chemotherapy was evaluated as a partial response, second-look laparoscopy was performed to evaluate the effects of chemotherapy on the peritoneal lesions. Lesions of peritoneal dissemination were found to have changed to white nodules, and no adenocarcinoma cells were found pathocytologically in the nodes of the omentum or in lavage fluid (Fig. 1C,D).

No gastrointestinal or bone marrow toxicities were recognized in the chemotherapy courses, except for a sole adverse effect on serum total bilirubin level (peak level of bilirubin, 3.5 mg/dl).

Operative findings

A gastric tumor was recognized on the greater curvature of the gastric body, showing invasion to the serosa. Although multiple white scars were recognized in the omentum and peritoneum, no tumor cells were observed histologically in frozen sections of the peritoneum and omentum. Also, peritoneal lavage cytology was negative, and we performed total gastrectomy with D2 lymph node dissection without splenectomy. Macroscopic findings of the resected specimen showed an irregular depressed lesion with fibrosis through the wall of the stomach (Fig. 2). Microscopically, the resected specimens showed poorly differentiated adenocarcinoma which had invaded to the subserosa, while most parts of the tumor showed severe fibrosis (Fig. 3), judged to be a grade 2 effect following chemotherapy. Because small numbers of cancer cells were detected in the largest nodule of the omentum, the final findings showed that the tumor was T2, N1 (#3), H0, P1, CY0, and stage IV according to the *Japanese classification of gastric carcinoma.*

Postoperative course

The patient did well after the operation. S-1 was administered orally as adjuvant chemotherapy, at a dose of 100 mg/day twice daily for 14 days, followed by a 1-week rest period. A solitary liver metastasis was recognized by abdominal CT 3 months after the operation. Intravenous administration of paclitaxel was added biweekly at the dose of 90 mg/body.

CT showed a complete response (CR) of the liver metastasis at 5 months after the beginning of this intravenous paclitaxel administration. Twelve months after the CR of liver metastasis, the patient maintained a good quality of life and the performance status remained at grade 0, according to the WHO grading, without any signs of peritoneal dissemination. However, the liver metastasis was found to be re-growing 21 months after the operation, and he died from liver metastasis 29 months after the initial chemotherapy.

Discussion

The most common cause of death in gastric cancer patients with noncurative resection and recurrence is peritoneal dissemination. Although patients with this disease have been treated after surgical resection with high-dose systemic or intraperitoneal chemotherapy, the results of these treatments have been poor, and most patients with peritoneal dissemination die within 6 months after diagnosis [1].

For patients with peritoneal dissemination, systemic chemotherapy with methotrexate (MTX)/5-FU or intraoperative chemohyperthermia has been performed. Konishi et al. [12] reported that an MTX/5FU regimen showed higher efficacy in patients with diffuse type of adenocarcinoma than in those with intestinal type. The response rate of patients with peritoneal dissemination in their study was 23% (6/26) and ascites was eliminated in 8 of 16 patients (50%). Tahara et al. [13] reported that sequential MTX/5FU therapy was effective for patients with confirmed peritoneal dissemination, and objective improvement of ascites was seen in 13 of 26 patients, including 5 who showed complete disappearance of the ascites. Although the median survival time and median time to treatment failure were 259 days and 167 days, respectively, the results of this therapy have been unsatisfactory.

S-1 is an oral fluoropyrimidine anticancer drug that combines three pharmacological agents: tegafur, gimeracil, and oteracil potassium [5]. Late phase II studies of S-1 in advanced gastric cancer obtained overall response rate of 46% and 49% [6, 7]. Also, several reports have demonstrated that S-1 was effective for the undifferentiated type of histology (such as poorly differentiated adenocarcinoma and signet-ring cell carcinoma), which is relevant to peritoneal dissemination [14]. Animal studies have revealed that the concentration of 5-FU in intraperitoneal fluid remained high after the oral administration of S-1. And we have demonstrated that S-1 was effective in preventing the development of peritoneal dissemination [8].

Although S-1 may be a promising agent for peritoneal dissemination due to gastric cancer, the effectiveness of S-1 for peritoneal dissemination is not clear, because the two aforementioned late phase II studies excluded patients with nonmeasurable metastatic lesions such as peritoneal dissemination [6, 7]. In our patient with severe peritoneal dissemination, we searched for a combined chemotherapy in the hope of achieving a more effective response in a short time.

Paclitaxel has a high molecular weight and bulky structure, delaying its clearance from the peritoneal cavity; a profound intraperitoneal exposure advantage for paclitaxel was demonstrated with intraperitoneal/systemic AUC ratios ranging from 336 to 2890 (mean +

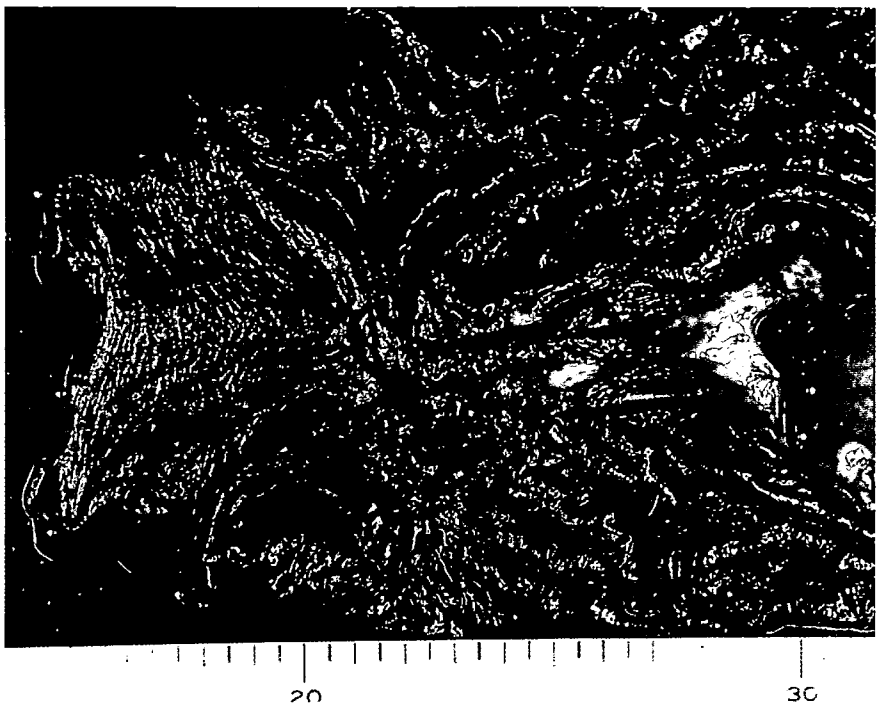

Fig. 2. Macroscopic findings of the resected specimen showed an irregular depressed lesion with fibrosis through the wall of the stomach

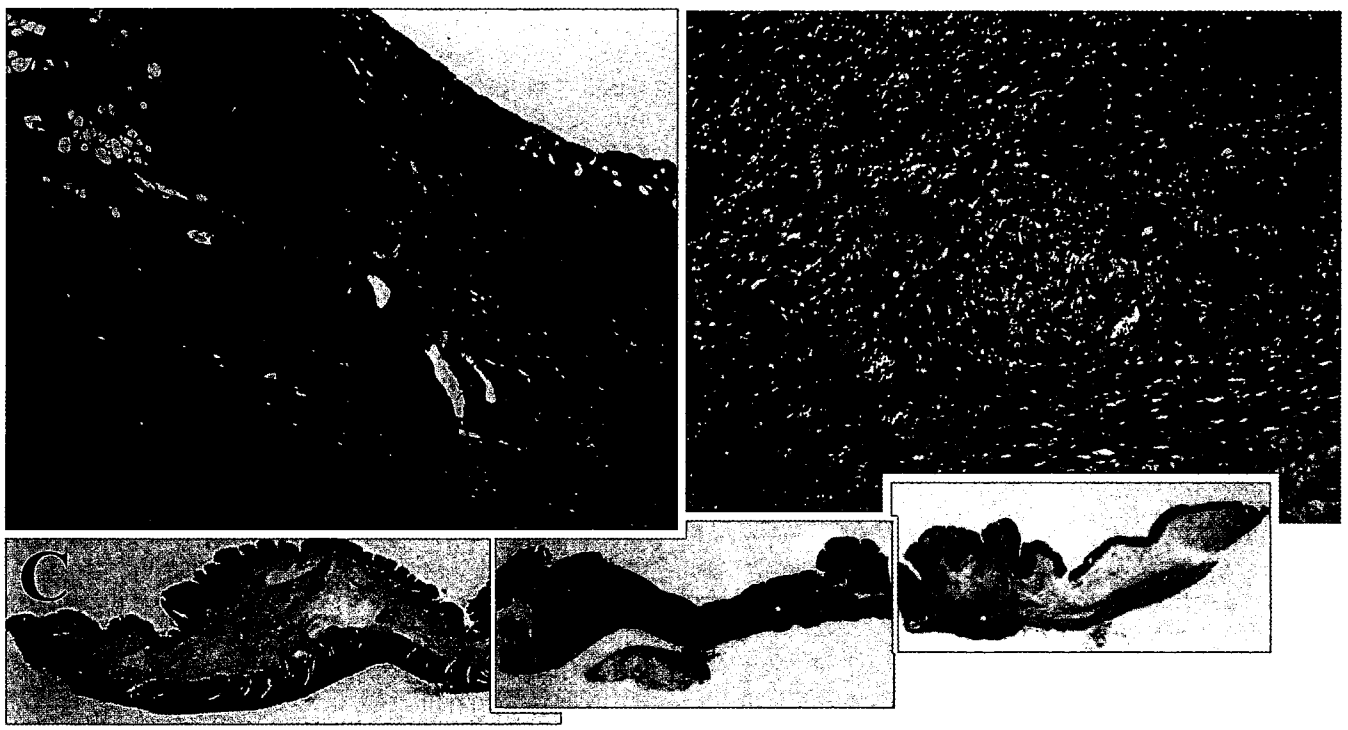

Fig. 3A–C. Microscopic findings of the excised specimen. The resected specimen showed poorly differentiated adenocarcinoma which had invaded to the subserosa, while most parts of the tumor from the submucosa to the subserosa showed change to severe fibrosis. **A** H&E, ×40; **B** H&E, ×100; **C** H&E, ×2

SE, 996 + 93) [10]. Concerning the dosing schedule of weekly intraperitoneal paclitaxel, Francis et al. [15] have demonstrated that doses up to 60 mg/m^2 per week were well tolerated, with minimal abdominal pain or systemic toxicity with potentially cytotoxic concentrations of paclitaxel of 5 to 7 days' duration. In addition, in a phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum, a weekly dosing schedule of intraperitoneal paclitaxel, for a total of 16 weeks, was tolerable and active in patients with microscopic residual disease [16]. In that study, although the patients with microscopic disease achieved a good response, patients with any macroscopic disease achieved only a limited effect. Therefore, we adopted a combination of intraperitoneal administration of paclitaxel and oral S-1 for the present patient with high peritoneal dissemination of gastric cancer in the hope of an effect on both microscopic and macroscopic diseases. Although several therapeutic methods have been reported concerning the intraperitoneal administration of taxanes in patients with gastric cancer [17, 18], there is no established schedule for their use in patients with peritoneal dissemination.

We confirmed the dramatic effect of our therapy by laparoscopic examination and we carried out ablative surgery and achieved a survival time of more than 2 years without any adverse effects. This chemotherapy can be applied as one of the promising candidates for the treatment of patients with peritoneal metastasis of gastric cancer. To obtain clear evidence about first-line chemotherapy for patients with peritoneal dissemination, a randomized clinical trial, comparing S-1 alone and S-1 plus other anticancer agents such as taxanes, will be necessary. In Japan, there are several problems concerning expansion of the clinical utilization of intraperitoneal administration of paclitaxel; thus, a phase I/II clinical trial for establishing the optimal dose and administration schedule of this drug is warranted in the near future.

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