A Case of Unresectable Gastric Cancer Successfully Treated with Conversion Surgery After Immunotherapy Including Treatment

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A 72-year-old woman diagnosed as unresectable advanced gastric cancer with both of direct invasion to liver and pancreas and peritoneal dissemination, received 11 courses of S-1 and oxaliplatin (SOX) + nivolumab combination therapy according to the Japanese Gastric Cancer Treatment Guideline because the tumor showed HER2-negative, microsatellite instability (MSI)-high, and PD-L1-positive. Since post-treatment endoscopic and other imaging findings showed a prominent reduction of the main tumor, release of surrounding organ infiltration, and disappearance of disseminated metastases, we planned the conversion surgery and could perform laparoscopic distal gastrectomy with D2 lymph node dissection. Postoperative histopathological examination showed no residual tumor cells both in the primary tumor and dissected lymph nodes. Postoperatively, the patient was treated with SOX therapy for 1 year and remains alive at 16 months postoperatively without recurrence.

Key words: Conversion surgery, Nivolumab combination chemotherapy, Pathological complete response

INTRODUCTION

In the 2021 Japanese Gastric Cancer Society Preliminary Treatment Guidelines, based on the results of two randomized trials (ATTRACTION-4 [1], CheckMate 649 [2]) investigating the efficacy of immune checkpoint inhibitors in the treatment of HER2-negative curatively unresectable advanced or recurrent gastric cancer, a combination of an immune checkpoint inhibitor, nivolumab and chemotherapy was approved as the recommended primary therapeutic regimen. Conversion surgery (CS) for gastric cancer (GC) has been defined as a surgical treatment aiming at an R0 resection after chemotherapy for tumors that were originally unresectable or marginally resectable for technical and/or oncological reasons [3]. However, due to the infrequency of CS against GC, further cases need to be accumulated regarding its indications, surgical difficulty, and mid-term prognosis. We here report on a patient with originally unresectable advanced gastric cancer with direct invasion to liver and pancreas and peritoneal dissemination who became eligible for laparoscopic CS after receiving a total of 11 courses of S-1 and oxaliplatin (SOX) plus nivolumab.

CASE REPORT

A 72-year-old woman was referred to our hospital for treatment of advanced gastric cancer. Esophagogastroduodenoscopy (EGD) performed at another clinic to investigate anemia identified a Type 3 tumor extending from the middle of the gastric body to the pyloric ring (Fig. 1). Contrast-enhanced CT showed an indistinct border between the thickened gastric wall and the pancreas and left lobe of the liver, suggesting invasion (Fig. 2). Positron emission tomography (PET)-computed tomography (CT) showed fluorodeoxyglucose (FDG) accumulation at the primary tumor (maximum standardized uptake value (SUVmax) 22.4) with multiple lymph node metastases. In addition, a nodule with FDG accumulation was detected just below the left upper abdominal wall, and peritoneal

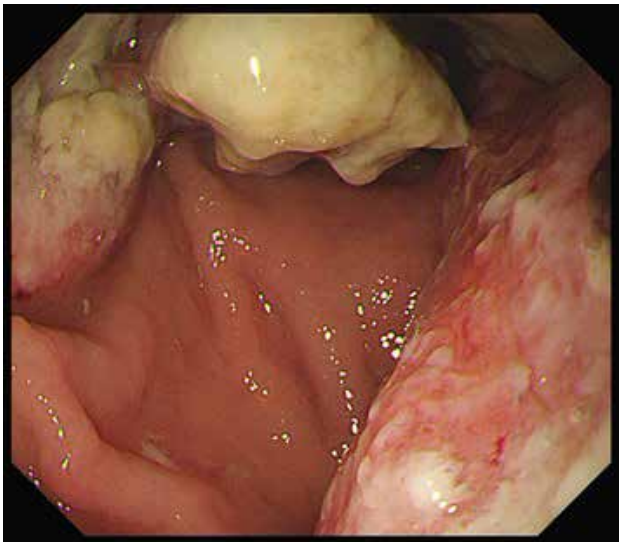

Fig. 1 A Type 3 lesion centered on the lesser curvature is seen from the gastric body to the pyloric ring.

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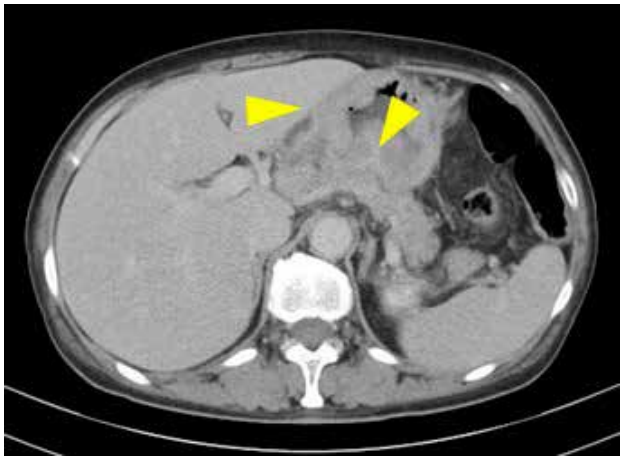

Fig. 2 Contrast-enhanced CT shows an indistinct border between the tumor and the left lobe of the liver and pancreas (arrows).

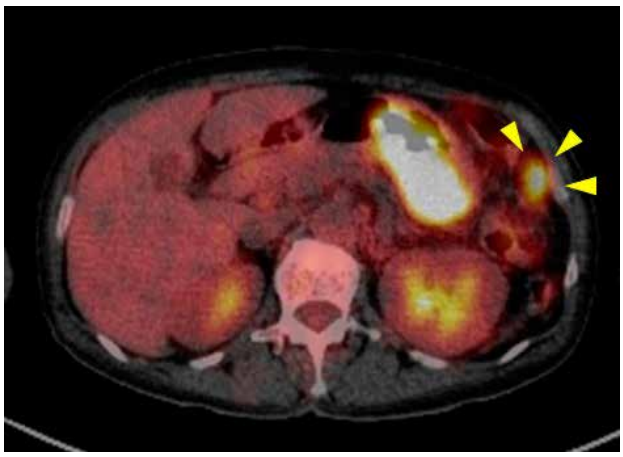

Fig. 3 Peritoneal dissemination is suspected due to a nodule with FDG accumulation just below the left abdominal wall (arrows).

dissemination was suspected (Fig. 3). Histopathological examination revealed adenocarcinoma, well and moderately differentiated tubular adenocarcinoma. Immunohistochemical staining of biopsy specimens showed HER2-negative, microsatellite instability (MSI)-high, and PD-L1-positive. Based on imaging findings, patient was diagnosed as stage IVB gastric cancer with direct invasion to liver and pancreas and peritoneal dissemination according to the Japanese Classification of Gastric Carcinoma 15th edition [4]. After 11 courses of SOX + nivolumab as primary treatment, EGD showed prominent reduction and scarring of the lesions (Fig. 4). Since PET-CT did not show any obvious abnormal accumulation of suspected primary tumor, lymph node metastasis, or disseminated nodules, we decided to perform laparoscopic surgery. Intraoperative findings showed that slight adhesions were present, but detachable, on the posterior surface of the gastric wall and the anterior surface of the pancreas (Fig. 5), and there was no evidence of peritoneal dissemination. Peritoneal wash cytology was negative. We could safely complete laparoscopic distal gastrectomy with lymph node dissection. The postoperative course was uneventful, and the patient discharged on postoperative days. Histopathological examinations on resected specimens showed fibrosis with foam cell aggregation and inflammatory cell infiltration from the submucosa to the serosa, but no tumor cells and no metastatic sites in any lymph nodes (pN0(0/42)). Final histopathological diagnosis was no residual carcinoma cells, and therapeutic grade was Grade 3. The patient was treated with SOX regimen as adjuvant chemotherapy for 1 year postoperatively and is currently recurrence-free 22 months after surgery.

DISCUSSION

Nivolumab was clinically approved to use in Japan in 2021 in combination with first-line chemotherapy in the patient with HER2-negative, curatively unresectable, or recurrent gastric cancer, and long-term benefit and safety have been described in subsequent reports of the ATTRACTION-4 trial [5]. Although S-1 + cisplatin combination therapy is considered to perform as the standard of care for neoadjuvant chemotherapy (NAC) in the gastric cancer patients with bulky lymph node metastasis in Japan, no superiority has been demonstrated for scirrhous type of gastric cancer [6], and furthermore, no consensus has been reached to introduce this therapy into daily practice. CS could be performed in the patient because of obvious downstaging of the tumor after preoperative SOX + nivolumab treatment. MSI status might be the

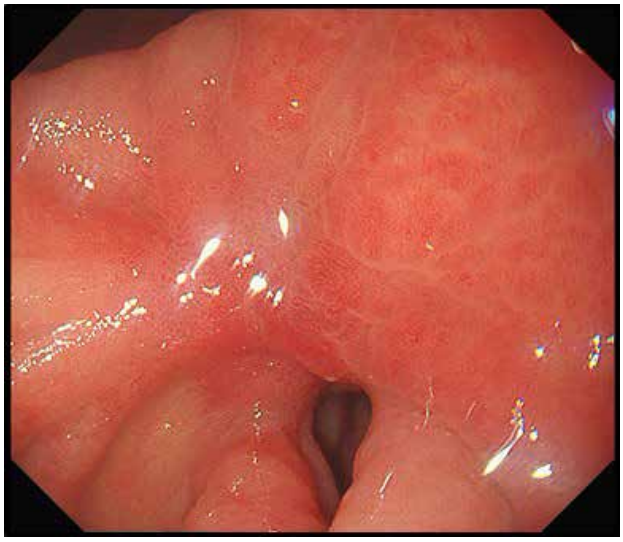

Fig. 4 The lesion is markedly reduced and scarred.

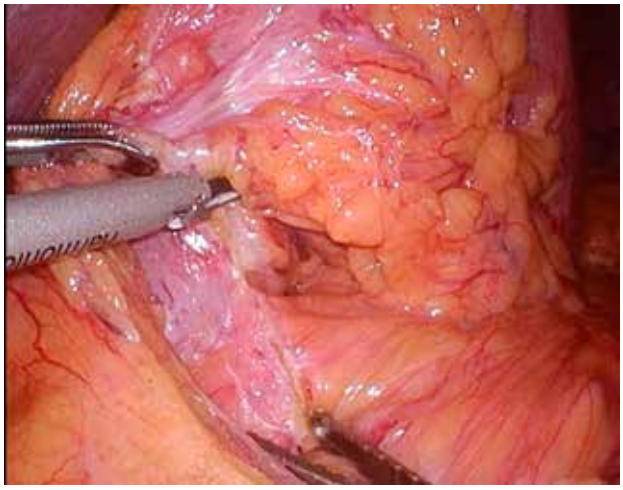

Fig. 5 Adhesions on the posterior surface of the gastric wall and the anterior surface of the pancreas were suspected to be traces of invasion, but were detachable.

primary reason to obtain the significant tumor shrinkage [2, 7], and there was a difference in the hazard ratio between the chemotherapy with nivolumab combination group and the chemotherapy alone group in the CheckMate 649 study [2]. In addition, a retrospective cohort study of patients who received CS versus those who received chemotherapy alone consistently demonstrated a survival benefit of CS on univariate and multivariate analyses [8]. Treatment by inhibiting the PD-1/PD-L1 axis with immune checkpoint inhibitors such as nivolumab has emerged as a new therapeutic strategy for gastric cancer [9]. A search in the Japan Medical Abstract Society database using the keywords "gastric cancer," "Nivolumab," and "conversion surgery" identified a total of nine reported cases, including our case. (Table 1) CS was performed following first-line treatment with Nivolumab combined chemotherapy. Seven cases demonstrated a treatment response of Grade 3, achieving pathological complete response. Almost cases showed MSI-high and CPS > 5, which is suggesting the therapeutic efficacy of immune checkpoint inhibitor combination therapy. Immune-related adverse events were not observed in any of the cases. In our case, the patient had no apparent adverse events from the immune checkpoint inhibitor and was able to continue for 11 courses of SOX + nivolumab treatment.

In a retrospective cohort study of Stage IV gastric cancer, the main regimen was a combination of S-1 and cisplatin, but oxaliplatin, capecitabine, irinotecan, docetaxel, 5-fluorouracil, and leucovorin have also been reported to improve the safety of CS and survival of patients with R0 resection [3]. Three cases of R0 resection after chemotherapy including nivolumab for unresectable gastric cancer with multiple liver metastases were reported [10], suggesting that nivolumab combination therapy for Stage IV gastric cancer may attract more attention in the future. Since CS could be performed safely in this case and there was little adhesion to surroundi ng organs, a regimen including immune checkpoint inhibitors for unresectable gastric cancer may be promising when considering treatment with CS. Laparoscopic surgery has a well-established safety profile in conventional gastric cancer surgery and is considered to have a high benefit in CS in terms of surgical invasiveness. However, there are no guide-

Table 1 Cases of conversion surgery performed after chemotherapy with nivolumab as first-line treatment

case	auther	year	age	sex	histological type	HER2	MSI	CPS	regimen	course	gastrectomy	therapic grade	adj	rec	prognosis (month)
1	Harada. K [11]	2023	78	F	por1, tub2	—	high	> 5	SOX + Nivo	4	TG	3	no	no	9
2	Okuda. T [12]	2023	78	F	tub1, pap	—	N/A	> 5	SOX + Nivo	3	PG	N/A	S1	no	10
3	Sato. T [13]	2024	63	F	N/A	—	N/A	1 < 5	SOX + Nivo	5	DG	3	S1	no	6
4	Egami. Y [14]	2024	77	M	hepatoid	N/A	N/A	N/A	FOLFOX + Nivo	3	TG	1a	no	no	9
5	Sekino. N [15]	2024	58	F	sig	—	N/A	> 5	SOX + Nivo**	5	TG	3	no	no	4
6	Uehara. H [16]	2024	59	M	por	—	high	< 1	SOX + Nivo	6	TG	3	no	no	12
7	Nozu. S [17]	2024	71	M	tub2, por	—	high	< 5	SOX + Nivo*	5	DG	3	no	no	6
8	Hayashishita. S [18]	2024	81	M	tub2	—	N/A	N/A	SOX + Nivo	5	DG	3	no	no	8
9	our case	2024	72	F	tub1, tub2	—	high	+	SOX + Nivo	11	DG	3	SOX	no	22

** Oxaliplatin was discontinued after 2 courses, due to peripheral neuropathy.
* Oxaliplatin was discontinued after 3 courses, due to peripheral neuropathy.

lines in Japan regarding the regimen and duration of NAC, and it is considered necessary to investigate a large number of cases. In addition, patients who have undergone preoperative chemotherapy often have hard tumor texture, edema of the surrounding tissue, evident fibrosis, and anatomical gaps that disappear, significantly increasing the difficulty of laparoscopic surgery and necessitating a switch to open surgery, which is recommended to be performed at an experienced gastric cancer center.

In conclusion, this case report demonstrated the achievement of pCR with nivolumab combination chemotherapy alone as first-line treatment for unresectable advanced gastric cancer, demonstrating the benefit for preoperative chemotherapy in future CS.

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CONFLICT OF INTEREST STATEMENT

Authors declare no Conflict of Interests for this article.

PATIENT CONSENT STATEMENT

Informed Consent Statement: Informed consent was obtained orally from the patient for this case report.

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REFERENCES

1) Kang YK, Chen LT, Ryu MH, *et al*. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-contr. *Lancet Oncol* 2022; 23: 234–247. doi: 10.1016/S1470–2045(21)00692–6.
2) Janjigian YY, Shitara K, Moehler M, *et al*. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; 398: 27–40. doi:10.1016/S0140–6736(21)00797–2.
3) Yoshida K, Yasufuku I, Terashima M, *et al*. International Retrospective Cohort Study of Conversion Therapy for Stage IV Gastric Cancer 1 (CONVO-GC-1). *Ann Gastroenterol Surg* 2022; 6: 227–240.
4) Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 15th ed. Tokyo: Kanehara; 2017.
5) Boku N, Omori T, Shitara K, *et al*. Nivolumab plus chemotherapy in patients with HER2-negative, previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: 3-year follow-up of the ATTRACTION-4 randomized, double-blind, placebo-controlled, phase 3 trial. *Gastric Cancer* 2024. doi: 10.1007/s10120–024–01535–0.
6) Terashima M, Iwasaki Y, Mizusawa J, *et al*. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). *Gastric Cancer* 2019; 22: 1044–1052.
7) Chao J, Fuchs CS, Shitara K, *et al*. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol* 2021; 7: 895–902.
8) Ohnuma H, Sato Y, Onoyama N, *et al*. Survival benefit of conversion surgery after intensive chemotherapy for unresectable metastatic gastric cancer: a propensity score-matching analysis. *J Cancer Res Clin Oncol* 2021; 147: 2385–2396.
9) Muro K, Chung HC, Shankaran V, *et al*. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016; 17: 717–726.
10) Kawai J, Yasufuku I, Fukada M, *et al*. Successful R0 resection after chemotherapy, including nivolumab, for gastric cancer with liver metastases: three case reports. *Surg Case Rep* 2024; 10: 138.
11) Harada K, Fukunaga K, Kashimoto K, *et al*. A case of curative resection of the local advanced gastric cancer after SOX plus Nivolumab chemotherapy, and the pathological diagnosis was complete response. *Jpn J Cancer Chemother* 50(13): 1712–1714, Dec. 2023.
12) Okuda T, Odagiri K, Yanagimoto Y, *et al*. Conversion surgery performed after SOX plus Nivolumab therapy for advanced gastric cancer with para-aortic lymph node metastasis. *Jpn J Cancer Chemother* 50(13): 1671–1673, Dec. 2023.
13) Sato T, Kawaoka T, Xaolin Y, *et al*. A case of conversion surgery after SOX plus Nivolumab for unresectable advanced gastric cancer. *Jpn J Cancer Chemother* 51(1): 75–77, Jan. 2024.
14) Egami Y, Sugimura K, Katsuyama S, *et al*. A case of conversion surgery for Stage Ⅳ ATP-producing gastric cancer with distant metastasis. c329–331, Mar. 2024.
15) Sekino N, Natsume T, Tanaka H, *et al*. A case of advanced gastric cancer treated with conversion surgery followed by Nivolumab combination chemotherapy. *Jpn J Cancer Chemother* 51(4): 417–420. Apr. 2024.
16) Uehara H, Sakaguchi Y, Kusumoto T, *et al*. A case of gastric

cancer with pathological complete response after chemotherapy using S-1, Oxaliplatin, and Nivolumab. *J Jpn Surg Assoc* 85(7): 892–897, 2024.
17) Nozu S, Musha H, Yamaga R, *et al*. Conversion surgery for a patient with cStage Ⅳ gastric cancer with para-aortic lymphatic metastases who achieved a complete pathological response after first line Nivolumab plus Tegafur-Gimeracil-Oteracil/Oxaliplatin therapy. *Jpn J Gastroenterol Surg* 57(10): 483–490, 2024.
18) Hayashishita S, Kaneta A, Utsumi A, *et al*. A case of conversion surgery after Nivolumab and chemotherapy for metastatic gastric cancer. *Jpn J Cancer Chemother* 51(13): 1455–1457, Dec. 2024.