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Recent Trend of Internal Hernia Occurrence After Gastrectomy for Gastric Cancer

Hiromichi Miyagaki · Shuji Takiguchi · Yukinori Kurokawa · Motohiro Hirao · Shigeyuki Tamura · Toshirou Nishida · Yutaka Kimura · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki

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Abstract
Background The incidence of internal hernia after gastrectomy can increase with the increasing use of laparoscopic surgery, although this trend has not been elucidated.
Methods Clinical information was collected from medical records and by questionnaire for 18 patients who underwent surgical treatment for internal hernia after gastrectomy for gastric cancer in 24 hospitals from January 2005 to December 2009.
Results Gastrectomy for gastric cancer was open/distal gastrectomy (DG) in five (28%) patients, open/total gastrectomy (TG) in seven (39%), laparoscopy-assisted/DG in three (17%), and laparoscopy-assisted/TG in 3 (17%). Reconstruction was by Roux-Y methods in all patients. The hernia orifice was classified as a jejunojejunostomy mesenteric defect in eight patients (44%), dorsum of the Roux limb (Petersen's space) in eight (44%), and one (5%) each of esophageal hiatus and mesenterium of the transverse colon. Among 8,983 patients who underwent gastrectomy for gastric cancer, a postoperative survey revealed that 13 patients underwent surgical treatment for internal hernia in the same hospitals. The 3-year incidence rate of the internal hernia was 0.19%, which was significantly higher after laparoscopy-assisted than open gastrectomy (0.53 vs. 0.15%, $p = 0.03$). Patients with an internal hernia had a mean (±SD) low weight at hernia operation (body mass index 17.9 ± 1.6 kg/m^2) and marked weight loss after gastrectomy (weight reduction 15.6 ± 5.8%).
Conclusions Gastrectomy with Roux-Y reconstruction for gastric cancer leaves several spaces that can cause internal hernia formation. Laparoscopic surgery and postoperative body weight loss are potential risk factors.

H. Miyagaki · S. Takiguchi (✉) · Y. Kurokawa · Y. Fujiwara · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan
e-mail: stakiguchi@gesurg.med.osaka-u.ac.jp

M. Hirao
Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

S. Tamura
Department of Surgery, Kansai Rosai Hospital, Hyogo, Japan

T. Nishida
Department of Surgery, Osaka Police Hospital, Osaka, Japan

Y. Kimura
Department of Gastroenterological Surgery, NTT West Hospital, Osaka, Japan

Introduction

Intraabdominal adhesions are the most common cause of postoperative bowel obstruction after abdominal surgery, accounting for ~62–75% of cases [1–3]. These adhesions increase the risk of various subsequent complications, such as massive bowel infarction and pulmonary disease [3, 4]. Therefore, various contrivances, such as the use of antiadhesive material [5, 6], are employed to protect against the development of postoperative adhesions. Laparoscopic surgery is the most effective method that can reduce postoperative intraabdominal adhesions, and the incidence of bowel obstruction after laparoscopic surgery has decreased markedly relative to that with open surgery [7–10].

Another complication that has attracted attention in recent years is the postoperative internal hernia, representing bowel obstruction often irrelevant to intraabdominal adhesions [11, 12]. Postoperative internal hernia is an

acute or chronic protrusion of a viscus through an iatrogenic mesenteric or peritoneal aperture [13]. With respect to gastrectomy, internal hernia often occurs after specific reconstruction procedures, such as Roux-Y [14] and Billroth II [15] reconstruction, probably because of the multiplicity and large size of the iatrogenically created artificial apertures compared with the less frequent incidence after other reconstruction procedures (e.g., Billroth I reconstruction, esophagogastrostomy after proximal gastrectomy).

Studies of complications after gastric Roux-Y bypass surgery for obesity have reported a a significantly higher incidence of internal hernia after laparoscopic surgery than open surgery [11], suggesting that a reduction of intraabdominal adhesion in fact increases the risk, contrary to adhesive bowel obstruction. For patients who undergo gastrectomy for gastric cancer, which often includes a similar reconstruction procedure, the incidence of internal hernia may be more frequent after laparoscopic surgery than after open surgery as reported after bariatric surgery [11]. It is thought that the development of internal hernia after gastrectomy for gastric cancer is rare compared to that with gastric bypass surgery. In today's era of laparoscopic surgery, we should pay more attention to postoperative internal hernia, but to our knowledge there are only a few reports on the incidence of internal hernia after gastrectomy. The present retrospective multicenter study was designed to determine the true status of internal hernia after gastrectomy, including its developmental pattern, incidence, treatment, and outcome.

Methods

Patients

The study included analysis of questionnaires and medical and surgical records of 18 patients who underwent surgical treatment for internal hernia after gastrectomy between January 2005 and December 2009 in 24 high-volume centers (>40 gastrectomies per year) in the Kinki area, Japan. Based on the operative records, cases of intestinal herniation through adhesive bands that were treated by synechiotomy were excluded. Among the 18 patients, 13 underwent surgery for internal hernia in the same hospital where their gastrectomy was performed; the remaining five patients underwent gastrectomy in the same hospitals beyond the study period or in hospitals other than the 24 participating centers. None of the 18 patients developed cancer recurrence at or after surgical treatment of the internal hernia.

During the study period, 8,983 patients underwent curative gastrectomy in the participating 24 centers and adequate postoperative follow-up every 3 months until December 2010. Also, the medical charts indicated that none underwent surgical treatment for internal hernia in other hospitals. The mean follow-up period after gastrectomy in these patients was 30.3 months. Patients with pathologic stage II or higher diagnosed after 2007 generally received postoperative chemotherapy using S-1 (tegafur, gimeracil, and oteracil potassium).

These 8,983 patients consisted of 7,721 who underwent open gastrectomy and 1,262 in whom laparoscopy-assisted gastrectomy (LAG) was performed. The former group was subdivided into 4,756 with open/distal gastrectomy (OPDG), 2,748 with open/total gastrectomy (OPTG), and 217 with open/proximal gastrectomy (OPPG). Of the LAG group, 1,028 patients underwent LA distal gastrectomy (LADG), 218 LA total gastrectomy (LATG), and 16 LA proximal gastrectomy (LAPG).

Statistical analysis

Data are expressed as the mean ± SD. The incidence and 3-year cumulative incidence rates were analyzed by the Kaplan–Meier method. Correlations between incidences of surgical procedures were evaluated by the log-rank test. All analyses were carried out using JMP software version 8.0.1 (SAS Institute, Cary, NC, SA) for Windows. A p value <0.05 denoted the presence of statistical significance.

Results

Clinical profile of internal hernia after gastrectomy

Eighteen patients underwent surgical treatment of internal hernia after gastrectomy for gastric cancer (Table 1). They included 4 women and 14 men, aged 51–81 years (median 72 years). The median interval between preceding gastrectomy and surgery for internal hernia was 411 days (range 3–3437 days). The mean body mass index (BMI) at time of surgery for the hernia was 17.9 ± 1.6 kg/m^2, and the mean body weight reduction after gastrectomy was 15.6 ± 5.8%: 16.5 kg/m^2 and 17.6%, respectively, for the 10 patients of the total gastrectomy group and 19.3 kg/m^2 and 13.5% for the eight patients of the distal gastrectomy group. The operative procedures for preceding gastrectomy were OPDG in five (27%) patients, OPTG in seven (39%), LADG in three (17%), and LATG in three (17%). Reconstruction was by the Roux-Y method with antecolic route in nine patients and the retrocolic route in nine patients. Details of the preceding gastrectomy were available for 14 patients and showed the use of antiadhesion material in five patients and closure or fixation of both of the mesenterium of the transverse colon and jejunojejunostomy mesenteric defect in 10 patients. Petersen's space was not closed in any of the patients.

Table 1 Preoperative parameters for 18 patients who underwent repair of postgastrectomy internal hernia

Parameter	Data
Age (years): median (range)	72 (51–81)
Sex (M/F)	14/4
Interval period (days): median, range	411 (3–3437) days
BMI (kg/m^2): mean ± SD	
Preceding gastrectomy	21.2 ± 2.6
Internal hernia operation	17.9 ± 1.6
Reduction ratio	15.6 ± 5.8%
Procedure of the preceding gastrectomy	
Open distal gastrectomy	5
Open total gastrectomy	7
Laparoscopy-assisted distal gastrectomy	3
Laparoscopy-assisted total gastrectomy	3
Antiadhesive material used in preceding gastrectomy	
Yes	5
No	9
Unknown	4

The most common presentation of internal hernia was abdominal pain ($n = 16$, 89%) followed by nausea/vomiting ($n = 6$, 33%). Abdominal computed tomography (CT) was conducted in all cases, and there was a preoperative diagnosis of internal hernia in 14 cases (78%), as shown in Fig. 1. Emergency operation was required in four cases (22%). With regard to the approach used for surgery of the internal hernia, a laparoscopic procedure was adopted for two patients (11%) who had undergone the preceding gastrectomy via a laparoscopic approach, whereas the open procedure was applied in the remaining 16 patients. Figure 2 indicates the various hernia orifices in these patients, including jejunojejunostomy mesenteric defect in eight patients (44%), dorsum of the Roux limb (Petersen's space) in eight (44%), and one (6%) each of esophageal hiatus and mesenterium of the transverse colon. Because of bowel necrosis, bowel resection was performed in three (17%) patients. The operating time was 270 ± 53 min, with intraoperative blood loss of 283 ± 126 ml (Table 2). With regard to the postoperative course, one (6%) patient developed sepsis with disseminated intravascular coagulation but recovered later and was discharged from the hospital without other complications. Another patient (6%), who underwent a 360-cm small bowel resection, developed short-bowel syndrome. There were no deaths in this series.

Analysis of frequency and cumulative incidence of internal hernia

The frequency and incidence of internal hernia were calculated, excluding five patients who had undergone preceding gastrectomy beyond the dates of the study period and/or the surgery was conducted in a hospital other than the 24 participating centers. The frequency of internal hernia was calculated according to each gastrectomy surgical procedure among 8,983 curative gastrectomies conducted during this period. The overall frequency of the internal hernia was 0.14% but was not observed after open and laparoscopy-assisted proximal gastrectomy (Table 3). The median latency between gastrectomy and the diagnosis of internal hernia was 12.0 months. A trend was noted of a gradual increase in laparoscopic surgery (data not shown). The cumulative incidence rate of internal hernia was calculated by the Kaplan–Meier method (Fig. 3). The 3-year incidence was 0.19% for all patients, which was significantly higher for LAG than in open gastrectomy (0.53 vs. 0.15%, $p = 0.03$) (Fig. 3a). In particular, the rate for LATG was highest among all other procedures (Fig. 3b).

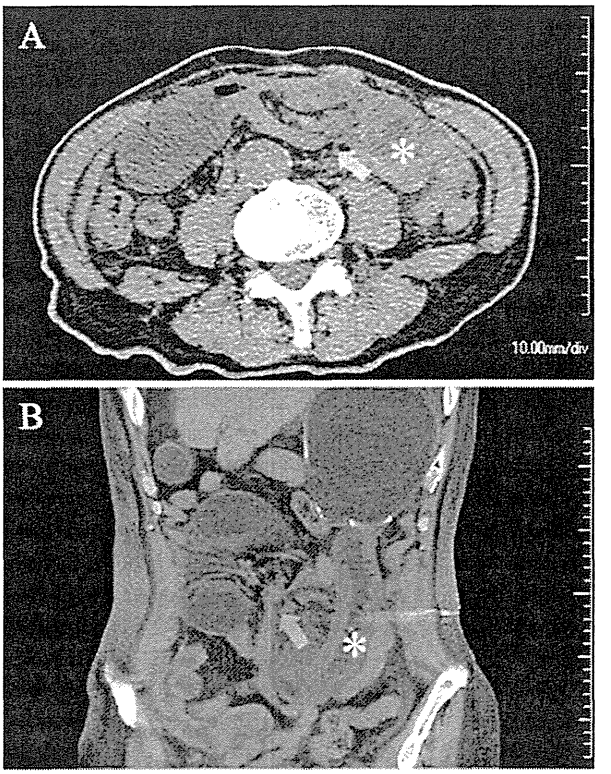

Fig. 1 Abdominal CT was used for the diagnosis of internal hernia. *Arrows*: orifice of the jejunojejunostomy mesenteric hernia; *: pedicled jejunum. **a** Horizontal section. **b** Coronal three-dimensional image viewed from the front

Discussion

This is the first multiinstitutional cohort study of the incidence of internal hernia after gastrectomy performed for gastric cancer. The results showed a 3-year incidence of

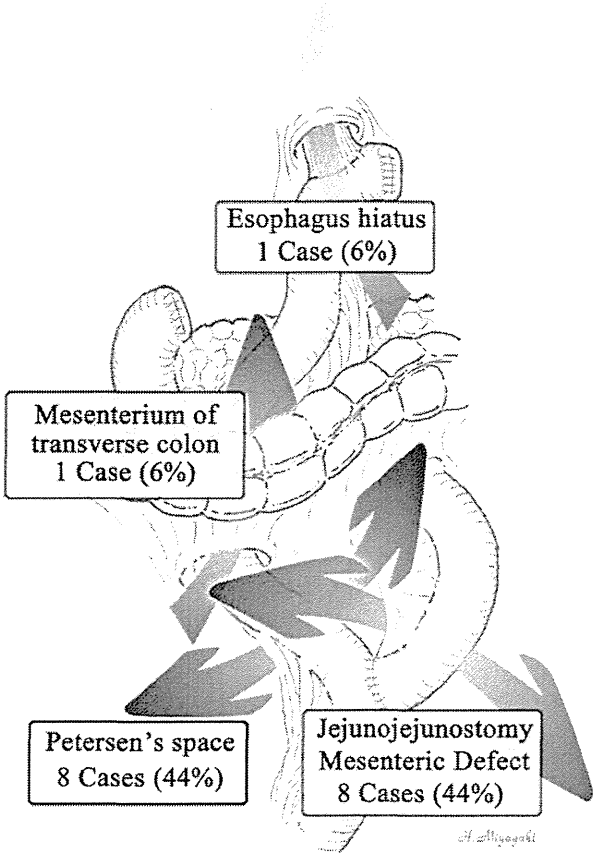

Fig. 2 Anatomic mapping of internal hernias. Although the figure is for total gastrectomy followed by retrocolic Roux-Y reconstruction, it serves to show the anatomic locations of internal hernias

0.19%, indicating that internal hernia is not a negligible postoperative complication.

The most considerable reason for this trend is the increased use of laparoscopic surgery. The decreased intraabdominal adhesions after laparoscopic surgery, which provides overall benefits associated with fewer various postoperative complaints and complications [7, 8], is widely regarded to be the major risk factor for the development of an internal hernia. For example, Capella et al. [11], who conducted a retrospective study of bariatric surgery, reported that the incidence of internal hernia following the Roux-Y gastric bypass was significantly higher after laparoscopic surgery than after open surgery (9.7 vs. 0%). In our study, although it included various surgical procedures, the cumulative incidence was also significantly higher after laparoscopic gastrectomy than after open gastrectomy (0.53 vs. 0.15%, $p = 0.03$). In Japan, the rate of LAG for gastric cancer has increased annually from 6.3% in 2000 to 25.7% in 2009 [16]. This rate could have a future impact on the incidence of internal hernia.

Another notable observation was that an internal hernia was observed only in patients with the Roux-Y reconstruction. Roux-Y reconstruction is the most popular procedure for total gastrectomy, being employed in more than 90% of the surgical procedures in Japan [17]. However, for distal gastrectomy, Billroth I and II and Roux-Y has been widely and preferentially used in many countries. Although there is no solid evidence based on randomized clinical trials, Billroth I, which allows physiological food

Table 2 Operative parameters for 18 patients who underwent repair of internal hernia

Parameter	No. of patients
Preoperative diagnosis	
Internal hernia	14
Other	4
Emergency operation	
Yes	4
No	14
Approach of operation	
Open procedure	16
Laparoscopic procedure	2
Hernia orifice	
Jejunojejunostomy mesenteric defect	8
Petersen's space	8
Mesenterium of transverse colon	1
Esophagus hiatus	1
Bowel resection	
Yes	3
No	15
Operating time (mean ± SD)	270 ± 53 min
Blood loss (mean ± SD)	283 ± 126 ml

Table 3 Frequency of internal hernia according to the type of gastrectomy

Procedure	Repair of internal hernia	Gastrectomy	Frequency (%)
Total gastrectomies	13	8,983	0.14
Open gastrectomy			
All procedures	9	7,721	0.12
OPDG	5	4,756	0.11
OPTG	4	2,748	0.15
OPPG	0	217	–
LAG			
All procedures	4	1,262	0.16
LADG	2	1,028	0.19
LATG	2	218	0.92
LAPG	0	16	–

OPDG open/distal gastrectomy, *OPTG* open/total gastrectomy, *OPPG* open/proximal gastrectomy, *LADG* laparoscopy-assisted/distal gastrectomy, *LATG* laparoscopy-assisted/total gastrectomy, *LAPG* laparoscopy-assisted/proximal gastrectomy

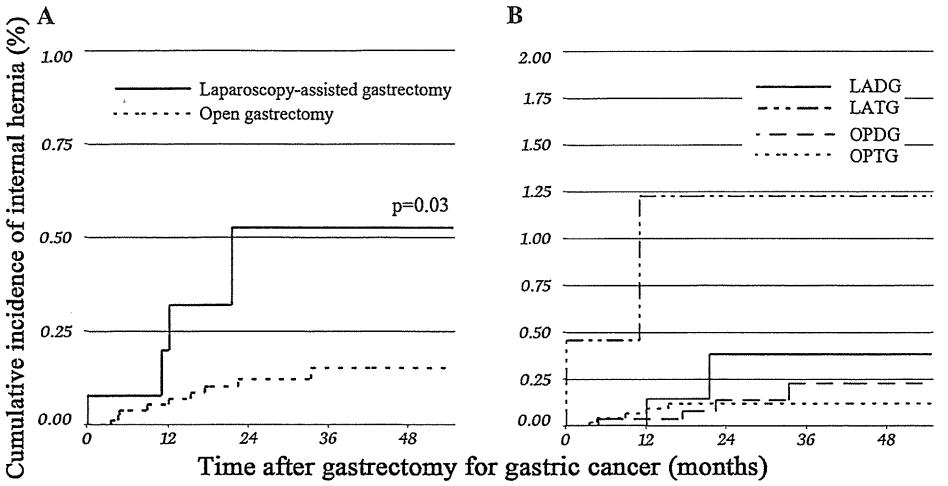

Fig. 3 Cumulative incidence of internal hernia after gastrectomy according to the gastrectomy procedure for gastric cancer. A total of 8983 patients underwent gastrectomy between January 2005 and December 2009 in 24 hospitals. Among these patients, 13 underwent surgical treatment for internal hernia. **a** The 3-year cumulative incidence rate of internal hernia after laparoscopic gastrectomy ($n = 4$) was 0.53%, which was significantly higher than that after open gastrectomy ($n = 9$) ($p = 0.03$). **b** The 3-year cumulative incidence of internal hernia according to the gastrectomy procedure. The cumulative rate was the highest after laparoscopy-assisted total gastrectomy (*LATG*) (1.22%, $p < 0.05$). *OPDG* open/distal gastrectomy, *OPTG* open/total gastrectomy, *LADG* laparoscopy-assisted distal gastrectomy

passage through the duodenum, is popular in Japan [17], whereas the Roux-Y reconstruction is still used infrequently in Japan [17]. Therefore, the incidence of internal hernia after gastrectomy with Roux-Y reconstruction was considered to be much higher than our observation. Moreover, use of the reconstruction has been gradually increasing in recent years [17], most likely to avoid anastomotic leakage and reflux inflammation of the remnant stomach [18, 19]. In our study, the incidence of internal hernia tended to be higher after total gastrectomy than distal gastrectomy (3-year incidence rates: 0.29 vs. 0.15%, $p = 0.358$). Although information on the reconstruction procedure for all registered cases was not available, except for those with internal hernia, this difference may be attributed in part to the difference in the frequency of Roux-Y reconstruction. Therefore, internal hernias may increase in the future in parallel with the change in the reconstruction method used.

The high risk of internal hernia after Roux-Y reconstruction is probably related to the abdominal spaces specifically created after Roux-Y reconstruction, with each space becoming a potential orifice for an internal hernia. Therefore, treatment of these artificial spaces is an important surgical issue to be discussed. The greatest factor possibly affecting the incidence of internal hernia after gastrectomy is closure of the mesenteric defects. Intuitively, an obliterated mesenteric defect should prevent the incidence of internal hernias, and several groups have recommended routine closure of all mesenteric defects, citing a decrease in the incidence of internal hernias after gastric bypass [20–25]. In our experience, jejunojejunostomy-associated mesenteric defects were surgically closed in six of eight patients with a jejunojejunostomy-repaired mesenteric hernia. Therefore, firmer closure with nonabsorbable surgical suture might be required. In general, we do not surgically close Petersen's spaces during gastrectomy. When the orifice is not closed, it is considered better to leave it large [25]. A large orifice may allow transposition of unfixed small intestine but rarely causes obstruction or strangulation, which clinically presents as an internal hernia. Management of the orifices during gastrectomy is still controversial, and further investigation should be carried out to identify the most effective procedure.

Body weight loss seems a risk factor for patients with a postgastrectomy internal hernia. In our study, the mean reduction in BMI in patients who developed an internal hernia after total gastrectomy was 17.6%, which was a larger loss than that reported in other studies (range 6.6–10.8%) [26, 27]. Similarly, the reduction (13.5%) after distal gastrectomy in our study was larger than in other studies (range 9.1–10.5%) [28, 29]. Weight loss, even when intentional after bariatric surgery, is considered a risk factor for internal hernia [21, 30]. The large decrease in mesenteric fat postoperatively constitutes a major part of the weight loss after surgery [31, 32]. Therefore, a large weight loss could increase the size of the mesenteric defect, thus enhancing the development of internal hernia [33].

The rare incidence and the associated nonspecific presentation make it difficult to diagnose an internal hernia preoperatively. However, CT can be helpful in depicting

signs of internal herniation [34, 35]. The swirled appearance of mesenteric fat or vessels was found to be the best single predictor of hernia, with a sensitivity of ~80% and specificity of 90% [36]. In the present study, a preoperative diagnosis was achieved in 14 cases (78%) via abdominal CT scans. CT resolution has markedly improved, and 3D images can be constructed easily (Fig. 1b) with improved diagnostic power [37–40].

Conclusions

Roux-Y reconstruction creates several intraabdominal spaces that can promote internal herniation. The 3-year incidence rate of internal hernia after gastrectomy performed for gastric cancer was 0.19%. Laparoscopic surgery and body weight loss may be risk factors for internal herniation. With the increase in popularity of LAG, attention must be focused on preventing morbidity associated with internal hernia formation.

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A Phase I Study of Bi-weekly Docetaxel for Recurrent or Advanced Gastric Cancer Patients Whose Disease Progressed by Prior Chemotherapy

Yutaka Kimura[1,*], Hiroshi Yano[2], Hirokazu Taniguchi[1], Takashi Iwazawa[3], Katsuki Danno[1], Naofumi Kagara[1], Toshiyuki Kanoh[1], Tadashi Ohnishi[1], Takeshi Tono[1], Yoshiaki Nakano[1], Takushi Monden[1] and Shingi Imaoka[1]

[1]Department of Surgery, NTT West Osaka Hospital, Osaka, [2]Department of Surgery, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo and [3]Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Osaka, Japan

*For reprints and all correspondence: Yutaka Kimura, Department of Surgery, NTT West Osaka Hospital, 2-6-40 Karasugatuji, Tennojiku, Osaka 543-8922, Japan. E-mail: y.kimura@mhc.west.ntt.co.jp

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Objective: Although docetaxel is active against gastric cancer, Grade 3 or 4 neutropenia occurs in the majority of patients in Japan when administered at 60 mg/m^2 every 3 weeks. To determine a more convenient and tolerable schedule than the tri-weekly schedule, we conducted a dose-escalation study of bi-weekly docetaxel. In this study, we investigated the maximum-tolerated dose and recommended dose.

Methods: Patients with advanced gastric cancer who had received prior chemotherapy were enrolled between April 2004 and March 2007. This study was designed to evaluate the escalated dose of docetaxel starting at 35 mg/m^2 (Level 1) given every 2 weeks. The dose was escalated in a stepwise fashion to 40 mg/m^2 (Level 2), 45 mg/m^2 (Level 3) and 50 mg/m^2 (Level 4).

Results: Fifteen patients completed at least two cycles of the therapy. Three episodes of Grade 3 neutropenia occurred in all patients and Grade 4 neutropenia was observed at Level 4 in six patients. Grade 3 or 4 thrombocytopenia and anemia were not observed. Grade 3 aspartate aminotransferase/alanine aminotransferase elevation ($n = 1$) and Grade 3 stomatitis ($n = 1$) were noted at Level 4. There was no other Grade 3 or 4 non-hematologic toxicity. The definition of dose-limiting toxicities of this docetaxel schedule at Level 4 are Grade 4 neutropenia, Grade 3 aspartate aminotransferase/alanine aminotransferase elevation and Grade 3 stomatitis.

Conclusions: The maximum-tolerated dose of docetaxel when administrated following the bi-weekly schedule was 50 mg/m^2 and the recommended dose was 45 mg/m^2. Bi-weekly administration of docetaxel may provide a better tolerated and efficacious use in gastric cancer.

Key words: gastric cancer – chemotherapy – bi-weekly docetaxel – Phase I

INTRODUCTION

In Japan, S-1 plus cisplatin (CDDP) is recognized as a standard chemotherapy for unresectable or recurrent gastric cancer (GC). This is based on the Japanese Phase III trial that showed a survival benefit of S-1 plus CDDP over S-1 (1). The median survival time and progression-free survival of S-1 plus CDDP were reported to be 13.0 and 6.0 months, respectively. Despite the survival benefit associated with first-line chemotherapy, the majority of patients experience relapse or disease progression. Second-line chemotherapy and additional therapy are thought to be important for survival benefit. Although docetaxel, paclitaxel and CPT-11 are used for second- or third-line chemotherapy, the standard chemotherapy for GC patients whose disease progressed by prior chemotherapy regimens has not yet been established (2–7).

Docetaxel is a semi-synthetic taxane that acts by stabilizing microtubules and is an active drug against GC (8,9).

A clinical trial of single-agent docetaxel given at 60 mg/m^2 every 3 weeks demonstrated a 17.1% response rate in advanced GC and 19.5% for its use as a second-line regimen. The dose-limiting toxicity (DLT) of docetaxel when administered at this dose and schedule is severe myelosuppression (10,11). Docetaxel exerts activity in various types of tumor including breast, lung and ovarian cancers when administered bi-weekly (12–14). The recommended dose (RD) of bi-weekly docetaxel is 50 mg/m^2 for breast cancer, 50 mg/m^2 for lung cancer and 60 mg/m^2 for ovarian cancer. The bi-weekly administration of docetaxel is well tolerated and produces substantially less myelosuppression than is observed with standard docetaxel administration every 3 weeks.

However, a clinical trial of bi-weekly docetaxel administration for GC has not yet been performed. Because patients with advanced GC often suffer from ascites and several gastrointestinal symptoms caused by peritonitis carcinomatosa, a bi-weekly docetaxel regimen given at the RD for GC must be tested.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: (i) patients must have histologically confirmed GC from excision or biopsy specimens; (ii) patients must have received more than one prior chemotherapy regimen; (iii) no prior docetaxel was permitted; (iv) prior chemotherapy must have been completed at least 2 weeks prior to study entry; (v) the age range was from 20 to 75 years; (vi) patients were required to have a performance status (PS) of 0–1 on the Eastern Cooperative Oncology Group scale; (vii) absence of serious organ dysfunction, namely, hemoglobin level $\geq$9.0 g/dl, neutrophil count $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3, adequate hepatic function (transaminases $<$2 times the upper limit of normal and total bilirubin level $<$1.5 mg/dl) and adequate renal function (serum creatinine level $<$1.5 mg/dl); (viii) the life expectancy was longer than 2 months; and (ix) all of patients gave their written informed consent to participate in this study.

The exclusion criteria included the following: (i) any organ failure; (ii) active concomitant malignancy; (iii) unfavorable medical condition, such as uncontrolled active infectious disease, cardiac disease or diabetes mellitus; (iv) pregnancy; (v) peripheral neuropathy; (vi) massive ascites or retention of pleural effusion; and (vii) ineligibility to the attending physician.

Treatment Plan

Patients who met the eligibility criteria were given docetaxel every 14 days. Docetaxel was dissolved in 500 ml of saline and was administered intravenously over the cycle of 60 min on day 1. All patients received premedication with 5-hydroxytryptamine3 agonist and dexamethasone (8 mg) intravenously on day 1 and oral dexamethasone (4 mg) given twice daily on days 2 and 3 of each cycle. The prophylactic use of granulocyte colony-stimulating factor and antibiotics was prohibited. This study was conducted using a 3 + 3 design. Docetaxel at a dose of 30 mg/m^2 was defined as Level 0. The starting dose of docetaxel was 35 mg/m^2 (Level 1) and the dose was escalated in a stepwise fashion to 40 mg/m^2 (Level 2), 45 mg/m^2 (Level 3) and 50 mg/m^2 (Level 4).

Definition of DLT

DLT was defined as follows: (i) Grade 4 neutropenia or leukopenia; (ii) Grade 3 febrile neutropenia; (iii) Grade 3 thrombocytopenia; (iv) Grade 3–4 non-hematologic toxicity (except for anorexia, nausea, vomiting and fatigue); and (v) postponement of the resumption of treatment by 29 or more days because of adverse reaction or other factors. DLT was assessed during the first two cycles of treatment.

Definition of Maximum-tolerated Dose and RD

At least three patients were enrolled at each dose level. If a DLT was not observed among these patients, the dose was increased to the next dose level. If two or three patients met the DLT criteria, dose was not increased. If a DLT was observed in one patient, an additional three patients were enrolled. If only one or two of the six patients assigned to this level had DLT, the dose was escalated to the next level. If two or three of the first three patients or three or more of the six patients had DLT during the initial two cycles, the level was defined as the maximum-tolerated dose (MTD). The RD was defined as the level one step below the MTD.

Treatment Delay and Discontinuation

Chemotherapy was postponed for any of the following reasons: (i) a leukocyte count $<$3000/mm^3, neutrophil count $<$1500/mm^3 and platelet count $<$75 000/mm^3 immediately before chemotherapy; (ii) hemoglobin $<$8.0 g/dl; and (iii) Grade 2 non-hematologic toxicity (Grade 3 for nausea, vomiting, anorexia and fatigue). Patients continued to receive the assigned treatment at the same dose level bi-weekly, provided that they did not develop progressive disease, refuse further treatment or experience unacceptable toxicity.

Evaluation and Assessment

Before the start of the study, physical examination, PS assessment, complete blood cell counts, chemistry profile, electrolyte determination, chest X-ray, electrocardiography and computed tomography of the abdomen were performed. Patients with measurable lesions had tumor measurements documented within 4 weeks of starting treatment. Physical

examination, PS assessment and clinical laboratory tests were repeated weekly. Side effects were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0, Japanese version issued by the Japan Clinical Oncology Group Study). Although determination of tumor response was not a primary objective of this study, patients with measurable or assessable disease were evaluated for response after two treatment cycles. Partial response and complete response had to be confirmed for at least 1 month. Tumor shrinkage was assessed according to the criteria of Response Evaluation Criteria in Solid Tumors (RECIST) (version 2).

This Phase I study was conducted in accordance with the Declaration of Helsinki and approved by Institutional Review Board at NTT West Osaka Hospital.

RESULTS

Clinical Profile

A total of 15 patients were enrolled from September 2004 to March 2007. The numbers of patients per dose level are shown in Table 1. Of the 15 patents, 3 received Level 1, 3 received Level 2, 3 received Level 3 and 6 received Level 4. The number of patients and cycles per dose level are presented in Table 1. All of them were evaluable for toxicity and 12 for response. The clinical profile of the patients is shown in Table 2. The median age of the patients was 64.0 (range, 57–75) years. Ten patients were men and five women. The PS was 0 in eight patients and 1 in seven patients. The histological type of the tumor was intestinal type in 5 patients and diffuse type in 10. Eight patients received prior chemotherapy with one regimen (six with S-1, one with S-1 + paclitaxel and one with S-1 + CPT-11), four with two regimens (two with paclitaxel and two with CPT-11 + CDDP followed by first line S-1 regimen) and three with three regimens including S-1, paclitaxel and CPT-11 + CDDP. The median number of treatment cycles was 4 (range, 2–16).

Table 1. Dose-escalation schedule for docetaxel

Dose level	Dose (mg/m^2)	No. of patients	No. of cycles
0	30	.....	.....
1	35	3	12
2	40	3	13
3	45	3	24
4	50	6	26

Table 2. Patient characteristics

	No
Age, years	
Median (range)	64 (57–75)
Gender (male/female)	10 / 5
ECOG performance status	
0	8
1	7
Prior gastrectomy	
−	10
+	5
Histology	
Intestinal type	10
Diffuse type	5
Metastatic site	
Lymph node	9
Liver	6
Peritoneum	4
No. of previous chemotherapy regimens	
1	6
2	4
≥3	5
Treatment cycle	
Median (range)	4 (2–16)

ECOG, Eastern Cooperative Oncology Group.

Toxicities

The toxicities during the first two cycles are shown in Table 3. Grade 3 neutropenia was observed in three patients and Grade 4 neutropenia as DLT in only one patient at Level 4. There were no actual episodes of neutropenic fever. Moreover, thrombocytopenia and Grade 3 or 4 anemia were not observed at any dose levels. Grade 3 non-hematologic toxicities were observed only at Level 4. Grade 3 stomatitis was noted in one patient and Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation in one patient at Level 4.

The total number of treatment cycles was 75 (12 cycles at Level 1, 13 cycles at Level 2, 24 cycles at Level 3, and 26 cycles at Level 4). The toxicities in all treatment cycles are summarized in Table 4. Neutropenia was the most commonly observed hematological toxicity. There were no episodes of neutropenic fever. Non-hematologic toxicities were mild except for stomatitis and AST/ALT elevation during the first two cycles. Neither treatment-related death nor delayed severe toxicities was observed.

Maximum-tolerated Dose and Recommended Dose

At Level 4, Grade 4 neutropenia was found in one patient, Grade 3 stomatitis in one and Grade 3 AST/ALT elevation in one, and these were considered DLTs. On the basis of

Table 3. Adverse events during the first two cycles

	Level 1 ($n=3$)				Level 2 ($n=3$)				Level 3 ($n=3$)				Level 4 ($n=6$)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	1				1			1	1			2	2		
Neutropenia		1	1		1	1				2				1	2	1
Anemia	2	1			1	2			3				1	4		
Thrombocytopenia																
Febrile neutropenia																
Anorexia	2								1					1		
Nausea/vomiting													2	1		
Diarrhea						1										
Stomatitis					1										1	
Fatigue	2				1								1	2		
Alopecia	2				1	1			2				4			
Dermatitis					1											
Neurotoxicity					1								1			
Peripheral edema	1													1		
AST/ALT elevation	1					1									1	

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4. Adverse events in all cycles

	Level 1 ($n=3$)				Level 2 ($n=3$)				Level 3 ($n=3$)				Level 4 ($n=6$)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	1				1			1	1			2	2		
Neutropenia		1	1		1	1				2				1	2	1
Anemia	2	1			1	2			3				1	4		
Thrombocytopenia									1				1			
Febrile neutropenia																
Anorexia	2				1				1					1		
Nausea/vomiting									1				2	1		
Diarrhea						1										
Stomatitis					1										1	
Fatigue	2				1				1				2	2		
Alopecia	2				2	1			3				4			
Dermatitis					1											
Neurotoxicity					1				1				1			
Peripheral edema	1												1	1		
AST/ALT elevation	1					1							1		1	

these results, Level 4 was considered the MTD. The RD of docetaxel was determined to be 45 mg/m^2 (Level 3).

Efficacy

Twelve patients had measurable tumors (RECIST). Of these 12 patients, 1 had a partial response at Level 3, yielding a response rate of 8.3%, and 6 patients had stable disease (Table 5).

DISCUSSION

In most clinical trials of docetaxel against several cancers, a dose of 60–100 mg/m^2 was administered every 3 weeks (15–18). At this dose range, >80% of the patients developed Grade 3 or 4 neutropenia, and hospitalization for the treatment of febrile neutropenia was relatively common. In Japan, two late Phase II clinical studies of tri-weekly docetaxel (60 mg/m^2) in patients with advanced GC showed the occurrence of Grade 3 or 4 neutropenia in 81.3–90.0% of the patients (10,11).

Bi-weekly docetaxel has been reported to be effective in various cancers including breast, lung and ovarian cancers as well as to prevent severe myelosuppression (12–14). Based on this observation, we investigated whether the bi-weekly administration of docetaxel for GC, which increases the dose intensity of docetaxel, would decrease the appearance and extent of toxicity while maintaining the effect of tri-weekly administration.

The results of this Phase I study for patients having advanced GC with prior chemotherapy demonstrate that the toxicity profile of docetaxel can be markedly altered when this drug is administrated bi-weekly. At Level 4 (50 mg/m^2), Grade 4 neutropenia, Grade 3 stomatitis and Grade 3 AST/ALT elevation appeared as DLTs. Accordingly, Level 4 was judged to be the MTD, and the RD was determined to be one level lower, that is, Level 3 (45 mg/m^2). Interestingly, severe myelosuppression, which occurs in a large majority of patients when docetaxel is administrated at 60 mg/m^2 every 3 weeks, was not observed following the bi-weekly schedule besides at the level of the MTD. Non-hematologic toxicity was not severe below the level of the RD. At Level 3, Grade 1 anorexia and Grade 1 alopecia appeared during the first two cycles. In all treatment cycles, cumulative toxicities with repeated cycles of treatment were not observed at the level of the RD. At a bi-weekly dose as high as 45 mg/m^2/week (equivalent in dose intensity to 67.5 mg/m^2 every 3 weeks), docetaxel was extremely well tolerated without Grade 3 or 4 toxicities even in previously treated patients.

The efficacy data obtained in this Phase I study are only preliminary. However, these data are not satisfactory on the grounds that many patients have received two or more regimens of prior chemotherapy. Therefore, the efficacy of bi-weekly docetaxel should be investigated by Phase II study.

In conclusion, bi-weekly docetaxel infusion is a possible regimen as salvage chemotherapy for advanced GC.

Table 5. Response (RECIST)

Response	Complete response	Partial response	Stable disease	Progressive disease	Response rate (%)	Disease control rate (%)
Overall ($n = 12$)	0	1	6	5	8.3	58.3
Level 1 ($n = 2$) (35 mg/m^2)	0	0	1	1	.....	.....
Level 2 ($n = 2$) (40 mg/m^2)	0	0	0	2	.....	.....
Level 3 ($n = 3$) (45 mg/m^2)	0	1	2	0	—	—
Level 4 ($n = 5$) (50 mg/m^2)	0	0	3	2	.....	.....

RECIST, Response Evaluation Criteria in Solid Tumors.

Bi-weekly docetaxel may be more convenient than a tri-weekly schedule because of the lack of severe toxicities. Based on the present results, we are planning a Phase II clinical study followed by first- or second-line chemotherapy to evaluate the efficacy of this schedule.

Conflict of interest statement

None declared.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial

Shuichi Hironaka, Shinya Ueda, Hirofumi Yasui, Tomohiro Nishina, Masahiro Tsuda, Takehiko Tsumura, Naotoshi Sugimoto, Hideki Shimodaira, Shinya Tokunaga, Toshikazu Moriwaki, Taito Esaki, Michitaka Nagase, Kazumasa Fujitani, Kensei Yamaguchi, Takashi Ura, Yasuo Hamamoto, Satoshi Morita, Isamu Okamoto, Narikazu Boku, and Ichinosuke Hyodo

Author affiliations appear at the end of this article.

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Clinical trial information: University Hospital Medical Information Network–Clinical Trials Registry Japan No. 000001252.

Corresponding author: Shuichi Hironaka, MD, Clinical Trial Promotion Department, Chiba Cancer Center, 666-2 Nitona-cho Chuo-ku Chiba-shi, Chiba, 260-8717 Japan; e-mail: shironaka@ta2.so-net.ne.jp.

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ABSTRACT

Purpose
This phase III study compared treatment with weekly paclitaxel and biweekly irinotecan in patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum.

Patients and Methods
Patients were randomly assigned to receive either paclitaxel (80 mg/m^2 on days 1, 8, and 15, every 4 weeks) or irinotecan (150 mg/m^2 on days 1 and 15, every 4 weeks). Primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS), response rate, adverse events, and proportion of patients who received third-line chemotherapy.

Results
Of 223 patients, 219 were eligible for analysis. Median OS was 9.5 months in 108 patients allocated to the paclitaxel group and 8.4 months in 111 patients allocated to the irinotecan group (hazard ratio [HR], 1.13; 95% CI, 0.86 to 1.49; P = .38). Median PFS was 3.6 months in the paclitaxel group and 2.3 months in the irinotecan group (HR, 1.14; 95% CI, 0.88 to 1.49; P = .33). Response rate was 20.9% in the paclitaxel group and 13.6% in the irinotecan group (P = .24). Common grade 3 to 4 adverse events were neutropenia (paclitaxel group, 28.7%; irinotecan group, 39.1%), anemia (21.3%; 30.0%), and anorexia (7.4%; 17.3%). Treatment-related deaths occurred in two patients (1.8%) in the irinotecan group. Third-line chemotherapy was administered in 97 patients (89.8%) after paclitaxel treatment and in 80 patients (72.1%) after irinotecan treatment (P = .001).

Conclusion
No statistically significant difference was observed between paclitaxel and irinotecan for OS. Both are reasonable second-line treatment options for advanced gastric cancer.

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INTRODUCTION

The outcomes in patients with unresectable gastric cancer are extremely poor; median survival times of 3 to 5 months have been reported with best supportive care (BSC) alone.[1-3] In randomized studies conducted in the 1990s, first-line chemotherapy for advanced gastric cancer provided survival benefit over BSC alone. After many clinical trials, at present, fluoropyrimidine plus platinum with or without epirubicin or docetaxel is regarded as standard first-line chemotherapy in the treatment of gastric cancer worldwide.[4-9]

Since S-1 was approved for treatment of advanced gastric cancer in Japan, several phase III studies have been conducted, such as the JCOG 9912 (Japan Clinical Oncology Group 9912; fluorouracil *v* S-1 *v* irinotecan plus cisplatin),[10] SPIRITS (S-1 Plus Cisplatin Versus S-1 in a Randomized Controlled Trial in the Treatment for Stomach Cancer; S-1 *v* S-1 plus cisplatin),[9] and GC0301/TOP-002 trials (Gastric Cancer 0301/Topotecin-002; S-1 *v* S-1 plus irinotecan).[11] On the basis of these study results, S-1 plus cisplatin is accepted as standard first-line chemotherapy for advanced gastric cancer

in Japan. Despite no robust evidence of survival benefit, > 70% of participants received second-line chemotherapy in these studies.[9-11]

Many phase II studies of second-line chemotherapy for advanced gastric cancer have been conducted.[12-20] In evaluations of taxanes, administration of both paclitaxel (210 mg/m^2) and docetaxel (60 mg/m^2) on a triweekly schedule resulted in high rates of grade 3 or 4 neutropenia (37% to 88%),[12-14] whereas lower rates of severe neutropenia (3% to 32%) were observed with weekly administration of paclitaxel (80 mg/m^2).[15-18] Regarding efficacy parameters, response rate (RR) and progression-free survival (PFS) were similar for patients on the triweekly and weekly schedules of paclitaxel. Two reports evaluated weekly paclitaxel as second-line chemotherapy, in which median overall survival (OS) was 5 and 6.9 months, respectively.[15,16] In other studies, combination chemotherapy including biweekly administration of irinotecan (150 mg/m^2) as second-line chemotherapy resulted in median OS of 8 to 10 months,[19,20] although toxicity seemed to be more severe than that seen with weekly paclitaxel. Thus, weekly paclitaxel has become the preferable second-line chemotherapy in Japan.

At present, taxanes and irinotecan are two main options for treatment of advanced gastric cancer refractory to fluoropyrimidine plus platinum. However, to our knowledge, no randomized study has directly compared the efficacy of these two treatments. The West Japan Oncology Group (WJOG) conducted a phase III trial (WJOG 4007) comparing paclitaxel with irinotecan in patients with advanced gastric cancer.

PATIENTS AND METHODS

Patients

Eligible patients were age 20 to 75 years with histologically confirmed metastatic or recurrent gastric adenocarcinoma. Other inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; disease progression confirmed by computed tomography (CT), endoscopy, or other imaging technique during or within 1 month after last dose of first-line chemotherapy with fluoropyrimidine plus platinum; no prior chemotherapy with taxanes or irinotecan; and no severe peritoneal metastasis. Severe peritoneal metastasis was defined as ileus or subileus suggested on barium enema examination and moderate to severe ascites exceeding the pelvic cavity on spine CT scan caused by peritoneal metastasis. In case of treatment with adjuvant or neoadjuvant chemotherapy consisting of fluoropyrimidine plus platinum, patients with disease progression during treatment or within 6 months after treatment completion were eligible. Adequate bone marrow, hepatic, and renal functions were also required.

Study Design

WJOG 4007 was a prospective, multicenter, randomized, open-label, parallel-group phase III clinical trial conducted at 37 centers in Japan. The protocol was approved by the independent ethics committee or institutional review board of each participating institution. This trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry. The trial was registered with the University Hospital Medical Information Network.

After checking eligibility, patients were randomly assigned at a 1:1 ratio to receive either paclitaxel or irinotecan. Random assignment was carried out centrally at the data center using minimization method with the following adjustment factors: institution, ECOG PS (0 to 1 *v* 2), and measurable lesions (presence *v* absence). Neither investigators nor patients were blinded to the allocated treatment.

Treatment

Paclitaxel (80 mg/m^2) was administered intravenously on days 1, 8, and 15, every 4 weeks. Patients were premedicated with histamine receptor-1 and -2 blockers and dexamethasone for prophylaxis of allergic reactions 30 minutes before paclitaxel administration. Irinotecan (150 mg/m^2) was administered intravenously on days 1 and 15, every 4 weeks. Dose reduction and/or cycle delays were permitted according to predefined toxicity criteria. Treatment continued until disease progression, occurrence of unacceptable serious toxicity, or patient refusal of further treatment. Subsequent chemotherapy was not specified.

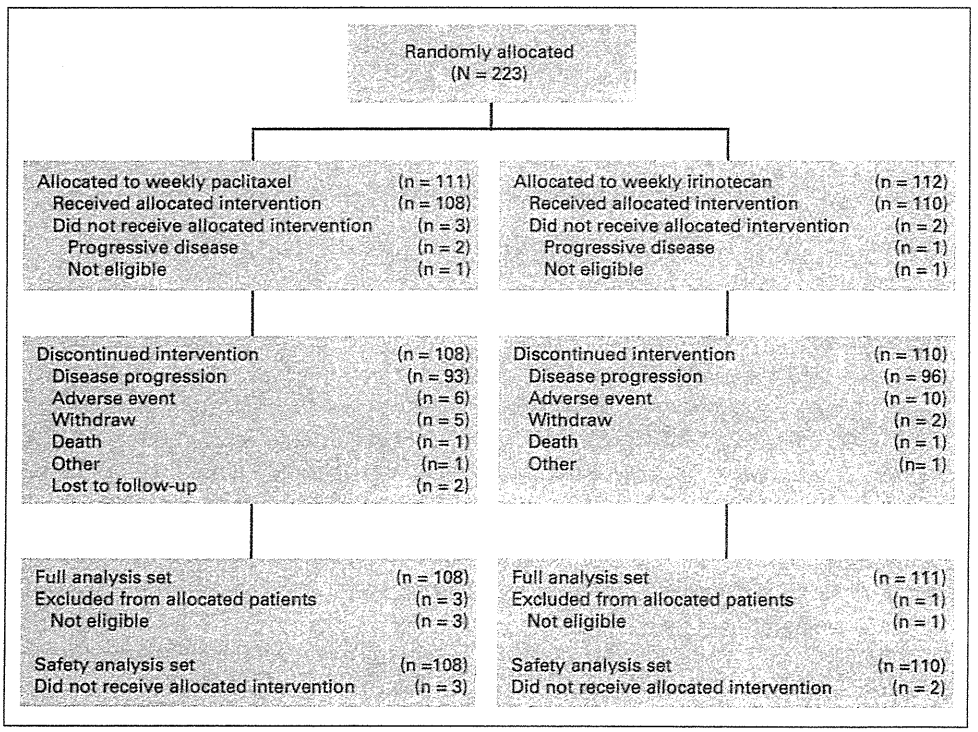

Fig 1. CONSORT diagram.

Assessments

Vital signs, ECOG PS, and laboratory tests were assessed within 7 days before study entry. Physical examinations and hematology and biochemistry tests were conducted during drug administration throughout the treatment course. Tumor assessments using CT scans of the chest, abdomen, and pelvis were performed within 28 days before study entry and repeated every 2 months after random assignment until discontinuation of protocol treatment. RECIST (version 1.0) was used to evaluate treatment responses.[21] Safety assessments were repeated every 2 weeks until initiation of subsequent chemotherapy or 6 weeks after the last protocol treatment. Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The WJOG Data and Safety Monitoring Committee reviewed serious adverse events for trial safety during the protocol treatment. Investigators assessed response, progression, and toxicities in their patients; independent central assessments of response and disease progression were not performed.

Statistical Analysis

The primary end point was OS, defined as time from random assignment to death resulting from any cause. Secondary end points were PFS, defined as time from random assignment to disease progression or death resulting from any cause; RR; toxicity; and proportion of patients who received subsequent chemotherapy.

Previous single-arm studies showed median OS of 5 and 6.9 months in paclitaxel-[15,16] and 8 and 10 months in irinotecan-containing regimen.[19,20] Irinotecan was contraindicated for patients with severe peritoneal metastasis, because its biliary-excreted metabolites caused severe toxicities. In gastric cancer, peritoneal metastasis often developed along with disease progression, and we therefore speculated that subsequent irinotecan after paclitaxel would be more difficult to apply in patients compared with the reverse treatment sequence. On the basis of these previous results and our assumption, this study was designed to detect 50% improvement in median OS from 5 months in the paclitaxel group to 7.5 months in the irinotecan group (hazard ratio [HR], 0.67). Assuming accrual and follow-up periods of 36 and 12 months, respectively, and using a two-sided log-rank test with 5% α and 20% β errors, 220 patients were required for the study. No interim analyses were planned.

A full analysis set (FAS) included all randomly assigned patients who met the eligibility criteria (patients found to be ineligible after random assignment were excluded). The safety analysis set (SAS) included all randomly assigned patients who received $\geq$ one dose of study medication. OS and PFS were analyzed in the FAS and estimated using the Kaplan-Meier method. RR was assessed in patients with $\geq$ one measurable lesion at baseline. Toxicity was analyzed in the SAS.

The primary analysis was planned for 1 year after enrollment of the last patient or approximately 205 events, whichever came first. An independent statistician and data analysis center performed the primary analysis for OS with unstratified log-rank test in the FAS population. All investigators remained blinded to the data until the analysis was completed. Cox proportional hazards models were used to calculate HRs and CIs. Fisher's exact test was used to assess differences in RR, incidence of

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Weekly Paclitaxel (n = 108) No.	%	Irinotecan (n = 111) No.	%
Sex				
Male	84	77.7	87	78.4
Female	24	22.2	24	21.6
Age, years				
Median	64.5		65	
Range	37-75		38-75	
ECOG PS				
0 to 1	104	96.3	107	96.4
2	4	3.7	4	3.6
Prior gastrectomy				
Yes	37	34.3	39	35.1
No	71	65.7	72	64.9
Prior chemotherapy				
S-1 plus cisplatin	92	85.2	102	91.9
Capecitabine plus cisplatin	13	12.4	8	7.2
S-1 plus oxaliplatin	3	2.8	1	0.9
Target lesion				
Yes	91	84.3	88	79.3
No	17	15.7	23	20.7
Histology				
Intestinal	54	50.0	54	48.6
Diffuse	54	50.0	57	51.4
Peritoneal metastasis				
Yes	28	25.9	28	25.2
No	80	74.1	83	74.8
No. of metastatic sites				
One	57	52.8	64	57.7
Two or more	51	47.2	47	42.3

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

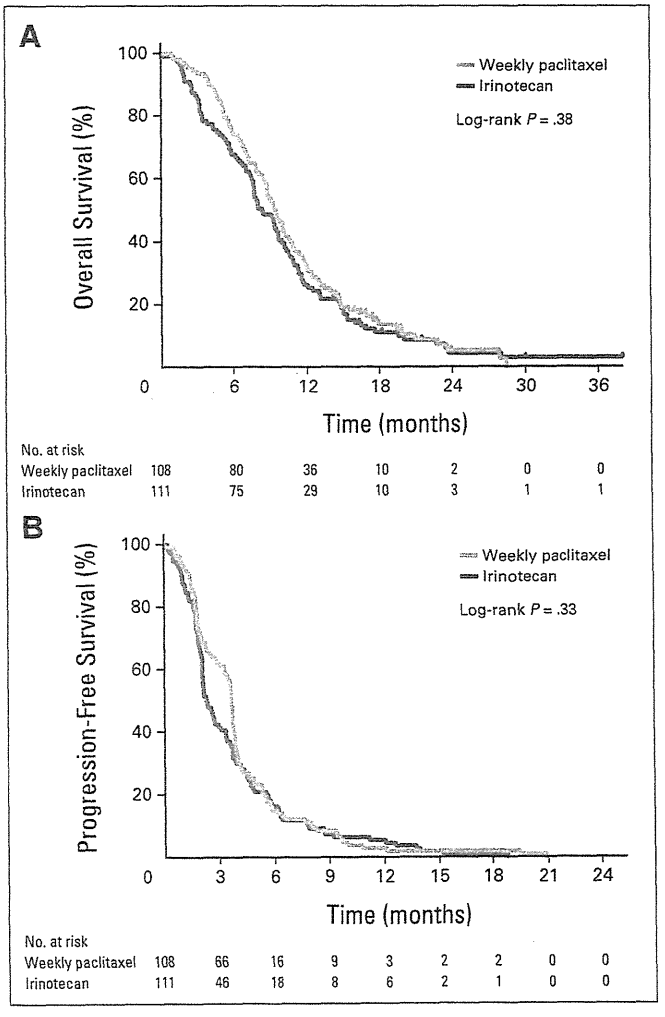

Fig 2. Kaplan-Meier curves of (A) overall and (B) progression-free survival.

adverse events, and proportion of patients who received third-line chemotherapy. Exploratory subgroup analyses of OS were performed using stratification and prognostic variables.

RESULTS

Patients

Between August 2007 and August 2010, 223 patients were enrolled from 37 centers in Japan. Of these patients, 111 were allocated to the paclitaxel group and 112 to the irinotecan group (Fig 1). Four patients, who either had received prior fluoropyrimidine monotherapy (paclitaxel group, n = 2; irinotecan group, n = 1) or had radiologically unconfirmed disease progression (paclitaxel group, n = 1), were ineligible for the study. Thus, the FAS consisted of 108 patients in the paclitaxel group and 111 patients in the irinotecan group. After random assignment, three patients in the paclitaxel group and two in the irinotecan group did not receive the protocol treatment. Thus, the SAS consisted of 108 patients in the paclitaxel group and 110 patients in the irinotecan group. Baseline characteristics of patients in the FAS were well balanced between the two treatment groups (Table 1). ECOG PS scores of 0 or 1 were found in a majority of patients. The most common first-line chemotherapy was S-1 plus cisplatin (88.6%), followed by capecitabine plus cisplatin with or without anti–epidermal growth factor receptor or anti–vascular endothelial growth factor antibodies (9.6%) and S-1 plus oxaliplatin (1.8%). One or more measurable lesions were present in approximately 80% of patients, and mild or moderate peritoneal metastasis was detected in approximately 25% of patients in both groups. Two or more metastatic sites were found in < 50% of patients.

Exposure to Chemotherapy

Median number of administrations was 11.5 (range, one to 46) in the paclitaxel group and 4.5 (range, one to 39) in the irinotecan group. Reasons for discontinuation of treatment included: disease progression (86.7%), adverse events (7.3%), withdrawal of consent (3.2%), and other reasons (2.8%). The proportion of patients in whom treatment was discontinued because of toxicity was 5.6% in the paclitaxel group and 9.1% in the irinotecan group.

Third-line chemotherapy was administered to 97 patients (89.8%) in the paclitaxel group and 80 patients (72.1%) in the irinotecan group ($P = .001$). In the paclitaxel group, third-line chemotherapy containing irinotecan was used in 81 patients (75.0%), and in the irinotecan group, a taxane-containing regimen was used in 67 patients (60.4%). Including later lines, 87 patients (80.6%) in the paclitaxel group received irinotecan, and 75 patients (67.6%) in the irinotecan group received paclitaxel.

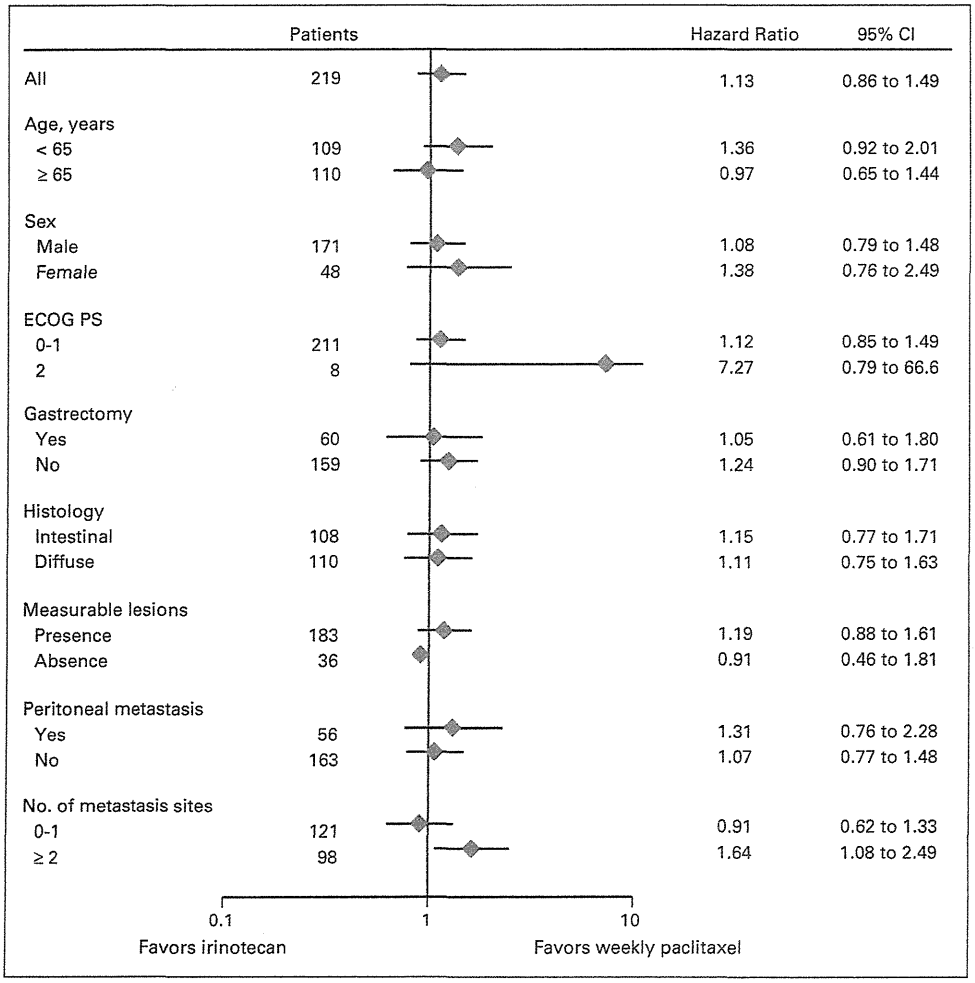

Fig 3. Forest plot of subgroup analyses. ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

In August 2011, after a median follow-up period of 17.6 months, 203 deaths (92.7%) were reported in the patient cohort. For the primary end point of OS, no statistically significant difference was observed between paclitaxel and irinotecan groups (HR, 1.13; 95% CI, 0.86 to 1.49; two-sided $P = .38$). Median OS was 9.5 months (95% CI, 8.4 to 10.7) in the paclitaxel group and 8.4 months (95% CI, 7.6 to 9.8) in the irinotecan group (Fig 2A). Median PFS was 3.6 months (95% CI, 3.3 to 3.8) in the paclitaxel group and 2.3 months (95% CI, 2.2 to 3.1) in the irinotecan group. This difference was not statistically significant (HR, 1.14; 95% CI, 0.88 to 1.49; two-sided $P = .33$; Fig 2B). RR was 20.9% (19 of 91 patients) in the paclitaxel group and 13.6% (12 of 88) in the irinotecan group (Fisher's exact $P = .24$).

Results of the subgroup analysis of OS are shown in Figure 3. Although treatment with weekly paclitaxel conferred a slight survival advantage in almost all subgroups, no significant interactions were observed in any subgroup. In an exploratory analysis, OS was analyzed in patients who received irinotecan and paclitaxel during second- and later-line chemotherapies. Median OS was 10.1 months in each group, and the survival curves of these two subgroups almost overlapped (HR, 0.96; 95% CI, 0.69 to 1.32; two-sided $P = .96$).

Safety

Table 2 lists adverse events and the proportion of patients experiencing adverse events during treatment in the SAS. The most common grade 3 or 4 adverse events were leukopenia (20.4%), neutropenia (28.7%), and anemia (21.3%) in the paclitaxel group. Leukopenia (19.1%), neutropenia (39.1%), anemia (30.0%), anorexia (17.3%), and hyponatremia (15.5%) were common in the irinotecan group. Grade 3 or 4 sensory neuropathy was observed in the paclitaxel group (7.4%) only. Grade 3 or 4 febrile neutropenia was more prevalent in the irinotecan group (9.1%) than in the paclitaxel group (2.8%). Three (2.7%) and four deaths (3.6%) resulting from any cause occurred within 30 days after the last administration in the paclitaxel and irinotecan groups, respectively. Treatment-related death confirmed by the independent data safety monitoring committee was observed in two patients (1.8%) in the irinotecan group. Causes of death included serious pneumonia in one patient and gastric perforation in the other.

Table 2. Adverse Events

	Weekly Paclitaxel (n = 108)				Irinotecan (n = 110)			
	All Grade		Grade 3 to 4		All Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Leukocytopenia	88	81.4	22	20.4	76	69.4	21	19.1
Neutropenia	85	78.7	31	28.7	77	70.0	43	39.1
Hemoglobin	69	63.9	23	21.3	84	76.4	33	30.0
Thrombocytopenia	6	5.6	1	0.9	15	13.6	2	1.8
Febrile neutropenia	3	2.8	3	2.8	10	9.1	10	9.1
Nausea	33	30.6	2	1.9	61	55.5	5	4.5
Vomiting	22	20.4	3	2.8	40	36.4	1	0.9
Anorexia	50	46.3	8	7.4	78	70.1	19	17.3
Diarrhea	21	19.4	1	0.9	49	44.5	5	4.5
Neuropathy (sensory)	62	57.4	8	7.4	2	1.8	0	0
Bilirubin	10	9.3	3	2.8	21	19.1	4	3.6
AST	32	29.6	4	3.7	42	38.2	9	8.2
ALT	24	22.2	3	2.8	41	37.3	3	2.7
Hyponatremia	21	19.4	4	3.7	35	31.8	17	15.5
Treatment-related death	0	0	0	0	2	1.8	2	1.8

DISCUSSION

To our knowledge, this was the first randomized phase III trial comparing paclitaxel and irinotecan in second-line chemotherapy for advanced gastric cancer. No statistically significant differences were observed between paclitaxel and irinotecan for the primary end point of OS or for other parameters evaluated in this study, including PFS and RR. Activity, feasibility, and tolerability of paclitaxel and irinotecan were comparable for second-line treatment of advanced gastric cancer.

When we planned this study, OS in patients who received second-line chemotherapy seemed to be longer than OS in patients who received BSC alone in previous trials.[12-16,19,20] Because > 70% of patients were receiving second-line chemotherapy as part of routine clinical practice at that time, conducting a trial of second-line chemotherapy compared with BSC alone was difficult in Japan. Since then, the survival benefit of second-line chemotherapy over BSC has been demonstrated in two randomized trials[22,23]: the AIO (Arbeitsgemeinschaft Internistische Onkologie) trial using irinotecan and Korean trial using irinotecan or docetaxel during the same time period as this WJOG 4007 study. On the basis of these results, second-line chemotherapy using irinotecan or docetaxel has been recognized as the standard of care for patients with gastric cancer. However, further comparison between irinotecan and taxane regimens would be valuable for strategic planning of treatment in patients with advanced gastric cancer.

In the Korean trial, choice of chemotherapy regimen—docetaxel or irinotecan—depended on investigator discretion. A subgroup analysis showed no significant difference in survival between regimens (median OS: docetaxel, 5.2 months *v* irinotecan, 6.6 months; $P = .116$).[23] In addition, Ji et al[24] conducted a retrospective analysis of 725 patients with gastric cancer treated with second-line chemotherapy; they found no relevant difference in OS between taxane and irinotecan treatment. In our exploratory subgroup analysis, no interaction was observed among several clinical factors; results favored neither paclitaxel nor irinotecan. Thus, either taxane or irinotecan can be recommended as a treatment option for second-line chemotherapy in patients with advanced gastric cancer.

Longer OS was achieved in this study than in previous phase III studies.[22,23] Many patients in good condition with small tumor burdens were enrolled onto our study. ECOG PS of 0 or 1 was recorded in almost all patients, and only one metastatic site was detected in > half of all patients. Additionally, excluding patients with severe peritoneal metastasis resulted in a lower proportion of patients (25.6%) with peritoneal metastasis, compared with those in the AIO (43%) and Korean (45%) trials.[22,23] These are well known as prognostic factors in advanced gastric cancer, and these patient-selection biases might have led to longer survival in our study.

In gastric cancer, peritoneal metastasis often develops along with disease progression, and irinotecan would be toxic for patients with

severe peritoneal metastasis. Indeed, the proportion of patients receiving subsequent irinotecan after second-line paclitaxel was only 24% in the previous report.[16] In this study, excluding patients with severe peritoneal metastasis seemed to result in a high proportion of patients (> 70%) receiving third-line chemotherapy, whereas 30% to 40% of patients did so in previous studies.[23,24] Although evidence is limited with regard to the efficacy of third-line chemotherapy in advanced gastric cancer, this therapy may have contributed to prolonged OS, and the unexpected higher proportion of those receiving third-line chemotherapy might have diluted a difference in OS between the paclitaxel and irinotecan groups.

Overall toxicity in both treatment arms was acceptable for second-line chemotherapy. In the paclitaxel group, common grade 3 or 4 toxicities (≥ 10%) included leukocytopenia, neutropenia, and anemia. Grade 3 sensory neuropathy, which was specific to paclitaxel, occurred at an incidence < 10% in this study. These toxicity profiles and severity levels are consistent with those in previous reports.[15,16] In the irinotecan group, leukocytopenia, neutropenia, anemia, anorexia, and hyponatremia were commonly observed. Frequency and severity of these toxicities were also consistent with those in previous reports.[22,23] Severe diarrhea, which is a well-known adverse reaction to irinotecan, generally occurs less frequently in Asian patients than in Western patients. In fact, grade 3 or 4 diarrhea was observed in 4.5% of patients in this trial, 8% of those in the Korean trial,[23] and 26% of those in the AIO trial.[22] Although ethnic diversity in metabolism of irinotecan has been suggested, the dosage of irinotecan is commonly higher in Western countries than in Asian countries. This may explain the different incidence of severe diarrhea between this and other studies.

Our study has several limitations. Participants were all Japanese; tumor biology may differ from that in Western patients.[25] In addition, a majority of patients received S-1 plus cisplatin as first-line chemotherapy, whereas S-1 is not popular in Western countries. However, a large, global phase III study (FLAGS [First-Line Therapy in Patients With Advanced Gastric Cancer Study] trial) demonstrated S-1 plus cisplatin to be similar in efficacy to fluorouracil plus cisplatin.[7] This difference in regimens used as first-line chemotherapy may have had little influence on interpretation of results of our study. Because patients with severe peritoneal metastasis were excluded from our study to avoid confounding effects of serious adverse events resulting from irinotecan, our results are not applicable to patients with severe peritoneal metastasis. Another trial is needed to determine the most appropriate treatment in such patients. As for statistical consideration, our hypothesis was 50% improvement in median OS in the irinotecan group over weekly paclitaxel group, and this resulted in a relatively small sample size. Therefore, if a small but true benefit existed in either group, this study may have been underpowered to detect it.

In conclusion, no difference in OS between paclitaxel and irinotecan groups was observed in this study. Both are considered reasonable second-line treatment options. The differences in toxicity profile and treatment schedule between both treatments will help in choosing either irinotecan or paclitaxel. Currently, several randomized trials investigating additional benefits of molecular targeting agents in second-line chemotherapy are planned or being conducted using weekly paclitaxel or irinotecan as a platform or reference regimen. The findings of our study are relevant to these future trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Shuichi Hironaka, Satoshi Morita, Narikazu Boku, Ichinosuke Hyodo
Administrative support: Takashi Ura, Isamu Okamoto, Narikazu Boku
Provision of study materials or patients: Shuichi Hironaka, Tomohiro Nishina, Toshikazu Moriwaki, Kensei Yamaguchi, Yasuo Hamamoto
Collection and assembly of data: Shuichi Hironaka, Shinya Ueda, Hirofumi Yasui, Tomohiro Nishina, Masahiro Tsuda, Takehiko Tsumura, Naotoshi Sugimoto, Hideki Shimodaira, Shinya Tokunaga, Toshikazu Moriwaki, Taito Esaki, Michitaka Nagase, Kazumasa Fujitani, Kensei Yamaguchi, Takashi Ura, Yasuo Hamamoto
Data analysis and interpretation: Shuichi Hironaka, Satoshi Morita, Isamu Okamoto, Ichinosuke Hyodo
Manuscript writing: All authors
Final approval of manuscript: All authors

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Affiliations

Shuichi Hironaka, Chiba Cancer Center, Chiba; Shinya Ueda and Isamu Okamoto, Kinki University, Osakasayama; Hirofumi Yasui, Shizuoka Cancer Center, Shizuoka; Tomohiro Nishina, National Hospital Organization Shikoku Cancer Center, Matsuyama; Masahiro Tsuda, Hyogo Cancer Center, Akashi; Takehiko Tsumura, Osaka Red Cross Hospital; Naotoshi Sugimoto, Osaka Medical Center for Cancer and Cardiovascular Diseases; Shinya Tokunaga, Osaka City General Hospital; Kazumasa Fujitani, Osaka National Hospital, Osaka; Hideki Shimodaira, Tohoku University Hospital, Sendai; Toshikazu Moriwaki and Ichinosuke Hyodo, University of Tsukuba, Tsukuba; Taito Esaki, National Kyushu Organization Kyushu Cancer Center, Fukuoka; Michitaka Nagase, Jichi Medical University, Shimono; Kensei Yamaguchi, Saitama Cancer Center, Saitama; Takashi Ura, Aichi Cancer Center Hospital, Nagoya; Yasuo Hamamoto, Tochigi Cancer Center, Utsunomiya; Satoshi Morita, Yokohama City University Graduate School of Medicine, Yokohama; and Narikazu Boku, St Marianna University School of Medicine, Kawasaki, Japan.

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