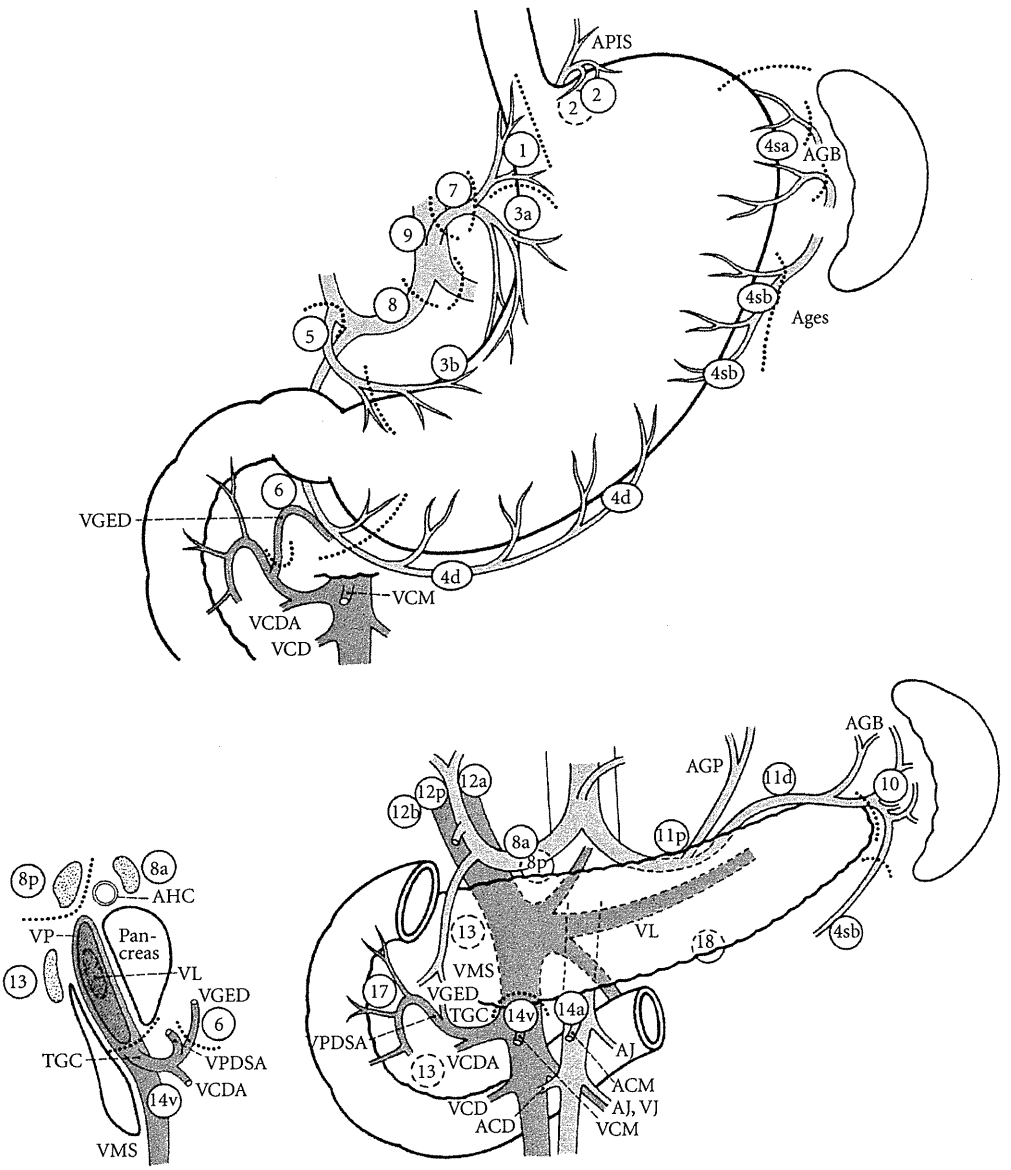

FIGURE 1: Lymph noses (LNs) are retrieved from the en bloc resected specimen and placed on the map exactly as they were in situ and numbered. Regional lymph node stations are defined as No. 1, right paracardial LN; No. 2, left paracardial; No. 3, LN along the lesser curvature; No. 4sa, LN along the short gastric vessels; No. 4sb, LN along the left gastroepiploic vessels; No. 4d, LN along the right gastroepiploic vessels; No. 5, suprapyloric LN; No. 6, infrapyloric LN; No. 7, LN along the left gastric artery; No. 8a LN along the common hepatic artery; No. 9, LN around the celiac artery; No. 10 LN at the splenic hilum; No. 11p, LN along the proximal splenic artery; No. 11d, LN along the distal splenic artery; No. 12a, LN in the hepatoduodenal ligament; No. 13, LN on the posterior surface of the pancreatic head; No. 14v, LN along the superior mesenteric vein; No. 16, LN around the abdominal aorta. APIS, left inferior phrenic artery; GB, short gastric artery; AGES, left gastroepiploic artery; VCM, middle colic vein; VGED, right gastroepiploic vein; VCDA, accessory right colic vein; VCD, right colic vein; AGP, posterior gastric artery; VL, splenic vein; AJ, jejunal artery; VJ, jejunal vein; ACM, middle colic artery; ACD, right colic artery; TGC, gastrocolic trunk; VMS, superior mesenteric vein; VPDIA, anterior inferior pancreaticoduodenal vein; AHC, common hepatic artery; VP, portal vein.

2.2. Patient Population. From 1994 to 2004, 505 patients with a single gastric adenocarcinoma located in the upper third portion underwent curative total gastrectomy at Niigata Cancer Center Hospital. Among them, 240 patients underwent total gastrectomy with splenectomy (ST), because the tumor involved the greater curvature or enlarged LN of No. 10 and/or No. 11. The remaining 265 patients underwent spleen-preserving lymphadenectomy (T) and remove No.

Table 1: Clinicopathological characteristics of the patients who underwent total gastrectomy with or without splenectomy (N = 505).

Characteristics	T N = 265 (%)	ST N = 240 (%)	P value
Age (year)			0.121
<70	163 (61.5)	18 (75.0)	
≥70	102 (39.5)	60 (25.0)	
Age (year)			0.481
Male	198 (74.7)	172 (71.7)	
Female	67 (25.3)	68 (28.3)	
Gross type			<0.001
Type 0, 1, 2	221 (83.4)	100 (41.7)	
Type 3, 4	44 (16.6)	140 (58.3)	
Tumor location			<0.001
U	191 (72.1)	159 (66.3)	
M, L	60 (22.6)	34 (14.2)	
UML	14 (5.3)	47 (19.6)	
Histological type			<0.001
Differentiated	151 (57.0)	97 (40.4)	
Undifferentiated	114 (43.0)	143 (59.6)	
Depth of invasion			<0.001
pT1, T2	228 (86.0)	78 (32.5)	
pT3, T4	37 (14.0)	162 (67.5)	
Lymph node metastasis			<0.001
pN0, N1	220 (83.0)	123 (51.3)	
pN2, N3	45 (17.0)	(48.8)	

* U; upper third, M; middle third, L; lower third.

11 but not No. 10. The clinicopathological features, stage and 5-year survival rates according to JCGC were compared between ST group and T group.

2.3. Procedures. Total gastrectomy with D2 and more extensive lymphadenectomy was performed according to the rules of the JCGC. The standard reconstruction was Roux-en Y method. In T group, No. 11 was dissected along the upper border of the pancreas but not No. 10 with or without mobilization of the spleen from the retroperitoneum. When the tumor involved the greater curvature and/or enlarged LN suspected metastasis at splenic hilum was found before or during operation, splenectomy was performed simultaneously as R0 resection. The index of estimated benefit from lymphadenectomy was calculated by multiplying the incidence of each nodal station by the 5-yer survival rate of patients with metastasis to that nodal station [9].

2.4. Statistical Analysis. All statistical analyses were conducted using the statistical program SPSS version 19 for Windows (SPSS, Chicago, IL, USA). Clinicopathological variables were analyzed using the chi-square test and the Student's t-test. The risk factors for No. 10 metastasis were determined using logistic regression analysis. Cumulative survival rates were calculated by the Kaplan-Meier method, and the significance of the differences in survival was determined by the log-rank test. P-value of <0.05 was considered statistically significant.

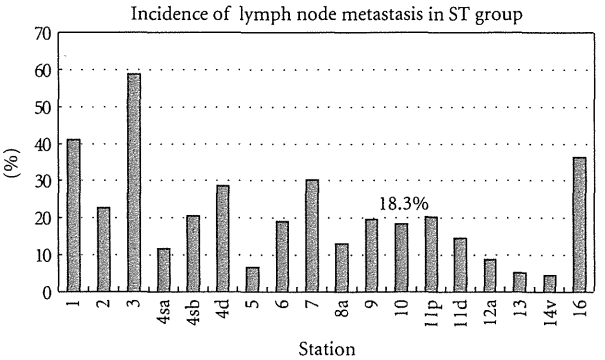

Figure 2: Incidence of each lymph node metastasis in ST group. The metastatic rate of the splenic hilar LN (No. 10) was 18.3%.

3. Results

3.1. Comparison of the Clinicopathological Features. Clinicopathological features are shown in Table 1. There was no statistical difference in age and gender between ST group and T group. But there were significant differences between two groups regarding gross type, tumor location, and histological type, depth of the tumor invasion, and status of lymph node metastasis. Namely, type 3 and type 4, UML (U; the upper, M; the middle, L; the lower), undifferentiated type, pT3 and pT4, and pN2 and pN3, are found frequently in ST group. Patients who underwent splenectomy showed more advanced lesions.

3.2. Perioperative Morbidity. Postoperative complications were listed in Table 2. There was no significant difference between two groups concerning nonsurgical complications. The incidence of surgical complications regarding anastomotic leakage, pancreatic fistula, postoperative ileus, and intra-abdominal bleeding was higher in ST group than in T group. But there was no statistical difference except for pancreatic fistula (P = 0.008).

3.3. Lymph Node Metastasis in ST Group. The lymph node metastatic rate in ST group was shown in Figure 2. No. 3 metastatic rate was highest (58.8%). The incidence of No. 10 metastasis was 18.3%, which was similar to that of No. 4sb (20.5%), No. 6 (19%), No. 9 (19.5%), and No. 11p (20.2%). No. 16 metastatic rate was 36.3% which was unexpectedly high.

The 5-year survival rate was 22.2% in patients with No. 10 metastasis and 50.8% in patients without its metastasis in ST group (Figure 3).

3.4. The Therapeutic Value of Lymph Node Dissection. The therapeutic value of extended lymph node dissection was estimated by multiplication of incidence of lymph node

Table 2: Perioperative morbidity following total gastrectomy with or without splenectomy.

Complication	T (without splenectomy)	ST (with splenectomy)	P value
Nonsurgical complication			
Cardiovascular	3 (1.1)	2 (0.8)	N.S.
Pulmonary	7 (2.6)	8 (3.3)	N.S.
Liver dysfunction	0	2 (0.8)	N.S.
Renal dysfunction	0	2 (0.8)	N.S.
CNS disorder	2 (0.8)	2 (0.8)	N.S.
Others	6 (2.3)	7 (2.9)	N.S.
Surgical complication			
Anastomotic leakage	1 (0.4)	4 (1.6)	N.S.
Panctreatic fistula	16 (6.0)	31 (12.9)	0.008*
Postoperative	22 (8.3)	21 (8.7)	N.S.
Bleeding	0	3 (1.3)	N.S.

N.S., not significant. *significant difference.

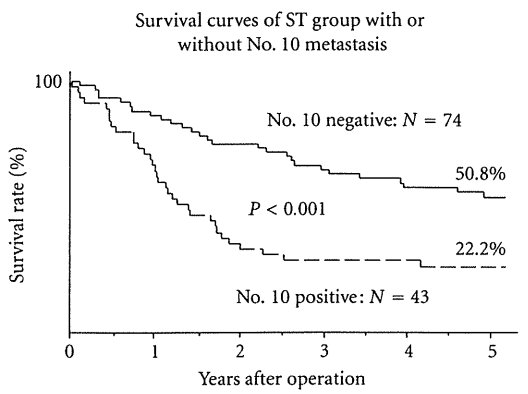

Figure 3: Comparison of cumulative survival curves of ST group between with or without No. 10 metastasis. The prognosis of the patients with No. 10 positive was poorer than that of the patients with No. 10 negative ($P < 0.001$).

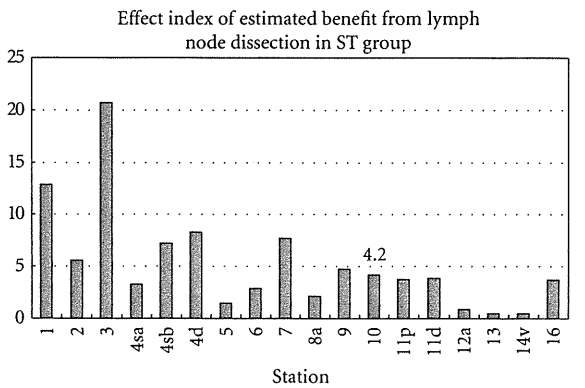

Figure 4: Effect index of estimated benefit from lymphadenectomy in ST group. The index was calculated by multiplication of the frequency of metastasis to the station and the 5-year survival rate of patients with metastasis to that station. The index of estimated benefit of No. 10 was approximately equal to that of No. 9, No. 11p, No. 11d, and No. 16.

metastasis and 5-year survival rate of patients with metastasis for each station. The index of estimated benefit of No. 10 was 4.2, which was similar to that of No. 9 (4.8), No. 11p (3.8), No. 11d (3.9), and No. 16 (3.7) (Figure 4). Almost all the regional lymph nodes of upper third portion of the stomach had high effect index of lymphadenectomy, but the treatment index of No. 4a and No. 8a was lower than that of No. 10.

3.5. Survival. In the survival rate according to depth of tumor invasion, ST group revealed lower prognosis compared with T group, but there was no significant difference between two groups in T2a and T2b (Figure 5(a)).

But the survival rate for patients with pSE (T3: tumor penetration of serosa), there was significantly difference between ST group (48.1%) and T group (67.7%). In the survival rate according to lymph node metastasis, there was no significant difference in the cumulative survival rates between two groups in pN0 and pN1 (Figure 5(b)).

But in the survival rate for patients with pN2, there was significantly difference between ST group (46.1%) and T group (66.7%). As for the survival rate according to stage, the survival of ST group was lower than that of T group in stages II, IIIA, and IIIB, but there was no significant difference (Figure 5(c)).

4. Discussion

The current standard treatment for proximal advanced gastric cancer in Japan is total gastrectomy with D2 lymphadenectomy. In order to accomplish D2 lymphadenectomy, splenectomy had been justified for complete removal of No. 10 as extended radical surgery. But extended resection which is regarded as a standard procedure in Asian countries is not effective in Western countries. The splenectomy caused

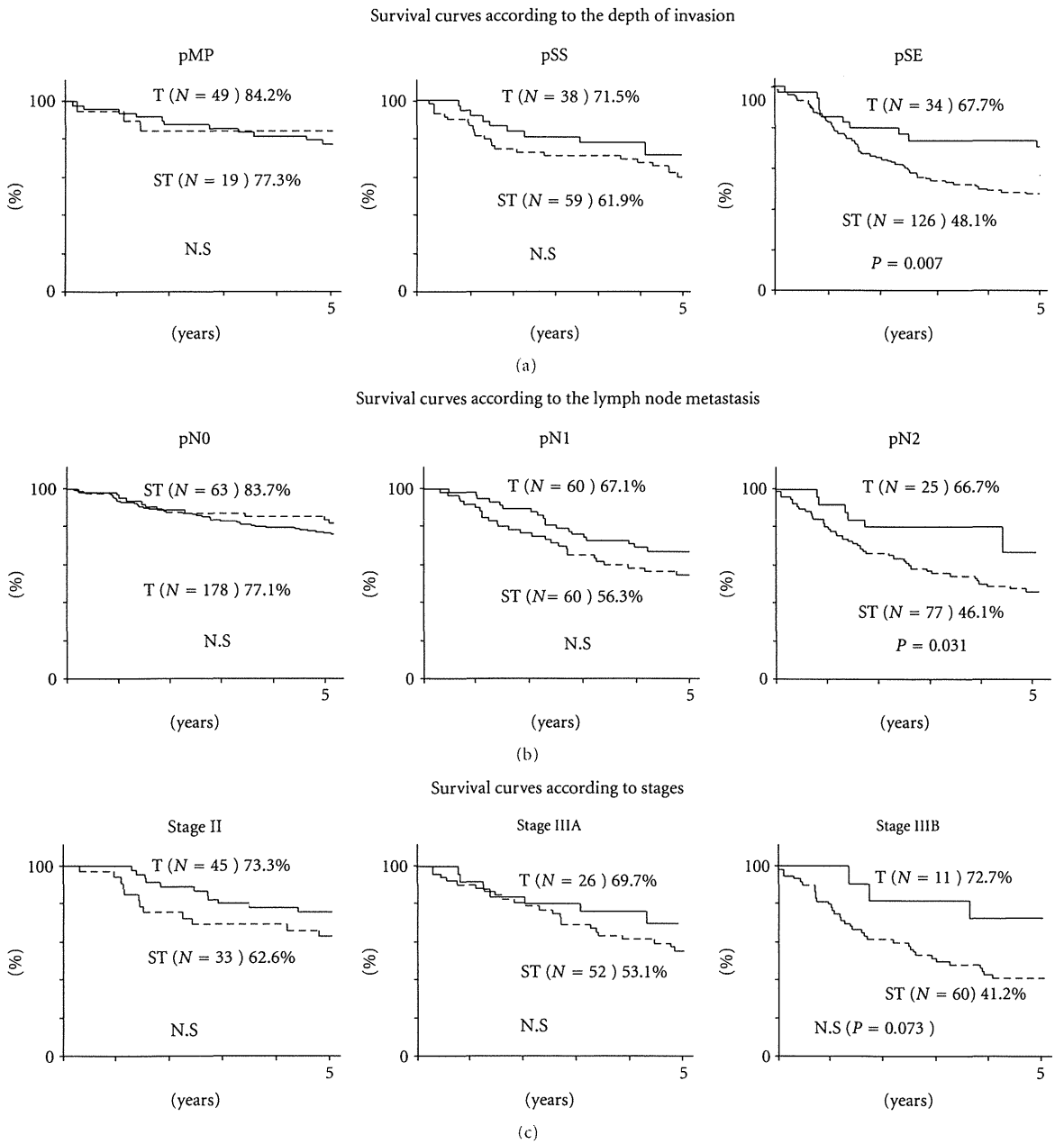

FIGURE 5: (a) Cumulative survival rates according to the depth of invasion (pT). As for pMP and pSS, there was no difference between T group and ST group, but the survival of the T group with pSE was better than that of ST group with pSE ($P = 0.007$). (b) Cumulative survival rates according to lymph node metastasis (pN). There was no difference in the cumulative survival rates between two groups with pN0 and pN1, but the survival of T group with pN2 was better than that of ST group with pN2 ($P = 0.031$). (c) Cumulative survival curves according to stage (pStage). There was no significant difference in the cumulative survival rates between two groups with Stage II, Stage IIIA, and Stage IIIB.

high morbidity and mortality, and it was shown to be an independent prognostic risk factor on multivariate analysis in node-negative patients in previous studies [10–15]. On the other hand, the splenectomy is considered to be a safe procedure that does not decrease surgical mortality [16]. A Korean trial has also reported that postoperative morbidity after splenectomy for D2 lymphadenectomy was not higher than simple total gastrectomy, but there was no significant difference in 5-year survival between with and without splenectomy [17]. Patients with proximal advanced gastric cancer localized on the greater curvature and type 4 might obtain relatively high survival benefits from No. 10

lymphadenectomy [18]. The splenectomy has become a safe technical procedure, but the surgical procedure of a total gastrectomy with splenectomy should be performed at a high volume hospital to avoid the postoperative complications.

The frequency of No. 10 metastasis was reported to be high in proximal advanced gastric cancer located on the greater curvature or in the posterior wall of the stomach, and lymphatic pathways along the posterior gastric artery, splenic artery, short gastric vessels, and/or gastroepiploic vessels were suggested to be important for No. 10 metastasis [19]. Lymphography has demonstrated that the lymphatic flow from the left upper region of the stomach enters the lymph node in the splenic hilum and travels to the nodes around the celiac trunk along the splenic artery [20]. In our study, the location involving the greater curvature, pN3 and No. 11d metastasis were risk factors for No. 10 metastasis, and the frequency of No. 10 metastasis was similar to that of No. 4sb, No. 9, and No. 11p metastasis. Furthermore, LN dissection effect index of No. 10 was almost as same as that of No. 9, No. 11p, and No. 11d. But the prognosis of patients with No. 10 metastasis was still poor even after its dissection. Furthermore, splenectomy does not improve survival of patients with proximal advanced gastric cancer even though curative resection was performed [21, 22]. Multivariate analysis demonstrated that nodal metastasis was independent prognostic factor, but splenectomy was not [23]. These reports suggested that the patients with No. 10 metastasis had already too extended LN metastasis to improve the prognosis. Accordingly, the splenectomy for D2 lymphadenectomy may be unnecessary in all the patients with advanced gastric cancer. On the contrary, some authors have found the survival benefit and recommended splenectomy for No. 10 lymphadenectomy. The splenectomy was one of the independent prognostic factors, and total gastrectomy with splenectomy is recommended for patients with No. 10 positive T3 proximal gastric cancer [24]. The survival of No. 10 positive patients was not to be different from that of No. 10 negative patients when curative surgery was performed [25]. The splenectomy was recommended when the tumor was located on the greater curvature or posterior wall of the stomach and had No. 4sa, No. 4sb, or No. 11 metastasis [19]. In fact, it is difficult to detect the depth of tumor invasion and No. 10 and/or No. 11 metastasis though a preoperative and intraoperative diagnostic technique. In Germany, No. 10 metastasis was observed only in advanced cancer, particularly in tumors located in the greater curvature and/or type 4 tumors [26]. Our current study showed that splenectomy adversely affected survival in pSE and pN2, while there was no significant difference in survival rates in pMP, pSS, pN0, and pN1 and among Stage II, IIIA, and IIIB. Though there were limitations of our study which was retrospectively conducted in a single institute, and there was selection bias, our study would suggest the benefit of spleen preservation on postoperative morbidity and long-term surgical outcomes. The overall survival rate stratified by stage was analyzed in a prospective randomized controlled trial [27], in which the 5-year overall survival rates of patients with stage I, stage II, and stage III were not significantly different between the 2 groups. Until 2005, our institute preferred to perform a total gastrectomy with splenectomy in advanced proximal gastric cancer for complete D2 lymphadenectomy. Recently we had a policy of splenectomy for the patients with No. 10 enlargement in the splenic hilum suggesting metastasis or tumor located in greater curvature or encircling in upper third portion of the stomach. A randomized controlled trail to evaluate total gastrectomy with splenectomy for proximal advanced gastric carcinoma with R0 resection (JCOG0110-MF) [28] has already recruited 505 patients and resulted that splenectomy was associated with higher morbidity and larger blood loss and was safely performed by specialized surgeons with low mortality. The precise impact of splenectomy on prognosis remains uncertain and the impact on long-term survival should be awaited.

In conclusion, although splenectomy for patients with proximal advanced gastric cancer was not an important risk factor for postoperative morbidity, splenectomy was not effective for patients with No. 10 metastasis in long-term survival. Spleen-preserving total gastrectomy will be feasible and be enough to accomplish radical surgery for locally advanced proximal gastric cancer.

Conflicts of Interest

There was no conflicts of interest in their submitted manuscripts.

References

[1] T. Toge, A. Kameda, K. Kuroi, Y. Seto, H. Yamada, and T. Hattori, "The role of the spleen in immunosuppression and the effects of splenectomy on prognosis in gastric cancer patients," *Nippon Geka Gakkai zasshi*, vol. 86, no. 9, pp. 1120–1123, 1985.

[2] K. Okajima and H. Isozaki, "Splenectomy for treatment of gastric cancer: Japanese experience," *World Journal of Surgery*, vol. 19, no. 4, pp. 537–540, 1995.

[3] S. Ishikawa, S. Shimada, N. Miyanari, M. Hirota, H. Takamori, and H. Baba, "Pattern of lymph node involvement in proximal gastric cancer," *World Journal of Surgery*, vol. 33, no. 8, pp. 1687–1692, 2009.

[4] T. Sano and T. Aiko, "Japanese gastric cancer treatment guidelines 2010 (ver. 3)," *Gastric Cancer*, vol. 14, no. 2, pp. 113–123, 2011.

[5] J. J. Bonenkamp, J. Hermans, M. Sasako, and C. J. H. Van De Velde, "Extended lymph-node dissection for gastric cancer," *New England Journal of Medicine*, vol. 340, no. 12, pp. 908–914, 1999.

[6] A. Cuschieri, P. Fayers, J. Fielding et al., "Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial," *Lancet*, vol. 347, no. 9007, pp. 995–999, 1996.

[7] S. S. Brar, R. Seevaratnam, R. Cardoso et al., "A systematic review of spleen and pancreas preservation in extended lymphadenectomy for gastric cancer," *Gastric Cancer*. In press.

[8] Japanese Gastric Cancer Association, "Japanese classification of gastric carcinoma: 2nd English edition," *Gastric Cancer*, vol. 1, pp. 10–24, 1998.

[9] M. Sasako, P. McCullouch, T. Kinoshita, and K. Maruyama, "New method to evaluate the therapeutic value of lymph node

dissection for gastric cancer," *British Journal of Surgery*, vol. 82, no. 3, pp. 346–351, 1995.

[10] M. S. Brady, A. Rogatko, L. L. Dent, and M. H. Shiu, "Effect of splenectomy on morbidity and survival following curative gastrectomy for carcinoma," *Archives of Surgery*, vol. 126, no. 3, pp. 359–364, 1991.

[11] J. P. Griffith, H. M. Sue-Ling, I. Martin et al., "Preservation of the spleen improves survival after radical surgery for gastric cancer," *Gut*, vol. 36, no. 5, pp. 684–690, 1995.

[12] S. J. Kwon, J. I. Lee, D. W. Choi et al., "Prognostic impact of splenectomy on gastric cancer: results of the Korean Gastric Cancer Study Group," *World Journal of Surgery*, vol. 21, no. 8, pp. 837–844, 1997.

[13] H. J. Wanebo, B. J. Kennedy, D. P. Winchester, A. K. Stewart, and A. M. Fremgen, "Role of splenectomy in gastric cancer surgery: adverse effect of elective splenectomy on longterm survival," *Journal of the American College of Surgeons*, vol. 185, no. 2, pp. 177–184, 1997.

[14] Y. Maehara, S. Moriguchi, M. Yoshida, I. Takahashi, D. Korenaga, and K. Sugimachi, "Splenectomy does not correlate with length of survival in patients undergoing curative total gastrectomy for gastric carcinoma: univariate and multivariate analyses," *Cancer*, vol. 67, no. 12, pp. 3006–3009, 1991.

[15] E. Otsuji, T. Yamaguchi, K. Sawai, K. Okamoto, and T. Takahashi, "Total gastrectomy with simultaneous pancreaticosplenectomy or splenectomy in patients with advanced gastric carcinoma," *British Journal of Cancer*, vol. 79, no. 11-12, pp. 1789–1793, 1999.

[16] Y. Tanizawa and M. Terashima, "Lymph node dissection in the resection of gastric cancer: review of existing evidence," *Gastric Cancer*, vol. 13, no. 3, pp. 137–148, 2010.

[17] W. Yu, G. S. Choi, and H. Y. Chung, "Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer," *British Journal of Surgery*, vol. 93, no. 5, pp. 559–563, 2006.

[18] T. Kosuga, D. Ichikawa, K. Okamoto et al., "Survival benefits from splenic hilar lymph node dissection by splenectomy in gastric cancer patients: relative comparison of the benefits in subgroups of patients," *Gastric Cancer*, vol. 14, no. 2, pp. 172–177, 2011.

[19] K. Aoyagi, K. Kouhuji, M. Miyagi et al., "Prognosis of metastatic splenic hilum lymph node in patients with gastric cancer after total gastrectomy and splenectomy," *World Journal of Hepatology*, vol. 27, no. 2, pp. 81–86, 2010.

[20] K. Maruyama, K. Okabayashi, and T. Kinoshita, "Progress in gastric cancer surgery in Japan and its limits of radicality," *World Journal of Surgery*, vol. 11, no. 4, pp. 418–425, 1987.

[21] C. H. Zhang, W. H. Zhan, Y. L. He, C. Q. Chen, M. J. Huang, and S. R. Cai, "Spleen preservation in radical surgery for gastric cardia cancer," *Annals of Surgical Oncology*, vol. 14, no. 4, pp. 1312–1319, 2007.

[22] S. H. Shin, H. Jung, S. H. Choi et al., "Clinical significance of splenic Hilar lymph node metastasis in proximal gastric cancer," *Annals of Surgical Oncology*, vol. 16, no. 5, pp. 1304–1309, 2009.

[23] K. Y. Lee, S. H. Noh, W. J. Hyung et al., "Impact of splenectomy for lymph node dissection on long-term surgical outcome in gastric cancer," *Annals of Surgical Oncology*, vol. 8, no. 5, pp. 402–406, 2001.

[24] C. M. Huang, J. B. Wang, H. S. Lu et al., "Prognostic impact of splenectomy on advanced proximal gastric cancer with No. 10 lymph node metastasis," *Chinese Journal of Surgery*, vol. 14, no. 19, pp. 1483–1486, 2009.

[25] M. Ikeguchi and N. Kaibara, "Lymph node metastasis at the splenic hilum in proximal gastric cancer," *American Surgeon*, vol. 70, no. 7, pp. 645–648, 2004.

[26] S. P. Monig, P. H. Collet, S. E. Baldus et al., "Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus," *Journal of Surgical Oncology*, vol. 76, no. 2, pp. 89–92, 2001.

[27] A. Csendes, P. Burdiles, J. Rojas, I. Braghetto, J. C. Diaz, and F. Maluenda, "A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma," *Surgery*, vol. 131, no. 4, pp. 401–407, 2002.

[28] T. Sano, S. Yamamoto, and M. Sasako, "Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan clinical oncology group study JCOG 0110-MF," *Japanese Journal of Clinical Oncology*, vol. 32, no. 9, pp. 363–364, 2002.

Original Paper

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

Hiroshi Yabusaki, Atsushi Nashimoto, Atsushi Matsuki and Masaki Aizawa

Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan

Corresponding author: Hiroshi Yabusaki, Department of Surgery, Niigata Cancer Center Hospital, 2-15-3 Kawagishicyo, Chuo-ku, Niigata 951-8566, Japan; Tel.: +81-25-266-5111, Fax: +81-25-266-9385; E-mail: yabu@niigata-cc.jp

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/m^2 for 21 consecutive days, followed by 14 days of rest. CDDP was administered intravenously on day 8 at a dose of 60mg/m^2 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/m^2/day, days 1-14) was administered every 3 weeks for 1 year. The treatments after R^2 resection or upon detection of recurrent disease were decided at the discre-

Hepato-Gastroenterology 2013; 60: 383-387 doi 10.5754/hge12653

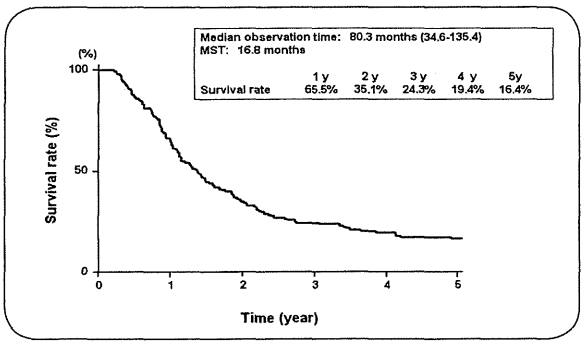

FIGURE 1. With a median follow-up of 80.3 months, the overall MST of the patients was 16.8 months, with a 5YSR of 16.4%.

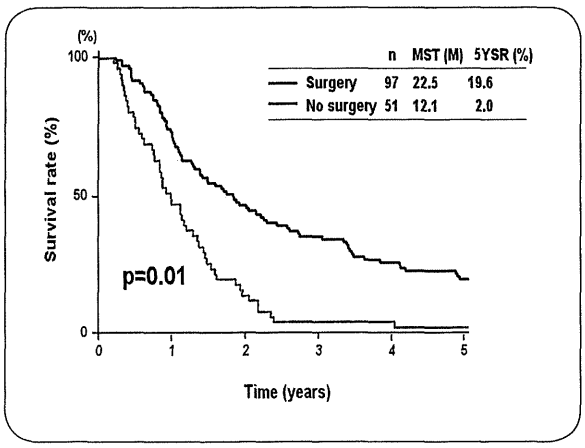

FIGURE 2. The MST of patients who went onto receive surgery was 22.5 months and the 5YSR was 19.6%. There was a statistically significant difference in the survival between these patients and those who did not receive a gastrectomy.

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 χ^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.

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 demographics (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

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 disease 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 com-

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

bined 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**).

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

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.

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

Variables	Hazard ratio	95% confidence limit	*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

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 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)

REFERENCES

1. **Macdonald JS, Smalley SR, Benedetti J, et al.:** Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345(10):725-730.
2. **Cunningham D, Allum WH, Stenning SP, et al.:** MAGIC Trial participants: Perioperative chemotherapy vs. surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1):11-20.
3. **Sakuramoto S, Sasako M, Yamaguchi T, et al.:** ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357(18):1810-1820.
4. Japanese Research Society for Gastric Cancer: Guideline for diagnosis and treatment of carcinoma of the stomach. Kanehara Tokyo, October 2010.
5. **Nashimoto A, Yabusaki H, Nakagawa S, et al.:** Perioperative chemotherapy with S-1 and cisplatin for highly advanced gastric cancer. Anticancer Res 2009; 29:4689-4696.
6. **Koizumi W, Tanabe S, Saigenji K, et al.:** Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003; 89:2207-2212.
7. **Therasse P, Arbuck SG, Eisenhauer EA, et al.:** New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3):205-216.
8. Japanese Research Society for Gastric Cancer: Japanese classification of gastric carcinoma. Kanehara, Tokyo, March 2010.
9. **Isobe Y, Nashimoto A, Akazawa K, et al.:** Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer 2011; 14:301-316.
10. **Hartgrink HH, Putter H, Klein KE, et al.:** Value of palliative resection in gastric cancer. Br J Surg 2002; 89:1438-1443.
11. **Kikuchi S, Arai Y, Morise M, et al.:** Gastric cancer with metastases to the distant peritoneum: a 20-year surgical experience. Hepato-gastroenterol 1998; 45(22):1183-1188.
12. **Sasako M, Sano T, Yamamoto S, et al.:** D2 lymphadenectomy alone or with paraaortic lymph node dissection for gastric cancer. N Engl J Med 2008; 359(5):453-462.
13. **Sasako M, Sano T, Yamamoto S, et al.:** Left thoracico-abdominal approach vs. abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomized controlled trial. Lancet Oncol 2006; 7(8):644-651.
14. **Satoh S, Hasegawa S, Ozaki N, et al.:** Retrospective analysis of 45 consecutive patients with advanced gastric cancer treated with neoadjuvant chemotherapy using an S-1/CDDP combination. Gastric Cancer 2006; 9:129-135.
15. **Nakajo A, Natsugoe S, Hokita S, et al.:** Successful treatment of advanced gastric cancer by surgical resection following combination chemotherapy with oral S-1 and biweekly paclitaxel. Gastric Cancer 2007; 10:58-62.
16. **Nakajima T, Ota K, Ishihara S, et al.:** Combined intensive chemotherapy and radical surgery for incurable gastric cancer. Ann Surg Oncol 1997; 4(3):203-208.
17. **Gallard RD, Onate LF, Calderillo RG.:** Neoadjuvant chemotherapy with P-ELF (cispl-atin, etoposide, leucovorin, 5-fluorouracil) followed by radical resection in patients with initially unresectable gastric adenocarcinoma: A phase II study. Ann Surg Oncol 2000; 7(1):45-50.
18. **Schumacher CP, Fink U, Becker K, et al.:** Neoadjuvant therapy for patients with locally advanced gastric carcinoma with etoposide, doxorubicin, and cisplatinum: Closing results after 5 years of follow-up. Cancer 2001; 91(5):918-927.
19. **Karoui M, Penna C, Amin HM, et al.:** Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastasis. Ann Surg 2006; 243(1):1-7.
20. **Raut CP, Posner M, Desai J, et al.:** Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitor. J Clin Oncol 2006; 24(15):2325-2331.
21. **Koizumi W, Narahara H, Hara T, et al.:** S-1 plus cisplatin versus S-1 alone for first-1ine treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9(3):215-221.
22. **Bang YJ, Van Cutsem E, Feyereislova A, et al.:** Trastuzumab in combination with chemotherapy vs. chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet 2010; 376:687-697.
23. **Brenner B, Shah MA, Karpeh MS, et al.:** A phase II trial of neoadjuvant cisplatin-fluorouracil followed by postoperative intraperitoneal floxuridine-leucovorin in patients with locally advanced gastric cancer. Ann Oncol 2006; 17(9):1404-1411.
24. **Biondi A, Persiani R, Cananzi F, et al.:** R0 resection in the treatment of gastric cancer: Room for improvement. World J Gastroenterol 2010; 16(27):3358-3370.

Cancer Chemother Pharmacol. 2013 Mar 5. [Epub ahead of print]

Phase II trial of paclitaxel and cisplatin as neoadjuvant chemotherapy for locally advanced gastric cancer.

Tsuburaya A, Nagata N, Cho H, **Hirabayashi N**, Kobayashi M, Kojima H, Munakata Y, Fukushima R, Kameda Y, Shimoda T, Oba K, Sakamoto J.

Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2, Nakao, Asahi, Yokohama, 2410815, Japan, tuburayaa@kcch.jp.

Abstract

PURPOSE: Paclitaxel-cisplatin (TC) combination is effective and well tolerated in patients with unresectable gastric cancer. We investigated the efficacy and safety of TC for locally advanced gastric cancers in a neoadjuvant setting.

METHODS: Patients received 2-4 courses of paclitaxel (80 mg/m2) and cisplatin (25 mg/m2) on days 1, 8, and 15 in a 4-weekly schedule, followed by radical gastrectomy. Primary endpoint was the pathological response rate: percentage of tumors in which one-third or more parts were affected.

RESULTS: All 52 patients enrolled were eligible. Thirty-six (69.7 %) patients completed two or more courses of chemotherapy. Forty-three patients (82.7 %) underwent surgery, 33 (63.5 %) had R0 resection, and there was no treatment-related death. The pathological response was 34.6 % (95 % CI 22.0-49.1) for all registered patients; the null hypothesis of tumor response ≤10 % was rejected ($p < 0.0001$). The 3-year overall survival was 41.5 % (95 % CI 27.4-55.0).

CONCLUSIONS: The neoadjuvant chemotherapy with TC was safe and effective for patients with locally advanced gastric cancer, and further study is needed to confirm the effectiveness of this regimen.

PMID: 23463482 [PubMed - as supplied by publisher]

Gastric Cancer (2012) 15:245–251
DOI 10.1007/s10120-011-0101-x

ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

Kohei Shitara · Satoshi Morita · Kazumasa Fujitani · Shigenori Kadowaki · Nobuhiro Takiguchi · Naoki Hirabayashi · Masazumi Takahashi · Masakazu Takagi · Yukihiko Tokunaga · Ryoji Fukushima · Yasuhiro Munakata · Kazuhiro Nishikawa · Akinori Takagane · Takaho Tanaka · Yoshiaki Sekishita · Junichi Sakamoto · Akira Tsuburaya

Received: 19 July 2011 / Accepted: 11 September 2011 / Published online: 13 October 2011

Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

K. Shitara (✉)
Department of Clinical Oncology,
Aichi Cancer Center Hospital, 1-1 Kanokoden,
Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: Kouheis0824@yahoo.co.jp

S. Morita
Department of Biostatistics and Epidemiology,
Yokohama City University Medical Center,
Yokohama, Japan

K. Fujitani
Department of Surgical Oncology,
National Osaka Medical Center, Suita, Japan

S. Kadowaki
Department of Gastroenterology,
Saitama Cancer Center Hospital, Saitama, Japan

N. Takiguchi
Department of Gastroenterological Surgery,
Chiba Cancer Center Hospital, Chiba, Japan

N. Hirabayashi
Department of Surgery, Hiroshima City Asa Hospital,
Hiroshima, Japan

M. Takahashi
Department of Gastroenterological Surgery,
Yokohama Municipal Citizens Hospital, Yokohama, Japan

M. Takagi
Department of Surgery, Shizuoka General Hospital,
Shizuoka, Japan

Y. Tokunaga
Department of Surgery, Osaka North Japan Post Hospital,
Osaka, Japan

R. Fukushima
Department of Surgery, Teikyo University School of Medicine,
Tokyo, Japan

Y. Munakata
Department of Surgery, Nagano Municipal Hospital,
Nagano, Japan

K. Nishikawa
Department of Surgery, Osaka General Medical Center,
Osaka, Japan

A. Takagane
Department of Surgery, Hakodate Goryoukaku Hospital,
Hakodate, Japan

T. Tanaka
Department of Surgery, Social Insurance Tagawa Hospital,
Tagawa, Japan

Y. Sekishita
Department of Surgery, Obihiro Kosei Hospital, Obihiro, Japan

J. Sakamoto
Young Leaders' Program in Medical Administration,
Nagoya University Graduate School of Medicine, Nagoya, Japan

A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer
Center, Yokohama, Japan

disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS. *Conclusions* S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

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

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All (*n* = 52)	RFI <6 months (*n* = 25)	RFI ≥6 months (*n* = 27)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

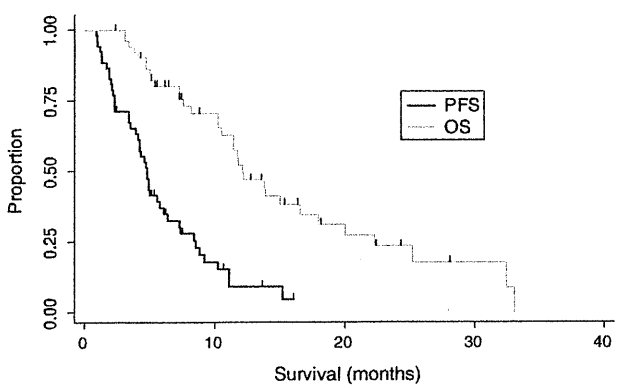

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

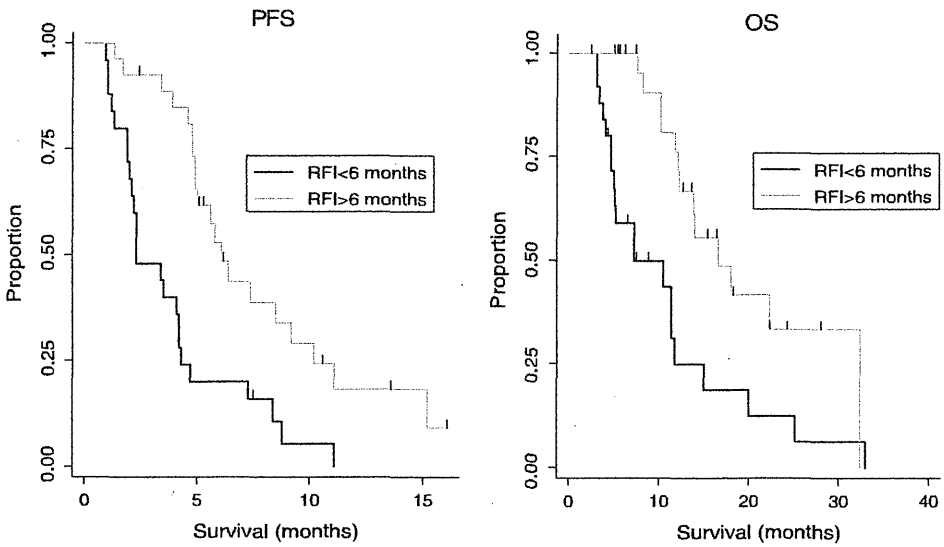

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29], and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

Acknowledgments This work was supported by the Epidemiological and Clinical Research Information Network (ECRIN).

Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

References

1. International Agency for Research on Cancer. GLOBOCAN. http://www-dep.iarc.fr/CancerMondial.htm (2008). Accessed April 2011
2. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991–7.
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
4. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
5. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20:666–73.
6. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.
7. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer. 1998;34:1715–20.
8. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology. 2000;58:191–7.
9. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
10. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
11. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. J Clin Oncol. 2011 Aug 15. [Epub ahead of print]
12. Shitara K, Muro K, Ura T, Takahari D, Yokota T, Sawaki A, et al. Chemotherapy for gastric cancer that recurs after adjuvant chemotherapy with S-1. Jpn J Clin Oncol. 2008;38:786–9.
13. Hasegawa H, Fujitani K, Kurokawa Y, Hirao M, Nakazuru S, Mita E, et al. Effect of S-1 adjuvant chemotherapy on survival following recurrence and efficacy of first-line treatment in recurrent gastric cancer. Chemotherapy. 2010;56:436–43.
14. Aoyama T, Yoshikawa T, Watanabe T, Hayashi T, Ogata T, Cho H, et al. Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1. Gastric Cancer. 2011;14:150–4.
15. Kang HJ, Chang HM, Kim TW, Ryu MH, Sohn HJ, Yook JH, et al. Phase II study of capecitabine and cisplatin as first-line combination therapy in patients with gastric cancer recurrent after fluoropyrimidine-based adjuvant chemotherapy. Br J Cancer. 2005;92:246–51.
16. Pujade-Lauraine E, Paraiso D, Cure H, Germann N, Lortholary A, Lucas V, et al. Predicting the effectiveness of chemotherapy (Cx) in patients with recurrent ovarian cancer (ROC): a GINECO study. Proc Am Soc Clin Oncol 2002;21:abstract 829.
17. Takashima A, Shirao K, Hirashima Y, Takahari D, Okita N, Akatsuka S, et al. Chemosensitivity of patients with recurrent esophageal cancer receiving perioperative chemotherapy. Dis Esophagus. 2008;21:607–11.
18. de Gramont Lesparre AH, Chibaudel B, Bourges O, Perez-Staub N, Tournigand C, Maindrault-Goebel F, et al. Definition of oxaliplatin sensitivity in patients with advanced colorectal cancer previously treated with oxaliplatin-based therapy. J Clin Oncol. 2009;27:15s. (abstr 4024).
19. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, et al. Late phase II study of irinotecan hydrochloride (CPT-11) in

advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho. 1994;21:1033–8.
20. Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). Gan To Kagaku Ryoho. 1998;25:1915–24.
21. Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: a Cooperative Study Group Trial (group B). Gan To Kagaku Ryoho. 1999;26:487–96.
22. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol. 2001;12:1133–7.
23. Nakae S, Hirao M, Kishimoto T, Iijima S, Ishida H, Morimoto T, et al. Phase II study of bi-weekly CPT-11 + CDDP for patients with gastric cancer refractory to S-1 (OGSG 0504 study). J Clin Oncol 2008;26 (May 20 suppl; abstr 4571).
24. Lee JJ, Kim TM, Yu SJ, Kim DW, Joh YH, Oh DY, et al. Single-agent capecitabine in patients with metastatic colorectal cancer refractory to 5-fluorouracil/leucovorin chemotherapy. Jpn J Clin Oncol. 2004;34:400–4.
25. Yasui H, Yoshino T, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Retrospective analysis of S-1 monotherapy in patients with metastatic colorectal cancer after failure to fluoropyrimidine and irinotecan or to fluoropyrimidine, irinotecan and oxaliplatin. Jpn J Clin Oncol. 2009;39:315–20.
26. Takiuchi H, Goto M, Imamura H, Furukawa H, Imano M, Imamoto H, et al. Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). Jpn J Clin Oncol. 2008;38:176–81.
27. Ono A, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yasui H, et al. Activity of S-1 in advanced or recurrent gastric cancer patients after failure of prior chemotherapy, including irinotecan + cisplatin or fluorouracil (except S-1). Jpn J Clin Oncol. 2009;39:332–5.
28. Yamamoto D, Yoshida H, Iwase S, Odagiri H, Kitamura K. TS-1 in patients with capecitabine-resistant breast cancer. J Clin Oncol 27:15s, 2009 (suppl; abstr 1103).
29. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.

Tolerability of adjuvant chemotherapy with S-1 after curative resection in patients with stage II/III gastric cancer

HIRONORI TSUJIMOTO, HIROYUKI HORIGUCHI, SHUICHI HIRAKI, YOSHIHISA YAGUCHI, RISA TAKAHATA, ISAO KUMANO, KAZUMICHI YOSHIDA, YUSUKE MATSUMOTO, SATOSHI ONO, JUNJI YAMAMOTO and KAZUO HASE

Department of Surgery, National Defense Medical College, Tokorozawa 359-8513, Japan

Received April 24, 2012; Accepted August 13, 2012

DOI: 10.3892/ol.2012.882

Abstract. The results of the Japan Clinical Oncology Group trial demonstrated that adjuvant chemotherapy with S-1 for stage II/III gastric cancer is effective and suggested that this therapy should be adopted as the standard treatment following curative D2 gastric dissection. We reviewed treatment outcomes in 58 consecutive patients who received adjuvant therapy with S-1 for stage II/III gastric cancer following curative D2 dissection; the standard dosage used was determined on the basis of the patient body surface area. Twenty-four patients (41.3%) discontinued treatment before 12 months. Patients who completed 12 months of adjuvant therapy with S-1 were younger and more frequently treated by senior doctors (>15 years of experience) than those who did not. However, no differences existed in pathological features and surgical procedures between groups. Overall survival and relapse-free survival were better in patients who completed 12 months of adjuvant therapy with S-1. Fatigue and nausea were associated with discontinuation of S-1 treatment. In conclusion, immediately after surgery, fatigue and gastrointestinal symptoms of ≤ grade 2 may have a major impact on treatment compliance. Prior to the commencement of S-1 administration, both patients and doctors should be made completely aware of the toxicity, compliance and efficacy issues associated with this adjuvant therapy.

Introduction

S-1 is an oral anticancer preparation composed of a mixture of tegafur [FT, a prodrug of 5-fluorouracil (5-FU)], 5-chloro-2,4-dihydroxypyridine (CDHP, a biochemical modulator that inhibits 5-FU biodegradation) and potassium oxonate (Oxo, added to reduce the gastrointestinal toxicity of 5-FU) (1-3). In the two registration phase II studies in Japan, the rate of response to treatment with S-1 alone exceeded 40% in patients with advanced or recurrent gastric cancer (4,5). The Japan Clinical Oncology Group (JCOG) conducted a randomized prospective controlled study to evaluate the efficacy of single-agent S-1 as adjuvant therapy for patients with stage II/III (Japanese Classification of Gastric Carcinoma, JCGC) (6) gastric cancer following curative D2 dissection (7). When the final analysis was performed in September 2006, 3-year overall survival (OS) was 80.5% for S-1 treated patients and 70.1% for patients who underwent surgery alone. The hazard ratio for death in S-1 treated patients was 0.68 (P=0.0024). The results of this trial demonstrated that adjuvant chemotherapy with S-1 for stage II/III gastric cancer is effective and suggested that this therapy should be adopted as the standard treatment following curative D2 gastric dissection (8).

To investigate the tolerability of adjuvant chemotherapy with S-1 for stage II/III gastric cancer following curative D2 dissection, we reviewed treatment outcomes in patients receiving this adjuvant therapy.

Materials and methods

Patients. Between August 2007 and July 2010, 283 patients underwent gastrectomy for adenocarcinoma of the stomach with curative intent at the National Defense Medical College Hospital (Tokorozawa, Saitama, Japan). Of these, 64 patients (41-84 years old) had pathological stage II/III disease according to the JCGC (6). All patients were informed of the efficacy of the adjuvant chemotherapy trial of S-1 for gastric cancer (ACTS-GC) and provided their consent to the study (7).

Treatment regimen. S-1 was orally administered twice daily for 4 weeks, followed by a 2-week rest. This schedule was repeated every 6 weeks for 12 months until tumor recurrence, observation of unacceptable toxicity levels or refusal by the patient to undergo further treatment. Dosages were assigned according to the patient body surface area: <1.25 m^2, 80 mg/day; 1.25-1.5 m^2, 100 mg/day; and ≥1.5 m^2, 120 mg/day. Dosage modification and treatment interruption were performed according to the protocol in the registration trial (5,7). The dose or treatment schedule was modified at the physician's discretion according to the toxicity profiles. In

Correspondence to: Dr Hironori Tsujimoto, Department of Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan
E-mail: tsujihi@ndmc.ac.jp

Key words: gastric cancer, adjuvant therapy, tolerability