2.9% of 1246 cases with *H. pylori* infection developed gastric cancer over a period of 7.8 years. A randomized controlled study in China also showed that *H. pylori* eradication was more effective in patients without atrophic gastritis than those with it (5). Dr Fukase in Japan reported that in a randomized controlled study comparing eradication of *H. pylori* with no eradication after endoscopic mucosal resection (EMR) of early gastric cancer at the 3-year follow-up point significantly reduced the number (9 versus 24) of metachronous gastric cancer developed in the eradication group compared with the control group. It was concluded that prophylactic eradication of *H. pylori* after EMR for early gastric cancer should be performed to prevent the development of metachronous gastric cancers (Fig. 5) (6). These results suggested that it was never too late to eradicate *H. pylori* for prevention of gastric cancer. An Italian group performed a meta-analysis of the published data regarding whether *H. pylori* eradication treatment can reduce the risk of gastric cancer. It was concluded that 1.1% of treated patients would develop gastric cancer, in contrast to 1.7% of untreated patients. In six studies with about 6700 participants followed for 4–10 years, the relative risk was 0.65, and it was concluded that *H. pylori* eradication treatment seemed to reduce gastric cancer (7). In Taiwan, a nationwide cohort study followed 80 000 patients with *H. pylori*-infected peptic ulcers for 10 years. These patients were divided into early- and late-eradication cohorts. It was concluded that early *H. pylori* eradication showed no significant difference in the gastric cancer risk compared with the general population, but late eradication was associated with an increased risk of gastric cancer. Older age, male gender, gastric ulcer, no regular NSAIDs use and late *H. pylori* eradication represented independent risk factors for gastric cancer development (Fig. 6) (8).

Fock et al. concluded that fruits and vegetables are associated with a reduced risk of gastric cancer in his paper in the *Journal of Gastroenterology and Hepatology*. Supplementation of vitamins and minerals may be unnecessary, at least in healthy subjects with no nutritional deficiencies (9). In a
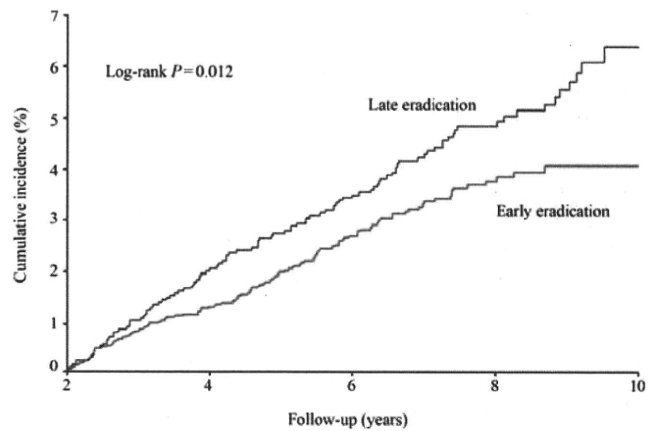

Figure 6. Cumulative incidence of gastric cancer in two groups, early eradication and late eradication groups. Source: Wu et al. (8).
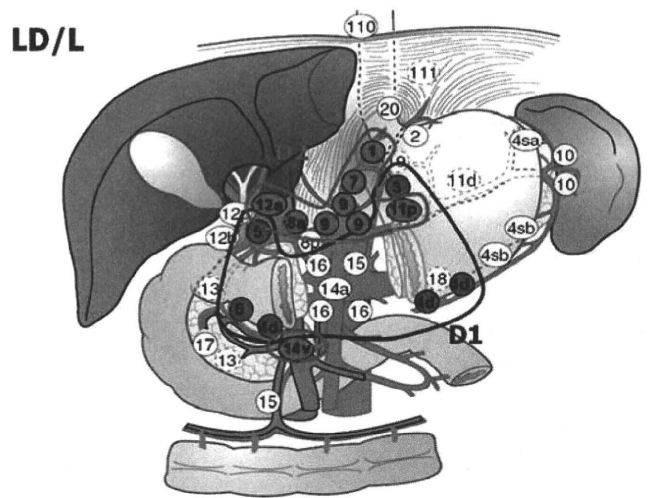

Figure 7. Regional lymph node group according to the location of tumor. Source: Sasako et al. (21) and Yoon and Yang (22).

meta-analysis study, all studies proved that both aspirin and NSAIDs are useful for preventing cardia and non-cardia gastric cancer (10). There is insufficient evidence for any benefit from green tea, vitamins and antioxidants. The biological behaviors of distal and proximal gastric cancers are quite different, but the prevention regimens have been the same, centered on eradication of *H. pylori* infection.

The Working Group concluded that the etiology of gastric cancer consists of genetic susceptibility, *H. pylori* infection and environmental risk factors. *Helicobacter pylori* eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and NSAIDs (11) seem to reduce the risk of gastric cancer.

Figure 5. Kaplan–Meier analysis of the cumulative incidence rate of new carcinoma. Source: Fukase et al. (6).

ENDOSCOPY AND DIAGNOSIS

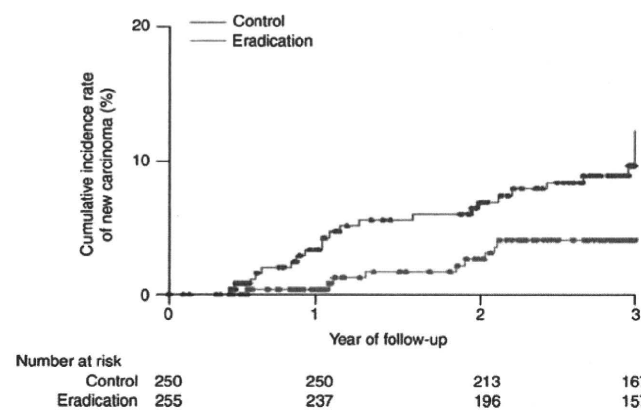Experience in Japan has shown that access to screening and early endoscopy increased the proportion of early-stage

gastric cancers, leading to improved survival (12). Cost is a major barrier to screening. Screening is considered to be cost-effective in high-incidence countries, but perhaps not where the incidence of gastric cancer is moderate or low. Risk stratification may help to focus limited resources on patients at greatest risk, and thereby increase the cost-effectiveness of screening (13). Serum pepsinogen-based tests may help to identify a subset of patients with atrophic gastritis, who are especially at a high risk. In a country with high incidence of gastric cancer, such as Japan, it is still very cost-effective to screen even if the cost of endoscopy is high. Singapore and some other countries in East Asia have a moderate incidence of gastric cancer, and screening these populations could be cost-effective if the cost were moderate (13). In Japan, the government-supported screening program has been based on barium, and although very successful, it accounts for less than 10% of all cancers that are diagnosed by screening. Most are detected due to early or easy access to endoscopy, either through outpatient clinics or through health screening outside of the government's screening program (14).

High-quality endoscopy is important and may be facilitated by endoscope preparation, such as lens cleaning, and by patient preparation ahead of endoscopy by the use of defoaming agents, mucolytics and antispasmodics, which make the field of interest much clearer. Techniques such as adequate air insufflation, systematic examination of the entire stomach, use of contrast agents, image enhancement and cognitive training may also help improve yield rates.

Accurate specimen collection and recording of endoscopic findings are important. There is some discordance between Western- and Japanese-trained pathologists in the biopsy definition of early gastric cancer. In the West, the gold standard for diagnosing cancer is to detect invasion of tumor cells into the lamina propria, muscularis mucosae or submucosal layer, whereas in Japan, it is more important to detect cellular atypia or structural atypia, regardless of invasion, when making a diagnosis of cancer. The revised Vienna classification has helped resolve some of these differences and may be a good starting point for consensus between Western and Japanese pathologists (15).

Gotoda et al. (16) reported that there is a clearly defined subgroup of patients with early gastric cancer that has a virtually negligible risk of nodal metastasis. Such patients could be treated definitively by local resection, with the expected long-term outcome equivalent to radical surgery. Further development led to the expanded criteria for endoscopic therapy of early gastric cancer, with *en bloc* resection being the primary goal (17). Endoscopic resection can be considered curative if the lesion shows differentiated histopathology, is limited to the mucosal layer or <500 μm submucosal invasion, with clear vertical and lateral margins, and no lymphovascular involvement. EMR has the advantages of short procedure time and low risk of perforation, which make it an attractive option for small lesions. EMR for differentiated, non-ulcerated early cancer <20 mm in

diameter is associated with an excellent 10-year survival rate of 99% (18). Endoscopic submucosal dissection (ESD) is associated with a lower local recurrence rate than EMR because the technique permits *en bloc* resection without size limitation. Procedure times for ESD are longer, however, with higher delayed bleeding and perforation risk (19). A recent long-term follow-up study showed that ESD for early gastric cancer, which met the expanded criteria, resulted in 5-year overall and disease-specific survival rates of 97% and 100%, respectively (20). Training opportunities in ESD for endoscopists from outside Japan and Korea, however, remain limited.

In conclusion, screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Barium meal-based screening is government-funded in Japan, but is less accurate than gastroscopy. Gastroscopic screening is desirable in high-risk populations. High-quality endoscopy may increase diagnostic yield in early cancer. Endoscopic resection is curative in a subset of patients with early cancer as defined by the expanded criteria. EMR has shown long-term outcomes comparable with surgery in patients with small lesions, and similar outcomes with ESD for larger lesions in experienced hands. Standardization between Western- and Japanese-trained pathologists in diagnosing gastric cancer is urgently needed. Structured training programs for ESD should be set up in high-volume centers and made accessible to suitable regional candidates.

SURGERY AND ADJUVANT TREATMENT

For gastric cancer, so-called D1, or perigastric lymph node, dissection is common in Western countries, whereas in high-incidence countries like Japan and Korea, so-called D2 dissection is considered to be the standard (Fig. 7) (21,22).

An RCT from UK comparing D1 versus D2 found very high mortality but failed to show a difference (23,24). The trial was flawed due to the very high mortality, inclusion of a large proportion of stage I and absence of any description regarding the quality of lymph node dissection. A Dutch trial started 20 years ago also showed much higher mortality for D2 compared with D1 dissection and demonstrated no survival benefit (25,26). These two trials were closed before reaching the plateau of the learning curve, and the high postoperative mortality offset the effect of the D2. D2 dissections should be carried out in specialized centers.

An RCT in Taiwan compared D1 and D2 showed survival benefit of D2 dissection with reasonable morbidity and mortality (Fig. 8) (27).

To investigate even more extensive dissection of gastric cancer, a Japanese group compared D2 with D2 plus para-aortic nodal dissection (28,29). The results showed slightly higher morbidity, but without increase in mortality. These morbidity and mortality results were acceptable. However,
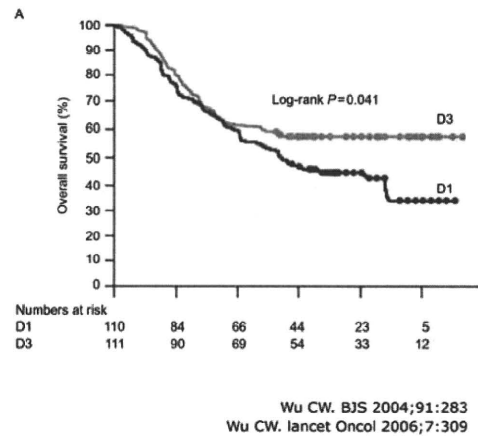
Figure 8. Nodal dissection for patients with gastric cancer: a randomized controlled trial. Source: Wu et al. (27).

no survival difference was observed, and D2 was thus the optimal surgery in that RCT. Comparison of reports from various countries reveals that the mortality is higher when the volume is lower, again demonstrating that D2 dissection should be performed in high-volume and/or specialized centers.

Regarding the role of adjuvant treatment, a major trial in Europe showed survival benefit from perioperative chemotherapy, but less than half of the patients underwent D2 dissection and the study also included esophageal cancer cases (30).

An RCT performed in the USA investigated the role of post-operative chemoradiotherapy and also showed significant survival benefit (31,32). However, only 10% of the patients underwent D2 dissection, there was a very high rate of local recurrence, and the surgery was not standardized among the participating hospitals. Subgroup analysis found survival benefit only in D0 or D1, but not in the D2-dissected group. The study thus showed that D0/D1 dissection was insufficient treatment.

In a Japanese randomized trial, curative D2 dissection alone was compared with D2 followed by post-operative chemotherapy by oral S-1 (33). In contrast to the Western studies, almost all of the cases in this study underwent D2 dissection, and the 3-year survival rate showed a 10% improvement (Fig. 9). A clinical trial of adjuvant treatment is being conducted in Korea, China and Taiwan, and 1024 cases have been enrolled. The results will be available within a few years. A Japanese group and a Korean group are working together to assess, for the first time, the role of reductive gastrectomy in Stage IV gastric cancer treatment (34). The chemotherapy applied in both arms is S-1 plus cisplatin. Although a very difficult project, it is very important,

and it is hoped that other Asian countries will join this collaboration in the future.

In conclusion, with regard to the extent of surgery, R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery. In areas with a high incidence of gastric cancer, the quality of treatment can be kept very high, with both endoscopic treatment and surgery. At the moment, at least in Asia, D2 dissection should be considered as the standard.

CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

There are now four active cytotoxic agents for advanced gastric cancer, consisting of fluorouracils, platinum, taxanes and irinotecan. The fluorouracils include 5-FU, S-1 and capecitabine, and the platinum include cisplatin and oxaliplatin. During the last decade, various randomized trials investigated the optimal combination of these four chemotherapy drug groups in Japan, Korea and China (Table 1). Capecitabine plus platinum was at least non-inferior to 5-FU plus cisplatin in terms of survival (35,36). S-1 plus cisplatin showed a comparable median time to progression to those in capecitabine or 5-FU plus cisplatin in Western studies (37,38), whereas the Japanese studies yielded relatively longer survival than the Western studies. These favorable survival in Japanese studies compared with the Westerns might be caused by longer survival after failure of the first-line therapy associated with higher rates of subsequent therapy than in the Western studies (Fig. 10).

ACTS-GC
trial

Topics	Summary		
Arms	Op	Op+postop CRx	
No. of patients	530	529	Total = 1059
Enroll period	2001–2004 (3 years)		
Indication	Stage II–III		
Exp. 5 Years	70%	HR = 0.70	
3 Years	70.1%	80.1%	HR = 0.68
3 years DFS	59.6%	72.2%	HR = 0.62
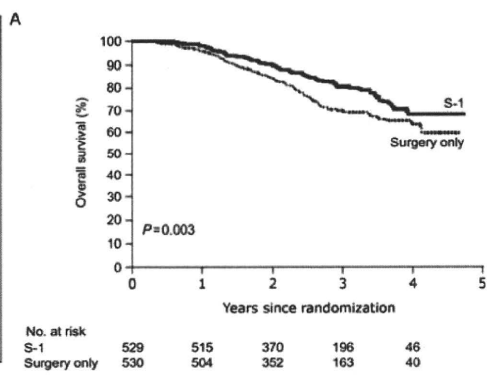
Sakuramoto S. NEJM 2007;357:1810

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

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

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

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

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

Table 2. Approval status of active agents in gastric cancer

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

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

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

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

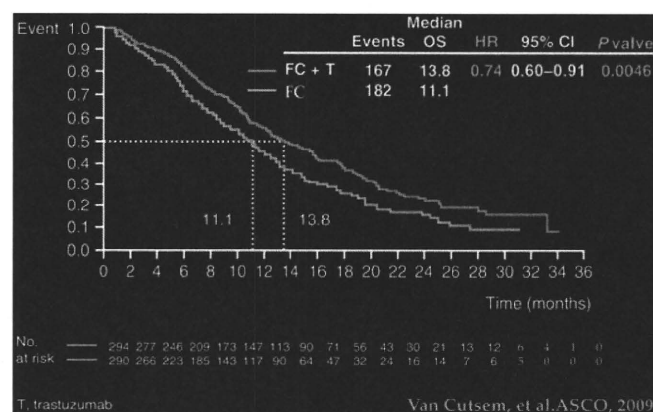| Agents	Study name	Leading country	Region	Enrollment status
Trastuzumab	ToGA	Korea	Asia, EU, SA	Published
Bevacizumab	AVAGAST	Japan	Asia, EU, N/S A	Completed
Cetuximab	EXPAND	Germany	EU, Asia	Recruiting
Lapatinib (first line)	LOGiC	Korea	Asia, EU, N/S A	Recruiting
Lapatinib (second line)	TYTAN	Japan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

Figure 11. Overall survival results in ToGA trial.

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

The ToGA study compared the cytotoxic combination (5-FU or capecitabine + cisplatin) with and without trastuzumab in patients with HER2-positive gastric cancer (Fig. 11) (39). This is a global randomized trial, but more than half of the patients have been recruited from East Asian countries, including Korea, Japan and China. Trastuzumab showed a significant survival advantage compared with the cytotoxic agent combinations, with a hazard ratio of 0.74. From the Asian point of view, the ToGA trial indicates that trastuzumab in combination with FU/platinum will be a new option for HER2-positive gastric cancer. Moreover, the HER2-positive population will become an independent entity, as in breast cancer, although further studies are needed. Regional differences, such as the HER2-positive rate, may be clarified by further analyses. Five of seven ongoing global RCTs for metastatic gastric cancer are led mainly by Japan and Korea. Asian countries are playing a major role in the development of new agents for gastric cancer (Table 3) (40).

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

Conflict of interest statement

None declared.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002:* Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0. Lyon: IARC Press 2004. Available from: http://globocan.iarc.fr
2. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., editors. Cancer Incidence in Five Continents, Vol. IX, IARC Scientific Publications No. 160. Lyon: IARC 2007.
3. Wu MS, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer (Review). *Cancer Epidemiol Biomarkers Prev* 2005;14: 1878–82.
4. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001;345:784–9.
5. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al., China Gastric Cancer Study Group. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
6. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al., Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392–7.
7. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151: 121–8.
8. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009;137: 1641–8.
9. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351–65.
10. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003;95:1784–91.
11. Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in *Helicobacter pylori*-infected patients. *J Clin Oncol* 2010;28:2952–7.
12. Yamazaki H, Oshima A, Murakami R, Endoh S, Ubukata T. A long-term follow-up study of patients with gastric cancer detected by mass screening. *Cancer* 1989;63:613–7.
13. Dan YY, So JB, Yeoh KG. Endoscopic screening for gastric cancer. *Clin Gastroenterol Hepatol* 2006;4:709–16.
14. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer* 2006;9:315–9.
15. Schlemper RJ, Kato Y, Stolte M. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 2001;36:445–56.
16. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–25.
17. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007;10:1–11.
18. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Longterm outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 2006;9:88–92.
19. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009;41:751–7.
20. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. ESD for early gastric cancer: a large-scale feasibility study. *Gut* 2009;58:331–6.
21. Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Surgical treatment of advanced gastric cancer: Japanese perspective. *Dig Surg* 2007;24:101–7.
22. Yoon SS, Yang HK. Lymphadenectomy for gastric adenocarcinoma: should west meet east? *Oncologist* 2009;14:871–82.
23. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995–9.
24. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;79:1522–30.
25. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745–8.
26. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340:908–14.
27. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:309–15.
28. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767–73.
29. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453–62.
30. Cunningham D, Allum WH, Stenning SP, Thompson JN, van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
31. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
32. Enzinger PC, Benedetti JK, Meyerhardt JA, McCoy S, Hundahl SA, Macdonald JS, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg* 2007;245:426–34.
33. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810–20.
34. Fujitani K, Yang HK, Kurokawa Y, Park do J, Tsujinaka T, Park BJ, et al., Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group; Korea Gastric Cancer Association. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. *Jpn J Clin Oncol* 2008;38:504–6.
35. Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III non-inferior trial. *Ann Oncol* 2009;20:666–73.
36. Cunningham D, Starling N, Rao S, Ivelson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Eng J Med* 2008;358:36–46.
37. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
38. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1

with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS Trial. *J Clin Oncol* 2009;27:1547–53.

39. Van Cutsem E, Kang YK, Chung H, Shen L, Sawaki A, Lordick F, et al. Efficacy results from ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer. *J Clin Oncol* 2009;27:18S (Abstract LBA 4509).

40. Ohtsu A. Chemotherapy for metastatic gastric cancer: past present and future. *J Gastroenterol* 2008;43:256–64.

A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study)

T. Yoshikawa [a,*], K. Omura [b], O. Kobayashi [a], A. Nashimoto [c], A. Takabayashi [d], T. Yamada [e], H. Yamaue [f], M. Fujii [g], T. Yamaguchi [h], T. Nakajima [i]

[a] *Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan*
[b] *Department of Surgery, Kanazawa University, 13-1 Takara-machi, Kanazawa, Japan*
[c] *Department of Surgery, Niigata Cancer Center, 2-15-3 Kawagishi-cho, Chuo-Ku, Niigata 951-8566, Japan*
[d] *Department of Surgery, Kitano Hospital, 2-4-20 Ogicho, Kita-Ku, Osaka 530-8480, Japan*
[e] *Department of Surgery, Ishikawa Prefectural Central Hospital, 2-1 Kuratsukihigashi, Kanazawa 920-8530, Japan*
[f] *Department of Surgery, Wakayama University, 811-1 Kimiidera, Wakayama 641-8510, Japan*
[g] *Department of Surgery, Nihon University, 1-8-13 Kandasurugadai, Chiyoda-Ku, Tokyo 101-8309, Japan*
[h] *Department of Gastrointestinal Tract Surgery, Cancer Institute Hospital, 3-10-6 Ariake, Koto-Ku, Tokyo 135-8550, Japan*
[i] *Japan Clinical Cancer Research Organization, 3-10-6 Ariake, Koto-Ku, Tokyo 135-8550, Japan*

Accepted 12 April 2010

Abstract

Aims: Clinically serosa-positive (T3–4) gastric cancer has a poor prognosis. This phase II trial explored the feasibility and safety of preoperative chemotherapy followed by D2 or D3 gastrectomy in this type of gastric cancer.
Methods: Patients with T3–4 gastric cancer received one course of S-1 (80 mg/m^2 daily for 3 weeks) and cisplatin (60 mg/m^2 on day 8) chemotherapy and then underwent D2 or D3 gastrectomy with curative intent. Primary endpoint was toxicities.
Results: Of 50 patients enrolled, 49 were eligible and received the treatment protocol. Chemotherapy-related toxicities were mild; grade 3 neutropenia in 2 patients, anorexia in 3, and nausea in 2, and no grade 4 toxicities. Clinical response was achieved in 13 of 34 evaluable patients. Of the 49 patients, 39 underwent D2 or D3 dissection. There was no surgical mortality. Operative morbidity occurred in 5 of 49 patients, including pancreatic fistula in 1 and abdominal abscess in 2.
Conclusion: This multi-modality treatment seems to be feasible and safe for T3–4 gastric cancer.
© 2010 Published by Elsevier Ltd.

Keywords: Gastric cancer; Chemotherapy; Surgery; Phase II

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe.[1] Complete

resection is essential for cure,[2] and because more than half of T3 and T4 tumors have metastasized to lymph nodes along the major branch arteries or in the para-aortic area, complete resection has involved D2 or D3 dissection in Japan.[3,4] However, despite resection of these tumors with curative intent, prognosis has been limited.[5] To improve the survival of these patients, new treatment strategies must be developed.

Most clinical trials of postoperative adjuvant chemotherapy have failed to prove a survival benefit.[6] However, a large phase III trial recently demonstrated that adjuvant chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M ostat potassium) significantly improved survival after D2 curative

gastrectomy in Japanese patients with T2N+ or T3 disease.[7] Based on this, D2 surgery and postoperative S-1 chemotherapy has been established as a standard treatment in Japan. Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for T3 tumors was not satisfactory.

Preoperative chemotherapy followed by extended surgery has some theoretical benefits when compared with postoperative chemotherapy.[8] If bulky tumors are reduced in size by chemotherapy, complete tumor removal could theoretically be easily achieved by extended surgery. If distant micrometastases are eliminated by chemotherapy, complete resection by extended surgery may improve survival and result in cure in some cases. However, preoperative chemotherapy followed by extended surgery has not been confirmed in phase III trial.

A high response rate and relatively low toxicity are required for preoperative chemotherapy, because target tumors are resectable or marginally resectable and the patients must receive potentially curative surgery after chemotherapy. Combined chemotherapy with S-1 plus cisplatin is an attractive regimen for preoperative chemotherapy for gastric cancer. A previous phase II trial of this regimen in metastatic gastric cancer reported a high response rate of 76% and acceptable toxicities.[9] Recently, a Japanese phase III trial of chemotherapeutic regimens for metastatic gastric cancer (SPIRITS trial) demonstrated that S-1 plus cisplatin led to significantly longer median overall survival than S-1 alone (13 months vs. 11 months).[10] Moreover, in the recent international phase III trial (FLAGS), S-1 plus cisplatin had lower toxicity but achieved equally overall survival compared with 5-FU plus cisplatin (CF) (Ajani JA, et al. presented at the 2009 Gastrointestinal Cancers Symposium). Triplet chemotherapy of CF plus epirubicin (ECF) or CF plus docetaxel (DCF) is effective but more toxic than CF.[11]

However, the influence of preoperative chemotherapy on D2 or D3 surgery has not been fully evaluated, although D2 and D3 gastrectomy are safe procedures in Japan.[12] Unlike D0 or D1 surgery, D2 or D3 gastrectomy involves nodal dissection along the pancreas, which can cause pancreatic fistula or abdominal abscess. These complications can be lethal and might be increased by preoperative chemotherapy. The effect of preoperative chemotherapy on surgical mortality or morbidity with these procedures has not been fully clarified. Recently, preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 dissection was tested in phase II trial to evaluate the efficacy and toxicity in Japan.[13] However, this trial has been terminated due to high treatment-related death during the accrual. A safe and effective regimen before extended surgery has yet to be reported.

The Japan Clinical Cancer Research Organization (JACCRO) therefore, conducted a multi-institutional phase II trial (JACCRO GC-01) to evaluate the feasibility and safety of preoperative chemotherapy with S-1 plus cisplatin followed by curative D2 or D3 gastrectomy for clinically serosa-positive (T3–4) gastric cancer.

Patients and methods

Eligibility criteria

Eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) stage clinically assessed as T3–4, N0–N3 which is classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma,[14] and M0; (3) age 20–75 years; (4) Eastern cooperative oncology group (ECOG) performance status 0–1; (5) no prior therapy; (6) sufficient organ function [white blood cell count (WBC) 4000–12,000 mm^3, platelet count (PLT) >100,000/mm^3, glutamic oxaloacetic transaminase (GOT) <80 IU/l, glutamic pyruvic transaminase (GPT) <80 IU/l, total bilirubin <1.5 mg/dl, alkaline phosphatase (ALP) < two times greater than upper limit of normal, creatinine <1.2 mg/dl, creatinine clearance >60 ml/min, and hemoglobin >8.0 g/dl]; and (7) written informed consent. Clinical diagnosis was based on gastric fiberscopy, upper gastrointestinal series, computed tomography, and ultrasonography. Serosal invasion of the primary tumor was evaluated by computed tomography. Endoscopic ultrasonography or diagnostic laparoscopy was not mandatory, because these remain outside of routine preoperative examinations in Japan. Exclusion criteria were (1) severe co-morbidities; (2) active and acute bleeding from the digestive tract; (3) insufficient oral intake; (4) synchronous or previous malignancy other than carcinoma *in situ*; and (5) contraindications to S-1 or cisplatin. All patients provided informed consent before registration and were registered centrally at the JACCRO Data Center by means of the online Flexible licence assisted data server (FLADS) system. The JACCRO Data Center conducted the data management, central monitoring, and statistical analysis.

Preoperative chemotherapy

On the basis of previous reports S-1 (80 mg/m^2) was given orally every day for 3 weeks and cisplatin (60 mg/m^2) was administered intravenously on day 8 as one course.[9,10] If the patient had a WBC of 2000/mm^3 or lower, neutrophil count of 1000/mm^3 or lower, PLT of 75,000/mm^3 or lower, diarrhea or mucositis of grade 3 or higher, GOT or GPT of grade 2, or serum creatinine of grade 1, chemotherapy was postponed until recovery from these adverse events and the next dose of S-1 was reduced to 70 mg/mm^2. For diarrhea or mucositis of grade 1, chemotherapy was postponed until recovery. In the case of GOT and/or GPT of grade 3 or higher or serum creatinine of grade 2 or higher, chemotherapy was terminated. If the patient had cardiac or neurologic toxicities, chemotherapy was postponed until recovery from these toxic effects and confirmation of their cause. For any other adverse events of grade 2 or higher, chemotherapy was postponed until recovery. If the chemotherapy was postponed but the toxicities had not resolved within 21 days, the chemotherapy was terminated after this period.

Surgery

Tumor resectability was assessed after completion of chemotherapy. Resection criteria were (1) R0 resection was anticipated by D2 or extended D2 gastrectomy; (2) sufficient organ function (WBC >3000/mm^3, neutrophils >1000/mm^3, PLT >100,000/mm^3, GOT <100 IU/l, GPT <100 IU/l, creatinine <1.5 mg/dl); and (3) no active infection. Patients who fulfilled these criteria were treated by D2 or D3 gastrectomy with curative intent between two and four weeks after finishing chemotherapy. The precise procedure of D2 and D3 dissection has been reported previously.[12,15] Combined resections of adjacent organs were permitted when these procedures were indispensable for curative resection.

Treatment defined by the protocol

The treatment protocol was defined as completed when a patient received preoperative chemotherapy and underwent R0 resection by gastrectomy with D2 or D3 dissection. The treatment protocol was stopped when: (1) response was evaluated as progressive disease during chemotherapy; (2) the patient did not meet the criteria for surgery after chemotherapy; (3) the patient underwent surgery after chemotherapy but this took the form of exploratory laparotomy, bypass, or non-R0 resection; (4) the patient refused further participation; or (5) the doctor recommended stopping the protocol. After the treatment protocol was stopped, any treatment was allowed and postoperative adjuvant therapy was not defined.

Endpoints

Primary endpoint was toxicities. Secondary endpoints included response rate and overall survival.

Evaluation

The response rate was evaluated only in patients with measurable lesions; Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used[16] and response to chemotherapy was evaluated by external review committee. Adverse reactions during chemotherapy were evaluated by National Cancer Institute — Common Toxicity Criteria Version 2.0.[17]

Statistical hypothesis

As it is difficult to predict the occurrence of severe adverse events or treatment-related deaths and to calculate sample size, feasibility and safety was evaluated in calculated sample size based on the response rate to be required in this setting. A Simon optimal two-stage design[18] was used to calculate the sample size, assuming an anticipated response rate of 50% and a threshold response rate of 30% with 10% alpha error and 10% beta error. Using this design, if at least 8 objective responses were observed among 22 patients in the first stage, an additional 24 patients would be recruited to the second stage. Taking into account tumors without measurable lesions and patients not fulfilling the eligibility criteria, sample size was determined to be 50. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC). This phase II trial was approved by the JACCRO Protocol Review Committee and the institutional review board of each of the 8 JACCRO institutions involved.

Results

Patients

Between February 2004 and January 2005, 50 patients were enrolled and the study was terminated. During the accrual, unpredicted severe adverse events or treatment-related death was not observed. One of these patients declined to participate, while the other 49 were eligible and received the treatment protocol. Table 1 shows patient demographics and tumor characteristics. Clinically apparent nodal disease was observed in 40 patients.

Preoperative chemotherapy and toxicities

Of all 49 eligible patients, 3 did not receive cisplatin because of S-1-related toxicity. The average proportion of actual dose to proposed dose was 94% (2219.2 mg/ 2348.6 mg) for S-1 and 94% for cisplatin (87.8 mg/

Table 1
Patient demographics and pre-treatment tumor characteristics (all eligible patients, $n = 49$).

Age (median, range)	62, 20–73
Sex (male/female)	36/13
PS (0/1)	46/3
Macroscopic type	
1	4
2	6
3	24
4	14
5	1
Histologic type	
Differentiated	17
Undifferentiated	31
Miscellaneous	1
Depth of tumor invasion	
T3	44
T4	5
Nodal status[a]	
N0	9
N1+, perigastric	17
N2+, along major branch arteries	12
N3+, para-aortic	11

[a] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

92.0 mg). Adverse events during chemotherapy are shown in Table 2. There were no grade 4 and a few grade 3 toxicities.

Clinical response

Clinical response could be evaluated in 34 patients who had enlarged lymph nodes as target lesions as defined by RECIST criteria. There were 13 responders (all showed partial response); 18 patients had stable disease and 3 had progressive disease. Thus, 13 of 34 evaluable patients demonstrated a clinical response (38%) with a 95% confidence interval from 22% to 56%.

Surgery

All of the 49 patients who completed chemotherapy underwent surgery. Surgical findings are shown in Table 3. Three patients underwent exploratory laparotomy due to massive peritoneal dissemination, and 7 underwent palliative D0 or D1 resection due to peritoneal dissemination or extended lymph node metastasis. Curative resection was intended for the remaining 39 patients; D2 was performed in 27 and D3 in 12. Thus, D2 or D3 was performed in 39 of all eligible 49 patients. Consequently, R0 resection was performed in 38 patients, R1 in 1 due to positive peritoneal cytology, and R2 in 7 due to peritoneal dissemination or extended lymph node metastases (Table 3). Thus, the proportion of R0 resections was 78% (38 of all eligible 49 patients), with a 95 per cent confidence interval from 66% to 89%.

Surgical morbidity and mortality

Surgical complications are shown in Table 4. There was no operative mortality. On the other hand, operative morbidity was observed in 5 of the 49 patients including pancreatic fistula in 1 and abdominal abscess in 2. No anastomotic leakage was observed and no patients required re-operation for morbidity.

Table 2
Adverse events during chemotherapy in all eligible patients ($n = 49$).

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	48	0	1	0	0
Neutrophils	38	4	5	2	0
Hemoglobin	40	7	2	0	0
Platelets	48	0	1	0	0
Total bilirubin	48	1	0	0	0
GOT	46	2	1	0	0
GPT	47	1	1	0	0
ALP	46	3	0	0	0
BUN	45	0	4	0	0
Urine creatinine	47	1	1	0	0
Urine protein	47	1	1	0	0
Anorexia	33	8	5	3	0
Nausea	37	6	4	2	0
Vomiting	42	3	4	0	0
Diarrhea	45	3	1	0	0
Pigmentation	45	3	1	0	0

Table 3
Surgical findings in all operated patients ($n = 49$).

Type of surgery	
Proximal gastrectomy	1
Distal gastrectomy	18
Total gastrectomy	27
Exploratory laparotomy	3
Dissection ($n = 46$)[a]	
D0	4
D1	3
D2	27
D3	12
Combined resection	
Spleen	13
Pancreas	4
Gall bladder	8
Spleen + pancreas	2
None	22
Operation time (minutes)	
Median, range	232, 25–590
Blood loss (ml)	
Median, range	342, 0–2760

[a] Three missing cases were exploratory laparotomy.

Pathological response

Details of pathological data are shown in Table 5. A total of 18 patients were diagnosed as pathological T1 or T2 disease. The pathological response rate in resected patients, defined by the degeneration/necrosis area $\geq 1/3$, was 39%. On the other hand, nodal status, which was classified by 2nd English Edition of Japanese Classification of Gastric Carcinoma, was evaluated in 39 patients who underwent D2 or D3 gastrectomy. Pathological N0 was observed in 8 patients.

Overall survival

Survival time was estimated in all 49 patients who were eligible. Median follow-up period was 31 months from 27 to 38 months. The overall survival curve is shown in Fig. 1. The three-year survival rate was 43.0% with a 95% confidence interval from 35.6% to 50.3%.

Discussion

This multi-institutional phase II prospective trial demonstrated neither treatment-related death nor severe adverse

Table 4
Surgical complications in all operated patients ($n = 49$).

	Number of patients	%
Anastomotic leakage	0	0
Pancreatic fistula	1	2
Abdominal abscess	2	4
Pneumonia	0	0
Ileus	0	0
Wound infection	1	2
Renal dysfunction	1	2

Table 5
Pathological results.

Depth of tumor invasion ($n = 46^a$)			
T1		3	
T2		15	
T3		19	
T4		9	

Nodal status[b] ($n = 39^c$)			
	D2	D3	D2/D3
N0	7	1	8
N1	12	3	15
N2	6	4	10
N3	2[d]	4	6

[a] Three missing cases were exploratory laparotomy.

[b] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

[c] Ten missing cases included exploratory laparotomy in 3, palliative D0 in 4 and palliative D1 gastrectomy in 3.

[d] Two cases were determined by a few lymph nodes of N3 dissected in addition to D2 dissection.

events by preoperative chemotherapy of S-1 plus cisplatin followed by extended surgery, suggesting that this multimodality treatment was safe and feasible.

Surgical mortality

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group
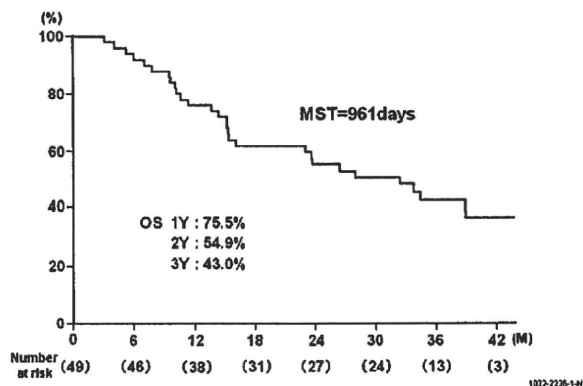

Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

Pancreas-related surgical morbidity

Pancreatic fistula is the major specific complication after D2 or greater extended surgery. In this study, pancreatic fistula was observed in 1 patient and abdominal abscess in 2 patients. As no apparent anastomotic leak was found in the latter 2 patients, the abdominal abscess might have been caused by pancreatic fistula. Thus, pancreatic fistula might have been a complication in a maximum of 3 of 49 patients in the present study, a proportion almost equivalent to that found in the JCOG 9501 phase III trial.[12] In that trial, tumors were diagnosed as T2–T4, N0–N2, and P0 by surgical findings.[12] In the present study, on the other hand, all tumors were clinically diagnosed as T3–T4. Moreover, 11 of the present patients had clinically apparent N3 disease. Hence, although the tumors were more advanced in this study, the rate of pancreatic fistula was not increased by preoperative chemotherapy with S-1 plus cisplatin. On the other hand, pancreatic fistula was observed in 12.2% in JCOG 0001 trial consisting of CPT-11 plus cisplatin followed by D3 dissection.[13] Toxic regimen could increase the rate of pancreatic fistula.

Overall surgical morbidity

In the present study, overall surgical morbidity was 5 of 49 which was slightly lower than the 20.9% to 28.1% observed in the JCOG 9501 trial.[12] In particular, anastomotic leakage and re-operation were not observed in this study, while rates of these events were 1.9% and 2.7%, respectively, in the JCOG 9501 study.[12] Thus, operative morbidity did not increase with the present preoperative chemotherapy regimen. In the MAGIC trial, morbidity was similar in both arms of the trial; 45.3% in the surgery alone group and 45.7% in chemotherapy group.[19] Because our preoperative chemotherapy was performed only short term, operative morbidity appears not to increase even after D2 or D3 surgery.

Chemotherapy-related toxicities

Chemotherapy-related toxicities were relatively mild in this study. There were no grade 4 toxicities and only a few grade 3 toxicities including neutropenia, anorexia, and nausea. In the SPIRITS trial,[10] grade 3/4 bone marrow suppression was more frequently observed when compared with the present trial. Chemotherapy was limited to one course in this study while it continued until disease

progression in the SPIRITS trial, which would explain the difference in the toxic profile between the two studies. Our results may also suggest that mild toxicities led to high compliance with this chemotherapy regimen and low morbidity and mortality of D2 or D3 resection.

Response to the chemotherapy

The present study achieved a relatively high response rate of 38%, which was almost the same as observed in the pathological response of the primary tumor. Previous trials in metastatic gastric cancer have demonstrated that response rate was 76% in a phase II trial[9] and 54% in the SPIRITS phase III trial.[10] The response rate in this study was slightly lower, which may be attributable to only one course of chemotherapy being administered in the present study. In the MAGIC phase III trial, three courses of ECF chemotherapy were performed preoperatively.[19] Considering the low toxicities of one course of S-1 plus cisplatin and the low mortality and morbidity of subsequent extended surgery, an additional two or three courses of this chemotherapy should be evaluated in another phase II study.

Survival

In the present study, all patients were clinically diagnosed with T3 or T4 disease before entry and overall 3-year survival rate was 43.0%. It has been reported that clinical diagnosis of T3–T4 was accurate in 74.4% in clinical T3 tumors and 87.0% in clinical T4 tumors.[5] M0 was evaluated by computed tomography and diagnostic laparoscopy was not mandatory in this study, therefore, peritoneal metastases may not be excluded in this series.[22] Retrospective analyses of Cancer Institute Hospital of Japan have reported 5-year survival rates of 25.3% and 1.8% in pathological T3 and T4 with any N, respectively.[5] In this series of patients, the 3-year survival rate was 43% despite that R0 resection was only performed in 77.6%. Although it may be difficult to compare these survival rates, our results appear to be worthy of further investigation using the same strategy.

Conclusion

In conclusion, preoperative chemotherapy with one course of S-1 plus cisplatin followed by gastrectomy with D2 or D3 dissection seems to be feasible and safe for clinically serosa-positive (T3–4) gastric cancer.

Acknowledgment

Conflict of interest

No authors have any conflict of interest.

References

1. Torrado J, Santiseban A, Ruiz-Ederra J. Genetic susceptibility to gastric cancer. *Hepato-Gastroenterology* 2001;**48**:1544–7.
2. Sasako M. Principles of surgical treatment for curable gastric cancer. *J Clin Oncol* 2003;**21**:274–5.
3. Maeta M, Yamashiro H, Saito H, et al. A prospective pilot study of extended (D3) and superextended para-aortic lymphadenectomy (D4) in patients with T3 or T4 gastric cancer managed by total gastrectomy. *Surgery* 1999;**125**:325–31.
4. Díaz de Liaño A, Yarnoz C, Aguilar R, et al. Rationale for gastrectomy with D2 lymphadenectomy in the treatment of gastric cancer. *Gastric Cancer* 2008;**11**:96–102.
5. Nakajima T, Yamaguchi T. *Gastric cancer database 1946–2004 in Cancer Institute Hospital.* Tokyo: Kanehara & Co; 2006.
6. Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. *J Clin Oncol* 2006;**24**:2188–96.
7. 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.
8. Ott K, Lordick F, Hermann K, et al. The new credo: induction chemotherapy in locally advanced gastric cancer: consequences for surgical strategies. *Gastric Cancer* 2008;**11**:1–9.
9. Koizumi W, Tanabe S, Saigenji K, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003;**89**:2207–12.
10. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;**9**:215–21.
11. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;**24**:4991–7.
12. Sano T, Sasako M, Yamamoto S, 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.
13. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009;**96**:1015–22.
14. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 2nd English ed. *Gastric Cancer* 1998;**1**:10–24
15. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;**359**:453–62.
16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–14.
17. National Cancer Institute. *Common Toxicity Criteria version 2.0 (CTC)* 1999;. Available from: http://ctep.cancer.gov/reporting/CTC-3.html.
18. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;**10**:1–10.
19. 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.
20. Baba H, Yamamoto M, Endo K, et al. Clinical efficacy of S-1 combined with cisplatin for advanced gastric cancer. *Gastric Cancer* 2003;**6**:45–9.
21. Satoh S, Hasegawa S, Ozaki N, et al. Retrospective analysis of 45 consecutive patients with advanced gastric cancer treated with neoadjuvant chemotherapy using S-1/CDDP combination. *Gastric Cancer* 2006;**9**:129–35.
22. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. *Gastric Cancer* 2007;**10**:29–34.

Functional outcomes after extended surgery for gastric cancer

Y. Kurokawa[1], M. Sasako[2], T. Sano[3], T. Shibata[8], S. Ito[4], A. Nashimoto[5], A. Kurita[6] and T. Kinoshita[7], for the Japan Clinical Oncology Group

Departments of Surgery, [1]Osaka National Hospital, Osaka, [2]Hyogo College of Medicine, Nishinomiya, [3]Cancer Institute Ariake Hospital, Tokyo, [4]Aichi Cancer Centre, Nagoya, [5]Niigata Cancer Centre Hospital, Niigata, [6]National Shikoku Cancer Centre, Matsuyama, and [7]National Cancer Centre Hospital East, Kashiwa, and [8]Japan Clinical Oncology Group Data Centre, Centre for Cancer Control and Information Services, National Cancer Centre, Tokyo, Japan
Correspondence to: Dr Y. Kurokawa, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2-E2, Yamadaoka, Suita, Osaka 565-0871, Japan (e-mail: ykurokawa@gesurg.med.osaka-u.ac.jp)

Background: Extended gastrectomy with para-aortic nodal dissection (PAND) or thorough dissection of mediastinal nodes using a left thoracoabdominal (LTA) approach is an alternative to D2 lymphadenectomy, with variable postoperative results.
Methods: Two randomized controlled trials have been conducted to compare D2 lymphadenectomy alone (263 patients) *versus* D2 lymphadenectomy plus PAND (260), and the abdominal–transhiatal (TH) approach (82) *versus* the LTA approach (85), in patients with gastric cancer. Prospectively registered secondary endpoints bodyweight, symptom scores and respiratory function were evaluated in the present study.
Results: Bodyweight was comparable after D2 and D2 plus PAND, but higher after TH than after LTA procedures at 1 and 3 years. At 1- and 3-year follow-up symptom scores were comparable between D2 and D2 plus PAND. A LTA approach resulted in significantly worse scores than a TH approach in terms of meal volume, return to work, incisional pain and dyspnoea up to 1 year. The decrease in vital capacity was significantly greater after LTA than TH procedures up to 6 months.
Conclusion: Bodyweight and postoperative symptoms were not affected by adding PAND to a D2 procedure. A LTA approach aggravated weight loss, symptoms and respiratory functions compared with a TH approach. Registration numbers: NCT00149279, NCT00149266 (http://www.clinicaltrials.gov).

Introduction

Radical gastrectomy with D2 lymphadenectomy is the standard treatment for patients with curable gastric cancer in east Asia[1]. To improve survival further, more extensive surgery has been attempted in specialized centres. Two multicentre randomized controlled trials have evaluated extended gastric surgery. In the Japan Clinical Oncology Group (JCOG) 9501 trial, D2 plus para-aortic nodal dissection (PAND) was compared with D2 lymphadenectomy for tumour category (T) 2b to T4 potentially curable gastric cancer[2,3]. In the JCOG9502 trial, a left thoracoabdominal (LTA) approach accompanied by thorough lower mediastinal lymphadenectomy was compared with an abdominal–transhiatal (TH) approach for proximal gastric cancer invading the oesophagus[4].

Contrary to expectations, there was no survival benefit from these extended procedures. D2 plus PAND or a LTA approach resulted in a longer duration of operation than D2 or a TH procedure. The morbidity was also worse after these extended procedures than after the standard operations. This has led to the conclusion that they should not be employed as prophylactic lymphadenectomy for curable gastric cancer[2,4]. Apart from survival and short-term morbidity, postoperative evaluation of symptom, bodyweight and respiratory function outcomes after extended surgery permits proper decision-making regarding surgical treatment for gastric cancer. In the present study, changes in the secondary endpoints bodyweight, various symptom-related scores and respiratory function in these two trials were assessed prospectively.

Methods

Japan Clinical Oncology Group 9501 trial

Patients younger than 75 years of age with histologically proven gastric adenocarcinoma considered potentially curable were enrolled in the JCOG9501 trial[2,3]. Additional eligibility criteria derived from intraoperative findings were T2b or higher, no gross metastases to para-aortic nodes, and negative cytology by peritoneal lavage. The surgeon confirmed the eligibility criteria during surgery and telephoned the JCOG Data Centre to register patients. Patients were then randomized to either standard D2 or extended D2 plus PAND using the minimization method according to clinical T category, Borrmann macroscopic type and institution. The surgeon then performed the allocated operation as described in the protocol.

The surgical procedures used in each group have been described previously[2,3]. In short, in the D2 group gastrectomy with D2 lymphadenectomy was carried out according to the 12th edition of the Japanese Classification of Gastric Carcinoma[5]. In the D2 plus PAND group the para-aortic lymph nodes were also dissected. The spleen was removed in patients having total or proximal subtotal gastrectomy. Pancreatectomy was confined to patients in whom the pancreas was involved by tumour. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149279).

Japan Clinical Oncology Group 9502 trial

The eligibility criteria for the JCOG9502 trial were: histologically proven adenocarcinoma of the gastric cardia or body with oesophageal invasion of 3 cm or less, clinically T2–4, patient no more than 75 years old, no distant metastasis, and no bulky node category (N) 3 or N4 metastasis[3]. Patients were randomized to either standard TH or extended LTA treatment using the minimization method according to clinical T stage, Borrmann macroscopic type and institution.

The surgical procedures used in each group have been described previously[4]. In short, a total gastrectomy with D2 and additional dissection of the left upper para-aortic nodes was performed in the TH group. The lower mediastinum was accessed through the oesophageal hiatus extended by a longitudinal incision of the median part of the diaphragm. In the LTA group a long oblique incision over the seventh intercostal space was extended into the right abdomen. In the abdominal cavity, the same procedure as that performed in the TH group was carried out and thorough mediastinal lymph node dissection below the inferior pulmonary vein was performed. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149266).

Subjective symptom-related scores

The primary endpoint of these trials was overall survival. Postoperative changes in bodyweight and symptoms (JCOG 9501 and 9502) and also in respiratory function (JCOG9502 only) were assessed prospectively as secondary endpoints. Bodyweight was measured before surgery, and at 6 months, 1 year and 3 years after operation.

Surgeons evaluated patient symptoms during outpatient clinic visits at 6 months, 1 year and 3 years after surgery, without being blinded to the procedure performed. Symptoms included appetite, meal volume, bowel habit, sleep and occurrence of pneumonia (JCOG 9501 and 9502), and also incisional pain and dyspnoea for JCOG9502. As a surrogate for total physical strength, the proportion of patients who were able regularly to leave their homes to perform daily activities and those who returned to their former work were evaluated. All items were dichotomized, and scoring was performed as shown in *Table 1*.

Respiratory function, including vital capacity, forced expiratory volume in 1 s (FEV1) and arterial partial pressure of oxygen (PaO_2) in room air, were also measured before, and at 1 and 6 months after surgery.

Statistical analysis

The group means of bodyweight, vital capacity, FEV1 and PaO_2 were determined using a mixed-effect model with pretreatment value, treatment arms, time and treatment–time interaction as co-variables. Items related to symptoms and respiratory function were dichotomized

Table 1 Nine symptom items evaluated in this study

	Score 0	Score 1
Appetite	Poor	Good
Meal volume	$< \frac{1}{2}$ preoperative amount	$\geq \frac{1}{2}$ preoperative amount
Bowel habit	Irregular, diarrhoea	Daily, normal
Sleep	Disturbed	Good
Leaving home	Seldom	Regularly
Return to work	No	Yes
Pneumonia	Experienced	Never
Incisional pain*	Always, often	Seldom, none
Dyspnoea*	Yes	No

*These parameters were evaluated only in the Japan Clinical Oncology Group 9502 trial.

and these group means were evaluated by marginal models fit via generalized estimating equations (GEEs), with treatment arms, time and treatment–time interaction as co-variables. All group means were compared at each time point between two groups. According to these models, point estimates with least-squares means, their confidence intervals and P value were calculated and compared at each time point between two groups. GEE is used to take into account the within-patient correlation that is inevitable when outcomes are measured repeatedly from the same patients[6].

Measurements were missing for those who were still in hospital as a result of major complications and those who developed recurrence, and these data points were excluded from the analysis. Because of the exploratory nature of between-group comparisons, the test results are reported with two-sided P values without multiplicity adjustment of type I error.

All statistical analyses were carried out with SAS® software release 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

In the JCOG9501 trial, 523 patients were assigned randomly to either the D2 group (263 patients) or the D2 plus PAND group (260) in 24 Japanese hospitals between July 1995 and April 2001 (*Fig. S1,* supporting information). Patient characteristics have been published previously[3]. Total gastrectomy was performed in 102 patients (38·8 per cent) in the D2 group and 97 (37·3 per cent) in the D2 plus PAND group. The most common method of reconstruction was the Roux-en-Y procedure in both groups (D2, 59·7 per cent; D2 plus PAND, 60·8 per cent). Splenectomy was performed in 98 (37·3 per cent) and 93 (35·8 per cent) patients in the D2 and D2 plus PAND groups respectively; only nine (3·4 per cent) and 12 (4·6 per cent) patients respectively underwent distal pancreatectomy.

In the JCOG9502 trial, 167 patients were randomly assigned to either the TH (82 patients) or LTA (85) approach in 27 Japanese hospitals between July 1995 and December 2003 (*Fig. S1,* supporting information). Details of patient and tumour characteristics have already been published[4]. Most patients in both TH and LTA groups underwent total gastrectomy with splenectomy. Distal pancreatectomy was performed in 22 patients (27 per cent) in the TH group and 13 (15 per cent) in the LTA group.

Table 2 Postoperative change in bodyweight between groups in Japan Clinical Oncology Group 9501 and 9502 trials

	Group	No. of patients	Bodyweight (kg)*	P
JCOG9501				
Before operation	D2	263	57·5 (56·3, 58·7)	—
	D2 + PAND	259	56·9 (55·7, 58·2)	
After 6 months	D2	255	51·1 (50·6, 51·6)	0·030†
	D2 + PAND	252	50·3 (49·8, 50·8)	
After 1 year	D2	242	51·1 (50·5, 51·7)	0·241†
	D2 + PAND	233	50·6 (49·9, 51·2)	
After 3 years	D2	192	51·1 (50·4, 51·8)	0·381†
	D2 + PAND	190	50·7 (50·0, 51·4)	
JCOG9502				
Before operation	TH	82	58·5 (56·4, 60·5)	—
	LTA	82	57·6 (55·6, 59·7)	
After 6 months	TH	75	49·7 (48·7, 50·6)	0·115‡
	LTA	71	48·5 (47·5, 49·6)	
After 1 year	TH	68	50·0 (49·0, 51·0)	0·031‡
	LTA	56	48·2 (47·0, 49·5)	
After 3 years	TH	47	50·7 (49·7, 51·7)	0·046‡
	LTA	40	49·0 (47·6, 50·3)	

*Values are mean (95 per cent confidence interval), crude mean for preoperative values and least-squares mean for the others. JCOG, Japan Clinical Oncology Group; PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal. †*Versus* D2 + PAND, ‡*versus* LTA (mixed-effect model).

Table 3 Postoperative change in respiratory function between abdominal–transhiatal and left thoracoabdominal groups

	Group	No. of patients	Mean	P*
Vital capacity (ml)				
Before operation	TH	82	3573 (3416, 3731)	—
	LTA	82	3421 (3225, 3617)	
After 1 month	TH	80	2944 (2855, 3034)	< 0·001
	LTA	74	2427 (2327, 2528)	
After 6 months	TH	73	3193 (3089, 3297)	< 0·001
	LTA	68	2658 (2552, 2764)	
FEV1 (%)				
Before operation	TH	82	80·2 (78·3, 82·1)	—
	LTA	82	80·4 (78·3, 82·5)	
After 1 month	TH	80	84·4 (82·7, 86·2)	0·416
	LTA	74	83·3 (81·1, 85·4)	
After 6 months	TH	73	84·7 (82·6, 86·7)	0·985
	LTA	68	84·7 (81·8, 87·6)	
Pao_2 in room air (mmHg)				
Before operation	TH	80	86·6 (84·5, 88·8)	—
	LTA	81	87·1 (85·1, 89·1)	
After 1 month	TH	72	87·6 (85·5, 89·8)	0·004
	LTA	69	82·8 (80·3, 85·2)	
After 6 months	TH	73	90·3 (87·9, 92·8)	0·057
	LTA	68	87·0 (84·7, 89·4)	

Values in parentheses are 95 per cent confidence intervals. TH, abdominal–transhiatal; LTA, left thoracoabdominal; FEV1, forced expiratory volume in 1 s; Pao_2, arterial partial pressure of oxygen. *Versus* LTA (mixed-effect model).
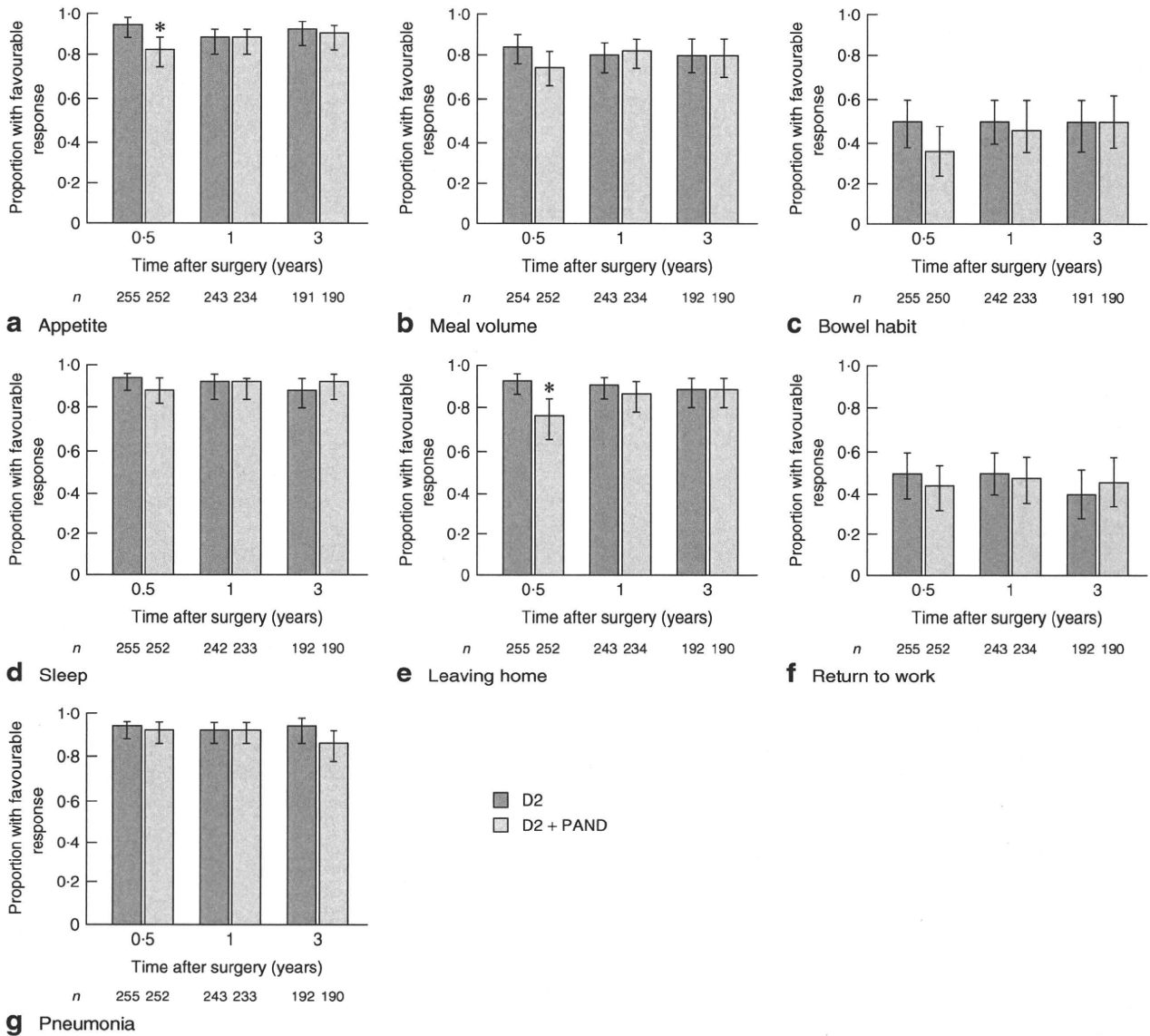
Fig. 1 Comparison of proportion of patients with a favourable response regarding seven symptoms between D2 and D2 + para-aortic nodal dissection (PAND) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work and **g** pneumonia. Group means are shown with 95 per cent confidence intervals. $*P < 0.050$ *versus* D2 (generalized estimating equations model)

Bodyweight

In the JCOG9501 trial, the decrease in mean bodyweight at 6 months was 6·4 kg in the D2 group and 6·6 kg in the D2 plus PAND group (*Table 2*). Postoperative bodyweight remained unchanged thereafter in both groups. Bodyweights were comparable between groups at 1 and 3 years' follow-up.

In the JCOG9502 trial, the decrease in mean bodyweight was 8·8 kg in the TH group and 9·1 kg in the LTA group at

6 months after surgery (*Table 2*). At 1 and 3 years' follow-up mean bodyweight was higher after a TH than a LTA procedure ($P = 0.031$ and $P = 0.046$ respectively).

Postoperative symptoms

Symptom scores after surgery are shown in *Figs 1* and *2*. In the JCOG9501 trial, appetite and the proportion of patients able to leave their home almost every day were significantly higher in the D2 group than in the D2
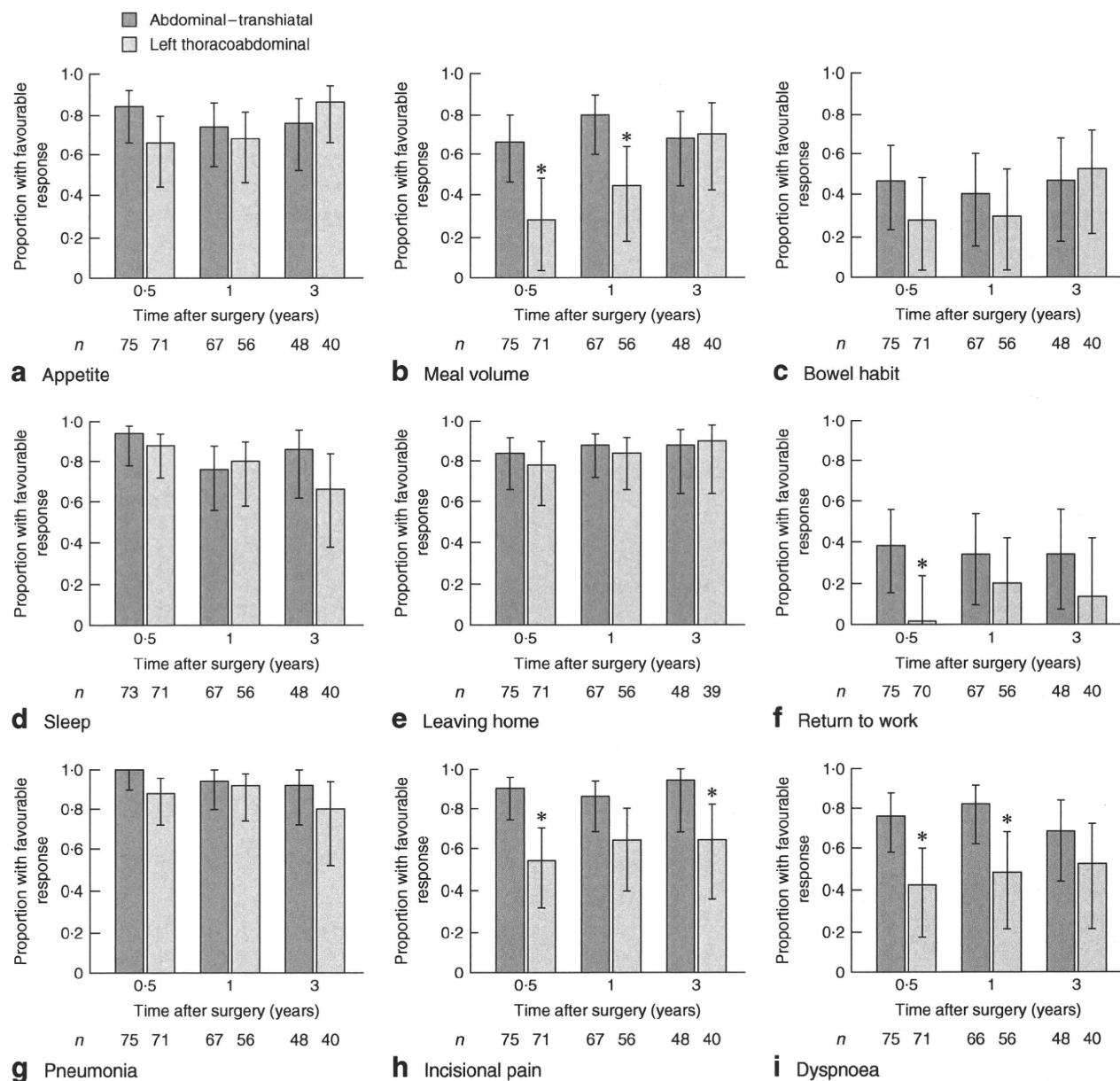
Fig. 2 Comparison of proportion of patients with a favourable response regarding nine symptoms between abdominal–transhiatal (TH) and left thoracoabdominal (LTA) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work, **g** pneumonia, **h** incisional pain and **i** dyspnoea. Group means are shown with 95 per cent confidence intervals. *$P < 0.050$ versus TH (generalized estimating equations model)

plus PAND group at 6 months. At 1- and 3-year follow-up symptom scores were comparable between the two groups.

In the JCOG9502 trial, meal volume and respiratory status (dyspnoea) were better in the TH group than in the LTA group up to 1 year after surgery. The proportion of patients with incisional pain was significantly higher in

the LTA group than in the TH group until the end of follow-up at 3 years.

Respiratory function in Japan Clinical Oncology Group 9502 trial

The LTA group showed a significantly greater decrease in vital capacity than the TH group at 1 and 6 months after

surgery (*Table 3*). There was no deterioration in FEV1 after surgery in either group. PaO_2 in the TH group did not change in the 6 months after surgery, whereas there was a transient decrease in the LTA group.

Discussion

The first randomized controlled trial compared two types of lymphadenectomy within the same surgical approach for gastric cancer, whereas the second trial compared two completely different surgical approaches, namely with and without thoracotomy. In the present study, secondary outcomes of patients without recurrence after gastrectomy were evaluated. Bodyweight was comparable after D2 and D2 plus PAND, whereas the difference in bodyweight between the TH and the LTA groups widened gradually owing to recovery in the TH group. This means that bodyweight change after gastrectomy is more dependent on surgical approach than on the extent of lymphadenectomy. Some of the clinical symptoms were particularly negatively affected by a LTA compared with a TH approach, whereas D2 and D2 plus PAND had comparable scores. The decrease in vital capacity was significantly greater after a LTA than a TH procedure.

Clinical symptoms in the D2 plus PAND group were limited to a short time after operation, and mostly related to changes in bowel habit. This may be due either to autonomic nerve damage or to lymphoedema of the jejunum caused by PAND. However, limited autonomic nerve dissection in PAND may not cause long-term impairment of intestinal function. A small-scale randomized controlled trial of PAND in patients with pancreatic cancer showed that dissection of such nodes frequently caused diarrhoea for up to 4 months after surgery[7]. Although changes in bowel habit may be the biggest disadvantage of PAND, these negative effects were limited to the early postoperative period and seemed to be acceptable clinically. Wu *et al.*[8] compared postoperative symptoms between D1 alone and D2 plus retropancreatic lymph node dissection in a single-institution randomized controlled trial[8]. They reported no significant difference in symptoms between the two groups and concluded that postoperative changes in symptoms were related largely to the scope of gastric resection, disease status and combined resection of the pancreas or spleen rather than the extent of lymph node dissection.

Pain and dyspnoea are well known sequelae of intercostal thoracotomy[9,10]. The negative impact of the thoracotomy procedure on symptoms within the first year agreed with the results of previous studies[11,12]. The difference in meal volume might arise from the location of the anastomosis, in the open thoracic cavity in LTA procedures *versus* the mediastinum in TH operations.

Although quality of life and symptoms are distinct entities, symptoms usually affect patients' quality of life quite strongly. Quality of life is usually assessed by questionnaire and is evaluated by the patients themselves to minimize information bias[13,14]. However, the Japanese versions of validated questionnaires such as the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy – General (FACT-G) were not available when these randomized controlled trials were conducted[14,15]. In the present study, the Gastric Cancer Surgical Study Group/JCOG Symptom Questionnaire, which consisted of only seven or nine queries, was used, because the more complicated the survey, the lower the compliance would have been. Moreover, this questionnaire evaluating patient-centred outcome such as symptom scores was completed by the doctor not the patient, which might have introduced observer bias.

The decrease in bodyweight and worsening of postoperative symptom scores following PAND was limited compared with D2 without PAND. Therefore, D2 plus PAND might be one option when R0 resection is impossible without dissection of such nodes. The LTA approach worsened both symptoms and respiratory function to a greater extent than the TH approach. Surgeons are advised to avoid the LTA approach based not only on previously published survival-related evidence but also on other parameters such as those evaluated in this study.

Acknowledgements

References

1 Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Modern surgery for gastric cancer – Japanese perspective. *Scand J Surg* 2006; **95**: 232–235.

2 Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A *et al*. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; **359**: 453–462.

3 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**: 2767–2773.

4 Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T *et al*. Left thoracoabdominal approach *versus* abdominal–transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 644–651.

5 Japanese Research Society for Gastric Cancer. *Japanese Classification of Gastric Carcinoma* (1st English edn). Kanehara: Tokyo, 1995.

6 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; **42**: 121–130.

7 Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR *et al*. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery* 2005; **138**: 618–628.

8 Wu CW, Chiou JM, Ko FS, Lo SS, Chen JH, Lui WY *et al*. Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial. *Br J Cancer* 2008; **98**: 54–59.

9 d'Amours RH, Riegler FX, Little AG. Pathogenesis and management of persistent postthoracotomy pain. *Chest Surg Clin N Am* 1998; **8**: 703–722.

10 Lewis RJ, Caccavale RJ, Bocage JP, Widmann MD. Video-assisted thoracic surgical non-rib spreading simultaneously stapled lobectomy: a more patient-friendly oncologic resection. *Chest* 1999; **116**: 1119–1124.

11 Barbour AP, Lagergren P, Hughes R, Alderson D, Barham CP, Blazeby JM. Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. *Br J Surg* 2008; **95**: 80–84.

12 de Boer AG, van Lanschot JJ, van Sandick JW, Hulscher JB, Stalmeier PF, de Haes JC *et al*. Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. *J Clin Oncol* 2004; **22**: 4202–4208.

13 Wilson KA, Dowling AJ, Abdolell M, Tannock IF. Perception of quality of life by patients, partners and treating physicians. *Qual Life Res* 2000; **9**: 1041–1052.

14 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–376.

15 Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A *et al*. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; **11**: 570–579.

Supporting information

Additional supporting information may be found in the online version of this article.

Fig. S1 CONSORT diagrams for **a** Japan Clinical Oncology Group (JCOG) 9501 and **b** JCOG9502 trials. PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal (Word file)

Please note: John Wiley & Sons Ltd is not responsible for the functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.