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Case Report

Clinical Complete Response after Chemotherapy and Palliative Surgery for Unresectable Gastric Cancer

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Chemotherapy · Gastric cancer · Clinical complete response

Abstract
Gastric cancer incidence is high in several countries, and management of advanced gastric cancer remains a challenge. Chemotherapy for unresectable gastric cancers is still evolving, and achieving a complete cure is difficult. Although a clinical complete response to chemotherapy has been reported in patients with unresectable gastric cancer, the chemotherapy duration for these patients is unclear. Here, we report the case of a 71-year-old man who presented with abdominal discomfort. Upper endoscopy revealed advanced gastric cancer on the upper gastric body. Histopathological examination revealed a poorly differentiated adenocarcinoma. Computed tomography revealed regional lymph node and multiple bilobar hepatic metastases. Radical surgery was not possible; therefore, palliative resection of the primary lesion was planned for symptomatic improvement. Tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate were administered prior to surgery, and proximal gastrectomy was performed. Tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate administration was reinitiated after surgery. A clinical complete response was achieved in the 8th postoperative month, with no hepatic metastases noted on radio imaging. Computed tomography performed in the 1st postoperative year revealed ascites; however, the cytological examination findings were negative. The initial chemotherapy was discontinued, and paclitaxel administration was commenced. Computed tomography performed annually thereafter demonstrated no recurrence, and paclitaxel was discontinued in the 9th postoperative

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year. The patient remained recurrence free at 12 years postoperatively. For elderly patients like the one presented here, it may be necessary to consider ceasing chemotherapy; however, because it is possible for a complete clinical response over the long term, it should be continued if the patient is well.

Introduction

Gastric cancer is a common disease worldwide [1] that is often diagnosed at an advanced stage. Patients diagnosed with early gastric cancer demonstrate a remarkable 5-year survival rate of over 90%. Conversely, those diagnosed with stage IV gastric cancer (based on the Japanese Classification of Gastric Carcinoma) have a poor 5-year survival rate of 16.6% [2]. Although chemotherapeutic options for unresectable gastric cancers are evolving, complete cure with chemotherapy is currently difficult. The therapeutic goals of chemotherapy are to improve the clinical symptoms associated with cancer progression and to prolong survival. The median survival of patients with unresectable, highly advanced gastric cancer is reported to be 13 months [3]. Occasionally, however, a clinical complete response (cCR) is achieved with chemotherapy. Here, we report a case involving an elderly man with unresectable gastric cancer who achieved a cCR and long-term survival with chemotherapy and palliative surgery.

Case Presentation

A 71-year-old man presented to a local physician with the chief complaint of discomfort in the epigastric region for 1 month. He did not smoke or consume alcohol and had no specific medical or family history. Upper endoscopy revealed an advanced gastric carcinoma (35 mm in length) on the lesser curvature of the upper gastric body (Fig. 1). Biopsy indicated a poorly differentiated solid-type adenocarcinoma. The patient was referred to our department 2 weeks after the initial visit for detailed investigations and treatment.

The results of his blood investigations were as follows: white blood cell count, 6,000/mm^3; hemoglobin, 14.6 g/dL; platelet count, 188,000/mm^3; total bilirubin, 0.77 mg/dL; aspartate aminotransferase, 25 IU/L; alanine aminotransferase, 22 IU/L; blood urea nitrogen, 15.6 mg/dL; creatinine, 1.0 mg/dL; sodium, 141 mEq/L; potassium, 4.1 mEq/L; chloride, 104 mEq/L; and albumin, 4.2 g/dL. The serum carbohydrate antigen 19-9 (CA19-9) level was elevated at 52.3 U/mL, whereas the serum carcinoembryonic antigen (CEA) level was normal at 2.7 ng/mL.

Contrast-enhanced thoracic and abdominal computed tomography (CT) revealed a contrast-enhancing, 24-mm-long, localized wall thickening with a central depression on the lesser curvature of the upper gastric body. A regional lymph node swelling of 17 mm in diameter and some irregular nodular shadows with slightly dark borders in both hepatic lobes were identified (Fig. 2). A preoperative diagnosis of T3, N2, H1, P0, M0, stage IV was made based on the Japanese Classification of Gastric Carcinoma [4]. While radical surgery was not possible in this case, the patient strongly wished to have the primary lesion resected for symptomatic improvement. As there was a long waiting period for surgery, following discussion with the patient, we initiated preoperative chemotherapy, which consisted of S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate) administration for 3 weeks (120 mg/day [80 mg/m^2]), followed by a 1-week break. Imaging was not performed immediately before the surgery, which included proximal gastrectomy and cholecystectomy. An ulcerated lesion measuring 28 × 17 mm was found in the extirpated specimen. Histopath-

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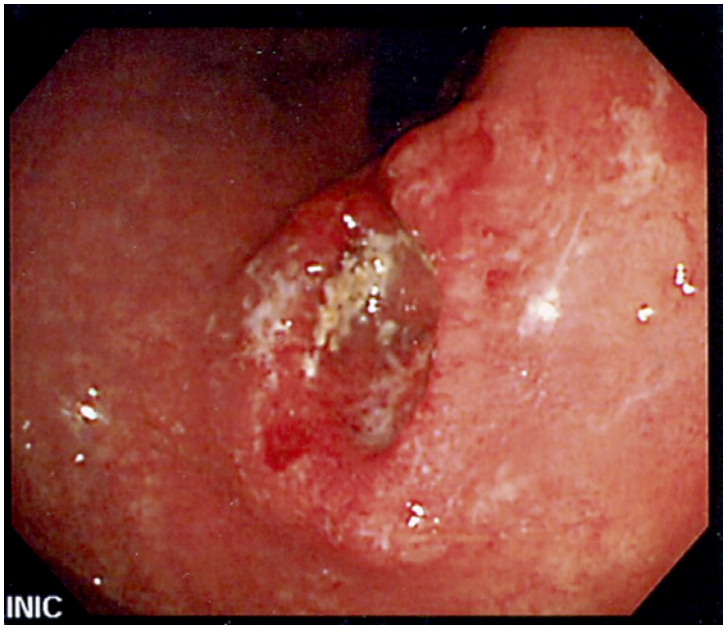

Fig. 1. Gastroscopic findings. Gastroscopy showing gastric cancer on the smaller curvature on the gastric fundus.

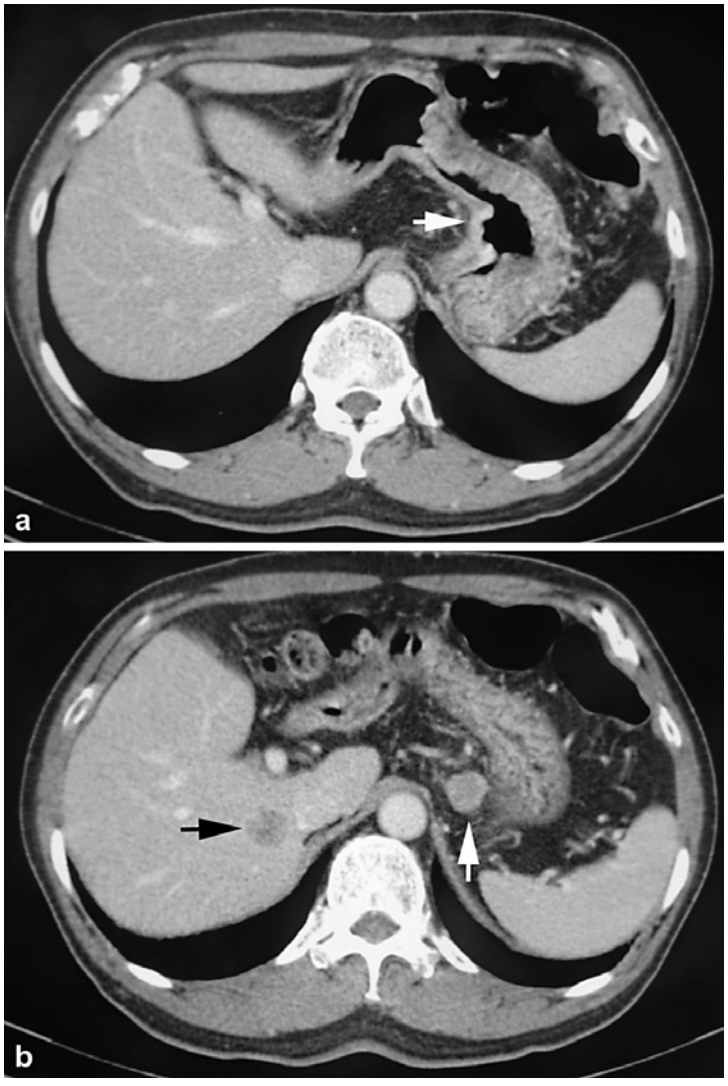

Fig. 2. Contrast-enhanced abdominal computed tomography (CT). **a** CT scan showing an enhanced area of 24 mm in diameter and localized wall thickening with a central depression on the lesser curvature of the gastric body (white arrow). **b** CT scan showing a regional lymph node measuring 17 mm (white arrow) and irregular nodular shadows (black arrow) with faint enhancements in the marginal regions in both lobes of the liver.

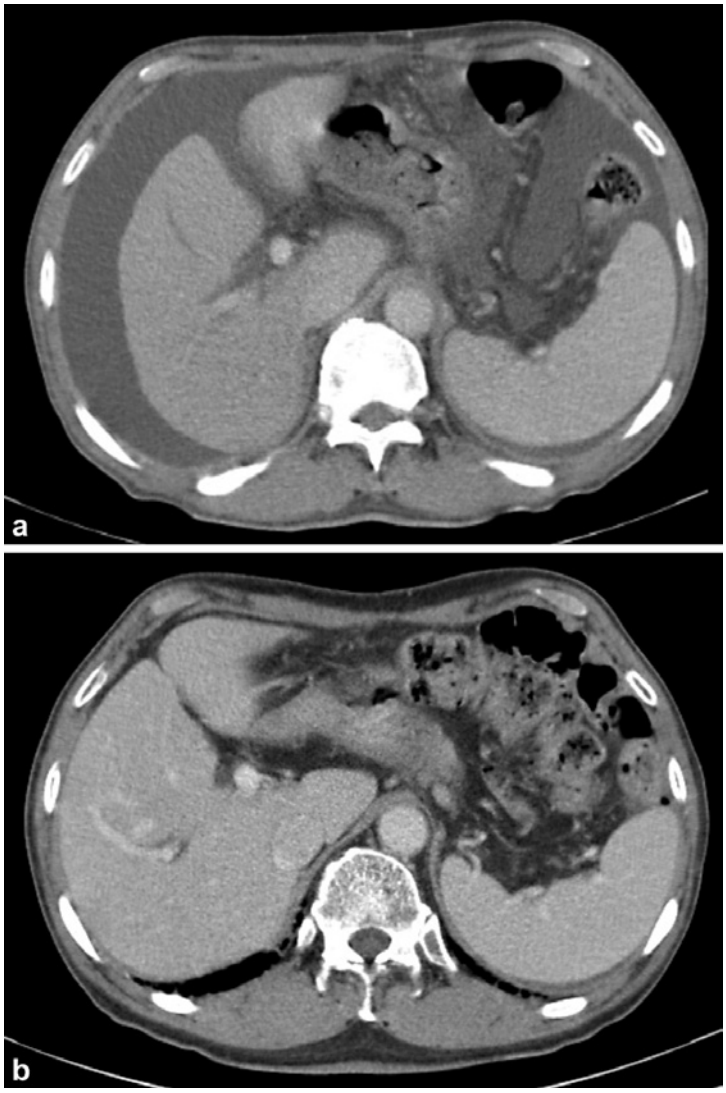

Fig. 3. Contrast-enhanced abdominal computed tomography (CT). **a** The CT scan acquired in the 1st postoperative year shows ascites. There are no signs of recurrence of liver metastasis. **b** The CT scan obtained in the 20th postoperative month shows resolution of the massive ascites and no evidence of recurrence.

ological examination revealed no residual malignancy. The preoperative invasion depth was estimated to be pT2 (pathological muscularis propria invasion) based on chronic phagocyte infiltration and granulation of the submucosa, and lymphoid follicles in the deep muscularis propria; the tumor was histologically assessed to be of grade 3, indicating the absence of viable tumor cells. Two of the 24 dissected lymph nodes were xanthogranulomatous and fibrotic; hence, the metastatic lymph nodes were also classified as grade 3.

The postoperative course was uneventful. On the 17th postoperative day, S-1 therapy was resumed at the preoperative dose; the patient was discharged on the 18th postoperative day. S-1 therapy was continued for 4 weeks, followed by a 2-week break. Magnetic resonance imaging (MRI) performed in the 3rd postoperative month showed a reduction in liver metastases. Serum CA19-9 and CEA normalized in the 3rd postoperative month. CT and MRI performed in the 8th postoperative month revealed no metastatic lesions; thus, the patient was deemed to have achieved a cCR. A CT scan acquired in the 1st postoperative year revealed ascites (Fig. 3a), of which 2,700 mL of fluid was removed by paracentesis; however, the cytological examinations resulted negative. Serum CEA increased to 5.9 ng/mL, while CA19-9 remained within the normal range. S-1 was discontinued, and because the chance of recur-

rence was not zero, paclitaxel 100 mg (80 mg/m^2) was initiated once a week for 3 weeks, followed by a 1-week break. The only side effects were manageable neutropenia and hair loss. The CEA level normalized 2 months after changing the chemotherapy. The ascites also reduced and was not visible on CT scans 20 months postoperatively. There were no other clear findings suggestive of recurrence (Fig. 3b). Follow-up was continued with regular CT examinations. There was no recurrence observed on CT scans obtained in the 5th postoperative year, nor was there clear recurrence on positron emission tomography/CT; therefore, paclitaxel was reduced to 1 dose every 2 weeks. CT performed annually thereafter also demonstrated no recurrence. The paclitaxel dose was further reduced to once every 3 weeks in the 6th postoperative year, and again to once every 4 weeks in the 7th postoperative year. Finally, 9 years postoperatively, chemotherapy was discontinued following discussions with the patient. The patient remained recurrence free at 12 years postoperatively.

Discussion

We experienced a case involving an elderly patient with unresectable gastric cancer who achieved a cCR with pre- and postoperative chemotherapy and palliative surgery. The duration of chemotherapy for cCR patients is unclear. Over the course of several years, we tapered and discontinued chemotherapy in consultation with the patient and managed to achieve long-term survival.

The median survival period among patients with unresectable gastric cancers is approximately 6–14 months [5, 6]. Based on the results of the SPIRIT [3] and JCOG9912 [7] trials, S-1 + cisplatin (CDDP) therapy is the recommended first-line therapy in Japan for unresectable gastric cancer. However, this approach can be considered too aggressive in patients scheduled for palliative resection of the primary lesion. Furthermore, elderly patients often have age-related complications and impaired heart, liver, kidney, and bone marrow functions, which make them less resistant to chemotherapy in comparison with younger patients. A subgroup analysis of a phase III trial that compared S-1 + CDDP therapy and S-1 monotherapy demonstrated that the overall survival rate among patients aged 70 years or above who were on S-1 + CDDP combined therapy was significantly higher than that among similar patients on S-1 monotherapy. However, adverse events were also significantly more frequent among the patients on S-1 + CDDP combined therapy [3]. Although there are no phase III trials currently investigating treatments for refractory advanced gastric cancer in elderly patients (70 years and above), S-1 + CDDP must be cautiously selected in elderly patients, and S-1 monotherapy should be selected if S-1 + CDDP is deemed inappropriate [8]. A previous study demonstrated that S-1 is a superior oral chemotherapy drug for advanced gastric cancer and suggested that it may be effective as preoperative chemotherapy [9]. Common side effects of S-1 include a low hematocrit count, leukopenia, granulocytopenia, diarrhea, lethargy, and proteinuria; a post-marketing survey revealed generally low toxicity and suggested that S-1 can be administered on an outpatient basis [10].

Our patient was initially not scheduled for preoperative chemotherapy; however, it was administered due to the long waiting period for surgery. Furthermore, he was older, and therefore, the surgery was performed after 3 weeks of preoperative outpatient S-1 monotherapy. Many reports have shown that a pathological CR can be achieved with preoperative chemotherapy. The patient herein also underwent resection of the stomach and regional lymph node dissection, and there were no malignant cells within the extent of the resection. Metastatic lesions of the liver appeared to be reduced on MR images obtained in the 3rd postoperative month, but were still present, nonetheless. Hence, liver metastasis was deemed to have been present at the time of the surgery. However, as liver metastasis was unidentifiable on CT and MR images acquired in the 8th postoperative month, the patient was deemed to have achieved a cCR.

As observed on CT scans, the patient's ascites worsened 1 year postoperatively. Although no malignant cells were found during cytological studies, clinically, the chance of recurrence was not zero. While the April 2004 version of the Japanese Gastric Cancer Society Guidelines for Diagnosis and Treatment of Carcinoma of the Stomach (version 2) recognized the efficacy of chemotherapy in unresectable gastric cancer, it did not recommend any specific regimen; thus, investigations were required to determine the optimal second-line chemotherapy following S-1 therapy. Hironaka et al. [11] reported the safety and efficacy of weekly paclitaxel as a second-line drug for metastatic recurrent gastric cancer; as such, we decided to use the same approach. CT performed in the 20th postoperative month did not reveal ascites or other findings of recurrence; thus, the patient was deemed to have achieved a cCR, and treatment was continued.

In recent years, there have been several reports of patients with advanced gastric cancer who achieved a cCR with several chemotherapy regimens. Koo et al. [12] reported that only 1 of 59 patients achieved a cCR following fluorouracil + CDDP chemotherapy. On the other hand, Elsing et al. [13] reported that no CR was observed in a retrospective analysis of 111 patients with advanced gastric cancer. However, many of these patients had only been followed up for a short time since therapy, and the long-term postoperative courses and prognoses in these patients were unknown. Currently, there is no consensus on the duration of chemotherapy in patients who have achieved a cCR. There are also some reports of prolonged survival despite discontinuation of chemotherapy after a cCR. In these cases, chemotherapy was discontinued due to side effects; moreover, chemotherapy had to be discontinued due to grade 2 enteritis in one case [14], and in another case report, the reason for discontinuation of chemotherapy was not stated [15].

To the best of our knowledge, this is the first case in which chemotherapy was tapered and discontinued in a planned manner over the course of several years, in consultation with the patient, along with achieving long-term survival. For this patient, tapering of chemotherapy began in the 5th postoperative year, and was discontinued in the 9th postoperative year. This patient has maintained a cCR for 12 years since surgery, and for over 3 years since discontinuing chemotherapy. Recurrence after discontinuation of chemotherapy is likely to be irreversible; thus, the decision to discontinue chemotherapy must be made in accordance with the patient's wishes and with acceptance of the worst possible scenario after thorough discussions. Further studies with larger sample sizes are warranted to identify the best practice guidelines regarding continuation of chemotherapy and methods for observation in patients who have achieved a cCR.

Statement of Ethics

The patient has provided written informed consent to publish this case (including publication of images).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M. Shishida designed the research study, drafted the manuscript, and contributed to the interpretation of data. K. Toyota and M. Ikeda helped with the interpretation of data. All authors treated the patient, acquired the clinical data, and have read and approved the final manuscript.

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