaging indicated cholecystolithiasis.

**Case 2:** Gastroscopic examination revealed type 3 gastric cancer in the lower third of the stomach. MDCT showed enlargement of two adjacent lymph nodes, No. 3 to 1.84 cm and 1.73 cm in diameter, respectively.

**Case 3:** Gastroscopic examination revealed type 3 gastric cancer in the upper third of the stomach. MDCT indicated enlargement of the No. 3-11p lymph nodes to 5.26 cm in diameter, with invasion of the pancreatic body.

**Case 4:** Gastroscopic examination indicated type 3 gastric cancer in the lower third of the stomach. MDCT showed enlargement of the No. 8a lymph node to 3.06 cm in diameter.

**Case 5:** Gastroscopic examination indicated type 2 gastric cancer in the middle to lower third of the stomach. MDCT showed enlargement of two adjacent lymph nodes, Nos. 9-11p to 1.82 cm and 1.52 cm in diameter, respectively.

### **FINAL DIAGNOSIS**

Pathological evaluation of the tumors indicated well to moderately differentiated adenocarcinoma of the stomach in all five patients. Table 1 shows the clinical characteristics of all five patients.

### **TREATMENT**

Table 1 shows details of the preoperative treatment in all five patients. Table 2 shows the operative findings of the five patients.

**Case 1:** The patient underwent 45 Gy irradiation (recommended by a radiotherapist considering the age of the patient and risk factors) and chemotherapy with S-1 at a dose of 100 mg/day for six weeks. Subjective symptoms and hematological toxicity > grade 3 did not occur. Findings of MDCT imaging indicated low signal intensity inside lymph

node No. 6, although this node was slightly enlarged (3.86 cm), indicating progressive disease (PD; Fig. 2). Levels of CEA increased once after CRT (211.8 ng/ml), subsequently decreasing to < 10% of pretherapy values (140.4 ng/ml to 9.8 ng/ml). Six weeks after completing CRT, the patient underwent total gastrectomy with D2 lymph node dissection, partial resection of the transverse colon, and cholecystectomy.

**Case 2:** The patient received a total of 50 Gy irradiation and 100-80 mg/day of S-1 for six weeks (i.e. an initial dose of 100 mg/day for 3 weeks, followed by 80 mg/day for 3 weeks after 2 weeks of rest). Thereafter, the size of the No. 3 metastatic two adjacent lymph nodes decreased (0.77 cm and 0.72 cm, respectively), indicating a partial response (PR). His CEA value decreased to < 20% of pretherapy levels (37.2 ng/ml to 4.9 ng/ml). Eight weeks after completing CRT, he underwent subtotal distal gastrectomy with D2 lymph node dissection.

**Case 3:** The primary tumor initially showed bleeding, but settled after starting CRT. The findings of MDCT showed areas of low intensity in the No. 3-11p lymph nodes after 30 Gy of irradiation and 80 mg/day of S-1 for three weeks. However, we switched her regimen to capecitabine (Xeloda), cisplatin and trastuzumab (Herceptin) (XP-HER)<sup>[13]</sup>, because of the presence of fatty liver that resembled liver metastasis and an increase in CEA values after CRT (74.9 ng/ml). Thereafter, her CEA decreased to < 20% of the pretherapy level (11.6 ng/ml to 2.2 ng/ml). Four weeks after completing two courses of XP-HER, total gastrectomy with resection of the pancreas (body to tail) and spleen was performed.

**Case 4:** The patient developed grade 3 anorexia after 30 Gy of irradiation and 120 mg/day of S-1 for three weeks. MDCT showed that the No. 8a metastatic lymph node had shriveled (1.86 cm), indicating PR. Distal gastrectomy with D2 lymph node dissection was performed six weeks after stopping CRT.

**Case 5:** The patient developed grade 3 anorexia after 30 Gy of irradiation and 100 mg/day of S-1 for three weeks. MDCT showed that metastatic lymph node Nos. 9-11p had shriveled (0.97 cm, 1.01 cm), indicating PR. Her CEA value decreased after CRT to < 10% of pretherapy levels (29.9 ng/ml to 1.3 ng/ml). Distal gastrectomy with D2 lymph node dissection was performed six weeks after stopping CRT.

## **OUTCOMES AND FOLLOW-UP**

Table 2 shows the details of postoperative clinicopathological features of the five patients.

**Case 1:** The histological findings were ypT1bN0H0P0cy0, Stage 1A. Furthermore, pathologically, colon cancer was not evident. The enlarged lymph nodes with low intensity on CT were cystic lesions, including necrotic tissue, with no cancerous tissue. There was no evidence of recurrence at 56 months postoperatively.

**Case 2:** The resected portion of the stomach was free of cancer cells, indicating a pathological complete response (pCR). The other histological findings were ypT0N0H0P0cy0. However, this patient died 18 months postoperatively due to peritoneal dissemination and multiple lung metastasis.

**Case 3:** The primary lesion was diagnosed as T3 (SS) and disappearance of the pancreatic invasion. The histological findings were ypT3(SS), N1 (Nos. 3a and 7) H0P0cy0, Stage IIB. This patient opted for postoperative adjuvant chemotherapy with S-1 for more than one year postoperatively. There was no evidence of recurrence at 45 months postoperatively.

**Case 4:** The main malignant lesion was mucosal cancer, although metastasis persisted in the No. 4d, 6, and 8a lymph nodes. The histological findings were ypT1a(M), N2H0P0cy0, Stage IIA. This patient underwent cholecystectomy to treat acute cholecystitis on POD 18. Since anorexia continued for two months, he needed some support of enteral nutrition in the interim. There was no evidence of recurrence 41 months postoperatively.

**Case 5:** The resected stomach was free of cancer cells, indicating pCR. Micrometastasis of adenocarcinoma (pN1(mi)) was evident only in fibrous tissues surrounding the No. 3b lymph node. The histological findings were ypT0, N1 (No. 3b) H0P0cy0. This patient opted for adjuvant chemotherapy with S-1 for more than one year after operation. There was no evidence of recurrence 24 months postoperatively.

Thank you once again for your comments that have helped to improve our manuscript. We hope that you will now find our paper suitable for publication.