type gastric carcinomas. Cancer Res. *54*, 3845–3852.

Bonenkamp, J.J., Hermans, J., Sasako, M., and van de Velde, C.J.H., for the Dutch Gastric Cancer Group. (1999). Extended lymph-node dissection for gastric cancer. N. Engl. J. Med. *340*, 908–914.

Cuschieri, A., Weeden, S., Fielding, J., Bancewicz, J., Craven, J., Joypaul, V., Sydes, M., and Fayers, P. (1999). Br. J. Cancer *79*, 1522–1530.

Ding, Y., Le, X.P., Zhang, Q.X., and Du, P. (2003). Methylation and mutation analysis of p16 gene in gastric cancer. World J. Gastroenterol. *9*, 423–426.

El-Omar, E.M., Carrington, M., Chow, W.H., McColl, K.E., Bream, J.H., Young, H.A., Herrera, J., Lissowska, J., Yuan, C.C., Rothman, N., et al. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature *404*, 398–402.

Fang, D.C., Wang, R.Q., Yang, S.M., Yang, J.M., Liu, H.F., Peng, G.Y., Xiao, T.L., and Luo, Y.H. (2003). Mutation and methylation of hMLH1 in gastric carcinomas with microsatellite instability. World J. Gastroenterol. *9*, 655–659.

Fenoglio-Preiser, C., Carneiro, F., Correa, P., Guilford, P., Lambert, R., Megraud, F., Munoz, N., Powell, S., Rugge, M., Sasako, M., et al. (1997). Gastric carcinoma. In Tumours of the digestive system, S. Hamilton and L. Aaltonen, eds. (Lyon, France: IARC Press), pp. 39–52.

Ferlay, J., Bray, F., Pisani, P., and Parkin, D.M. (2001). GLOBOCAN 2000: Cancer Incidence, Mortality, and Prevalence Worldwide, Version 1.0, Vol. *5* (Lyon: IARC Press).

Fertitta, A.M., Comin, U., Terruzzi, V., Minoli, G., Zambelli, A., Cannatelli, G., Bodini, P., Bertoli, G., Negri, R., Brunati, S., et al. (1993). Clinical significance of gastric dysplasia: a multicenter follow-up study. Gastrointestinal Endoscopic Pathology Study Group. Endoscopy *25*, 265–268.

Gotoda, T., Yanagisawa, A., Sasako, M., Ono, H., Nakanishi, Y., Shimoda, T., and Kato, Y. (2000). Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer *3*, 219–225.

Guilford, P., Hopkins, J., Harraway, J., McLeod, M., McLeod, N., Harawira, P., Taite, H., Scoular, R., Miller, A., and Reeve, A.E. (1998). E-cadherin germline mutations in familial gastric cancer. Nature *392*, 402–405.

Gut, M.O., Parkkila, S., Vernerova, Z., Rohde, E., Zavada, J., Hocker, M., Pastorek, J., Karttunen, T., Gibadulinova, A., Zavadova, Z., et al. (2002). Gastric hyperplasia in mice with targeted disruption of the carbonic anhydrase gene Car9. Gastroenterol. *123*, 1889–1903.

Hasegawa, S., Furukawa, Y., Li, M., Satoh, S., Kato, T., Watanabe, T., Katagiri, T., Tsunoda, T., Yamaoka, Y., and Nakamura, Y. (2002). Genome-wide analysis of gene expression in intestinal-type gastric cancers using a complementary DNA microarray representing 23,040 genes. Cancer Res. *62*, 7012–7017.

Judd, L.M., Alderman, B.M., Howlett, M., Shulkes, A., Dow, C., Moverley, J., Grail, D., Jenkins, B.J., Ernst, M., and Giraud, A.S. (2004). Gastric cancer development in mice lacking the SHP2 binding site on the IL-6 family co-receptor gp130. Gastroenterol. *126*, 196–207.

Kaneda, A., Kaminishi, M., Yanagihara, K., Sugimura, T., and Ushijima, T. (2002). Identification of silencing of nine genes in human gastric cancers. Cancer Res. *62*, 6645–6650.

Kang, G.H., Lee, S., Kim, W.H., Lee, H.W., Kim, J.C., Rhyu, M.G., and Ro, J.Y. (2002). Epstein-barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. Am. J. Pathol. *160*, 787–794.

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

Lee, J.H., Abraham, S.C., Kim, H.S., Nam, J.H., Choi, C., Lee, M.C., Park, C.S., Juhng, S.W., Rashid, A., Hamilton, S.R., and Wu, T.T. (2002). Inverse relationship between APC gene mutation in gastric adenomas and development of adenocarcinoma. Am. J. Pathol. *161*, 611–618.

Lefebvre, O., Chenard, M.P., Masson, R., Linares, J., Dierich, A., LeMeur, M., Wendling, C., Tomasetto, C., Chambon, P., and Rio, M.C. (1996). Gastric mucosa abnormalities and tumorigenesis in mice lacking the pS2 trefoil protein. Science *274*, 259–262.

Li, Q.L., Ito, K., Sakakura, C., Fukamachi, H., Inoue, K., Chi, X.Z., Lee, K.Y., Nomura, S., Lee, C.W., Han, S.B., et al. (2002). Causal relationship between the loss of RUNX3 expression and gastric cancer. Cell *109*, 113–124.

MacDonald, J.S., Smalley, S.R., Benedetti, J., Hundahl, S.A., Estes, N.C., Stemmermann, G.N., Haller, D.G., Ajani, J.A., Gunderson, L.L., Jessup, J.M., and Martenson, J.A. (2001). Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N. Engl. J. Med. *345*, 725–730.

Machado, J.C., Oliveira, C., Carvalho, R., Soares, P., Berx, G., Caldas, C., Seruca, R., Carneiro, F., and Sobrinho-Simoes, M. (2001). E-cadherin gene (CDH1) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. Oncogene *20*, 1525–1528.

Maesawa, C., Tamura, G., Suzuki, Y., Ogasawara, S., Sakata, K., Kashiwaba, M., and Satodate, R. (1995). The sequential accumulation of genetic alterations characteristic of the colorectal adenoma-carcinoma sequence does not occur between gastric adenoma and adenocarcinoma. J. Pathol. *176*, 249–258.

Miwa, H., Go, M.F., and Sato, N. (2002). H. pylori and gastric cancer: the Asian enigma. Am. J. Gastroenterol. *97*, 1106–1112.

Nakajima, T. (2002). Gastric cancer treatment guidelines in Japan. Gastric Cancer *5*, 1–5.

Noda, N., Sasako, M., Yamaguchi, N., and Nakanishi, Y. (1998). Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. Br. J. Surg. *85*, 831–834.

Oberhuber, G., and Stolte, M. (2000). Gastric polyps: an update of their pathology and biological significance. Virchows Arch. *437*, 581–590.

Ono, H., Kondo, H., Gotoda, T., Shirao, K., Yamaguchi, H., Saito, D., Hosokawa, K., Shimoda, T., and Yoshida, S. (2001). Endoscopic mucosal resection for treatment of early gastric cancer. Gut *48*, 225–229.

Oshima, A. (1997). Secondary prevention: Screening methods in high-incidence area. In Gastric Cancer, T. Sugimura and M. Sasako, eds. (Oxford: Oxford University Press), pp. 199–212.

Oue, N., Motoshita, J., Yokozaki, H., Hayashi, K., Tahara, E., Taniyama, K., Matsusaki, K., and Yasui, W. (2002). Distinct promoter hypermethylation of p16INK4a, CDH1, and RAR-beta in intestinal, diffuse-adherent, and diffuse-scattered type gastric carcinomas. J. Pathol. *198*, 55–59.

Palli, D. (2000). Epidemiology of gastric cancer: an evaluation of available evidence. J. Gastroenterol. *35* (*Suppl 12*), 84–89.

Park, W.S., Oh, R.R., Park, J.Y., Lee, S.H., Shin, M.S., Kim, Y.S., Kim, S.Y., Lee, H.K., Kim, P.J., Oh, S.T., et al. (1999). Frequent somatic mutations of the beta-catenin gene in intestinal-type gastric cancer. Cancer Res. *59*, 4257–4260.

Potter, J.D., Chavez, A., Chen, J., Ferro-Luzzi, A., Hirohata, T., James, W.P.T., Kadlubar, F.F., Kavishe, F.P., Kolonel, L.N., Kono, S., et al., eds (1997). Stomach. In Food, Nutrition and the Prevention of Cancer: A global perspective (Washington, D.C.: World Cancer Research Fund/American Institute for Cancer Research), pp. 148–175.

Sasako, M. (2003). Principles of surgical treatment for curable gastric cancer. J. Clin. Oncol. *21*, 274s–275s.

Schlemper, R.J., Itabashi, M., Kato, Y., Lewin, K.J., Riddell, R.H., Shimoda, T., Sipponen, P., Stolte, M., Watanabe, H., Takahashi, H., and Fujita, R. (1997). Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. Lancet *349*, 1725–1729.

Shimizu, N., Inada, K.I., Tsukamoto, T., Nakanishi, H., Ikehara, Y., Yoshikawa, A., Kaminishi, M., Kuramoto, S., and Tatematsu, M. (1999). New animal model of glandular stomach carcinogenesis in Mongolian gerbils infected with Helicobacter pylori and treated with a chemical carcinogen. J. Gastroenterol. *34*, 61–66.

Takada, K. (2000). Epstein-Barr virus and gastric carcinoma. Mol. Pathol. *53*, 255–261.

Tatematsu, M., Tsukamoto, T., and Inada, K. (2003). Stem cells and gastric

cancer: role of gastric and intestinal mixed intestinal metaplasia. Cancer Sci. *94*, 135–141.

Tsubono, Y., and Hisamichi, S. (2000). Screening for gastric cancer in Japan. Gastric Cancer *3*, 9–18.

Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Yamakido, M., Taniyama, K., Sasaki, N., and Schlemper, R.J. (2001). Helicobacter pylori infection and the development of gastric cancer. N. Engl. J. Med. *345*, 784–789.

Waki, T., Tamura, G., Tsuchiya, T., Sato, K., Nishizuka, S., and Motoyama, T. (2002). Promoter methylation status of E-cadherin, hMLH1, and p16 genes in nonneoplastic gastric epithelia. Am. J. Pathol. *161*, 399–403.

Xu, X., Brodie, S.G., Yang, X., Im, Y.H., Parks, W.T., Chen, L., Zhou, Y.X., Weinstein, M., Kim, S.J., and Deng, C.X. (2000). Haploid loss of the tumor suppressor Smad4/Dpc4 initiates gastric polyposis and cancer in mice. Oncogene *19*, 1868–1874.

Yamashita, S., Wakazono, K., Sugimura, T., and Ushijima, T. (2002). Profiling and selection of genes differentially expressed in the pylorus of rat strains with different proliferative responses and stomach cancer susceptibility. Carcinogenesis *23*, 923–928.

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Original article

Feasibility study of adjuvant chemotherapy with S-1 (TS-1; tegafur, gimeracil, oteracil potassium) for gastric cancer

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Abstract

Background. **We conducted a feasibility study using S-1, a novel oral derivative of 5-fluorouracil, as postoperative adjuvant chemotherapy for curatively resected gastric cancer patients.**

Methods. **Adjuvant chemotherapy consisted of eight courses (4-week administration and 2-week withdrawal) of S-1, at 80–120 mg/body per day. Forty-one patients from 11 institutions were enrolled in this pilot study, from November 1999 to October 2000.**

Results. **Thirty-five patients were eligible. In 7 patients, S-1 administration was discontinued due to recurrence. Among the 28 patients without recurrence, the planned eight courses of S-1 were administered to 17 patients (60.7%). In 4 patients, S-1 administration was discontinued due to subjective symptoms, such as anorexia, in the first course. Adverse reactions such as neutropenia, leukopenia, elevated total bilirubin, anorexia, general fatigue, diarrhea, nausea, and stomatitis were seen in more than half of the patients. Although grade 3 neutropenia (29.3%), leukopenia (9.8%), and diarrhea (9.8%) were observed, no grade 4 adverse effects appeared. Compared with the treatment of unresectable or recurrent gastric cancer with S-1, the incidence of adverse reactions in the adjuvant setting was slightly higher, probably due to the influence of gastrectomy.**

Conclusion. **Except for the early development of anorexia, most likely due to adverse effects of surgery, postoperative administration of S-1 for 1 year seems feasible as adjuvant chemotherapy for gastric cancer.**

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Key words Gastric cancer · S-1 · Adjuvant chemotherapy · Feasibility study

Introduction

The results of surgical treatment for gastric cancer have been improved by early detection and meticulous surgical procedures in Japan. However, we still face recurrence in patients with advanced gastric cancer, even with extended surgical treatment [1].

Many clinical trials of adjuvant chemotherapy could not prove survival benefits. Only a few metaanalyses of adjuvant trials reported the possibility of survival benefits [2,3]. According to the guidelines from the Japanese Gastric Cancer Association [4], the efficacy of adjuvant chemotherapy after curative resection for gastric cancer has not been established. A well-designed large-scale phase III trial is needed, with a surgery-alone arm, to prove the benefit of adjuvant chemotherapy.

S-1 is a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine (DIF), which showed the highest response rate among many oral anticancer agents against unresectable advanced gastric cancer in early and late phase II studies [5–7]. In these phase II trials, S-1 showed 40% and higher response rates with acceptable low toxicity. Based on these results, a phase III trial to compare S-1 with two other regimens is underway as a JCOG (Japan Clinical Oncology Group) trial for unresectable and recurrent gastric cancer.

At the same time, the high response rate and low toxicity of S-1 has led to its adjuvant use. Oral anticancer drugs are also attractive for outpatient use. A feasibility study to confirm the safety of S-1 for adjuvant chemotherapy after curative surgery was necessary before starting the phase III trial.

Patients and methods

Design of the trial

The trial was non-blinded and open-label. The primary endpoint was the rate of accomplishment of the scheduled adjuvant chemotherapy. Secondary endpoints were the incidence and grade of adverse reactions.

In this trial, the sample size was 50, without any calculations based on statistical assumptions.

Patient eligibility

Patient eligibility required compliance with the following criteria: gastric adenocarcinoma with histological proof; operative findings revealing advanced gastric cancer (T2 or more); curability B resection, defined in the *Japanese classification of gastric carcinoma* [8]; sufficient oral intake; no prior treatment except for surgery; and more than 19 and less than 76 years of age. Patients also had to have adequate organ function ($4000 \leq$ leukocytes $< 12000/mm^3$; thrombocytes, $\geq 100000/mm^3$; total bilirubin, ≤ 1.5 mg/dl; GOT and GPT, less than twice the normal limits at each institution; creatinine, ≤ 1.5 mg/dl). Patients expected to receive medication and to be followed-up regularly for more than 48 weeks. Patients with a history of drug hypersensitivity, serious surgical and non-surgical complications, or active secondary cancer were excluded. Pregnant or lactating women were excluded. This study was approved by the institutional review board at each site, and written informed consent was obtained from all patients.

Treatment schedule

Chemotherapy consisted of eight courses (4-week administration and 2-week withdrawal) of S-1 (tegafur, gineracil, oteracil potassium; Taiho Pharmocentical, Tokyo, Japan) at 80–120 mg/body per day according to the body surface area (BSA): BSA $< 1.25\,m^2$, 80 mg/day; $1.25 \leq$ BSA $< 1.5\,m^2$, 100 mg/day; $1.5\,m^2 \leq$ BSA, 120 mg/day. S-1 was administered orally, twice daily after meals for 4 weeks after surgery. Doses were modified in accordance with the following guidelines. When adverse reactions appeared, the dose was reduced from 120 to 100 mg/day or from 100 to 80 mg/day, or administration was temporarily discontinued. The withdrawal period due to adverse reactions was less than 16 days in the same course, with a maximum of 28 days' administration of the drugs in total. Treatment was discontinued when the patient showed recurrence of disease or adverse reactions that were uncontrollable by dose modification and temporary withdrawal of drug administration. A 48-week period of temporary drug withdrawal was the limit set for a patient not being able to enter a new course.

Evaluation of toxicity

The National Cancer Institute Common Toxicity Criteria (NCI-CTC; 1998) were adopted to determine the toxicity of the chemotherapy.

Results

In November 2000, an interim analysis was performed in order to determine whether to continue further recruitment of patients. Because information from the periodic safety report of use-results surveillance (September 24, 2000) from Taiho Pharmaceutical to the Ministry of Health, Labor, and Welfare revealed there were no specific adverse reactions in up to two courses in 110 patients who received S-1 within 30 days after surgical resection of gastric cancer, and because a feasible result was obtained by monitoring the patients in the present study, we decided to complete recruitment at 41 patients.

Of the 41 patients, 6 patients were ineligible. Four patients had received curable A resection, 1 patient had received intraoperative chemotherapy with cisplatin (CDDP), and the other patient had distant metastasis at the time of the operation. Thirty-five patients were eligible (full analysis set [FAS]).

Table 1 shows the characteristics of the FAS. Thirty of the 35 patients (85.7%) had rather advanced stage disease (TNM stage IIIA or more; Table 1).

Table 2 shows drug compliance in each course and the reasons for discontinuation of drug administration. In 7 of the 35 patients (FAS), administration of S-1 was discontinued due to recurrence. The planned eight courses of S-1 were administered to 17 patients (60.7%). In 4 patients, drug administration was discontinued in the first course at the patient's request, due to anorexia. The main reason for discontinuation was recurrence of disease.

Table 3 shows the drug compliance of the FAS (days and total amount of the drug). In every course, drug compliance was maintained at more than 85% (86.0%–90.4%). In the total of 35 patients (FAS), the percentage of actual administration days against the total number of planned administration days (28 days × 8;

Table 1. Patient characteristics

		Number of patients	Percentage
Sex	Male	20	57.1
	Female	15	42.9
Age (years)	20–29	1	2.9
	30–39	2	5.7
	40–49	5	14.3
	50–59	4	11.4
	60–69	12	34.3
	70–79	11	31.4
	Mean, 60.3; median, 65.0		
BSA (m^2)	1.20–1.39	10	28.6
	1.40–1.59	20	57.1
	1.60–1.79	5	14.3
	Mean, 1.47; median 1.47		
Lymph node dissection	D2	24	68.6
	D3	11	31.4
Type of resection	Distal gastrectomy	15	42.9
	Total gastrectomy	19	54.3
	Proximal gastrectomy	1	2.9
Combined resection	No	11	31.4
	Yes	24	68.6
Reconstruction	Billroth I	5	14.3
	Billroth II	8	22.9
	Roux-Y	20	57.1
	Interposition	1	2.9
	Other	1	2.9
Japanese Stage	IB	1	2.9
	II	3	8.6
	IIIA	12	34.3
	IIIB	9	25.7
	IV	10	28.6
TNM Stage	IB	2	5.7
	II	3	8.6
	IIIA	9	25.7
	IIIB	8	22.9
	IV	13	37.1

BSA, body surface area

224) was 79.0% (median) and 69.7% (mean). Concerning the amount of the drug, compliance was 75.2% (median) and 67.3% (mean).

Table 4 shows summaries of the adverse reactions that developed in more than 10% of the 41 patients in total, grouped as laboratory findings-based and clinical findings-based. Of the laboratory findings-based adverse reactions, neutropenia was the most frequent, in 35 of the 41 patients (85.4%) followed by leukopenia (75.6%), increase in serum total bilirubin (53.7%), GOT (41.5%), anemia (hemoglobin [Hb]; 41.5%), anemia (RBC; 34.1%), alkaline phosphatase (ALP; 26.8%), GPT (26.8%), lactate dehydrog-enase (LDH; 24.4%), thrombocytopenia (24.4%), proteinuria (24.4%), lymphopenia (19.5%), anemia (hematocrit [Hct]; 14.6%), hyperkalemia (12.2%), blood urea nitrogen (BUN; 12.2%), and hypoalbuminemia (12.2%). Among the clinical findings-based adverse reactions, anorexia was the most frequent (68.3%), followed by fatigue (61.0%), diarrhea (58.5%), nausea (51.2%), stomatitis (51.2%), pigmentation changes (46.3%), weight loss (39.0%), rash (31.7%), and vomiting (19.5%). Concerning the incidence and grade of laboratory findings-based adverse reactions, grade 3 adverse reactions were seen with neutropenia, leucopenia, lymphopenia, anemia (Hb), GOT, and GPT. However, there were no grade 4 adverse reactions. In the clinical findings-based adverse reactions, grade 3 adverse reactions were observed with anorexia, fatigue, diarrhea, and weight loss. There were also no grade 4 adverse reactions.

Figure 1 shows comparisons of the incidences of the main adverse reactions in a late-phase II study [9] and those in the present study. When compared with the

Table 2. Drug compliance (each course)

Course no.	FAS full analysis set; $n = 35$		Excluding patients with recurrence ($n = 28$)		Reasons for discontinuation of drug administration
	Number of patients entering the course	Percentage	Number of patients entering the course	Percentage	
1	35	—	28	—	Patient refusal (anorexia; $n = 4$) Complication, (varicose; $n = 1$)
2	30	85.7	23	82.1	
3	30	85.7	23	82.1	Recurrence ($n = 1$)
4	29	82.9	23	82.1	Patient refusal (anorexia; $n = 1$) Dr's judgment (poor general condition; $n = 1$)
5	27	77.1	21	75.0	Recurrence ($n = 3$)
6	24	68.6	21	75.0	Recurrence ($n = 2$) Adverse reaction (arrhythmia; $n = 1$)
7	21	60.0	20	71.4	Recurrence ($n = 1$) Unable to enter the eight course ($n = 3$)[a]
8	17	48.6	17	60.7	Patient refusal (adverse reaction; $n = 1$)

[a] Because of prolongation of the period during which the drug was temporarily withdrawn

Table 3. Drug compliance (days and total amount of the drug)

Course no.	No. of patients entering the course	Percent administration days (mean)[a]	Percent administration amount (mean)[b]
1	35	85.9	87.9
2	30	91.4	90.4
3	30	91.7	88.1
4	29	92.3	87.4
5	27	96.1	90.4
6	24	92.1	89.0
7	21	93.7	86.0
8	17	91.8	87.1
Overall mean ($n = 35$)		69.7	67.3
Overall median ($n = 35$)		79.0	75.2

[a] Days actually administered as a percentage of planned number of days
[b] Amount of drug as actually administered a percentage of planned amount

data from the late-phase II study [9], a higher incidence of adverse reactions was observed in the present study.

Discussion

As mentioned in the "Introduction", S-1 is an attractive oral anticancer agent for advanced gastric cancer, with a high response rate and low toxicity. The possibility of outpatient use of S-1 has increased the convenience for both doctors and patients, and it has led to the idea of using S-1 as an adjuvant chemotherapeutic agent. Up to 1999, there were no trials of S-1 use in the adjuvant setting. Therefore, as a prerequisite to conducting a large-scale clinical trial of adjuvant S-1, the present study was carried out to confirm the feasibility of adjuvant S-1 given after curative gastrectomy.

Survival benefits of adjuvant chemotherapy after curative resection of gastric cancer have not yet been proved by a large-scale prospective randomized trial, as stated in the guidelines of the Japanese Gastric Cancer Association (Japanese guidelines). Even though

Table 4. Adverse reactions (n = 41)

	Grade				
	4	3	2	1	Total (incidence; percentage)
Laboratory findings					
Neutropenia		12	16	7	85.4
Leukopenia		4	15	12	75.6
Lymphopenia		2	5	1	19.5
Thrombocytopenia			2	8	24.4
Anemia (Hb)		3	8	6	41.5
Anemia (RBC)			5	9	34.1
Anemia (Hct)			3	3	14.6
GOT		2	1	14	41.5
GPT		1	2	8	26.8
LDH				10	24.4
ALP			1	10	26.8
Total bilirubin			8	14	53.7
Hypoalbuminemia			1	4	12.2
Hyperkalemia				5	12.2
BUN				5	12.2
Proteinuria			1	9	24.4
Clinical findings					
Anorexia		4	5	19	68.3
Nausea			3	18	51.2
Vomiting				8	19.5
Diarrhea		4	5	15	58.5
Stomatitis			2	19	51.2
Fatigue		1	5	19	61.0
Pigmentation changes			3	16	46.3
Rash			5	8	31.7
Weight loss		1	9	6	39.0

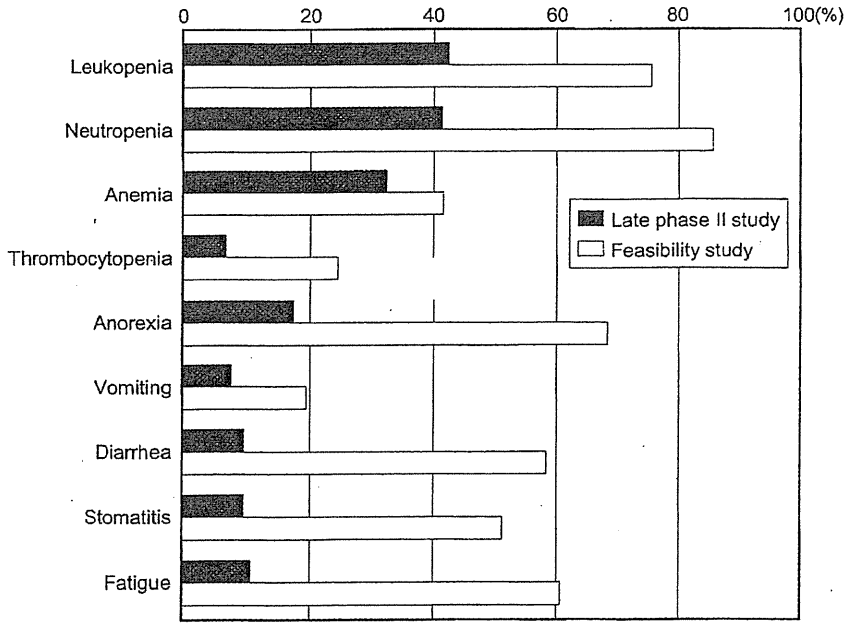

Fig. 1. Comparison of incidence of adverse reactions with that in a late phase II study [9]

Macdonald et al. [9], in 2001, confirmed the effectiveness of the combination of 5-fluorouracil with radiotherapy as an adjuvant after curative gastric surgery in a randomized clinical trial, the Japanese guidelines have not changed up to now, probably because of differences in the local control rates after different types of surgery between the United States and Japan. The local recurrence rate is negligible after systematic lymph node dissection (D2 or more) in Japan. However, in the United States, the local recurrence rate is usually much higher with less aggressive surgery (D0 or D1). The incidence of local, invisible, residual cancer cells in eligible patients in the study of Macdonald et al. [9] were quite different from those in the Japanese candidates for adjuvant therapy. That is why we still think that survival benefits of adjuvant chemotherapy after curative resection of gastric cancer have not yet been proved in Japan; only metaanalyses will show the survival benefit of adjuvant chemotherapy.

S-1 is expected to be a promising agent for adjuvant use. The high response rate of S-1 in advanced gastric cancer gives a rationale for expecting a certain survival benefit with S-1 in the adjuvant setting.

Because the standard treatment of locally advanced gastric cancer is still surgery, a randomized controlled trial with a surgery-alone arm is essential to prove the efficacy of adjuvant chemotherapy.

According to the "Results", no grade 4 adverse reactions were observed.

In the FAS, excluding the patients with recurrence, 17 of the 28 patients (60.7%) received the planned eight courses of S-1. Drug compliance was acceptable. In every course, drug compliance was over 85% in the FAS.

Problems in this study were a higher incidence of adverse reactions when compared with that in the phase II trials and postmarketing surveillance [10], and a high incidence of patient refusal, due to adverse reactions in the first course, which was not seen during the postmarketing surveillance of 110 patients who received S-1 within 30 days after surgical resection of gastric cancer (as mentioned in "results"). The reasons for these problems, especially the early appearance of anorexia, may be the influence of surgery, because the patients in this study had rather advanced disease and had received D2 or more aggressive gastrectomy with frequent combined organ resections. It is difficult to deny the possibility of gastro-intestinal (GI) toxicity of S-1; however, the adverse reaction was not bone marrow suppression, which is a dose-limiting toxicity of S-1. In this protocol, S-1 administration was started within 4 weeks after surgery. In the early postoperative period, patients have not yet recovered from surgical stress, and the limitation of food intake due to aggressive gastrectomy is a possible cause of exacerbation of adverse reactions such as anorexia and nausea. To prevent these problems, a delay in the start of drug administration seems necessary for adjuvant use. Except for these problems, the administration of S-1 for 1 year seems feasible as postoperative adjuvant chemotherapy for gastric cancer.

Based on this feasibility study, a prospective randomized controlled trial was started in 2001 to evaluate the efficacy of S-1 as adjuvant chemotherapy; in this trial S-1 administration is started within 6 weeks after surgery.

We expect that a significant survival benefit of S-1, with less toxicity, will be shown by this trial, and that this could be the standard treatment after curative gastrectomy.

References

1. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987;11:418–25.
2. Nakajima T, Ohta K, Ohyama S, Hamashima N. Meta-analysis of adjuvant chemotherapy trial for gastric cancer at the Cancer Institute Hospital, Tokyo. In: Nakajima T, Yamaguchi T. editors. Multimodality therapy for gastric cancer. Heidelberg Berlin New York Tokyo: Springer-Verlag; 1988. pp. 27–31.
3. Hermans J, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441–47.
4. Nakajima T. Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002;5:1–5.
5. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Miyachi Y, et al. An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. Oncology 1999;57:202–10.
6. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998;34:1715–20.
7. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. Oncology 2000;58:191–7.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 2nd English Ed. Gastric Cancer 1998;1:10–24.
9. 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.
10. Maehara Y. S-1 in gastric cancer: a comprehensive review. Gastric Cancer 2003;6 (Suppl 1):2–8.

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ORIGINAL REPORT

Extended Lymph Node Dissection for Gastric Cancer: Who May Benefit? Final Results of the Randomized Dutch Gastric Cancer Group Trial

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ABSTRACT

Purpose
The extent of lymph node dissection appropriate for gastric cancer is still under debate. We have conducted a randomized trial to compare the results of a limited (D1) and extended (D2) lymph node dissection in terms of morbidity, mortality, long-term survival and cumulative risk of relapse. We have reviewed the results of our trial after follow-up of more than 10 years.

Patients and Methods
Between August 1989 and June 1993, 1,078 patients with gastric adenocarcinoma were randomly assigned to undergo a D1 or D2 lymph node dissection. Data were collected prospectively, and patients were followed for more than 10 years.

Results
A total of 711 patients (380 in the D1 group and 331 in the D2 group) were treated with curative intent. Morbidity (25% *v* 43%; $P < .001$) and mortality (4% *v* 10%; $P = .004$) were significantly higher in the D2 dissection group. After 11 years there is no overall difference in survival (30% *v* 35%; $P = .53$). Of all subgroups analyzed, only patients with N2 disease may benefit of a D2 dissection. The relative risk ratio for morbidity and mortality is significantly higher than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years.

Conclusion
Overall, extended lymph node dissection as defined in this study generated no long-term survival benefit. The associated higher postoperative mortality offsets its long-term effect in survival. For patients with N2 disease an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy and age. Extended lymph node dissections may be of benefit if morbidity and mortality can be avoided.

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INTRODUCTION

Gastric cancer is a common malignancy worldwide. Even in a low-incidence country like the Netherlands, it is ranked fifth with respect to incidence. Despite declining incidence, mortality of gastric cancer remains high. Surgery is the only possible curative treatment, and results of gastrectomy have improved throughout the years with respect to survival, morbidity, and postoperative mortality.[1,2]

It is not clear, however, if extended lymph node dissection contributes to this improvement. Despite promising results in nonrandomized studies, improved survival has never been demonstrated in randomized trials.[3-6] In all these randomized trials, postoperative morbidity and mortality were significantly higher in the extended (D2) dissection group. Within the Dutch Gastric Cancer Trial (DGCT), the number of early gastric cancers was surprisingly high, and it has been argued that any beneficial effect of extended lymph node dissection, which would be expected in more advanced disease, might have been attenuated. We have

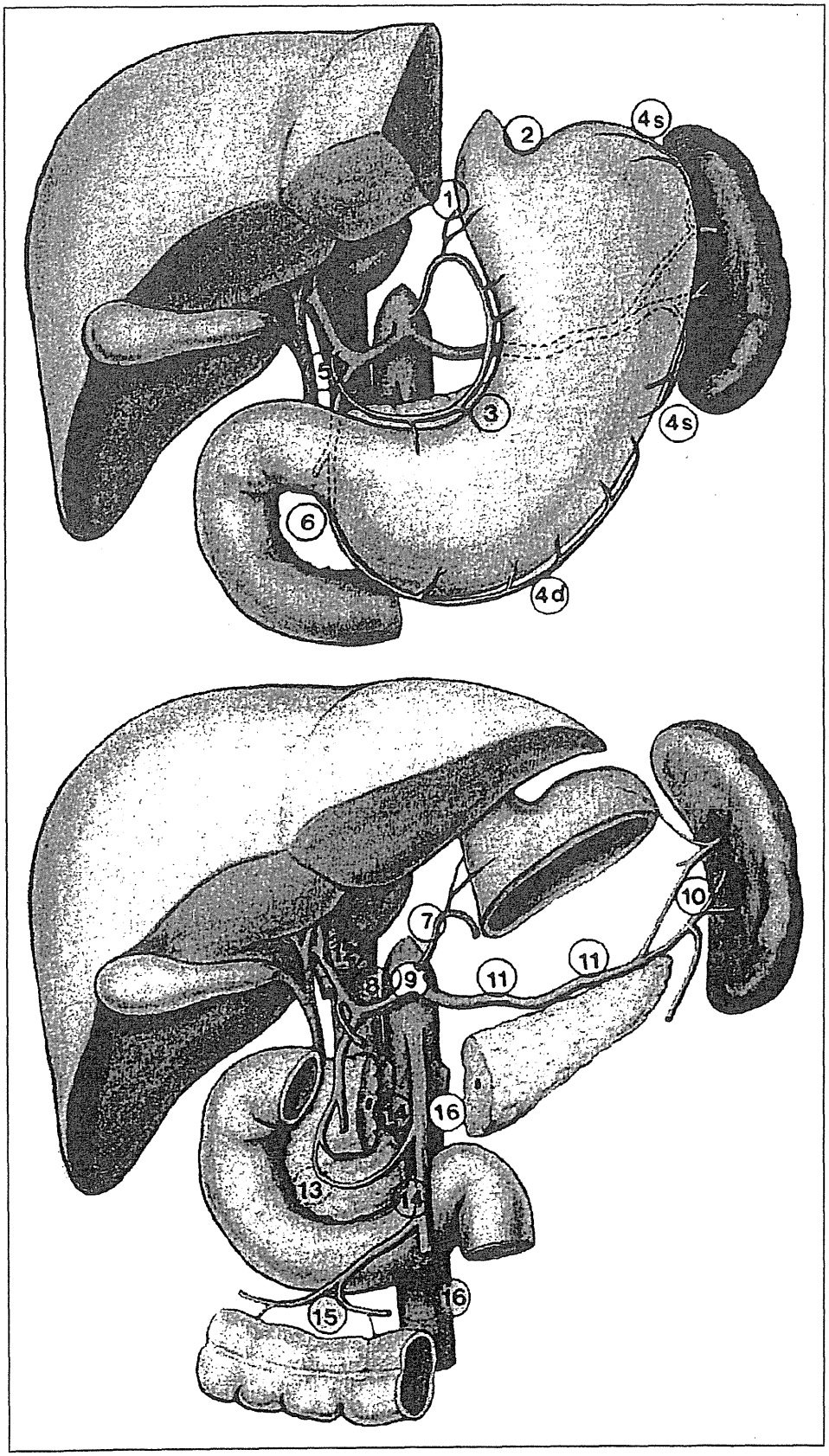

Fig 1. Lymph node stations surrounding the stomach. 1, right cardial nodes; 2, left cardial nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes along the common hepatic artery; 9, nodes around the celiac axis; 10, nodes at the splenic hilus; 11, nodes along the splenic artery; 12, nodes in the hepatoduodenale ligament; 13, nodes at the posterior aspect of the pancreas head; 14, nodes at the root of the mesenterium; 15, nodes in the mesocolon of the transverse colon; 16, para-aortic nodes.

Table 1. Characteristics of 711 Patients and Tumors After Resection With Curative Intent* and Status at Last Follow-Up

Characteristic	Dissection Group			
	D1 (n = 380)		D2 (n = 331)	
	No. of Patients	%	No. of Patients	%
Median age, years	67		65	
Sex				
Male	215		187	
Female	165		144	
Median No. of lymph nodes investigated	17		30	
Status after resection				
Location of tumor				
More than two thirds of stomach	25	7	24	7
Upper third (C)	39	10	34	10
Middle third (M)	108	28	92	28
Distal third (A)	207	54	180	54
Unknown	1	< 1	1	< 1
Pathologic stage of disease				
T0	2	< 1	3	< 1
T1	98	26	85	26
T2	181	48	152	46
T3	94	25	82	25
T4	3	< 1	9	2
Tx	2	< 1	0	0
Lymph node involvement	205	54	185	56
R0 resection	339	89	293	89
Type of gastrectomy				
Total	115	30	128	38
Partial	265	70	205	62
Resection of spleen	41	11	124	37
Resection of tail of pancreas	10	3	98	30
Status at last follow-up				
Alive				
Without recurrence	112	98	116	99
With recurrence	2	2	1	1
Dead				
Hospital death	15	4	32	10
Without recurrence†	82	31	86	40
With recurrence				
Locoregional	56	21	40	19
Locoregional and distant	98	37	55	26
Distant	30	11	33	15

NOTE. Some data have previously been reported.[6]
Abbreviations. D1, limited lymph node dissection group; D2, extended lymph node dissection group.
*Because of rounding, percentages may not total 100.
†These numbers include hospital deaths.

therefore reviewed the results of our randomized limited lymph node dissection (D1) versus extended lymph node dissection (D2) trial after follow-up of more than 10 years and focused on subgroups and prognostic factors.

PATIENTS AND METHODS

Patients with gastric adenocarcinoma were enrolled in the DGCT between August 1989 and July 1993. Eligible patients were randomly assigned for D1 (conventional) or D2 (extended) lymph node dissection if at laparotomy, no signs of distant lymph node, hepatic or peritoneal metastases were found. In case of metastases, palliative surgery without formal lymph node dissection was done. The trial protocol has previously been published.[7]

D1 and D2 dissection were defined according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer.[8] These guidelines are also recommended by the American Joint Committee on Cancer, in its fourth Manual for Staging of Cancer, and by the International Union Against Cancer.[9,10] In these guidelines, 16 different lymph node compartments (stations) are identified surrounding the stomach (Fig 1). In general, the perigastric lymph node stations along the lesser (stations 1, 3, and 5) and greater (stations 2, 4, and 6) curvature are grouped N1, whereas the nodes along the left gastric (station 7), common

hepatic (station 8), celiac (station 9), and splenic (stations 10 and 11) arteries are grouped N2.

D1 dissection entails removal of the involved part of the stomach (distal or total), including greater and lesser omentum. The spleen and pancreas tail are only resected when necessitated by tumor invasion. For a D2 dissection, the omental bursa is removed with the front leave of the transverse mesocolon, and the mentioned vascular pedicles of the stomach are cleared completely. Standard resection of the spleen and pancreatic tail was only done in proximal tumors to achieve adequate removal of D2 lymph node stations 10 and 11.

Patients were randomly assigned before surgery to ensure standardization of surgery. Patients randomly assigned to D1 dissection had their operation performed by their local surgeon, supervised by the trial coordinator. For D2 dissections, one of nine referent surgeons performed the operation at the local hospital. These referent surgeons had been trained in D2 dissection by a Japanese surgeon from the National Cancer Center Hospital in Tokyo. Apart from standardizing surgery, they ensured that the specimen was adequately divided into lymph node stations, which were then further investigated by the local pathologist. Operations were classified as R0 if there was microscopic complete tumor removal, without N3 or N4 involvement and no malignant cells on cytology of abdominal washing. For analysis of differences in relapse rates, only patients were included who had had a R0 resection and who did not die because of complications. None of the curative patients had adjuvant radiotherapy or chemotherapy.

In the hospital, death was defined as death within 30 days of surgery or during hospital stay, if this was longer than 30 days. For stage grouping, the new (2002) tumor-node-metastasis system classification system was used.[11] In this new classification lymph nodes are no longer characterized by location but by the number of metastatic regional lymph nodes. N1 stands for 1 to 6, N2 for 7 to 15, and N3 for more than 16 metastatic regional lymph nodes.

For statistical analysis the SPSS program (SPSS Inc, Chicago, IL) was used. A P value of .05 was considered statistically significant. Overall survival was calculated from the day of random assignment until either day of death (event) or day of last follow-up (censored). Relapse was also calculated from the day of random assignment; the data of a patient were censored when at last follow-up contact the patient was alive with no evidence of disease. The χ^2 test was applied to evaluate differences in proportions, and the Mann-Whitney test was used to assess the significance of differences in hospital stay. The log-rank test was used to evaluate difference between survival and relapse curves, although the assumption of proportional hazards was not always satisfied. The Cox proportional hazard model was used to test for interaction between prognostic factors and lymph node dissection.

For the subgroup analysis, no adjustment for multiple testing was applied. Interpretation of the results of subset analyses have to be judged carefully and any significant results must be viewed as hypotheses that require validation in subsequent studies. A P value of .05 may not be strict enough for these subgroups.

RESULTS

Of 1,078 patients randomly assigned in the DGCT, 996 were eligible. At the time of surgery, 285 patients (29%) had peritoneal, hepatic or distant lymph node metastasis, or locally irresectable tumor and they underwent noncurative treatment deemed appropriate by their surgeon.

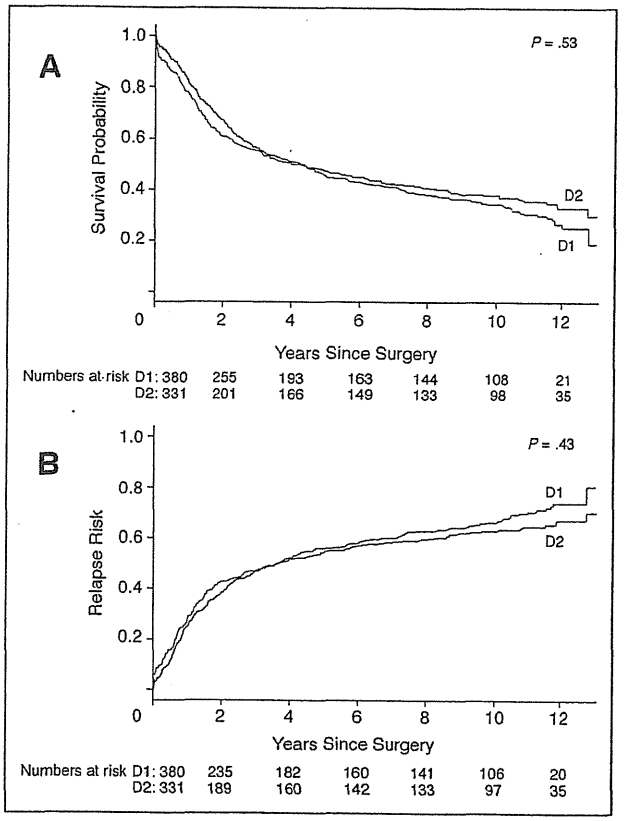

Fig 2. Survival probability (A) and relapse risk (B) of all patients treated with curative intent (n = 711). D1, limited lymph node dissection group; D2, extended lymph node dissection group.

This analysis focuses on the 711 patients (71%) who had a curative resection with D1 (n = 380) or D2 (n = 331) lymph node dissection. The characteristics of the 711 curative patients are well balanced between the two treatment groups, except for pancreatico-splenectomy, which was expected according to the protocol (Table 1).

Follow-up was continued until January 2003. Median follow-up for all eligible patients is 11 years (range, 6.8 to 13.1 years). Four-hundred eighty patients (68%) are now deceased, 35% without and 65% with recurrent disease (Table 1). In the hospital, death was 4% (n = 15) for the D1 group and 10% (n = 32) for the D2 group (P = .004). At 11 years, survival rates are 30% for D1 and 35% for D2 (P = .53) The risk of relapse is 70% for D1 and 65% for D2 (P = .43; Fig 2).

In a univariate analysis of all 711 patients, for none of the subgroups based on the selected prognostic variables was a significant impact found on survival rates between D1 and D2 dissection (Table 2). Analysis of interaction between covariates and lymph node dissection shows no significance. The only subgroup with a trend to benefit is the N2 disease group (Fig 3). Furthermore, there is no difference in survival after 11 years

Table 2. Univariate Analysis of Survival Rates 11 Years After Resection With Curative Intent (N = 711)

Variable	Dissection Group				
	D1		D2		
	No. of Patients	Survival %	No. of Patients	Survival %	*P**
Age, years					
≤ 70	252	37	229	41	.74
> 70	128	19	102	24	.68
Pathologic stage					
T1	98	57	85	55	.90
T2	181	28	152	35	.54
T3	94	8	82	17	.80
Lymph nodes					
Negative	171	52	144	51	.93
Positive	209	13	187	23	.28
Lymph node stage					
N0	171	52	144	51	.93
N1	138	20	113	30	.46
N2	50	0	47	21	.08
N3	21	0	27	0	.30
Tumor-node-metastasis stage‡					
IA	75	60	69	58	.84
IB	97	47	72	44	.65
II	93	23	77	37	.10
IIIA	60	4	54	22	.38
IIIB	24	0	20	10	.55
IV	28	0	36	3	.19
Gastrectomy					
Partial	265	35	205	43	.20
Total	115	20	126	24	.94
All patients	380	31	331	35	.53

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; TNM, tumor-node-metastasis.
*P values were derived by the log-rank test for the difference between the D1 and D2 groups.
†Stages T0 and T4 (five patients in the D1 group and 12 in the D2 group) have been omitted.
‡Stages according to the sixth edition of the TNM classification manual.[11] TNM stage 0 (four patients in the D1 group and three in the D2 group) has been omitted.

whether less than 15 lymph nodes, between 15 and 25 lymph nodes, or more than 25 lymph nodes are harvested.

Lymph node stations 10 and 11 were resected in 112 and 124 patients, respectively. In the group of 18 patients with metastasis in station number 10, survival after 11 years is only 11%. In the group of 24 patients with lymph node metastasis in station 11, survival after 11 years is only 8%. If there are no metastases in lymph node stations 10 and 11, the 11-year survival is 27% and 35%, respectively.

The relative risk ratio for morbidity and mortality is significantly greater than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years (mortality only; Table 3).

Patients older than 70 years have significantly higher morbidity and hospital mortality and significantly shorter survival compared with patients younger than 70 years. (Table 4).

DISCUSSION

For many years it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure. Such resection, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into a systemic disease, or if resection increases morbidity and mortality substantially.

Long-term follow-up of the largest randomized study of D1 and D2 dissection now clearly demonstrates that overall, no improved survival or decreased relapse rates can be obtained by D2 dissection. Extended lymph node dissection is even harmful in terms of increased morbidity and hospital mortality, although many reports deny this. Specifically, Japanese investigators have reported low operative morbidity and mortality,[12] but so far, studies have not been randomized. A randomized Japanese study between D2 and D4 dissections, that included 523 patients and closed in April 2001 found a hospital mortality of 0.8% in both groups. Dedicated centers in Western Europe have reported hospital mortality rates of less then 5% for extended lymph node dissections in selected patients.[13-15] In our study, patients younger than 70 years had a hospital mortality rate of 5.9%.

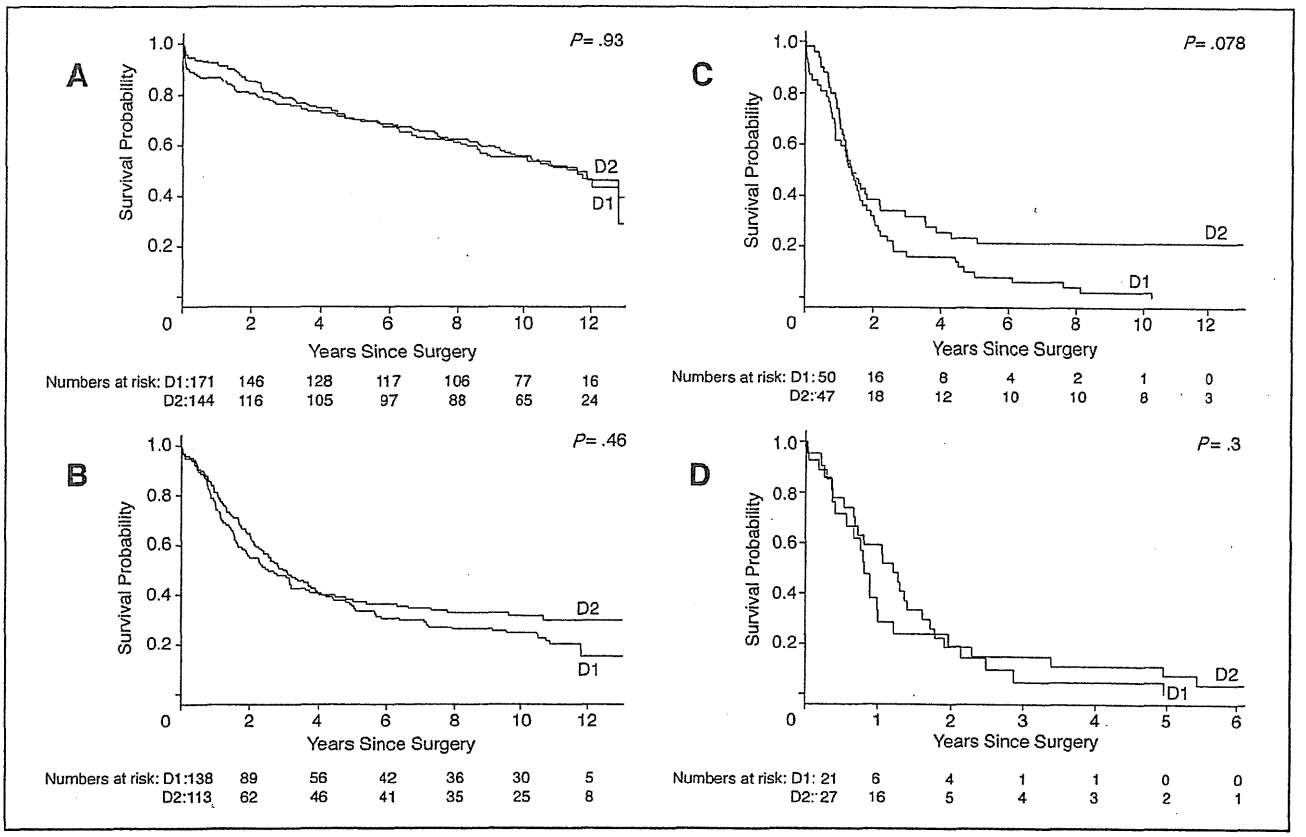

Fig 3. Survival of patients treated with curative intent according to N stage. (A), N0; (B), N1; (C), N2; (D), N3. D1, limited lymph node dissection group; D2, extended lymph node dissection group.

Splenectomy and pancreatectomy are important risk factors for morbidity and hospital mortality after D2 dissection,[16,17] with a significant adverse effect on survival as well.[18] Two Japanese studies showed no beneficial effect on survival if pancreatosplenectomy was combined with total gastrectomy, whereas morbidity was increased in these patients.[19,20] A randomized trial in Chile found no survival benefit from a splenectomy in patients with total gastrectomy, whereas morbidity was again significantly increased.[21] Another randomized trial to study the effect of splenectomy is underway in Japan.[22] In our study the risk ratio for morbidity and mortality was significant for pancreatectomy and splenectomy. The question is whether a survival benefit can be achieved with an extended lymph node dissection, if morbidity- and mortality-increasing procedures such as pancreatectomy and splenectomy can be avoided. A randomized English study supports this hypothesis for patients with stage II and III disease.[23] Pancreas and spleen sparing procedures have now become standard in Japan as well as many Western countries.

The main reason to do pancreatectomy and splenectomy in D2 dissection was not to compromise an adequate dissection of lymph node stations 10 and 11. Metastasis in these lymph nodes, however, confers a poor prognosis. In our study, patients with metastasis in these lymph nodes have a survival rate at 11 years of 8% and 11%, respectively, whereas patients without metastases have a survival rate of 27% and 35%, respectively. So the relevance of the dissection of these nodes has to be questioned as the survival benefit is small and morbidity and hospital mortality are significantly increased.

Total gastrectomy has a higher morbidity and hospital mortality rate than partial gastrectomy. A randomized trial in Italy showed that there is no survival benefit from a total gastrectomy if resection margins are free of tumor.[18] So total gastrectomy should only be performed if the localization of the tumor requires to do so.

With the aging of the populations of industrialized countries, more elderly patients with gastric cancer will be diagnosed. Population-based data from the Netherlands show that from 1982 to 1992, 27% of newly diagnosed patients were older than 80 years.[24] In a study on gastric cancer in the elderly by Klein Kranenbarg et al,[25] it was shown that there is no difference in resectability and curability rate between different age groups, but hospital mortality increases with increasing age, especially older than 70

Table 3. Relative Risk Ratio for Morbidity and Mortality After Resection With Curative Intent (n = 711)

Factor	Total No. of Patients	Morbidity				Mortality			
		No. of Patients	%	RR	95% CI	No. of Patients	%	RR	95% CI
Dissection									
D1	380	94	25			15	4		
D2	331	142	43	1.73	1.40 to 2.15	32	10	2.45	1.35 to 4.44
Splenectomy									
D1	41								
D2	124								
No, both groups	546	59	11			26	5		
Yes, both groups	165	54	33	3.03	2.19 to 4.19	21	13	2.67	1.55 to 4.62
Pancreatectomy									
D1	10								
D2	98								
No, both groups	603	70	12			34	5		
Yes, both groups	108	43	40	3.43	2.49 to 4.72	13	12	2.14	1.17 to 3.91
Age, years									
≤ 70	481	152	32			20	4		
> 70	230	80	37	1.10	0.88 to 1.37	27	12	2.82	1.62 to 4.93

Abbreviations: RR, relative risk; D1, limited lymph node dissection group; D2, extented lymph node dissection group.

years. Differentiation between D1 and D2 dissections for the age groups younger and older than 70 years shows that the morbidity and hospital mortality is higher in the D2 dissection group compared with the D1 dissection group. Although some authors do not regard age as an important prognostic variable for survival, we believe that gastrectomies should not be withheld from elderly patients but that extended lymph node dissection should be avoided in Western patients older than 70 years.

The new (2002) tumor-node-metastasis system classification system[11] offers a better insight in subgroups with different prognosis.[26-28] Using this new classification system, we studied the effect of D1 and D2 dissections in the N0, N1, N2, and N3 groups and found what theoretically might be expected—that the largest advantage is for the N2 disease group if they had a D2 dissection. This advantage was less for the N0, N1, and N3 groups. So a D2 dissection probably is the only possible cure for N2 patients. Given that only 12% of all patients had N2 disease, it is not possible to find this difference through the randomized groups. We calculated that with exclusion of postoperative deaths, 21% of the population ought to have N2 disease to make an overall difference between D1 and D2 significant. Including postoperative death, no such percentage will make the difference between the D1 and D2 significant.

At this moment N classification can only be concluded postoperatively after histologic examination. Although we have tested many possible prognostic factors and their combinations, such as T stage, tumor location in the stomach, histologic characteristics (well *v* poorly differentiated, WHO classification, Lauren classification, and Goseki classification), oncogene markers (p53, Rb, Myc, and Nm23), adhesion molecules (Ep-CAM, E-Cadherin, CD44v5, and CD44v6), and sucrose maltase expression, we have so far not been able to identify any factor that can identify N2 patients preoperatively.[29,30] We hope that promising results from genomic profiling in the near future may help to discriminate between patients with a high risk of lymph node metastasis.[31]

The extent of surgery will especially be of influence on locoregional control. Relapse after curative surgery because of local recurrence or regional lymph node metastasis has been shown in up to 87.5% of patients.[32] In our trial, locoregional recurrence was registered in 58% of the D1 group and in 45% of the D2 group. In studies with extensive surgery (D2 or more) local recurrence rates of less than 1% are reported.[33] Another approach to improve locoregional control is postop-

Table 4. Impact of Age on Morbidity, Mortality, and Survival After Resection With Curative Intent (N = 711)

	Age (years)		
	≤ 70	> 70	*P*
Morbidity, %			
D1	20.4	31.7	.01
D2	41.1	46.4	NS
Mortality, %			
D1	1.7	7.6	.005
D2	5.9	17.0	.002
Mean survival, years			
D1	6.27	4.43	.0001
D2	6.13	4.73	.009

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; NS, not significant.

erative chemoradiotherapy, which has recently been suggested as the standard of care treatment in the United States after a curative resection of gastric adenocarcinoma.[34] Because only 10% of these patients had the advised D2 lymph node dissection and 54% of the patients in that trial had a D0 lymph node dissection, the question has raised whether the adjuvant treatment given in that trial only compensates for inadequate surgery. Five-year survival rates of the group that received adjuvant chemoradiotherapy resemble those of the Dutch Gastric Cancer Trial, where no adjuvant treatment was given. Although the population of the INT 0116 trial[34] had more advanced stages of disease compared with our trial, we believe that this conclusion seems justified. Many comments on this trial support our opinion.[35-37] The effect of a limited lymph node dissection on survival was also reported by the study group itself.[38] It is therefore doubtful if any survival advantage of chemoradiotherapy would have been found if patients would have had adequate surgery.

We conclude that there is no long-term overall survival benefit from an extended lymph node dissection in Western patients with gastric cancer. The associated higher postoperative mortality offsets its long-term effect in survival. For patients with N2 disease, an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy, and age. Extended lymph node dissections may be of benefit if morbidity and mortality can be reduced.

Acknowledgment

We are indebted to the participating surgeons and pathologists of the Dutch Gastric Cancer Group and to the data center of the Surgery Department at the Leiden University Medical Center for its contribution to this trial.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Macintyre IMC, Akoh JA: Improving survival in gastric cancer: Review of operative mortality in English language publications from 1970. Br J Surg 78:771-776, 1991
2. Akoh JA, Macintyre IMC: Improving survival in gastric cancer: Review of 5-year survival rates in English language publications from 1970. Br J Surg 79:293-299, 1992
3. Dent DM, Madden MV, Price SK: Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. Br J Surg 75:110-112, 1988
4. Robertson CS, Chung SCS, Woods SDS, et al: A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann Surg 220:176-182, 1994
5. Cuschieri A, Weeden S, Fielding J, et al: Patient survival after D1 and D2 resections for gastric cancer: Long-term results of the MRC randomized surgical trial. Br J Cancer 79:1522-1530, 1999
6. Bonenkamp JJ, Sasako M, Hermans J, et al: Extended lymph-node dissection for gastric cancer. N Engl J Med 340:908-914, 1999
7. Bunt AMG, Hermans J, Boon MC, et al: Evaluation of the extent of lymphadenectomy in a randomized trial of Western versus Japanese type surgery in gastric cancer. J Clin Oncol 12:417-422, 1994
8. Kajitani T: Japanese Research Society for the Study of Gastric Cancer. The general rules for gastric cancer study in Surgery and Pathology. Jpn J Surg 11:127-145, 1981
9. American Joint Committee of Cancer. Manual for staging of cancer (ed 4). Philadelpia, PA, Lippincott Company, 1992
10. International Union Against Cancer: TNM Classification of Malignant Tumors (ed 4). Berlin, Springer, 1992
11. International Union Against Cancer: TNM Classification of Malignant Tumors (ed 6). New York, NY, Wiley-Liss, 2002
12. Sano T, Katai H, Sasako M, et al: One thousand consecutive gastrectomies without operative mortality. Br J Surg 89:123, 2002
13. Siewert JR, Böttcher K, Stein HJ, et al: Relevant prognostic factors in gastric cancer: Ten year results of the German gastric cancer study. Ann Surg 228:449-461, 1998
14. Marubini E, Bozzetti F, Miceli R, et al: Lymphadenectomy in gastric cancer: Prognostic role and therapeutic implications. Eur J Surg Oncol 28:406-412, 2002
15. Sue-Ling HM, Johnston D, Martin IG, et al: Gastric cancer: A curable disease in Britain. BMJ 307:591-596, 1993
16. Griffith JP, Sue-Ling HM, Martin I, et al: Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 36: 684-690, 1995
17. Roukos DH, Lorenz M, Encke A: Evidence of survival benefit of extended (D2) lymphadenectomy in Western patients with gastric cancer based on a new concept: A prospective long-term follow-up study. Surgery 123:573-578, 1998
18. Bozzetti F, Marubini E, Bonfanti G, et al: Subtotal versus total gastrectomy for gastric cancer: Five-year survival rates in a multicenter randomised Italian trial. Ann Surg 230:170-178, 1999
19. Kodera Y, Yamamura Y, Shimizu Y, et al: Lack of benefit of combined pancreaticosplenectomy in D2 resection for proximal-third gastric carcinoma. World J Surg 21:622-628, 1997
20. Kitamura K, Nishida S, Ichikawa D, et al: No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer. Br J Surg 86:119-122, 1999
21. Csendes A, Burdiles P, Rojas J, et al: A prospective randomised study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. Surgery 131:401-407, 2002
22. Sano T, Yamamoto S, Sasako M: Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. Jpn J Clin Oncol 32:363-364, 2002
23. Edwards P, Blackshaw PG, Barry J, et al: Randomised comparison of D1 versus modified D2 gastrectomy for gastric cancer. Br J Surg 90:30, 2003 (suppl 1)
24. Damhuis RA, Tilanus HW: The influence of age on resection rates and postoperative mortality in 2773 patients with gastric cancer. Eur J Cancer 31A:928-931, 1995
25. Klein Kranenbarg E, van de Velde CJH: Gastric cancer in the elderly. Eur J Surg Oncol 24:384-390, 1998
26. Hermanek P, Altendorf-Hofmann A, Mansmann U, et al: Improvements in staging of gastric carcinoma using the new edition of TNM classification. Eur J Surg Oncol 24:536-541, 1998
27. Katai H, Yoshimura K, Maruyama K, et al: Evaluation of the new international union against cancer TNM staging for gastric cancer. Cancer 88:1796-1800, 2000
28. Klein Kranenbarg EK, Hermans J, van Krieken JHJM, et al: Evaluation of the fifth edition of the TNM classification for gastric cancer: Improved prognostic value. Br J Cancer 84:64-71, 2001
29. Songun I, Hermans J, van de Velde CJH, et al: Expression of oncoproteins and eosinophilic and lymphocytic infiltrates can be used as

prognostic factors in gastric cancer. Br J Cancer 74:1783-1788, 1996

30. Songun I, van de Velde CJH, Arends JW, et al: Classification of gastric carcinoma using the Goseki system provides prognostic information additional to TNM staging. Cancer 85:2114-2118, 1999

31. Weiss M, Kuipers E, Postma C, et al: Genomic profiling of gastric cancer predicts lymph node status and survival. Oncogene 22: 1872-1879, 2003

32. Gunderson LL, Sosin H: Adenocarcinoma of the stomach: Areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 8:1-11, 1982

33. Nashimoto A, Nakajima T, Furukawa H, et al: Randomised trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan clinical oncology group 9206-1. J Clin Oncol 21:2282-2287, 2003

34. 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 345:725-730, 2001

35. Schwarz RE: Postoperative adjuvant chemoradiation therapy for patients with resected gastric cancer: Intergroup 116. J Clin Oncol 19:1879, 2001

36. Cuschieri A: Does chemoradiotherapy after intended curative surgery increase survival of gastric cancer patients? Gut 50:751, 2002

37. Roukos DH: Adjuvant chemoradiotherapy in gastric cancer: Wave goodbye to extensive surgery? Ann Surg Oncol 9:220-221, 2002

38. Hundahl SA, Macdonald JS, Benedetti J, et al: Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: The effect of undertreatment. Ann Surg Oncol 9:278-286, 2002

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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

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

Patients and Methods
Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

Results
A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications, while one from each group died of rapid progressive cancer while inpatient.

Conclusion
Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

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INTRODUCTION

Gastric cancer is the second most common malignancy in the world, and surgical resection remains the only curative treatment option. Lymph node metastases occur during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus.

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s.[1] This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% to 40% of patients

Table 1. Eligibility Criteria of the Study

Before operation
Entry criteria
Histologically proven adenocarcinoma
75 years or younger
Forced expiratory volume in 1 second ≧ 50%
Arterial oxygen pressure in room air ≧ 70 mm Hg
Creatinine clearance ≧ 50 mL/min
Written consent
Exclusion criteria
Carcinoma in the remnant stomach
Borrmann type 4 (linitis plastica)
Synchronous or metachronous malignancy in other organs except for cervical carcinoma in situ and colorectal focal cancer in adenoma
Past history of myocardial infarction or positive results of exercise ECG
Liver cirrhosis or chronic liver disease with indocyanine green test ≧ 10%
During operation
Macroscopic T staging is T2-subserosa, T3, or T4
Potentially curative operation is possible
No gross metastasis in para-aortic nodes (frozen section diagnosis not allowed)
Peritoneal lavage cytology is negative for cancer cells

with positive lymph node metastases including the second tier lymph nodes, have survived longer than 5 years with D2 lymphadenectomy.[2] However, D2 gastrectomy has a steep learning curve,[3] and may be associated with a higher-than-expected operative morbidity and mortality.

Two European randomized controlled trials comparing D1 and D2 gastrectomy revealed a high operative mortality exceeding 10% in the D2 group.[4,5] Based on these reports, the British National Health Service Cancer Guidance discourages the use of D2 technique in routine clinical practice.[6] In contrast, D2 gastrectomy is considered a standard and safe procedure in Japan, where 100,000 cases of gastric cancers are diagnosed every year. General surgeons are taught this technique early during their surgical training.[7] The Japanese nationwide registry reported an operative mortality of less than 2%, and in specialized institutions, less than 1% for D2 gastrectomy.[8,9]

Since the eighties, even more radical extended lymphadenectomy procedures had been practiced in many Japanese specialized centers. It was reported that 20% to 30% of patients with nonearly gastric cancer had microscopic metastasis present in the para-aortic nodes.[10-13] The 5-year survival for these patients has reached 14% to 30% after extended systematic dissection. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected, primarily for ultimate local tumor control. However, this extended dissection may not only increase operative morbidity but also may effect the function of other abdominal organs.

There has never been a prospective study to assess the perioperative morbidity and mortality in Japanese patients after D2 gastrectomy or more extended surgery. To evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection in gastric cancer surgery, a multi-institutional randomized controlled trial was conducted on behalf of the Japan Clinical Oncology Group (JCOG). The accrual closed with 523 patients. We hereby present the data on the operative morbidity and mortality, which are the secondary end points of this trial. Survival analysis is scheduled to take place in August 2006.

PATIENTS AND METHODS

Objectives and End Points of the Study

A prospective randomized controlled trial was designed to compare the two surgical techniques: the standard lymphadenectomy and the standard lymphadenectomy with the addition of para-aortic node dissection for gastric cancer. Only surgeons with sufficient experience of para-aortic dissection for gastric cancer participated in the trial. Since the role of neoadjuvant and adjuvant chemotherapy was not established, no patients received chemotherapy until recurrent disease was diagnosed.

The primary end point was the overall survival, while the secondary end points were the relapse-free survival, operative morbidity, hospital mortality, and quality of life. Randomization and data handling for this study was performed by the Data Centre of the JCOG, a government-sponsored organization for multi-institutional clinical trials.[14]

Eligibility Criteria

Eligibility criteria for this study are shown in Table 1. Patients with advanced gastric cancer deemed curable and fit for surgery were recruited into the trial following informed consent. Borrmann type 4 tumors (linitis plastica) were excluded because of their very poor prognosis after surgery. Liver cirrhosis and ischemic heart disease were important risk factors for mortality after surgery and hence were excluded from the study. Para-aortic lymph node metastasis is extremely rare in T1 (invasion confined

to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

Surgical Methods

Group A: Standard D2 gastrectomy. Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

Group B: D2 gastrectomy combined with para-aortic lymphadenectomy. Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

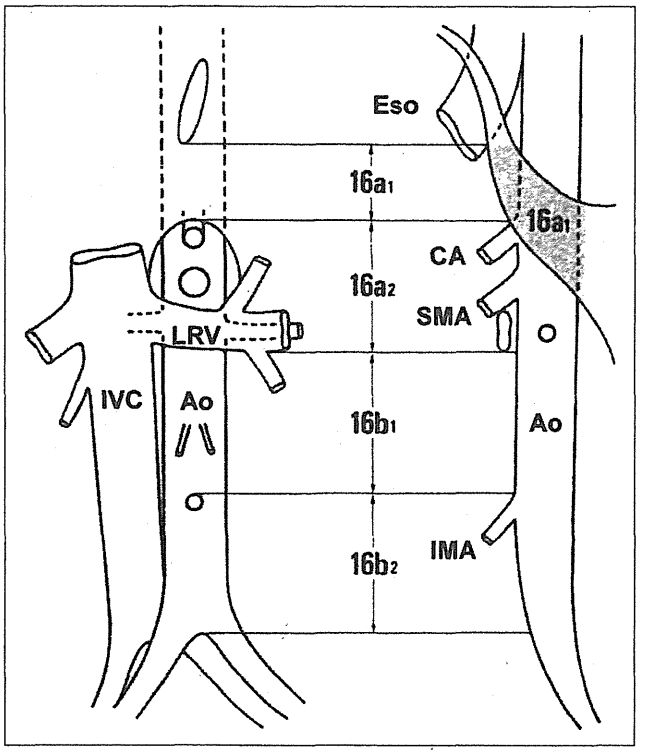

Fig 1. Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided α error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to