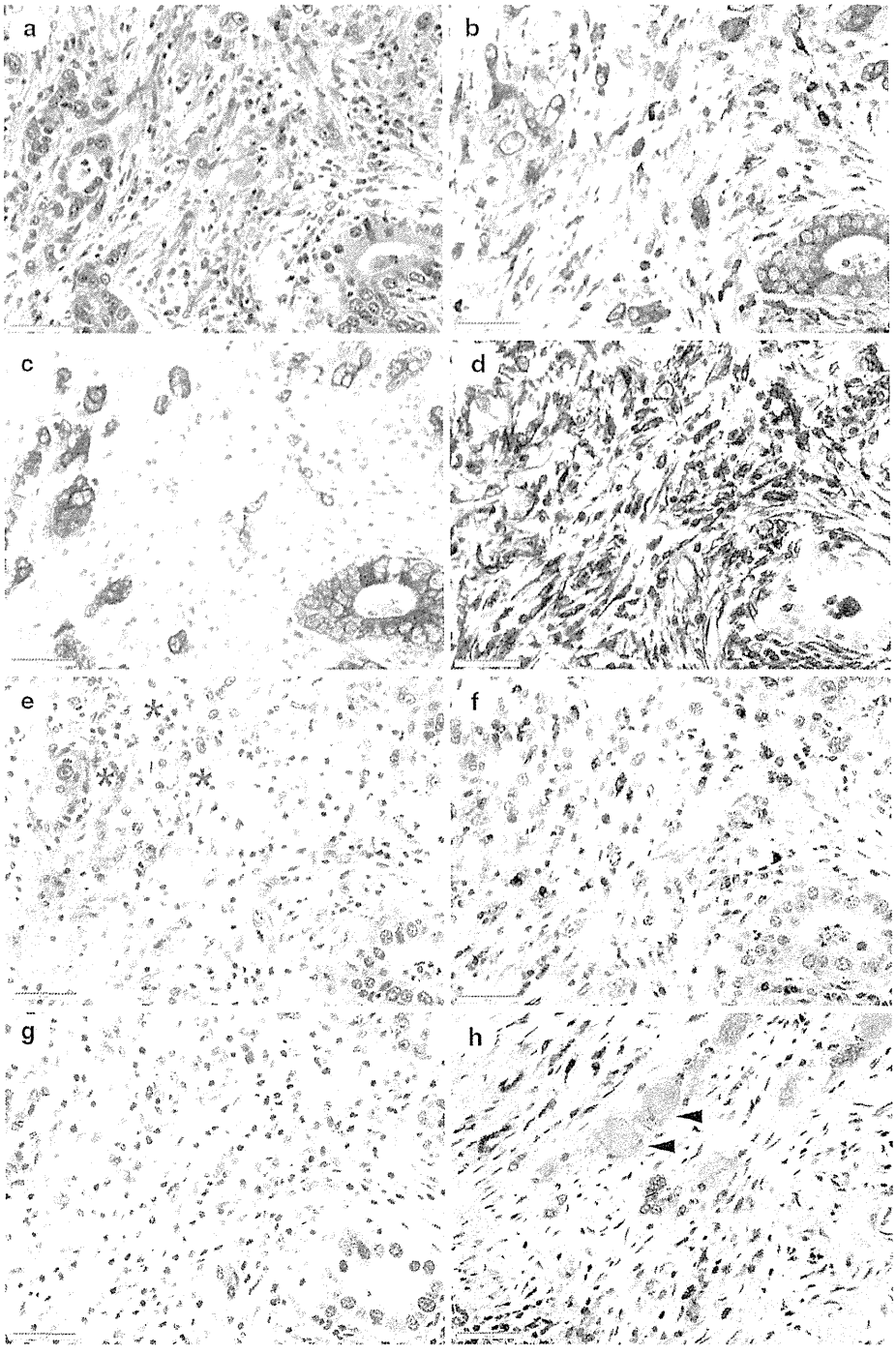

Fig. 3 Intermingling of scattered cancer cells and GCSC expressing Ephrin A2 receptors (IC/A2+). Immunohistochemistry analyzed phenotype of IC/A2-positive lesion. **a** Hematoxylin-eosin staining of ICs, showing intermingling of scattered cancer cells and stromal cells in invasive lesions. **b** EphA2 expression in both of cancer cells and stromal cells. Expression of keratin (**c**) and vimentin (**d**) in cancer cells and mesenchymal cells. Fibroblasts, endothelial cells, and hematopoietic cells were positive for vimentin, but negative for keratin. **e** alpha-SMA expression in vascular vessels and myofibroblasts. Most stromal cells were alpha-SMA negative in ICs. Large spread stromal cells were positive for alpha-SMA (*asterisks*), whereas other most small stromal cells in ICs were alpha-SMA negative. **f** CD31 was expressed in endothelial cells and hematopoietic cells, not in most stromal cells (**g**) D2-40 expression in lymphatic endothelial cells. **h** Expression of EphA2 in the soma of Auerbach's plexus (*black arrow heads*). Original magnification ×40

but that EphA2 expression alone is insufficient to distinguish patients at high risk of tumor recurrence. In contrast, IC/A2+ was significantly predictive of relapse. Of 26 patients classified as IC/A2+, 14 (53.8 %) developed recurrence, including eight with peritoneal metastasis, three with LN metastasis, and three with blood-borne metastasis, with a median RFS of 378 days, significantly shorter than in patients classified as IC/A2−Ca/A2− (1,298 days) or IC/A2−Ca/A2+ (1,120 days). Invisible/micro-metastases may have been present in IC/A2+ patients at the time of gastrectomy. These patients require another treatment strategy, since many relapsed while receiving adjuvant chemotherapy. Even for a high-risk patient, second or third line chemotherapy was effective in

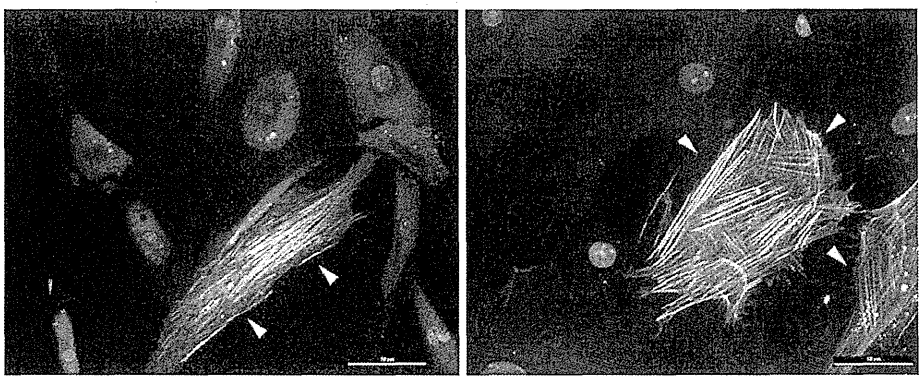

Fig. 4 Immunofluorescent microscopy of primary cultured GCSC. Expression of EphA2 (*red*) and α-SMA (*green*) was analyzed in primary cultured GCSC by immunofluorescent microscopy. In left panel, GCSC looks EphrinA2-positive (*red*) and one cell strongly expressed α-SMA (*white arrow head*). In *right panel*, all cells were EphA2 negative and widespread cells were α-SMA-positive (*white arrow head*). Primary cultured GCSC expressed different levels of α-SMA. These data suggested that the status of GCSC in IC/A2+ might be different from that in cultured and activated myofibroblasts. Original magnification ×40 (color figure online)

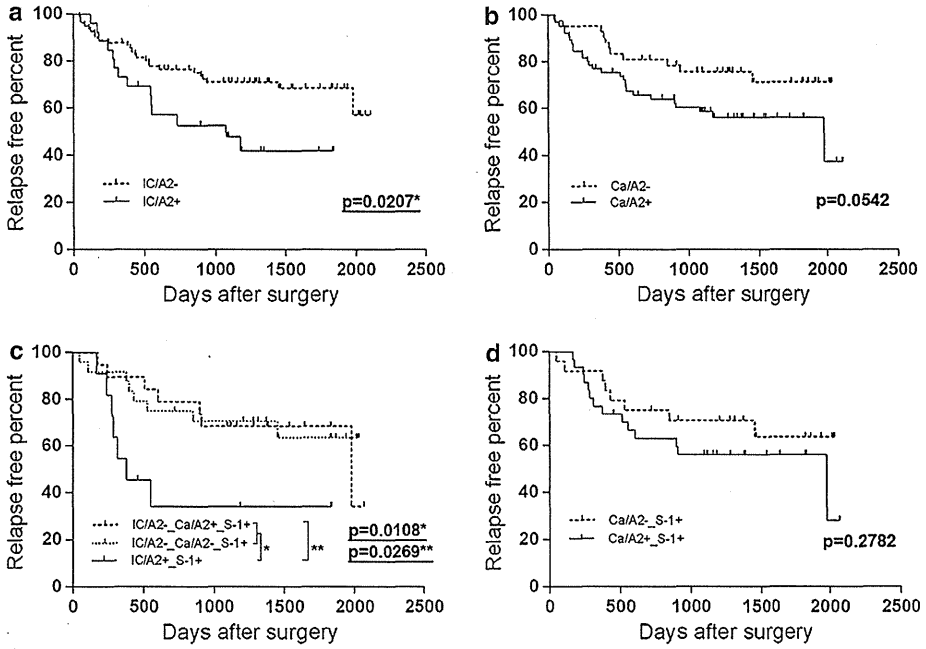

Fig. 5 Relapse free survival of all patients ($n = 107$) and of patients who received adjuvant chemotherapy (S-1, $n = 54$). Kaplan–Meier curves showing the relationship between RFS and expression of EphA2 in IC parts (**a**), in cancer cells (**b**) in all patients, and in patients who received adjuvant chemotherapy (**c**, IC/A2+ vs. IC/A2− Ca/A2± vs. IC/A2−Ca/A2−; **d**, Ca/A2). **a** The relapse rate was significantly higher in IC/A2+ than in IC/A2− patients (HR, 2.12; 95 % CI, 1.16–5.41; $p = 0.0207$). **b** The recurrence rate was higher in patients classified as Ca/A2+ than in those classified as Ca/A2− [HR, 1.96; 95 % confidence interval (CI), 0.99–3.51; $p = 0.0542$], not significant. **c** IC/A2+ was significantly associated with poorer RFS during adjuvant chemotherapy (HR, 3.00; 95 % CI, 1.47–17.03; $p = 0.0108$). Stromal reaction may have been prognostic, because patients classified as IC/A2+ had significantly reduced median RFS compared to those classified as IC/A2− (378 vs. 1,120 days; HR, 2.99; 95 % CI, 1.22–13.63; $p = 0.0269$). **c**, and **d** Fifty-four patients received six to eight cycles of adjuvant chemotherapy with S-1 (tegafur–gimeracil–oteracil potassium) without severe adverse effects. **b** Fourteen of 30 patients (46.7 %) classified as Ca/A2+ experienced recurrence during treatment, compared with seven of 11 (63.6 %) IC/A2+ patients. Almost half of the patients classified as IC/A2+ relapsed within 1 year after R0 operation, even while receiving adjuvant chemotherapy

IC/A2+ patients. Overall survival wasn't significantly different between IC/A2 and Ca/A2 without regard for adjuvant chemotherapy. When cancer was relapsed, most patients received additional chemotherapy, and our data proved effectiveness of additional chemotherapy in relapse cases. IC/A2+ in gastric cancer exactly indicated a risk of

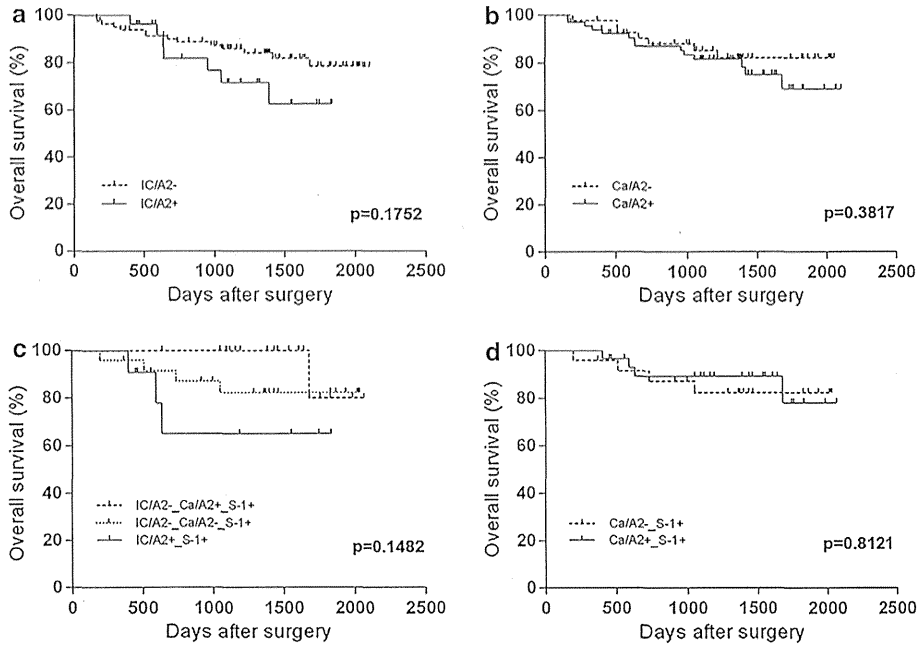

Fig. 6 Overall survival of all patients ($n = 107$) and of patients who received adjuvant chemotherapy (S-1, $n = 54$). Kaplan–Meier curves showing the relationship between overall survival (OS) and expression of EphA2 in IC parts (**a**), in cancer cells (**b**) in all patients, and in patients who received adjuvant chemotherapy (**c**, IC/A2+ vs. IC/A2− Ca/A2± vs. IC/A2−Ca/A2−; **d**, Ca/A2). **a**, and **b** Overall survival wasn't significant in IC/A2+ and IC/A2− patients ($p = 0.1752$), and in Ca/A2+ and Ca/A2− patients ($p = 0.3817$). **c** Median overall survival in IC/A2+ (633 days) was shorter than in IC/A2− (1,398 days), and not significant. **d** Ca/A2 wasn't a prognostic factor in patients who received adjuvant chemotherapy ($p = 0.8121$). When cancer was relapsed, most patients received additional chemotherapy, and these data had also proved effectiveness of second or third line chemotherapy in relapse cases. IC/A2+ in gastric cancer exactly indicated a risk of relapse, not the biological malignancy of cancer

relapse, not the biological aggressiveness of cancer. In patients who received adjuvant chemotherapy, median RFS and median OS in IC/A2+ was 378 and 633 days. However, median RFS and median OS in IC/A2− was 1,280 and 1,398 days, respectively. Our data indicated that careful follow-up and earlier diagnosis of relapse might improve survival of high-risk patients.

The EphA2–ephrin signaling axis regulates multiple events critical for the malignant transformation of normal cells. The key downstream molecules in this signaling pathway include the phosphatidylinositol 3′ kinases, Src family kinases, Rho and Rac1 GTPases, mitogen activated protein kinases and integrins. Moreover, there is cross talk between these molecules and other oncogene receptors (e.g., EGFR), which regulate cell adhesion, proliferation, and migration; modulate the cytoskeletal architecture, and control the development of vascular networks. The ephrin RTKs and their ephrin ligands have intriguing expression patterns in cancer and stromal cells, suggesting the importance of their bidirectional signals in many aspects of tumor development and progression. Targeting EphA2 overexpression may be beneficial in cancer therapeutics. Among the molecules targeting Eph receptors and ephrin currently in development are RTKs in the forward signaling pathway [26, 27], siRNA/oligonucleotides as inhibitors of Eph expression [28, 29], peptides/mAb that inhibit Eph–ephrin interactions [30, 31], cytotoxic mAbs and mAb conjugates [32, 33], and nanoparticles/mAb as imaging agents [34–36]. Most of these molecules were found to target cancer cells but not stromal cells, and their effects on tumor progression involving cancer stromal cell interactions were unclear. These interactions through the Eph–ephrin axis may be flexible and adaptable for survival in various microenvironments. EphA2 targeting should regulate deleterious cancer stromal cell interactions and be cytotoxic to cancer cells.

In conclusion, IC/EphA2 expression in invasive parts of tumors was useful in determining a high risk of relapse after curative (R0) surgery for gastric cancer. Further examination of the EphA2–ephrin signaling pathway in cancer stromal cells is essential in the development of agents that target Eph and ephrin.

Acknowledgments The authors thank Prof. Kenji Nakanishi, who provided continuing support and constant encouragement throughout this project. We also thank Yuko Yasui of the Department of Surgery, and Nobuyuki Adachi and Ryota Shinozaki of the HCM Joint-Use Research facilities for technical contributions. This work was supported in part by a Grant-in-Aid for Scientific Research

(C) 25460466, Grant-in-Aid for Researchers, Hyogo College of Medicine, 2012, to Shojiro Kikuchi; a Ministry of Education, Culture, Sports, Science and Technology of Japan—Supported Program for the Strategic Research Foundation at Private Universities, 2012–2015 and a Grant-in-Aid for Scientific Research (C) 23591949 to Mitsuru Sasako; and a grant from the Third-Term Comprehensive Control Research for Cancer conducted by the Ministry of Health, Labour and Welfare of Japan, and Charitable Trust Laboratory Medicine Foundation of Japan to Mitsuru Sasako.

Conflict of interest None of the authors had any financial interests or potential conflicts of interest.

References

1. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36–46.
2. 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(3):215–21.
3. Dodelet VC, Pasquale EB. Eph receptors and ephrin ligands: embryogenesis to tumorigenesis. Oncogene. 2000;19(49):5614–9.
4. Ireton RC, Chen J. EphA2 receptor tyrosine kinase as a promising target for cancer therapeutics. Curr Cancer Drug Targets. 2005;5(3):149–57.
5. Nakamoto M, Bergemann AD. Diverse roles for the Eph family of receptor tyrosine kinases in carcinogenesis. Microsc Res Tech. 2002;59(1):58–67.
6. Miyazaki T, Kato H, Fukuchi M, Nakajima M, Kuwano H. EphA2 overexpression correlates with poor prognosis in esophageal squamous cell carcinoma. Int J Cancer. 2003;103(5):657–63.
7. Fang WB, Brantley-Sieders DM, Parker MA, Reith AD, Chen J. A kinase-dependent role for EphA2 receptor in promoting tumor growth and metastasis. Oncogene. 2005;24(53):7859–68.
8. Kullander K, Klein R. Mechanisms and functions of Eph and ephrin signalling. Nat Rev Mol Cell Biol. 2002;3(7):475–86.
9. Bhowmick NA, Chytil A, Plieth D, Gorska AE, Dumont N, Shappell S, et al. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. Science. 2004;303(5659):848–51.
10. Bhowmick NA, Neilson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. Nature. 2004;432(7015):332–7.
11. Ding L, Saunders TL, Enikolopov G, Morrison SJ. Endothelial and perivascular cells maintain haematopoietic stem cells. Nature. 2012;481(7382):457–62.
12. Ding ZY, Zou XL, Wei YQ. Cancer microenvironment and cancer vaccine. Cancer Microenviron. 2012;5(3):333–44.
13. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer. 2004;4(1):71–8.
14. Zander CS, Soussi T. Breast-cancer stromal cells with TP53 mutations. N Engl J Med. 2008;358(15):1635 (author reply 6).
15. Patocs A, Zhang L, Xu Y, Weber F, Caldes T, Mutter GL, et al. Breast-cancer stromal cells with TP53 mutations and nodal metastases. N Engl J Med. 2007;357(25):2543–51.
16. Japanese classification of gastric carcinoma. 3rd English edition. Gastric Cancer. 2011;14(2):101–12.
17. Kinch MS, Moore MB, Harpole DH Jr. Predictive value of the EphA2 receptor tyrosine kinase in lung cancer recurrence and survival. Clin Cancer Res. 2003;9(2):613–8.
18. Zelinski DP, Zantek ND, Stewart JC, Irizarry AR, Kinch MS. EphA2 overexpression causes tumorigenesis of mammary epithelial cells. Cancer Res. 2001;61(5):2301–6.
19. Zeng G, Hu Z, Kinch MS, Pan CX, Flockhart DA, Kao C, et al. High-level expression of EphA2 receptor tyrosine kinase in prostatic intraepithelial neoplasia. Am J Pathol. 2003;163(6):2271–6.
20. Abraham S, Knapp DW, Cheng L, Snyder PW, Mittal SK, Bangari DS, et al. Expression of EphA2 and Ephrin A-1 in carcinoma of the urinary bladder. Clin Cancer Res. 2006;12(2):353–60.
21. Thaker PH, Deavers M, Celestino J, Thornton A, Fletcher MS, Landen CN, et al. EphA2 expression is associated with aggressive features in ovarian carcinoma. Clin Cancer Res. 2004;10(15):5145–50.
22. Xu F, Zhong W, Li J, Shanshen Z, Cui J, Nesland JM, et al. Predictive value of EphA2 and EphrinA-1 expression in oesophageal squamous cell carcinoma. Anticancer Res. 2005;25(4):2943–50.
23. Mudali SV, Fu B, Lakkur SS, Luo M, Embuscado EE, Iacobuzio-Donahue CA. Patterns of EphA2 protein expression in primary and metastatic pancreatic carcinoma and correlation with genetic status. Clin Exp Metastasis. 2006;23(7–8):357–65.
24. Kataoka H, Igarashi H, Kanamori M, Ihara M, Wang JD, Wang YJ, et al. Correlation of EPHA2 overexpression with high microvessel count in human primary colorectal cancer. Cancer Sci. 2004;95(2):136–41.
25. Miyazaki K, Inokuchi M, Takagi Y, Kato K, Kojima K, Sugihara K. EphA4 is a prognostic factor in gastric cancer. BMC Clin Pathol. 2013;13(1):19.
26. Choi Y, Syeda F, Walker JR, Finerty PJ Jr, Cuerrier D, Wojciechowski A, et al. Discovery and structural analysis of Eph receptor tyrosine kinase inhibitors. Bioorg Med Chem Lett. 2009;19(15):4467–70.
27. Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, et al. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol. 2008;26(1):127–32.
28. Carles-Kinch K, Kilpatrick KE, Stewart JC, Kinch MS. Antibody targeting of the EphA2 tyrosine kinase inhibits malignant cell behavior. Cancer Res. 2002;62(10):2840–7.
29. Duxbury MS, Ito H, Zinner MJ, Ashley SW, Whang EE. EphA2: a determinant of malignant cellular behavior and a potential therapeutic target in pancreatic adenocarcinoma. Oncogene. 2004;23(7):1448–56.
30. Coffman KT, Hu M, Carles-Kinch K, Tice D, Donacki N, Munyon K, et al. Differential EphA2 epitope display on normal versus malignant cells. Cancer Res. 2003;63(22):7907–12.
31. Landen CN Jr, Lu C, Han LY, Coffman KT, Bruckheimer E, Halder J, et al. Efficacy and antivascular effects of EphA2 reduction with an agonistic antibody in ovarian cancer. J Natl Cancer Inst. 2006;98(21):1558–70.
32. Jackson D, Gooya J, Mao S, Kinneer K, Xu L, Camara M, et al. A human antibody–drug conjugate targeting EphA2 inhibits tumor growth in vivo. Cancer Res. 2008;68(22):9367–74.
33. Lee JW, Han HD, Shahzad MM, Kim SW, Mangala LS, Nick AM, et al. EphA2 immunoconjugate as molecularly targeted chemotherapy for ovarian carcinoma. J Natl Cancer Inst. 2009;101(17):1193–205.
34. Cai W, Ebrahimnejad A, Chen K, Cao Q, Li ZB, Tice DA, et al. Quantitative radioimmunoPET imaging of EphA2 in tumor-bearing mice. Eur J Nucl Med Mol Imaging. 2007;34(12):2024–36.
35. Scarberry KE, Dickerson EB, McDonald JF, Zhang ZJ. Magnetic nanoparticle-peptide conjugates for in vitro and in vivo targeting and extraction of cancer cells. J Am Chem Soc. 2008;130(31):10258–62.
36. Scarberry KE, Dickerson EB, Zhang ZJ, Benigno BB, McDonald JF. Selective removal of ovarian cancer cells from human ascites fluid using magnetic nanoparticles. Nanomedicine. 2010;6(3):399–408.

Gastric Cancer (2014) 17:542–547
DOI 10.1007/s10120-013-0293-3

ORIGINAL ARTICLE

Early phase II study of robot-assisted distal gastrectomy with nodal dissection for clinical stage IA gastric cancer

Masanori Tokunaga · Norihiko Sugisawa · Junya Kondo · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Masanori Terashima

Received: 13 March 2013 / Accepted: 4 August 2013 / Published online: 5 September 2013

Abstract
Background Robot-assisted distal gastrectomy (RADG) is increasingly performed in Japan and Korea and is thought to have many advantages over laparoscopic gastrectomy. However, a prospective study investigating the safety of RADG has never been reported. The present study evaluated the safety of RADG with nodal dissection for clinical stage IA gastric cancer.
Methods This single-center, prospective phase II study included patients with clinical stage IA gastric cancer located within the lower two-thirds of the stomach. The primary endpoint was the incidence of postoperative intraabdominal infectious complications including anastomotic leakage, pancreas-related infection, and intraabdominal abscess. The secondary endpoints included all in-hospital adverse events, RADG completion rate, and survival outcome.
Results From May 2012 to November 2012, 18 eligible patients were enrolled for this study. The incidence of intraabdominal infectious complication was 0 % (90 % CI, 0–12.0 %). The overall incidence of in-hospital adverse events was 22.2 % (90 % CI, 8.0–43.9 %). No patient required conversion to laparoscopic or open gastrectomy; thus, the RADG completion rate was 100 %.
Conclusions This early phase II study suggested that RADG might be a safe and feasible procedure for stage IA gastric cancer, providing experienced surgeons perform the surgery. This conclusion should be clarified in subsequent late phase II studies with a larger sample size.

Keywords da Vinci · Gastric cancer · Gastrectomy · Clinical trial · Safety

Introduction

Laparoscopy-assisted distal gastrectomy (LADG) is performed increasingly often, particularly in East Asian countries where the incidence of early gastric cancer is higher than in Western countries. The safety of LADG was clarified by prospective studies [1, 2], and survival outcome of LADG compared with open gastrectomy was under investigation in two large, nationwide, randomized controlled trials in Japan and Korea [1, 3]. However, current laparoscopic procedures have several drawbacks, including a limitation in range of forceps movement and the two-dimensional surgical view available to the operating surgeons.

Robot-assisted distal gastrectomy (RADG) may enable us to overcome these drawbacks. Using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), surgeons were able to attain a three-dimensional surgical view, instrument flexibility, tremor suppression, and improved ergonomics, although RADG still has disadvantages such as high cost and lack of tactile sensation [4–8]. In addition, a shorter learning curve has been reported for robotic surgery compared to laparoscopic surgery [9–11].

Reported studies rate RADG as a feasible procedure, although most such studies involved a retrospective or prospective study cohort [4, 5, 8–10, 12–22]. So far, no prospective clinical trials have focused on the feasibility of RADG, a step that is necessary before RADG could be

M. Tokunaga · N. Sugisawa · J. Kondo · Y. Tanizawa · E. Bando · T. Kawamura · M. Terashima (✉)
Division of Gastric Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: m.terashima@scchr.jp

explored further with greater number of patients. To this end, the current prospective study evaluated the safety of RADG with nodal dissection for clinical stage IA gastric cancer.

Methods

The present study was designed as a single-center, prospective phase II trial. The institutional review board of Shizuoka Cancer Center approved the study protocol, which had the following inclusion criteria: histologically confirmed adenocarcinoma of the stomach, clinical stage IA early gastric cancer according to the International Union Against Cancer classification system (UICC) [23], no indication for endoscopic submucosal dissection (ESD), a tumor located in the lower two-thirds of the stomach, no involvement of the duodenum, patient age of 20–80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, a body mass index (BMI) less than 30 kg/m^2, no prior upper abdominal surgery or intestinal resection other than appendectomy, no prior chemotherapy or radiotherapy for any malignancy, adequate organ function, and written informed consent. The study was registered with clinical trials.gov (clinical trials.gov identifier: NCT 1504997).

In this study period, medical cost for hospital admission, including surgical fee, was funded by the Shizuoka Cancer Center because the national insurance system in Japan did not reimburse patients for RADG.

Surgical procedure

All RADG operations were performed using the da Vinci Surgical System with four robotic arms; a central arm for a dual-channel endoscope, and the other three for a Cadiere forceps, fenestrated bipolar forceps, and bipolar Maryland forceps or monopolar electrocautery, respectively. One assistant port was placed in the right umbilical level. The surgical procedures were similar to that used in LADG, with a standardized surgical field to achieve omentum preservation, D1+ lymph node dissection according to the Japanese gastric cancer treatment guidelines [24–27], and vagal nerve preservation [28, 29]. Removal of resected specimens and reconstruction were performed by a 4- to 5-cm upper midline incision. In the case of distal gastrectomy, a Billroth I reconstruction with circular stapler was selected in general. In the case of pylorus-preserving gastrectomy, reconstruction was performed by hand-sewn sutures.

In this study, the operations were separated into three parts. The docking time was defined as the time from skin incision to completion of docking. The console time was the time that the da Vinci system was used by the surgeon at the console. The anastomosis time was the time spent from the creation of the mini-laparotomy to the completion of the surgery.

Training for RADG

A team of two gastric surgeons who were board certified by the Japanese Society of Endoscopic Surgery (JSES) as experts in laparoscopic surgery performed RADG in all cases. To be board certified by the JSES as an expert laparoscopic surgeon, an applicant is required to perform more than 20 laparoscopic gastrectomies or alternative advanced laparoscopic surgeries within 3 years and to submit a non-edited video of one of the surgeries for a review by at least two board-qualified referees. The strict review process, which takes place once a year, allows only one-third of the applicants to be certified. Before introducing RADG at Shizuoka Cancer Center, the two surgeons completed a fixed training program for RADG as recommended by the JSES. The program consisted of e-learning, training sessions at an animal laboratory, and site visits to a specified high-volume center to observe actual RADG. In addition, surgeons with sufficient experience in RADG were invited as instructors in the initial two cases of RADG at our institution.

Endpoints

The primary endpoint in this study was the incidence of postoperative intraabdominal infectious complications, which included anastomotic leakage, pancreas-related infection, and intraabdominal abscess. Patients who developed Clavien–Dindo classification grade II or more complications by discharge were regarded as having complications [30, 31]. The secondary endpoints were overall survival (OS), relapse-free survival (RFS), RADG completion rate, and the incidence of all surgical morbidities.

Anastomotic leakage was diagnosed by radiologic examination using orally administered contrast media. Pancreas-related infection was defined as amylase-rich purulent discharge. Intraabdominal abscess was defined as an abscess not associated with anastomotic leakage or pancreas-related infection. The completion of RADG was defined as the proportion of patients without conversion from RADG to LADG or open distal gastrectomy (ODG).

Study design and statistical methods

In this phase II trial, the sample size was 18 cases, providing 70 % power under the hypothesis of a primary endpoint with an expected value of 4 % and a threshold

value of 15 %, using one-sided testing at a 10 % significance level. The expected value was decided according to the postoperative outcome of 265 patients who had undergone an ODG or LADG for early gastric cancer in the lower two-thirds of the stomach at the Shizuoka Cancer Center; the incidence of intraabdominal infectious complication among these patients was 4.5 % [32]. All statistical analyses were conducted using R Statistics version 2.13.1.

Results

A total of 18 patients were recruited in this phase II study from May 2012 to November 2012. Table 1 summarizes the patient characteristics. The male-to-female ratio was 1.57, median body mass index was 21.1 kg/m^2, and all patients had stage IA gastric cancer located within the lower two-thirds of the stomach. Undifferentiated histology was more frequently observed than differentiated histology.

Table 2 shows details of the surgical procedure. The median duration of the surgery was 311.5 min; median docking, console, and anastomosis times were 22, 212.5, and 63 min, respectively. Distal gastrectomy and pylorus-preserving gastrectomy were performed in nine patients each, and all patients underwent D1 + lymph node dissection. No patient required conversion to laparoscopic or open surgery; thus, the RADG completion rate was 100 %. Median blood loss was 32.5 ml; blood transfusion was not required in any of the patients.

Postoperative clinical course is shown in Table 3. The median duration of postoperative hospital stay was 8 days. Incidence of intraabdominal infectious complication was 0 % [0/18; 90 % confidence interval (CI), 0–12.0 %]. The overall proportion of in-hospital adverse events was 22.2 % (90 % CI, 8.0–43.9 %), with all rated as grade II, from which all patients recovered well with medical treatment only and no surgical interventions.

Table 1 Patient characteristics

Number of patients	18
Sex (cases)	
Male	11
Female	7
Age (years)	
Median	65.5
Range	53–80
Body mass index (kg/m^2)	
Median	21.1
Range	16.2–25.8
Tumor location (cases)	
Upper third	0
Middle third	11
Lower third	7
Histological type (cases)	
Differentiated	6
Undifferentiated	12
Tumor size (cm)	
Median	
Range	
Clinical stage (cases)	
IA	18
IB	0

Table 2 Details of surgical procedures

Operation time (min)	
Median	311.5
Range	225–375
Docking time (min)	
Median	22
Range	11–41
Console time (min)	
Median	212.5
Range	161–291
Anastomosis time (min)	
Median	63
Range	41–111
Blood loss (ml)	
Median	32.5
Range	0–160
Perioperative blood transfusion (cases)	
Yes	0
No	18
Type of gastrectomy (cases)	
PPG	9
DG	9
Reconstruction method	
Roux-en-Y	1
Billroth I	8
Gastro-gastrostomy	9
Extent of lymph node dissection (cases)	
D1+	18
D2	0
Number of retrieved lymph nodes (cases)	
Median	40
Range	26–89
Completion of RADG (cases)	
Yes	0
No	18

PPG pylorus-preserving gastrectomy

DG distal gastrectomy

Table 3 Postoperative clinical course

Postoperative hospital stay (days)	
Median	8
Range	7–10
Postoperative morbidities (cases)	
Intraabdominal infectious complications	0
Anastomotic leakage	0
Pancreas-related infection	0
Intraabdominal abscess	0
Other complications	
Wound infection	2
Delayed gastric emptying	1
Liver dysfunction	1

Discussion

The present study showed RADG is feasible in terms of safety if experienced laparoscopic surgeons perform the surgery, with a zero incidence of intraabdominal infectious complications recorded (90 % CI, 0–12.0 %).

Before May 2012, we had performed five RADGs as an institute, and based on this experience, we assessed RADG as technically feasible. In addition, none of these five patients developed any postoperative complications. We therefore decided to more thoroughly assess the safety of RADG in the present prospective study.

Previous retrospective studies demonstrated that RADG was a feasible treatment for gastric cancer [4, 5, 10, 12, 14, 18, 19]. Surgeons generally believed that much more meticulous surgery could be performed with the da Vinci Surgical System because of the three-dimensional surgical view provided and the flexibility of instrumentation. However, RADG required longer operation times [5, 14, 17–19, 21] and was more expensive than laparoscopic or open gastrectomy [14, 16, 21, 33]. In addition, the advantages of RADG compared to conventional procedures were not clear from these previous studies, and no prospective study investigating the safety of RADG was reported.

The incidence of postoperative intraabdominal infectious complication in the present study was 0 % (90 % CI, 0–12.2 %) with a 22.2 % overall proportion of in-hospital adverse events (90 % CI, 8.0–43.9 %) in this study. A similar complication rate (0–47.3 %) has been reported in previous retrospective studies, although none had focused on the incidence of intraabdominal infectious complication [4, 5, 8–10, 12, 17, 18, 22, 33]. With the three-dimensional magnified view available with RADG, surgeons were able to recognize anatomical structures much more precisely than with the standard two-dimensional view. In addition, the flexibility of instruments used helped surgeons perform meticulous surgery. We propose that these advantages of RADG resulted in the low complication rate.

Other possible reasons for the low complication rate recorded in this study were involving only experienced laparoscopic surgeons to perform the procedures and the relatively lower BMI of the patients compared with that reported in Western series. High BMI is a possible risk factor for postoperative complications after open and laparoscopic gastrectomy, although this association remains controversial [34–38]. The present study included only one overweight patient (BMI, 25.8). The feasibility of RADG in overweight or obese patients is still unclear and must be clarified in a future trial.

RADG procedures required longer surgical times than LADG. Indeed, there was a difference of 86.5 min in our institute between RADG and LADG [31]. We considered that the meticulousness of the procedure was inversely proportional to operation time to some degree. With the magnified and three-dimensional magnified view and instrument flexibility, surgeons were able to perform much more meticulous surgery at the expense of increased operation time.

There were other possible reasons for the longer operation times. First, RADG was performed during our learning curve period whereas LADG was not. Second, we did not use ultrasonic shears provided for RADG because such usage is not allowed in Japan with the da Vinci Surgical System. Thus, if we achieve our learning curve with RADG and the usage of ultrasonic devices is permitted in the future, we will be able to reduce the operation time.

We believe that the advantages of the da Vinci Surgical System would be enhanced when we use it for more complicated surgery such as gastrectomy with extended (D2) lymph node dissection or mediastinal lymph node dissection. During extended lymph node dissection, we were able to recognized layers precisely as well as small vessels because of the three-dimensional magnified view. In addition, the flexibility of instruments and tremor suppression enabled us to do each procedure meticulously, resulting in high-quality lymph node dissection. Similar advantages would be obtained when we perform lower mediastinal lymph node dissection for adenocarcinoma of esophagogastric junction in which the surgical field is narrow and linear instruments used in laparoscopic surgery frequently interfere. Thus, our next step is to indicate the da Vinci Surgical System for these complicated surgeries.

In the present study, early surgical outcomes of RADG were not compared with conventional open or laparoscopic surgery; thus, it is still unclear if RADG is superior to conventional surgeries in this regard. Although previous retrospective studies compared surgical outcomes of RADG with LADG or ODG, there is no prospective randomized trial comparing RADG and other procedures [5, 17, 18, 20, 22]. In addition, survival outcomes of RADG

remain unclear. Future trials are needed to clarify the superiority of RADG over other procedures, including both short- and long-term outcomes, before it can be accepted as a standard treatment for gastric cancer.

The present study had limitations including the relatively small sample size. The Japanese national insurance system does not reimburse patients for RADG; thus, either the patient or the hospital has to pay the entire admission fee in addition to the surgical fee (around USD $20,000). It was therefore challenging to recruit sufficient patient numbers even for a small phase II trial, and so long as this situation persists, the cost of such surgeries will be an issue and the forthcoming surgeries will be paid by the hospital or the patient in our hospital. We consider that the future practical use of RADG in Japan as an advanced medical technology will require a well-planned prospective trial involving sufficient patient numbers to provide important information about issues such as reimbursement. However, we also believe that accumulated evidence from smaller prospective studies such as ours will help future, larger-scale trials for RADG.

In conclusion, this early phase II study suggested that RADG might be a safe and feasible procedure for stage IA gastric cancer, providing experienced surgeons perform the surgery. This conclusion should be clarified in subsequent late phase II studies with a larger sample size.

References

1. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, et al. 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(3):417–20.
2. Katai H, Sasako M, Fukuda H, Nakamura K, Hiki N, Saka M, et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with supra-pancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). Gastric Cancer. 2010;13(4):238–44.
3. Nakamura K, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashima M, et al. A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer (JCOG0912). Jpn J Clin Oncol. 2013;43(3):324–7.
4. 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(6):927–32.
5. Song J, Kang WH, Oh SJ, Hyung WJ, Choi SH, Noh SH. Role of robotic gastrectomy using da Vinci system compared with laparoscopic gastrectomy: initial experience of 20 consecutive cases. Surg Endosc. 2009;23(6):1204–11.
6. Hashizume M, Sugimachi K. Robot-assisted gastric surgery. Surg Clin N Am. 2003;83(6):1429–44.
7. Kakeji Y, Konishi K, Ieiri S, Yasunaga T, Nakamoto M, Tanoue K, et al. Robotic laparoscopic distal gastrectomy: a comparison of the da Vinci and Zeus systems. Int J Med Robot. 2006;2(4):299–304.
8. Isogaki J, Haruta S, Man IM, Suda K, Kawamura Y, Yoshimura F, et al. Robot-assisted surgery for gastric cancer: experience at our institute. Pathobiol J Immunopathol Mol Cell Biol. 2011;78(6):328–33.
9. Park SS, Kim MC, Park MS, Hyung WJ Rapid adaptation of robotic gastrectomy for gastric cancer by experienced laparoscopic surgeons. Surg Endosc. 2012;26(1):60–7.
10. Lee HH, Hur H, Jung H, Jeon HM, Park CH, Song KY. Robot-assisted distal gastrectomy for gastric cancer: initial experience. Am J Surg. 2011;201(6):841–5.
11. Heemskerk J, van Gemert WG, de Vries J, Greve J, Bouvy ND. Learning curves of robot-assisted laparoscopic surgery compared with conventional laparoscopic surgery: an experimental study evaluating skill acquisition of robot-assisted laparoscopic tasks compared with conventional laparoscopic tasks in inexperienced users. Surg Laparosc Endosc Percutan Tech. 2007;17:171–4.
12. D'Annibale A, Pende V, Pernazza G, Monsellato I, Mazzocchi P, Lucandri G, et al. Full robotic gastrectomy with extended (D2) lymphadenectomy for gastric cancer: surgical technique and preliminary results. J Surg Res. 2011;166(2):e113–20.
13. Pugliese R, Maggioni D, Sansonna F, Costanzi A, Ferrari GC, Di Lernia S, et al. Subtotal gastrectomy with D2 dissection by minimally invasive surgery for distal adenocarcinoma of the stomach: results and 5-year survival. Surg Endosc. 2010;24(10):2594–602.
14. Patriti A, Ceccarelli G, Bellochi R, Bartoli A, Spaziani A, Di Zitti L, et al. Robot-assisted laparoscopic total and partial gastric resection with D2 lymph node dissection for adenocarcinoma. Surg Endosc. 2008;22(12):2753–60.
15. Pugliese R, Maggioni D, Sansonna F, Ferrari GC, Forgione A, Costanzi A, et al. Outcomes and survival after laparoscopic gastrectomy for adenocarcinoma. Analysis on 65 patients operated on by conventional or robot-assisted minimal access procedures. Eur J Surg Oncol. 2009;35(3):281–8.
16. Anderson C, Ellenhorn J, Hellan M, Pigazzi A. Pilot series of robot-assisted laparoscopic subtotal gastrectomy with extended lymphadenectomy for gastric cancer. Surg Endosc. 2007;21(9):1662–6.
17. Kim MC, Heo GU, Jung GJ. Robotic gastrectomy for gastric cancer: surgical techniques and clinical merits. Surg Endosc. 2010;24(3):610–5.
18. Woo Y, Hyung WJ, Pak KH, Inaba K, Obama K, Choi SH et al. Robotic gastrectomy as an oncologically sound alternative to laparoscopic resections for the treatment of early-stage gastric cancers. Arch Surg. 2011;146(9):1086–92.
19. Caruso S, Patriti A, Marrelli D, Ceccarelli G, Ceribelli C, Roviello F, et al. Open vs. robot-assisted laparoscopic gastric resection with D2 lymph node dissection for adenocarcinoma: a case-control study. Int J Med Robot. 2011;7(4):452–8.
20. Yoon HM, Kim YW, Lee JH, Ryu KW, Eom BW, Park JY, et al. Robot-assisted total gastrectomy is comparable with laparoscopically assisted total gastrectomy for early gastric cancer. Surg Endosc. 2012;26(5):1377–81.
21. Park JY, Jo MJ, Nam BH, Kim Y, Eom BW, Yoon HM, et al. Surgical stress after robot-assisted distal gastrectomy and its economic implications. Br J Surg. 2012;99(11):1554–61.
22. Hyun MH, Lee CH, Kwon YJ, Cho SI, Jang YJ, Kim DH et al. Robot versus laparoscopic gastrectomy for cancer by an experienced surgeon: comparisons of surgery, complications, and surgical stress. Ann Surg Oncol. 2013;20(4):1258–65.
23. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley-Blackwell; 2009.
24. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113–23.

25. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer. 2011;14(2):97–100.
26. Hiki N, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Ohyama S, et al. The benefits of standardizing the operative procedure for the assistant in laparoscopy-assisted gastrectomy for gastric cancer. Langenbecks Arch Surg. 2008;393(6):963–71.
27. Fukunaga T, Hiki N, Tokunaga M, Nohara K, Akashi Y, Katayama H, et al. Left-sided approach for supra-pancreatic lymph node dissection in laparoscopy-assisted distal gastrectomy without duodenal transection. Gastric Cancer. 2009;12(2):106–12.
28. Nunobe S, Hiki N, Fukunaga T, Tokunaga M, Ohyama S, Seto Y, et al. Laparoscopy-assisted pylorus-preserving gastrectomy: preservation of vagus nerve and infrapyloric blood flow induces less stasis. World J Surg. 2007;31(12):2335–40.
29. Tokunaga M, Hiki N, Fukunaga T, Ohyama S, Nunobe S, Yamada K, et al. Is preservation of the celiac branch of the vagal nerve effective in preventing stasis following pylorus-preserving gastrectomy? Hepatogastroenterology. 2011;58(107-108):1046–50.
30. 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(2):205–13.
31. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
32. Tokunaga M, Kondo J, Tanizawa Y, Bando E, Kawamura T, Terashima M. Postoperative intra-abdominal complications assessed by the Clavien-Dindo classification following open and laparoscopy-assisted distal gastrectomy for early gastric cancer. J Gastrointest Surg. 2012.
33. Clark J, Sodergren MH, Purkayastha S, Mayer EK, James D, Athanasiou T, et al. The role of robotic assisted laparoscopy for esophagogastric oncological resection; an appraisal of the literature. Dis Esophagus. 2011;24(4):240–50.
34. Tokunaga M, Hiki N, Fukunaga T, Ogura T, Miyata S, Yamaguchi T. Effect of individual fat areas on early surgical outcomes after open gastrectomy for gastric cancer. Br J Surg. 2009;96(5):496–500.
35. Noshiro H, Shimizu S, Nagai E, Ohuchida K, Tanaka M. Laparoscopy-assisted distal gastrectomy for early gastric cancer: is it beneficial for patients of heavier weight? Ann Surg. 2003;238(5):680–5.
36. Yamada H, Kojima K, Inokuchi M, Kawano T, Sugihara K. Effect of obesity on technical feasibility and postoperative outcomes of laparoscopy-assisted distal gastrectomy: comparison with open distal gastrectomy. J Gastrointest Surg. 2008;12(6):997–1004.
37. Makino H, Kunisaki C, Izumisawa Y, Tokuhisa M, Oshima T, Nagano Y, et al. Effect of obesity on laparoscopy-assisted distal gastrectomy compared with open distal gastrectomy for gastric cancer. J Surg Oncol. 2010;102(2):141–7.
38. Hiki N, Fukunaga T, Yamaguchi T, Ogura T, Miyata S, Tokunaga M, et al. Increased fat content and body shape have little effect on the accuracy of lymph node retrieval and blood loss in laparoscopic distal gastrectomy for gastric cancer. J Gastrointest Surg. 2009;13(4):626–33.

Sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy as adjuvant chemotherapy for T4a/b gastric cancer (SAMIT): a phase 3 factorial randomised controlled trial

Akira Tsuburaya, Kazuhiro Yoshida, Michiya Kobayashi, Shigefumi Yoshino, Masazumi Takahashi, Nobuhiro Takiguchi, Kazuaki Tanabe, Naoto Takahashi, Hiroshi Imamura, Naokuni Tatsumoto, Akinori Hara, Kazuhiro Nishikawa, Ryoji Fukushima, Isao Nozaki, Hiroshi Kojima, Yumi Miyashita, Koji Oba, Marc Buyse, Satoshi Morita, Junichi Sakamoto

Lancet Oncol 2014; 15: 886–93
Published Online
June 19, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70025-7

See Comment page 788

Yokohama City University, Yokohama, Japan (A Tsuburaya MD); Gifu University Graduate School of Medicine, Gifu, Japan (K Yoshida MD); Department of Human Health and Medical Sciences, Kochi Medical School, Nankoku, Japan (M Kobayashi MD); Yamaguchi University Graduate School of Medicine, Ube, Japan (S Yoshino MD); Yokohama Municipal Citizen's Hospital, Yokohama, Japan (M Takahashi MD); Chiba Cancer Centre, Chiba, Japan (N Takiguchi MD); Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan (K Tanabe MD); Jikei University Hospital, Tokyo, Japan (N Takahashi MD); Sakai Municipal Hospital, Sakai, Japan (H Imamura MD); Miyoshi Central Hospital, Miyoshi, Japan (N Tatsumoto MD); Saiseikai Suita Hospital, Suita, Japan (A Hara MD); Osaka General Medical Centre, Osaka, Japan (K Nishikawa MD); Teikyo University School of Medicine, Tokyo, Japan (R Fukushima MD); National Hospital Organization Shikoku Cancer Centre, Matsuyama, Japan (I Nozaki MD); Aichi Cancer Centre Aichi Hospital, Okazaki, Japan (H Kojima MD); NPO Epidemiological and Clinical Research Information Network, Okazaki, Japan (Y Miyashita RN); Translational Research and Clinical Trial Centre, Hokkaido University Hospital, Sapporo, Japan (K Oba PhD); International Drug

Summary

Background The prognosis for locally advanced gastric cancer is poor despite advances in adjuvant chemotherapy. We did the Stomach cancer Adjuvant Multi-Institutional group Trial (SAMIT) to assess the superiority of sequential treatment (paclitaxel then tegafur and uracil [UFT] or paclitaxel then S-1) compared with monotherapy (UFT or S-1) and also the non-inferiority of UFT compared with S-1.

Methods We did this randomised phase 3 trial with a two-by-two factorial design at 230 hospitals in Japan. We enrolled patients aged 20–80 years with T4a or T4b gastric cancer, who had had D2 dissection and a ECOG performance score of 0–1. Patients were randomly assigned to one of four treatment groups with minimisation for tumour size, lymph node metastasis, and study site. Patients received UFT only (267 mg/m² per day), S-1 only (80 mg/m² per day) for 14 days, with a 7-day rest period or three courses of intermittent weekly paclitaxel (80 mg/m²) followed by either UFT, or S-1. Treatment lasted 48 weeks in monotherapy groups and 49 weeks in the sequential treatment groups. The primary endpoint was disease-free survival assessed by intention to treat. We assessed whether UFT was non-inferior to S-1 with a non-inferiority margin of 1·33. This trial was registered at UMIN Clinical Trials Registry, number C000000082.

Findings We randomly assigned 1495 patients between Aug 3, 2004, and Sept 29, 2009. 374 patients were assigned to receive UFT alone, 374 to receive S-1 alone, 374 to received paclitaxel then UFT, and 373 to receive paclitaxel then S-1. We included 1433 patients in the primary analysis after at least 3 years of follow-up (359, 364, 355, and 355 in each group respectively). Protocol treatment was completed by 215 (60%) patients in the UFT group, 224 (62%) in the S-1 group, 242 (68%) in the paclitaxel then UFT group, and 250 (70%) in the paclitaxel then S-1 group. 3-year disease-free survival for monotherapy was 54·0% (95% CI 50·2–57·6) and that of sequential treatment was 57·2% (53·4–60·8; hazard ratio [HR] 0·92, 95% CI 0·80–1·07, p=0·273). 3-year disease-free survival for the UFT group was 53·0% (95% CI 49·2–56·6) and that of the S-1 group was 58·2% (54·4–61·8; HR 0·81, 95% CI 0·70–0·93, p=0·0048; $p_{non\text{-}inferiority}$=0·151). The most common grade 3–4 haematological adverse event was neutropenia (41 [11%] of 359 patients in the UFT group, 48 [13%] of 363 in the S-1 group, 46 [13%] of 355 in the paclitaxel then UFT group, and 83 [23%] of 356 in the paclitaxel then S-1 group). The most common grade 3–4 non-haematological adverse event was anorexia (21 [6%], 24 [7%], seven [2%], and 18 [5%], respectively).

Interpretation Sequential treatment did not improve disease-free survival, and UFT was not non-inferior to S-1 (and S-1 was superior to UFT), therefore S-1 monotherapy should remain the standard treatment for locally advanced gastric cancer in Japan.

Funding Epidemiological and Clinical Research Information Network.

Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer mortality.[1] The prognosis of locally advanced tumours remains poor despite advances in adjuvant chemotherapy.[2–4] More effective adjuvant chemotherapy treatments are needed for curatively resected but locally advanced gastric cancer.

Oral fluoropyrimidines and taxanes are often used to treat both gastric and breast cancer,[5–7] and taxanes are important drugs for breast and ovarian cancer given singly or in combination.[8,9] Docetaxel provided modest but better survival than did paclitaxel every 3 weeks in a trial of advanced breast cancer; but its toxic effects were worse,[10] and it has not been compared with dose-dense paclitaxel once per week, which is superior to paclitaxel every 3 weeks for ovarian cancer.[9,11] Sequential treatment with single taxanes is often preferred owing to fewer toxic effects and quality of life seems to be better.[12,13]

Peritoneal metastasis are the most common site of relapse in patients with gastric cancer,[3] for whom serosal

exposure is a major risk.[14,15] Paclitaxel is effective for treatment of malignant ascites from gastric cancer,[16] and in studies[17,18] of paclitaxel for the second-line chemotherapy, it was especially effective for peritoneal metastasis. Fluoropyrimidine monotherapy has been used for adjuvant chemotherapy in Asia, and a combination of tegafur and uracil (UFT) was for a time the Japanese community standard treatment for gastric cancer because of its efficacy, good compliance, and safety.[5] In 2007, the NSAS-GC study[19] showed that UFT plus surgery was more effective than surgery alone for Japanese patients who had had a D2 dissection for T2 and lymph node positive gastric cancer. UFT has since been replaced by S-1 in Japan because of the results of ACTS-GC,[3] which was a large randomised controlled trial for stage II and III tumours, although no direct comparison of these two drugs has been done. Combination of paclitaxel and oral fluoropyrimidine is a candidate treatment for curatively resected gastric cancer at high risk of peritoneal recurrence (ie, serosa-positive tumours).[14] However, no comparison has been done of concurrent and sequential regimens. Because of the poor nutrition of patients after gastrectomy[20] and the interaction between paclitaxel and fluorouracil,[21] we tested the effect of sequential paclitaxel followed by S-1 for locally advanced gastric cancer in the single group trial,[22] with favourable results.

We did the Stomach cancer Adjuvant Multi-institutional group (SAMIT) trial for T4a or T4b[23] gastric cancer to assess (1) the effect on survival of paclitaxel followed by oral fluoropyrimidine (sequential treatment) compared with fluoropyrimidine alone (monotherapy), and (2) the non-inferiority of UFT compared with S-1.[24]

Methods

Study design and participants

We did this phase 3, randomised controlled study at 230 hospitals in Japan. We used a two-by-two factorial design, with four treatment groups: UFT alone, S-1 alone, paclitaxel followed by UFT, and paclitaxel followed by S-1. This design enabled us to evaluate the superiority of sequential treatment compared with monotherapy as well as the non-inferiority of UFT compared with S-1. The design of the study has been described previously.[24]

Panel 1 shows the eligibility criteria. In the original protocol, the control group for the non-inferiority comparison was 24 weeks of UFT. However, following the results of ACTS-GC, showing the effectiveness of 1 year of adjuvant S-1 compared with surgery alone, the control group was changed to 48 weeks of S-1 through a protocol amendment dated May 10, 2007. The non-inferiority margin for S-1 was initially set as 1·25; however, in ACTS-GC, the risk reduction of recurrence-free survival by S-1 was 0·62, therefore the data and safety monitoring committee approved changing the margin to 1·33.

The trial was approved by the institutional review board of each participating institution and done in accordance with the Declaration of Helsinki. All patients provided written informed consent before or after surgery.

Randomisation and masking

Randomisation was done centrally and independently at the non-profit organisation Epidemiological and Clinical Research Information Network (Okazaki, Japan). The minimisation method was applied to obtain a balance for tumour size (<8 cm *vs* ≥8 cm), lymph node metastasis (positive *vs* negative), and study site. A unique random sequence was generated before the enrollment by an independent statistician and sequentially applied to each patient's allocation. The detailed procedures of randomisation were not disclosed to researchers at the participating sites. Participants, investigators, and other staff were not masked to treatment allocation.

Procedures

Gastrectomy was only done by laparotomy—laparoscopy was not permitted. Immediately after opening the abdomen, the investigator had to search for tumours in the abdomen by visual inspection and palpation. Gastrectomy by laparotomy had to be attempted first if oesophageal invasion was less than 3 cm, irrespective of thoracotomy. Peritoneal cytology was not necessary for enrolment purposes but was done according to the usual policy of each institution where performed. Tumour exposure to serosa or adjacent invasion, T4a or T4b, was assessed during surgery for clinical staging. Because tumour size is related to prognosis,[25,26] the size was determined macroscopically in surgical specimen.

Panel 1: Eligibility criteria

Inclusion criteria

- Histologically proven gastric adenocarcinoma
- Clinical stage including surgical findings: T4a–b, N0–2, P0, H0, and M0
- D2 or equivalent dissection done, and macroscopically no residual disease (R0 or R1 including lavage cytology 1 or X)
- No previous chemotherapy or radiotherapy
- Age 20–80 years
- Preoperative Eastern Cooperative Oncology Group performance status of either 0 or 1
- Sufficient main organ function
- Able to start chemotherapy 14–56 days after surgery
- Without active synchronous cancer

Exclusion criteria

- Serious concomitant disease
- History of serious drug hypersensitivity
- Acute inflammatory disease
- Pregnant, possibly pregnant, or lactating
- Other active cancer that may affect survival or adverse events
- Determined by the investigator to be unsuitable for other reasons

Development Institute, Louvain-la-Neuve, Belgium (M Buyse ScD); Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan (S Morita PhD); and Tokai Central Hospital, Kakamigahara, Japan (J Sakamoto MD)

Correspondence to: Dr Kazuhiro Yoshida, Department of Surgical Oncology, Gifu University, Graduate School of Medicine, 1-1 Yanagido, Gifu 5011194, Japan
kyoshida@gifu-u.ac.jp

In the UFT only group, patients were given oral UFT 267 mg/m² in two or three doses per day, for 28-day courses for 48 weeks. In the S-1 only group, patients were given S-1 80 mg/m² orally twice per day for 14 days followed by 7 days rest for 48 weeks. In the paclitaxel then UFT group, patients were given an intravenous infusion of paclitaxel 80 mg/m² administered over 1 h on days 1 and 8, followed by a 1-week rest beginning on day 15 in course 1 (21 days), and on days 1, 8, and 15 followed by a 1-week rest from day 22 following courses 2 and 3 (28 days), for 11 weeks. Patients then received nine courses (36 weeks) of UFT 14 days after the last infusion of paclitaxel. In the paclitaxel then S-1 group, three courses (11 weeks) of paclitaxel treatment, and 12 courses (36 weeks) of S-1 were given.

See Online for appendix

The protocol treatment was discontinued for the following reasons: (1) recurrence or death, (2) withdrawal of consent, (3) protocol violation or ineligibility, (4) a pathological finding of intramucosal cancer, (5) investigator's discretion, (6) adverse events: more than 29 days of unresolved events that prevent starting or continuing a course, more than two dose reductions needed, grade 3 hypersensitivity reaction, or grade 4 non-haematological toxic effect. Criteria for continuation of treatment included white blood cell count at least 3000 per mL or neutrophil counts at least 1500 per mL; platelet count at least 75 000 per mL; serum creatinine concentration no more than 1·5 mg/L; alanine aminotransferase and aspartate aminotransferase concentrations no more than 100 IU; no worse than grade 1 nausea, vomiting, diarrhoea, or stomatitis; performance score 0–1; other non-haematological toxic effect no worse than grade 2; body temperature less than 38°C.

Toxic effects were assessed with the Common Toxicity Criteria for Adverse Events (version 3.0), with a defined protocol for modifications and delays (appendix). All patients were followed up until death or until 3 years after the last patient enrolled. During treatment, patients physical and blood examinations were done every 1–4 weeks. During and after protocol treatment, patients were physically checked for recurrence every 3 months for 3 years. Abdominal CT or ultrasound scans were done every 3 months in the first 2 years after assignment and every 6 months thereafter.

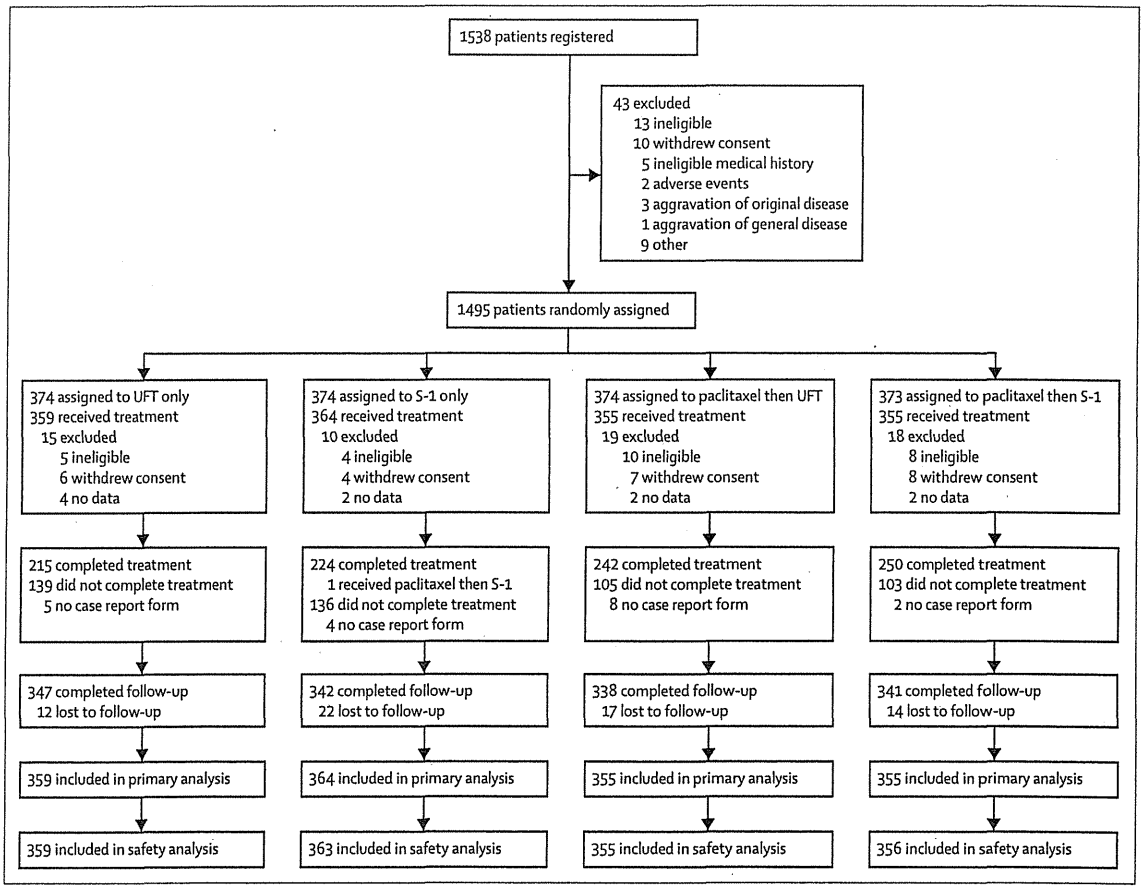

Figure 1: **Trial profile**
One patient assigned to S-1 only received paclitaxel followed by S-1: they were analysed by intention to treat for the primary analysis and per protocol for the safety analysis.

Data were collected and quality checked centrally at the Epidemiological and Clinical Research Information Network data centre. Quality control was done with CluePoints (version 1.2). No atypical data patterns that would affect the analysis were found.

Outcomes

The primary endpoint was disease-free survival, defined as the time between randomisation and the first event (all-cause death, relapse of stomach cancer, or occurrence of a second cancer). The secondary endpoints were overall survival, incidence of adverse events, and proportion of patients who completed the protocol treatment. Overall survival was defined as time between randomisation and all-cause death. Patients who had not had an event were censored at the last follow-up date. All outcomes were assessed for the intention-to-treat population, which included all patients except those who did not receive any treatment at all, who were ineligible after randomisation, or who withdrew consent.

Statistical analysis

We calculated the sample size assuming 3-year disease-free survival of 50% for the monotherapy group, and accrual and follow-up periods of 3 years. We calculated that 1480 patients (370 per treatment group) were needed to achieve 90% power to reject the null hypothesis of an equal chance of disease-free survival with sequential treatment and monotherapy at a two-sided significance level of 5%, assuming that the risk reduction in the sequential treatment group would be 20% and that 5% of patients would be lost to follow-up. This sample size would also provide 88% power to show the non-inferiority of UFT compared with S-1, using a non-inferiority margin of 1·33. We did no interim analyses.

Before the primary analysis, we tested the independence of the two hypotheses with a stratified Cox regression model for the primary endpoint including a corresponding interaction term, and then did the primary analysis if we detected no statistically significant interaction. We compared groups for the primary outcome by stratified log-rank statistics. We estimated the hazard ratio (HR) and its two-sided Wald-type 95% CI with the stratified Cox regression model, stratified by tumour size (<8 cm *vs* ≥8 cm) and N (N0 *vs* N1–2). We tested non-inferiority with a one-tailed Wald statistic. We assessed time-to-event endpoint with the Kaplan-Meier method. No statistical adjustment to control the overall type I error rate was needed because of the two-by-two design.

We did prespecified exploratory analyses of pairwise treatment comparisons with Cox regression models, adjusted using Bonferroni's method. We produced forest plots for subgroup analyses based on the patients' characteristics for disease-free survival and overall survival. Because the protocol was amended to increase the duration of oral drug treatments on May 10, 2007 (from 24 weeks to 48 weeks for monotherapy group, and from 12 weeks to 36 weeks for sequential treatment group), we assessed whether treatment effects on disease-free survival were different before and after the amendment.

We used a significance level of 5%. We did the statistical analyses with SAS (version 9.3) and produced forest plots with Stata (version 12).

This trial is registered at UMIN Clinical Trials Registry, number C000000082.

Role of the funding source

The funder participated in study design, data collection, and data management, but had no role in data analysis or data interpretation, or the writing of the report. The corresponding and the first authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 3, 2004 and Sept 24, 2009, 1495 patients were randomly assigned to a treatment group (figure 1). 62 patients were excluded because of ineligibility (n=27), withdrawal of consent (n=25), or no data (n=10). 1368 (96%) patients were followed up. Baseline characteristics were well balanced between the four treatment groups (table 1). Full protocol treatment was completed by 215 (60%) of 359 patients in the UFT only

	UFT only (n=359)	S-1 only (n=364)	Paclitaxel then UFT (n=355)	Paclitaxel then S-1 (n=355)
Tumour size				
≥8 cm	246 (69%)	247 (68%)	241 (68%)	240 (68%)
<8 cm	113 (31%)	117 (32%)	114 (32%)	115 (32%)
Lymph node metastasis				
Positive	305 (85%)	309 (85%)	302 (85%)	301 (85%)
Negative	54 (15%)	55 (15%)	53 (15%)	54 (15%)
Sex				
Women	109 (30%)	120 (33%)	119 (34%)	105 (30%)
Men	250 (70%)	244 (67%)	236 (66%)	250 (70%)
Age (years)				
≥65	187 (52%)	186 (51%)	198 (55%)	192 (54%)
<65	172 (48%)	178 (49%)	157 (44%)	163 (46%)
Eastern Cooperative Oncology Group performance status				
0	317 (88%)	314 (86%)	301 (85%)	302 (85%)
1	42 (12%)	50 (14%)	54 (15%)	53 (15%)
Pathological stage*†				
IA or IB	18 (5%)	15 (4%)	20 (6%)	19 (5%)
II	72 (20%)	90 (25%)	79 (22%)	77 (22%)
IIIA	132 (37%)	128 (35%)	126 (35%)	123 (35%)
IIIB	91 (25%)	94 (26%)	94 (26%)	92 (26%)
IV	40 (11%)	35 (10%)	33 (9%)	40 (11%)
Lavage cytology 1	26 (7%)	29 (8%)	24 (7%)	27 (8%)

Data are n (%). *Recorded according to the Japanese Classification of Gastric Carcinoma.[27] †Data missing for 15 patients.

Table 1: Baseline characteristics

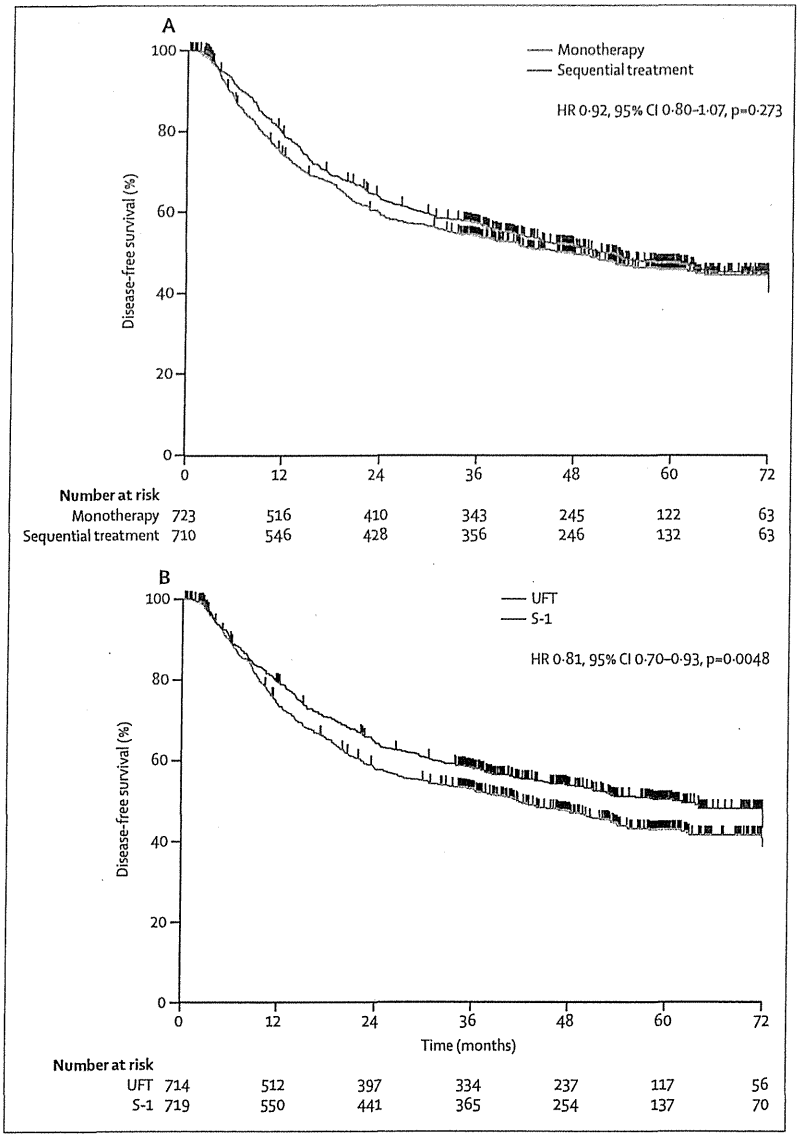

Figure 2: Kaplan-Meier analysis of disease-free survival for UFT versus S-1 (A), and by treatment group (B)

group, 224 (62%) of 364 in the S-1 only group, 242 (68%) of 355 in the paclitaxel then UFT group, and 250 (70%) of 355 in the paclitaxel then S-1 group. The median number of treatment courses was 6 (IQR 4–6) in the UFT only group, 8 (IQR 6–10) in the S-1 only group, 6 (IQR 6–10) in the paclitaxel then UFT group, and 7 (IQR 7–12) in the paclitaxel then S-1 group.

Median follow-up was 62·5 months (IQR 48·3–80·7) for UFT only, 62·8 months (47·9–80·5) for S-1 only, 65·5 months (48·7–81·0) for paclitaxel then UFT, and 61·3 months (47·8–78·9) for paclitaxel then S-1. For the primary endpoint, 728 events had occurred and 592 (41%) patients had died at the time of analysis.

Disease-free survival at 3 years with monotherapy was 54·0% (95% CI 50·2–57·6) and with sequential treatment was 57·2% (95% CI 53·4–60·8), with no significant difference between the two groups (HR 0·92, 95% CI 0·80–1·07, p=0·273; figure 2A). Disease-free survival at 3 years for patients given UFT was 53·0% (95% CI 49·2–56·6) and for those given S-1 it was 58·2% (95% CI 54·4–61·8; HR 0·81, 95% CI 0·70–0·93, p=0·0048; $p_{non\text{-}inferiority}$=0·151; figure 2B). Figure 3 shows disease-free survival for each group. We recorded no interaction between the two hypotheses ($p_{interaction}$=0·886). We also detected no effect of the protocol amendment on treatment efficacy (for monotherapy *vs* sequential treatment $p_{interaction}$=0·390, for UFT *vs* S-1 $p_{interaction}$=0·781; appendix).

3-year overall survival with monotherapy was 55·8% (95% CI 51·7–59·6) and that with sequential treatment was 59·3% (95% CI 55·3–63·0), with no significant difference between groups (HR 0·93, 95% CI 0·79–1·09, p=0·342). 3-year overall survival with UFT was 54·3% (95% CI 50·3–58·2) and that with S-1 was 60·7% (95% CI 56·7–64·5; HR 0·81, 95% CI 0·69–0·93, p=0·013).

The most common grade 1 or 2 adverse events were anaemia (1102 [77%] of 1433 patients), followed by neutropenia (767 [54%] of 1433), leucopenia (710 [50%] of 1433), anorexia (600 [42%] of 1433), and fatigue (547 [38%] of 1433); which were rarer in the UFT only group than in the other treatment groups (appendix). The most common grade 3–4 haematological adverse event was neutropenia (table 2), whereas leucopenia occurred in less than 7% of patients in each treatment group (table 2). Thrombocytopenia and febrile neutropenia occurred in less than 1% of patients. Grade 3–4 non-haematological adverse events mostly occurred in less than 5% of patients, except for anorexia (table 2). We recorded no unexpected toxic effects and no treatment-related deaths.

Subgroup analyses for disease-free survival showed no interaction between factors used for randomisation and other characteristics in the comparison of monotherapy and sequential treatment or the comparison of UFT and S-1 (appendix). S-1 had a stronger treatment effect in more advanced cases according to cytological staging ($p_{interaction}$=0·038) and pathological staging, ($p_{interaction}$=0·093). Sequential treatment was better than was monotherapy for patients with stage IIIb disease, but not significantly so. Peritoneal recurrence occurred in 93 (26%) patients taking UFT only, 75 (22%) taking S-1 only, 81 (22%) taking paclitaxel then UFT, and 60 (17%) taking paclitaxel then S-1.

Discussion

Sequential paclitaxel did not improve disease-free survival and UFT was not non-inferior to S-1; S-1 was superior to UFT as adjuvant treatment for T4a or T4b gastric cancer. These results suggest that S-1 monotherapy should remain the standard treatment for locally advanced gastric cancer in Japan.

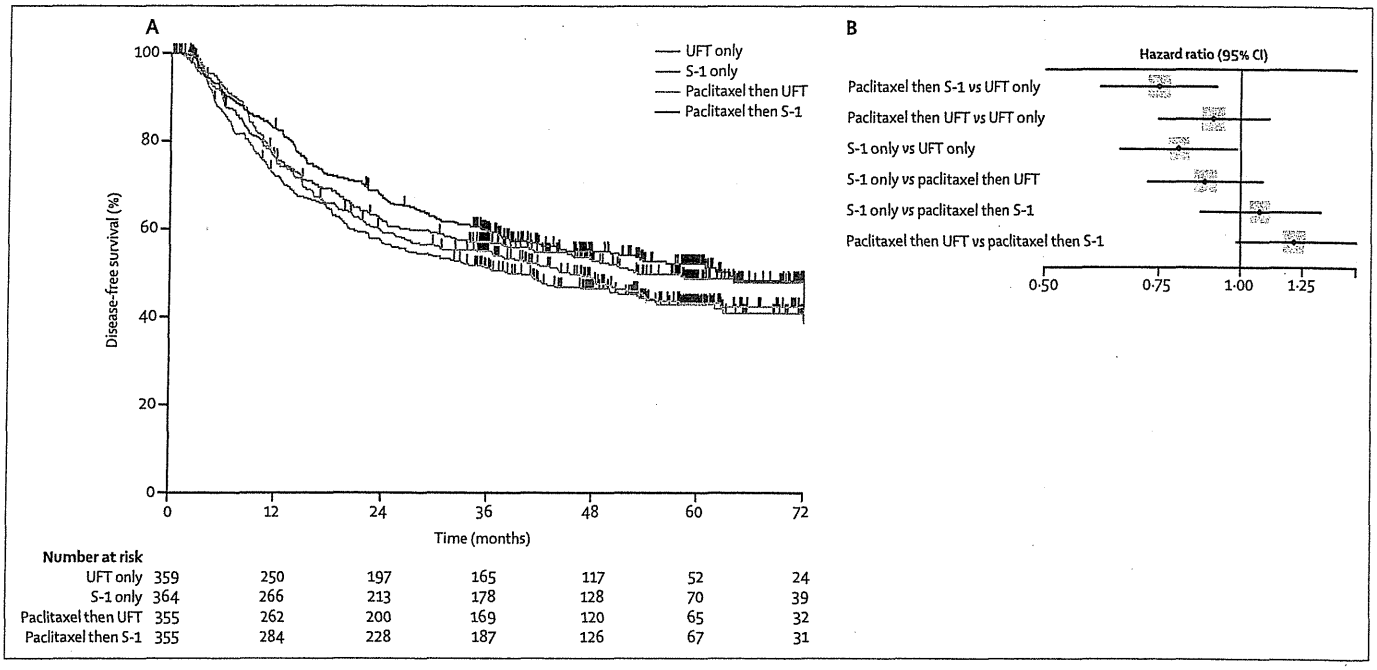

Figure 3: **Analysis of overall survival, by Kaplan-Meier (A) and forest plot (B)**

To our knowledge, the SAMIT trial is the largest-ever adjuvant trial for gastric cancer. Few other large randomised adjuvant trials have been done for gastric cancer, especially after radical lymph node dissection (panel 2). D2 gastrostomy was done for only 10% of patients in the INT 0116 trial[33] and 38% in the MAGIC trial.[2] ACTS-GC,[3] CLASSIC,[4] and ARTIST[34] included patients only after D2 dissection. Adjuvant chemotherapy showed a survival benefit in two of these studies: S-1 in ACTS-GC and capecitabine and oxaliplatin in CLASSIC. Although not the primary analyses, our findings showed the superiority of S-1 compared with UFT. S-1 monotherapy has been considered a robust adjuvant regimen after radical gastrectomy. Patients' characteristics were different in ACTS-GC and SAMIT: about 55% of patients had stage III disease and 0% had stage IV disease in ACTC-GC, compared with 60% and 10% in SAMIT. This difference could explain the difference in survival and compliance between the studies. The subgroup analysis in ACTS-GC suggested that treatment might have less of an effect in patients with stage III disease than in those with stage II disease.[3,35] In SAMIT, we recorded numerically but not statistically improved survival and fewer peritoneal recurrences in patients who received sequential treatment; however, sequential treatment was only effective for patients with stage IIIB disease. A meta-analysis[36] suggests that treatment with several drugs could be more effective than treatment with using fewer (or lower doses), but this finding has not been confirmed in the adjuvant setting.[37]

Weight loss after surgery is an independent risk factor for discontinuation of S-1 adjuvant chemotherapy for

	UFT only (n=359)	S-1 only (n=363)	Paclitaxel then UFT (n=355)	Paclitaxel then S-1 (n=356)
Haematological				
Leucopenia	6 (2%)	8 (2%)	22 (6%)	16 (4%)
Neutropenia	41 (11%)	48 (13%)	46 (13%)	83 (23%)
Abnormal platelets	3 (1%)	1 (<1%)	0 (0%)	2 (1%)
Anaemia	1 (<1%)	11 (3%)	3 (1%)	6 (2%)
Non-haematological				
Allergic reaction	0 (0%)	0 (0%)	2 (1%)	3 (1%)
Fever	0 (0%)	1 (<1%)	3 (1%)	3 (1%)
Fatigue	8 (2%)	12 (3%)	11 (3%)	16 (4%)
Anorexia	21 (6%)	24 (7%)	7 (2%)	18 (5%)
Nausea	6 (2%)	7 (2%)	1 (<1%)	4 (1%)
Vomiting	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)
Stomatitis	0 (0%)	2 (1%)	0 (0%)	1 (<1%)
Diarrhoea	4 (1%)	8 (2%)	2 (1%)	11 (3%)
Hypotension	0 (0%)	2 (1%)	1 (<1%)	0 (0%)
Dyspnoea	0 (0%)	1 (<1%)	1 (<1%)	2 (1%)
Motor neuropathy	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Sensory neuropathy	0 (0%)	1 (<1%)	2 (1%)	1 (<1%)
Abnormal total bilirubin	8 (2%)	10 (3%)	2 (1%)	2 (1%)
Abnormal AST concentration	6 (2%)	3 (1%)	8 (2%)	4 (1%)
Abnormal ALT concentration	5 (1%)	3 (1%)	13 (4%)	4 (1%)
Serum creatinine concentration	0 (0%)	2 (1%)	0 (0%)	0 (0%)

Data are n (%). One patients allocated to UFT only was treated with paclitaxel then S-1. Grade 3-4 febrile neutropenia, infection, myalgia, arthralgia, arrhythmia, pigmentation, and albumin decrease occurred in less than 0·5% of patients in each group. AST=asparatate aminotransferase. ALT=alanine aminotransferase.

Table 2: **Grade 3 and 4 toxic effects**

Panel 2: Research in context

Systematic review

We searched Medline, PubMed, and The Cochrane Library with the terms "gastric cancer" (or "stomach cancer"), "adjuvant chemotherapy", and "Japan" for clinical trials published between Jan 1, 1980, and March 31, 2005.[5] We retrieved 12 reports, but only four trials[28–31] met the inclusion and exclusion criteria for our meta-analysis. The eight reports were excluded because they used historical controls, were retrospective studies, control was not surgery alone, or not adjuvant chemotherapy. For the four trials the estimated hazard ratio for surgery plus adjuvant chemotherapy compared with surgery alone for overall survival was 0·73 (95% CI 0·60–0·89, p=0·002). Meta-analysis focused of UFT produced similar results,[32] however, most of the included trials were small and adjuvant chemotherapy was not recognised as a standard treatment. In 2007, the ACTS-GC trial[3] showed the superiority of S-1 compared with surgery alone. S-1 has since become a standard treatment in Japan.

Interpretation

Sequential paclitaxel did not improve disease-free survival and UFT was not non-inferior to S-1, while S-1 was superior to UFT as adjuvant treatment for T4a or T4b gastric cancer. Taken together with ACTS-GC,[3] S-1 monotherapy should be the standard treatment in this setting, at least in Asian populations. Because sequential paclitaxel is safe with good compliance and improves survival, it could be considered for patients with advanced disease.

gastric cancer.[20] In patients with inssuficient oral intake, gastrointestinal adverse events (eg, anorexia, nausea, and vomiting) can cause major distress; such events were less frequent in the sequential groups in SAMIT. In a randomised controlled trial[10] for metastatic breast cancer, the incidence of grade 3–4 nausea, vomiting, or diarrhoea was 3·2% for patients given paclitaxel and 14·0% for those given docetaxel. 10–50% of patients have morbidity after surgery[38] and post-gastrectomy disturbances for 3 months,[39,40] therefore a low toxicity, albeit less effective, regimen is preferable for this initial period. In general practice, the number of elderly patients with cancer who have more comorbidities is increasing;[41] such patients are under-represented in clinical trials.[42] Taxane-containing adjuvant chemotherapy is feasible for older patients with breast cancer and toxic effects can be reduced by sequential treatment regimens.[43]

Our study has some limitations. Staging for randomisation was intraoperative and lavage cytology was not mandatory, but this approach was taken for practical reasons; also, an early and adequate clinical decision to start adjuvant treatment would benefit both patients and clinicians. We used disease-free survival as the primary endpoint because it enabled us to assess the data sooner than if we had used overall survival, although overall survival is the gold standard endpoint for trials of adjuvant treatment for gastric cancer. Nevertheless, the GASTRIC group has said[44] that disease-free survival is an acceptable surrogate for overall survival in trials of cytotoxic drugs for gastric cancer in the adjuvant setting, which suggests that any observed benefit for disease-free survival could translate into a benefit for overall survival in the future.

Contributors

AT, KY, YM, KO, SM, MB, and JS formed the coordinating committee, designed, developed, and revised the protocol, analysed and interpreted data, and prepared the report. KO and MB did statistical analyses. All other authors collected data, and reviewed and helped to revise the report.

Declaration of interests

KY has received honoraria from Taiho, Pfizer, Chugai, Kyowa Hakko, and Yakult, and is a consultant or advisor for Taiho and Hoffman La Roche. RF has received personal fees from Medicon, and grants from Otsuka and Ajinomoto. SM has received personal fees from Bristol and Taiho. NT has received honoraria from Taiho, Chugai, and Pfizer. MB is a shareholder of International Drug Development Institute. The other authors declare no competing interests.

Acknowledgments

This study was supported by the Epidemiological & Clinical Research Information Network. The independent data and safety monitoring committee was Yasuo Ohashi (School of Public Health, University of Tokyo), Akira Kurita (Department of Surgery, Shikoku Cancer Centre), and Kuniaki Shirao (Department of Medical Oncology, Oita University). We thank Aimery de Gramont (Saint-Antoine Hospital) and J Patrick Barron (Emeritus Tokyo Medical University and Permanent Advisory Professor Bundang University, Seoul National University) for editing and proofreading the report.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893–917.

2 Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11–20.

3 Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; 357: 1810–20.

4 Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; 379: 315–21.

5 Oba K, Morita S, Tsuburaya A, Kodera Y, Kobayashi M, Sakamoto J. Efficacy of adjuvant chemotherapy using oral fluorinated pyrimidines for curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials in Japan. *J Chemother* 2006; 18: 311–17.

6 Wilson PM, Danenberg PV, Johnston PG, Lenz HJ, Ladner RD. Standing the test of time: targeting thymidylate biosynthesis in cancer therapy. *Nat Rev Clin Oncol* 2014; 11: 282–98.

7 Jimenez P, Pathak A, Phan AT. The role of taxanes in the management of gastroesphageal cancer. *J Gastrointest Oncol* 2011; 2: 240–49.

8 Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012; 379: 432–44.

9 Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; 374: 1331–38.

10 Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005; 23: 5542–51.

11 Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev* 2010; 36: 69–74.

12 Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; **21**: 1431–39.

13 Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst* 2008; **100**: 121–33.

14 Sakamoto J, Matsui T, Kodera Y. Paclitaxel chemotherapy for the treatment of gastric cancer. *Gastric Cancer* 2009; **12**: 69–78.

15 Sun Z, Xu YY, Wang ZN, et al. Macroscopic serosal classification predicts peritoneal recurrence for patients with gastric cancer underwent potentially curative surgery. *Ann Surg Oncol* 2011; **18**: 1068–80.

16 Kobayashi M, Sakamoto J, Namikawa T, et al. Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. *World J Gastroenterol* 2006; **12**: 1412–15.

17 Boku N. JCOG trials of systemic chemotherapy for unresectable or recurrent gastric cancer. *Gastric Cancer* 2009; **12** (suppl 1): 43–49.

18 Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; **31**: 4438–44.

19 Nakajima T, Kinoshita T, Nashimoto A, et al. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. *Br J Surg* 2007; **94**: 1468–76.

20 Aoyama T, Yoshikawa T, Shirai J, et al. Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. *Ann Surg Oncol* 2013; **20**: 2000–06.

21 Grem JL, Nguyen D, Monahan BP, Kao V, Geoffroy FJ. Sequence-dependent antagonism between fluorouracil and paclitaxel in human breast cancer cells. *Biochem Pharmacol* 1999; **58**: 477–86.

22 Kobayashi M, Tsuburaya A, Nagata N, Miyashita Y, Oba K, Sakamoto J. A feasibility study of sequential paclitaxel and S-1 (PTX/S-1) chemotherapy as postoperative adjuvant chemotherapy for advanced gastric cancer. *Gastric Cancer* 2006; **9**: 114–19.

23 Biondi A, Hyung WJ. Seventh edition of TNM classification for gastric cancer. *J Clin Oncol* 2011; **29**: 4338–39.

24 Tsuburaya A, Sakamoto J, Morita S, et al. 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**: 672–75.

25 Iwasaki Y, Sasako M, Yamamoto S, et al. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). *J Surg Oncol* 2013; **107**: 741–45.

26 Aoyama T, Yoshikawa T, Watanabe T, et al. 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. *Gastric Cancer* 2011; **14**: 274–78.

27 Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma 2nd Edn. *Gastric Cancer* 1998; **1**: 10–24.

28 Nakajima T, Takahashi T, Takagi K, Kuno K, Kajitani T. Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. *J Clin Oncol* 1984; **2**: 1366–71.

29 Nakajima T, Nashimoto A, Kitamura M, et al; and theGastric Cancer Surgical Study Group. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. *Lancet* 1999; **354**: 273–77.

30 Nashimoto A, Nakajima T, Furukawa H, et al; and the Gastric Cancer Surgical Study Group, Japan Clinical Oncology Group. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosanegative gastric cancer: Japan Clinical Oncology Group 9206-1. *J Clin Oncol* 2003; **21**: 2282–87.

31 Fujii M, Sakabe T, Wakabayashi K, et al. The optimal period for orally administered fluoropyrimidines as an adjuvant chemotherapy for gastric cancer: a pilot study using 5-FU tablets compared with surgical operation alone. *Gan To Kagaku Ryoho* 1994; **21**: 1199–208 [in Japanese].

32 Sakamoto J, Tsuburaya A, Morita S, et al. Adjuvant chemotherapy with tegafur/uracil (UFT) for gastric cancer. A meta-analysis of centrally randomized clinical trials. *J Clin Oncol* 2006; **24** (18 suppl): 4033.

33 Macdonald JS, Smalley SR, Benedetti J, 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.

34 Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012; **30**: 268–73.

35 Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387–93.

36 Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903–09.

37 Paoletti X, Oba K, Burzykowski T, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303**: 1729–37.

38 Bickenbach K, Strong VE. Comparisons of gastric cancer treatments: east vs. west. *J Gastric Cancer* 2012; **12**: 55–62.

39 Kim AR, Cho J, Hsu YJ, et al. Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea. *Ann Surg* 2012; **256**: 1008–13.

40 Kong H, Kwon OK, Yu W. Changes of quality of life after gastric cancer surgery. *J Gastric Cancer* 2012; **12**: 194–200.

41 Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol* 2005; **55**: 231–40.

42 Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J Clin Oncol* 2012; **30**: 2036–38.

43 Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res* 2008; **10**: R77.

44 Oba K, Paoletti X, Alberts S, et al. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. *J Natl Cancer Inst* 2013; **105**: 1600–07.

Gastric Cancer
DOI 10.1007/s10120-014-0398-3

ORIGINAL ARTICLE

HER2 expression in locally advanced gastric cancer with extensive lymph node (bulky N2 or paraaortic) metastasis (JCOG1005-A trial)

Tomohiro Matsumoto · Mitsuru Sasako · Junki Mizusawa · Seiichi Hirota · Atsushi Ochiai · Ryoji Kushima · Hitoshi Katai · Yoichi Tanaka · Norimasa Fukushima · Atsushi Nashimoto · Akira Tsuburaya · Stomach Cancer Study Group of the Japan Clinical Oncology Group

Received: 1 February 2014 / Accepted: 11 June 2014

Abstract

Background Human epidermal growth factor receptor 2 (HER2) is likely overexpressed and/or amplified in locally advanced gastric cancer with extensive (bulky N2 or paraaortic) lymph node metastasis, and patients may benefit from treatment with anti-HER2 antibodies. This study evaluated the frequency of HER2 overexpression and amplification in The Japanese Gastric Cancer Association (JGCA)-N3 and JGCA-bulky N2 tumors and the correlation between HER2 status and survival.

Methods HER2 status was assessed using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in tumor tissue samples from 89 patients with gastric adenocarcinoma enrolled in the phase II JCOG0001 and JCOG0405 trials. HER2 positivity was defined as IHC3+ or IHC2+ with confirmatory FISH results.

Results Of the 89 tumor samples, 24 (27 %) showed HER2 positivity, including 16 scored as IHC3+ and 8 as IHC2+ and FISH positive. Multivariate analysis showed that the HER2 positivity rate was significantly higher in evaluable differentiated tumors than in undifferentiated tumors [18/44 (40.9 %) vs. 5/42 (11.9 %)]. Although the apparent OS curve of HER2 positive was superior to that of HER2 negative patients, HER2 status was not a statistically significant prognostic factor in multivariate analysis.

Conclusion The HER2 positivity rate was relatively high in patients with JGCA-bulky N2 and JGCA-N3 gastric adenocarcinoma, suggesting that HER2 evaluation is essential to select the therapeutic regimen for neoadjuvant chemotherapy for this group of patients.

T. Matsumoto · M. Sasako (✉)
Department of Upper Gastrointestinal Surgery, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: msasako@hyo-med.ac.jp

J. Mizusawa
Japan Clinical Oncology Group Data Center, Multi-Center Clinical Trial Support Center, National Cancer Center, Tokyo, Japan

S. Hirota
Department of Surgical Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

A. Ochiai
Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

R. Kushima
Pathology and Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan

H. Katai
Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Y. Tanaka
Division of Gastroenterological Surgery, Saitama Cancer Center, Saitama, Japan

N. Fukushima
Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan

A. Nashimoto
Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan

A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan

Published online: 04 July 2014

Keywords Gastric adenocarcinoma · HER2 status · Immunohistochemistry · Trastuzumab

Introduction

Gastric cancer is one of the most common types of malignant tumors and the second leading cause of cancer-related deaths in the world [1]. Complete tumor removal (R0 resection) is essential for cure [2, 3]. The Japanese Gastric Cancer Association (JGCA) used to define para-aortic lymph nodes (PAN) as regional lymph node stations (JGCA-N3) in contrast to the tumor node metastasis (TNM) staging of the International Union Against Cancer (UICC), which defines paraaortic metastasis as distant metastasis [4]. Prophylactic PAN dissection for T3 (subserosa) or deeper gastric cancer is no longer recommended in Japan based on the results of a randomized controlled trial (RCT) by the Japan Clinical Oncology Group (JCOG 9501) [5]. However, Japanese surgeons have not given up yet to cure patients with extensive nodal disease [bulky nodal metastasis surrounding the celiac artery and its branches (JGCA-bulky N2) or PAN metastasis] using preoperative chemotherapy with D2 plus PAN dissection (PAND) if they have no other distant metastasis. These patients are regarded as unresectable in the West and treated by palliative chemotherapy with or without radiation. The Stomach Cancer Study Group of the JCOG considers these tumors to be a specific type and has carried out two phase II studies on this subject with remarkably better results than historical controls [6, 7]. We consider that more intensive chemotherapy such as triplet therapy or the addition of molecular targeted agents is needed to further improve the prognosis of patients with this disease.

Human epidermal growth factor receptor 2 (HER2; also known as ERBB2) is a member of a family of receptors associated with tumor cell differentiation, migration, proliferation, and survival [8], and it is recognized as an important biomarker. In gastric carcinoma, the frequency of HER2 overexpression and/or amplification has been reported to vary widely from 7 to 34 % [8–11]. Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, has been shown to confer a survival benefit in both primary and metastatic breast carcinoma cases with high levels of HER2 expression and amplification, and it is used as the standard regimen in adjuvant therapy [12–14]. Findings in a multicenter and international phase III trial to evaluate trastuzumab for gastric cancer (ToGA trial) revealed that the combination of trastuzumab with chemotherapy consisting of fluoropyrimidine and cisplatin improved survival in patients with advanced HER2-positive gastric carcinomas or gastroesophageal junction carcinomas as compared to chemotherapy alone [15]. Thus, molecular targeted therapies have begun to play an important role in improving the prognosis of patients with gastric carcinomas.

A close relationship between HER2 overexpression and/or amplification and intestinal histologic type in gastric carcinomas has been reported in recent studies and confirmed in the ToGA trial [10, 16–18]. Approximately 50 % of all patients entered in the JCOG0001 and JCOG0405 trials were pathologically diagnosed as having well-to-moderately differentiated tumors corresponding to the intestinal type. Thus, we speculated that tumors with JGCA-N3 or JGCA-bulky N2 have a high frequency of HER2 expression and/or amplification and considered it necessary to clarify whether the HER2 status of these tumors should be taken into account for development of new therapies.

The aims of this study were to evaluate the frequency of HER2 overexpression and/or amplification in tumors with JGCA-N3 or JGCA-bulky N2 using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) findings and to analyze the correlation between HER2 status and survival.

Patients and methods

Patients and material

All gastric cancer patients enrolled in the JCOG0001 and JCOG0405 trials were included in this study [6, 7]. Eligibility criteria, treatment schedules, monitoring, and statistical analysis in these trials have been described in detail elsewhere [6, 7]. Briefly, these were phase II studies involving patients with histologically proven gastric adenocarcinoma with JGCA-N3 or JGCA-bulky N2 confirmed by contrast-enhanced computed tomography (CT) between 2000 and 2007. Eligibility criteria included no distant nodal metastasis outside the paraaortic region, as confirmed by contrast-enhanced CT, no peritoneal or pleural effusion, no clinically apparent brain or bone metastasis, no peritoneal metastasis or negative cytology obtained in staging laparoscopy, non-scirrhous macroscopic type by endoscopy or upper gastrointestinal X-ray study, and no previous chemotherapy or radiotherapy. Following preoperative chemotherapy (JCOG0001 trial: irinotecan plus cisplatin; JCOG0405 trial: S-1 plus cisplatin), a gastrectomy with D2 plus PAND was performed if curative resection was deemed possible. To examine the HER2 status of archival tumor samples surgically resected or biopsies, 3-μm-thick paraffin block samples from enrolled cases were obtained from institutions belonging to the Stomach Cancer Study