Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(6) 2524–2532

DOI: 10.1177/0300060519845491
journals.sagepub.com/home/imr
SAGE

Tumor blood supply may predict neoadjuvant chemotherapy response and survival in patients with gastric cancer

Xiang Ji, Qiaoyun Yang, Hui Qin, Jie Zhou and Wenming Liu

Abstract

Objectives: We investigated the prognostic value of tumor blood supply in patients with advanced gastric cancer (GC) receiving neoadjuvant chemotherapy.

Methods: We retrospectively reviewed 53 patients with advanced GC treated with FLEEOX chemotherapy. The tumor computed tomography (CT) enhancement value was measured before chemotherapy (CT1; arterial phase CT–plain phase CT). The liver parenchyma CT enhancement value (CT2) was also measured using the same method, to eliminate individual differences. Tumor blood supply was defined as good or poor based on the median CT1/CT2 values. We evaluated the relationships between tumor blood supply and response to chemotherapy, clinicopathologic characteristics, and overall survival (OS).

Results: A good blood supply (GBS) was associated with significantly better clinical and pathological responses to chemotherapy than a poor blood supply (PBS). The 3-year OS was 65.8% for the entire cohort. Patients with a GBS had a significantly higher OS (78.57%) than those with a PBS (54.44%). Additionally, patients with Bormann type III GC had a better blood supply than those with type II GC.

Conclusion: Patients with advanced GC and a GBS are more likely to benefit from neoadjuvant chemotherapy than those with a PBS. Blood supply may thus be a predictor for chemotherapy response.

Changzhou No. 2 People's Hospital, Affiliated Hospital of Nanjing Medical University, Changzhou, China

Corresponding author:
Wenming Liu, Changzhou No. 2 People's Hospital, Affiliated Hospital of Nanjing Medical University, Gehu Middle Road, Changzhou, 213000, China.
Email: LWMICU@163.com

Keywords
Advanced gastric cancer, neoadjuvant chemotherapy, intra-arterial chemotherapy, blood supply, prognostic value, survival

Date received: 27 September 2018; accepted: 1 April 2019

Introduction

Gastric cancer (GC) is the second most common cause of cancer-related deaths worldwide, with almost 50% of all cases occurring in China.[1] Most patients are already at an advanced stage when a diagnosis of GC is made.[2,3] Although surgical resection is the main treatment for localized/regional GC, many patients with advanced GC fail to achieve satisfactory R0 resection rates after surgery alone. Two previous studies reported unsatisfactory postoperative survival rates of patients with stage III GC, but adjuvant chemotherapy with S-1[4] or capecitabine/oxaliplatin after D2 gastrectomy improved the survival of patients with stage II/III GC.[5] Compared with adjuvant chemotherapy, preoperative or neoadjuvant chemotherapy (NAC) is a promising approach that has been shown to improve the R0 resection rate, the response to intensive regimens, and the rate of chemotherapy initiation, while reducing chemotherapy toxicities and unnecessary surgery.[6] Among many randomized, controlled trials, the MAGIC and FNCLCC/FFCD trials showed that NAC improved progression-free survival and overall survival (OS) rates compared with surgery alone.[7,8] Although advances in treatments and understanding of GC have improved chemotherapy response rates to $\geq$50%,[7,9] this remains unsatisfactory, and further research thus aims to identify more accurate and effective methods for improving patient survival. However, given that the same treatment regimen cannot be applied to everyone, extensive attention has been focused on individualized treatments, including the identification of markers for screening out patients likely to benefit from chemotherapy.

In the current study, we examined the association between tumor blood supply and response to NAC in patients with advanced GC, and also analyzed its relationships with OS and clinicopathologic characteristics.

Patients and methods

Patients

This retrospective study included 53 patients with advanced GC (stage III, Bormann type II and III) who underwent preoperative intra-arterial and intravenous infusion chemotherapy at Changzhou No. 2 People's Hospital, Affiliated Hospital of Nanjing Medical University, Changzhou, China, from January 2010 to August 2013. All patients were diagnosed with GC by gastroscopic biopsy and were evaluated by contrast-enhanced computed tomography (CT) scan. Patients with potential peritoneal metastases were evaluated by laparoscopy and peritoneal cytology. Preoperative staging was carried out according to the 6th edition UICC TNM classification and the number of lymph node stations was determined according to the Japanese Gastric Cancer Association (JGCA) classification.[10]

Preoperative chemotherapy and follow-up

Preoperative intra-arterial infusion chemotherapy was administered using Seldinger's approach via the femoral artery. The FLEEFOX chemotherapy protocol was administered as follows: 5-fluorouracil (370 mg/m^2) and leucovorin (200 mg/m^2) by intravenous infusion on days 1–5, and intra-arterial administration of etoposide (80 mg/m^2), oxaliplatin (80 mg/m^2), and epirubicin (30 mg/m^2) via the Seldinger method on days 6 and 20, repeated for two cycles. The chemotherapeutic response was evaluated by contrast-enhanced CT scan independently by two experienced radiologists who were blinded to the clinical data, according to the criteria of the JGCA.[10] All patients were reappraised by CT after NAC. Patients considered to be resectable underwent gastrectomy with D2 lymphadenectomy, or D2+ lymphadenectomy if preoperative CT indicated N3 lymph node metastasis. Patients received six cycles of postoperative adjuvant chemotherapy with XELOX, involving oxaliplatin (130 mg/m^2) on day 1 and capecitabine (1000 mg/m^2) on days 1–14 of a 28-day cycle. Patients considered to be unresectable or who declined surgery received other regimens and/or best supportive care. The protocol was approved by the Chinese Ethics Committee of Registering Clinical Trials, and the independent Institutional Review Board and Ethics Committee of Changzhou No. 2 People's Hospital. All patients provided written informed consent.

Tumor CT values

The CT imaging system automatically measured the CT value. We measured each tumor CT enhancement value before chemotherapy (CT1; arterial phase CT value−plain phase CT value; average of five). To eliminate individual differences, we also measured the liver parenchyma CT enhancement value (CT2) using the same method. The tumor blood supply was defined as good or poor according to the median CT1/CT2 value. This method is illustrated in Supplemental Figure 1.

Clinical response and histological evaluation of surgical specimens

Each patient was examined by contrast-enhanced CT scan after two cycles of preoperative chemotherapy. Tumors were staged based on the JGCA criteria[10] (Tables 1 and 2).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software Inc., San Diego, CA, USA). OS was calculated from the date of first NAC to the date of death or last follow-up. Comparisons between groups were analyzed by unpaired test or Fisher's exact test. Survival curves were estimated according to the Kaplan–Meier method, and differences between the curves were analyzed using the log-rank test. Hazard ratios were determined using Cox proportional hazards regression. P values < 0.05 were considered to be significant.

Results

Clinical response

The characteristics of the 53 patients are shown in Table 3. Thirty-six patients were responders. Three patients (5.66%) obtained a complete response (CR), including two with a good blood supply (GBS) and one with a poor blood supply (PBS). Thirty-three patients (62.26%) obtained a partial response (PR), including 18 with a GBS and 15 with a PBS. Thirteen patients

Table 1. Definition of clinical response in primary lesion.

Complete response (CR)	Disappearance of all tumor lesions and no diagnosis of carcinoma; biopsy specimens negative for carcinoma
Partial response (PR)	
a-lesions	At least a 30% decrease in total size
b-lesions	Remarkable regression and flattening of tumor on X-ray/endoscopic examinations, roughly corresponding to at least 50% decrease in tumor size
c-lesions	At least 50% enlargement of gastric lumen in the area of the lesions by X-ray examination
Stable disease (SD)	Changes in tumor size or shape less than PR, but not progressive disease (PD)
Progressive disease (PD)	Increase in tumor size and/or worsening of shape (20% or more increase in a-lesions), or new intragastric lesions

CR or PR cases were considered as responders.

Table 2. Histological evaluation criteria for tumor response after preoperative therapy.

Grade 0 (no effect)	No evidence of effect
Grade 1 (slight effect)	
Grade 1a (very slight effect)	Viable tumor cells occupy more than 2/3 of the tumorous area
Grade 1b (slight effect)	Viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area
Grade 2 (considerable effect)	Viable tumor cells remain in less than 1/3 of the tumorous area
Grade 3 (complete response)	No viable tumor cells remain; recommended that the finding is confirmed on additional sectioning

Patients with grade 0–1a lesions were regarded as pathological non-responders and those with grades 1b–3 lesions were regarded as pathological responders.

(24.52%) achieved stable disease (SD), including three with a GBS and 10 with a PBS, and four patients (7.54%) achieved progressive disease (PD), including one with a GBS and three with a PBS. The overall response rate was 67.92% (36/53 cases) and the response rates in the GBS and PBS groups were 83.33% (20/24 cases) and 55.17% (16/29 cases), respectively ($P = 0.039$) (Figure 1).

Pathological findings

The pathological findings are summarized in Tables 4 and 5. Four patients refused surgery and the tumors in another four patients could not be resected because of syncretic lymph nodes enclosing the pivotal arteries. Pathological response (grade 1b–3) was observed in 34 patients (75.55%). Eight patients (17.78%; 6 GBS, 2 PBS) obtained CR. The pathological response rates were 90.91% (20/22) and 60.87% (14/23) in patients with a GBS and PBS, respectively ($P = 0.0351$) (Figure 2).

Relationships between blood supply and clinicopathologic characteristics

The relationships between blood supply and clinicopathologic characteristics are shown in Table 6. There was no significant

Table 3. Patient characteristics (n=53).

Characteristic	No. patients	%
Median age (range) (years)	58 (30–73)	
Sex		
Male	35	66
Female	18	34
Macroscopic type		
Type 2	17	32.1
Type 3	25	4.2
Type 4	11	20.7
Tumor location		
UM	21	39.6
ML/MU/MUL	8	15.1
LM	24	45.3
Histopathology subtype		
Well-differentiated adenocarcinoma	18	33.9
Moderately differentiated	26	49.1
Poorly differentiated adenocarcinoma	2	3.8
Signet-ring cell carcinoma	7	13.2
TNM stage		
IIIB	32	60.4
IIIC	21	39.6

Lesion location classified according to the JCGA (3nd English Edition). U, M, L: bulk of tumor located in the upper, middle, or lower third of the stomach, respectively.

Table 4. Pathological findings (n = 45).

Pathological finding	No. patients (%)
No tumor (PCR)	8 (17.78)
pT1	3 (6.67)
pT2	5 (11.11)
pT3	0 (0)
pT4	29 (64.44)
Lymph node metastasis	
pN0	14 (31.11)
pN1	8 (17.78)
pN2	9 (20)
pN3	6 (13.33)
Pathological tumor stage	
IA, IB	3 (6.67)
IIA, IIB	15 (33.33)
IIIA, IIIB	19 (42.22)
IV	0 (0)

Table 5. Pathological response to FLEEOX therapy according to blood supply.

	Grade 0	Grade 1a	Grade 1b	Grade 2	Grade 3
GBS	1	1	11	3	6
PBS	2	7	8	4	2

GBS: good blood supply, PBS: poor blood supply.

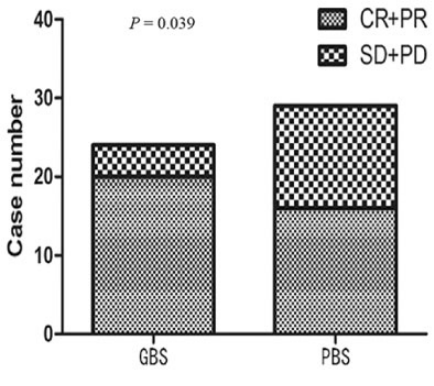

Figure 1. Clinical response in patients with GBS and PBS.
GBS: good blood supply, PBS: poor blood supply, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

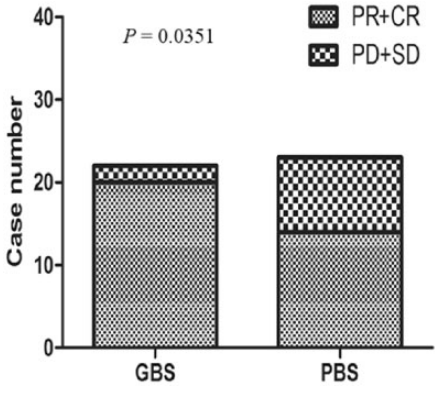

Figure 2. Pathological response in patients with GBS and PBS.
GBS: good blood supply, PBS: poor blood supply, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

relationship between tumor blood supply and any clinicopathologic parameter except tumor macroscopic type (B3 vs. B2, $P < 0.001$). We also assessed the relationship between tumor blood supply and response to chemotherapy, and showed that tumor blood supply was significantly related to both radiographic and pathological chemotherapy responses ($P = 0.039$ and $P = 0.035$, respectively).

Correlation between blood supply and OS

Patients were followed-up for a median of 35 months (range 4 to 71 months). OS at 3 years was 65.8% for the entire cohort (Figure 3). Univariate analysis identified GBS as significantly correlated with superior OS (GBS vs. PBS: 3-year OS 78.57% vs 54.44%, hazard ratio = 0.3773, 95% confidence interval 0.1614–0.8823, $P = 0.0245$) (Figure 4).

Discussion

Preoperative chemotherapy, or NAC, was first proposed in the 1980s and has since become an essential adjuvant chemotherapy for patients with advanced GC.[11] Preoperative chemotherapy is known to play an important role in the treatment of GC by decreasing tumor cell activity and tumor volume, reducing iatrogenic tumor cell diffusion during surgery, and by improving the R0 resection rate. However, the optimal way of administering the drugs remains controversial. Local intra-arterial administration of chemotherapeutic agents was reported to produce 10-fold higher tumor serum concentrations than systemic intravenous chemotherapy; however, this

Table 6. Relationships between blood supply and clinicopathologic characteristics.

	P value
Age (years)	
≥58 vs. <58	0.595
Sex	
Male vs. female	0.6
TNM stage	
IIIB vs. IIIC	0.732
Tumor site	
Upper vs. lower	0.425
Macroscopic type	
B2 vs. B3	**<0.001**
Histological subtype	
G1 vs. G2	0.159

Median value of CT enhancement was used as a cut-off point to separate patients into high or low blood supply groups. Significant results indicated in bold.

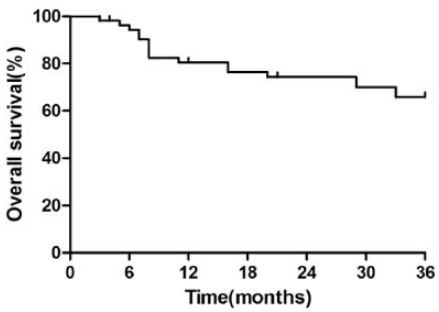

Figure 3. Overall survival in the entire cohort.

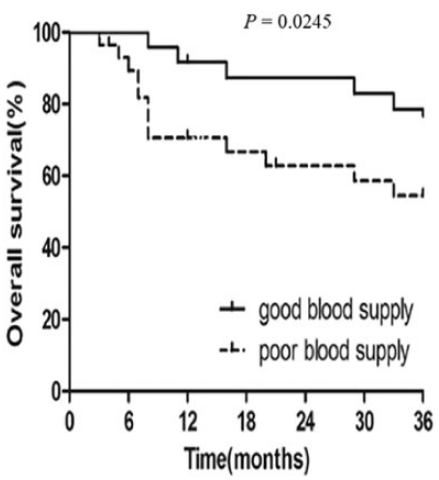

Figure 4. Kaplan–Meier survival curves showing significantly higher overall survival in patients with good blood supply compared with poor blood supply.

route had weaker efficiency in metastatic tissues compared with the systemic intravenous route.[12] Kosaka et al.[13] compared the therapeutic efficacies of intra-arterial infusion and systemic intravenous chemotherapy in patients with advanced GC and found that the intra-arterial route was associated with a higher overall chemotherapy response rate than the systemic intravenous route. Intra-arterial infusion chemotherapy was also shown to improve the overall chemotherapy response rate of gastric carcinomas, possibly by promoting apoptosis of cancer cells and by pathological tumor necrosis, thus restraining tumor cell proliferation.[14]

Various studies have indicated that the partial response rate (PRR) could significantly affect survival in GC patients treated with NAC, implying that PRR was a suitable endpoint in patients with advanced GC treated with NAC.[15–19] Patients with a high pathological response had better survival rates than those with a low pathological response.[15] These results suggest that increasing the PRR could improve survival among patients with advanced GC. Although several studies reported mean PRRs of NAC of 14.5% to 51% based on the same Japanese criteria used in our previous study,[16–19] this remained unsatisfactory. However, recent studies showed greatly improved PRRs of NAC as high as 70% to 72%,[20,21] while the current study demonstrated even higher PRRs of 83.33% by radiography and 90.91% by pathology for patients with advanced GC with a GBS. Furthermore, to the best of our knowledge, information on the relationship between tumor blood supply and response to chemotherapy and OS in patients with advanced GC is lacking. The current results indicated significant associations between GC blood supply and both radiographic and pathological responses to chemotherapy (GBS vs. PBS, 83.33% vs 55.17% and 90.91% vs 60.87%, respectively) and OS (GBS vs. PBS, 3-year OS 78.57% vs 54.44%). Furthermore, a PRR >80% and 3-year OS of 78.57% support the application of blood supply values in decisions regarding individualized treatment plans for patients with GC.

Borrmann developed a classification system for GC in 1926, which has since been used to describe the endoscopic and gross findings of GC. Borrmann IV GCs, including linitis plastica, are characterized by poorly differentiated tumor cells with diffusely infiltrative involvement of the stomach.[22–25] Although the diagnosis and treatment of GC have been greatly improved, most early stage Borrmann IV GCs remain undetected and their prognosis is thus still very poor.[26,27] The 5-year survival rate after gastrectomy for Borrmann IV GCs is 0% to 17%, while rates for other types can reach 35% to 70%.[28–31] The poor prognosis of Borrmann type IV GCs is associated with their characteristic biological behavior, including poorly differentiated and undifferentiated tumor cells resulting in early lymph node and adjacent organ metastases.[32] Borrmann IV GCs are therefore generally considered as a special type and are usually studied separately, and were thus not included in the current study.

This study was limited by the relatively small number of samples, and further large-scale, multicenter studies are needed to confirm the results.

There is currently a need for individualized and accurate treatment of patients with advanced GC, and identifying potential subgroups of patients who might benefit from a chemotherapy regimen is therefore vital. The results of the current study suggested that neoadjuvant intra-arterial and intravenous chemotherapy was more effective in patients with a GBS. Tumor blood supply may thus be a useful marker for predicting the response of patients to NAC, thus allowing intra-arterial and intravenous chemotherapy to be applied more precisely.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Xiang Ji https://orcid.org/0000-0003-2856-4070

References

1. Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012; 380: 1840–1850. DOI: 10.1016/S0140-6736(12)60919-2.
2. Chen W, Zheng R, Zhang S, et al. Report of incidence and mortality in China cancer registries, 2009. *Chin J Cancer Res* 2013; 25: 10–21. DOI: 10.3978/j.issn.1000-9604.2012.12.04.
3. He Q, Li Y, Ma L, et al. Application of FLEEOX preoperative chemotherapy via intra-arterial and intravenous administration in treatment of unresectable locally advanced gastric cancer. *J Gastrointest Surg* 2016; 20: 1421–1427. DOI: 10.1007/s11605-016-3153-8.
4. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; 357: 1810–1820. DOI: 10.1056/NEJMoa072252.
5. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; 379: 315–321. DOI: 10.1016/S0140-6736(11)61873-4.
6. Yoshikawa T, Rino Y, Yukawa N, et al. Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. *Surg Today* 2014; 44: 11–21. DOI: 10.1007/s00595-013-0529-1.
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11–20. DOI: 10.1056/NEJMoa055531.
8. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; 29: 1715–1721. DOI: 10.1200/JCO.2010.33.0597.
9. Fuentes E, Ahmad R, Hong TS, et al. Adjuvant therapy completion rates in patients with gastric cancer undergoing perioperative chemotherapy versus a surgery-first approach. *J Gastrointest Surg* 2016; 20: 172–179; discussion 179. DOI: 10.1007/s11605-015-2954-5.
10. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; 14: 101–112. DOI: 10.1007/s10120-011-0041-5.
11. Leong T, Michael M, Foo K, et al. Adjuvant and neoadjuvant therapy for gastric cancer using epirubicin/cisplatin/5-fluorouracil (ECF) and alternative regimens before and after chemoradiation. *Br J Cancer* 2003; 89: 1433–1438. DOI: 10.1038/sj.bjc.6601311.
12. Tokairin Y, Maruyama M, Baba H, et al. [Pharmacokinetics of "subselective" arterial infusion chemotherapy]. *Gan To Kagaku Ryoho* 2001; 28: 1795–1798.
13. Kosaka T, Ueshige N, Sugaya J, et al. [Evaluation of intra-arterial infusion chemotherapy for advanced gastric cancer]. *Gan To Kagaku Ryoho* 1998; 25: 1288–1291.
14. Dong XC, Li B and Li YP. [Effect of preoperative intra-arterial chemotherapy on apoptosis and p53 expression of gastric cancer]. *Ai Zheng* 2002; 21: 1078–1080.
15. Kurokawa Y, Shibata T, Sasako M, et al. Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A). *Gastric Cancer* 2014; 17: 514–521. DOI: 10.1007/s10120-013-0294-2.
16. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study of neoadjuvant

chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009; 96: 1015–1022. DOI: 10.1002/bjs.6665.
17. Yoshikawa T, Omura K, Kobayashi O, et al. A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). *Eur J Surg Oncol* 2010; 36: 546–551. DOI: 10.1016/j.ejso.2010.04.011.
18. Iwasaki Y, Sasako M, Yamamoto S, et al. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). *J Surg Oncol* 2013; 107: 741–745. DOI: 10.1002/jso.23301.
19. Tsuburaya A, Mizusawa J, Tanaka Y, et al. 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: 653–660. DOI: 10.1002/bjs.9484.
20. Okabe H, Hata H, Ueda S, et al. A phase II study of neoadjuvant chemotherapy with S-1 and cisplatin for stage III gastric cancer: KUGC03. *J Surg Oncol* 2016; 113: 36–41. DOI: 10.1002/jso.24096.
21. Migita K, Nashimoto A, Yabusaki H, et al. Efficacy of neoadjuvant chemotherapy with docetaxel, cisplatin and S-1 for resectable locally advanced gastric cancer. *Int J Clin Oncol* 2016; 21: 102–109. DOI: 10.1007/s10147-015-0851-2.
22. Furukawa H, Hiratsuka M and Iwanaga T. A rational technique for surgical operation on Borrmann type 4 gastric carcinoma: left upper abdominal evisceration plus Appleby's method. *Br J Surg* 1988; 75: 116–119.
23. Shin SH, Jung H, Choi SH, et al. Clinical significance of splenic hilar lymph node metastasis in proximal gastric cancer. *Ann Surg Oncol* 2009; 16: 1304–1309. DOI: 10.1245/s10434-009-0389-5.
24. Zhao X, Huang K, Zhu Z, et al. Correlation between expression of leptin and clinicopathological features and prognosis in patients with gastric cancer. *J Gastroenterol Hepatol* 2007; 22: 1317–1321. DOI: 10.1111/j.1440-1746.2007.04941.x.
25. Kim DY, Kim HR, Kim YJ, et al. Clinicopathological features of patients with Borrmann type IV gastric carcinoma. *ANZ J Surg* 2002; 72: 739–742.
26. Liu Y, Yoshimura K, Yamaguchi N, et al. Causation of Borrmann type 4 gastric cancer: heritable factors or environmental factors? *Gastric Cancer* 2003; 6: 17–23. DOI: 10.1007/s101200300002.
27. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005; 241: 27–39.
28. Ahn HS, Lee HJ, Yoo MW, et al. Changes in clinicopathological features and survival after gastrectomy for gastric cancer over a 20-year period. *Br J Surg* 2011; 98: 255–260. DOI: 10.1002/bjs.7310.
29. Takeda J, Hashimoto K, Koufuji K, et al. A retrospective study of resected gastric cancers. *Kurume Med J* 1992; 39: 141–145.
30. Park JC, Lee YC, Kim JH, et al. Clinicopathological features and prognostic factors of proximal gastric carcinoma in a population with high Helicobacter pylori prevalence: a single-center, large-volume study in Korea. *Ann Surg Oncol* 2010; 17: 829–837. DOI: 10.1245/s10434-009-0785-x.
31. Flores Cabral JA, Vojvodic I, Ortega D, et al. [Factors associated with postoperative mortality following gastric adenocarcinoma surgery at the Edgardo Rebagliati Martins Hospital]. *Rev Gastroenterol Peru* 2004; 24: 212–222.
32. Yokota T, Teshima S, Saito T, et al. Borrmann's type IV gastric cancer: clinicopathologic analysis. *Can J Surg* 1999; 42: 371–376.