

Successful Conversion Surgery for Advanced Gastric Cancer With Multiple Liver Metastases Following Ramucirumab Plus Paclitaxel Combination Treatment

TSUTOMU NAMIKAWA¹, AKIRA MARUI¹, KEIICHIRO YOKOTA¹, YUKI FUJIEDA¹,
MASAYA MUNEKAGE¹, SUNAO UEMURA¹, HIROMICHI MAEDA¹, HIROYUKI KITAGAWA¹,
MICHIYA KOBAYASHI² and KAZUHIRO HANAZAKI¹

¹Department of Surgery, Kochi Medical School, Kochi, Japan;

²Department of Human Health and Medical Sciences, Kochi Medical School, Kochi, Japan

Abstract. *Aim:* To present the case of a patient with unresectable gastric cancer showing a remarkable effect by second-line drug treatment with ramucirumab plus paclitaxel and conversion surgery. *Case Report:* A 68-year-old woman who was diagnosed with gastric cancer was referred to us. Esophagogastroduodenoscopy showed an ulcerated lesion with an irregular nodulated border in the lower third of the stomach, and histology of biopsied specimens indicated a poorly differentiated adenocarcinoma. Enhanced computed tomography revealed extensive invasion of the liver, and the patient was treated using S-1 plus oxaliplatin as first-line chemotherapy. Because she developed liver metastases, the treatment regimen was changed to ramucirumab plus paclitaxel as the second-line treatment. After four cycles of weekly paclitaxel with ramucirumab treatment, the liver metastases had completely disappeared. Because no other metastatic lesions in other organs were detected, we performed total gastrectomy with D2 lymphadenectomy. The macroscopic findings of the surgically resected specimen revealed an ulcerated lesion with an irregularly modulated lesion measuring 9.5×4.5 cm. Pathological analysis demonstrated a poorly differentiated adenocarcinoma in the stomach, with invasion to the liver through the serosal layer, and seven lymph node metastases. The postoperative course was unremarkable, and she received ramucirumab in

combination with paclitaxel treatment. However, liver metastasis appeared at 4 months after the operation, for which she was treated with irinotecan. Although the patient continued to receive irinotecan chemotherapy for 10 months, her general condition gradually deteriorated, and she was started on best supportive care 13 months after conversion surgery. *Conclusion:* Conversion surgery may prolong survival not only through first-line but also second-line treatments in selected patients with unresectable advanced gastric cancer; however, assessments of additional cases and further studies are required to establish this treatment strategy.

Gastric cancer remains one of the most common gastrointestinal malignancies, and is the second leading cause of cancer-related mortality worldwide (1). In the Japanese gastric cancer treatment guidelines, systemic drug treatment using anticancer agents or molecular targeted agents is recommended for patients with unresectable advanced and recurrent gastric cancer, with preservation of major organ function (2). Recent advances in systemic drug treatment have resulted in these therapies becoming the standard treatment for prolonging survival and have dramatically affected the prognostic impact of unresectable metastatic gastric cancer (3).

In the past few years, several investigators focused on the efficacy of surgical interventions in patients initially diagnosed with unresectable gastric cancer who were then able to undergo surgical resection after systemic drug treatment (4-8). Conversion surgery is a challenging treatment in an attempt at curative resection after downstaging or disease control obtained by use of systemic treatment (9). However, conversion surgery after second- or third-line systemic treatment is generally a difficult strategy, while conversion surgery following first-line systemic treatment did result in some survival benefit in selected patients (10, 11).

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Correspondence to: Tsutomu Namikawa, Department of Surgery, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan. Tel: +81 888802370, Fax: +81 888802371, e-mail: tsutomun@kochi-u.ac.jp

Key Words: Advanced gastric cancer, unresectable metastases, conversion treatment, second line treatment.

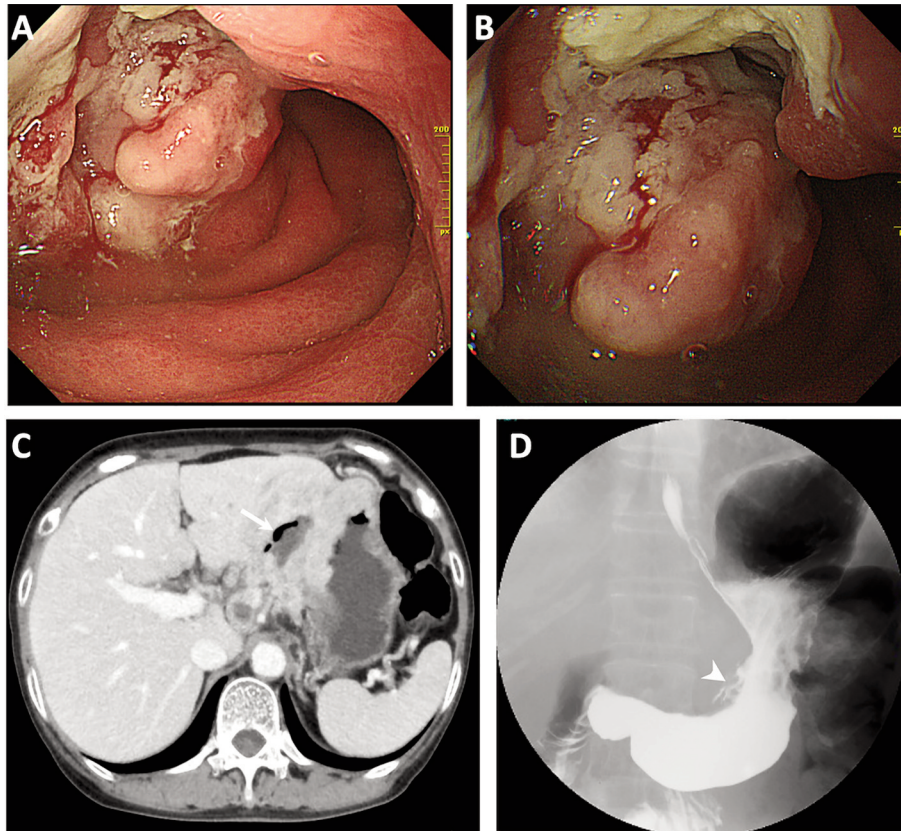


Figure 1. Initial esophagogastroduodenoscopy, computed tomography, and double-contrast upper gastrointestinal imaging. Esophagogastroduodenoscopy revealed an obviously elevated lesion with a central depression in the middle third of the stomach (A and B). Abdominal contrast-enhanced computed tomography showed thickening of the gastric wall and fluid retention with air density in the perigastric area under the lateral segment of the liver (C, arrow). Fluoroscopy of the upper gastrointestinal tract showed a deformity of the gastric contour, poor extension of the gastric wall, and leakage of contrast agent into the perigastric area on the lesser curvature side (D, arrowhead).

Herein, we present a case of patient with advanced gastric cancer who underwent conversion surgery after successful tumor downgrade by systemic second-line treatment using ramucirumab plus paclitaxel.

Case Report

A 68-year-old woman with a complaint of appetite loss and body weight presented to our Department for further evaluation after a diagnosis of gastric cancer by her local hospital. Her blood analysis showed the following: Reduced red blood cell count ($355 \times 10^4/\text{mm}^3$; normal range: $386\text{--}492 \times 10^4/\text{mm}^3$), elevated white blood cell count ($10.6 \times 10^3/\text{mm}^3$; normal range: $3.3\text{--}8.6 \times 10^3/\text{mm}^3$), and high C-reactive protein level (5.5 mg/dl; normal range: <0.14 mg/dl). A high level of the serum tumor marker carbohydrate antigen-125 (CA125) (48.0 U/ml; normal range: <35 U/ml) was confirmed, and levels of the serum tumor markers carcinoembryonic antigen, CA19-9 and alpha-fetoprotein were within the normal limits.

Esophagogastroduodenoscopy revealed an irregular ulcerated lesion with a nodulated border in the lower third of the stomach (Figure 1A and B). The pathological examination for biopsied specimens of the lesion demonstrated a poorly differentiated adenocarcinoma, and immunohistochemical examination of the tumor revealed negative reactivity for human epidermal growth factor receptor 2 (HER2). Abdominal contrast-enhanced computed tomography showed extensive wall thickening with heterogeneous enhancement on the lesser curvature of the stomach, with lymph nodes swelling around the stomach, and an obscured boundary between the stomach and liver, with a low-density lesion in the area between the stomach and the liver (Figure 1C). Upper gastrointestinal imaging using a water-soluble contrast agent revealed a deformity of the gastric contour with poor extension and leakage of the contrast agent into the perigastric area on the lesser curvature side (Figure 1D).

We diagnosed cT4N2M0, stage IV gastric cancer accompanied by liver invasion according to the Japanese

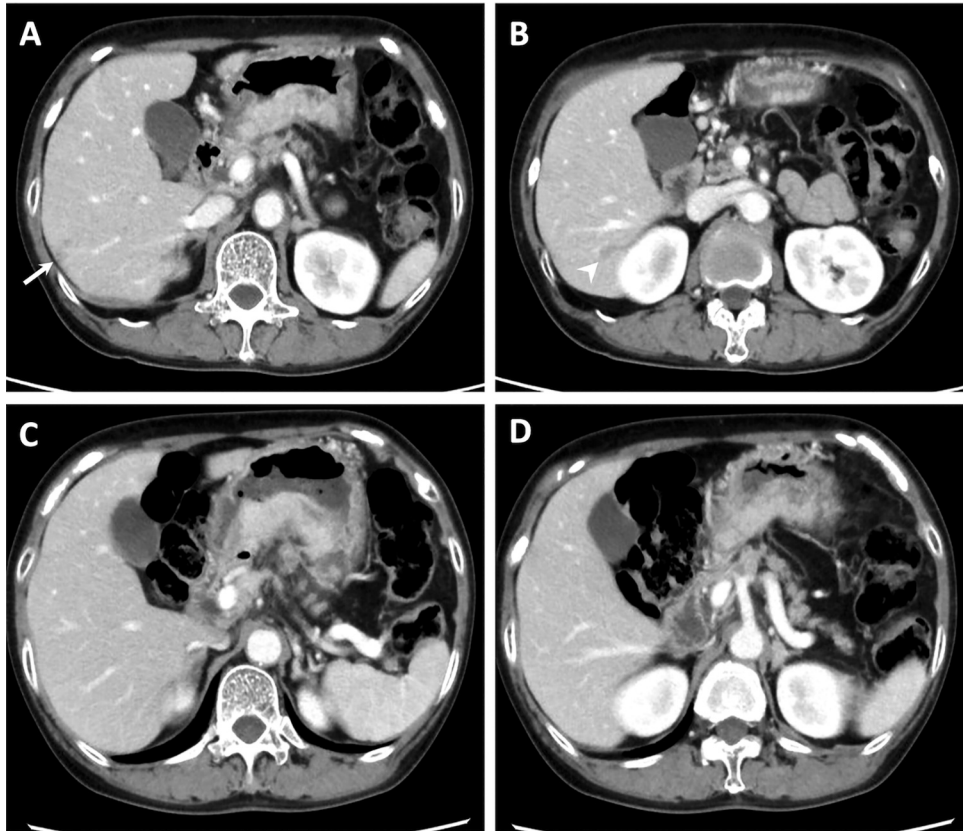


Figure 2. Abdominal contrast-enhanced computed tomography before (A and B) and after (C and D) systemic treatment using ramucirumab plus paclitaxel. Abdominal contrast-enhanced computed tomography before ramucirumab plus paclitaxel treatment showed liver metastases (A, arrow; B, arrowhead). After four cycles of weekly paclitaxel with ramucirumab treatment, the liver metastases completely disappeared.

classification system (12), treating the patient with S-1 plus oxaliplatin as the first-line chemotherapy. S-1 was administered at 80 mg/m² body surface area per day for 2 weeks, followed by 1 week of no chemotherapy. On day 1 of the 21-day cycle, the patient was also intravenously administered 100 mg/m² per day of oxaliplatin. After four courses of chemotherapy, liver metastases were detected on abdominal contrast-enhanced computed tomography (Figure 2A and B). Therefore, the regimen was changed to ramucirumab in combination with paclitaxel chemotherapy as the second-line treatment. After four cycles of weekly paclitaxel with ramucirumab, the liver metastases had completely disappeared (Figure 2C and D).

Since enhanced computed tomography showed no further metastatic lesions in any other organs, conversion surgery was planned. Intraoperatively, there were dense adhesions with sclerotic tissue changes between the liver and stomach, and we performed total gastrectomy with D2 lymphadenectomy followed by Roux-en-Y reconstruction. The operative time was 312 min, and the estimated blood loss was 450 ml.

The macroscopic findings of the surgically resected specimen revealed an ulcerated lesion with an irregularly modulated lesion measuring 9.5×4.5 cm in the middle third of the stomach (Figure 3A). Pathological analysis of the specimen demonstrated a poorly differentiated adenocarcinoma in the stomach, with invasion to the liver through the serosal layer and seven lymph node metastases (Figure 3B). The tumor after preoperative therapy was classified as ypT4N3M0 stage IIIC, and the histological response after preoperative therapy was grade 1a according to the Japanese classification system (12).

The patient was discharged on postoperative day 14 without complications, and she received ramucirumab in combination with paclitaxel treatment. However, the patient developed liver metastasis at 4 months after the operation, for which she was started on treatment with irinotecan. Despite a 10-month course of irinotecan chemotherapy, her general condition gradually deteriorated, and her treatment plan was changed to best supportive care 13 months after conversion surgery.

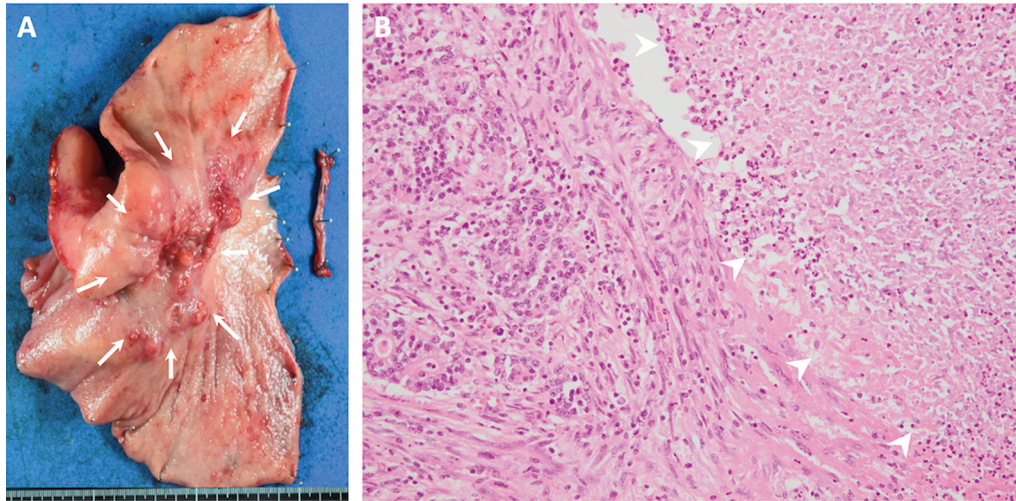


Figure 3. The gross appearance and pathological examination of the surgically resected specimen. The macroscopic appearance of the resected specimen revealed an ulcerated tumor, with an irregularly modulated lesion measuring 9.5×4.5 cm in the middle third of the stomach (A, arrows). Hematoxylin and eosin-stained sections of the gastric tumor demonstrated serosal invasion of a poorly differentiated adenocarcinoma with necrotic change (B, arrowheads).

Discussion

We herein describe the case of a patient with initially unresectable advanced gastric cancer who underwent conversion surgery after the control of distant metastases by second-line systemic treatment with ramucirumab plus paclitaxel. We analyzed conversion surgery for gastric cancer after second-line systemic treatment reported from 2000 and 2021 in the English literature as found in a search of the Medline and PubMed databases using the key words “unresectable gastric cancer”, “second- or third-line treatment” and “conversion surgery.” Articles published only in abstract form were excluded, and we obtained clinicopathological data for each patient. To the best of our knowledge, this is only the third reported case for which the conversion surgery after second-line systemic treatment for initially unresectable advanced gastric cancer is described in the English literature.

Table I lists the clinicopathologic characteristics of the two previously reported cases (13, 14) and the present case. The median age of the patients was 68 (range=68-77) years, and the male-to-female ratio was 1:2. Gastric tumor in the middle third of the stomach was reported in all cases, and the macroscopic type was also ulcerated lesions. The first-line regimen for systemic treatment was S-1 plus cisplatin for one patient and S-1 plus oxaliplatin for the other two. The second-line systemic treatment was ramucirumab plus paclitaxel for all patients. Conversion surgery was performed after second-line treatment in two patients and after third-line treatment in one. Treatment consisted of total gastrectomy in one patient and distal gastrectomy in two.

Histological examinations of the gastric adenocarcinomas showed two intestinal types and one diffuse-type carcinoma.

According to the Japanese guidelines for gastric cancer, S-1 plus cisplatin is the recommended systemic treatment as first-line chemotherapy for patients with HER2-negative disease (2, 15, 16). S-1 plus oxaliplatin is also recommended chemotherapy regimen for unresectable advanced gastric cancer and was proven to be effective in pivotal trials (17-20). Recent developments in second-line and further treatments, such as ramucirumab, nivolumab, and trifluridine/tipiracil, for metastatic gastric cancer have improved overall survival and quality of life (21-23). In particular, the recent advances in newly developed molecular targeted drugs, such as trastuzumab, ramucirumab, and nivolumab combined with chemotherapy, have had a significant effect on improving the prognosis in patients with initially unresectable advanced gastric cancer (21, 22).

Several investigators demonstrated that the survival of patients who were able to undergo conversion surgery was longer than those who continued chemotherapy (8, 10, 24). These studies have shown the practical benefits of conversion surgery following first-line systemic treatment in selected patients. However, it remains unclear whether conversion surgery after second-line treatment is an effective strategy, following which a patient’s condition generally deteriorates and often worsens due to exhaustion.

Ramucirumab is a molecular targeted angiogenesis inhibitor, that is a humanized monoclonal antibody directed against vascular endothelial growth factor receptor-2 (21, 25). Considering its characteristics as an angiogenesis inhibitor and the circulating half-life of this drug, a more than 28-day

Table 1. Clinicopathological data for reported cases of conversion surgery after second- or third-line treatment for metastatic advanced gastric cancer.

Author (Ref)	Year	Age, years	Gender	Gross appearance	Initial staging*	Treatment regimen			Surgery	Histological type	Postoperative staging*	Survival, months
						First line	Second line	Third line				
Maki <i>et al.</i> (13)	2019	77	M	Ulcerated	T4N0M0, Stage III	S-1 plus cisplatin	Ramucirumab plus paclitaxel	None	TG	Intestinal	ypT4N0M0, Stage III	30
Matsumoto <i>et al.</i> (14)	2020	68	F	Ulcerated	T2N0M1, Stage IV	S-1 plus oxaliplatin	Ramucirumab plus paclitaxel	Nivolumab	DG	Diffuse	ypT0N0M0, pCR	3
Present case	2021	68	F	Ulcerated	T4N3M0, Stage IV	S-1 plus oxaliplatin	Ramucirumab plus paclitaxel	None	DG	Intestinal	ypT4N3M1, Stage IV	13

DG: Distal gastrectomy; F: female; M: male; TG: total gastrectomy; pCR: pathological complete response. Tumors were located in the middle third of the stomach in all patients. *According to the Japanese Classification of Gastric Carcinoma (12).

interval between the last administration and an operation is recommended when surgery is planned (14). In the present case, the interval between the last administration of ramucirumab and surgery was set at 30 days. These considerations may also be needed to minimize the occurrence of complications associated with conversion surgery.

Yoshida *et al.* classified stage IV gastric cancer into four categories for conversion surgery on the basis of the biology and heterogeneous characteristics of the tumor (9). According to this new therapeutic classification, the present case was classified as category 2, which was a marginally resectable metastasis, and the operation would not be considered to be the best choice for initial treatment. Yamaguchi *et al.* reported that among 135 patients with gastric cancer classified as category 2, the median survival was significantly longer in patients who underwent conversion surgery than in those without surgery (30.5 months *vs.* 11.0 months; $p < 0.001$) (8). However, the preoperative determination of whether curative resection with negative resection margins is possible remains clinically challenging for patients with category 2 disease (8, 9).

Previous studies reported that additional systemic treatment should be continued even if conversion therapy can be performed with curative resection (8, 9, 17, 26). The present patient developed liver metastasis at 4 months after the operation despite the continuation of postoperative ramucirumab plus paclitaxel treatment. Further assessments of additional cases are required to determine the benefit of conversion surgery following second- or third-line systemic treatment.

In conclusion, conversion surgery after second- or third-line systemic treatment might be a treatment option for patients with initially unresectable gastric cancer, even if first-line treatment fails to improve treatment outcomes. Although prospective randomized control studies are unrealistic due to the small number of patients, further investigations, including case-control studies with large sample sizes, are required to validate the use of conversion surgery following late line systemic treatment.

Conflicts of Interest

None declared.

Authors' Contributions

T. Namikawa, A. Marui, K. Yokota and Y. Fujieda performed the surgical procedure; T. Namikawa and H. Maeda reviewed literature data; T. Namikawa, M. Munekage, S. Uemura and H. Kitagawa performed preoperative investigation the patient; T. Namikawa prepared the draft of the article; M. Kobayashi was advisor of the surgical procedures; T. Namikawa and K. Hanazaki reviewed the final version of the article. All Authors read and approved the final version of the article.

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Received May 15, 2021
Revised June 11, 2021
Accepted June 15, 2021