Int Surg 2013;**98:**181–187
DOI: 10.9738/INTSURG-D-12-00027.1

Prognostic Factors for Stage IV Gastric Cancer

Hiroyuki Baba, Koki Kuwabara, Toru Ishiguro, Kensuke Kumamoto, Yoichi Kumagai, Keiichiro Ishibashi, Norihiro Haga, Hideyuki Ishida

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan

Gastric cancer is the fourth leading cause of cancer in the world with the incidence of nearly 1 million cases (7.8% of the total). Regionally, half of the world cases occur in Eastern Asia. It is a second leading cause of cancer death worldwide (738,000 deaths, 9.7% of the total).[1] Although early diagnosis and standardized treatment strategies have contributed to the improvement of survival, stage IV patients still suffer from poor prognosis. Previous reports from Japan and Korea have shown the 5-year survival rate to be 15.3% and 18%, respectively.[2,3]

Guidelines published by the Japanese Gastric Cancer Association (JGCA)[4,5] recommend selection from among 5 treatments for stage IV patients in clinical practice: surgery (extended or palliative), chemotherapy, radiation therapy or palliative care. Principles are still controversial, and clinical study is advocated. The nature of the disease does not allow us to conduct prospective studies; however, retrospective study plays an important role by means of clinical study.

This study is a retrospective study based on clinical practice and aims to clarify the favorable factors contributing to better prognosis of stage IV gastric cancer patients. Furthermore, we aim to assess the optimal treatment strategies.

Patients and Methods

Between April 2005 and March 2011, a total of 123 patients with pathologically confirmed stage IV gastric cancer at Saitama Medical Center were investigated according to the data collected from the chart. Clinicopathologic factors evaluated in this study were age, sex, performance status (PS), tumor location, gross tumor appearance, histologic type, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), tumor depth (T), regional lymph node metastasis (N), liver metastasis (H), peritoneal dissemination (P), and peritoneal lavage cytology (CY). Distant metastasis besides H, P, and CY are relatively rare, except for lymph node metastasis beyond regional nodes [M (LYM)] We categorized these rare M factors as "other M" and included them as one of the variables in this study. Removal of the primary tumor or not and introducing systemic chemotherapy or not was also included as one of the variables for statistical analysis.

Reprint requests: Hiroyuki Baba, MD, PhD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama, 350-8550, Japan.
Tel.: +81 49 228 3619; Fax: +81 49 222 8865; E-mail: hirobaba@saitama-med.ac.jp

The staging process was based on the tumor-node-metastasis (TNM) staging system adopted by Union for Cancer Control (UICC; 7th edition, 2010).[6] To avoid unnecessary terminological confusion, we followed the terminology defined in the English version of guidelines for diagnosis and treatment of carcinoma of the stomach,[7] published by JGCA. PS was evaluated on admission in every patient using the method proposed by the Eastern Cooperative Oncology Group (ECOG).[8] Diagnosis of stage IV was made by preoperative radiologic findings, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US), otherwise at laparotomy or staging laparoscopy. Peritoneal lavage cytology (CY) was performed at the time of the laparotomy, and diagnostic information was given from the pathologic department during the operation. Pathologic reports of the specimens were investigated by the board-certified pathologists at our institution.

JGCS defines stage IV patients as having no absolute treatment strategy in the treatment guideline.[2] Therefore, we do not have a particular treatment algorithm against stage IV patients at this time. However, we weigh patients' clinical symptoms for decision making. Gastric outlet syndrome (GOS) is a most concerning and irritating symptom for patients, and if recognized, surgery tends to be our first choice. If not, chemotherapy can be an option. If poor patient status is remarkable, best supportive care is considered. Patients may start with chemotherapy and go on to have surgery with the emergence of GOS or bleeding. Whatever the treatment order may be, all patients in this retrospective study provided written informed consent before starting anything.

Whether to introduce chemotherapy first or not and the most effective surgical procedure were briefly discussed with patients and their family members. Decision making was based on the patients' wishes and objective judgment by the physician in charge. Attempt to carry out extended surgery often ended up with removal of the primary tumor after all, achieving only R1 surgery. Especially, when palliative surgery was anticipated, sufficient informed consent to the patient was made, and the operation was carried out on the premises. Chemotherapy regimen was based on tegafur, gimeracil, and oteracil potassium combined antitumor drug (S-1), an oral pyrimidine derivative, which is the major anti-gastric cancer agent today.[9–11] Combination with cisplatin (CDDP) is considered to be the first choice regimen today.[12] However, other agents were used in practice on a daily basis, such as irinotecan (CPT-11) and taxans (paclitaxel and docetaxel), and these patients were also included in the study.[13–15]

Statistical Analysis

Statistical analyses were performed between the groups using the χ^2 or Mann-Whitney U tests where appropriate. Survival curves were analyzed using the Kaplan-Meier method, and differences were determined by the log-rank test. The multivariate Cox proportional hazards model was used to identify independent prognostic factors. For determining the independent prognostic factors, a factor with a P value < 0.1 by univariate analysis was introduced into multivariate analysis with a forward stepwise selection. Overall survival was defined as a period starting from the initial treatment (chemotherapy, surgery, or best supportive care) until death of any reason. Tests were considered significant at a P value < 0.05.

Results

Demographic and clinicopathologic characteristics are shown in Table 1. There were 91 men and 32 women, with a median age of 69 years (range, 26–88). PS 0 and 1 combined counted 102 patients (82.9%). The number of patients whose tumor location involved the proximal area of the stomach was 55 (44.7%). Sixty-eight patients (55.3%) had their tumor localized at the distal part of the stomach. Gross appearance of the tumor varied from Borrman type 0 to type 5, counting 1, 6, 18, 57, 33, and 18, respectively. All tumors were pathologically diagnosed as adenocarcinoma. Thirty-five (28.5%) of them were tubular type, and 88 (71.5%) were nontubular type, suggesting that adenocarcinoma that were potentially invasive in nature were dominant in stage IV. The number of T4 patients was 82 (66.7%) and N3 patients, 67 (54.5%). Distant metastasis defined by H, P, and CY counted 46 (37.4%), 62 (50.4%), and 39 (45.3%) patients, respectively. The number of CY1 patients being less than P1 seems odd, but this phenomenon can be explained by understanding the actual peritoneal lavage cytology (CY) carried out upon operation. According to the chart review, CY was routine for P0 patients (n = 61) and among them, 14 were CY1. The rest of the patients (n = 62) being P1, CY was not a routine procedure. The total number of patients

Table 1 Clinicopathological features of stage IV gastric cancer patients

Parameters	Total
Number of patients	123
Sex (male/female)	91/32
Age (median; years)	69 (26–88)
Performance status (0/1/2 or more)	72/30/21
Tumor location (distal only/including proximal)	68/55
Gross tumor appearance[a] (type 0/1/2/3/4/5)	1/6/18/57/33/8
Histologic type[a]	
tubular type	35
nontubular type	88
Tumor markers	
CEA [median (range)] (ng/mL)	6.05 (0.8–3136.5)
CA19-9 [median (range)] (ng/mL)	15.5 (1–67867)
TNM factors	
Depth of tumor invasion (T) (1/2/3/4)	0/4/37/82
Lymph node metastasis (N) (0/1/2/3)	15/22/19/67
Distant metastasis (M)	
H1	46
P1	62
CY1 (n = 86)	39
Other M[b]	55

[a]Tumor appearance as described in the English version of JGCA 14th edition.[30]

[b]Metastasis other than H, P, and CY.

with CY being 86, 25 patients were P1 and naturally enough CY1. Therefore, the sum of 14 patients (P0CY1) and 25 patients (P1CY1) was the number of total CY1 patients (n = 39). If we consider all P1 patients as CY1, the number of CY1 would sum up to 76, instead of 39, CY1 being more than P1. Other M counted 55 (44.7%) patients, and they were all a result of the extensive lymph node involvement, which can be classified as M (LYM). The median of CEA and CA19-9 was 6.05 ng/mL and 15.5 ng/mL, respectively.

Figure 1 shows the flow diagram of the treatments undertaken in stage IV patients. A total of 78 patients underwent a surgical procedure. Among them, 37 patients underwent reduction surgery, and 41 patients had palliative surgery. The decision whether to resect the primary tumor was entrusted to the surgical team on laparotomy. Thirteen patients did not receive postoperative chemotherapy mostly because of the worsening of their performance status. Others wished to have best supportive care after all. Thirty-eight patients did not have surgery and received chemotherapy alone or went to have best supportive care (n = 7). Chemotherapy was carried out with S-1 based regimen (n = 99). Among them, patients with S-1 only, or in combination with CDDP, taxans, and CPT11 were 45, 45, 8, and 1, respectively (Table 2).

Univariate analysis of prognostic factors for overall survival is listed in Table 3. Age (70 or more versus under 70; $P = 0.03$), performance status (PS2 or more versus PS0 or 1; $P < 0.01$), liver metastasis (H1 versus H0; $P = 0.02$), other M (positive versus negative; $P < 0.01$), CA19-9 (37 ng/mL or more versus less than 37 ng/mL; $P < 0.01$), reduction surgery (nonresection versus resection; $P < 0.01$), chemotherapy (No versus Yes; $P < 0.01$) were found to be significant prognostic factors for overall survival. As also listed in Table 3, PS, other M, reduction surgery, and chemotherapy were calculated as independent prognostic factors. Considering these results, the survival curve of the subgroup of stage IV patients (*i.e.*, better PS patients without other M) who underwent reduction surgery plus systemic chemotherapy showed significantly better survival curve than those who lack any one of these 4 favorable variables (Fig. 2).

Discussion

We have clearly demonstrated in this study that on the premises of conducting both reduction surgery and systemic chemotherapy, stage IV patients with good PS and M factors limited within H1, P1, and CY1 can prolong survival significantly. Conducting reduction surgery and systemic chemotherapy for poor prognostic patients seems too aggressive when comprehensive treatment strategy is still yet to be defined. Therefore, treatment strategy for stage IV gastric cancer patients is always a controversial issue in clinical practice owing to their poor prognosis. However, our results may be good news for these patients. Furthermore, it may be a cornerstone for optimal treatment strategy for future stage IV gastric cancer patients. To our knowledge, we are the first to conclude that certain subgroup of stage IV patients can benefit from conducting both reduction surgery and chemotherapy.

Treatment options for stage IV gastric cancer patients are limited since the spread of the disease is far beyond its origin. According to the JGCA data, cumulative 5-year survival of stage IV patients was 15.3%,[2] and Korean data also showed similar results with 18%.[3] Moreover, among all stage IV patients, 4% to 9% of them are said to be too advanced with no chance of curative surgery and their prognosis is absolutely poor showing less than 10% at 3 years after diagnosis.[16]

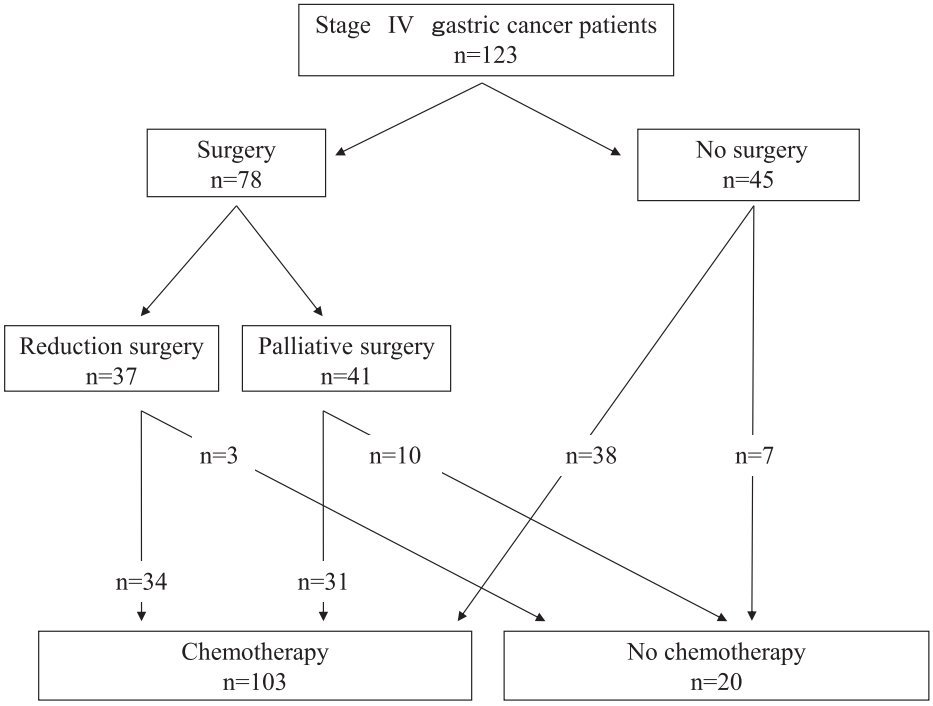

Fig. 1 Flow diagram of 123 patients.

JGCA suggests extended surgery or palliative surgery as clinical practice and reduction surgery as a clinical study for stage IV patients (T4 and N3 patients are classified as stage IV in this suggestion). Past literatures have proven that when stage IV is diagnosed by only one M factor, conducting resection may prolong survival.[17–22] Therefore, removing the primary tumor is an option even if responsive chemotherapy is available today.

Table 2 Treatment data of patients

Treatment	Patients
Surgery	78 (63.4%)
Reduction surgery	37
Palliative surgery	41
Chemotherapy	103 (83.7%)
S-1–based regimen	99 (96.1%)
S-1 + CDDP	45
S-1 + taxan	8
S-1 + irinotecan	1
S-1 alone	45
Treatment combination	
Chemotherapy and no surgery	38
Chemotherapy and reduction surgery	34
Chemotherapy and palliative surgery	31
Best supportive care	7

S-1 has gained an ultimate position as a standard antitumor agent for gastric cancer treatment. Together with other agents such as CDDP, CPT-11, and taxans (paclitaxel and docetaxel), the response rate of chemotherapy has improved dramatically. They have provided better prognosis for stage IV patients.[9–11] S-1 with CDDP was proven to have a high response rate and is chosen as the first line chemotherapy.[12]

Adjuvant chemotherapy trials against advanced gastric cancer have shown promising results.[23,24] On the other hand, chemotherapy is said to have no influence on survival for the elderly.[25] Nevertheless, S-1 alone can be used safely for the elderly and poor PS patients, which most stage IV patients are.[26,27] Neoadjuvant chemotherapy settings have been discussed lately to give an adequate amount of antitumor agent and if possible, downstage the non-curative tumor to perform R0 operation. The European group has reported recently that R0 surgery increased but did not affect overall survival.[28] Kochi and his colleagues have reported the efficacy of neoadjuvant S-1+CDDP.[29] Before any conclusive results come out by the well-organized studies, we should be careful in adopting neoadjuvant chemotherapy in the clinical settings.

Table 3 Univariate and multivariate analysis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinicopathologic factors				
Age (≥70 versus <70)	1.52 (1.03–2.24)	0.03	1.25 (0.83–1.89)	0.28
Sex (female/male)	0.77 (0.49–1.19)	0.24		
Performance status (≥2 versus 0)	2.88 (1.76–4.70)	<0.01	2.21 (1.26–3.87)	<0.01
Tumor location (including proximal versus distal only)	0.95 (0.65–1.41)	0.82		
Gross tumor appearance (Borrman 4/5 versus 0/1/2/3)	1.10 (0.73–1.64)	0.66		
Histologic type (nontubular versus tubular)	1.21 (0.79–1.86)	0.38		
CEA (>6.7 ng/mL versus <6.7 ng/mL)	1.23 (0.83–1.82)	0.3		
CA19-9 (>37 ng/mL versus <37 ng/mL)	1.75 (1.16–2.64)	<0.01	1.31 (0.85–2.02)	0.22
TNM factors				
Tumor status (T4 versus T3 or less)	0.84 (0.56–1.26)	0.4		
Nodal status (N3 versus N2 or less)	1.24 (0.84–1.83)	0.28		
Liver metastasis (H1 versus H0)	1.58 (1.07–2.34)	0.02	1.35 (0.84–2.17)	0.21
Peritoneal carcinomatosis (P1 versus P0)	1.17 (0.80–1.73)	0.41		
Peritoneal lavage cytology (CY1 versus CY0)	1.36 (0.85–2.17)	0.2		
Other M[a] (positive versus negative)	1.90 (1.29–2.80)	<0.01	2.23 (1.47–3.40)	<0.01
Treatment factors				
Primary tumor (nonresection versus resection)	3.89 (2.56–5.93)	<0.01	3.39 (2.04–5.65)	<0.01
Chemotherapy (No versus Yes)	2.18 (1.21–3.94)	<0.01	2.45 (1.25–4.79)	<0.01

HR, hazard ratio; CI, confidential index.

[a]Other M, metastasis other than H, P, and CY.

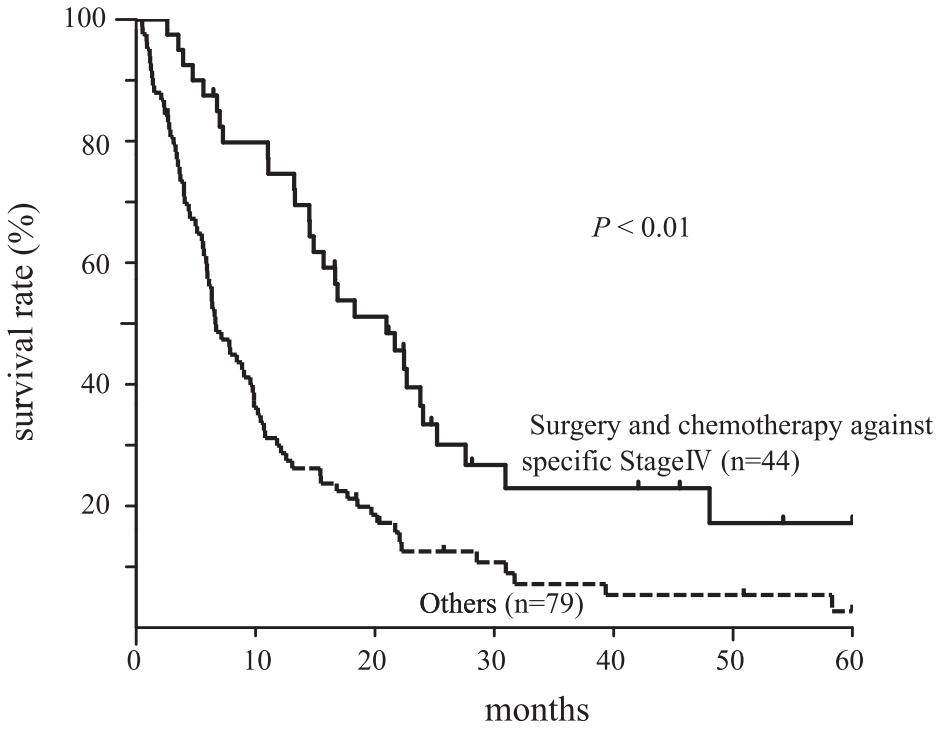

Fig. 2 Survival curves of patients with stage IV gastric cancer who underwent both reduction surgery and chemotherapy. Solid line represents patients with specific M (H, P, and CY). Dotted line represents patients with other M as described in the text.

In this study, our patient treatment strategy was nothing but practice based, and the decision whether to operate first or begin chemotherapy first was not randomly selected. We always tried to provide surgical treatment not only for better oncologic outcome but also for the settlement of the uncomfortable gastrointestinal symptoms caused by the tumor often described as GOS. Moreover, ensuring the passage by surgery may contribute to achieve better compliance of S-1 treatment along with the increase of oral diet. If the patients had a strong will to start chemotherapy rather than surgery, we respected their decision and carried it out without any delay.

Nevertheless, 13 patients who had surgery as initial treatment failed to move on to chemotherapy. Some had lost their wish to continue treatment, some had failed to improve or keep their performance status, and some had to move on to best supportive care. In a sense, these 13 patients could only enjoy the benefit of reducing unfavorable gastrointestinal symptoms caused by the tumor. But from the quality of life point of view, it may be considered as the right choice for them. Patient performance status and their will may change during the treatment course, and we should be flexible in all circumstances with decision making.

As shown in the survival curve in Fig. 2, we clearly demonstrated that regardless of treatment order, if both reduction surgery and chemotherapy are carried out, we can improve the prognosis of certain stage IV patients, that is, patients diagnosed stage IV with H, P, and CY (redundant included). Therefore, we should not hesitate to carry out both reduction surgery and systemic chemotherapy as long as patient PS is well enough. Moreover, metastatic-site specific treatment strategy was not necessary to achieve this result. Our study excluded M (LYM) from the favorable factor that extended lymph node metastasis is truly an unfavorable factor for stage IV patients.

The current study was based on a small number of data acquired retrospectively at a single institution in Japan. Although the extent of the disease does not permit us to carry out prospective studies, our results may be rationalized and validated in a larger randomized control trial. It is beyond the objective of this study, but clinically, it is very interesting to find out the treatment order or when to convert to surgery after neo-adjuvant chemotherapy. These questions could be clarified by a future randomized control trial.

Acknowledgments

The authors would like to thank Professor Tomoyuki Kawada, Nippon Medical School, for his assistance with statistical analysis.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;**127**(12):2893–2917
2. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y *et al*. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* 2013;**16**(1):1–27
3. Lee HK, Yang HK, Kim WH, Lee KU, Choe KJ, Kim JP. Influence of the number of lymph nodes examined on staging of gastric cancer. *Br J Surg* 2001;**88**(10):1408–1412
4. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer* 2011;**14**(2):97–100
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;**14**(2): 113–123
6. International Union Against Cancer. In: Sobin LH, Gospodarowicz M, Wittelkind C, eds. *TNM Classification of Malignant Tumors*. 7th ed. New York, NY: Wiley-Blackwell, 2009:84–95
7. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. *Gastric Cancer* 1998; **1**(1):10–24
8. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**(6):649–655
9. 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**(11):1715–1720
10. 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. *Oncology* 2000;**58**(8):191–197
11. Maehara Y. S-1 in gastric cancer: a comprehensive review. *Gastric cancer* 2003;**6**(suppl 1):2–8
12. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M *et al*. Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (The SPIRITS trial) SPIRITS: S-1 plus cisplatin vs S-1 in RCT in the treatment for stomach cancer. *Lancet Oncol* 2008;**9**(3):215–221
13. Takiuchi H, Narahara H, Tsujinaka T, Gotoh M, Kawabe S, Katsu K *et al*. Phase I study of S-1 combined with irinotecan

(CPT-11) in patients with advanced gastric cancer (OGSG 0002). *Jpn J Clin Oncol* 2005;**35**(1):520–525
14. Fujitani K, Narahara H, Takiuchi H, Tsujinaka T, Satomi E, Gotoh M *et al*. Phase I and pharmacokinetic study of S1 combined with weekly paclitaxel in patients with advanced gastric cancer. *Oncology* 2005;**69**(5):414–420
15. Yoshida K, Ninomiya M, Takakura N, Hirabayashi N, Takiyama W, Sato Y *et al*. Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. *Clin Cancer Res* 2006;**12**(11):3402–3407
16. Japanese Gastric Cancer Association Registration Committee. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. *Gastric Cancer* 2006;**9**(2):51–66
17. Bozzetti F, Bonfanti G, Audisio RA, Doci R, Dossena G, Gennari L *et al*. Prognosis of patients after palliative surgical procedures for carcinoma of the stomach. *Surg Gynecol Obstet* 1987;**164**(2):151–154
18. Kikuchi S, Arai Y, Morise M, Kobayashi N, Tsukamoto H, Shimao H *et al*. Gastric cancer with metastases to the distant peritoneum: a 20-year surgical experience. *Hepatogastroenterology* 1998;**45**(22):1183–1188
19. Koga S, Kawaguchi H, Kishimoto H, Tanaka K, Miyano Y, Kimura O *et al*. Therapeutic significance of noncurative gastrectomy for gastric cancer with liver metastasis. *Am J Surg* 1980;**140**(3):356–359
20. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ; Dutch Gastric Cancer Group. Value of palliative resection in gastric cancer. *Br J Surg* 2002;**89**(11): 1438–1443
21. Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJ. Tumor load and surgical palliation in gastric cancer. *Hepatogastroenterology* 2001;**48**(44):1219–1221
22. Maekawa S, Saku M, Maehara Y, Sadanaga N, Ikejiri K, Anai H *et al*. Surgical treatment for advanced gastric cancer. *Hepatogastroenterology* 1996;**43**(7):178–186
23. 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**(18): 1810–1820
24. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN *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
25. Endo S, Yoshikawa Y, Hatanaka N, Tominaga H, Shimizu Y, Hiraoka K *et al*. Treatment for gastric carcinoma in the oldest old patients. *Gastric Cancer* 2011;**14**(2):139–143
26. Tsushima T, Hironaka S, Boku N, Machida N, Yamazaki K, Yasui H *et al*. Safety and efficacy of S-1 monotherapy in elderly patients with advanced gastric cancer. *Gastric Cancer* 2010; **13**(4):245–250
27. Tsushima T, Hironaka S, Boku N, Machida N, Yamazaki K, Yasui H *et al*. Comparison of safety and efficacy of S-1 monotherapy and S-1 plus cisplatin therapy in elderly patients with advanced gastric cancer. *Int J Clin Oncol* 2013;**18**(1):10–16
28. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF *et al*. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010;**28**(35):5210–5218
29. Kochi M, Fujii M, Kanamori N, Kaiga T, Takahashi T, Kobayashi M et al. Neoadjuvant chemotherapy with S-1 and CDDP in advanced gastric cancer. *J Cancer Res Clin Oncol* 2006; **132**(12):781–785
30. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**(2):101–112