recurrence during follow-up and monitoring the response to treatment is now standard practice. PET provides information that is complementary to that obtained by CT. The most important application of PET may be the selection of potential responders for various treatment modalities. Its survival benefit during multidisciplinary therapy for esophageal cancer is limited to those who display a pathological response.[61–66] Pathological responses can be seen only when the patient undergoes surgery, but FDG-PET has the potential to predict an exact pathological response after induction therapy. That is, second-line therapy may be chosen based on FDG-PET results. The precision of FDG-PET and PET/CT needs improvement. Larger studies may better clarify whether there is indeed an incremental diagnostic improvement with FDG-PET.

In conclusion, FDG-PET is an important diagnostic modality in the therapeutic strategy for esophageal cancer. If higher-precision FDG-PET can be developed, it will contribute to improving the survival statistics for esophageal cancer patients. Also, with the identification of new FDG-PET tracers, we expect further expansion of the application of PET imaging in the field of esophageal cancer.

Disclosure Statement

Masanobu Nakajima and other co-authors have no conflict of interest.

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Adult Intussusception Caused by Descending Colon Cancer during Chemotherapy of Stomach Cancer Recurrence

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Key Words
Intussusception · Descending colon cancer · Stomach cancer recurrence · Chemotherapy

Abstract
Intussusception in adults is uncommon, and it is rare in the descending colon because of its fixation to the retroperitoneum. We herein describe a case of intussusception caused by descending colon cancer. A 74-year-old man was admitted to our hospital for treatment of vomiting and abdominal pain. He had undergone chemotherapy for lymph node recurrence of stomach cancer for about 4 years. Computed tomography revealed a 'target mass' with a tumor in the descending colon. We diagnosed his illness as intussusception of a descending colon tumor and performed emergency laparotomy. Conservative resection was performed following anastomosis after reduction of the intussusception. The tumor was pathologically diagnosed as poorly differentiated adenocarcinoma with neuroendocrine features. To the best of our knowledge, this is the first report of an intussusception caused by descending colon cancer incidentally diagnosed during chemotherapy for stomach cancer recurrence.

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Introduction

Intussusception is most commonly encountered in infants and children, although approximately 5% of cases occur in adults. In fact, it accounts for an estimated 1% of all cases of bowel obstruction in adults. Adult intussusception of the colon is rare and often originates from neoplasia [1]. This condition generally does not present with any specific symptoms. The diagnosis can be in emergency situations, with the aid of integrated examinations. The association of readily available diagnostic means, such as radiological and ultrasonographic studies, may yield reliable findings [2, 3]. These help in formulating a diagnosis of the nature and site of occlusion. However, this condition is often subsequently confirmed intraoperatively. Preoperative diagnosis of this condition can be difficult in emergency cases.

We herein describe a case of adult intussusception of the descending colon caused by a malignant tumor. Intussusception of the descending colon generally does not readily occur because the descending colon is anatomically fixed to the retroperitoneum [4]. Moreover, this patient had undergone chemotherapy for lymph node recurrence of stomach cancer for about 4 years, which could not prevent colon cancer. The progression of this patient's condition seemed to indirectly suggest a difference in biological malignancy between stomach cancer and colon cancer.

Case Report

A 74-year-old Japanese man was admitted to our hospital for treatment of vomiting and abdominal pain on June 15, 2011. Physical examination revealed a temperature of 36.9°C, blood pressure of 175/105 mm Hg and a pulse rate of 65 beats/min. His abdominal pain continued intermittently for approximately 12 h in the night. Clinical examination revealed a distended abdomen with provocative pain in the left upper quadrant and a palpable, fist-sized mass. Blood tests showed a slightly elevated C-reactive protein level of 1.15 mg/dl, although other tests, including tumor markers, were within normal limits.

The patient had a past history of distal gastrectomy for stomach cancer in December 2003 and was visiting our hospital for chemotherapy for lymph node recurrence around the aorta approved since March 2007. This patient underwent 12 courses of irinotecan (100 mg/m^2 weekly for 3 weeks followed by 2 weeks of rest) followed by 14 courses of S-1 (80 mg/m^2 weekly for 4 weeks followed by 2 weeks of rest) and 5 courses of paclitaxel (100 mg/m^2 weekly for 3 weeks followed by 1 week of rest). Computed tomography (CT) indicated that the lymph node recurrence had disappeared on June 1, 2011, resulting in a complete response.

At his visit to our hospital, CT revealed a 'target mass' in the descending colon, suggesting the existence of a tumor in the head of the intussusception (fig. 1), whereas colonoscopic examination had revealed normal results in June 2008. We diagnosed his illness as intussusception of a colon tumor and performed emergency laparotomy. At surgery, the descending colon was intussuscepted into itself by the tumor. The intussusceptum was easily isolated because the fixation between the descending colon and the retroperitoneum was relatively weak. Reduction of the intussusception was performed before the resection following anastomosis because of the shortness and tension in the neighboring colon. The left colon, including the ischemic area and tumor, and regional lymph nodes were removed. An end-to-end anastomosis was primarily fashioned between the transverse colon and sigmoid colon. The postoperative course was uneventful, and the patient was discharged 14 days after surgery.

Macroscopically, the surgical specimen contained a 5.3 × 3.5 cm protuberant tumor at the proximal edge of the 16-cm-long ischemic area in the descending colon (fig. 2). Microscopic examination revealed poorly differentiated adenocarcinoma with invasion into the subserosa and ischemic wall on the anal side of the tumor by hematoxylin-eosin staining (fig. 3a). The regional

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lymph nodes did not have metastasis. The tumor was partially positive for chromogranin A, KIT, and CD56 by immunohistological staining, resulting in an adenocarcinoma with neuroendocrine features (fig. 3b–d).

Discussion

Most colon intussusceptions in adults are caused by malignant tumors, although other causes and idiopathic forms of intussusception have been reported [1–3]. These intussusceptions are frequently located in the flexible portions of the colon, for example the sigmoid colon or cecum [5, 6]. Intussusception of the descending colon is rarer because the descending colon is anatomically fixed to the retroperitoneum [4]. Incomplete fixation between the retroperitoneum and descending colon might result in the presently described condition.

Few general surgeons encounter more than one or two patients with colon intussusception during their careers, and most cases are undiagnosed before surgery. Previous papers reported that CT is the most accurate imaging modality for diagnosing intussusception [1, 2]. The characteristic CT findings of intussusception include an early target mass with enveloped, eccentrically located areas of low density [7].

Reduction of intussusceptions with suspected malignancy is not generally advisable because it may cause bowel perforation and tumor cell dissemination [8]. However, reduction may be advisable to accurately determine the range of resection for minimally invasive surgery [6]. In our case, conservative resection was performed following anastomosis after reduction of the intussusception. If the intussusception had been operatively reduced, it would have been difficult to anastomose primarily because of the shortness and tension in the neighboring colon.

It was thought that colon cancer in this case occurred during the past 3 years, because colonoscopic examination had revealed a normal study in 2008. On the other hand, our patient had received several kinds of chemotherapy for lymph node recurrence of stomach cancer for about 4 years and had obtained a complete response. Thus chemotherapy seems to be generally effective for both gastric cancer and colon cancer, but could not prevent colon adenocarcinoma in our case. One reason could be the mixture of neuroendocrine features, because neuroendocrine carcinomas often show resistance to chemotherapy [9].

Colon intussusception in adults is generally rare. To the best of our knowledge, this is the first report of an intussusception caused by descending colon cancer incidentally diagnosed during chemotherapy for stomach cancer recurrence. The progression of this patient's condition also suggested a difference in the biological malignancy between stomach cancer and colon cancer.

Disclosure Statement

The authors have no conflicts of interest.

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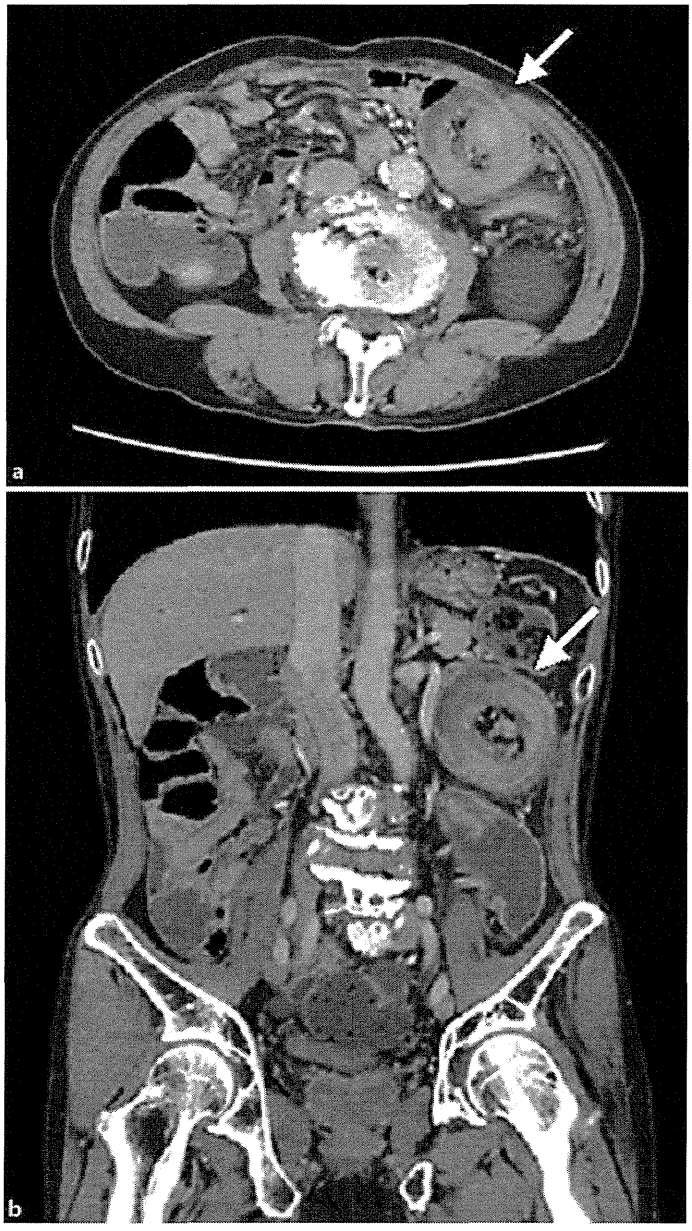

Fig. 1. Abdominal CT indicated enlargement of the descending colon wall within the intussusception (arrows), suggesting the existence of a tumor in the head. **a** Transverse slice. **b** Sagittal slice.

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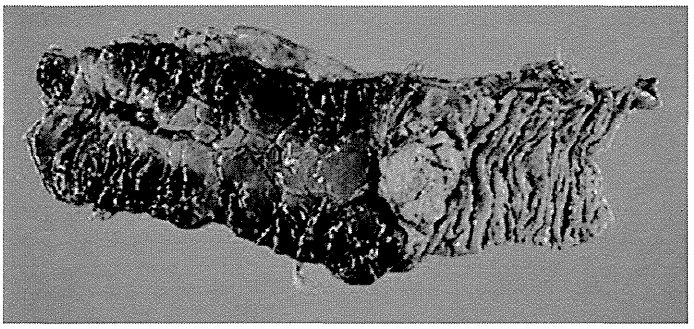

Fig. 2. The surgical specimen contained a 5.3 × 3.5 cm protuberant tumor that was thought to be the lead point of the intussusception. The ischemic area of the wall was 16 cm along the anal side of the tumor.

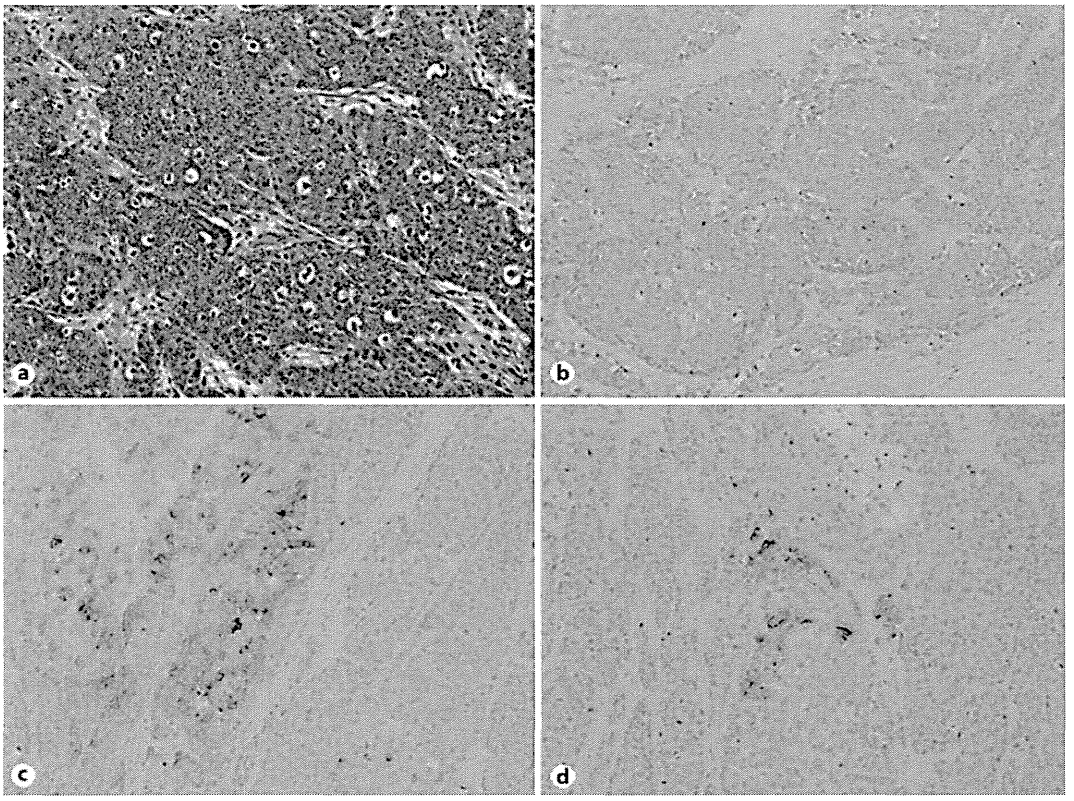

Fig. 3. Microscopic examination. **a** The tumor was a poorly differentiated adenocarcinoma with invasion into the subserosa (hematoxylin-eosin staining, ×100). **b–d** The tumor was partially positive for chromogranin A, KIT, and CD56 by immunohistological staining (×100).

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INTERNATIONAL SURGERY

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A Case of Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis Successfully Treated by a Combination of Intra-Arterial Infusion 5-Fluorouracil, Cisplatin, and Systemic Interferon-α Therapies

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Case Report

A Case of Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis Successfully Treated by a Combination of Intra-Arterial Infusion 5-Fluorouracil, Cisplatin, and Systemic Interferon-α Therapies

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A 58-year-old female with hepatitis C was referred to our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. After thorough examination, tumor thrombosis was detected on the main trunk of the portal vein, and we decided to administer a combination of subcutaneous interferon-alfa and intra-arterial 5-fluorouracil. However, after 2 cycles of treatment, this regimen was ineffective, and thus cisplatin (CDDP) was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography. Hence, chemotherapy was considered effective and stopped. Two years after chemotherapy, Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II) levels were within normal limits. Combination therapies have been recognized recently, and judging from the above case, the addition of CDDP to the combination regimen can prove beneficial.

Key words: Hepatocellular carcinoma – Portal vein tumor thrombosis – INF-α – Intra-arterial chemotherapy

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There is no effective treatment for cases of hepatocellular carcinoma (HCC) with main portal vein tumor thrombosis (PVTT). Moreover, the prognosis of inoperable cases is extremely poor, and some authors have reported that the average life span after diagnosis is 3 to 6 months. Recently, however, a combination of systemic interferon-alfa (INF-α) and intra-arterial 5-fluorouracil (FU) has been reported to improve the prognosis of the disease. Furthermore, partial and complete response cases are reported to achieve high survival rates of 100% at 1 year and 80% at 3 years. The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis and is therefore being considered a standard treatment option for HCC with PVTT. If the treatment is not effective, the patient can be administered additional medication. In this case study, it was seen that systemic INF-α therapy and intra-arterial infusion of 5-FU in combination with cisplatin (CDDP) were effective for both recovery and long-term survival of a patient with HCC and PVTT.

Case report

A 58-year-old female was referred to the outpatient clinic of our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. The patient was infected with hepatitis C virus (HCV) by blood transfusion 35 years ago, but she did not receive treatment and visited our hospital for a thorough examination and treatment. Clinical tests on admission indicated abnormal liver function, and laboratory data showed abnormally high levels of aspirate aminotransferase (AST; 166 IU/L) and alanine aminotransferase (ALT; 188 IU/L). The levels of total bilirubin were normal (0.8 mg/dL). The prothrombin time was 82%, and the indocyanine green retention rate at 15 minutes was 36.8%. The levels of tumor markers AFP and PIVKA were found to be elevated at 48.2 ng/mL and 19,362 U/mL, respectively, indicating advanced HCC. Liver cirrhosis was defined as grade A according to Child's classification. CT and abdominal angiography revealed PVTT, which was then treated by INF-α and intra-arterial 5-FU combination chemotherapy. Hepatectomy and embolization therapy were contraindicated in this case. Pretreatment images are shown in Fig. 1. CT arterial portography and CT hepatic arteriography revealed that the tumor was in the right lobe of her liver and had infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium revealed a flow defect at the main trunk of the portal vein. ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed abnormal uptake in the right lobe of her liver (maximum standardized uptake value, 3.0; Fig. 1). The protocol of this combination therapy was as follows: 5-FU 500 mg/d (days 1–7, weeks 1–2), INF-α 5 million units (days 1, 3, and 5; weeks 1–4). However, after 2 cycles of treatment, this regimen was ineffective, thus CDDP was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET (Fig. 2). Hence, chemotherapy was considered effective and stopped. A combination therapy of INF-α and revabirin was started to combat hepatitis C. Two years after chemotherapy, AFP and PIVKA-II levels were within normal limits. However, 3 years and 6 months after chemotherapy, a new lesion was detected in the left lobe of the liver on CT scan, along with increased HCV titers; and the lesion was treated by radiofrequency ablation (RFA). New lesions were detected in the right lobe of the liver after 1 year and after 2 years of RFA treatment, and were treated by transcatheter arterial embolization (TAE) therapy. After treatment with TAE, no lesion was detected, and the patient achieved a 5-year survival. Changes in tumor marker levels and HCV titers are shown in Fig. 3.

Discussion

The incidence of HCC, one of the most common cancers, has been on the rise in Japan for the past 30 years.[1] Recent developments in imaging techniques have made it possible to detect even a small lesion at an early stage. Although prognosis of total HCC has improved, that of advanced cases with PVTT continues to be poor. Numerous therapies have been implemented to treat advanced cases with PVTT, but none have been effective. The prognosis of inoperable cases that have been reported is estimated to be extremely poor, with an average life span of only 3 to 6 months after diagnosis.[2,3] Recently, a combination of intra-arterial 5-FU and systemic INF-α was reported to be more effective than treatment with arterial 5-FU alone for inoperable cases, resulting in an improved prognosis compared with operable cases.[4–6] Obi reported that the complete response cases of HCC with PVTT, which constitute 15%, showed a 1-year survival rate of over 80%.[4] The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis.[7,8] Prognosis of high-expression

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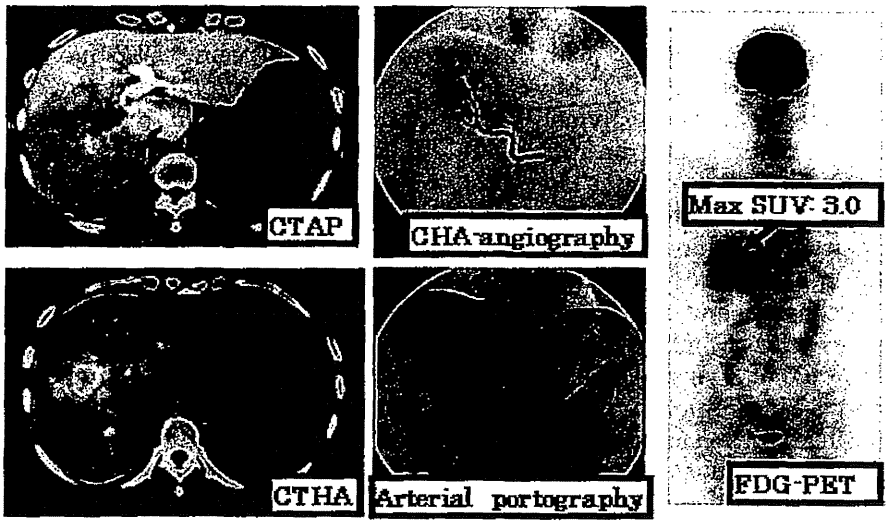

Fig. 1 CT arterial portography and CT hepatic arteriography reveal a tumor, in the right lobe of the liver, that infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium reveals a flow defect at the main trunk of the portal vein. FDG-PET reveals abnormal uptake in the right lobe of the liver (maximum standardized uptake value, 3.0).

groups of type-I interferon receptor is reported to be better than that of low-expression groups for gastrointestinal cancer; however, the function of this receptor in HCC has not been identified.[7,8] In our case, the above-mentioned combination therapy was only slightly effective and complete response was achieved with the addition of CDDP. Addition of other chemotherapy drugs is considered to be effective in cases that do not respond to standard combination therapy. The recent developments in radiation techniques have enabled the use of local radiation therapy. Radiation-induced hepatitis usually occurs after whole liver irradiation to total 30 Gy; however, three-dimensional conformal radiation therapy (3DCRT) for PVTT has been reported to be effective, even with high focal doses (60 Gy), without causing any damage to the normal liver parenchyma tissue.[9–11] Some studies conducted on TAE and 3DCRT have reported significantly high survival rates in the responders compared with the nonresponders, while others have reported no difference in survival rates between the 2 groups.[10,11] The drawback of this TAE-3DCRT combination therapy was that the therapy failed to suppress intrahepatic metastasis.[10] Large-scale studies of 3DCRT and arterial chemotherapy have not yet been conducted, thus making the findings of our study on combination therapy valuable. We experienced one case of HCC with PVTT that showed complete recovery with local radiation therapy for PVTT and intra-arterial 5-FU infusion. The patient is currently alive having survived for

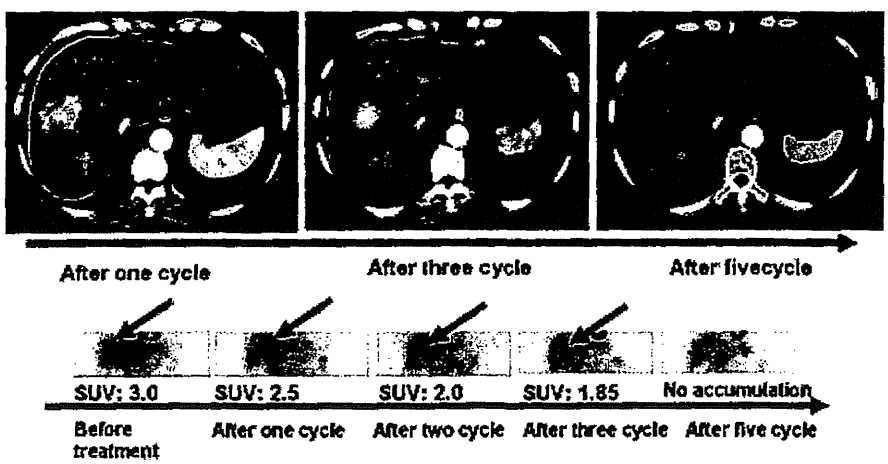

Fig. 2 On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET.

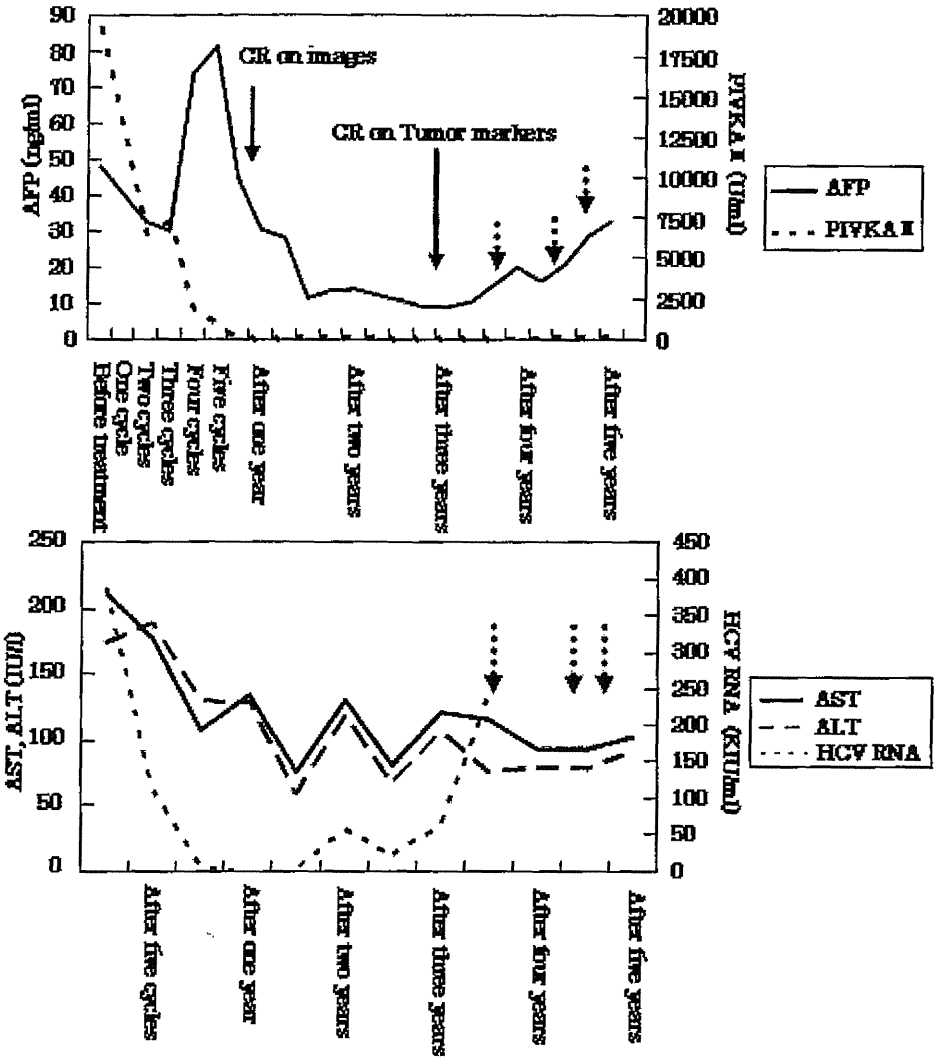

Fig. 3 The top graph shows changes in tumor markers. The bottom graph shows AST, ALT and HCV titers. The broken arrow indicates a period of recurrence.

over 5 years without recurrence. We might include local radiation in the treatment regimen for similar/future cases. In the future, a combination of local radiation therapy along with INF-α, intra-arterial 5-FU, and other carcinostatic drugs should be considered as the basic protocol for HCC with PVTT.

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Phase II multi-institutional prospective randomised trial comparing S-1 + paclitaxel with S-1 + cisplatin in patients with unresectable and/or recurrent advanced gastric cancer

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BACKGROUND: A combination of S-1 and cisplatin has been shown to be effective with acceptable safety for the first-line treatment of far-advanced gastric cancer in Japan. This is the first randomised phase II trial to compare S-1 + paclitaxel with S-1 + cisplatin in this setting.

METHODS: Patients with unresectable and/or recurrent advanced gastric cancer were randomly assigned to receive one of the two regimens: S-1 (40 mg m^{-2} twice daily) on days 1–14 plus paclitaxel (60 mg m^{-2}) on days 1, 8, and 15 of a 4-week cycle (S-1 + paclitaxel) or S-1 (40 mg m^{-2} twice daily) on days 1–21 plus cisplatin (60 mg m^{-2}) on day 8 of a 5-week cycle (S-1 + cisplatin). The primary end point was the response rate (RR). Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

RESULTS: A total of 83 patients were eligible for safety and efficacy analyses. In the S-1 + paclitaxel and S-1 + cisplatin groups, RRs (52.3% *vs* 48.7%; $P=0.74$) and median PFS (9 *vs* 6 months; $P=0.50$) were similar. The median OS was similar in the S-1 + paclitaxel and S-1 + cisplatin groups (16 *vs* 17 months; $P=0.84$). The incidence of grade 3 or higher haematological toxicity was 19.0% with S-1 + paclitaxel and 19.5% with S-1 + cisplatin. The incidence of grade 3 or higher non-haematological toxicity was 14.2% with S-1 + paclitaxel and 17.1% with S-1 + cisplatin.

CONCLUSION: S-1 + paclitaxel was suggested to be a feasible and effective non-platinum-based regimen for chemotherapy in patients with advanced gastric cancer. Our results should be confirmed in multicenter, phase III-controlled clinical trials.

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Gastric cancer is the second most common cause of cancer-related mortality worldwide. Patients with unresectable or recurrent gastric cancer have extremely poor outcomes, with 5-year survival rates of <5%. Various chemotherapeutic agents have been used in the hope of improving overall survival (OS), progression-free survival (PFS), response rate (RR), and quality of life in patients with advanced gastric cancer.

The SPIRITS trial established that S-1 + cisplatin is a standard first-line regimen for advanced gastric cancer in Japan (Koizumi *et al*, 2003; Koizumi *et al*, 2008). This randomised phase III study compared OS between patients who were given S-1 + cisplatin and those who were given S-1 alone (Koizumi *et al*, 2008). Median OS was significantly longer in the S-1 + cisplatin group than in the S-1 alone group. On the other hand, the S-1 + cisplatin group had more toxic events, such as neutropenia, anaemia, nausea, and anorexia; however, there was no treatment-related mortality. Subsequently, the JCOG 9912 study confirmed that oral S-1 could replace infusional 5-fluorouracil without compromising efficacy or causing excessive toxicity (Boku *et al*, 2009). Based on these findings, S-1 + cisplatin has been recognised as a standard chemotherapy regimen for advanced gastric cancer in Japan. However, no alternative standard regimen is currently available for this indication. Some patients with impaired renal function cannot receive S-1 + cisplatin as a first-line treatment for advanced gastric cancer. Therefore, other regimens with low toxicity are needed.

Paclitaxel is a taxane derivative that was originally isolated from *Taxus brevifolia*, a type of Western yew (Wani *et al*, 1971). Paclitaxel has activity against a broad range of tumour types, including breast, ovarian, and lung cancers (Holmes *et al*, 1991; Einzig *et al*, 1992; Chang *et al*, 1993). Paclitaxel is also an effective drug for gastric cancer, with RRs ranging 20–28% in single-agent phase II studies (Ajani *et al*, 1998; Ohtsu *et al*, 1998; Yamada *et al*, 2001; Yamaguchi *et al*, 2002). The recommended dosage of paclitaxel in Japan was determined to be 210 mg m^{-2} once every 3 weeks (Yamaguchi *et al*, 2002). Recently, good results have been

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obtained with a weekly regimen of paclitaxel in patients with ovarian cancer and gastric cancer (Fennelly *et al*, 1997; Hironaka *et al*, 2006). To further improve outcomes, many phase II studies have been performed to evaluate the safety profile and efficacy of weekly paclitaxel-based combination regimens for advanced and metastatic gastric cancer (Sakamoto *et al*, 2009). In 2006, we performed a phase I/II study of weekly paclitaxel combined with S-1 in patients with unresectable and/or recurrent advanced gastric cancer (Mochiki *et al*, 2006). The RR was 54.1%, and the median survival time was 15.5 months. Our results showed that S-1 + paclitaxel is effective and well tolerated (Mochiki *et al*, 2006). To confirm our findings, we planned the present randomised phase II study to compare the efficacy and safety of S-1 + paclitaxel with those of S-1 + cisplatin, currently the standard treatment in Japan, in patients with advanced gastric cancer.

PATIENTS AND METHODS

Patients

Patients between 20 and 75 years of age who had advanced, unresectable, histologically confirmed adenocarcinoma of the stomach were eligible for enrolment in this study. Eligible patients also had to have measurable or evaluable lesions, the ability to orally intake medications, an Eastern Clinical Oncology Group performance status of 0 or 1, and adequate liver, kidney, and bone marrow functions, similar to our previous study (Mochiki *et al*, 2006). Patients were excluded if they had brain metastases, significant gastrointestinal bleeding, serious comorbidity, concomitant use of drugs that potentially interact with S-1 (flucytosine, allopurinol, warfarin, or phenytoin), or an inability to comply with the protocol requirements. Pregnant women were also excluded.

Study design and randomisation

This randomised, open-label, phase II study was conducted at six institutions in Gunma and Saitama Prefectures in Japan between January 2006 and November 2010. The protocol was approved by the ethics committee of each participating institution, and all patients gave written informed consent. The primary end point of the study was the clinical response (RR) to the study treatment (S-1 + paclitaxel) as compared with the response to the control treatment (S-1 + cisplatin) in patients with advanced gastric cancer. Secondary end points were median OS, PFS, and safety. These variables were compared between the treatment groups.

A central data centre confirmed patient eligibility, and eligible patients were randomly assigned to treatment automatically according to stratification factors (prior therapy and performance status). Randomisation was centrally performed by the Coordination Centre of Gunma University.

Treatment regimens

Patients who were assigned to the S-1 + paclitaxel group received S-1 orally ($40\,mg\,m^{-2}$ twice daily) on days 1–14 plus paclitaxel ($60\,mg\,m^{-2}$) as an intravenous infusion on days 1, 8, and 15 of a 4-week cycle (Mochiki *et al*, 2006). Patients who were assigned to the S-1 + cisplatin group received S-1 orally ($40\,mg\,m^{-2}$ twice daily) on days 1–21 plus cisplatin ($60\,mg\,m^{-2}$) as an intravenous infusion on day 8 of a 5-week cycle (Koizumi *et al*, 2003).

Before treatment with paclitaxel in the S-1 + paclitaxel group, patients received an antihistamine (e.g., diphenhydramine hydrochloride 50 mg), dexamethasone 8 mg, and cimetidine 300 mg (or a comparable H2 blocker) to prevent paclitaxel-related hypersensitivity reactions. To reduce the risk of cisplatin-induced renal damage in the S-1 + cisplatin group, patients received hydration with 1500 ml of 5% glucose before treatment with cisplatin. Furosemide was given 30 min before starting the cisplatin infusion, and hydration with 4000 ml of 5% glucose, 24 g NaCl, 1.2 g KCl and 0.8 g $CaCl_2$ was continued for 48 h. Treatment was discontinued at the onset of disease progression, severe toxic effects, or at the patient's request.

Response and toxicity criteria

Tumour response was assessed objectively after each course of treatment, according to the Response Evaluation Criteria in Solid Tumours. OS was estimated from the date of study entry to the date of death or the last follow-up visit according to the Kaplan–Meier method. The log-rank test was used to compare survival between treatment groups. Progression free survival was measured from the date of study entry to the first objective observation of disease progression or death from any cause. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Follow-up schedule

Disease progression and the development of new lesions were evaluated as needed by abdominal radiography, abdominal and thoracic computed tomography, and measurement of the tumour markers carcinoembryonic antigen (CEA) and CA 19–9, performed at baseline and at least every 4–5 weeks during treatment. Responses were evaluated every 8 weeks or earlier in patients who had an evidence of treatment failure. Physical examinations, complete blood counts, serum chemical analyses, and other laboratory tests were performed before treatment and at least every 2 weeks during treatment.

Statistical analysis

The required sample size was estimated according to the criteria of Simon *et al* (1985). We estimated that 36 patients per treatment group would allow selection of the better treatment with 90% accuracy, given that the absolute difference in the RR of the better treatment is at least 15%, with an expected baseline RR of 50%. To compensate for the possible enrolment of ineligible patients, the sample size was set at 80 (40 patients per group).

The Kaplan–Meier estimates and a Cox proportional hazards model were used to analyse time-event variables. The distributions of discrete variables were compared between the two treatment groups with the use of the χ^2-test or Fisher's exact test as appropriate. To compare continuous variables, the Mann–Whitney *U*-test for nonparametric data was used. All the tests were two-sided, and P values <0.05 were considered to indicate statistical significance. SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

Patient characteristics

Between January 2006 and November 2010, a total of 83 patients (61 men and 22 women) were registered at six hospitals. In all, 42 patients were assigned to S-1 + paclitaxel and 41 patients were assigned to S-1 + cisplatin. The characteristics of the assessable patients, including sex, median age, performance status, histological type, prior therapy, and sites of metastasis, are shown in Table 1. The mean age of the patients was 63.3 years in the S-1 + paclitaxel group and 63.0 years in the S-1 + cisplatin group. The baseline characteristics were well balanced between the two treatment groups.

Response rate

The confirmed RR was 52.3% (22 out of 42) in the S-1 + paclitaxel group (95% confidence interval (CI), 39–61%) and 48.7% (20 out

Table 1 Characteristics of patients

	S-1 + paclitaxel	S-1 + cisplatin	*P*-value
Sex: male/female	31/11	30/11	0.48
Mean age ± s.e.; years	63.3 ± 1.4	63.0 ± 1.3	0.91
Performance status 0/1	38/4	39/2	0.42
Histological type			
Intestinal	16	16	0.47
Diffuse	26	25	
Prior therapy			
None	33	33	0.73
Gastrectomy	2	3	
Gastrectomy + chemotherapy	7	5	
Site of metastasis			
Liver	14	12	0.57
Lymph nodes	40	33	
Peritoneum	11	8	

Table 2 Overall response to treatment

	S-1 + paclitaxel	S-1 + cisplatin	*P*-value
CR	1	0	0.72
PR	21	20	
SD	12	10	
PD	6	8	
NE	2	3	

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SR = stable disease.

of 41) in the S-1 + cisplatin group (95% CI, 39–61%) (Table 2). All the responses were partial, except for one complete response (CR) in the S-1 + paclitaxel group. The RR in the S-1 + paclitaxel group was slightly, but not significantly, higher than that in the S-1 + cisplatin group ($P = 0.74$). The tumour control rate (CR + partial response + stable disease) was 80% (34 out of 42) in the S-1 + paclitaxel group and 73% (30 of 41) in the S-1 + cisplatin group.

Progression-free survival and overall survival

The median PFS was 9 months in the S-1 + paclitaxel group (95% CI, 6–12 months) and 6 months in the S-1 + cisplatin group (95% CI, 4–9 months; Figure 1). The hazard ratio for disease progression or death (S-1 + paclitaxel/S-1 + cisplatin) was 0.84 (95% CI, 0.50–1.4). When the treatment groups were compared by log-rank test, there was no significant difference in median PFS ($P = 0.50$). At a median follow-up of 14 months, the median OS was 16 months in the S-1 + paclitaxel group (95% CI, 15–22 months) and 17 months in the S-1 + cisplatin group (95% CI, 11–23 months); the hazard ratio for death (S-1 + paclitaxel/S-1 + cisplatin) was 0.94 (95% CI, 0.55–1.63). Efficacy of the treatments thus appeared to be similar (log-rank test; $P = 0.84$; Figure 2). The estimated survival rates at 1 and 2 years were 70% and 26%, respectively, in the S-1 + paclitaxel group and 63% and 30%, respectively, in the S-1 + cisplatin group.

A total of 14 patients (S-1 + paclitaxel, 6 patients; S-1 + cisplatin, 8 patients) underwent gastrectomy after chemotherapy and had no critical chemotherapy-related adverse effects. On average, the number of administered courses of chemotherapy before surgery was 5.1 (range 2–15) in the S-1 + paclitaxel group and 4.1 (range 2–8) in the S-1 + cisplatin group. Total gastrectomy was performed in 13 patients and distal gastrectomy was done in 1. The six patients in the S-1 + paclitaxel group had a median survival of 28

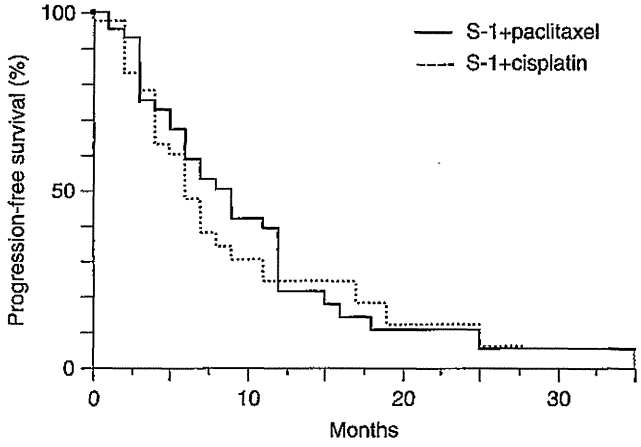

Figure 1 Progression free survival.

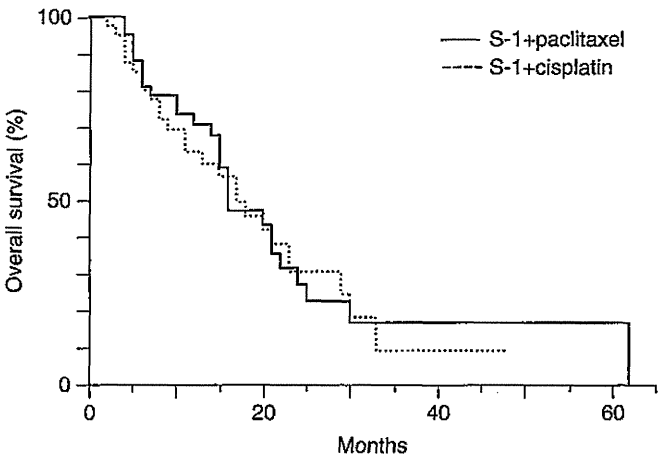

Figure 2 Overall survival.

months (range 21–60), and two patients were alive at the time of this analysis. The eight patients in arm C had a median survival of 25.5 months (range 11–48), and all were alive at the time of this analysis. Responses of all the patients who underwent gastrectomy were partial.

Toxic effects

The median number of administered cycles of chemotherapy was 5 (range 2–30) in the S-1 + paclitaxel group and 4 (range 1–15) in the S-1 + cisplatin group. Myelosuppression was the most frequent toxic effect in both groups (Table 3). In the S-1 + paclitaxel group, grade 3 or 4 haematological toxicity occurred in 19.0% (8 out of 42) of the patients and grade 3 or 4 non-haematological toxicity occurred in 14.2% (6 out of 42) of the patients. The most common types of severe (grade 3 or 4) haematological toxicity were leucopenia (3 patients, 7.1%), neutropenia (3 patients, 7.1%), and anaemia (2 patients, 4.7%) (Table 3). The most common types of all grade non-haematological toxicity were peripheral neuropathy (7 patients, 16.6%), anorexia (6 patients, 14.2%), diarrhoea (5 patients, 11.9%), nausea (5 patients, 11.9%), and stomatitis (5 patients, 11.9%). In the S-1 + cisplatin group, grade 3 or 4 haematological toxicity occurred in 19.5% (8 out of 41) of the patients and grade 3 or 4 non-haematological toxicity occurred in 17.1% (7 out of 41). The frequent types of severe (grade 3 or 4) haematological toxicity were neutropenia (4 patients, 9.7%), leucopenia (3 patients, 7.5%), and anaemia (2 patients, 5%) (Table 3). There was one episode of febrile neutropenia. The most

Table 3 Toxic effects and number of patients with toxicity

	S-1 + paclitaxel		S-1 + cisplatin	
Grade	**1-2**	**3-4**	**1-2**	**3-4**
Haematological toxicity				
Leucopenia	10	3	11	2
Neutropenia	10	3	6	4
Anaemia	3	2	8	2
Thrombocytopenia	1	0	8	0
Non-haematological toxicity				
Anorexia	6	0	12	2
Nausea	5	0	10	2
Diarrhoea	3	2	9	1
Fatigue	3	0	6	0
Stomatitis	4	1	3	0
Peripheral neuropathy	4	3	2	0
Hypoalbuminemia	2	0	6	0
Bilirubin	1	0	1	0
AST/ALT	2	0	0	1
Hyperkalemia	3	0	0	0
Hyponatremia	0	0	0	1

Abbreviations: ALT = alanine aminotransferase; AST = aminotransferase.

common types of all grade non-haematological toxicity were anorexia (14 patients, 34.1%), diarrhoea (10 patients, 24.3%), and nausea (12 patients, 29.2%). Treatment was discontinued during the first course of S-1 + cisplatin in three patients because of grade 3 liver dysfunction, grade 3 anorexia, and grade 4 neutropenia, respectively. There was no treatment-related death or severe delayed toxicity in either group. The overall incidence of grade 3 or 4 toxic effects did not differ significantly between the treatment groups ($P = 0.53$).

DISCUSSION

The efficacy of S-1-based combination chemotherapy in advanced gastric cancer has been assessed in a number of phase I/II studies. The SPIRITS trial, a phase III study, established S-1 + cisplatin as a standard first-line regimen for advanced gastric cancer in Japan (Koizumi *et al*, 2008). However, the FLAGS trial, a non-Asian global phase III study, concluded that S-1 + cisplatin did not prolong the OS of patients with advanced gastric or gastroesophageal adenocarcinoma as compared with cisplatin + infusional fluorouracil, but did have a significantly better safety profile (Ajani *et al*, 2010). Cisplatin can cause renal toxicity, emesis, and peripheral neuropathy, and the intravenous hydration required during its use lengthens outpatient visits and can necessitate overnight admission. Consequently, drug combinations, such as S-1 + cisplatin, are considered too toxic for elderly patients or patients with a poor performance status. S-1 + cisplatin regimens also have other limitations. Therefore, alternative drug combinations with similar efficacy but lower toxicity than S-1 + cisplatin are needed. Our previous phase I/II study showed that a combination of S-1 + paclitaxel is highly effective in advanced and recurrent gastric cancer, with an acceptable and manageable toxicity profile (Mochiki *et al*, 2006). This combination regimen produced promising results, with an overall RR of 54.1%, a median time to progression of 9.5 months (95% CI, 5–11.6 months), and a median OS of 15.5 months) (95% CI, 11.6–19.4 months). Haematological and non-haematological toxicities associated with S-1 + paclitaxel were generally mild. Based on the positive results of our previous study, we initiated the present randomised phase II trial to compare S-1 + paclitaxel with S-1 + cisplatin in a similar setting.

To our knowledge, this is the first randomised trial to compare S-1 + paclitaxel with S-1 + cisplatin in patients with unresectable and recurrent gastric cancer. Although this was a phase II study and had limited power to detect significant differences between the treatment groups, we could estimate the relative efficacy and safety of the two regimens. To assess the primary end point (RR), all images were reviewed and all responses were confirmed. The RR was 52.3% in the S-1 + paclitaxel group and 48.7% in the S-1 + cisplatin group, suggesting that both regimens have similar activity in patients with unresectable and recurrent gastric cancer. The RRs for S-1 + paclitaxel and S-1 + cisplatin are largely consistent with the results of previous studies in advanced gastric cancer (Koizumi *et al*, 2003; Mochiki *et al*, 2006). Furthermore, median PFS and OS were also similar for both regimens in this study. The promising median survival time obtained in the present study (16 months) raises hope that S-1 + paclitaxel may improve survival outcomes in patients with advanced gastric cancer. The longer median OS in our study may have been related to the good performance status of many patients. Performance status was 0 or 1 in all patients; no patient had a performance status of 2. Survival outcomes in our study are consistent with the results of phase II studies of similar regimens of S-1 + paclitaxel in patients with advanced gastric cancer (Narahara *et al*, 2008; Lee *et al*, 2009; Ueda *et al*, 2010). Lee *et al* (2009) obtained an RR of 40% and a median survival time of 12.1 months with a combination regimen of weekly paclitaxel and S-1 in advanced gastric cancer. Nakajo *et al* (2008) reported a median OS of > 17.0 months in their feasibility study of paclitaxel and S-1 in 52 patients with advanced gastric cancer treated at a single institution. In the present study, combination therapy with S-1 and weekly paclitaxel was associated with very tolerable levels of gastrointestinal toxicity as well as high antitumour effectiveness. Furthermore, the survival outcomes with S-1 + paclitaxel were similar to those reported for S-1 + docetaxel, another S-1 taxane-based regimen (Yoshida *et al*, 2006). It is not necessarily surprising that taxanes + S-1 markedly improved outcomes in patients with advanced and metastatic gastric cancer because patients eligible to receive a combination of paclitaxel and oral agents must have the possibility of oral intake, suggesting that they are in better general condition.

Human epidermal growth factor receptor 2 (HER2) is an important biomarker and a key driver of tumourigenesis in gastric cancer, with studies showing overexpression in 7–34% of tumours (Tanner *et al*, 2005; Gravalos and Jimeno, 2008). The ToGA study recently showed that the addition of trastuzumab to chemotherapy improves survival in patients with advanced gastric or gastro-oesophageal junction cancer as compared with chemotherapy alone (Bang *et al*, 2010). The ToGA study also found that OS was longer in patients with high expression of HER2 protein than in those with low expression. Information on the HER2 status of the patients in our study is unfortunately unavailable. However, recent studies have also shown an association of HER-2-positive tumours with poor outcomes and aggressive disease (Tanner *et al*, 2005; Gravalos and Jimeno, 2008). Further studies are thus needed to address the issue of whether HER2 has an effect on outcomes in gastric cancer and to determine whether it confers a good or poor prognosis.

Studies of patients with gastric cancer who receive chemotherapy before gastrectomy may show a survival benefit with the use of perioperative chemotherapy as compared with chemotherapy alone. Neoadjuvant (preoperative) chemotherapy is attractive for a number of reasons, including good compliance of patients with preoperative treatment, higher surgical cure rates as a result of tumour downstaging, and sparing patients with biologically aggressive disease from induction chemotherapy. The MAGIC trial showed that neoadjuvant chemotherapy resulted in tumour downstaging, significantly improved OS from 23–36%, and did not increase the rate of postoperative complications (Cunningham *et al*, 2006). However, favourable outcomes have been obtained