Table 6 JCOG phase II trials of neoadjuvant chemotherapy for extensive nodal disease

Study	Number of patients	Trial type	Test arm	Primary endpoint	TRD	3y-OS	Pathological response
JCOG 0001	55	Phase II single arm	CPT/CDDP X2 → D3	3y-OS/TRD	5.5 %	27 %	15 %
JCOG 0405	53	Phase II single arm	S-1/CDDP X2 → D3	%R0 resection	0.0 %	58.8 %	51 %
JCOG 1002	50	Phase II single arm	DCSX2 → D3 → S-1	%Clinical response	–	–	–

TRD treatment-related death, *3y-OS* 3-year overall survival rate

Table 7 JCOG phase II or III trials of neoadjuvant chemotherapy for scirrhous type

Study	Number of patients	Trial type	Test arm	Primary endpoint	OS	%TRC	Pathological response
JCOG 0002	55	Phase II single arm	S-1X2 → D2	2y-OS	59 %/2y	81 %	33 %
JCOG 0210	50	Phase II single arm	S-1/CDDP X2 → D2	%Treatent completion (%TRC)	24.5 %/3y	73.5 %	51.0 %
JCOG 0501	316	Phase III	S-1/CDDP → D2 → S-1	3y-OS	–	–	–

OS overall survival, *2y-OS* 2-year overall survival rate, *2y* 2-year overall survival rate, *3y* 3-year overall survival rate, *%TRC* %treatment completion

underwent R0 resection was greater than 50 %, and a sample size of 50 was calculated to ensure sufficient precision when the %R0 resection was 65 %. A total of 53 patients were enrolled. The feasibility and safety of S-1 and CDDP were found to be superior compared with that of CPT-11 + CDDP of JCOG-0001. The %R0 resection was 88 %, which met the primary endpoint. The 3-year overall survival rate was 58.8 %, which was extremely high compared with the 27 % observed in the JCOG-0001 and the 10 % historical control. A triplet regimen of docetaxel, S-1 and CDDP (DCS) is now being tested in a single arm Phase II trial (JCOG-1002).

For patients with scirrhous gastric cancer, two trials have been completed and one Phase III trial is now ongoing (Table 7). The JCOG-0002 Phase II study was conducted to evaluate the safety and efficacy of neoadjuvant chemotherapy consisting of two courses of S-1, followed by curative gastrectomy [45]. The primary end point was to determine whether the 2-year survival rate was 60 %, which was 15 % higher than the historical control of 45 %. The required sample size was calculated to be 55. Although treatment with S-1 was determined to be feasible and safe, the 2-year survival rate was 59 %, which did not quite meet the primary end point. Neoadjuvant chemotherapy with S-1 + CDDP was evaluated in the subsequent JCOG-0210 Phase II study [46]. The primary goal was to determine whether the proportion of curative resection was greater than 45 % at the lower limit of the 95 % interval and whether it reached to 60 % at the expected value. The sample size required to demonstrate a significant difference was calculated to be 50. The proportion of curative resection was 62 %, which met the primary end point. Based on these findings, a Phase III trial was conducted to compare the survival benefit of neoadjuvant chemotherapy consisting of two courses of S-1 + CDDP, followed by surgery and postoperative adjuvant S-1 chemotherapy, with those of standard therapy consisting of primary surgery, followed by postoperative adjuvant S-1 chemotherapy (JCOG-0501). This trial is now ongoing.

The use of neoadjuvant chemotherapy for stage III disease or tumors invading the serosa has also been evaluated by other groups. The JACCRO conducted the GC-01 trial to confirm the safety and feasibility of one course of S-1 + CDDP, followed by curative surgery for serosa-positive gastric cancer that could be resected curatively [47]. A total of 50 patients were enrolled in the study. Surgery-related morbidity was observed in five of 49 patients without mortality, which confirmed the safety and feasibility of one course of S-1 + CDDP.

Questions to be answered in the future

As mentioned above, neoadjuvant chemotherapy consisting of two courses of S-1 + CDDP is promising and has been tested in a Phase III trial for scirrhous gastric cancer in Japan. Meanwhile, neoadjuvant chemotherapy consisting of three courses of ECF, combined with surgery and three postoperative courses of ECF, is currently the standard treatment in Europe. The main issues to be resolved in future studies are the optimal regimen and number of courses. To address these issues, two randomized Phase II trials are now ongoing (Table 8). One is the COMPASS trial comparing neoadjuvant chemotherapy using two and four courses of S-1 + CDDP, paclitaxel and CDDP with a two-by-two factorial design for stage III gastric cancer

Table 8 Randomized phase II trials of neoadjuvant chemotherapy to compare the regimens and courses

Study	Number of patients	Trial type	Test arm	Primary endpoint
COMPASS	80	Randomized phase II	S-1/CDDP X2 → D2	3y-OS
			S-1/CDDP X4 → D2	
			Paclitaxel/CDDP X2 → D2	
			Paclitaxel + CDDP X4 → D2	
COMPASS-D	120	Randomized phase II	S-1/CDDP X2 → D2 → S-1	3y-OS
			S-1/CDDP X4 → D2 → S-1	
			S-1/docetaxel/CDDP X2 → D2 → S-1	
			S-1/docetaxel/CDDP X4 → D2 → S-1	

3y-OS 3-year overall survival rate

[48, 49]. The other is the COMPASS-D trial comparing neoadjuvant chemotherapy using two and four courses of S-1 plus CDDP and S-1, CDDP and docetaxel with a two-by-two factorial design for macroscopically resectable serosa-positive gastric cancer [50]. The COMPASS and COMPASS-D trials should be able to answer these unresolved questions in the future.

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Accuracy of CT Staging of Locally Advanced Gastric Cancer after Neoadjuvant Chemotherapy: Cohort Evaluation within a Randomized Phase II Study

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ABSTRACT

Background. Accuracy of the radiologic diagnosis of gastric cancer staging after neoadjuvant chemotherapy remains unclear.

Methods. Patients enrolled in the COMPASS trial, a randomized phase II study comparing two and four courses of S-1 plus cisplatin and paclitaxel and cisplatin followed by gastrectomy, were examined. The radiologic stage was determined by using thin-slice computed tomography (CT) or multidetector low CT by following Habermann's method.

Results. A total of 75 patients registered in the COMPASS study who underwent surgical resection were examined in this study. The radiologic T and pathologic T stages were not significantly correlated ($p = 0.221$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 42.7, 10.7, and 46.7%, respectively. When patients were stratified according to the pathologic response of the primary tumor, the correlation was not significant in either the responders ($n = 32$, $p = 0.410$) or the nonresponders ($n = 43$, $p = 0.742$). The radiologic accuracy was 37.5% in the responders and 42.7% in the nonresponders. The radiologic N and pathologic N stages were significantly correlated ($p = 0.000$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 44, 29.3, and 26.7%, respectively. When stratifying the patients with measurable lymph nodes according only to the radiologic response, the correlation was significant in the nonresponders ($n = 23$, $p = 0.035$) but not in the responders ($n = 28$, $p = 0.634$). The radiologic accuracy was 39.3% in the responders and 52.1% in the nonresponders.

Conclusions. Restaging using CT after neoadjuvant chemotherapy for gastric cancer is considered to be inaccurate and unreliable. In particular, the radiologic T-staging determined after neoadjuvant chemotherapy should not be considered in clinical decision-making.

Gastric cancer is the second leading cause of cancer death worldwide, accounting for 736,000 deaths in 2008.[1] Complete surgical resection is essential for curing gastric cancer. Recent large phase III studies have demonstrated that multimodality treatment including surgery significantly improves the survival of locally advanced disease compared with surgery alone, postoperative adjuvant chemotherapy with S-1 in Japan, postoperative adjuvant chemotherapy with capecitabine plus oxaliplatin in Korea and the United States, and preoperative and postoperative chemotherapy with epirubicin, cisplatin, and fluorouracil in the United Kingdom.[2–8]

Neoadjuvant chemotherapy is a promising treatment for gastric cancer when considering intensive chemotherapy with a relatively toxic regimen.[2] Even with treatment

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including D2 gastrectomy and adjuvant chemotherapy, the prognosis of stage III tumors is not satisfactory.[5] Neoadjuvant chemotherapy has been tested in several phase III trials in eastern Asia where D2 gastrectomy and adjuvant chemotherapy is a standard treatment.[2] After administering neoadjuvant chemotherapy, physicians must evaluate tumor progression and the response to treatment in order to continue or stop the chemotherapy and to assess resectability with respect to surgery and determine the most appropriate surgical procedure to fit the tumor stage considering the benefits and risks of surgery.

Endoscopic ultrasonography (EUS) and computed tomography (CT) are standard approaches for staging primary gastric cancer. The diagnostic accuracy of T-staging is 77.1 to 88.9% on CT and 65 to 92.1% on EUS, whereas that of N-staging is 51 to 71% on CT and 63 to 78% on EUS.[9,10] However, there are no reliable data with respect to restaging after neoadjuvant chemotherapy. Previously, several small studies demonstrated that preoperative EUS is inaccurate in patients who receive neoadjuvant chemotherapy.[11,12] Regarding CT, Park et al.[13] reported that the accuracy of T- and N-staging after neoadjuvant chemotherapy using CT is 57 and 37%, respectively. However, the sample size was only 38 in their study, and the evaluation criteria for assessing tumor depth were not defined. Moreover, the criteria for determining nodal metastasis were not optimized.

To evaluate the radiologic accuracy of restaging after neoadjuvant chemotherapy using CT, the present study was conducted as an exploratory analysis of a randomized phase II study that strictly defined primary staging, neoadjuvant chemotherapy, restaging after neoadjuvant chemotherapy, and the surgical procedures.

PATIENTS AND METHODS

Patients registered into the randomized phase II COMPASS trial who received gastrectomy with nodal dissection were examined in this study. The details of the COMPASS trial have been described in a previous article.[14] Briefly, the key eligibility criteria included T2–3/N+ or T4aN0 in cases of scirrhous or junctional tumors, T2–3 with nodal metastasis to the major branched artery, T4aN+ , T4b, paraaortic nodal metastases, or resectable minimal peritoneal metastases confirmed on laparoscopy. The use of staging laparoscopy was mandatory to diagnose peritoneal metastasis. The eligible patients were randomized to receive two courses of S-1 plus cisplatin, four courses of S-1 plus cisplatin, two courses of paclitaxel plus cisplatin, or four courses of paclitaxel plus cisplatin. The primary end point of the COMPASS trial is the 3-year overall survival rate and will recruit 60 to 80 subjects. This study was conducted in a cohort of consecutive patients recruited into the COMPASS trial.

Regarding the S-1 plus cisplatin regimen, S-1 (80 mg/m^2) was given orally twice daily for the first 3 weeks of a 4-week cycle, and cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle, as previously described.[15] With respect to the paclitaxel plus cisplatin regimen, paclitaxel (60 mg/m^2) and cisplatin (25 mg/m^2) were administered on days 1, 8, and 15 as one course repeated every 4 weeks.[16] The neoadjuvant chemotherapy was discontinued in cases of documented disease progression, unacceptable toxicity, or withdrawal of consent.

Two to six weeks after the completion of neoadjuvant chemotherapy or when the tumors progressed during treatment, the patients proceeded to surgery. R0 resection was achieved with gastrectomy and standard D2 lymphadenectomy.[17] Paraaortic nodal dissection or combined resection of a small portion of the peritoneum or adjacent organs was permitted for curative intent; however, more invasive procedures, such as pancreaticoduodenectomy or Appleby's surgery, were not. When macroscopically curative surgery was achieved, the protocol treatment was terminated.

The radiologic diagnosis of T and N was determined by using thin-slice CT with a 5- to 7-mm thickness or multidetector low CT by following Habermann's method.[18,19] T1 tumors were defined as tumors that could not be found on images or that had focal thickening of the inner layer with a visible outer layer of the gastric wall and a clear fat plane around the lesion. T2 tumors were defined as tumors with focal or diffuse thickening of the gastric wall with transmural involvement and a smooth outer border of the wall or only a few small linear strands of soft tissue extending into the fat plane involving less than one-third of the tumor extent. T3 tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent or wide reticular strands surrounding the outer border of the tumor. T4 tumors were defined as tumors with obliteration of the fat plane between the gastric tumor and the adjacent organ or invasion of an adjacent organ. The regional lymph nodes were considered to be involved by metastases if they measured larger than 8 mm in the short-axis diameter. Tumor progression was evaluated according to the 7th edition of the International Union against Cancer TNM classification.[20,21] The radiologic response of the lymph nodes was evaluated according to version 1.0 of the Response Evaluation Criteria for Solid Tumors.[22] The surgical specimens were pathologically evaluated as grade 0 when degeneration and/or necrosis were absent within the tumor, grade 1a when these areas accounted for less than one-third of the tumor, grade 1b when these areas accounted for more than one-third and less than two-thirds of the tumor, grade 2a when these areas accounted for more

than two-thirds of the tumor, although tumor tissue apparently remained, grade 2b when only minimal tumor cells remained, and grade 3 when no residual tumor was detected.[17] Patients with grade 1b, 2a, 2b, or 3 tumors were classified as responders, whereas those with grade 0 or 1 tumors were classified as nonresponders.

All statistical analyses were performed by using the SPSS version 18.0 software program. Correlations between the two groups were analyzed with the chi-square test.

RESULTS

Between October 2009 and July 2011, a total of 83 patients were enrolled in the COMPASS study. All patients were eligible and received neoadjuvant chemotherapy. Among these 83 patients, 6 did not proceed to surgery because of tumor progression, 2 received bypass surgery because of peritoneal metastasis, and 75 underwent surgical resection and were entered into this study. The background characteristics of these 75 patients are shown in Table 1.

The relationship between the radiologic T and pathologic T stage is demonstrated in Table 2. No significant correlation was found in the 75 patients ($p = 0.221$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 42.7% (32 of 75), 10.7% (8 of 75), and 46.7% (35 of 75), respectively.

A pathologic response of the primary tumor was observed in 32 patients. When stratifying the patients according to the pathologic response (Table 3), the correlation was not significant in either the responders ($n = 32$, $p = 0.410$) or the nonresponders ($n = 43$, $p = 0.742$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 37.5% (12 of 32), 3.1% (1 of 32), and 59.4% (19 of 32), respectively, in the responders and

TABLE 1 Background of the patients ($n = 75$)

Variable	Data	
Age (years)	Median	66
	Range	32–80
Sex	Male/Female	53/22
Performance status	0/1	74/1
Macroscopic type	0	1
	1	5
	2	20
	3	34
	4	8
	5	7
Histologic type	Differentiated	14
	Undifferentiated	56
Clinical T	T2	1
	T3	6
	T4a	64
	T4b	4
Clinical N	N0	12
	N1	37
	N2	17
	N3	9
Regimen	Two courses of S-1 plus cisplatin	20
	Four courses of S-1 plus cisplatin	18
	Two courses of paclitaxel plus cisplatin	18
	Four courses of paclitaxel plus cisplatin	19

TABLE 2 Relationship between clinical T after neoadjuvant chemotherapy and pathologic T

Clinical T	Pathologic T						Total
	T0	T1	T2	T3	T4a	T4b	
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	2[a]	0[a]	2[b]	2[c]	0[c]	0[c]	6
T3	0[a]	3[a]	0[a]	6[b]	4[c]	1[c]	14
T4a	2[a]	3[a]	6[a]	18[a]	24[b]	1[c]	54
T4b	0[a]	0[a]	0[a]	1[a]	0[a]	0[b]	1
Total	4	6	8	27	28	2	75

[a] Overdiagnosis
[b] Accurate diagnosis
[c] Underdiagnosis

TABLE 3 Relationship between clinical T after neoadjuvant chemotherapy and pathologic T by stratifying the pathologic response of the primary tumor

Clinical T	Pathologic T						Total
	T0	T1	T2	T3	T4a	T4b	
Responder							
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	2[a]	0[a]	2[b]	1[c]	0[c]	0[c]	5
T3	0[a]	2[a]	0[a]	4[b]	0[c]	0[c]	6
T4a	2[a]	2[a]	4[a]	5[a]	6[b]	0[c]	19
T4b	0[a]	0[a]	0[a]	0[a]	2[a]	0[b]	2
Total	4	4	6	10	8	0	32
Nonresponder							
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	0[a]	0[a]	0[b]	1[c]	0[c]	0[c]	1
T3	0[a]	1[a]	0[a]	2[b]	4[c]	1[c]	8
T4a	0[a]	1[a]	2[a]	12[a]	18[b]	1[c]	34
T4b	0[a]	0[a]	0[a]	0[a]	0[a]	0[b]	0
Total	0	2	2	15	22	2	43

[a] Overdiagnosis
[b] Accurate diagnosis
[c] Underdiagnosis

46.5% (20 of 43), 16.3% (7 of 43), and 37.2% (16 of 43), respectively, in the nonresponders.

The relationship between the radiologic N and pathologic N stage is shown in Table 4. A significant correlation was found in all 75 patients ($p = 0.000$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 44% (33 of 75), 29.3% (22 of 75), and 26.7% (20 of 75), respectively. For the diagnosis of nodal positivity, the radiologic accuracy, sensitivity, and specificity were 70.7% (53 of 75), 84.9% (45 of 53), and 36.4% (8 of 22), respectively.

Fifty-one patients had measurable lymph nodes according to RECIST version 1.0. Among these patients, a radiologic response was observed in 28 cases. When the 51 patients with measurable lymph nodes were stratified according to the radiologic response (Table 5), the correlation was significant in the nonresponders ($n = 23$, $p = 0.035$) but not in the responders ($n = 28$, $p = 0.634$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 39.3% (11 of 28), 21.4% (6 of 28), and 39.3% (11 of 28), respectively, in the responders and 52.1% (12 of 23), 21.7% (5 of 23), and 26.1% (6 of 23), respectively, in the nonresponders.

TABLE 4 Relationship between clinical N after neoadjuvant chemotherapy and pathologic N

Clinical N	Pathologic N				Total
	N0	N1	N2	N3	
N0	8[a]	5[c]	3[c]	0[c]	16
N1	12[b]	9[a]	11[c]	0[c]	32
N2	2[b]	6[b]	15[a]	3[c]	26
N3	0[b]	0[b]	0[b]	1[a]	1
Total	22	20	29	4	75

[a] Accurate diagnosis

[b] Overdiagnosis

[c] Underdiagnosis

TABLE 5 Relationship between clinical N after neoadjuvant chemotherapy and pathologic N by stratifying the radiologic response of the lymph node

Clinical N	Pathologic N				Total
	N0	N1	N2	N3	
Responder					
N0	1[a]	0[c]	1[c]	0[c]	2
N1	6[b]	4[a]	4[c]	0[c]	14
N2	2[b]	3[b]	6[a]	1[c]	12
N3	0[b]	0[b]	0[b]	0[a]	0
Total	9	7	11	1	28
Nonresponder					
N0	0[a]	0[c]	0[c]	0[c]	0
N1	3[b]	3[a]	3[c]	0[c]	9
N2	0[b]	3[b]	8[a]	2[c]	13
N3	0[b]	0[b]	0[b]	1[a]	1
Total	3	6	11	3	23

[a] Accurate diagnosis

[b] Overdiagnosis

[c] Underdiagnosis

Discussion

This study evaluated the accuracy of radiologic diagnosis after neoadjuvant chemotherapy in 75 patients enrolled in the prospective randomized phase II COMPASS study, which predefined radiologic criteria for T- and N-staging. The radiologic overall accuracy was 42.7% for T-staging and 44% for N-staging. Previously, we examined the radiologic accuracy of primary staging determined according to the same criteria using CT in 315 patients with primary resectable gastric cancer and demonstrated that the radiologic accuracy was 71.4% for T-staging and 75.9% for N-staging.[19] Compared with the primary staging, restaging after neoadjuvant chemotherapy was found to be inaccurate and unreliable.

With respect to T-staging after neoadjuvant chemotherapy, the radiologic T and pathologic T stages were not significantly correlated. The overall accuracy was only 42.7%. These results suggest that T-staging using CT provides no clinical information and should not be considered in clinical decision-making. Previously, Park et al.[13] reported that the accuracy of T restaging was 47% on EUS and 57% on CT. The accuracy reported in their study was slightly better than that observed in the present results. In this study, the radiologic accuracy was 37.5% in the responders and 46.5% in the nonresponders, which suggests that the radiologic accuracy is affected by the response of the primary tumor. In Park and colleagues' study, the response rate and accuracy stratified according to the response were not demonstrated.[13]

Most cases of misdiagnosis of the T stage are due to overdiagnosis. Park et al.[13] also reported similar results. Chemotherapy acts on tumor tissue and induces a variety of changes of in both the tumor and stroma, including necrosis, inflammation, and fibrosis.[23] The depth of tumor invasion may become shallow if these changes occur in the tumor tissue. Chemotherapy-induced stromal changes can cause difficulties in distinguishing the wall layer of the stomach on CT, by which overdiagnosis and/or misdiagnosis can occur. When the T stage was examined by separating the patients according to the pathologic response of the primary tumor, the radiologic accuracy was lower and the rate of overdiagnosis was higher in the responders than in the nonresponders. However, the radiologic accuracy was not significantly high, even in the nonresponders. It should be clarified whether chemotherapy-

induced stromal changes occur regardless of the tumor response.

The radiologic N and pathologic N stages were significantly correlated even though the radiologic overall accuracy of N-staging was only 44%. Moreover, the radiologic accuracy and sensitivity of the diagnosis of nodal positivity were both high: 70.7 and 84.9%, respectively. These results suggest that N-staging using CT is not accurate for diagnosing each N category, although it is useful for diagnosing nodal positivity. Previously, Park et al. [13] reported that the accuracy of N restaging was 39% on EUS and 37% on CT, whereas that of nodal positivity was 68% on both EUS and CT in 38 patients. Their results support our data. The sensitivity for diagnosing nodal positivity in this study was high, at 84.9%; however, the specificity was low, at 36.4%, thus suggesting that radiologically determined positive findings are reliable, whereas negative findings are not.

We next examined the accuracy of N-staging by stratifying the radiologic nodal response. The radiologic accuracy was low, at 39.3%, in the responders and higher, at 52.1%, in the nonresponders, which suggests that the radiologic accuracy of N-staging decreases when metastatic nodes respond to chemotherapy. The rates of underdiagnosis and overdiagnosis were almost half in the overall cohort and the nonresponders; however, overdiagnosis was a major cause of misdiagnosis in the responders. Among the responders, eight (89%) of nine patients with pathologic N0 disease were radiologically misdiagnosed as being node-positive. This result suggests that the enlarged nodes did not disappear even though the nodal metastasis pathologically disappeared.

In conclusion, restaging of gastric cancer after neoadjuvant chemotherapy by using CT is inaccurate and unreliable. In particular, the radiologic T stage determined after neoadjuvant chemotherapy should not be considered in clinical decision-making.

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SHORT COMMUNICATION

Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer

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Abstract

Background We previously reported that S-1 plus cisplatin was feasible as adjuvant chemotherapy for stage III gastric cancer after D2 gastrectomy. Herein we evaluate the recurrence-free survival and overall survival rates as secondary endpoints based on updated follow-up data.

Methods Patients with stage III gastric cancer who underwent D2 gastrectomy were enrolled. Treatment consisted of 3 cycles of S-1 (40 mg/m^2 PO) twice daily on days 1–21 and cisplatin (60 mg/m^2 IV) on day 8, and S-1 was given on days 1–28 every 6 weeks until 1 year after surgery.

Results From August 2007 to September 2009, 63 patients were accrued. Overall, 34 and 25 patients had stage IIIA and IIIB disease, respectively. After a median follow-up of 3.9 years, 16 patients experienced recurrence and 11 patients died. The 3-year recurrence-free survival rate was 74.1 % (95 % CI: 60.8–83.5 %, IIIA 81.8 %, IIIB 64.0 %). The 3-year overall survival rate was 84.5 % (95 % CI: 72.3–91.6 %, IIIA 87.9 %, IIIB 80.0 %).

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Recurrence sites included the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$).
Conclusion The present results indicate that adjuvant therapy with S-1 plus 3 cycles of cisplatin may provide a survival benefit to patients with stage III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

In 2007, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated the efficacy of S-1 for stage II–III Gastric Cancer (GC) patients who underwent curative resection with D2 gastrectomy [1, 2]. The addition of S-1 improved the overall survival (OS) rate, with a low incidence of adverse events and good compliance. According to this result, in Japan, the currently recommended adjuvant treatment after D2 gastrectomy is S-1 for 1 year. However, the 5-year OS rates in stage III patients receiving S-1 have been less satisfactory: 67.1 and 50.2 % for stage IIIA and IIIB, respectively. Therefore, identification of more effective treatments for stage III GC is urgently needed. So firstly we evaluated the feasibility of S-1 plus cisplatin, that is now considered to be one of the standard regimens for metastatic or recurrent GC [3] as adjuvant chemotherapy for Stage III GC after D2 gastrectomy.

As results, treatment completion rates after 3 cycles of S-1 plus cisplatin were 72 % (42/58; 95 % CI: 60–84 %; 57 % [12/21] before and 81 % [30/37] after the protocol amendment). Grade 3/4 toxicities included neutropenia (40 %), anorexia (28 %), and febrile neutropenia (4 %) before the protocol amendment, and neutropenia (37 %), anorexia (8 %), and febrile neutropenia (3 %) after the amendment implementation. Therefore, we concluded that the amended S-1 plus cisplatin regimen is feasible as adjuvant chemotherapy [4].

In this report, we evaluate the recurrence-free survival (RFS) and OS as secondary endpoints based on updated follow-up data.

Methods

Patients eligible for this trial had either stage IIIA (T2,N2; T3,N1; T4,N0) or stage IIIB (T3,N2; T4,N1) [5] gastric adenocarcinoma and had undergone D2 gastrectomy with R0 surgical resection. Additional details were described as previously [4]. The protocol was approved by the institutional review board at each participating center. Treatment according to the original protocol was initiated 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin (SP) followed by S-1 for up to 1 year. In the SP step, each cycle consisted of 40 mg/m^2 S-1 taken orally twice-daily for 21 days plus a 2-hour infusion of 60 mg/m^2 cisplatin on day 8. Each cycle was administered at 5-week intervals. In the S-1 step, 40 mg/m^2 S-1 was taken for 28 days at 6-week intervals. During enrollment, some toxicity was reported during the first cycle of SP, particularly neutropenia and anorexia. To minimize patient's risk, we elected to amend the protocol. Treatment according to the amended protocol was initiated 4–6 weeks after surgery and consisted of the following: the first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 was administered for up to 1 year. Tumor assessments with ultrasonography, computed tomography, and GI endoscopy and radiography were performed every 6 months for first 2 years after surgery, and annually thereafter (maximum follow-up 5 years). RFS was defined as the time from enrollment to the recurrence or death, whichever occurred first. OS was defined as the time from enrollment to death from any cause.

Results

From August 2007 to July 2009, 63 patients (25 patients in the original protocol, 38 patients in the amended protocol) were accrued from five Japanese institutions. Overall, 34 patients (54 %) had stage IIIA disease and 25 (40 %) had stage IIIB disease. The patient clinical characteristics have been reported previously [4]. After enrollment, 5 patients were deemed ineligible due to confirmed stage II disease ($n = 2$), stage Ib disease ($n = 1$), stage IV disease ($n = 1$), and cancer other than GC ($n = 1$).

OS and RFS were analyzed in 58 eligible patients. At the time of data cut-off on July 31, 2012, 11 patients had died, 5 patients were alive with recurrence, and the remaining 42 patients were alive without recurrence. The median follow-up period was 46 months. All patients could be followed-up for at least 3 years from the date of surgery. Kaplan–Meier estimates are shown that the 3-year OS rate was 84.5 % (95 % CI: 72.3–91.6 %) (Fig. 1a); and the 3-year RFS rate was 74.1 % (95 % CI: 60.8–83.5 %) (Fig. 1b). According to disease stage, the 3-year OS rate of patients with stage IIIA disease was 87.9 % (95 % CI: 70.9–95.3 %) (Fig. 2a), and the 3-year RFS rate was 81.8 % (95 % CI: 63.9–91.4 %) (Fig. 2b). The 3-year OS rate of patients with stage IIIB disease was 80.0 % (95 % CI: 58.4–91.1 %) (Fig. 2a). The 3-year RFS rate was 64.0 % (95 % CI: 42.2–79.4 %) (Fig. 2b).

In addition, there was no significant difference in survival between the original protocol and the amended

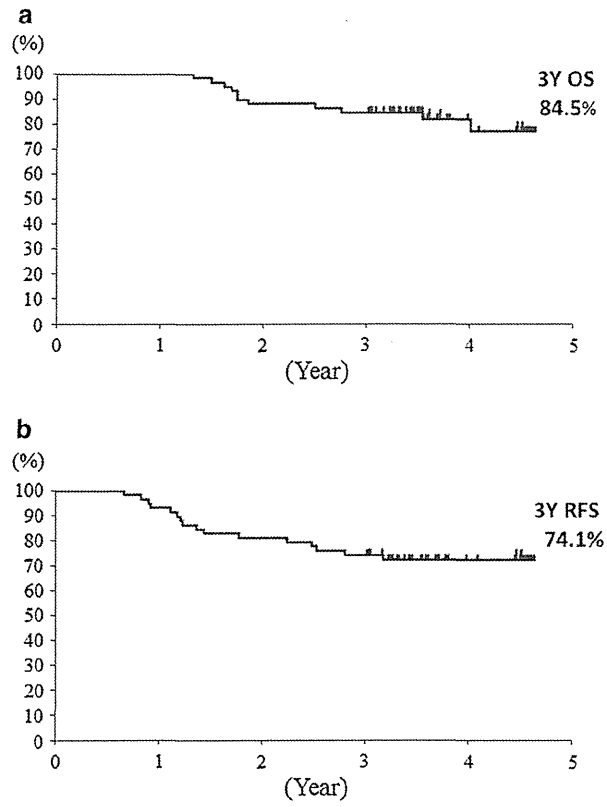

Fig. 1 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for all eligible patients

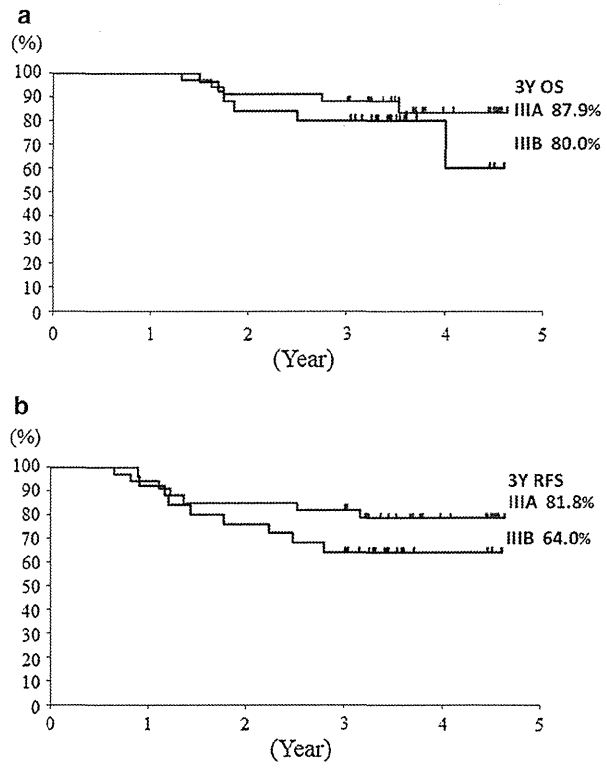

Fig. 2 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for patients with stage IIIA and IIIB gastric cancer

protocol. The 3-year OS rate of patients with stage IIIA disease in the original protocol ($n = 16$) and the amended ($n = 17$) was 87.5 and 88.2 %, respectively, and the 3-year RFS rate was 75.0 and 82.4 %, respectively. The 3-year OS rate of patients with stage IIIB disease was 80.0 % in the original protocol ($n = 5$) and the amended protocol ($n = 20$), and the 3-year RFS rate was 60.0 and 65.0 %, respectively.

The most common sites of relapse were the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$). Two patients experienced relapses simultaneously in the liver and the lymph nodes. No local relapse was observed. After relapse, the median survival time was estimated to be 351 days. Subsequent therapies were taxanes ($n = 7$), SP ($n = 4$), S-1 ($n = 3$), and CPT-11 ($n = 1$), and 1 case underwent surgery (oophorectomy) followed by paclitaxcel.

Discussion

In this study, postoperative S-1 plus 3 cycles of cisplatin demonstrated promising efficacy with respect to 3-year RFS and OS for stage III GC.

Recently, the results of the CLASSIC trial indicated that adjuvant capecitabine and oxaliplatin improved 3-year disease-free survival (DFS) compared with surgery alone in GC patients [6]. The subgroup analysis suggested that combined capecitabine and oxaliplatin were beneficial not only for stage II patients but also for stage IIIA and stage IIIB patients (the hazard rates compared to surgery alone were 0.57 and 0.57, respectively). This result suggests that combination therapy with fluoropyrimidine and a platinum agent may be more beneficial than fluoropyrimidine alone in patients with stage III disease after D2 gastrectomy.

Although small-sample comparisons should be made with caution, there was no significant difference in survival between the original protocol and the amended protocol. It is suggested that delay of cisplatin administration in our amended protocol didn't sacrifice the efficacy in terms of survival. Consequently, we believe that completion of 3 cycles of cisplatin is important, even though we changed the first cycle to S-1 monotherapy and delayed additional cisplatin until cycles 2, 3, and 4. Moreover, our amended protocol was beneficial in the reduction of grade 3/4 anorexia and nausea, even though we did not use NK-1 receptor antagonists, because they were not approved in Japan at that time. Now we could manage the

cisplatin-induced emesis easier by using NK-1 receptor antagonists with this regimen.

In conclusion, adjuvant therapy with S-1 plus 3 cycles of cisplatin may reduce recurrence and improve survival in patients with stage III GC who underwent D2 gastrectomy. This treatment should be considered for use as an experimental arm for comparison to S-1 in future postoperative adjuvant phase III trials.

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Conflict of interest The authors have declared no conflicts of interest.

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