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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

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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.

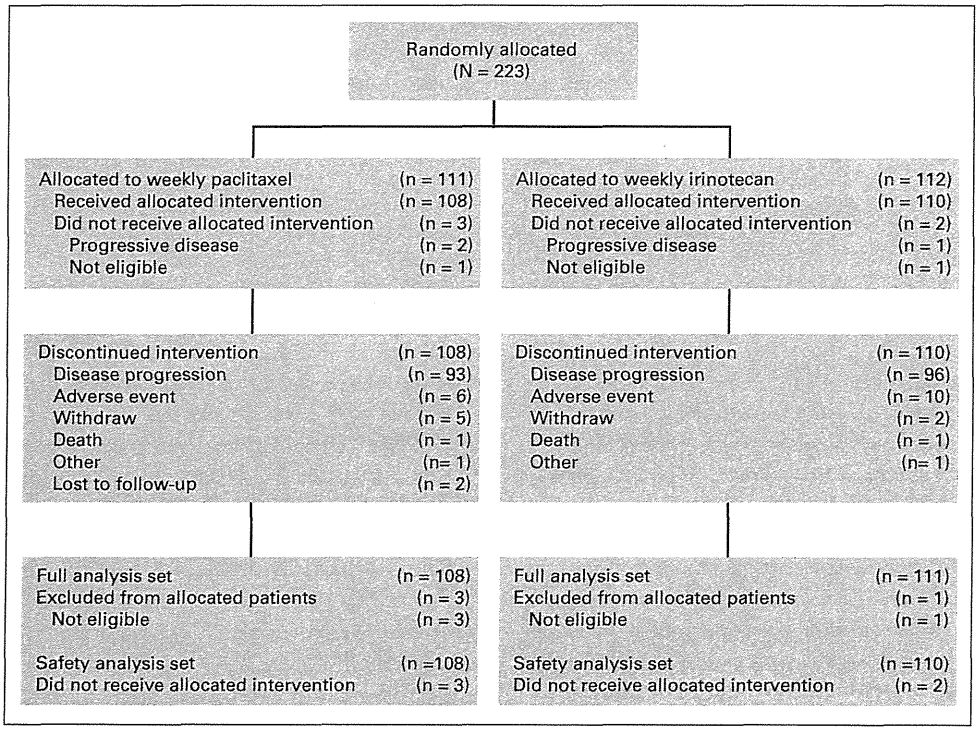

Fig 1. CONSORT diagram.

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 ≥ 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 ≥ 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.

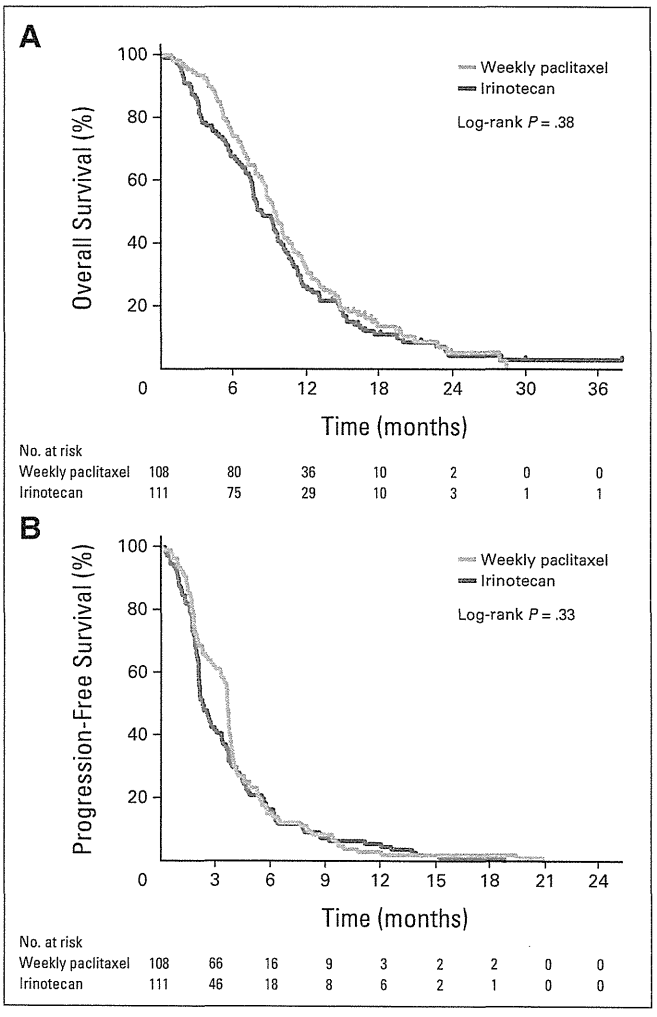

Fig 2. Kaplan-Meier curves of (A) overall and (B) progression-free survival.

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.

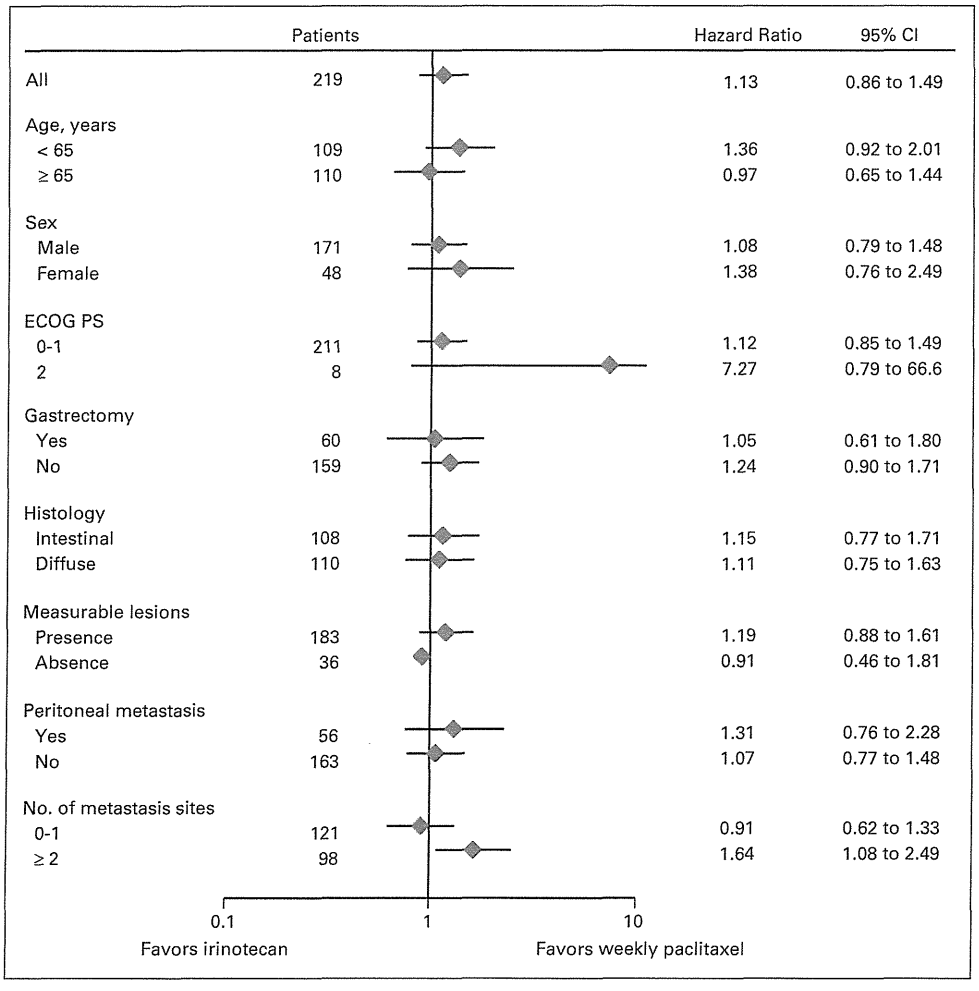

Fig 3. Forest plot of subgroup analyses. ECOG PS, Eastern Cooperative Oncology Group performance status.

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

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Original Paper

Significance of Surgical Treatment in Multimodal Therapy for Stage IV Highly Advanced Gastric Cancer

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ABSTRACT

Background/Aims: The purpose of this study was to evaluate the efficacy of surgical treatment following a response to chemotherapy to improve stage IV gastric cancer and to identify the factors contributing to survival benefit. **Methodology:** In total, 148 patients with cStage IV gastric cancer were treated with S-1 and CDDP. We retrospectively evaluated the factors contributing to a survival benefit and the significance of surgical treatment. **Results:** The 148 cStage IV patients included 107 males with a median age of 61 years. The overall response rate was 54.7%. After chemotherapy, 97 patients underwent surgery. R0 resection was successfully performed in 51 (52.6%) patients. The overall median survival time (MST) of the patients was 16.8 months, with a 5YSR of 16.4%. The MST of patients who went on to receive surgery was 22.5 months, and the 5YSR was 19.6%. In the multivariate analysis of 97 patients who underwent surgery, R0 resection, lymph node dissection of D2/D3 and obtaining a CR/PR from chemotherapy were the only independently prognostic factors. **Conclusions:** The use of multi-modal treatment, including surgical treatment, at an appropriate time was well tolerated and effective for patients with stage IV gastric cancer.

Key Words: Gastric cancer; cStage IV; Surgical treatment; Multimodal therapy.

INTRODUCTION

Currently, gastric cancer treatment incorporating individualization is being explored to improve the performance of new multimodal treatments including a combination of chemotherapy, radiation therapy and surgery. Postoperative chemoradiotherapy in the United States (1), and peri-operative ECF (epirubicin, cisplatin (CDDP), 5-FU) in Europe (2) are the standard treatments for adenocarcinoma of the stomach or gastroesophageal junction. On the other hand, adjuvant S-1 chemotherapy followed by D2 surgery has been established as a standard treatment in Japan (3). Nonetheless, the prognosis for stage III/IV tumors is not satisfactory in any of these regions, and evidence has not been established for stage IV gastric cancer (4). This retrospective study evaluated the significance of surgical treatment as part of multimodal therapy for cStage IV gastric cancer, and the factors contributing to a survival benefit were analyzed.

METHODOLOGY

Patients

Between October 2000 and April 2009, 236 consecutive patients underwent S-1+CDDP combination chemotherapy as the initial treatment for far advanced gastric cancer at our institution, and we have previously reported their outcomes (5). Among these patients were those who underwent surgical resection with curative intent after chemotherapy. As a result, we began to experience some cases of long-term survival. Of the 236 patients given S-1 + CDDP combination therapy, 148 patients with cStage IV gastric cancer were retrospectively reviewed to compare the outcomes between surgical and non-surgical treatments and to determine the appropriate timing of surgery and the optimal extent of resection.

Treatment schedule

All patients received systemic chemotherapy consisting of S-1 and CDDP. S-1 was orally administered at a dose of 80mg/m2 for 21 consecutive days, followed by 14 days of rest. CDDP was administered intravenously on day 8 at a dose of 60mg/m2 with hydration. The treatment was repeated every 5 weeks (6) and administered for at least two cycles. An objective measurable tumor response was evaluated using the response evaluation criteria in solid tumors (RECIST) version 1.0 (7) on the basis of the CT findings. The primary lesion, was not considered to be measurable by the RECIST criteria and was assessed by a barium contrast study and/or endoscopic examinations according to the Japan Gastric Cancer Association (JGCA) clinical criteria for response assessment of chemotherapy and radiotherapy (8). The pretreatment stage was diagnosed according to the JGCA staging system (8) on the basis of the CT, upper GI series, endoscopy and staging laparoscopic findings. Surgery after chemotherapy was indicated when diagnostic imaging confirmed a reduction or disappearance of the primary lesion or massive nodal metastases in response to chemotherapy, and when extended resection or combined resection with curative intent was considered possible. Patients who continued to have clear evidence of unresectable disease and those who did not respond to the chemotherapy were discouraged from receiving surgery. Surgery with intent to cure was performed 3 to 4 weeks after the final cycle of chemotherapy. The standard surgical procedure was gastrectomy with D2 nodal dissection. For an R0 resection, a para-aortic nodal dissection (D3), splenectomy and/or distal pancreatectomy, or a partial hepatectomy was attempted if the cytological findings were negative. Most patients were treated with S-1 monotherapy as adjuvant therapy after surgery. S-1 (80mg/m2/day, days 1-14) was administered every 3 weeks for 1 year. The treatments after R2 resection or upon detection of recurrent disease were decided at the discre-

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tion of each physician. The postoperative final tumor status was diagnosed comprehensively based on the clinical, surgical and pathological findings according to the criteria provided by the JGCA classification (8).

Statistical analysis

The terms used here are based on the Japanese classification of gastric carcinoma (8). Variables were expressed as the means ±SD. Comparisons between groups were performed using Student's t-test, the $\chi 2$ test and the Mann-Whitney U non-parametric test. The univariate and multivariate analyses using Cox's proportional hazards model were performed to identify independent prognostic factors. The median survival time (MST) and the 5-year survival rate (5YSR) were calculated from the time of initiation of chemotherapy to death. The survival analysis was performed using the Kaplan-Meier method. The log-rank test was used to calculate the statistical significance of the differences in the survival rates between the groups. A bilateral $p<0.05$ was considered to be significant.

Figure 1. Overall survival (n = 148)

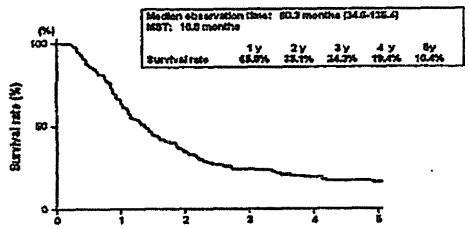

FIGURE 1. With a median follow-up of 80.3 months, the overall MST of the patients was 16.8 months, with a 5YSR of 16.4%.

Figure 2. Overall survival in the surgery and no-surgery groups as estimated by the Kaplan-Meier method

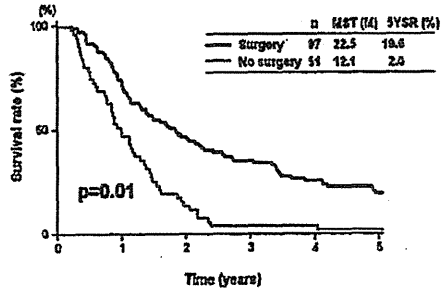

FIGURE 2. The MST of patients who went onto receive surgery was 22.5 months and the 5YSR was 19.6%. There was a statistically significant difference in the survival between these patients and those who did not receive a gastrectomy.

RESULTS

Patient demographics

The characteristics of the 148 cStage IV patients are shown in Table 1. There were 107 males and 41 females with a median age of 61 years. The distribution of the cStage IV factors included liver metastasis in 20 patients, peritoneal metastasis in 78 patients (including 36 POCY1 patients), involvement of abdominal para-aortic lymph nodes in 76 patients and locally advanced and potentially unresectable gastric cancer (cT4N2) in 14 patients. There were overlapping cases, i.e. 1 factor in 120 patients, 2 factors in 26 patients and 3 factors in 2 patients.

TABLE 1. Patient demographisc (n=148)

Value	No. of cases
Age median (range)	61(32-83)
Gender	male/female 107/41
PS	0/1/2 80/50/158
Location	L,M,U/LMU 114/34
Macroscopic type	1,2/3,4 29/119
Histology	diff./undiff. 56/90
cT	T2/T3/T4 3/131/14
cN	N0,N1/N2,N3 42/106
cH	H0/H1 128/20
cP	P0/P1 106/42
CY	0/1/X 22/65/61
Resection	Yes/No 97/51

TABLE 2. Clinical response to chemotherapy

	No. of case	CR	PR	SD	PD	NE	RR(%)	DCR(%)
Overall	148	1	80	53	13	1	54.7	90.5
Metastatic focus								
Lymph node	123	4	62	49	6	2	53.7	95.1
Liver	22	1	7	9	4	1	36.4	77.3
Peritoneum	63	0	9	50	2	2	14.9	96.8
Primary lesion	148	2	73	69	3	1	50.7	97.3

Clinical response to chemotherapy

Measurable lesions were confirmed in 141 patients. The objective response rate for these lesions, according to the RECIST, was 46.1%. As shown in Table 2, the overall response rate (ORR) was 54.7%. There were 81 responders (one complete response (CR) and 80 partial responses (PR)). The response rates for regional/para-aortic lymph nodes, liver metastases, peritoneal metastases and primary gastric tumors were 53.4% (66/123), 36.4% (8/22), 14.9% (9/63) and 50.7% (75/148), respectively. Fifty-four other patients (36.5%) had stable disease (SD) and only 13 patients (8.8%) had progressive disease (PD). Of the 81 responders, the residual tumor was completely resected in 32 (39.5%) patients. Out of the 88 patients who underwent staging laparoscopy, 69 were found to have peritoneal metastasis; of these, complete remission of the peritoneal dis-

ease was confirmed at surgery in 20 (29.0%) patients.

Surgery

After chemotherapy, 97 patients underwent surgery, and a gastrectomy was performed in all patients. The remaining 51 patients were not treated surgically, generally because of persistent metastatic disease after chemotherapy. The median number of chemotherapy courses, median number of cStage IV factors, and response rates significantly differed between patients with and without surgery (2 vs. 4, 1 vs. 2 and 58.8% vs. 49.0%, respectively; $p<0.05$). The patients who underwent surgery included 73 males and 24 females, with a median age of 61 years. The surgical procedure was a total gastrectomy in 56 patients and a distal gastrectomy in 41 patients. Fourteen patients underwent extended lymphadenectomy, and gastrectomy with D0/D1 resection was performed in 31 patients, and a total of 64 patients received a combined resection. The median hospital stay, duration of surgery and blood loss were 14 days, 200 minutes and 310mL, respectively. R0 resection was successfully performed in 51 (52.6%) patients. Postoperative complications were recognized in 19 patients. The pathological response rate was 40.2%. The distribution of the pStage was as follows; 1 patient in pathological CR, 14 patients in pStage I/II, 16 in pStage III and 66 in pStage IV. Downstaging was obtained in 31 (32.0%) patients (Table 3).

TABLE 3. Demographics of surgery group (n=97)

Value	
Total gastrectomy	56
Distal gastrectomy	41
Lymph node dissection	
D1	31
D2	52
D3	14
Combined resection*	
Spleen	32
Pancreas	11
Diaphragm	11
Liver	6
Others	37
Surgical stress median (range)	
Hospital stay (days)	14(9-195)
Duration of surgery (minutes)	200(90-406)
Blood loss (mL)	310(20-2460)
Residual tumor	
R0	51
R1	18
R2	28
R0 resection rate	52.60%
Complications	
Pancreatic fistel	8
Ileus	6
Abdominal abscess	2
Leakage	2
Pneumonia	1
Mortality	0
Pathological response	
Grade	
3	1
2	13
1b	25
1a	57
0	1
Pathological stage	
Pathological CR	1
p Stage	
I	8
II	6
III	16
IV	66

**include overlapping cases.*

Survival and analysis of prognostic factors

With a median follow-up of 80.3 months, the overall MST of the patients was 16.8 months, with a 5YSR of 16.4% (Figure 1). The MST of patients who went on to receive surgery was 22.5 months, and the 5YSR was 19.6%. There was a statistically significant difference in the survival between these patients and those who did not receive a gastrectomy (Figure 2). For all 148 patients included in the multivariate analysis, undergoing surgery (hazard ratio 0.373, $p<0.01$), obtaining a CR/PR following chemotherapy (0.307, $p<0.01$), and having one stage IV factor (0.359, $p<0.05$) were predictive of the overall survival (Table 4). In the univariate analysis of 97 patients who underwent surgery, a PS of 1 or less, 2 courses or fewer of chemotherapy, CY0 at surgery, cH0, obtaining a CR/PR following chemotherapy, lymph node dissection of D2 or more, pN1 or less, R0 and histological effects of 1b or more, were identified as significant prognostic determinants (Table 5). In the multivariate analysis of 97 patients who underwent surgery, R0 resection (0.109, $p<0.01$), lymph node dissection of D2/D3 (0.170, $p<0.05$) and obtaining a CR/PR from chemotherapy (0.221, $p<0.05$) were the only independently prognostic factors (Table 6).

DISCUSSION

According to the data of the Japanese stomach cancer registry in 2001, the 5YSR of patients with stage IV is extremely poor, at 15.8% (9), and the efficacy of surgery for stage IV patients is unknown (10,11). Further improvements in radical surgical techniques are unlikely to lead to any notable progress in the outcome (12,13). Thus, the present guidelines recommend the use of chemotherapy and other non-surgical treatments (4), and the development of an effective multimodal strategy has been sought. In recent years, the development of new anticancer drugs has improved the treatment outcomes. Chemotherapy performed in patients with hepatic metastasis, peritoneal dissemination, or distant lymph node metastasis resulted in a reduction of their tumor size or disappearance of metastatic foci, which often allows R0 surgery to be performed (14,15). Although chemotherapy is the standard of care for cStage IV metastatic gastric cancer, it does not cure the disease. However, if chemotherapy makes it possible to perform a R0 resection during the treatment process, it will be easier to control the dose and rest periods for the anticancer drugs that will be continuously required as postoperative adjuvant chemotherapy. Therefore, surgery remains an important option as a part of multimodal therapy for patients with resectable metastases. Nakajima et al. (16) reported that FLEP

therapy (5-FU, Leucovorin, etoposide, CDDP) yielded survival times of 12.7 months and 4.7 months in responders and non-responders, respectively. Gallard-Rincon et al. (17) reported that the survival time was 13.3 months in responders and 7.46 months in non-responders with combination therapy using CDDP, etoposide, leucovorin and 5-FU. Furthermore, Schumacher et al. (18) reported that when EAP therapy (etoposide, doxorubicin, CDDP) was administered to patients with stage III-IV disease, the survival time was 7.6 months in patients with non-curative resection, compared to 28.4 months in patients who were able to undergo curative resection. With regard to other types of cancer, surgical therapy performed at an appropriate time after chemotherapy is also useful for the treatment of hepatic metastases from colorectal cancer or recurrent GIST (19,20). In Japan, S-1 plus CDDP combination therapy is currently the first-line chemotherapy for unresectable/recurrent gastric cancer based on the results of the SPIRITS trial (21).The MST in the patients treated with S-1 plus CDDP was 13.0 months, and the RR obtained with this regimen was 54% in the present study. We have used this S-1 plus CDDP combination therapy regimen for unresectable/recurrent gastric cancer for several years. The advent of molecular-targeted drugs will contribute to further increase the response rate and/or the histological CR rate (22). An R0 resection is reported to be one of the most reliable prognostic indicators for patients after preoperative chemotherapy (23,24). Postoperative S-1 alone has proven to be beneficial for treating stage II and III gastric cancer (3). Hence, one of the potentially favorable multimodal treatments for stage IV gastric cancer would be a combination of preoperative administration of S-1 plus CDDP, subsequent gastrectomy with D2 or more lymphadenectomy to achieve R0, and postoperative S-1 administration. In the present study, the multi-modal treatment including surgery also showed good results in patients with poor-prognosis, highly advanced gastric cancer (stage IV). If curative resection is obtained by performing D2 or more dissection for chemotherapy responders, more favorable treatment outcomes will be obtained. The results of the present study indicate that the multi-modal treatment including surgical treatment at an appropriate time was well tolerated and effective for patients with stage IV gastric cancer.

TABLE 4. The results of the multivariate analysis of 148 patients.

Variables	hazard ratio	95% confidence limits	*p* value
Surgery/No surgery	0.373	(0.204-0.683)	0.001
Response (CR,PR/SD,PD)	0.307	(0.128-0.734)	0.004
No. of stage IV factors (~1/2)	0.359	(0.158-0.811)	0.013

TABLE 5. The results of the univariate analysis of the surgery group (n=97)

Variables	n	MST(M)	5YSR (%)	*p* value
PS				
0,1	83	23.0	22.2	
2	14	12.4	7.4	0.0324
No. of courses				
<2	67	18.3	18.2	
>2	30	26.1	23.3	0.0156
Location				
L,M,L	69	24.5	22.1	
LMU	28	13.7	14.3	0.0997
CY				
CY0	68	27.8	25.8	
CY1	29	13.5	3.4	0.0008
cH				
cH0	85	24.5	22.6	
cH1	12	10.0	0.0	0.0411
Response				
CR/PR	57	26.9	22.8	
SD/PD	40	16.0	15.4	0.0472
Dissection				
D0,1	31	13.4	6.5	
D2,3	66	26.9	26.2	0.0037
pN				
pN0,1	42	40.8	35.7	
pN2,3	55	14.0	7.4	0.0006
Residual tumor				
R0	48	41.8	38.3	
R1,2	49	13.4	2.0	<0.0001
Pathological response				
1a	59	16.9	20.7	
~1b	38	27.8	18.4	0.0434

TABLE 6. The results of the multivariate analysis of the surgery group (n=97)

Variables	Hazard ratio	95% confidence limits	*p* value
Residual tumor (R0,R1,2)	0.109	(0.028-0.429)	0.004
Dissection (D2,3/D0,1)	0.170	(0.039-0.739)	0.014
Response (CR,PR/SD,PD)	0.221	(0.056-0.817)	0.029)

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ORIGINAL ARTICLE

Comparison of the surgical treatment strategies for Siewert type II squamous cell carcinoma in the same area as esophagogastric junction carcinoma: data from a single Japanese high-volume cancer center

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Abstract

Purpose Siewert type II esophagogastric junction adenocarcinoma (ADC) and squamous cell carcinoma (SCC) existing in the same area have distinct clinicopathological characteristics. The objective of this study was to examine differences in the surgical treatment and survival data, according to the histological subtype, in a single high-volume cancer center.

Methods We retrospectively examined data from a total of 123 patients. Seventy-two patients with Siewert type II ADC and 51 patients with SCC in the same area.

Results In terms of the clinicopathological factors, the SCC patients had more advanced stage disease and thoracotomy was more frequently performed than in the ADC patients. The 5-year overall survival (OS) rates did not differ significantly between SCC and ADC, regardless of whether or not mediastinal, splenic hilum and para-aortic lymph node dissection was performed. Based on the calculated index for the frequency of nodal metastasis and the five-year OS rate for involvement at each level, only node nos. 1, 2, 3 and 7 had a high index (>5) in both groups. The multivariate Cox regression analysis showed that only age (<65), the pN category and residual tumor classification were independently associated with the outcome.

Conclusions Differences in the histological type of esophagogastric junction cancer were not independent prognostic factors for survival, and there appears to be a benefit to dissecting the number 1, 2, 3 and 7 lymph nodes.

Keywords Siewert type II · Squamous cell carcinoma · Surgical treatment

Introduction

In recent years in Western countries, the dominant histological subtype of carcinoma found in the lower esophagus and esophagogastric junction (EGJ) has shifted from squamous cell carcinoma (SCC) to adenocarcinoma (ADC) [1, 2]. While SCC still accounts for the majority of these malignancies in Japan, the current availability of *Helicobacter pylori* eradication therapy is anticipated to change the proportions of these cancers, giving rise to a trend similar to that observed in Western countries [3].

At the 2nd International Gastric Cancer Congress held in Munich in 1997, a consensus was reached to classify ADC in the EGJ into three subtypes according to the Siewert classification [4]. Using the anatomical classification of the esophagus, ADC of the EGJ was defined as ADC with esophageal invasion with the epicenter of a tumor within 5 cm of the EGJ in the TNM Classification of Malignant Tumors 7th Edition [5] In Japan, Nishi's classification system is also used to classify carcinoma of the gastric cardia, and cancer at the EGJ is defined as a tumor with the epicenter within 2 cm proximal and distal to the EGJ, regardless of its histological subtype [6–8].

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As described above, EGJ carcinoma comprises two histological subtypes, ADC and SCC. ADC and SCC have distinct predisposing risk factors and clinicopathological features. However, the carcinoma subtypes were not distinguished in some of the previous clinical trials, and it is unclear whether the optimal treatments differ among these subtypes [9]. For example, the most appropriate surgical procedures and extents of lymph node dissection for ADC and SCC [10], considered separately in the ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up, as well as in the NCCN Clinical Practice Guidelines in Oncology, have not yet been established. It is of the utmost importance to investigate the biological characteristics of ADC and SCC, and to identify the optimal treatment strategies for these distinct EGJ carcinomas [11].

Type II tumors, carcinomas of the true cardia, with the epicenter within an area 1 cm above and 2 cm below the cardia, in particular, are most likely to contain both ADC and SCC. Histologically specific treatment strategies, like those used in lung cancer and urinary bladder carcinoma, may be an important clinical issue, especially for SCC occurring at the same site as ADC. The objectives of this study were to examine the differences between SCC and ADC in terms of the surgical treatment, lymph node metastasis status and survival data, based on the histological subtype, in a single Japanese high-volume cancer center.

Methods

We diagnosed type II EGJ carcinoma if the epicenter was within 1 cm proximal and 2 cm distal to the anatomical EGJ based on a photograph of the resected specimen [12]. Between January 1985 and December 2008, a total of 6356 patients, 5658 patients with gastric carcinoma and 698 with esophageal carcinoma, underwent surgery at the Division of Surgery, Niigata Cancer Center Hospital, Niigata, Japan. We retrospectively examined the data from a total of 123 of these patients (72 with Siewert type II carcinoma undergoing at least D1 lymph node dissection and 51 patients with SCC in the same area with the lesion extending to the esophagus and stomach).

The tumor staging and nodal classification were performed according to the International Union Against Cancer (UICC) TNM staging system for EGJ cancer [5]. The lymph node levels were numbered according to the definition established by the Japanese Gastric Cancer Association and Japanese Esophageal Society [7, 8].

Surgical procedures

In principle, proximal or total gastrectomy without splenectomy via the abdominal approach was carried out for cT1 carcinoma, and thoracic esophagectomy or total gastrectomy with or without splenectomy via the thoracic or abdominal approach was carried out for cT2–T4 carcinoma. All procedural decisions were made by the primary surgeon.

Statistical analysis

Variables were expressed as the mean ± SD. Comparisons between groups were performed with Student's t test, the χ^2 test and the Mann–Whitney U nonparametric test. The multivariate analyses using Cox's proportional hazards model were performed to identify independent prognostic factors. The calculated mean survival time (MST) and the 5-year overall survival (OS) rates were calculated from the initiation of surgery until death. A survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to calculate the statistical significance of the differences in OS rates between groups. A two-tailed value of $p < 0.05$ was considered to indicate a statistically significant difference. We evaluated the therapeutic benefit obtained by node dissection at each lymph node level, based on the index of the estimated benefit of lymph node dissection calculated by multiplying the incidence of metastasis by the 5-year OS rate of patients with metastasis at each node level [13].

Results

Patient backgrounds and surgical procedures

With regard to the clinicopathological factors, SCC had more invasive characteristics, including more extensive esophageal invasion, deeper tumor invasion and more advanced pathological stages, than ADC. Furthermore, the intestinal type was more frequently observed in SCC patients (Table 1).

Thoracic esophagectomy via right thoracotomy or a left thoracoabdominal (TA) approach was more frequently performed in SCC patients, whereas total gastrectomy with caudal pancreatectomy and splenectomy via the abdominal-transhiatal (TH) approach were the most common procedures for ADC (Table 1).

Treatment results and survival

The median follow-up was 9.0 years (range 3.8–24.8). The MST was 48.8 months, and the 5-year OS rate was 45.1 % for the SCC patients. The corresponding values for the ADC patients were 60.2 months and 47.2 %. Thus, there were no significant survival differences between the SCC and ADC patients (Fig. 1).

Table 1 Demographics and surgical procedures of the 123 patients with EGJ carcinoma

	SCC (51)	ADC (72)	*p* value
Tumor size (cm)	5.8 ± 2.0	5.3 ± 2.7	0.2839
Length of esophageal invasion (cm)	3.1 ± 1.8	1.8 ± 1.2	<0.0001
Macroscopic type			
Borrmann Type 1, 2	47 (92.2)	42 (58.3)	
Borrmann Type 3, 4	4 (7.8)	30 (41.7)	<0.0001
Histological type			
Differentiated type	37 (72.5)	48 (66.7)	
Undifferentiated type	14 (27.5)	24 (33.3)	0.5392
Depth of tumor invasion			
pT1/2	6 (11.8)	37 (51.4)	
pT3/4	45 (88.2)	35 (48.6)	<0.0001
Lymph node metastasis			
Negative	17 (33.3)	27 (37.5)	
Positive	34 (66.7)	45 (62.5)	0.5546
Peritoneal metastasis			
Negative	51 (100)	70 (97.2)	
Positive	0 (0.0)	2 (2.8)	0.2462
Liver metastasis			
Negative	51 (100)	70 (97.2)	
Positive	0 (0.0)	2 (52.8)	0.2462
Venous invasion			
Negative	25 (49.0)	29 (40.3)	
Positive	26 (51.0)	43 (59.7)	0.2550
Lymphatic invasion			
Negative	10 (19.6)	17 (23.6)	
Positive	41 (80.4)	55 (76.4)	0.6089
Stage			
I/II	18 (35.3)	37 (51.4)	
III/IV	33 (64.7)	35 (48.6)	0.0004
Residual tumor			
R0	46 (90.2)	67 (93.1)	
R1/2	5 (9.8)	5 (6.9)	0.6133
Length of operation (min)	249 ± 63	225 ± 88	0.3470
Blood loss (ml)	216 ± 150	259 ± 217	0.5095
Approaches			
Right thoracotomy	11 (21.6)	2 (2.8)	<0.0001
Left thoracophrenicolaparotomy	25 (49.0)	20 (27.8)	0.0035
Laparotomy	15 (29.4)	50 (69.4)	<0.0001
Combined resection			
Spleen	23 (43.1)	42 (58.3)	0.0474
Pancreas	5 (9.8)	21 (29.2)	0.0011

0; %

pT pathological depth of tumor invasion, *pT1* invasion of the mucosa or submucosa, *pT2* invasion of the muscularis propria, *pT3* invasion of the subserosa, *pT4* invasion of the serosa

The 5-year OS rates also did not differ significantly between SCC and ADC patients with/without dissection of the lower mediastinal lymph nodes, such as Nos. 108, 110, 111 and 112. There were no differences in the five-year OS rates between SCC and ADC patients with/without splenic hilum (No. 10) and para-aortic (No. 16) lymph node dissection.

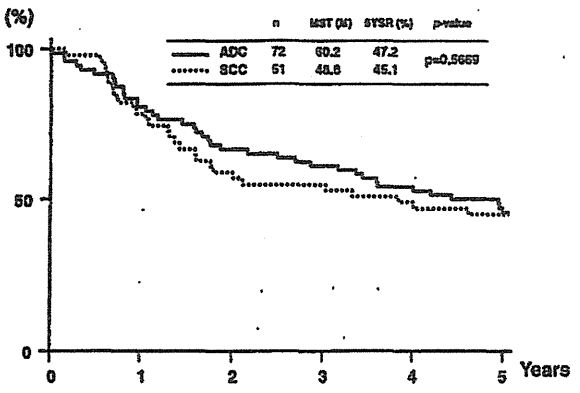

Fig. 1 Overall survival after resection of esophagogastric junction carcinoma according to histologic subtype

Distributions of the metastatic nodes and the index of estimated benefit from lymph node dissection

As shown in Table 2, nodal metastases frequently involved the abdominal lymph nodes, followed in frequency by node Nos. 1, 3, 2 and 7 in both ADC and SCC patients. Mediastinal lymph node dissection was performed in a total of 84 patients, and the metastatic rate was 22.9 % in SCC patients and 13.9 % in ADC patients. The metastatic rate of the No. 10 lymph node was low, at 0 % in SCC and 7.0 % in ADC patients. Only 31 patients underwent No. 16 lymph node dissection, and the metastatic rate was 28.6 % in SCC and 20.8 % in ADC cases (Table 2). Extended lymph node dissection was performed for regions where metastasis was suspected based on the preoperative clinical imaging findings.

Table 2 Distribution of the metastatic nodes and index of the estimated benefit from lymph node dissection

Lymph node station	SCC (51)					ADC (72)				
	Dissected cases	Metastasis cases	Metastatic rate	5YSR of metastasis cases	Index	Dissected cases	Metastasis cases	Metastatic rate	5YSR of metastasis cases	Index
1	49	20	40.8	27.8	11.3	72	33	45.8	24.2	11.1
2	49	9	18.4	33.3	6.1	72	16	22.2	37.5	8.3
3	49	17	34.7	33.3	11.6	72	29	40.3	27.6	11.1
4s	37	0	0	–	0.0	57	1	1.8	0	0.0
4d	35	0	0	–	0.0	66	2	3.0	50	1.5
5	31	0	0	–	0.0	60	1	1.7	0	0.0
6	36	1	2.8	0	0.0	63	3	4.8	33.3	1.6
7	47	9	19.1	33.3	6.4	71	20	28.2	20	5.6
8a	44	1	2.3	0	0.0	66	5	7.6	20	1.5
9	45	4	8.9	0	0.0	69	11	15.9	9.1	1.4
10	24	0	0	–	0.0	43	3	7.0	33.3	2.3
11p	39	5	12.8	20.0	2.6	64	6	9.4	16.7	1.6
11d	30	0	0	–	0.0	40	0	0	–	0.0
12a	6	1	16.7	0	0.0	36	0	0	–	0.0
16	7	2	28.6	0	0.0	24	5	20.8	20	4.2
a2lat	6	1	16.7	0	0.0	21	5	23.8	20	4.8
a2int	1	1	100	–	0.0	3	1	33.3	0	0.0
b1lat	4	1	25.0	0	0.0	10	1	10.0	0	0.0
b1int	0	0	0	–	0.0	6	0	0	–	0.0
ML	48	15	31.3	9.1	2.1	36	5	13.9	20	2.8
108	21	1	4.8	50.0	2.4	9	0	0	–	0.0
110	46	14	30.4	14.7	4.5	34	4	11.7	25	2.9
111	36	3	8.3	0	0.0	32	0	0	–	0.0
112	12	1	8.3	0	0.0	8	1	12.5	0	0.0

An index of the benefit gained by the dissection of each station was calculated by multiplication of the frequency of metastasis at the station by the 5-year survival rate of patients with metastasis at that station; metastatic rate × 5-year OS/100

Table 3 The total number of cases with lymph node metastasis with and without mediastinal lymph node metastasis

	All $n = 84$	SCC $n = 48$	ADC $n = 36$
Mediastinal LN metastasis (+)	6.7 ± 5.8	5.3 ± 3.5	9.8 ± 8.8
Mediastinal LN metastasis (−)	2.5 ± 3.6	2.0 ± 3.1	3.0 ± 4.1
p value	0.0003	0.0047	0.0063

Table 4 The number of patients with each site of first recurrence

	SCC	ADC	Total
Hematogenous	10	15	25
Liver	8	9	17
Lung	0	3	3
Bone	2	1	3
Brain	0	1	1
Skin	0	1	1
Lymphatic	11	3	14
Para-aortic	5	1	6
Mediastinal	3	0	3
Cervical	2	1	3
Other abdominal	1	1	2
Peritoneal	1	8	9
Local	1	0	1

Based on the index calculated employing the frequency of nodal metastasis and the 5-year OS rate for involvement at each lymph node level, only node Nos. 1, 2, 3 and 7, in both SCC and ADC patients, had a high index (>5). Although the estimated therapeutic index of lymph node dissection was 5 or less, the dissection of No. 110 in SCC and dissection of No. 16a2 lat in ADC patients were found to be effective (Table 2).

Lymph node metastasis status, recurrence sites and the results of the multivariate cox regression analysis

In 16 patients with mediastinal lymph node metastasis, the average total number of metastatic lymph nodes was 6.7, which was significantly higher than that (2.5) in the 68 patients who were positive for metastasis to only the abdominal lymph nodes. Similar results were obtained when metastases were examined according to the histological subtypes of SCC and ADC (Table 3).

Hematogenous metastasis was noted in 25 (10 SCC and 15 ADC) patients, and liver metastasis accounted for 17 of these patients. Lymphatic metastasis was observed in 14 (11 SCC and 3 ADC) patients; No. 16 lymph node metastasis in six patients, and mediastinal and cervical lymph node metastases in three patients each (Table 4).

Table 5 The results of the multivariate Cox regression analysis for the overall survival in patients with EGJ carcinoma ($n = 123$)

Variables	Hazard ratio	95 % confidence limits	p value
Age (< 65/≥ 65)	0.365	(0.215–0.618)	<0.01
Lymph node metastasis (n (−)/n (+))	0.370	(0.205–0.666)	<0.01
D-number (D0/D1, D2)	0.398	(0.158–0.998)	<0.01

A multivariate Cox regression analysis showed that only the age (<65 years), pN category (pN0) and residual tumor classification (R0) were independently associated with the outcome. Neither the histological subtype nor lower mediastinal, No. 10 and 16 node dissections were independently associated with the outcomes (Table 5).

Discussion

No standard procedure has yet been established for the surgical treatment of EGJ carcinoma in terms of the presence/absence of the need for thoracotomy, extent of esophageal and gastric resection, extent of mediastinal and abdominal lymph node dissection and the need for splenectomy. In the present study, we identified clear differences in the clinicopathological factors, approaches and surgical procedures used for SCC and ADC in our center.

A Dutch trial involving patients with Siewert type I/II carcinoma, treated in two high-volume centers, examined the superiority of two-field lymphadenectomy via the right TA over D1 lymphadenectomy via the TH approach [14]. It was recommended that right TA be performed for patients with type I tumors and TH for those with type II carcinoma based on a subsequent subset analysis [15].

In Japan, a randomized controlled trial (RCT) was conducted by the Stomach Cancer Study Group of the Japan Clinical Oncology Group to compare the left TA approach with the abdominal-TH approach in patients with Siewert Type II/III carcinoma (JCOG9502) [16]. The results failed to demonstrate the superiority of the left TA approach in terms of the OS. Accordingly, it was concluded that the abdominal-TH approach with para-esophageal lymph node dissection to a feasible extent should be recommended for Siewert Type II/III tumors.

Moreover, based on a study involving 1,002 patients, Siewert et al. [17] justified applying right TA for type I carcinoma of the esophagus and the abdominal-TH approach and D2 dissection of abdominal lymph nodes for type II and III gastric tumors. In addition, Yamashita et al.

[18] examined the optimal extent of lymph node dissection for Siewert type II carcinoma in a study including 225 patients, and determined that dissection of the paracardial and lesser curvature nodes is essential for achieving the therapeutic benefit of surgery. However, all of these studies were conducted for ADC. Therefore, further studies are needed to investigate the effects of histological differences on the distribution of lymph node metastasis and outcomes. However, to the best of our knowledge, there have been no reports on the surgical procedures or survival data based on the tumor histology of EGJ carcinoma.

The survival data in our series included a MST of 60.2 months and a 5-year OS rate of 47.2 % for ADC patients. The index calculated employing the frequency of nodal metastasis and the 5-year OS rate for involvement at each lymph node level indicated that the only lymph nodes which should be dissected were Nos. 1, 2, 3 and 7 in ADC patients. The multivariate Cox regression analysis showed that age, the pN category and the residual tumor classification were independently associated with the outcome. These results are in good agreement with those obtained in other studies [14, 16–19]. Therefore, the data from our series are highly consistent with those of previous studies, indicating the reliability of our present investigation.

In our series, the clinicopathological background factors and surgical procedures differed between the SCC and ADC groups, while there were no significant differences in the outcomes or therapeutic benefits provided by lymph node dissection. However, only three of the 51 SCC patients did not undergo mediastinal lymph node dissection. Because of this possible bias in the data, we cannot directly assess the clinical significance of mediastinal lymph node dissection in SCC cases.

The rate of mediastinal lymph node metastasis in our series was 22.9 % (11/48) in SCC and 13.9 % (5/36) in ADC patients, which was not significantly different. In addition, the values of the index of estimated benefit from the mediastinal lymph node dissection were similar in SCC and AC cases (2.9–2.2).

In our series of 123 patients, none exhibited mediastinal lymph nodes metastasis alone, suggesting that metastasis to mediastinal lymph nodes basically occurs after that to abdominal lymph nodes. In 16 patients with mediastinal lymph nodes metastasis, the average total number of metastatic lymph nodes was 6.7, which was significantly higher than that (2.5) in the 68 patients who were positive only for metastasis to abdominal lymph nodes. Similar results were obtained when the metastases were examined according to the histological subtypes. These results indicate that metastasis of EGJ carcinoma of Siewert type II occurs first to the abdominal lymph nodes, and then to mediastinal lymph nodes, regardless of the histopathological subtype of the tumor. Thus, patients with mediastinal lymph node metastasis probably already have abdominal lymph node metastasis, and the total number of metastatic lymph nodes would inevitably be high. Consequently, the addition of mediastinal lymph node dissection with additional thoracotomy may not provide a meaningful clinical benefit.

Our examination of the recurrence sites revealed that hematogenous recurrence, mainly in the liver, accounted for the majority of relapses in both SCC and AC, followed by No. 16 lymph node recurrence. Only three SCC patients and none of the ADC patients had mediastinal lymph nodes recurrence. This revealed hematogenous metastasis to the liver to be common in EGJ carcinoma cases, an observation consistent with other studies [18, 20].

Perioperative chemo-radiotherapy for EGJ carcinoma, including SCC, reportedly improves the outcomes [9]. Since patients with EGJ carcinoma are potentially at high risk of hematogenous micrometastasis, prophylactic dissection of mediastinal lymph nodes would offer no apparent benefits in terms of the local control or prognostic improvement. Among our patients with mediastinal lymph nodes metastasis, one SCC patient with three metastatic nodes (one at No. 108 and two at No. 110), and only one ADC patient with one metastatic lymph node, at No. 110, survived longer than 5 years. Based on these findings, we speculated that the effectiveness of mediastinal lymph node dissection is nearly as low in SCC as it is in ADC.

Conclusions

Overall, taking the surgical invasiveness into account, it can be assumed that the appropriate procedures for both SCC and ADC include dissection of the abdominal lymph nodes, focusing on the paracardial area and the lesser curvature of the stomach, para-esophageal lymph nodes (No. 110) for SCC, and a part of the para-aortic lymph nodes (No. 16 a2 lat) for ADE via the abdominal-TH approach.

A multivariate Cox regression analysis showed that histological subtype (SCC and ADE) was not an independent prognostic factor.

In this study, two datasets for esophageal and gastric tumors treated in our center were integrated for the analysis. Thus far, patients with lesions on the esophageal side have undergone esophageal surgery performed by specialists, while those with lesions on the gastric side have been treated by surgeons specializing in gastric surgery. This historical background may have yielded apparently contradictory outcomes. Further evidence is needed to confirm the present findings and establish the outcomes of each of the skilled approaches used for SCC and ADC. Such evidence is needed to prepare for the anticipated increase in the number of patients with EGJ carcinoma.

Conflict of interest The authors have no conflicts of interest to declare.

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