agents with more effective and reduced adverse effects were called for, but until recently, palliative chemotherapy was regarded as the standard strategy in stage IV or recurrent gastric cancer patients.

Adjuvant Surgery

As described in the previous section, after the new chemotherapeutic agents were developed including S-1, docetaxel, paclitaxel, irinotecan, oxaliplatin and molecular targeting agents, the RR and survival of patients have improved dramatically. Interestingly, it was often reported that with newly developed chemotherapeutic regimens, the tumors were downstaged and the curative resections or R0 resections were performed in stage IV gastric cancer patients [24]. It is only recently that those cases were often found successful after treatment with S-1 + CDDP and S-1 + docetaxel regimens [45]. These operations are called 'adjuvant surgery' as previously reported [24]. The indications for adjuvant surgery are that curative resection (not palliative) can be expected, based on the response to chemotherapy, the absence or CR of other distant metastases such as peritoneal dissemination, extensive lymph node metastases or lung metastasis. The macroscopically complete removal of liver deposits is feasible, and minimal residual tumors after chemotherapy in distant lymph nodes can be extensively removed. Palliative chemotherapy is the standard strategic approach for stage IV gastric cancer. However, if treatment has been successful with CR or PR and the tumors are considered resectable or R0 resection is deemed possible, it could be feasible to perform aggressive operations to remove the residual tumors, although these operations can be regarded as adjuvant. Of course, it might be required to continue chemotherapy after these surgeries, even after R0 resections, because these cases were treated as stage IV gastric cancer. This chemotherapeutic strategy is called perioperative chemotherapy [10]. In other words, so-called neoadjuvant chemotherapy (NAC) was performed, downstaging of the tumors followed, and as a result of this, the R0 resections could take place. It must be clarified that, strictly speaking, NAC is the chemotherapy which is conducted in patients with potentially curative resectable tumors before treatment [46]. NAC is performed in order to improve the prognosis or improve the resectability of the tumors. For aggressive operations in stage IV gastric cancer patients, it can be termed adjuvant surgery with perioperative chemotherapy. The merit of adjuvant surgery in stage IV gastric cancer with a favorable response to chemotherapy is that the compliance with chemotherapy is better before surgery compared to afterwards, and secondly, it can be regarded as an in vivo sensitivity test. Thirdly, tumors definitely acquire resistance to chemotherapy, which is why aggressive operations are preferred while the tumor growth is well controlled with chemotherapy, because it is well known that tumor growth is enhanced by the cytokines after surgical treatment [47]. The best timing for the operation is when the best response of the tumor to chemotherapy is observed, not when the tumor is increasing in size or has acquired the ability to regrow. Generally, we estimate the best timing for the removal of the tumor to be when the CR or PR is detected when 4–6 cycles of S-1 + CDDP or S-1 + docetaxel regimens have been performed. This strategy is regarded as rescue surgery, oncosurgery or conversion therapy (recently conducted in metastatic liver tumors from colorectal cancer) [48–52]. In the REGATTA trial, palliative surgery followed by chemotherapy for stage IV gastric cancer is now being conducted in Japan and Korea in order to evaluate the significant roles of tumor volume reduction and interesting results are expected.

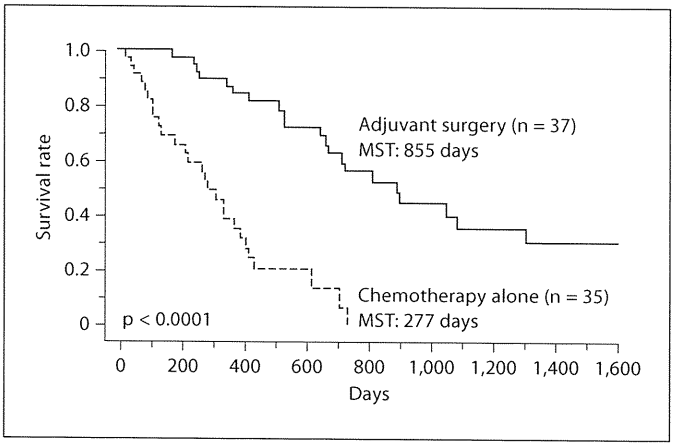

Fig. 5. Survival of the patients with adjuvant surgery in stage IV gastric cancer.

From 2001 to 2009, we treated 158 stage IV gastric cancer patients who had received S-1 + CDDP and S-1 + docetaxel treatment. We performed adjuvant surgery aiming at R0 resection of the primary and metastatic disease on 37 of these patients. The median survival of the patients who underwent surgery was 855 days after the initial start of the chemotherapy, while for those without an operation it was 277 days (fig. 5). As we reported in a preliminary retrospective analysis [24], this type of surgery might be effective in patients diagnosed as stage IV

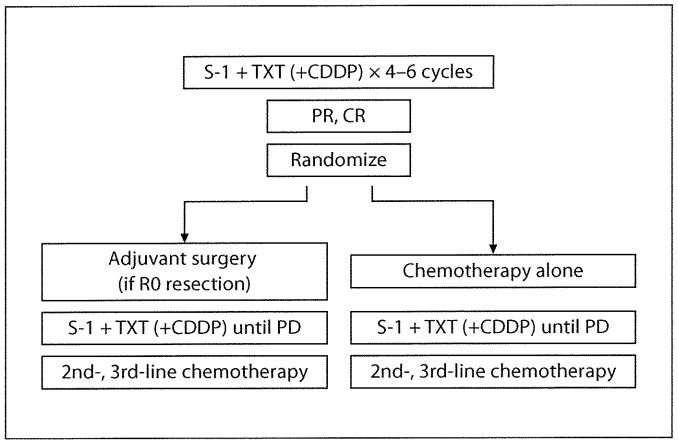

Fig. 6. Future trial of adjuvant surgery. Perioperative chemotherapy in stage IV gastric cancer: a randomized controlled trial of S-1 + docetaxel with or without CDDP. PD = Progressive disease; TXT = docetaxel.

due to liver metastasis or distant lymph node metastasis, but not for cases of peritoneal dissemination. Of course, there is a bias that the adjuvant surgery group had a good response to chemotherapy and the others not. In order to prove the significance of the adjuvant surgery, further analysis will be needed. Under investigation by a randomized phase II/III study, using S-1 + docetaxel and/or CDDP among patients who had had CR or PR and were considered curatively resectable, patients were randomized to a 'continuation of chemotherapy' group or an 'adjuvant surgery followed by chemotherapy (perioperative chemotherapy)' group (fig. 6).

Salvage Surgery

Salvage surgery is regarded as the surgery that is performed after curative radiation or chemoradiation therapy to remove the residual or regrown tumors which have invaded adjacent organs (as described in the Japanese guidelines of esophageal cancer [53, 54]). Salvage surgery is conducted in locally advanced tumors, but adjuvant surgery is conducted in metastatic cancer. Indeed, using the term 'adjuvant' in palliative surgery, even if it is after successful chemotherapy in stage IV gastric cancer, might be criticized. Because, in general, the term 'adjuvant' can be used when the tumor does not exist macroscopically, the term 'adjuvant chemotherapy' is used for chemotherapy when an R0 resection has been performed. In this sense, the term 'adjuvant surgery' could be defined as the curative surgery after CR was detected by chemotherapy in stage IV cancer. Further discussion might be required to determine the most appropriate terminology.

References

1 GLOBOCAN database. http//www-dep.jarc.fr/globocan/globocan.html.
2 Tajim K: Recent Advances of Cancer in Japan; in Saji S (ed): Recent Advances of Cancer in Asian Countries (commemorative book of the 9th ACOS 2010 in Gifu). Tokyo, Cancer and Chemotherapy, 2010, pp 26–34.
▶3 Yoshida K, Yamaguchi K, Osada S, Kawaguchi Y, Takahashi T, Sakashita F, Tanaka Y: Challenge for a better combination with basic evidence. Int J Clin Oncol 2008;13:212–219.
4 Aikou T (ed): Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma. Tokyo, Kanehara Shuppan, 2010.
5 Sano T (ed): Japanese Gastric Cancer Association: Japanese Guideline for Gastric Carcinoma. Tokyo, Kanehara Shuppan, 2010.
▶6 Shiraishi N, Yasuda K, Kitano S: Laparoscopic gastrectomy with lymph node dissection for gastric cancer. Gastric Cancer 2006;9:167–176.
▶7 Kitano S, Shiraishi N, Uyama I, Sugihara K, Tanigawa N, Japanese Laparoscopic Surgery Study Group: A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg 2007;245:68–72.
▶8 Uyama I, Sakurai Y, Komori Y, Nakamura Y, Syoji M, Tonomura S, Yoshida I, Masui T, Ochiai M: Laparoscopic gastrectomy with preservation of the vagus nerve accompanied by lymph node dissection for early gastric carcinoma. J Am Coll Surg 2005;200:140–145.
▶9 Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ: Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439–449.
▶10 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
▶11 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–730.
▶12 Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K, Japan Clinical Oncology Group: D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008;359:453–462.
▶13 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–1820.
▶14 Sano T: Adjuvant and neoadjuvant therapy of gastric cancer: a comparison of three pivotal studies. Curr Oncol Rep 2008;10:191–198.

15 Tsuburaya A, Sakamoto J, Morita S, Kodera Y, Kobayashi M, Miyashita Y, Macdonald JS: A randomized phase III trial of post-operative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: the Stomach Cancer Adjuvant Multi-institutional Trial Group (SAMIT) Trial. Jpn J Clin Oncol 2005;35:672–675.

16 Park YH, Lee JL, Ryoo BY, Ryu MH, Yang SH, Kim BS, Shin DB, Chang HM, Kim TW, Yuh YJ, Kang YK: Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. Cancer Chemother Pharmacol 2008;61: 623–629.

17 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S: Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group study (JCOG 9205). J Clin Oncol 2003;21: 54–59.

18 Wilson D, Hiller L, Geh I: ECF in gastric cancer. Clin Oncol (R Coll Radiol) 2004;16: 381–382.

19 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR, Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the UK: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36–46.

20 Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Marabotti C, Van Cutsem E: Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007;25: 3210–3216.

21 Overman MJ, Kazmi SM, Jhamb J, Lin E, Yao JC, Abbruzzese JL, Ho L, Ajani J, Phan A: Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010;116:1446–1453.

22 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M: 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;9:215–221.

23 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK, ToGA Trial Investigators: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–697.

24 Suzuki T, Tanabe K, Taomoto J, Yamamoto H, Tokumoto N, Yoshida K, Ohdan H: Preliminary trial of adjuvant surgery for advanced gastric cancer. Oncology Lett 2010;1:743–747.

25 Satoh S, Okabe S, Teramukai S, Hasegawa N, Ozaki S, Ueda A, Tsuji S, Sakabayashi Y, Sakai Y: Early outcome of phase II study of preoperative chemotherapy (CX) with S-1 plus cisplatin for stage IV gastric cancer: 2010 ASCO Annual Meeting Proceedings (abstract 4124). J Clin Oncol 2010;28:15s.

26 Adam R, Aloia T, Lévi F, Wicherts DA, de Haas RJ, Paule B, Bralet M-P, Bouchahda M, Machover D, Ducreux M, Castagne V, Azoulay D, Castaing D: Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. J Clin Oncol 2007;25:4593–4602.

27 Poston GP, Adam R, Alberts S, Curley S, Figueras J, Haller D, Kunstlinger F, Mentha G, Nordlinger B, Patt Y, Primrose J, Roh M, Rougier P, Ruers T, Schmoll HJ, Valls C, Nick Vauthey NJ-N, Cornelis M, Kahan JP: OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol 2005;23:7125–7134.

28 Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D: Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009; 27:1829–1835.

29 Song J, Oh SJ, Kang WH, Hyung WJ, Choi SH, Noh SH: Robot-assisted gastrectomy with lymph node dissection for gastric cancer: lessons learned from an initial 100 consecutive procedures. Ann Surg 2009;249: 927–932.

30 Yoshida K, Yamaguchi K, Sakashita F, Tanaka Y, Sanada Y, Takahashi T, Osada S: Complete laparoscopic gastrectomy preserving autonomic nerves in early gastric cancer (in Japanese). Shoukakigeka 2009;32:1–11.

31 Yoshida K, Tanabe K, Ukon K, Hihara J, Ohta K, Toge T: Laparoscopy assisted distal gastrectomy (LADG) preserving autonomic nerves; in Kitajima M and Otani Y (eds): Proceedings of the 6th International Gastric Cancer Congress, Yokohama, 2005, pp 389–393.

32 Ohtani H, Tamamori Y, Noguchi K, Azuma T, Fujimoto S, Oba H, Aoki T, Minami M, Hirakawa K: Meta-analysis of laparoscopy-assisted and open distal gastrectomy for gastric cancer. J Surg Res 2010, E-pub ahead of print.

33 Kurokawa Y, Katai H, Fukuda H, Sasako M, Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group: Phase II study of laparoscopy-assisted distal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG 0703. Jpn J Clin Oncol 2008;38:501–503.

34 Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, Lee HJ, Song KY: Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report – a phase III multicenter, prospective, randomized trial (KLASS Trial). Ann Surg 2010;251:417–420.

35 Kanaya S, Gomi T, Momoi H, Tamaki N, Isobe H, Katayama T, Wada Y, Ohtoshi M: Delta-shaped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy. J Am Coll Surg 2002;195:284–287.

36 Fujii M, Kochi M, Takayama T: Recent advances in chemotherapy for advanced gastric cancer in Japan. Surg Today 2010;40:295–300.

37 Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M: Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003;89:2207–2212.

38 Komatsu Y, Yuki S, Tateyama M, Kudo M, Asaka M: Irinotecan plus oral S-1 in patients with advanced gastric cancer-biweekly IRIS regimen. Gan to Kagaku Ryoho 2006;33 (suppl 1):131–134.

39 Yoshida K, Hirabayashi N, Takiyama W, Ninomiya M, Takakura N, Sakamoto J, Nishiyama M, Toge T: Phase I study of combination therapy with S-1 and docetaxel (TXT) for advanced or recurrent gastric cancer. Anticancer Res 2004;24:1843–1852.

40 Yoshida K, Ninomiya M, Takakura N, Hirabayashi N, Takiyama W, Sa to Y, Todo S, Terashima M, Goto M, Sakamoto J, Nishiyama M: Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006;12: 3402–3407.

41 Wada Y, Yoshida K, Suzuki T, Mizuiri H, Konishi K, Ukon K, Tanabe K, Sakata Y, Fukushima M: Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. Int J Cancer 2006;119:783–791.

42 Shigematsu H, Yoshida K, Sanada Y, Osada S, Takahashi T, Wada Y, Konishi K, Okada M, Fukushima M: Rapamycin enhances chemotherapy-induced cytotoxicity by inhibiting the expressions of TS and ERK in gastric cancer cells. Int J Cancer 2010;126:2716–2725.

43 Imamura H, Iishi H, Tsuburaya A, Hatake K, Imamoto H, Esaki T, et al: Randomized phase III study of irinotecan plus S-1 (IRIS) versus S-1 alone as first-line treatment for advanced gastric cancer (GC0301/TOP-002). Gastric Cancer 2011;14:72–80.

44 Kim YH, Koizumi W, Lee KH, Kishimoto T, Chung HC, Hara T, Cho JY, Nakajima T, Kim HK, Fujii M: Japan Clinical Cancer Research Organization (JACCRO) and Korean Cancer Study Group (KCSG) inter-group study: randomized phase III study of S-1 alone versus S-1 + docetaxel in the treatment for advanced gastric cancer: the START trial. Gastrointestinal Cancers Symposium General Session (abstract 7). J Clin Oncol 2011; 29(suppl 4).

45 Tanabe K, Suzuki T, Tokumoto N, Yamamoto H, Yoshida K, Ohdan H: Combination therapy with docetaxel and S-1 as a first-line treatment in patients with advanced or recurrent gastric cancer: a retrospective analysis. World J Surg Oncol 2010;8:40.

46 Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM: 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, E-pub ahead of print.

47 Wada Y, Yoshida K, Hihara J, Jyunya T, Suzuki T, Mizuiri H, Konishi K, Ukon K, Tanabe K: A specific neutrophil elastase inhibitor, sivelestat, suppresses the growth of gastric carcinoma cells by preventing the release of TGF-α. Cancer Sci 2006;97:1037–1043.

48 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F, Bismuth H: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy a model to predict long-term survival. Ann Surg 2004;240:644–658.

49 Adam R, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, Guettier C, Kunstlinger F, Delvart V, Azoulay D, Castaing D: Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol 2008;26:1635–1641.

50 Adam R, de Haas RJ, Wicherts DA, Aloia T, Delvart V, Azoulay D, Bismuth H, Castaing D: Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol 2008;26:3672–3680.

51 Nuzzo G, Giuliante F, Ardito F, Vellone M, Pozzo C, Cassano A, GiovanniniI, Barone C: Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. J Gastrointest Surg 2007;11:318–324.

52 Saif MW: Secondary hepatic resection as a therapeutic goal in advanced colorectal cancer. World J Gastroenterol 2009;15:3855–3864.

53 Makuuchi H (ed): The Japan Esophageal Society: Japanese Guideline for Diagnosis and Treatment for Esophageal Cancer.. Tokyo, Kanehara Shuppan, 2007, pp 70–71.

54 Nakamura T, Hyashi K, Ota M, Eguchi R, Ide H, Takasaki K, Mitsuhashi N: Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. Am J Surg 2004;188:161–166.

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ORIGINAL ARTICLE

Usefulness of enhanced recovery after surgery protocol as compared with conventional perioperative care in gastric surgery

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Abstract
Background Radical gastrectomy for gastric cancer is among the most invasive procedures in gastrointestinal surgery. Several studies have found that an enhanced recovery after surgery (ERAS) protocol is useful in patients who undergo colorectal surgery, but its value in gastric surgery remains uncertain. The aim of this study was to assess the usefulness of an ERAS protocol for gastric surgery.
Methods We studied the clinical characteristics, oncological factors, surgical factors, and outcomes in patients who underwent elective radical gastrectomy for gastric cancer before and after the introduction of an ERAS protocol.
Results The first days of oral intake, oral intake recovery, flatus, and defecation were significantly earlier in the ERAS group ($n = 91$) than in the conventional care (CONV) group ($n = 100$). Maximum pain evaluated on a visual analog scale and the number of additional analgesics on demand were significantly less in the ERAS group than in the CONV group. The ratio of the postoperative body weight at 1 week to the preoperative body weight was significantly higher in the ERAS group than in the CONV group (0.95 vs. 0.94, respectively, $P = 0.01$).
Conclusion Our results suggest that the ERAS protocol is useful in patients who undergo elective radical gastrectomy.

Keywords Gastric cancer · Perioperative care · ERAS

Introduction

Surgery for gastric cancer remains a high-risk procedure with clinically significant postoperative stress, complications, and sequelae. Morbidity and mortality from radical gastrectomy range from 20 to 46% and 0.8 to 10%, respectively [1–3]. Conventionally, patients scheduled to undergo gastrectomy fast for 1 day before the surgery and then receive intensive bowel preparation. Thoracic and upper abdominal surgical wounds are associated with the most severe pain. Patients usually have epigastric wound pain after the surgery. In addition, oral intake is not allowed for a long period after the surgery because it is anticipated that intraluminal pressure on the anastomosis would induce leakage.

Enhanced recovery after surgery (ERAS) programs have been proposed to maintain physiological function and thereby facilitate postoperative recovery. Several studies have shown that an ERAS protocol was useful in patients undergoing colorectal surgery [4–8], but its value in gastric surgery remains uncertain. ERAS programs consist of many elements, including preoperative education, preoperative carbohydrate loading, omission of bowel preparation, epidural analgesia without opioids, early postoperative enteral feeding, early mobilization of patients, and thromboprophylaxis. These elements are independent, but are directed

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toward the same goal: reducing surgical stress and optimizing recovery.

In June 2009, we revised our gastrectomy clinical pathway, referring to an ERAS protocol for colorectal resection [6–8]. In the present study, we compared postoperative outcomes between patients who received perioperative care according to our modified ERAS protocol and those who received conventional perioperative care, to evaluate the clinical relevance of the protocol in gastric surgery.

Patients and methods

Patients

We studied consecutive patients who underwent elective gastrectomy for gastric cancer at the Department of Gastrointestinal Surgery, Kanagawa Cancer Center, from November 2008 through December 2009. Patients who received conventional perioperative care underwent surgery from November 2008 through May 2009 (CONV group). Patients who received perioperative care according to the ERAS protocol underwent surgery from June 2009 through December 2009 (ERAS group).

All procedures were performed by the same team of surgeons. In principle, the patients diagnosed as being stage I preoperatively received laparoscopic surgery, and the others received open surgery. Anesthesia consisted of a combination of epidural analgesia (Th7-11) and general anesthesia. The amount of intravenous fluid used both during and after the operation was the same in the two groups. Steroids were not used in either group.

Conventional perioperative care protocol

Patients in the CONV group were allowed to have a liquid diet until lunch of the day before surgery and were allowed to drink the contents of two 500-ml plastic bottles of oral rehydration solution [OS-1®; Fructlact injection (classified as a drug in Japan); Otsuka Pharmaceutical, Tokushima, Japan] until midnight of the day before surgery. Patients with gastric stenosis were not given OS-1®. Intensive bowel preparation (10 ml 0.75% sodium picosulfate hydrate and 34 g magnesium citrate) was administered the day before surgery. One or two drains were always used for both total and distal gastrectomy. The nasogastric tube was removed on postoperative day (POD) 1. After surgery, a continuous thoracic epidural infusion of analgesics was given for 3 days. Additional analgesics were administered only when the patient had pain. On POD 3, patients were allowed to drink only water. Oral intake was started on POD 4, with the same step-by-step oral intake as in the ERAS protocol. An antithrombotic agent was not administered prophylactically (Table 1).

Modified ERAS protocol

The modified ERAS protocol evaluated in the present study was developed by a team of surgeons and anesthesiologists working in close cooperation with a data safety monitoring committee (DSMC). A feasibility and safety audit by the DSMC was completed in September 2009, when 50 patients had been treated according to the ERAS protocol. Patients were allowed to eat until midnight of the day before surgery and were allowed to drink the contents of two 500-ml plastic bottles of OS-1® 3 h before surgery. Patients with gastric stenosis were not given OS-1®. Mild bowel preparation (1 g magnesium oxide and a New Lecicarbon® suppository [Zeria Pharmaceutical, Tokyo, Japan]) was administered the day before surgery. After the surgery, a continuous thoracic epidural infusion of analgesics was given for 2 days. The epidural catheter was removed 6 h before subcutaneous injection of an antithrombotic agent (enoxaparin sodium 2000 IU, twice daily). No drain was used in distal gastrectomy; one or two drains were used in total gastrectomy. The nasogastric tube was removed immediately after surgery. To prevent postoperative pain, a nonsteroidal anti-inflammatory drug (NSAID) (50 mg flurbiprofen axetil) was administered intravenously twice daily after the surgery until the resumption of oral intake. Patients were encouraged to sit out of bed for more than 6 h on postoperative day (POD) 1. On POD 2, oral intake was started, beginning with water and an oral nutrition supplement (250 ml Ensure Liquid®; Abbott Japan, Tokyo, Japan). After the resumption of oral intake, 100 mg of acetaminophen was administered orally three times daily. The patients were encouraged to walk the length of the ward. On POD 3, the patients started to eat solid food, starting with rice gruel and soft food on POD 3 and advancing in three steps to regular food on POD 7. Discharge criteria were: adequate pain relief, soft food intake, return to preoperative mobility level, and normal laboratory data on POD 7 (Table 2).

Data collection

All data were retrieved from the patients' database and clinical records. The following data were extracted: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), comorbidity (diabetes mellitus, hypertension, ischemic heart disease, respiratory disease, liver disease), smoking, American Society of Anesthesiologists Physical Status (ASAPS), tumor size, pathological T factor, pathological N factor, pathological stage, curability, approach, procedure, dissection level, reconstruction, splenectomy, operation time, bleeding, complications,

Table 1 Timetable of CONV protocol

Operative day	−1	0	+1	+2	+3	+4 +5 +6 +7
Oral intake	Liquid diet until lunch; oral hydration solution (OS-1®) until midnight	No oral intake	→	→	Drink only water	Liquid diet (3 steps up to a soft diet every 2 days)
Bowel preparation	10 ml 0.75% sodium picosulfate hydrate and 34 g magnesium citrate					
Anesthesia and analgesics		Combination of epidural analgesia (TH7-11) and general anesthesia during surgery				
		Continuous thoracic epidural infusion of analgesics after surgery	→	→	Remove epidural catheter	
		No anti-inflammatory drug given routinely	→	→	→	→ → → →
Drain and NGT		Always NGT and one or two drains after both total and distal gastrectomy	Remove NGT		Remove drain(s)	
ADL			Mobilization on bed	Encouraged to sit out of bed	Encouraged to walk the length of the ward	→ → → →
Thromboprophylaxis			None	→	→	→ → → →
X-ray and blood examination		○	○			○ (check discharge criteria)

CONV conventional care, *NGT* nasogastric tube, *ADL* activities of daily life, → continue, ○ check these examination

mortality, accomplishment of clinical pathway, first day of walking, first day of oral intake, day of oral intake recovery, first day of flatus, first day of defecation, allowed day of discharge, postoperative hospital stay, maximum pain on a visual analog scale, the number of additional doses of analgesics, and the ratio of postoperative body weight (1 week, 1 month, and 3 months after surgery) to preoperative body weight. Pathological findings were categorized according to the 2nd English edition of the *Japanese classification of gastric carcinoma* [9]. Complications were defined as grade 2 or higher complications, according to the Clavien–Dindo classification, within 30 days after surgery [10]. Oral intake recovery was defined as the ability to ingest more than 50% of a second-step meal.

Statistical analysis

Data were analyzed on an intention-to-treat basis. The ERAS protocol was compared with conventional perioperative care by using the χ^2 test for binary outcomes and the Mann–Whitney *U*-test for continuous outcomes. All statistical analyses were performed using the Dr. SPSS II program, version 11.0.1J for Windows (SPSS, Chicago, IL, USA). Two-sided *P* values were calculated, and a difference was considered statistically significant at $P < 0.05$. Continuous data are expressed as medians (ranges).

Results

One hundred patients received conventional perioperative care, and ninety-one patients were treated according to the ERAS protocol.

Comparison of characteristics between CONV group and ERAS group

There were no significant differences between the CONV group and ERAS group with respect to sex, age, PS, comorbidity, smoking, or ASAPS. However, the ERAS

Table 2 Timetable of ERAS protocol

Operative day	−1	0	+1	+2	+3 +4 +5 +6 +7
Oral intake	Normal diet until midnight	Oral hydration solution (OS-1®) 3 h before surgery		Drink water and an oral nutrition supplement (Ensure Liquid®)	Liquid diet (3 steps up to a soft diet every 2 days)
Bowel preparation	1 g magnesium oxide and a New Lecicarbon® suppository				
Anesthesia and analgesics		Combination of epidural analgesia (TH7-11) and general anesthesia during surgery			
		Continuous thoracic epidural infusion of analgesics after surgery	→	Remove epidural catheter	
		Nonsteroidal anti-inflammatory drug intravenously after surgery twice daily	→	Acetaminophen three times daily, orally	→ → →
Drain and NGT		No drain in distal gastrectomy, one or two drains in total gastrectomy. NGT was removed immediately after surgery		Remove drain(s)	
ADL			Encouraged to sit out of bed for more than 6 h	Encouraged to walk the length of the ward	→ → → → →
Thromboprophylaxis			None	Subcutaneous injection of antithrombotic agent (enoxaparin sodium)	→ → None → →
X-ray and blood examination		○	○		○ (Check discharge criteria)

ERAS enhanced recovery after surgery, *NGT* nasogastric tube, *ADL* activities of daily life, → continue, ○ check these examination

Table 3 Comparison of characteristics between CONV group and ERAS group

	CONV group ($n = 100$)	ERAS group ($n = 91$)	*P* value
Sex (M/F)	72/28	62/29	0.34
Age (years)	65.0 (29–84)	67.0 (42–84)	0.10
PS (0/1/2)	90/7/3	80/11/0	0.13
DM (−/+)	92/8	77/14	0.09
HT (−/+)	69/31	65/26	0.42
IHD (−/+)	99/1	89/2	0.46
Respiratory disease (−/+)	86/14	77/13	0.55
Liver disease (−/+)	94/6	88/3	0.30
Smoking (−/+)	79/21	73/18	0.55
ASAPS (0/1)	40/59	32/59	0.28

CONV conventional care, *ERAS* enhanced recovery after surgery, *PS* Eastern Cooperative Oncology Group performance status, *DM* diabetes mellitus, *HT* hypertension, *IHD* ischemic heart disease, *ASAPS* American Society of Anesthesiologists Physical Status

Table 4 Comparison of oncological factors and surgical factors between the CONV group and ERAS group

	CONV group ($n = 100$)	ERAS group ($n = 91$)	P value
Tumor size (mm)	35.0 (0–190)	39.0 (0–200)	0.75
T factor (1/≥2)	50/50	52/39	0.24
N factor (0/1/2)	58/24/18	61/15/15	0.38
Stage (1/2/3/4)	58/14/18/10	59/17/7/8	0.40
Curability (A/B/C)	65/23/12	68/16/7	0.36
Approach (open/lap)	57/43	43/48	0.12
Procedure (TG/DG)	52/48	57/34	0.21
Dissection (D0–1/D2)	59/41	54/37	1.00
Reconstruction (B1/B2/RY)	42/6/52	45/3/43	0.32
Splenectomy (−/+)	86/14	78/13	0.57
Operation time (min)	206.0 (106–369)	177.0 (80–329)	0.00
Bleeding (ml)	102.5 (0–1240)	80.0 (0–1620)	0.10
Complications (Clavien–Dindo grade 0–1/≥2)	88/12	84/7	0.47
Mortality (−/+)	100/0	91/0	1.00

CONV conventional care, *ERAS* enhanced recovery after surgery, *lap* laparoscopy-assisted, *TG* total gastrectomy, *DG* distal gastrectomy, *B1* Billroth-I reconstruction, *B2* Billroth-II reconstruction, *RY* Roux-en-Y reconstruction

Table 5 Comparison of postoperative outcomes between CONV group and ERAS group

	CONV group ($n = 100$)	ERAS group ($n = 91$)	P value
Accomplish clinical pathway	96.0% (96/100)	94.5% (86/91)	0.74
First day of walking	2 (1–8)	2 (1–3)	0.43
First day of oral intake	**4 (2–17)**	**2 (1–6)**	**<0.01**
Day of oral intake recovery	**7 (5–34)**	**6 (3–45)**	**<0.01**
First day of flatus	**3 (2–12)**	**2 (1–5)**	**0.01**
First day of defecation	**6 (2–12)**	**4 (1–66)**	**<0.01**
Allowed day of discharge	7 (8–84)	7 (4–46)	0.50
Postoperative hospital stay (days)	9 (8–86)	9 (7–47)	0.98
Maximum pain on visual analog scale	**5 (1–10)**	**4 (0–10)**	**0.05**
Number of additional doses of analgesics	**10 (0–43)**	**3 (0–50)**	**<0.01**
The ratio of postoperative (1 week) to preoperative body weight	**0.94 (0.88–1.09)**	**0.95 (0.87–1.03)**	**0.01**
The ratio of postoperative (1 month) to preoperative body weight	0.92 (0.83–1.09)	0.93 (0.72–1.24)	0.69
The ratio of postoperative (3 months) to preoperative body weight	0.89 (0.77–1.11)	0.89 (0.59–1.02)	0.40

CONV conventional care, *ERAS* enhanced recovery after surgery

Items in boldface indicate significant differences between the groups

group tended to be older, have a worse PS, and have a higher prevalence of diabetes mellitus (Table 3).

Comparison of oncological factors and surgical factors between the CONV group and ERAS group

There were no significant differences between the CONV group and the ERAS group with respect to tumor size, pathological T factor, pathological N factor, pathological stage, curability, approach, procedure, dissection level, reconstruction, splenectomy, bleeding, or complications. The only difference was that operation time was shorter in the ERAS group than in the CONV group. Morbidity did not differ significantly between the groups (Table 4). Complications in the CONV group were gastrointestinal obstruction ($n = 1$), intra-abdominal abscess ($n = 1$), biliary tract infection ($n = 1$), postoperative bleeding ($n = 1$), anastomotic leakage ($n = 2$), postoperative anemia ($n = 3$), and pancreatic fistula ($n = 3$). Complications in the ERAS group were ascites ($n = 1$), pancreatic fistula ($n = 1$), anastomotic leakage ($n = 1$), postoperative bleeding on POD 1 before administration of an antithrombotic agent ($n = 1$), and gastrointestinal obstruction ($n = 3$).

Comparison of postoperative outcomes between CONV group and ERAS group

There were no significant differences between the CONV group and the ERAS group in accomplishment of the

clinical pathway, the first day of walking, the allowed day of discharge, or the postoperative hospital stay. However, the first days of oral intake, oral intake recovery, flatus, and defecation were significantly earlier in the ERAS group than in the CONV group. Maximum pain on a visual analog scale and the number of additional doses of analgesics required were significantly less in the ERAS group than in the CONV group. The ratio of postoperative to preoperative body weight was significantly higher in the ERAS group than in the CONV group 1 week after surgery, but the ratio did not differ between the groups at 1 or 3 months (Table 5).

Discussion

In the present study, the ERAS protocol as a whole was novel in gastric surgery, although the individual components are in practice at some Japanese high-volume centers. In accordance with the DSMC's suggestions and audit, the ERAS protocol was evaluated by comparison with the CONV protocol, in a group comprised of patients who underwent surgery and were followed for the same length of time as the ERAS group (7 months) as a historical control before the introduction of the ERAS protocol.

Clinical characteristics, oncological factors, and surgical factors, apart from operation time, did not differ significantly between the ERAS group and the CONV group. Operation time was shorter in the ERAS group than in the CONV group. However, the effect of a reduction of only 30 min in median operation time on postoperative outcomes was unclear. In the Japan Clinical Oncology Group (JCOG) 9501 trial comparing D2 versus D2 and extended para-aortic lymphadenectomy, the median operation time was 63 min longer in the latter group, without any difference in morbidities [11].

Avoidance of a full stomach is much more important in gastric resection than in colorectal resection, not only for the prevention of aspiration at the induction of anesthesia, but also for ensuring intraoperative maneuverability of the stomach and decreasing the risk of surgical-site infection. In the ERAS protocol for colorectal resection, patients receive 12.5% carbohydrate loading [12]. We used OS-1® (2.5% carbohydrate) for preoperative rehydration before surgery because of its rapid clearance from the stomach. Taniguchi et al. [13] reported that the volume of esophageal–pharyngeal fluid and gastric fluid following the induction of anesthesia was only 6.03 ± −9.14 ml and that no adverse event or adverse reaction occurred after preoperative OS-1® loading. But 12.5% carbohydrate clearance from the stomach is unclear. Further study is needed to determine whether OS-1® is effective as a carbohydrate loading and whether 12.5% carbohydrate is safe for gastric surgery.

No abdominal drain was used routinely in the patients in the ERAS group who underwent distal gastrectomy. There were no complications associated with drains in either of the groups. Alvarez Uslar et al. [14], in a study in Chile, reported that operative morbidity and hospital stay were significantly higher in the group of patients who underwent total gastrectomy with abdominal drains than in the group of patients without drains. However, we refrained from abolishing the use of drains for total gastrectomies at this time, since the degree of lymph node dissection is more extensive in Japan than in the West, and often calls for splenectomy, possibly leading to a higher risk for of surgical-site infection. The use of drains after total gastrectomy continues to be an issue for debate in the future development of the ERAS program.

Bowel movement recovery (i.e., the first days of oral intake, oral intake recovery, flatus, and defecation) was earlier in the ERAS group than in the CONV group in our study. Wang et al. [15] reported that the first day of flatus after gastric surgery was earlier in patients who received fast-track surgery care than in those who received conventional care (3 vs. 4 days). Teeuwen et al. [5] found that oral intake in their ERAS group was higher than that in the conventional group after colorectal surgery. Prolonged perioperative fasting, preoperative bowel preparation, and nasogastric tube intubation are likely to induce nausea and delay bowel-function recovery. Previous studies have reported that the patients without a postoperative nasogastric tube recovered postoperative bowel movement earlier than the patients with one, and that routine postoperative nasogastric tube intubation is unnecessary after an elective operation [16, 17]. On the other hand, complications potentially caused by a short fasting period, such as aspiration pneumonia or anastomotic leakage, did not increase in our ERAS group, and accomplishment of the clinical pathway did not differ between our groups. Suehiro et al. [18] reported that early feeding 2 days after gastrectomy was safe, with no increase in morbidity.

In our study, the epidural catheter was removed earlier in the ERAS group than in the CONV group, in accordance with an antithrombotic agent being administered prophylactically on POD 2. Moreover, an NSAID and acetaminophen were used as baseline analgesics throughout the postoperative course in the ERAS group. Consequently, maximum pain assessed on a visual analog scale and the number of additional doses of analgesics were significantly less in the ERAS group. It was not clear whether the total dose of analgesics (baseline plus additional analgesics) was different between the two groups. Baseline NSAID analgesics could be sufficient for the prevention of postoperative pain regardless of the short-term action of the epidural analgesic. Less pain facilitated early mobilization. Bed rest not only increases muscle loss and insulin resistance, but

also decreases pulmonary function and tissue oxygenation [19].

According to the National Comprehensive Cancer Network (NCCN) guideline, after surgery for cancer, all in-patients and out-patients are recommended to receive prophylactic anticoagulation therapy for up to 4 weeks after the surgery [20]. Also, the American Society of Clinical Oncology (ASCO) guidelines recommend that all patients undergoing major surgical intervention should be considered for thromboprophylaxis, starting as early as possible after the surgery and continuing for at least 7–10 days unless there is a contraindication [21]. To minimize the risk of epidural hematoma at the time of removing an epidural catheter, we do not start thromboprophylaxis on POD 1 before the removal of the epidural catheter on POD 2. There were no thromboembolic events or epidural hematomas in either of our groups, and there was no postoperative bleeding associated with thromboprophylaxis. Jeong et al. [22] reported that perioperative low-molecular-weight heparin as thromboprophylaxis significantly increased the risk of bleeding after gastric surgery. Therefore, an optimal thromboprophylaxis regimen of should be determined in further trials.

The day when discharge was allowed and the duration of the postoperative hospital stay did not differ between our ERAS group and the CONV group. This lack of a difference was attributed to the discharge criteria and the Japanese Diagnosis Procedure Combination-based Payment System (DPC). Because laboratory testing was performed on POD 7 in both groups, the mean day of discharge did not differ significantly. Wang et al. [15] reported that the postoperative hospital stay after gastric surgery was shorter in patients who received fast-track surgery care than in those who received conventional care.

In our study, the ratio of the postoperative body weight at 1 week to the preoperative body weight was higher in the ERAS group than that in the CONV group, despite the relatively higher proportion of elderly patients in the former group. Holte et al. [23] reported that preoperative bowel preparation caused dehydration and fluid electrolyte abnormalities, particularly in elderly patients. We attribute the prompter body weight recovery in the ERAS group not only to less postoperative muscle loss and fat loss, but also to their well-hydrated status during the perioperative period.

In conclusion, our results suggest that the ERAS protocol described here is useful in patients who undergo elective gastrectomy. Further study is needed to confirm the effectiveness of this protocol in terms of the recovery of the patients and to decide whether or not to include other components of the ERAS program.

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References

1. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med. 1999;340:908–14.
2. 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.
3. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359:453–62.
4. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29:434–40.
5. Teeuwen PH, Bleichrodt RP, Strik C, Groenewoud JJ, Brinkert W, van Laarhoven CJ, et al. Enhanced recovery after surgery (ERAS) versus conventional postoperative care in colorectal surgery. J Gastrointest Surg. 2010;14:88–95.
6. King PM, Blazeby JM, Ewings P, Longman RJ, Kipling RM, Franks PJ, et al. The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. Colorectal Dis. 2006;8:506–13.
7. Fearon KC, Luff R. The nutritional management of surgical patients: enhanced recovery after surgery. Proc Nutr Soc. 2003;62:807–11.
8. Mohn AC, Bernardshaw SV, Ristesund SM, Hovde Hansen PE, Røkke O. Enhanced recovery after colorectal surgery. Results from a prospective observational two-centre study. Scand J Surg. 2009;98:155–9.
9. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1998;1:10–24.
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
11. 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.
12. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg. 2009;144:961–9.
13. Taniguchi H, Sasaki T, Fujita H, Takamori M, Kawasaki R, Momiyama Y, et al. Preoperative fluid and electrolyte management with oral rehydration therapy. J Anesth. 2009;23:222–9.
14. Alvarez Uslar R, Molina H, Torres O, Cancino A. Total gastrectomy with or without abdominal drains. A prospective randomized trial. Rev Esp Enferm Dig. 2005;97:562–9.
15. Wang D, Kong Y, Zhong B, Zhou X, Zhou Y. Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care. J Gastrointest Surg. 2010;14:620–7.

16. Carrère N, Seulin P, Julio CH, Bloom E, Gouzi JL, Pradère B. Is nasogastric or nasojejunal decompression necessary after gastrectomy? A prospective randomized trial. World J Surg. 2007; 31:122–7.
17. Yoo CH, Son BH, Han WK, Pae WK. Nasogastric decompression is not necessary in operations for gastric cancer: prospective randomised trial. Eur J Surg. 2002;168:379–83.
18. Suehiro T, Matsumata T, Shikada Y, Sugimachi K. Accelerated rehabilitation with early postoperative oral feeding following gastrectomy. Hepatogastroenterology. 2004;51:1852–5.
19. Soop M, Carlson GL, Hopkinson J, Clarke S, Thorell A, Nygren J, et al. Randomized clinical trial of the effects of immediate enteral nutrition on metabolic responses to major colorectal surgery in an enhanced recovery protocol. Br J Surg. 2004; 91:1138–45.
20. Wagman LD, Baird MF, Bennett CL, Bockenstedt PL, Cataland SR, Fanikos J, et al. Venous thromboembolic disease. NCCN. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2008;6:716–53.
21. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol. 2007;25:5490–505.
22. Jeong O, Ryu SY, Park YK, Kim YJ. The effect of low molecular weight heparin thromboprophylaxis on bleeding complications after gastric cancer surgery. Ann Surg Oncol. 2010;17:2363–9.
23. Holte K, Nielsen KG, Madsen JL, Kehlet H. Physiologic effects of bowel preparation. Dis Colon Rectum. 2004;47:1397–402.

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ORIGINAL ARTICLE

Macroscopic tumor size as an independent prognostic factor for stage II/III gastric cancer patients who underwent D2 gastrectomy followed by adjuvant chemotherapy with S-1

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Abstract
Background In patients with stage II/III gastric cancer, tumors often recur even after curative D2 gastrectomy followed by adjuvant S-1 chemotherapy. The objective of this retrospective study was to clarify the prognostic factors in these patients that might be useful for future patients.
Methods Overall survival (OS) was examined in 82 gastric cancer patients who underwent curative D2 surgery; were diagnosed with stage IIA, IIB, IIIA, IIIB, or IIIC pathologically; and received adjuvant S-1 after surgery between June 2002 and March 2010.
Results When length of OS was evaluated by the log-rank test, significant differences were observed with regard to macroscopic tumor diameter and the depth of tumor invasion. A macroscopic tumor diameter >70 mm was regarded as a critical point of classification considering survival. Univariate and multivariate Cox's proportional hazard analyses demonstrated that macroscopic tumor diameter was the only significant independent prognosticator. The 5-year survival was 64.9% in patients with a macroscopic tumor diameter <70 mm, and 33.1% in patients with a macroscopic tumor diameter ≥70 mm ($P = 0.022$).
Conclusions The macroscopic tumor diameter was the most important prognostic factor for survival in patients with stage II/III gastric cancer who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy. Prognostic factors can be affected by adjuvant chemotherapy.

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Keywords Gastric cancer · Adjuvant chemotherapy · S-1 · Prognostic factor

Introduction

Every year, more than 934,000 people develop gastric cancer worldwide. Gastric cancer is the second most frequent cancer-related cause of death after lung cancer [1]. Complete resection is essential for the cure of gastric cancer. Stage IV cancers are unresectable, and these patients have a poor prognosis. Stage I cancers, in which the tumor is limited to T1N0–1 and T2N0, rarely develop a recurrence, and patients have an excellent prognosis. On the other hand, patients with stage II/III gastric cancer often develop tumor recurrence even after complete curative resection. Therefore, it is important to identify prognostic factors for patients with stage II and III gastric cancer in order to select patients for more aggressive treatment. Previously, lymph node metastasis [2, 3] and the depth of tumor invasion [4, 5] were reported to be significant prognostic factors that could be used to predict survival. However, these reports only analyzed patients who were treated with surgery alone or with surgery followed by adjuvant chemotherapy of unknown efficacy, because effective adjuvant chemotherapy had not been verified in these patients.

In 2007, the adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) trial demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who had undergone a D2 curative gastrectomy for locally advanced gastric cancer and had been diagnosed with pathological stage II or III disease [6]. Based on the ACTS-GC trial, S-1 adjuvant chemotherapy became the standard treatment for patients with stage II and III gastric cancer.

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This trial suggested that S-1 could improve patient survival by inhibiting peritoneal metastases. Therefore, it seems that prognostic factors might be altered following effective S-1 adjuvant chemotherapy.

In this study, we investigated the prognostic factors for patients with stage II and III gastric cancer who underwent D2 gastrectomy followed by adjuvant chemotherapy with S-1.

Patients and methods

Patients

The patients were selected from the prospective database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma; (2) patients underwent a curative D2 resection for gastric cancer as a primary treatment between June 2002 and March 2010; (3) stage IIA, IIB, IIIA, IIIB, or IIIC disease was diagnosed pathologically according to the Japanese classification of gastric carcinoma 14th edition published by the Japanese Gastric Cancer Association [7]; (4) patients received adjuvant S-1 chemotherapy after surgery at a starting dose of 80 mg/m^2/day.

Following the rule defined by the protocol of the ACTS-GC trial, patients received S-1 chemotherapy and were followed at outpatient clinics [6]. Written informed consent was obtained from each patient prior to treatment initiation. Survival data were obtained from hospital records or from the city registry system.

Measurement of tumor diameter

Tumor diameter was measured according to the Japanese classification of gastric carcinoma, 14th edition published by the Japanese Gastric Cancer Association [7]. The resected specimen was opened along the greater curvature to observe the mucosal surface clearly. The opened stomach was placed on a flat board, and the longest tumor diameter was measured and used in the analysis.

Evaluation and statistical analyses

The overall survival (OS) was evaluated by univariate and multivariate analyses. The survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and multivariate survival analyses. A P value of <0.05 was defined to be statistically significant.

An SPSS software package (v11.0J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 240 patients underwent surgical resection and were diagnosed with stage IIA, IIB, IIIA, IIIB, or IIIC disease pathologically. Among them, 82 patients were eligible for the present study. All patients had received S-1 as the standard therapy after 2007, when the results of the ACTS-GC trial were presented, or as the test treatment in clinical trials of ACTS-GC or the stomach cancer adjuvant multi-institutional trial group (SAMIT) study. Patients who had received other chemotherapy in other clinical trials and those who did not receive adjuvant chemotherapy were excluded. The patients' ages ranged between 36 and 80 years (mean 62.0). Fifty-six patients were male, and 26 were female. The pathological stage was IIA in 1 patient, IIB in 23 patients, IIIA in 10 patients, IIIB in 23 patients, and IIIC in 25 patients. The median follow-up period was 24.2 months (range 2.8–76.5 months). The median duration of adjuvant S-1 administration was 7.6 months (range 0.2–34.8 months). The S-1 treatment was continued for 1–3 months in 74 patients, 3–6 months in 61 patients, and 6–12 months in 47 patients. Three patients continued treatment for more than 13 months at the patient's request. When OS, stratified by clinical factors, was compared by the log-rank test, a significant difference was observed in regard to macroscopic tumor diameter and the depth of tumor invasion (Table 1). Lymph node metastasis was marginally significant. A macroscopic tumor diameter of 70 mm was regarded as the optimal critical point of classification, considering the 3-year survival rate, which was regarded as more reliable than the 5-year survival rate because median follow-up was only 24.2 months. Each clinicopathological factor was categorized, as shown in Table 2, and was analyzed for prognostic significance. Univariate analyses for OS demonstrated that macroscopic tumor diameter was a significant prognostic factor, but that tumor depth and nodal metastasis were only marginally significant (Table 2). Macroscopic tumor diameter was selected for the final model to be analyzed by multivariate analysis (Table 3). The 5-year survival was 64.9% in patients with a macroscopic tumor diameter <70 mm, and it was 33.1% in those with a macroscopic tumor diameter ≥ 70 mm (Fig. 1).

Discussion

In this report, we first evaluated the potential prognostic factors in stage II/III gastric cancer patients who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy, and clarified that macroscopic tumor diameter was the most important prognostic factor, based on the hazard ratio and p values.

Table 1 Comparison of survival rates stratified by patient characteristics

Characteristics	3-Year survival rate (%)	5-Year survival rate (%)	*P* value
Age (years)			0.5451
<70	70.4	52.5	
≥70	70.9	70.9	
Performance status (ECOG)			0.2743
0	73.7	59.9	
1	54.3	40.7	
Site of tumor			0.2228
Entire	33.3	0	
Upper third	83.6	65.0	
Middle third	67.6	67.6	
Lower third	70.9	56.8	
Macroscopic tumor diameter (mm)			0.0390
<30	85.7	68.6	
≥30 to <50	78.6	78.6	
≥50 to <70	79.4	54.4	
≥70 to <90	67.0	50.2	
≥90	17.9	17.9	
Histological type			0.1874
Differentiated	76.7	68.2	
Undifferentiated	68.6	49.2	
Depth of invasion			0.0415
pT2, pT3	85.7	85.7	
pT4a, pT4b	66.4	47.7	
Lymph node metastasis			0.0997
pN0	57.1	38.1	
pN1	–	–	
pN2	72.7	72.7	
pN3	64.3	33.1	
Lymphatic invasion			0.5798
Negative	75.2	58.5	
Positive	68.1	54.5	
Vascular invasion			0.3664
Negative	52.1	52.1	
Positive	75.6	58.5	

ECOG Eastern Cooperative Oncology Group

Table 2 Univariate Cox proportional hazards analysis of clinicopathological factors

Factors (category)	No. of patients	HR	95% CI	*P* value
Age (years)				0.547
<70	56	1.000		
≥70	26	0.712	0.235–2.157	
Performance status (ECOG)				0.281
0	70	1.000		
1	12	1.599	0.631–4.885	
Site of tumor				0.275
Entire	4	1.000		
Upper third	25	0.062	0.058–1.075	
Middle third	35	0.104	0.083–1.262	
Lower third	18	0.124	0.069–1.380	
Macroscopic tumor diameter (mm)				0.028
<70	55	1.000		
≥70	27	2.776	1.116–6.857	
Histological type				0.198
Differentiated	28	1.000		
Undifferentiated	54	2.068	0.685–6.246	
Depth of invasion				0.075
pT2, pT3	21	1.000		
pT4a, pT4b	61	6.222	0.830–46.638	
Lymph node metastasis				0.072
pN0–pN2	53	1.000		
pN3	29	2.295	0.929–5.671	
Lymphatic invasion				0.371
Negative	20	1.000		
Positive	62	0.621	0.218–1.766	
Vascular invasion				0.581
Negative	26	1.000		
Positive	56	1.315	0.497–3.475	

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group

Table 3 Stepwise multivariate Cox proportional hazards analysis of clinicopathological factors

Factor (category)	No. of patients	*P* value	HR	95% CI
Macroscopic tumor diameter (<70 vs. ≥70 mm)	55 and 27	0.028	2.766	1.116–6.857

Some authors have reported the significance of the macroscopic tumor diameter in the prognosis of gastric cancer patients. For example, Kunisaki et al. [8] examined 1215 patients with gastric cancer and classified them into groups with smaller tumors and those with larger tumors, by setting 100 mm as the cutoff value for the maximal tumor diameter. They found that OS was markedly different between stage II/III patients with smaller and larger tumors. Saito et al. [9] evaluated 1473 patients with gastric cancer and divided them into two groups using a cutoff value of 80 mm for the tumor size. They found that the prognosis of patients with the large tumors was significantly worse than the prognosis for those with the small tumors. However, these reports only examined patients

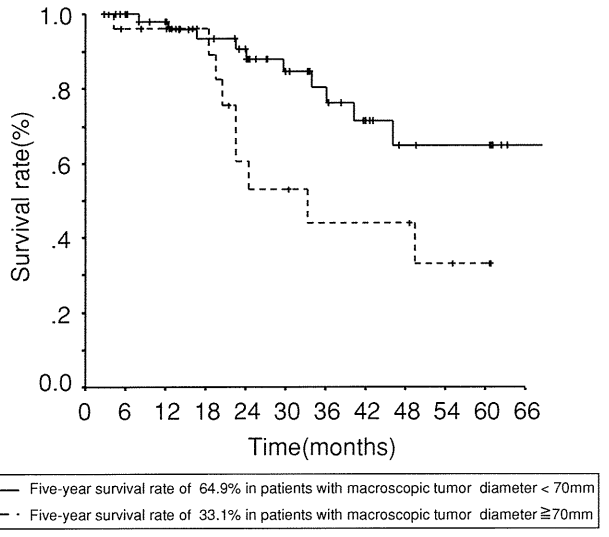

Fig. 1 Survival curves of patients with macroscopic tumor diameters of <70 and ≥70 mm

who had undergone surgery only, or those who had undergone surgery with adjuvant therapy of unproven efficacy. In the present study, evaluating patients who received S-1 adjuvant chemotherapy, we set the cutoff value for tumor size at 70 mm, considering the 3-year survival rate, and found that tumor size was a strong independent prognostic factor. The optimal cutoff value was different between the previous reports and the present one, which may be explained by the use of S-1 adjuvant chemotherapy in our study; by differences in the durations of the follow-up periods and the numbers of patients; and by inter-institutional variability.

Previously, the depth of tumor invasion had been considered to be the key prognostic factor in gastric cancer patients who underwent curative resection [4, 5]. Several authors indicated that serosal invasion correlated with peritoneal recurrence and a poorer prognosis. In the ACTS-GC trial, the incidence of peritoneal recurrence was 11.2% in the S-1 group and 15.8% in the surgery-only group ($P = 0.009$) [6]. On the other hand, the incidence of hematogenous recurrence was 10.2% in the S-1 group and 11.3% in the surgery-only group. These results suggest that S-1 was more effective in reducing peritoneal recurrence than in reducing hematogenous recurrence. The depth of tumor invasion might no longer be a useful prognostic factor, because S-1 can reduce the incidence of peritoneal recurrence.

Lymph node metastasis has also been considered as a strong prognostic factor in gastric cancer patients [2, 3]. The ACTS-GC trial demonstrated that hazard ratios for death were better in N0 and N1 than in N2 patients. In the present study, nodal metastasis was found to be a marginally significant factor according to our univariate analysis, and it remained in the final model, but did not reach statistical significance by multivariate analysis. Our results suggest that nodal metastasis may be an inferior prognostic factor compared to the tumor size when the examination is limited to patients who receive S-1 chemotherapy. However, the marginal significance might become more important if the number of patients is increased or if there is longer-term follow-up.

There were many limitations in this study. First, this was a retrospective single-center study with a small sample size. Our findings in this series may have been observed by chance only. Second, the median follow-up period was only 24.2 months, which is not enough to lead to a definite conclusion. Third, the optimal tumor size cutoff value is unclear. In our study, the cutoff value was set at 70 mm by considering the 3-year survival rate. However, regardless of whether the cutoff value was 70, 80, or 90 mm, tumor size remained an independent significant prognosticator (data not shown). Thus, large tumors seemed to have a poor prognosis. An appropriate cutoff value should be determined in other validation studies. Fourth, the depth of tumor invasion and nodal metastasis had prognostic impact in the ACTS-GC study although the tumor size was not examined. When comparing the ACTS-GC trial and our present study, there are some differences in the backgrounds of the patients. The depth of invasion was deeper in the present study (pT4a, pT4b, 61/82; 74.3%) than in the ACTS-GC trial (pT4a, pT4b, 239/529; 45.1%). The incidence of nodal metastases was higher in the ACTS-GC trial (478/529; 90.4%) than in the present study (68/82; 82.9%), while that of TNM-N3 was higher in the present study (29/82; 35.%) than in the ACTS-GC trial (147/529; 27.8%). Because many patients in the present series received S-1 adjuvant chemotherapy as a test arm of the SAMIT trial (a 2 × 2 phase III trial for surgical serosa-positive disease), the incidence of T4a and N3 may be high in this series. Also, differences in background factors could affect prognosticators in stage II/III disease. Considering these limitations, our results should be validated in different series with large sample sizes and sufficient follow-up periods.

In conclusion, the macroscopic tumor diameter was found to be the only significant independent prognostic factor in patients who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy. Therefore, it appears that the value of prognostic factors can be altered by the use of effective adjuvant chemotherapy.

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Conflict of interest None declared.

References

1. Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. J Clin Oncol. 2006;24:2188–96.
2. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. Cancer. 2000;89:255–61.
3. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi K. Prediction of early and late recurrence after curative resection for gastric carcinoma. Cancer. 1996;77:2445–8.
4. Bozzetti F, Bonfanti G, Morabito A, Bufalino R, Menotti V, Andreola S, et al. A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. Surg Gynecol Obstet. 1986;162:229–34.
5. Maruyama K. The most important prognostic factors for gastric cancer patients: a study using univariate and multivariate analyses. Scand J Gastroenterol. 1987;22:63–8.
6. 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.
7. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 14th Japanese ed. Tokyo: Kanehara-shuppan; 2010. p. 5–17.
8. Kunisaki C, Makino H, Takagawa R, Oshima T, Nagano Y, Kosaka T, et al. Tumor diameter as a prognostic factor in patients with gastric cancer. Ann Surg Oncol. 2008;15:1959–67.
9. Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Oro S, et al. Macroscopic tumor size as a simple prognostic indicator in patients with gastric cancer. Am J Surg. 2006;192:296–300.

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ORIGINAL ARTICLE

Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1

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Abstract
Background Some patients experience a recurrence of cancer even after curative D2 gastrectomy followed by adjuvant S-1 chemotherapy. The objective of this retrospective study was to clarify the survival and prognosticators in these patients.
Methods The study selected patients who underwent curative D2 surgery, were diagnosed with stage II, IIIA, or IIIB cancer, received adjuvant S-1 for more than 4 weeks, and experienced recurrence confirmed by an imaging study.
Results A total of 34 patients were evaluated. The median overall survival (OS) was significantly longer in the 26 patients who received palliative chemotherapy than that in the 8 who did not (8.5 vs. 2.5 months, $P = 0.002$). Only 1 patient received S-1, 21 received taxane-containing regimens, and 4 received irinotecan plus cisplatin as the first-line chemotherapy. Univariate and multivariate analyses showed that the histological type was only independent significant prognosticator.
Conclusions These results suggested that the survival did not reach the level expected for first-line chemotherapy. The histological type was a significant prognosticator in patients who experienced recurrence after adjuvant S-1 therapy and thereafter received palliative chemotherapy.

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

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Introduction

5-Fluorouracil (5-FU)-based chemotherapy is widely used for unresectable advanced or recurrent gastric cancer and has a survival benefit in comparison to the best supportive care [1]. Two phase III studies to evaluate chemotherapy regimens for gastric cancer were recently reported from Japan [2, 3]. The JCOG9912 trial compared 5-FU to S-1 alone or cisplatin (CDDP) plus irinotecan (CPT-11), and found S-1 alone to be comparable to 5-FU alone, but CDDP plus CPT-11 therapy failed to demonstrate superiority to 5-FU alone in overall survival (OS; 11.4 vs. 12.3 vs. 10.8 months). The SPIRITS trial compared the efficacy of S-1 plus CDDP to that of S-1 alone, and found that S-1 plus CDDP showed a significantly longer overall survival (OS; 13 vs. 11 months; $P = 0.037$). These trials included patients with recurrent gastric cancer who did not receive adjuvant chemotherapy or those who received an oral fluoropyrimidine other than S-1. However, prior to these studies, no drugs had been confirmed to be effective as adjuvant chemotherapy after curative surgery.

The ACTS-GC trial first demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who underwent curative gastrectomy for locally advanced gastric cancer and were diagnosed as pathological stage II or III [4]. Therefore, adjuvant S-1 chemotherapy has been established as the standard therapy for stage II or III gastric cancer in Japan. However, about 30% of the patients still develop recurrence after a curative resection followed by adjuvant S-1. The survival of patients who experience recurrence after adjuvant S-1 has not been fully clarified. It is unclear whether these patients should be treated as candidates for first-line chemotherapy.

The present study investigated the survival, and the factors that could predict the survival, in gastric cancer

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patients who experienced recurrence after adjuvant chemotherapy with S-1 and thereafter received palliative chemotherapy.

Patients and methods

Patients

Patients were selected from the database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma, (2) patients who underwent a curative surgical resection for gastric cancer as a primary treatment between June 2002 and December 2009, (3) stage II, IIIA, or IIIB determined pathologically according to the guidelines of the Japanese Gastric Cancer Association[5], (4) patients who received adjuvant S-1 chemotherapy after surgery for more than 4 weeks at a starting dose of 80 mg/m^2, (5) recurrence was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), barium enema, laparoscopy, or bone scintigraphy.

Evaluation and statistical analyses

The overall survival (OS) was calculated from the date of the imaging study that confirmed the recurrence to the date of any cause of death or last follow-up. Unpaired Student's *t*-test or the χ^2 method was used to compare two groups. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and stepwise multivariate survival analyses. A P value of <0.05 was defined to be statistically significant, and the data were expressed as medians ± ranges.

An SPSS software package (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 233 patients underwent surgical resection and were pathologically diagnosed as stage II, IIIa, or IIIb. Among them, 92 patients received adjuvant chemotherapy with S-1. Thirty-four patients were eligible for the present study. The median follow-up was 21.5 months (range from 4.3 to 57.2 months). The median OS was 7.3 months (95% confidence interval [CI], 5–9.6 months). Twenty-six patients received palliative chemotherapy after recurrence, while 8 did not, due to renal dysfunction in 2, liver dysfunction in 1, mechanical intestinal obstruction in 1, and patient's refusal in 4. The median OS was 8.5 months (95% CI, 4.4–12.5 months) in the patients who received chemotherapy and 2.5 months (95% CI, 0.7–4.3 months) in those who did not, and the difference was statistically significant ($P = 0.0022$; Fig. 1).

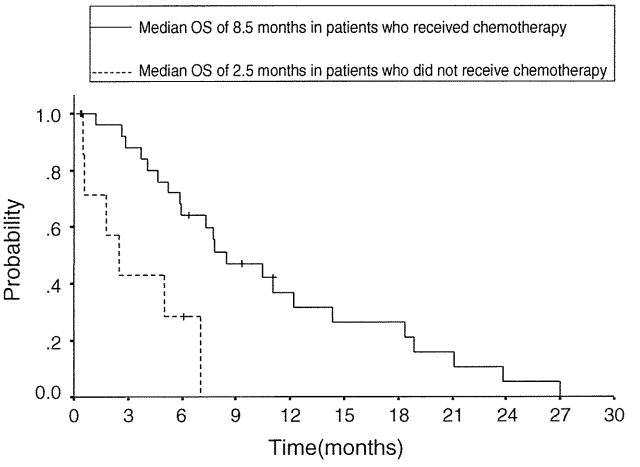

Fig. 1 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients who received chemotherapy (*solid line*) and those who did not receive chemotherapy (*broken line*; $P = 0.0022$)

The backgrounds of the 26 patients who received chemotherapy are shown in Table 1. None of the 26 patients received any other therapies, such as a surgical resection or radiological treatment, in addition to chemotherapy during the clinical course.

Prognosticators in these patients were analyzed by univariate and multivariate analyses. The median duration of adjuvant S-1 administration was 6.2 months, with a range from 1 to 19.9 months. Six patients stop S-1 for ≦3 months due to toxicity. The treatment was withdrawn in 8 of the remaining patients before 6 months, due to recurrence in 5, toxicity in 2, and for other reasons in 1. The treatment was withdrawn in 6 of the remaining patients before 9 months, due to recurrence in 3 and for other reasons in 3. As a result, 8 patients discontinued S1 due to recurrence and 12 patients discontinued S1 due to toxicity or other reasons. The chemotherapy regimens after recurrence were individually selected by the patient's physician. One patient received S-1, 21 received taxane-containing regimens [taxane group (i.e., paclitaxel and docetaxel)], and 4 received irinotecan plus cisplatin (CPT-11 group).

A univariate analysis of factors affecting OS demonstrated that histological type was the only significant factor (Table 2). The OS of the differentiated type was significantly better than that of the undifferentiated type ($P = 0.009$; Fig. 2). The multivariate analysis revealed that histological type remained the only independent significant prognosticator (Table 3). However, the duration of

Table 1 Background of patients who received chemotherapy

Age (years)	58.6 ± 11.6
Gender	
Male	16
Female	10
PS (ECOG) at recurrence	
0	18
1	8
Histological type	
Differentiated	9
Undifferentiated	17
Pathological stage	
Stage II	4
Stage III A	9
Stage III B	13
Site of recurrence	
Peritoneum	14
Liver	5
Lymph node	5
Other	2
Disease-free interval, months median (range)	13.1 (3.9–38.9)
Duration of adjuvant S-1	
<3 Months	6
≧3 Months	20
Treatment-free interval (since last S-1)	
<6 Months	13
≧6 Months	13
Disease-free interval (since surgery)	
<12 Months	12
≧12 Months	14
First-line chemotherapy after recurrence	
Taxane group	21
CPT-11 group	4
S-1	1
Second-line chemotherapy after recurrence	
Taxane group	5
CPT-11 group	6

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *CPT* irinotecan

Table 2 Univariate Cox proportional hazards analysis of clinicopathologic factors

Factor (category)	No. of patients	OR	95% CI	*P* value
Age				0.164
<65 Years	17	1.000		
≧65 Years	9	2.204	0.724–6.716	
PS (ECOG)				0.136
0	18	1.000		
1	8	2.315	0.768–6.975	
Histological type				0.009
Differentiated	9	1.000		
Undifferentiated	17	4.117	1.420–11.931	
Duration of adjuvant S-1				0.173
<3 Months	6	1.000		
≧3 Months	20	0.477	0.164–1.384	
Treatment-free interval (since last S-1)				0.161
<6 Months	13	1.000		
≧6 Months	13	2.026	0.755–5.433	
Recurrence-free interval (since surgery)				0.242
<12 Months	12	1.000		
≧12 Months	14	1.737	0.689–4.383	
Site of recurrence				0.412
Peritoneum	14	1.000		
Other	12	0.688	0.282–1.682	
First-line chemotherapy after recurrence				0.483
S-1	1	1.000		
CPT-11 group	4	0.590	0.076–4.545	
Taxane group	21	0.427	0.097–1.886	

OR odds ratio, *CI* confidence interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

chemotherapy tended to be significant according to the univariate analysis, but not based on the multivariate analysis.

Figure 3 shows details of the regimens of the first- and second-line chemotherapy in 9 patients with the differentiated type and 17 with the undifferentiated type. Most patients received taxane-containing regimens as the first-line chemotherapy. The proportion of patients who received both taxanes and irinotecan was higher in those with the differentiated type (6 of 9 patients, 66.7%) than in those with the undifferentiated type (3 of 17 patients, 17.6%), and the difference was statistically significant ($P = 0.012$).

Discussion

Only Shitara et al. [6] retrospectively examined the efficacy and survival of the treatment in patients who developed recurrence after adjuvant S-1 chemotherapy. The response rate to S-1-containing chemotherapy was 0%. They recommended other chemotherapeutic regimens in this setting. Most patients in the present study received taxane-containing regimens. Only 1 patient received palliative S-1 after recurrence. Despite the use of taxanes in most patients, the median OS of the 26 patients who received chemotherapy after recurrence was only 8.5 months, which did not reach the level expected for