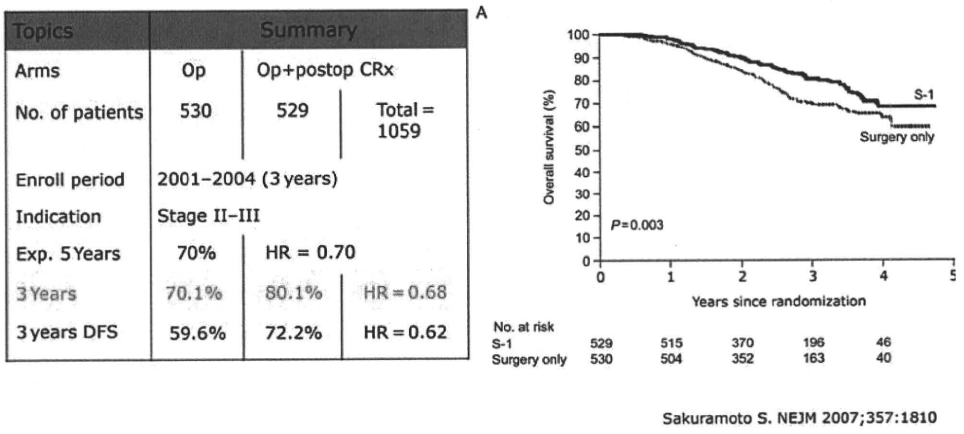

Figure 9. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. Source: Sakuramoto et al. (33).

Table 1. Results of randomized trials using newer regimens: advanced gastric cancer

Study	Treatment	*n*	RR (%)	MTTP (months)	MST (months)	*P* value[a]
V325 (JCO2006)	CDDP + FU (CF)	230	25	3.7	8.6	
	Docetaxel + CDDP + FU (DCF)	227	37	5.6	9.2	0.02
V306 (ASCO2005)	CDDP + FU (CF)	163	26	4.2	8.7	
	CPT-11 + FU (IF)	170	32	5.0	9.0	NS
ML07132 (ASCO2006)	FU + CDDP (FP)	156	29	5.0	9.3	
	Capecitabine + CDDP (XP)	160	41	5.6	10.5	NS
JCOG9912 (ASCO2007)	FU	234	9	2.9[b]	10.8	
	S-1	234	28	4.2[b]	11.4	NS
	CPT-11 + CDDP	236	38	4.8[b]	12.3	NS
SPIRITS (ASCO2007)	S-1	150	31	4.0[b]	11.0	
	S-1 + CDDP	148	54	6.0[b]	13.0	0.037
TOP002 (ASCO-GI2008)	S-1	162	27		10.5	
	S-1 + CPT-11	164	42		12.8	NS

[a]Test for superiority in OS.
[b]PFS.

The approval status of active agents for gastric cancer differs among four East Asian countries. Capecitabine and oxaliplatin are not yet available in Japan, and S-1 and oxaliplatin are not available in Taiwan (Table 2). In Japan, approval is always associated with medical reimbursement, but that is not always the case in other countries. The differences caused by the medical insurance systems may affect the survival results larger than by ethnic differences in biology or pharmacokinetics. In countries with limitations on medical reimbursement for second- or further line chemotherapy, such as Western countries and Asian countries other than Japan, triplet regimen such as docetaxel + cisplatin + 5-FU is becoming more popular. However, in Japan, all agents that have been approved are covered by medical reimbursement at any line of chemotherapy, which cause that FUs plus platinum are the most popular first-line

Table 2. Approval status of active agents in gastric cancer

Agents	Japan	Korea	China	Taiwan
5-FU	○	○	○	○
S-1	○	○	○	×
Capecitabine	×	○	○	○
Cisplatin	○	○	○	○
Oxaliplatin	×	○	○	×
Paclitaxel	○	○	○	○
Docetaxel	○	○	○	○
Irinotecan	○	○	○	○

○, medical reimbursement in Japan; ×, medical reimbursement in ex-Japan.

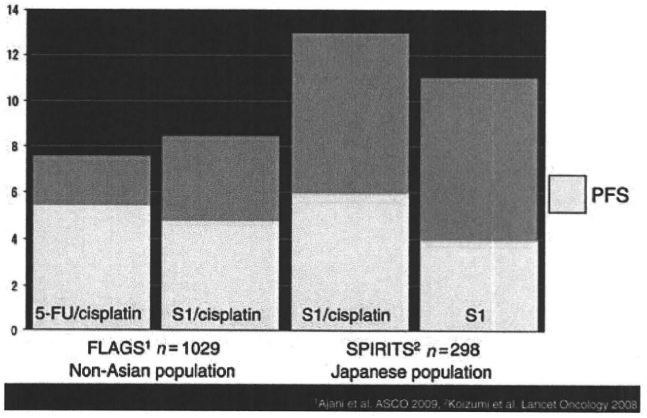

Figure 10. Survival in advanced gastric cancer: Japanese versus Western population.

regimens followed by taxane or irinotecan. In conclusion, no global standard regimen has been established yet as the first-line standard chemotherapy for metastatic cancer. In Asian countries, FU and platinum combinations are the most widely used regimens, with median progression-free survivals of 5–6 months. Differences in the approval and medical insurance systems may influence the status of these regimens.

The ToGA study compared the cytotoxic combination (5-FU or capecitabine + cisplatin) with and without trastuzumab in patients with HER2-positive gastric cancer (Fig. 11) (39). This is a global randomized trial, but more than half of the patients have been recruited from East Asian countries, including Korea, Japan and China. Trastuzumab showed a significant survival advantage compared with the cytotoxic agent combinations, with a hazard ratio of 0.74. From the Asian point of view, the ToGA trial indicates that trastuzumab in combination with FU/platinum will be a new option for HER2-positive gastric cancer. Moreover, the HER2-positive population will become an independent entity, as in breast cancer, although further studies are needed. Regional

Table 3. International investigational new drug registration randomized controlled trials for metachronous gastric cancer: leading countries

Agents	Study name	Leading country	Region	Enrollment status
Trastuzumab	ToGA	Korea	Asia, EU, SA	Published
Bevacizumab	AVAGAST	Japan	Asia, EU, N/S A	Completed
Cetuximab	EXPAND	Germany	EU, Asia	Recruiting
Lapatinib (first line)	LOGiC	Korea	Asia, EU, N/S A	Recruiting
Lapatinib (second line)	TYTAN	Japan	Asia	Recruiting
Panitumumab	REAL3	UK	EU	Recruiting
Everolimus	GRANITE-1	Japan	Asia, EU, N/S A	Recruiting

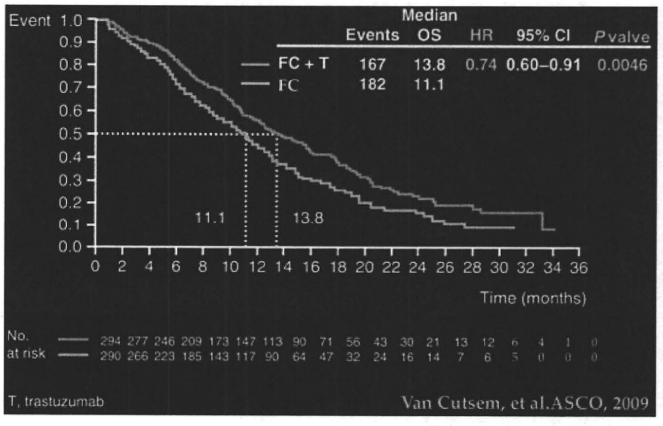

Figure 11. Overall survival results in ToGA trial.

differences, such as the HER2-positive rate, may be clarified by further analyses. Five of seven ongoing global RCTs for metastatic gastric cancer are led mainly by Japan and Korea. Asian countries are playing a major role in the development of new agents for gastric cancer (Table 3) (40).

In conclusion, FUs plus platinum are the most widely accepted first-line regimens for gastric cancer, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens, and the improvement in these status is hopefully done in many countries. Trastuzumab in combination with FUs/platinum will be a standard regimen for HER2-positive gastric cancer, and the recent phase II/III trials showed favorable median survival times exceeding 1 year. Many new targeting agents are currently under investigation and the roles of Asian countries in the development of new agents will become important.

Conflict of interest statement

None declared.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002:* Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0. Lyon: IARC Press 2004. Available from: http://globocan.iarc.fr
2. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., editors. Cancer Incidence in Five Continents, Vol. IX, IARC Scientific Publications No. 160. Lyon: IARC 2007.
3. Wu MS, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer (Review). *Cancer Epidemiol Biomarkers Prev* 2005;14:1878–82.
4. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;345:784–9.
5. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al., China Gastric Cancer Study Group. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
6. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al., Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392–7.
7. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151:121–8.
8. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009;137:1641–8.
9. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351–65.
10. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003;95:1784–91.
11. Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in *Helicobacter pylori*-infected patients. *J Clin Oncol* 2010;28:2952–7.
12. Yamazaki H, Oshima A, Murakami R, Endoh S, Ubukata T. A long-term follow-up study of patients with gastric cancer detected by mass screening. *Cancer* 1989;63:613–7.
13. Dan YY, So JB, Yeoh KG. Endoscopic screening for gastric cancer. *Clin Gastroenterol Hepatol* 2006;4:709–16.
14. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer* 2006;9:315–9.
15. Schlemper RJ, Kato Y, Stolte M. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 2001;36:445–56.
16. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–25.
17. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007;10:1–11.
18. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Longterm outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 2006;9:88–92.
19. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009;41:751–7.
20. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. ESD for early gastric cancer: a large-scale feasibility study. *Gut* 2009;58:331–6.
21. Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Surgical treatment of advanced gastric cancer: Japanese perspective. *Dig Surg* 2007;24:101–7.
22. Yoon SS, Yang HK. Lymphadenectomy for gastric adenocarcinoma: should west meet east? *Oncologist* 2009;14:871–82.
23. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995–9.
24. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;79:1522–30.
25. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745–8.
26. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340:908–14.
27. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:309–15.
28. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767–73.
29. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453–62.
30. Cunningham D, Allum WH, Stenning SP, Thompson JN, van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
31. 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;345:725–30.
32. Enzinger PC, Benedetti JK, Meyerhardt JA, McCoy S, Hundahl SA, Macdonald JS, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg* 2007;245:426–34.
33. 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.
34. Fujitani K, Yang HK, Kurokawa Y, Park do J, Tsujinaka T, Park BJ, et al., Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group; Korea Gastric Cancer Association. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. *Jpn J Clin Oncol* 2008;38:504–6.
35. Kang Y, 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 randomized phase III non-inferior trial. *Ann Oncol* 2009;20:666–73.
36. Cunningham D, Starling N, Rao S, Ivelson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Eng J Med* 2008;358:36–46.
37. 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.
38. 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* 2009;27:1547–53.
39. Van Cutsem E, Kang YK, Chung H, Shen L, Sawaki A, Lordick F, et al. Efficacy results from ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer. *J Clin Oncol* 2009;27:18S (Abstract LBA 4509).
40. Ohtsu A. Chemotherapy for metastatic gastric cancer: past present and future. *J Gastroenterol* 2008;43:256–64.

Prognostic significance of preoperative bowel obstruction in stage III colorectal cancer

Hiroshi Katoh, MD, PhD [1], Keishi Yamashita, MD, PhD [1], Guoqin Wang, MD, PhD [2], Takeo Sato, MD [1], Takatoshi Nakamura, MD, PhD [1] and Masahiko Watanabe, MD, PhD, FACS [1].

[1] Department of Surgery, Kitasato University School of Medicine

[2] Department on Community-based Perinatal and Emergency Medicine, Kitasato Clinical Research Center, Kitasato University School of Medicine

Corresponding author: Masahiko Watanabe, MD, PhD, FACS, Professor of Department of Surgery, Kitasato University, School of Medicine

Tel.: +81-42-778-8735; Fax: +81-42-778-8735

E-mail: gekaw@med.kitasato-u.ac.jp

Running head: Preoperative obstruction in stage III CRC

Synopsis

In this study, we suggest that preoperative obstruction predicts systemic recurrence in stage III colon and rectal cancer. This may be a potential tool to identify patients with high-risk stage III colon cancer or rectal cancer.

Abstract

BACKGROUND: Previous studies have suggested a detrimental prognostic effect of preoperative obstruction proximal to colorectal cancer (CRC). If such a detrimental effect is preserved in each stage of advanced (stage II or III) CRC, we can identify high-risk patients. METHODS: We enrolled 641 patients with pathologically confirmed advanced CRC (stage II, n=207; stage III, n=434) who had undergone curative resection of the primary lesion. The association of preoperative obstruction with clinicopathologic parameters was evaluated. Kaplan-Meier analysis and Cox proportional hazards models were used to estimate the effect of preoperative obstruction on disease-free survival (DFS) in each stage. RESULTS: Preoperative obstruction was seen in 63 patients (9.8%) (stage II, n=16; stage III, n=47).

Multivariable analysis showed that preoperative obstruction was significantly associated with preoperative elevation of CEA level in patients with colon cancer (odds ratio [OR]=3.59; p<0.001), while it was correlated with poor differentiation in patients with rectal cancer (OR=3.99; p=0.016). Preoperative obstruction was a significant prognostic factor in stage III CRC (p<0.001), but not in stage II disease. Multivariable prognostic analysis showed that preoperative obstruction was a remnant independent prognostic factor in stage III CRC. This finding was confirmed by separate analyses of colon and rectal cancer. Preoperative obstruction was associated with systemic recurrence (p=0.003) rather than peritoneal or local recurrence. CONCLUSION:

These findings suggest that preoperative obstruction may predict worse long-term prognosis in patients with stage III CRC and may be a potential clinical marker to identify patients with high-risk stage III CRC.

Keywords: colorectal cancer, obstruction, stage III, patient selection, prognosis.

Introduction

Preoperative obstruction has been reported to occur in 7-47% of patients with colorectal cancer (CRC) [1-8]. However, whether preoperative obstruction is prognostic is controversial [1,5-11]. This controversy may arise due to variations in study designs including different stages and/or mixed curability.

Recently, increasing application of adjuvant chemotherapy and advances in chemotherapy regimens have improved the prognoses in stage III CRC [12,13]; moreover, stage II patients may now be candidates for adjuvant chemotherapy. However, not all patients who undergo curative surgery receive optimal adjuvant chemotherapy because of cost issues and the capacity of medical facilities. Additionally, prognostic heterogeneity occurs in each cancer stage. Therefore, understanding significant differences in prognostic clinical parameters other than staging is important when considering individual treatment strategies after curative surgery.

Because few reports have analyzed the role of preoperative obstruction in each stage, the objectives of this study were: (1) to evaluate the relationship between preoperative obstruction and clinicopathologic parameters of CRC; (2) to evaluate the prognostic impact of obstruction on advanced CRC patients with stage II and stage III disease separately; and (3) if a prognostic significance of preoperative obstruction was

confirmed, to determine its impact on patients' prognoses in different tumor location (colon vs. rectum) and consider the potential suitability for identifying high-risk patients.

Patients and Methods

Between 1991 and 2005, 641 sporadic CRC patients who had been clinically diagnosed with advanced disease (TNM stage II and III) and underwent curative resection of the colon or the rectum at Kitasato University Hospital were analyzed. Through the observation period, our treatment policy was curative resection of the primary lesion with sufficient margin and appropriate lymph node dissection even for patients with obstruction. Except for unavoidable cases, such as perforation or suspicion of bowel necrosis, we first performed emergency ileostomy/colostomy, or insertion of a decompression tube if bowel obstruction required emergency decompression. After a thorough examination and nutritional improvement, we performed curative resection. We excluded the patients with prior chemo-immunotherapy or radiotherapy, and with severe systemic complications in other organs (heart, kidney, and liver). Patient demographics, tumor characteristics, and the postoperative course were assessed. Thirty-five surgeons performed curative resections, and all had at least 6 years of experience. Perioperative transfusion was defined as allogeneic blood transfusion during surgery or in the first 2 postoperative days [14], and was performed at the discretion of the treating surgeons and anesthesiologists. Pathological TNM classification was made according to the UICC (Unio Internationalis Contra Cancrum) staging.

Preoperative intestinal obstruction was defined as total absence of flatus or bowel movements for at least 24 h, accompanied by clinical signs of obstruction (abdominal distension, peristaltic abdominal pain, nausea, or vomiting) and by

radiographic evidence of obstruction (dilated intestinal loops).

When adjuvant chemotherapy was used, it was started within 7 weeks after surgery. Adjuvant chemotherapy regimens consisted of 5-fluorouracil (5FU) alone (infusion or oral), 5FU/PSK (protein-bound polysaccharide K), 5FU/leucovorin (LV), 5FU/LV/CPT-11 (irinotecan), 5FU/CPT-11, and others for at least 3 months or 3 cycles. Patients were followed up until cancer-related death, the recurrence of cancer, or the study end-point (March 31, 2007) if they survived. All patients were followed up at least every 3 months for the first year and every 6 months thereafter. Follow-up assessment involved a medical history, physical examination, biologic tests, measurement of serum CEA and CA19-9 levels, colonoscopy, chest radiography, abdominal ultrasonography (US), and chest/abdominal CT. Serum CEA and CA19-9 levels were usually evaluated at every visit, and abdominal US and CT were performed every 6 months. Chest CT and colonoscopy were performed every year. Recurrence was diagnosed on the basis of imaging and, if necessary, either cytologic analysis or biopsy was performed. Postoperative therapy for recurrence or metastasis included surgical resection, 5FU-based chemotherapy, or radiation therapy.

Statistical analysis

The relationship between preoperative obstruction and clinicopathologic features was assessed by chi-square test or Fisher's exact test, and multivariable logistic regression analysis was performed to obtain an adjusted effect. The follow-up time was calculated from the surgical date for the primary lesion to the date of recurrence or cancer-related death. Cumulative disease-free survival (DFS) was estimated using the Kaplan-Meier method, and statistical significance was tested using the log-rank test. For the Kaplan-Meier estimate, we truncated the data at a follow-up period of 5 years to avoid having the number at risk be too small. Those with a survival time of more than 5 years were reported 5 years, and events after the end of 5-year follow-up period were

computed as censored data. Multivariable analysis was performed using the Cox proportional hazards model to examine the interaction between obstruction and other variables and estimate the independent prognostic effect of preoperative obstruction by adjusting for confounding factors. Within the present study population, there were 184 recurrences of CRC (27 for stage II, 157 for stage III) which allowed up to 18, 3, or 15 variables to be included in a multivariable regression model for estimating in all stages, stage II or stage III, respectively. When data were separated by the colon and rectal cancer, the numbers of events were 76 and 81, respectively. To avoid over-fitting, all potential confounding factors of preoperative obstruction were reduced to a single composite characteristic by applying a propensity score [15]. A P value (two-sided) < 0.05 indicated statistical significance. Analyses were performed independently at our clinical research center using the SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Patients' characteristics and association with preoperative obstruction

Clinicopathologic features are shown in Table 1. A total of 380 men and 261 women were analyzed (mean age, 61.3±11.1). Of these patients, 207 had stage II CRC and 434 had stage III. Preoperative obstruction occurred in 16 (7.7%) and 47 (10.8%) of patients with stage II and III CRC, respectively. Among these 63 patients, only 1 patient underwent emergency primary resection with curative intent. All other patients underwent curative resection electively after decompression of the bowel obstruction. Emergency ileostomy or colostomy was initially performed in 15 patients; the remaining 47 patients were initially treated by non-oral intake with/without a nasal or anal decompression tube. During the study period, two patients with bowel obstruction were resected primary cancer without radicality (not included in the study). Therefore, 63 patients (96.9%) among the 65 obstructed patients had radical resection

regardless of one- or two-stage surgery.

For all subjects, preoperative obstruction was more common in colon cancer (p=0.058), related to preoperative CEA elevation (p=0.001), T factor (p=0.007), and poor differentiation (p=0.009) (Table 1). Preoperative obstruction was significantly associated with preoperative CEA (odds ratio (OR)=3.56; p<0.001) for colon cancer, while for rectal cancer, preoperative obstruction was related with poor differentiation (OR=3.99; p=0.016) and metastatic lymph node ratio (ND, node density) ≥ 20% (OR=3.18, p=0.021), by multivariable logistic regression analyses. Among patients with stage III colon cancer, preoperative CEA values were significantly higher in those with obstructive colon cancer (14.80±7.55) than those with non-obstructive colon cancer (3.88±0.54) (p<0.001, Fig. 1A), contrarily, that was not true in stage III rectal cancer (Fig. 1B). The mean number of total dissected lymph nodes tended to be greater in obstructed cases than in non-obstructed cases (stage II: 33.25±5.24 and 25.23±1.15, respectively; stage III: 26.17±2.45, 23.01±0.87), although there was no difference in the distribution of patient numbers categorized by the recovered node number (Table 1).

Kaplan-Meier estimate of disease-free survival

The overall follow-up period ranged from 2 to 207 months (median, 77 months), and the mean DFS was 46.7 months during our 5-year follow-up. Because a cumulative DFS probability of 50% was not reached by the end of the 5-year follow-up, the overall median DFS time was not determined. Five-year cumulative DFS was 51.4% for the obstructed group and 72.9% for the non-obstructed group. The median survival time was 32 months for patients with obstruction; median survival time was not available for patients without obstruction at the end of the 5-year follow-up period, indicating a significantly poorer prognosis in the obstructed group (p<0.001, Supplemental Table 1). Preoperative obstruction was significantly associated with

poorer prognosis for stage III patients (p<0.001, Fig. 2A), but not for stage II patients (p=0.478, Supplemental Table 2). For stage III patients, DFS was 41.0% for obstructed vs. 65.6% for non-obstructed patients; for stage II patients, DFS was 81.3% vs. 87.4%, respectively. There was no statistical difference in prognosis between primary resection and delayed (two-stage) resection in stage III patients (data not shown).

When tumor location was analyzed separately, preoperative obstruction was significantly associated with a poor outcome in patients with stage III colon cancer or rectal cancer (Tables 2 and 3). Among patients with stage III colon cancer, the DFS was 48.1% in those with obstruction compared with 70.0% in those without obstruction (p=0.004, Fig. 2B). Among patients with stage III rectal cancer, the DFS was 26.7% in those with obstruction compared with 59.8% in those without obstruction (p=0.001, Fig. 2C).

Multivariable prognostic analysis of preoperative obstruction

The Cox proportional hazards model was applied to estimate the effect of preoperative obstruction on survival. The crude hazard ratio (HR) of obstructed patients compared to non-obstructed patients was 2.21 (95% confidence interval [CI], 1.50-3.27; p<0.001). After controlling for clinicopathologic factors, the adjusted HR of preoperative obstruction was 2.05 (95% CI, 1.35-3.11, p=0.001). We also performed an analysis using a propensity score to adjust for the preoperative effect by transforming all other confounding variables into a single estimator. After the adjustment, the HR of preoperative obstruction became 1.92 (95% CI, 1.28-2.89, p=0.002), suggesting that preoperative obstruction is an independent risk factor for prognosis (Supplemental Table 1).

The unadjusted effect of preoperative obstruction on DFS was 1.24 (95% CI, 0.60-2.10; p=0.506) in stage II and 2.25 (95% CI, 1.49-3.41; p<0.001) in stage III.

Next, an evaluation of each stage was performed. The adjusted HR was not significant for stage II CRC (1.96; 95% CI, 0.48-7.97; p=0.347), but was significant for stage III CRC (1.98; 95% CI, 1.26-3.09; p=0.003). These respective values decreased to 1.62 (95% CI, 0.38-7.07; p=0.506) and 1.88 (95% CI, 1.22-2.89; p=0.004) after propensity score adjustment (Supplemental Table 3).

Prognostic effect of preoperative obstruction in stage III colon and rectal cancer

Preoperative obstruction occurred in 32 cases (12.6%) of patients with stage III colon cancer (n=253). Preoperative obstruction indicated significant poor outcome in stage III colon cancer (HR, 2.18; p=0.005) (Table 2). Tumor location (p=0.014), N factor (p<0.001), and preoperative CEA (p=0.001) were also significantly associated with patient prognosis in univariable analysis. Cox's proportional hazard model revealed that preoperative obstruction remained a potential independent prognostic factor in stage III colon cancer with an adjusted HR (95% CI) of 1.83 (1.02-3.25) (p=0.041), after propensity score adjustment (Table 2).

We similarly analyzed stage III rectal cancer (n=181). Preoperative obstruction occurred in 15 cases (8.3%) and showed a significant poor prognosis (HR, 2.78; p=0.002) (Table 3). Differentiation (p=0.017), T4 factor (p=0.019), N factor (p<0.001), ND ≥ 20 (p=0.004), preoperative CEA level (p=0.046), and preoperative CA19-9 (p=0.005) were also significantly associated with patient outcome in univariable analysis. Subsequent analyses suggested that preoperative obstruction also had a tendency to have a detrimental effect on clinical outcome in stage III rectal cancer, with an adjusted HR (95% CI) of 2.17 (0.98-4.79) (p=0.056) after propensity score adjustment (Table 3). Preoperative obstruction had a prognostic impact, especially on patients with poorly differentiated stage III rectal cancer (Supplemental Fig. 1).

First recurrence site and preoperative obstruction in stage III CRC patients

First recurrence sites in stage III patients were analyzed with consideration of preoperative obstruction. Preoperative obstruction was significantly correlated with hepatic recurrence (p=0.019 by Fisher's exact test) but not with other forms of recurrence (Supplemental Table 4).

Discussion

In the present study, the prognostic value of preoperative obstruction was examined in curatively operated patients with advanced CRC (stage II and III). Multivariable analysis revealed that preoperative obstruction detrimentally affected on long-term prognosis in stage III colon and rectal cancer, but not in stage II CRC. Moreover, preoperative obstruction was associated with systemic recurrence rather than local, lymph node, and peritoneal recurrence with regard to the first recurrent site in stage III CRC, suggesting that micrometastasis may occur in cases of preoperative obstruction. The tumor factors associated with preoperative obstruction differed between colon (preoperative CEA elevation) and rectal cancer (poor differentiation). Actually, the preoperative CEA level was significantly greater in obstructive colon cancer than in non-obstructive colon cancer, while this was not true for rectal cancer (Fig. 1A and B).

These findings suggest that obstructed CRC reflects a more advanced disease, possibly with radiologically undetectable occult metastases, which may be partly reflected by an elevated CEA level in colon cancer. This hypothesis could explain why bowel obstruction was associated with worse survival in stage III, but not in stage II disease. In addition, the preoperative CEA level was correlated with obstruction in stage II CRC (Fig. 1C), but neither obstruction nor preoperative CEA level was associated with a poor prognosis in stage II CRC. Collectively, factors other than the bowel obstruction itself (such as occult metastatic disease as reflected by elevated CEA

level) may contribute to a worse outcome.

The prognostic effect of preoperative obstruction is controversial [1,5-11] and may be due to the inclusion of several stages, and/or mixed curability. In this study, each stage and tumor location was analyzed separately in curatively operated CRC, and preoperative obstruction predicted a poor prognosis in stage III, but not in stage II. This result in stage II is different from a previous report [16]. In the present study, preoperative obstruction was particularly associated with a poor prognosis in right-sided stage III colon cancer ($p=0.008$), corresponding to previous studies, although these reports included patients with both stage II and III [1,8]. Additionally, there is an argument in favor of two-stage curative surgery [3,17]. In our study, there was no significant difference in long-term prognosis between one-stage and two-stage curative surgery, but this comparison should be made with a large number of cases of obstructive CRC in the future.

The initiation of metastasis is suggested to begin earlier in tumorigenesis than previously thought [18]. Tumor cells are frequently present in the circulation or bone marrow of patients with cancer before clinical or histopathological metastasis [19,20]. Luminal distension or related inflammation was proved to increase the mucosal permeability of capillaries to macromolecules [21], and mucosal inflammation produces inflammatory cytokines, including IL-1, IL-6, receptor activator of nuclear factor-κB and TNFα, which are known to promote distant metastasis [22,23]. Thus, obstruction proximal to colorectal cancer may lead to a favorable environment for systemic metastasis.

Many parameters have been reported to be independent prognostic factors for stage III CRC, including the number of metastatic lymph nodes [24,25], negative lymph node count [26], metastatic lymph node ratio [27-30], the number of evaluated lymph nodes [31,32], and preoperative CEA [33]. Among these factors, the number of metastatic lymph nodes has only been available in clinical practice as TNM sub-staging

[34] and has been prospectively confirmed. Interestingly, preoperative obstruction was the only prognostic discriminator in both colon cancer and rectal cancer in the present study. However, a negative lymph node count, metastatic lymph node ratio (which we called node density, ND factor), and the number of evaluated lymph nodes did not have prognostic significance in colon cancer or rectal cancer (data not shown). Preoperative CEA are insufficient to use as a prognostic marker [35], and recently we noted a diminishing impact of preoperative CEA on prognosis in stage III with the advancement of adjuvant chemotherapy and diagnostic tools [36]. One study also suggested that intraperitoneal free cancer cells were a significant prognostic marker in stage III [14]. In our current study, we present a novel prognostic marker in stage III.

In terms of molecular and genetic markers, DNA ploidy in patients with right-sided colon cancer alone has been prospectively confirmed in stage III CRC [37]. Ki-ras mutation on codon 12 was also reported a risk factor for relapse or cancer-related death in stage III [38]. TP53 mutation status is reported a prognostic predictor in stage III [39]. Other numerous markers have also been reported to indicate poor prognosis; however, all such genetic and molecular tools are unsuitable for routine application at present because they have not been validated. Additionally, testing for these markers is time consuming and expensive at present. In contrast, preoperative obstruction is easily identifiable for practical examinations and may have potential for patient selection after curative operation, in addition to intraperitoneal free cancer cells.

In conclusion, preoperative obstruction affected the long-term prognosis in patients with stage III CRC. To our knowledge, this study is the first to evaluate the prognostic impact of preoperative obstruction in each stage of advanced CRC among patients who underwent curative surgery. Preoperative obstruction may be a clinically applicable marker, and a potential tool to identify patients with high-risk stage III CRC, at least in colon cancer.

Acknowledgement

We thank Forte, Tokyo, Japan for correcting grammatical errors.

References

1. Cho YB, Yun SH, Hong JS, et al.: Carcinoma obstruction of the left colon and long-term prognosis. Hepatogastroenterology 2008;55:1288-1292.
2. Deans GT, Patterson CC, Parks TG, et al.: Colorectal carcinoma: importance of clinical and pathological factors in survival. Ann R Coll Surg Engl 1994;76:59-64.
3. Jiang JK, Lan YT, Lin TC, et al.: Primary vs. delayed resection for obstructive left-sided colorectal cancer: impact of surgery on patient outcome. Dis Colon Rectum 2008;51:306-311.
4. Lee JS: Distension pressure on subserosal and mesenteric lymph pressures of rat jejunum. Am J Physiol 1986;251:G611-614.
5. Mulcahy HE, Skelly MM, Husain A, O'Donoghue DP: Long-term outcome following curative surgery for malignant large bowel obstruction. Br J Surg 1996;83:46-50.
6. Ohman U: Prognosis in patients with obstructing colorectal carcinoma. Am J Surg 1982;143:742-747.
7. Umpleby HC, Williamson RC: Survival in acute obstructing colorectal carcinoma. Dis Colon Rectum 1984;27:299-304.
8. Wang HS, Lin JK, Mou CY, et al.: Long-term prognosis of patients with obstructing carcinoma of the right colon. Am J Surg 2004;187:497-500.
9. Fitchett CW, Hoffman GC: Obstructing malignant lesions of the colon. Surg Clin North Am 1986;66:807-820.
10. Garcia-Peche P, Vazquez-Prado A, Fabra-Ramis R, Trullenque-Peris R: Factors of prognostic value in long-term survival of colorectal cancer patients. Hepatogastroenterology 1991;38:438-443.
11. Omejc M, Stor Z, Jelenc F, Repse S: Outcome after emergency subtotal/total colectomy compared to elective resection in patients with left-sided colorectal carcinoma. Int Surg 1998;83:241-244.
12. Andre T, Boni C, Mounedji-Boudiaf L, et al.: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med

2004;350:2343-2351.

13. Jessup JM, Stewart A, Greene FL, Minsky BD: Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. JAMA 2005;294:2703-2711.
14. Katoh H, Yamashita K, Sato T, et al.: Prognostic significance of peritoneal tumour cells identified at surgery for colorectal cancer. Br J Surg 2009;96:769-777.
15. Rubin DB: Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757-763.
16. Burdy G, Panis Y, Alves A, et al.: Identifying patients with T3-T4 node-negative colon cancer at high risk of recurrence. Dis Colon Rectum 2001;44:1682-1688.
17. Baccari P, Bisagni P, Crippa S, et al.: Operative and long-term results after one-stage surgery for obstructing colonic cancer. Hepatogastroenterology 2006;53:698-701.
18. Psaila B, Lyden D: The metastatic niche: adapting the foreign soil. Nat Rev Cancer 2009;9:285-293.
19. Alix-Panabieres C, Riethdorf S, Pantel K: Circulating tumor cells and bone marrow micrometastasis. Clin Cancer Res 2008;14:5013-5021.
20. Podsypanina K, Du YC, Jechlinger M, et al.: Seeding and propagation of untransformed mouse mammary cells in the lung. Science 2008;321:1841-1844.
21. Granger DN, Kvietys PR, Mortillaro NA, Taylor AE: Effect of luminal distension on intestinal transcapillary fluid exchange. Am J Physiol 1980;239:G516-523.
22. Mantovani A: Cancer: Inflaming metastasis. Nature 2009;457:36-37.
23. Mantovani A, Allavena P, Sica A, Balkwill F: Cancer-related inflammation. Nature 2008;454:436-444.
24. Vaccaro CA, Bonadeo FA, Benati ML, et al.: Colorectal cancer staging: reappraisal of N/PN classification. Dis Colon Rectum 2004;47:66-69.
25. Wolmark N, Fisher B, Wieand HS: The prognostic value of the modifications of the Dukes' C class of colorectal cancer. An analysis of the NSABP clinical trials. Ann Surg 1986;203:115-122.
26. Johnson PM, Porter GA, Ricciardi R, Baxter NN: Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. J Clin Oncol 2006;24:3570-3575.
27. Berger AC, Sigurdson ER, LeVoyer T, et al.: Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol

2005;23:8706-8712.

28. Lee HY, Choi HJ, Park KJ, et al.: Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. Ann Surg Oncol 2007;14:1712-1717.
29. Schumacher P, Dineen S, Barnett C, Jr., et al.: The metastatic lymph node ratio predicts survival in colon cancer. Am J Surg 2007;194:827-831; discussion 831-822.
30. Wang J, Hassett JM, Dayton MT, Kulaylat MN: Lymph node ratio: role in the staging of node-positive colon cancer. Ann Surg Oncol 2008;15:1600-1608.
31. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA: Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433-441.
32. Le Voyer TE, Sigurdson ER, Hanlon AL, et al.: Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-2919.
33. Ishida H, Miwa H, Tatsuta M, et al.: Ki-67 and CEA expression as prognostic markers in Dukes' C colorectal cancer. Cancer Lett 2004;207:109-115.
34. Sobin LH, Wittekond Ch (eds): "International Union Against Cancer (UICC): "TNM classification of malignant tumors." 6th ed." New York: Wiley, 2002.
35. Locker GY, Hamilton S, Harris J, et al.: ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313-5327. Epub 2006 Oct 5323.
36. Katoh H, Yamashita K, Kokuba Y, et al.: Diminishing impact of preoperative carcinoembryonic antigen (CEA) in prognosis of Dukes' C colorectal cancer. Anticancer Res 2008;28:1933-1941.
37. Lanza G, Gafa R, Santini A, et al.: Prognostic significance of DNA ploidy in patients with stage II and stage III colon carcinoma: a prospective flow cytometric study. Cancer 1998;82:49-59.
38. Andreyev HJ, Norman AR, Cunningham D, et al.: Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. Br J Cancer 2001;85:692-696.
39. Ahmed IA, Kelly SB, Anderson JJ, et al.: The predictive value of p53 and p33(ING1b) in patients with Dukes'C colorectal cancer. Colorectal Dis 2008;10:344-351.

Legends for figures

Figure 1. Preoperative CEA values were compared between obstructed cases and non-obstructed cases, respectively in (A) colon cancer (n=253), (B) rectal cancer (n=181) and stage II CRC (n=207).

Figure 2. Kaplan-Meier analysis of 5-year disease-free survival (DFS) according to preoperative obstruction in patients with stage III CRC. (A) All stage III colorectal cancer (n=434). (B) Stage III colon cancer (n=253). (C) Stage III rectal cancer (n=181).

Supplemental Figure 1. Kaplan-Meier analysis of 5-year DFS according to preoperative obstruction in patients with stage III rectal cancer. (A) Patients with poorly differentiated rectal cancer (n=24). (B) Patients with non-poorly differentiated rectal cancer (n=157).