Available online at www.sciencedirect.com

ScienceDirect

EJSO

the Journal of Cancer Surgery

EJSO 41 (2015) 1354–1360

www.ejso.com

Efficacy of conversion gastrectomy following docetaxel, cisplatin, and S-1 therapy in potentially resectable stage IV gastric cancer

J. Kinoshita, S. Fushida*, T. Tsukada, K. Oyama, K. Okamoto, I. Makino, K. Nakamura, T. Miyashita, H. Tajima, H. Takamura, I. Ninomiya, T. Ohta

Department of Gastroenterologic Surgery Division of Cancer Medicine, Graduate School of Medicine Science, Kanazawa University, 13-1 Takaramachi, Kanazawa, 920-8641, Japan

Accepted 24 April 2015
Available online 15 May 2015

Abstract

Background: Recent advances in gastric cancer chemotherapy have made macroscopic complete resection possible in some patients with stage IV disease.

Methods: We retrospectively investigated the efficacy of multimodal therapy with combined docetaxel, cisplatin, and S-1 (DCS) and conversion gastrectomy in 57 patients with stage IV gastric cancer.

Results: Of the 57 patients, 15 patients were categorized into potentially resectable case, which is defined as patients with single incurable factor including the upper abdominal para-aortic lymph node metastasis (16a2b1 PAN metastasis) or fewer than three peripheral liver metastases. The other 42 were categorized as initially unresectable. All of patients underwent DCS therapy, and then 34 patients underwent conversion gastrectomy. The 3-year overall survival (OS) rate among the patients who underwent conversion gastrectomy was 50.1% with MST of 29.9 months. They had significantly longer OS than patients who underwent DCS therapy alone ($p < 0.01$). Univariate analysis among the patents with conversion gastrectomy identified 16a2b1PAN metastasis, peritoneal metastasis, potential resectable case, R0 resection as significant prognostic factors. A 3-year OS in potential resectable cases was 92.9%. Multivariate analysis identified potential resectability as the only independent prognostic factor contributing to OS (HR 0.133, 95%CI 0.024-0. 744, $p = 0.021$). In contrast, clinical response was selected as the only independent prognostic factor in the subgroup of initially unresectable cases (HR 0.354, 95%CI 0.151-0.783, $p = 0.021$).

Conclusion: Patients with potentially resectable disease had a remarkably good prognosis among stage IV gastric cancer patients, and might be ideal candidates for conversion gastrectomy following DCS therapy.

Keywords: Gastric cancer; Stage IV; Chemotherapy; Conversion gastrectomy

Introduction

Chemotherapy is the main treatment for stage IV gastric cancer associated with distant metastasis. Although there is currently no established global standard chemotherapy for stage IV gastric cancer, combination therapy with a fluoropyrimidine and platinum is commonly used worldwide.[1]

The orally administered, 5-FU analog S-1 has been used as a good alternative to continuous infusion of 5-FU in unresectable gastric cancer in Japan, according to the JCOG 9912 Trial.[2] A multicenter phase III trial of unresectable gastric cancer (SPIRITS trial) comparing S-1 alone with S-1 plus cisplatin yielded a significantly higher response rate and improved overall survival (OS) in patients receiving the combined treatment.[3] S-1 plus cisplatin is thus the current standard treatment regimen for advanced gastric cancer in Japan. Moreover, several Phase I and

* Corresponding author. Tel.: +81 76 265 2362; fax: +81 76 234 426.
E-mail address: fushida@staff.kanazawa-u.ac.jp (S. Fushida).

http://dx.doi.org/10.1016/j.ejso.2015.04.021

Phase II trials have been conducted to evaluate a combination of docetaxel, cisplatin and S-1 (DCS) in patients with highly advanced gastric cancer, and these trials demonstrated high response rate: 76.9–87.1%.[4–6] DCS therapy is expected to become the standard regimen for advanced gastric cancer in Japan.

These advances in gastric cancer chemotherapy have raised new clinical issues regarding the treatment of stage IV gastric cancer. The response rate of newly-developed chemotherapeutic regimens has improved dramatically, allowing the down-staging of many tumors and the further management of gastric cancer patients whose distant metastases have clinically disappeared or which are well controlled by chemotherapy. Surgical intervention in such patients may result in long-term survival after the excision of macroscopically remaining lesions. This type of surgery, referred to as conversion gastrectomy, aims to be curative rather than just palliative, on the basis of the response to chemotherapy. However, the clinical value of such multimodal therapy involving chemotherapy and conversion gastrectomy for stage IV gastric cancer remains controversial, especially in initially unresectable patients, because of the presence of widespread advanced systemic disease.

In this study, we retrospectively investigated the feasibility and efficacy of multimodal DCS therapy and conversion gastrectomy for stage IV gastric cancer patients, with particular focus on the potential to select patients who might benefit from surgical resection.

Materials and methods

Patients

We retrospectively identified patients with a clinical diagnosis of stage IV gastric adenocarcinoma who underwent DCS therapy as primary chemotherapy at our institute between April 2006 and March 2012. The inclusion criteria were as follows: (1) newly diagnosed with gastric adenocarcinoma; (2) clinically diagnosed with unresectable and/or metastatic lesions; (3) underwent at least one cycle of DCS therapy as primary chemotherapy; (4) Eastern Cooperative Oncology Group performance status 0–1; and (5) no prior chemotherapy, radiotherapy, or major surgical procedure; (6) provision of signed written informed consent.

A total of 57 patients were included in the current study. The patients enrolled in this study had one or more of the following factors indicating incurable cancer: liver metastasis, peritoneal metastasis, and/or distant lymph node metastasis clearly enlarged (≧1.0 cm) on CT scans with 2.5 mm slice thickness.

We also stratified patients into two categories depending on their cancer status at the time of initial diagnosis: (1) potentially resectable cases, who had single incurable factor including para-aortic lymph node (PAN) metastasis between the upper margin of the celiac artery and the lower border of the inferior mesenteric artery which are defined as lymph node station No. 16a2 and b1 according to JCGC 3rd English edition (16a2b1PAN),[7] or fewer than three peripheral liver metastasis lesions; and (2) initially unresectable cases who had other incurable factor or more than one incurable factor. In the current study, para-aortic lymph node metastasis around the upper side of the celiac artery (16a1) or lower side of inferior mesenteric artery (16b2) was defined as distant lymph node metastasis.

This study was approved by the institutional review board of Kanazawa University Graduate School of Medical Sciences. Written informed consent was obtained from all patients.

Treatment regimen

DCS therapy consisted of docetaxel 35 mg/m2 and cisplatin 35 mg/m2 as an intravenous infusion on Days 1 and 15, and S-1 administered at a dose of 80 mg/m2/day divided into two split daily doses for 14 days, followed by 14 days of rest, as described previously.[4]The clinical response for measurable metastatic tumors was evaluated based on the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0. The clinical response for primary lesions was defined according to JCGC 3rd edition.[7]

Clinical assessment of surgery and histological evaluation of surgical specimen

In patients in whom distant lesions were controlled or disappeared during the course of chemotherapy, the indication for surgery was determined based on the response to chemotherapy. In the present study, conversion gastrectomy was defined as surgery with curative intent aimed at leaving no macroscopic residual tumor. Complete regression of immeasurable lesions such as peritoneal metastasis was confirmed by laparoscopic examination before gastrectomy.

To ensure the feasibility of conversion surgery, this study included all surgeries that eventually resulted in incomplete resection. Surgical complications were assessed according to the Clavien–Dindo classification. All resected specimens were examined by the same pathologist to assess the extent of residual disease, disease stage, and effect of chemotherapy according to the criteria of JCGC 3rd edition.[7] Tumors were graded as 0–3 based on the degree of necrosis or disappearance of the tumor in relation to the estimated total amount of the lesion.

Statistical analysis

OS was calculated from the date of chemotherapy initiation to death from any cause or the latest follow-up. The median OS was estimated using the Kaplan–Meier method and differences in survival were evaluated using the log-

rank test. The effects of prognostic factors on patient survival were analyzed by multivariate analyses using the Cox proportional hazards method. All statistical evaluations were performed using the SPSS 11.5J software package (SPSS Japan Inc., Tokyo, Japan). A p value <0.05 (two-tailed) was considered statistically significant.

Results

Patient characteristics and clinical outcomes of DCS therapy

Table 1 shows the clinicopathological characteristics and clnical outcomes of DCS thepray in all patients enrolled in this study. Incurable factors included 16a2b1 PAN metastasis in 23 patients, liver metastasis in 18, distant lymph node metastasis in 17, peritoneal metastasis in 15, and bone metastasis in 2. Some of these numbers of patients according to incurable factors included overlapped data. Among those with liver metastases, 13 patients had multiple metastatic lesions and five had fewer than three peripheral lesions. Fifteen patients were categorized as potentially resectable according to metastatic status (10 with 16a2b1 PAN metastasis, 5 with liver metastasis), and the remaining 42 were categorized as initially unresectable.

Table 1
Patient characteristic and clinical outcomes of DCS therapy.

Characteristic	Number of patients
Sex (male/female)	38/19
Age (years), range (median)	30–78 (65)
Performance status 0/1/2/3/4	40/17/0/0/0
Tumor location U/M/L/Whole	15/13/18/11
Depth of tumor invasion T1/T2/T3/T4a/T4b	0/11/20/20/6
Histological type intestinal/diffuse	29/28
Borrmann macroscopic type 1/2/3/4	0/19/28/10
Incurable factor	
16a2b1Para-aortic lymph node metastasis	23
Distant lymph node metastasis	17
Peritoneal metastasis	15
Liver metastasis	18
Other hematogenous metastasis	2
Number of incurable factors, 1/2/3/4	31/17/2/7
Potentially resectable/Initially unresectable cases	15 (16a2b1PAN: 10 liver: 5)/42
Number of treatment cycles, range (median)	1–7 (2)
Clinical response of DCS therapy CR/PR/SD/PD/NE	0/42/8/3/4
% of Grade 3 or 4 toxicity	
Leukopenia	17.5
Neutropenia	31.6
Thrombocytopenia	1.8
Anemia	7.0
Anorexia	7.0
GI bleeding	5.3
Hyponatremia	3.5
Febrile neutropenia	7.0
Conversion gastrectomy +/−	34/23

All patients enrolled in this study underwent primary chemotherapy with DCS. The median number of courses of DCS was two (range 1–7). The clinical overall responses were partial response in 42 (73.7%), stable disease in eight (14.0%), progressive disease in three (5.3%), and not evaluable in four patients (7.0%). No patient had a complete response during DCS therapy. The overall response rate was 73.7% and the disease-control rate was 87.7%. The treatment-related toxicities of grade 3 or above included neutropenia (31.6%), leukopenia (17.5%), and febrile neutropenia (7.0%). Three patients experienced grade 3 gastrointestinal bleeding from the primary tumor. There were no patients who could not undergo conversion gastrectomy due to DCS-related toxicities and there were no treatment-related deaths in this study.

Thirty four patients (59.6%), including all the potentially resectable cases, underwent conversion gastrectomy following DCS therapy, while the other 23 (40.4%) underwent chemotherapy alone.

Surgical outcomes

A total of 34 patients underwent conversion surgery with curative intent after DCS therapy. The surgical procedures and outcomes are shown in Table 2. The median duration from the initiation of DCS therapy to surgery was 85 days (range 43–414 days). D2 lymphadenectomy plus PAN dissection was performed in 17 patients. Complete resection with no residual tumor (R0) was achieved in 27 of 34 patients, microscopic residual tumor status (R1) in one (positive for peritoneal washing cytology), and macroscopic residual tumor (R2) in six (peritoneal metastasis in four, lymph node metastasis in two). Eleven patients (32.4%) developed postoperative complications. Pathological response ($\geq$grade 1b) in the primary lesion was observed in 64.7% of patients, with grade 3 in two patients.

Postoperative chemotherapy

In this study, 32 of 34 patients were given postoperative chemotherapy after conversion gastrectomy. S-1-combined regimens were selected in 22 patients; DCS therapy in 4, S-1 plus paclitaxel in one, and S-1 alone in 17. Weekly paclitaxel treatment was administered to four patients, irinotecan to five patients, and capecitabine plus cisplatin to one. The median number of courses of postoperative S-1-combined chemotherapy was five (range 1–16 courses).

Survival and prognostic factors

Among all 57 patients, the 1-, 2-, and 3-year OS rates were 70.6%, 49.6%, and 41.3%, respectively with an MST of 20.9 months (Fig. 1A). The 3-year OS in the 34 patients who underwent conversion gastrectomy was 50.1%,

Table 2
Surgical outcomes in 34 patients who underwent conversion gastrectomy.

Variable	Number of patients (%)
Total number of patients who underwent conversion gastrectomy	34 (100%)
Surgical procedures	
Total gastrectomy	22 (64.7%)
Distal gastrectomy	9 (26.5%)
Proximal gastrectomy	3 (8.8%)
Surgical time (min), range (median)	170–690 min (338)
Intraoperative blood loss (ml), range (median)	70–2810 ml (750)
D2 lymphadenectomy plus PAN dissection	17 (50.0%)
Resection of the other organs	
Spleen	7 (20.1%)
Liver	5 (14.7%)
Colon	2 (5.9%)
Lower esophagus with median phrenotomy	3 (8.8%)
Distal pancreas	2 (5.9%)
Peritoneal lavage cytology +/−	1 (3.2%)/30 (96.8%)
Residual tumor status	
R0	27 (79.4%)
R1	1 (2.9%)
R2	6 (17.7%)
Pathological response	
Grade 0	3
Grade 1a	9
Grade 1b	9
Grade 2	11
Grade 3	2
Morbidity Clavien–Dindo classification	
Pancreatic fistulae	3 (8.8%) grade II/IIIa:1/2
Lymphatic fistulae	5 (14.7%) grade I/II: 1/4
Anastomotic leakage	1 (2.9%) grade IIIa
Intra-abdominal abscess	1 (2.9%) grade IIIa
Post operative ileus	1 (2.9%) grade II
Mortality	0 (0%)

with an MST of 29.9 months, whereas, the 3-year OS in the 23 patients with chemotherapy alone was 0% with MST of 9.6 months (Fig. 1B). Among the patients who underwent conversion gastrectomy, the 15 potentially resectable cases exhibited the 3-year OS of 92.9% and the OS rate of potentially resectable cases was significantly higher than that of initially unresctable cases ($p < 0.01$) as shown in Fig. 1C. All potentially resectable cases underwent surgical resection after DCS therapy, whereas 19 of 42 patients underwent surgical resection in initially unresectable cases.

MSTs and 3-year OS rates according to various prognostic factors in 34 patients who underwent conversion gastrectomy are shown in Table 3. Among these patients, univariate analysis identified 16a2b1 PAN metastasis, peritoneal metastasis, potential resectability, and residual tumor status as significant prognostic factors. Multivariate analysis revealed potential resectability as the only independent prognostic factor contributing to OS (hazard ratio 0.133, 95%CI 0.024-0.744, $p = 0.021$).

Subsequently, various prognostic factors in 42 patients who were categorized as initially unresectable were investigated as shown in Table 4. Univariate analysis identified clinical response and conversion surgery as the significant prognostic factor ($p = 0.023$, 0.048, respectively). Subsequent multivariate analysis of prognostic factors with $p < 0.1$ in univariate analysis identified clinical response to chemotherapy as the only independent prognostic factor contributing to OS (hazard ratio 0.354, 95% CI 0.151–0.783, $p = 0.036$) in the subgroup of initially unresectable cases.

Discussion

Advances in gastric cancer chemotherapy including the introduction of new anticancer agents and the development of multi-agent regimens, have made macroscopic complete resection possible in some patients with stage IV gastric cancer. This type of surgery is referred to as conversion gastrectomy with curative intent, and differs from palliative gastrectomy. Surgical resection for residual tumors has been reported as salvage gastrectomy, adjuvant gastrectomy, or secondary surgery.[8–14] They reported clinical benefits of gastrectomy following various combination chemotherapies and presented median survival that ranged from 22 to 53 months. However, the chemotherapeutic regimens administered in most of these studies, such as S-1 plus paclitaxel or S-1 plus docetaxel were not the current standard treatments for stage IV gastric cancer, while some reports included more than one regimen in the same study. These clinical issues make it difficult to draw firm conclusions about the optimum role of chemotherapy in the setting of conversion gastrectomy.

In the current study, we investigated stage IV gastric cancer patients who underwent DCS therapy, regardless of conversion gastrectomy. This triple combined therapy showed high response rate in several phase I and II trials: 76.9–87.1%[4–6] and is expected to become the standard regimen for advanced gastric cancer in Japan. Our data show that the rate of conversion gastrectomy following DCS therapy was 59.6% and patients undergoing conversion gastrectomy have longer survival compared with patients receiving chemotherapy alone. The resection rate of our study is high compared with that of the previous studies with double combined therapy. In the SPIRITS trial, 7 of 148 patients (4.7%) underwent surgical resection following S-1 plus cisplatin.[3] Fukuchi et al. reported 40 of 151 patients (26.5%) with stage IV gastric cancer underwent conversion surgery following S-1 plus cisplatin or paclitaxel.[14] Our data also reveal that the 3-year OS rate of potentially resectable cases was 92.9%, compared with a 3-year OS rate in unresectable cases of only 35.1% ($p < 0.01$). Multivariate analysis indentified potentially resectable disease is the only significant and independent factor associated with OS in patients undergoing conversion gastrectomy. These results indicate the potentially resectable cases can be expected long-term survival by conversion gastrectomy following DCS therapy and be ideal candidates for this

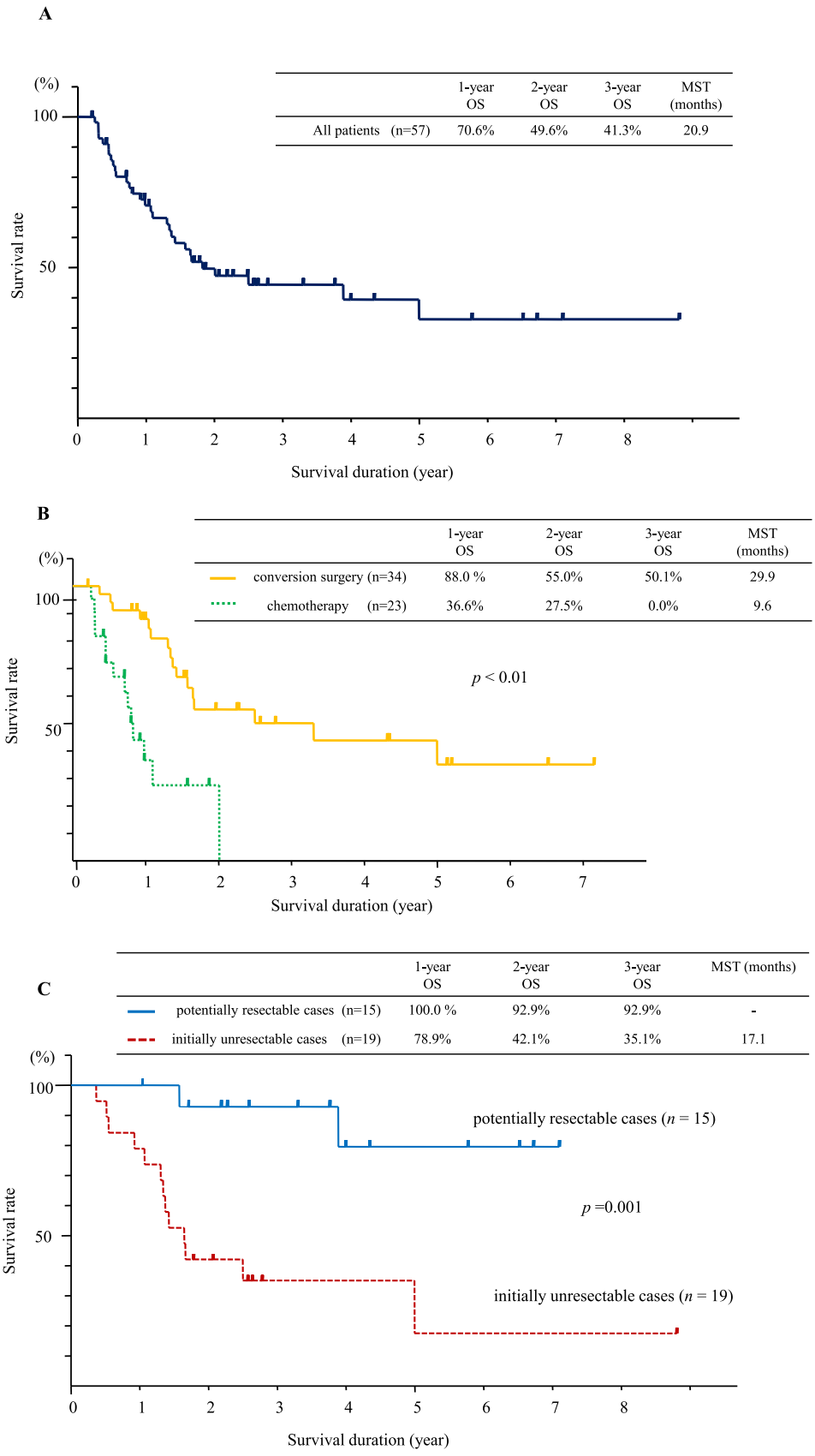

Figure 1. (A) Overall survival rates in all study patients. (B) Overall survival rates in patients with conversion surgery and those with chemotherapy alone. (C) The differences in overall survival rates between potentially resectable and initially unresectable cases who underwent conversion gastrectomy.

Table 3
Survival and various prognostic factors in 34 patients who underwent conversion gastrectomy.

Variable	Univariate analysis				Multivariate analysis		
	Number of patients	MST (months)	3-yr OS (%)	*p* value	HR	95% CI	*p* value
Sex, male/female	23/11	59.9/27.3	61.7/37.9	0.327	–	–	–
Age (<70/≧70 years)	23/11	47.7/18.8	53.7/48.7	0.909	–	–	–
ECOG performance status (0/1)	26/8	24.7/20.0	56.2/37.5	0.456	–	–	–
Bormann macroscopic type (2 or 3/4)	10/24	18.9/47.7	48.2/54.0	0.994	–	–	–
Differentiation (intestinal/diffuse)	24/10	47.7/18.7	58.2/35.6	0.386	–	–	–
Number of incurable factors (1/≧2)	24/10	59.9/20.0	64.6/25.9	0.067	–	–	–
16a2b1 PAN metastasis (+/−)	18/16	−/18.9	72.9/15.2	0.047	1.229	0.278–5.426	0.786
Liver metastasis (+/−)	11/23	18.9/33.4	40.4/57.9	0.367			
peritoneal metastasis (+/−)	4/30	6.54/52.1	0.0/27.9	<0.01	3.173	0.613–16.42	0.169
Potentially resectable/Initially unresectable	15/19	−/17.1	90.1/26.3	<0.01	0.133	0.024–0.744	0.021
Clinical response (PR/SD, PD or NE)	29/5	27.0/−	49.8/66.7	0.455	–	–	–
Residual tumor status R0/R1 or 2	27/7	−/15.6	63.5/16.0	<0.01	0.494	0.108–2.252	0.362
Pathological response grade ≧1b/0 or 1a	21/13	51.8/17.1	59.7/47.0	0.316	–	–	–

Table 4
Survival and various prognostic factors in initially unresectable cases.

	Univariate analysis				Multivariate analysis		
Variable	Number of patients	MST (months)	3-yr OS (%)	*p* value	HR	95% CI	*p* value
Sex (male/female)	27/15	13.1/15.9	38.2/0.0	0.838	–	–	–
Age (<70/≧70 years)	35/7	17.0/15.6	22.6/15.1	0.264	–	–	–
ECOG performance status (0/1)	27/15	16.0/9.6	22.2/23.8	0.377	–	–	–
Differentiation (intestinal/diffuse)	17/25	19.9/12.7	35.7/0	0.085	2.167	0.709–4.165	0.231
Number of incurable factors (1/≥2)	16/26	11.7/19.9	26.2/24.5	0.167	–	–	–
clinical response (PR/SD,PD or NE)	31/11	17.05/6.6	27.2/0.0	0.023	0.354	0.151–0.783	0.036
Conversion surgery (+/−)	19/23	19.6/9.6	24.7/0.0	0.048	1.876	0.207–1.219	0.128
Peritoneal metastasis (+/−)	15/27	9.6/16.3	9.3/27.6	0.155	–	–	–
16a2b1 PAN metastasis (+/−)	13/29	16.0/13.1	37.0/10.6	0.171	–	–	–
Liver metastasis (+/−)	13/29	15.6/16.0	27.5/20.2	0.994	–	–	–

curative strategy among patients with stage IV gastric cancer.

PAN metastasis is generally recognized as a non-curative factor because the 5-year overall survival rate of patients with PAN metastasis can be as high as 20% even after radical dissection.[15] Therefore, additional therapies besides curative resection have been developed to improve treatment outcome. Recently, several studies presented the efficacy of preoperative chemotherapy and curative resection in patients with pathologically positive PAN.[4,16] The results of the current study are consistent with recent findings regarding multimodality therapy in patients with PAN metastasis arising from gastric cancer.

Liver metastasis is present in 4–14% of gastric cancer patients at diagnosis.[17,18] The role of hepatectomy in gastric cancer is controversial. Only a few patients with limited liver metastasis are thought to gain a survival benefit from hepatectomy, because it usually occurs in the setting of multiple lesions in gastric cancer. Takemura et al. reported 1-, 3-, and 5-year OS rates after macroscopically complete liver resection (n = 64) of 84%, 50%, and 37%, respectively, in patients with fewer than three metastatic lesions.[19] However, previous studies showed that recurrence rate after hepatectomy for liver metastasis from gastric cancer was 63.6–91.0%.[20–25] This result indicates the importance of controlling the micrometastasis by additional systemic therapy. Chen et al. reported on the use of preoperative chemotherapy for liver metastases as an adjunct to surgery with MST of 22.3 months.[26] In this study, we defined potentially resectable liver metastases as those involving fewer than three peripheral lesions, because synchronous major hepatectomy with gastrectomy after DCS therapy may increase morbidity and mortality as a result of operative stress. We found 1-, 2-, and 3-year OS rates of 100%, 80%, and 80%, with no operative mortality.

In contrast, it remains unclear whether conversion gastrectomy improves the prognosis in initially unresectable cases; although univariate analysis indicated that initially unresectable patients who underwent conversion gastrectomy had significantly longer survival than those who received chemotherapy alone ($p = 0.048$), multivariate analysis showed that clinical response to chemotherapy was the most important factor affecting prognosis in initially unresectable cases ($p = 0.021$). Our results thus suggest that conversion gastrectomy in initially unresectable patients should be considered with caution, even if

distant metastases have disappeared or are controlled by chemotherapy. This represents an important issue in terms of deciding which patients are most likely to benefit from multimodality therapy, including conversion gastrectomy.

In the current study, the MST for stage IV gastric cancer patients treated with multimodality therapy including DCS followed by conversion gastrectomy was 29.9 months. Among these patients, those with potentially resectable disease had a remarkably good prognosis and were selected as the only significant prognostic factor.

Potentially resectable cases might be ideal candidates for this curative strategy. However, the conclusions are complicated by the fact that surgical cases are considered to have relatively high chemosensitivity and good performance status, leading to selection bias. The limitations of our study also include its retrospective design in single institute and small sample size. Because potentially resectable cases are very small population in gastric cancer, further prospective multicenter trials with longer OS as the primary endpoint are needed on the basis of our results to allow the identification of patients who are likely to gain a survival benefit from conversion surgery.

Conflict of interest

All the authors declare that there is no financial interest or any other potential conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2015.04.021

References

1. Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group study (JCOG 9205). *J Clin Oncol* 2003;**21**:54–9.
2. Boku N, Yamamoto S, Fukuda H, 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. http://dx.doi.org/10.1016/S1470-2045(09)70259-1.
3. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of ad- vanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;**9**:215–21.
4. Fushida S, Fujimura T, Oyama K, Yagi Y, Kinoshita J, Ohta T. Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with paraaortic lymph node metastases. *Anticancer Drugs* 2009;**20**:752–6. http://dx.doi.org/10.1097/CAD.0b013e32832ec02b.
5. Sato Y, Takayama T, Sagawa T, et al. Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Cancer Chemother Pharmacol* 2010;**66**:721–8. http://dx.doi.org/10.1007/s00280-009-1215-2.
6. Nakayama N, Koizumi W, Sasaki T, et al. A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). *Oncology* 2008;**75**:1–7. http://dx.doi.org/10.1159/000151613.
7. Japanese classification of gastric carcinoma: 3rd English edition. *Jpn Gastric Cancer Assoc Gastric Cancer* 2011;**14**:101–12.
8. Nakajima T, Ota K, Ishihara S, et al. Combined intensive chemotherapy and radical surgery for incurable gastric cancer. *Ann Surg Oncol* 1997;**4**:203–8. http://dx.doi.org/10.1007/BF02306611.
9. Ishigami S, Natsugoe S, Nakajo A, et al. Salvage gastrectomy following a combination of biweekly paclitaxel and S-1 for stage IV gastric cancer. *J Gastrointest Surg* 2008;**12**:1370–5. http://dx.doi.org/10.1007/s11605-008-0539-2.
10. Kanda T, Yajima K, Kosugi S, Ishikawa T, Ajioka Y, Hatakeyama K. Gastrectomy as a secondary surgery for stage IV gastric cancer patients who underwent S-1-based chemotherapy: a multi-institute retrospective study. *Gastric Cancer* 2012;**15**:235–44. http://dx.doi.org/10.1007/s10120-011-0100-y.
11. Suzuki T, Tanabe K, Taomoto J, et al. Preliminary trial of adjuvant surgery for advanced gastric cancer. *Oncol Lett* 2010;**1**:743–7.
12. Yano M, Shiozaki H, Inoue M, et al. Neoadjuvant chemotherapy followed by salvage surgery: effect on survival of patients with primary noncurative gastric cancer. *World J Surg* 2002;**26**:1155–9. http://dx.doi.org/10.1007/s00268-002-6362-0.
13. Yabusaki H1, Nashimoto A, Matsuki A, Aizawa M. Significance of surgical treatment in multimodal therapy for stage IV highly advanced gastric cancer. *Hepatogastroenterology* 2013;**60**:377–81.
14. Fukuchi M, Ishiguro T, Ogata K, et al. Prognostic role of conversion surgery for unresectable gastric Cancer. *Ann Surg Oncol* 2015. [Epub ahead of print] PMID: 25663597.
15. Yonemura Y, Segawa M, Matsumoto H, et al. Surgical results of performing R4 gastrectomy for gastric cancer located inthe upper third of the stomach. *Surg Today* 1994;**24**:488–93.
16. Tsuburaya A, Mizusawa J, Tanaka Y, et al. Stomach Cancer Study Group of the Japan Clinical Oncology Group. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014;**101**:653–60. http://dx.doi.org/10.1002/bjs.9484.
17. Shin A, Kim J, Park S. Gastric cancer epidemiology in Korea. *J Gastric Cancer* 2011;**11**:135–40. http://dx.doi.org/10.5230/jgc.2011.11.3.135.
18. Schlansky B, Sonnenberg A. Epidemiology of noncardia gastric adenocarci- noma in the United States. *Am J Gastroenterol* 2001;**106**:1978–85.
19. Takemura N, Saiura A, Koga R, et al. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. *Langenbecks Arch Surg* 2012;**397**:951–7. http://dx.doi.org/10.1007/s00423-012-0959-z.
20. Okano K, Maeba T, Ishimura K, et al. Hepatic resection for metastatic tumors from gastric cancer. *Ann Surg* 2002;**235**:86–91.
21. Sakamoto Y, Sano T, Shimada K, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. *J Surg Oncol* 2007;**95**:534–9.
22. Cheon SH, Rha SY, Jeung HC, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 2008;**19**:1146–53.
23. Roh HR, Suh KS, Lee HJ, Yang HK, Choe KJ, Lee K. Outcome of hepatic resection for metastatic gastric cancer. *Am Surg* 2005;**71**:95–9.
24. Ambiru S, Miyazaki M, Ito H, et al. Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 2001;**181**:279–83.
25. Shirabe K, Shimada M, Matsumata T, et al. Analysis of the prognostic factors for liver metastasis of gastric cancer after hepatic resection: a multi-institutional study of the indications for resection. *Hepatogastroenterology* 2003;**50**:1560–3.
26. L1 Chen, Song MQ, Lin HZ, et al. Chemotherapy and resection for gastric cancer with synchronous liver metastases. *World J Gastroenterol* 2013;**19**:2097–103. http://dx.doi.org/10.3748/wjg.v19.i13.2097.