sense, oral S-1 monotherapy is easy to accept, reserving other combination regimens for disease recurrence. In future trials, it will become more important to categorize patients according to the risk of relapse and to set appropriate experimental arms.

After the emergence of the strong evidence by these pivotal studies, it is clear that "surgery alone" will disappear from adjuvant trials for gastric cancer, and this will facilitate patient recruitment. The study design to compare various combinations of treatments will surely become complicated, and international collaboration may become necessary. The role of the surgeons should not be underestimated here, because, in this stage of disease, surgery still plays the central role in multimodality therapy, and different surgical standards may yield inconsistent results.

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Disclosures of Potential Conflicts of Interest

Dr. Sano has no potential conflicts of interest to disclose.

Pathology International 2007; **57**: 315–321 doi:10.1111/j.1440-1827.2007.02102.x

Original Article

Two distinct pathways of tumorigenesis of adenocarcinomas of the esophagogastric junction, related or unrelated to intestinal metaplasia

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It is still uncertain whether intestinal metaplasia (IM) of the esophagogastric junction (EGJ) plays a role in the development of adenocarcinoma of the esophagogastric junction (AEGJ). The purpose of the present study was to clarify the relationship between AEGJ and IM in Japanese patients. Forty-eight AEGJ, <3 cm and centered within 1 cm of the EGJ, were investigated. The frequency of IM around AEGJ and the correlation between IM and clinicopathological features were examined. IM was present in the surrounding mucosa in 22 of 48 cases (46%), and was seen more frequently in older patients ($P = 0.008$). Lymph node metastasis was observed only in cases in which the tumors were not associated with IM ($P = 0.017$). The gastric phenotype was seen almost exclusively in the group without IM, while the intestinal phenotype was predominant in the group with IM ($P = 0.003$). The present study found a lower incidence of associated IM than Western studies, and there were significant differences in clinicopathological features between AEGJ with and without IM. It is suggested that AEGJ may develop via two distinct pathways in Japanese patients: IM-related and IM-unrelated.

Key words: adenocarcinoma, esophagogastric junction, gastric/intestinal phenotypic expression, intestinal metaplasia

In parallel with the rising incidence of adenocarcinoma of the esophagus, adenocarcinoma of the esophagogastric junction (AEGJ) has been observed with increasing frequency in Western countries.[1,2] Intestinal metaplasia (IM) is recognized as a precancerous lesion of Barrett's esophagus or the distal stomach,[3–5] but its role in the development of AEGJ is still unclear. Some Western studies have noted a variable frequency of IM in the background mucosa of AEGJ, ranging from 38% to 100%.[6–11] For instance, the frequency of accompanying IM was reportedly as high as 69–100% for tumors with a mean size of <2.3 cm,[8–10] whereas it was as low as 42% for tumors >3.5 cm[6,7] Cameron *et al.* have suggested that large-sized AEGJ probably overgrow and conceal the underlying specialized columnar epithelium (SCE) from which they arise, whereas small tumors preserve their background mucosa of origin.[6,10] They concluded that all AEGJ might arise from IM of the esophagogastric junction (EGJ). In contrast, in Japanese patients, Tsuji *et al.* found IM adjacent to the tumor in the resected specimen in 21 (38%) of 54 cases of AEGJ <4 cm[11] They reported that there were two different types of AEGJ in Japan: tumors straddling the EGJ and tumors occurring entirely below the EGJ, the former having less IM in the surrounding mucosa.

In the present study we reviewed 48 small AEGJ to clarify the relationship between AEGJ and IM in Japanese patients. AEGJ was defined as an adenocarcinoma with its center located within 1 cm of the EGJ, strictly excluding adenocarcinoma arising from gastric fundic gland mucosa. The present study involves the largest number of cases of AEGJ <3.0 cm reported to date.

MATERIALS AND METHODS

Cases

We reviewed files of consecutive cases of AEGJ resected surgically with lymph node dissection, or endoscopic

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Received 8 September 2006. Accepted for publication 26 January 2007.

Table 1 Antibodies and cell types recognized

Antigen (clone)	Clonality	Dilution	Source	Expression in normal tissue
MUC5AC (45M1)	Monoclonal	1:100	Novocastra, Newcastle upon Tyne, UK	Gastric foveolar epithelial cell
MUC6 (CLH5)	Monoclonal	1:100	Novocastra, Newcastle upon Tyne, UK	Mucous neck cell, pyloric gland cell
MUC2 (Ccp58)	Monoclonal	1:200	Novocastra, Newcastle upon Tyne, UK	Goblet cell in small intestine and colon
CD10 (56C6)	Monoclonal	1:200	Novocastra, Newcastle upon Tyne, UK	Brush border on luminal surface
Cdx2 (CDX2-88)	Monoclonal	1/200	BioGenex, San Roman, CA, USA	Intestinal epithelial cells
CK7 (OV-TL 12/30)	Monoclonal	1/500	Dako, Carpinteria, CA, USA	–
CK20 (Ks 20.8)	Monoclonal	1/50	Dako, Carpinteria, CA, USA	–

mucosal resection (EMR), between January 1989 and December 2003 at the National Cancer Center Central Hospital. In the present study AEGJ was defined as an adenocarcinoma with its center located within 1 cm of the EGJ, strictly excluding adenocarcinoma arising from gastric fundic gland mucosa. Patients who had tumors <3 cm in maximum diameter were selected. Those who had received neoadjuvant therapy were excluded. Finally, 48 patients with small AEGJ met the study criteria. Of these 48 cases, we obtained 32 specimens by surgical resection with lymph node dissection and 16 by EMR.

Clinicopathological review

Clinicopathological characteristics, including patient age and gender, macroscopic type of tumor, tumor size, depth of tumor invasion, lymph node metastasis, and histological type, were reviewed. Pathological stage of AEGJ was determined according to the TNM Classification of Malignant Tumors established by the International Union Against Cancer.[12] The tumors were classified macroscopically as elevated, depressed, combined (combination of elevated and depressed type), or ulcerated type.

Histological examination

The resected specimens were fixed in 10% buffered formalin, and cut into serial 5 mm-wide slices in the case of surgical specimens and into 2 mm-wide slices in the case of EMR specimens. The slices were embedded in paraffin, cut into 3 μm-thick sections, and stained with HE.

The tumors were divided into differentiated or undifferentiated type according to the histological classification of Nakamura *et al.*[13] Each tumor was primarily classified on the basis of its predominant histological features, and then the presence or absence of a focal undifferentiated component was recorded. Undifferentiated component was defined as the presence of even a little undifferentiated type tumor according to Nakamura's classification, despite its predominant histology. The surrounding mucosa adjacent to cancer tissue was checked, the presence of IM was examined. IM was defined as the presence of goblet cells detected by HE staining and by immunohistochemical staining for MUC2.

Immunohistochemistry was performed on representative tissue sections of each lesion, using monoclonal antibodies to examine the gastric and intestinal phenotypic expression, as shown in Table 1.

Except for Cdx2, immunohistochemistry was performed using the avidin–biotinyl–peroxidase complex (ABC) method, as described previously.[14] An avidin–biotin horseradish peroxidase complex kit (StreptABComplex/HRP, Dako, Glostrup, Denmark) was used for the ABC method, in accordance with the manufacturer's instructions. For Cdx2, we used the L-SAB method with a Super Sensitive Ready-to-Use kit (BioGenex, San Ramon, CA, USA), also in accordance with the instructions supplied. 3,3′-Diaminobenzidine tetrachloride was used as a chromogen. Nuclear counterstaining was carried out with Mayer's hematoxylin. Negative controls involved substitution of similar dilutions of control mouse IgG1. Sections containing gastric foveolar cells, deep gastric gland cells and small-intestinal epithelial cells were used as positive controls for MUC5AC, MUC6, MUC2, CD10 and Cdx2, respectively.

Staining for MUC5AC, MUC6, MUC2, CD10, and Cdx2 was judged positive when >25% of the tumor cells were stained. Staining for MUC5AC, MUC6, and MUC2 was judged positive when it occurred in the cytoplasm, that for CD10 when the luminal surface was stained, and that for Cdx2 when nuclei were stained. MUC5AC and MUC6 were used as gastric phenotype markers, and MUC2, CD10, and Cdx2 as intestinal phenotype markers. Based on the immunohistochemical results, tumors were classified as having the gastric phenotype when they were positive for MUC5AC and/or MUC6 and negative for MUC2, CD10 and Cdx2, and the intestinal phenotype when they were positive for at least one of MUC2, CD10, and Cdx2, and negative for MUC5AC and MUC6, and the mixed phenotype when both gastric and intestinal characteristics were present. If a tumor was negative for all five of these antigens, it was judged as unclassified. We also examined the correlation between the gastric or intestinal phenotype and the presence of undifferentiated components.

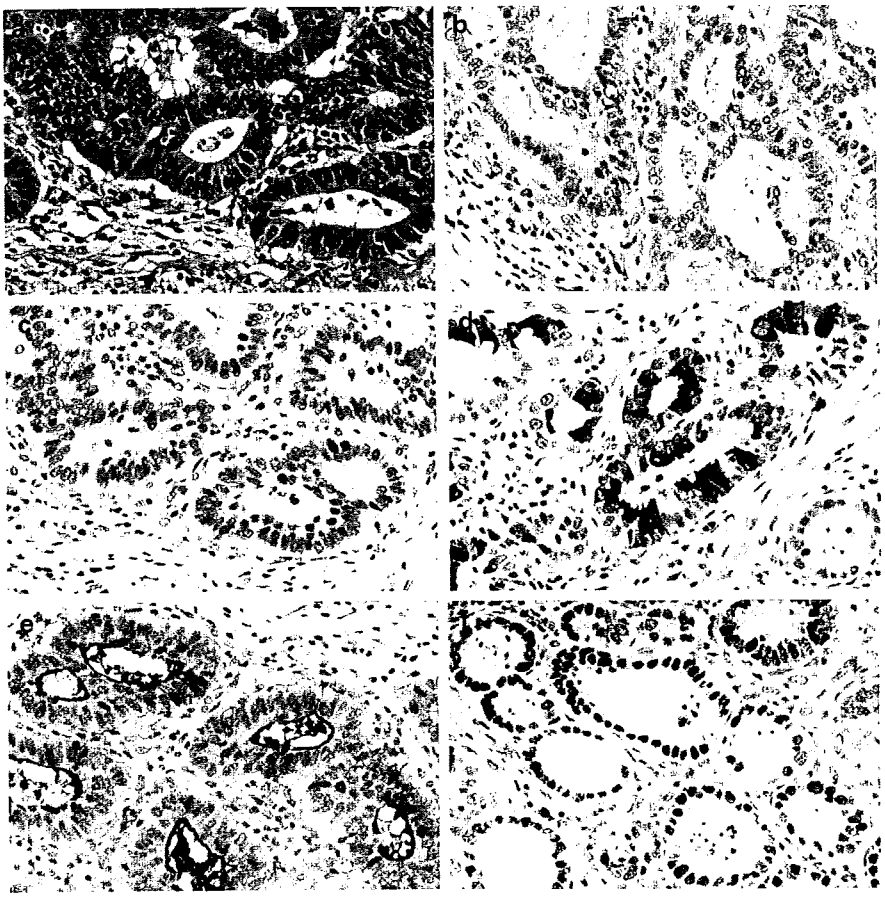

Figure 1 Adenocarcinoma of esophagogastric junction with intestinal phenotype. (**a**) Tumor cells have eosinophilic cytoplasm (HE). (**b**) MUC5AC and (**c**) MUC6 are not expressed in the cytoplasm of the tumor cells. Tumor cells are positive for (**d**) MUC2, (**e**) CD10, and (**f**) Cdx2.

The histological and immunohistochemical studies were reviewed by three pathologists (S. N., Y. N. and T. S.) without knowledge of the patients' clinical background.

Statistics

Statistical analysis was performed with the SPSS statistical software package (SPSS Japan, Tokyo, Japan). Comparisons between groups were made using χ^2 test or Mann–Whitney *U*-test as appropriate. Statistical significance was defined as $P < 0.050$.

RESULTS

Clinicopathological characteristics

The mean age of the patients was 65.0 years (range, 37–85 years). There was a strong predominance of men in the present series (male : female ratio, 43:5). The mean tumor width was 1.9 cm (range, 0.6–3.0 cm). On the basis of macroscopic appearance, the tumors were divided into four groups: 18 cases (38%) of the elevated type, 20 cases (42%) of the depressed type, nine cases (19%) of the combined type (combination of elevated and depressed), and one case (2%) of the ulcerated type. Histologically, most of the tumors were differentiated (45 cases; 94%) and there were only three cases (6%) of undifferentiated type. Undifferentiated components were found in 14 of the 48 patients (29%), and were frequently present at the invasive front in differentiated tumors. Carcinoma *in situ* or intramucosal cancer (Tis) was observed in 16 cases (33%), T1 in 26 (54%), T2 in four (8%), and T3 in two (4%) by the tumor nodes metastases (TNM) classification. Six (19%) of the 32 patients whose tumors were resected surgically had lymph node metastasis. Fifteen of the 48 patients had Barrett's epithelium.

The tumors were classified immunohistochemically into the gastric phenotype in 13 (27%) cases, the intestinal phenotype in 18 (38%), the mixed phenotype in 15 (31%), and

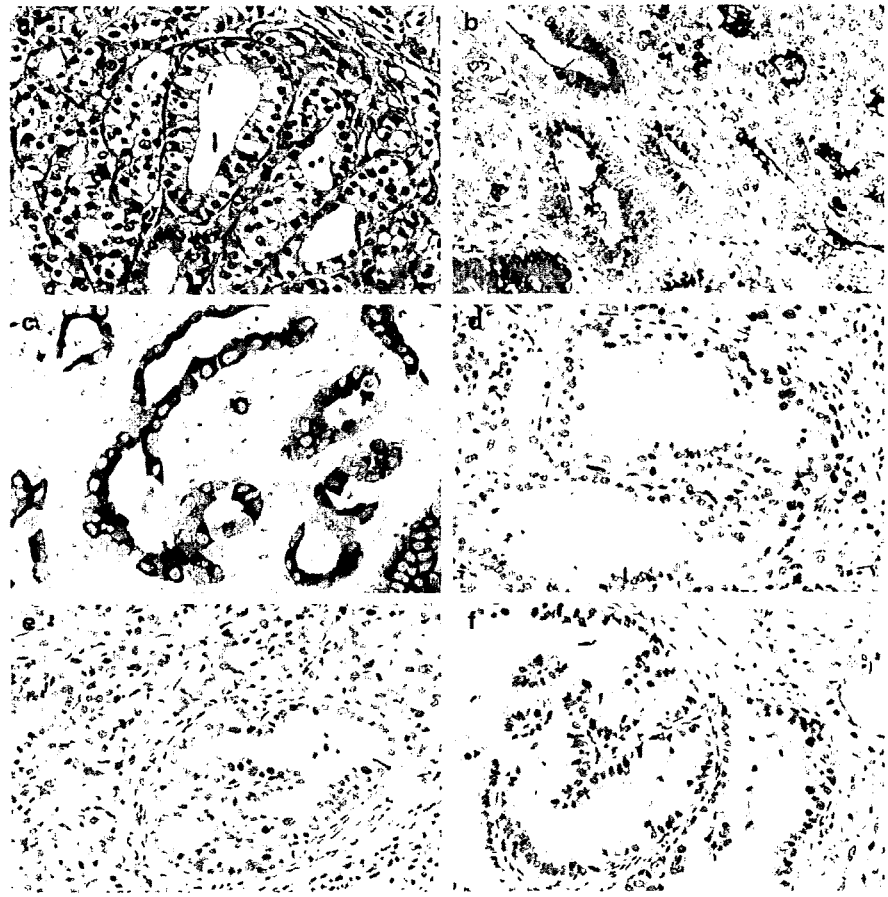

Figure 2 Adenocarcinoma of the esophagogastric junction with a gastric phenotype. (**a**) Tumor cells have clear cytoplasm (HE) and show cytoplasmic positivity for (**b**) MUC5AC and (**c**) MUC6. (**d**) MUC2, (**e**) CD10 and (**f**) Cdx2 are not expressed in the tumor cells.

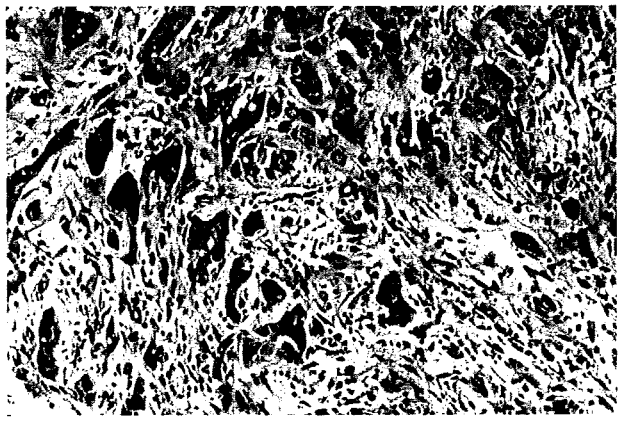

Figure 3 Undifferentiated component of the tumor. Tumor cells permeate as single cells or as small nests.

unclassified in two (4%). The tumors with an intestinal phenotype tended to have eosinophilic cytoplasm, whereas those with a gastric phenotype tended to have clear cytoplasm in the sections stained with HE (Figs 1,2).

Correlation between clinicopathological features and the presence of IM in surrounding non-neoplastic mucosa

IM, also known as SCE, was found in the surrounding non-neoplastic mucosa in 22 of the 48 patients (46%), while the remaining 26 (54%) were not associated with IM. Tumors associated with IM were seen more frequently in older patients ($P = 0.008$), and lymph node metastasis was seen only in patients whose tumors were unassociated with IM ($P = 0.017$; Table 2). Other factors, such as gender, tumor size, gross appearance, and pT staging, had no significant difference between tumors associated and unassociated with IM.

The differentiated type was the predominant histological feature observed in both groups. However, tumors without IM had undifferentiated components more frequently than those with IM ($P = 0.030$, Fig. 3).

A gastric phenotype was seen almost exclusively in tumors without IM (12 of 13 cases, 92%), whereas an intestinal phenotype was predominant in those with IM (12 of 18 cases,

Table 2 Clinicopathological characteristics of small AEGJ

	With IM $n=22$	Without IM $n=26$	P
Gender (M/F)	18/4	25/1	0.126
Age (years)			
≥60	19	13	
<60	3	13	0.008
Mean (range)	68.7 (54–84)	61.9 (37–85)	
Mean tumor size (mm)	19.5	19.1	0.641‡
Gross appearance			
Elevated	7	11	
Depressed	10	10	
Combined†	5	4	
Ulcerated		1	0.642
pT			
Tis	7	5	
T1	13	17	
T2	2	2	
T3		2	0.466
pN (surgical cases)			
Negative	14	12	
Positive	0	6	0.017
Histological type			
Differentiated	21	24	
Undifferentiated	1	2	0.564
Undifferentiated component			
Present	3	11	
Absent	19	15	0.030
Gastric and intestinal phenotype (mucosa)§			
Gastric phenotype	1 (1)	12 (16)	0.003
Intestinal phenotype	12 (15)	6 (5)	(0.000)
Mixed phenotype	9 (6)	6 (3)	
Unclassified	0 (0)	2 (2)	

†Combination of elevated and depressed type.
‡Mann–Whitney U-test.
§Incidence of the intramucosal phenotype of the tumor.
AEGJ, adenocarcinoma of the esophagogastric junction; IM, intestinal metaplasia.

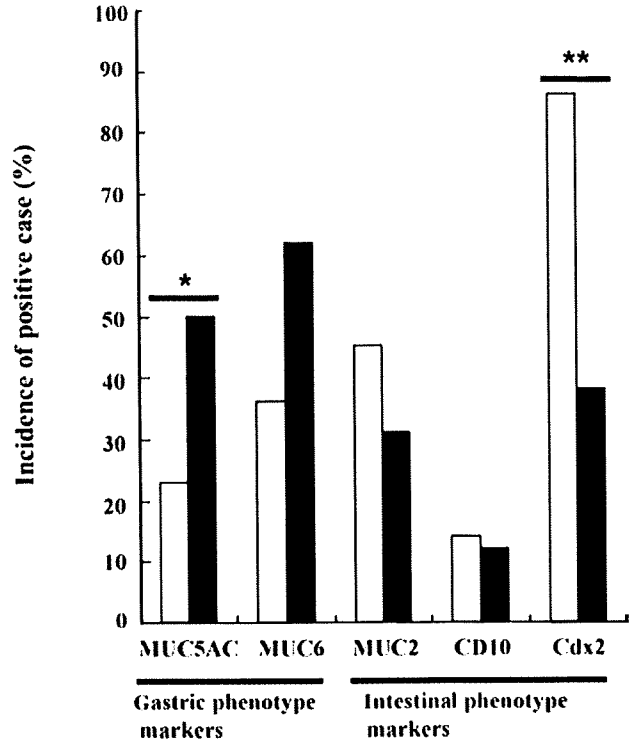

Figure 4 Expression of gastric and intestinal phenotype markers of adenocarcinoma of esophagogastric junction (AEGJ). The proportion of positive cases is shown on the vertical axis. There is a significant difference in MUC5AC and Cdx2 expression between AEGJ (□) with and (■) without intestinal metaplasia in the background mucosa. $^{*}P=0.049$; $^{**}P=0.001$.

Table 3 Correlation between presence of undifferentiated components and phenotype of AEGJ

	Undifferentiated component	
	Present	Absent
Gastric phenotype	9 (9)	4
Intestinal phenotype	1 (1)	17
Mixed phenotype	3 (2)	12
Unclassified	1 (1)	1

$P=0.001$.
(n), incidence of the phenotype in the undifferentiated components.
AEGJ, adenocarcinoma of esophagogastric junction.

67%; $P=0.003$). In the intramucosal phenotype, a gastric phenotype was also seen almost exclusively in tumors without IM (16 of 17 cases), whereas an intestinal phenotype was predominant in those with IM (15 of 20 cases; $P=0.000$). In some cases, gastric or intestinal phenotype were seen to be mixed type according to deeper invasion of the tumor. Expression of each of the gastric phenotype makers, MUC5AC and MUC6, was observed more frequently in tumors without IM than in those with IM, while expression of each of the intestinal phenotype markers, MUC2, CD10 and Cdx2, was observed more often in tumors with IM than in those without IM. There were significant differences in the incidence of positivity for MUC5AC and Cdx2 between AEGJ with IM and those without IM (Fig. 4, $P=0.049$ and 0.001, respectively).

Table 3 illustrates the correlation between phenotypic expression and the presence of undifferentiated components. The gastric phenotype was significantly related to the presence of undifferentiated components in the tumor ($P=0.001$). In cases of undifferentiated components, the phenotype in the undifferentiated components did follow the phenotype in almost all of the cases.

DISCUSSION

IM in Barrett's esophagus and the distal stomach is generally considered to be an important risk factor for the development of adenocarcinoma.[3–5] However, its contribution to

Table 4 Published reports on IM in background mucosa of AEGJ

Authors, year	*n*	Mean tumor size (cm)	IM, *n* (%)
Clark *et al.* (1994)[7]	31	3.5	13 (42%)
Cameron *et al.* (1995)[6]	24	6.0	10 (42%)
Van Sandick *et al.* (2000)[8]	12	2.3	12 (100%)
Ruol *et al.* (2000)[9]	16	2.0	11 (69%)
Cameron *et al.* (2002)[10]	22	1.4	19 (86%)
Tsuji *et al.* (2004)[11]	54‡	–†	21 (38%)
Present study	48‡	2.0	22 (46%)

†<4 cm.
‡Japanese patients.
AEGJ, adenocarcinoma of the esophagogastric junction; IM, intestinal metaplasia.

the development of AEGJ is still a matter of debate. The incidence of AEGJ is about the same as that of adenocarcinoma of the esophagus,[15] but gastroscopy has shown that the prevalence of IM at the EGJ (up to 15%),[2,16–19] is considerably higher than that of long Barrett's esophagus (up to 1%).[20] Clearly, then, the risk of cancer is lower in IM of the EGJ than in Barrett's esophagus. In the present study of small AEGJ located within 1 cm of the EGJ, only 46% of tumors were found to be associated with IM. Although some claim that IM plays an etiological role in the development of AEGJ, our findings suggest that a significant proportion of AEGJ arises in a background without IM.

Table 4 compares the prevalence of IM in reported cases of AEGJ between the West and Japan. A higher prevalence of IM has been observed in several Western studies confined to small tumors.[8–10] In contrast, the frequency of IM is much lower in Japanese subjects than in the West, irrespective of tumor size. Western reports have postulated that the absence of specialized IM in many patients with AEGJ may be caused by complete replacement of the metaplastic epithelium. Because IM is usually confined to ultrashort segments in these tumors, it may be easily concealed by the overgrown tumor. Furthermore, epidemiological differences between the West and Japan may affect the frequency of IM at the EGJ in each country. Although Western studies have shown correlations between AEGJ and body mass index, smoking, alcohol drinking, Barrett's esophagus and gastroesophageal reflux disease (GERD),[2,21–24] Okabayashi *et al.* found no correlation between AEGJ and these clinicopathological factors in Japanese cases of early AEGJ.[25]

It is well known that both gastric and intestinal phenotypic markers are expressed in gastric carcinomas, irrespective of their histological type, and that gastric carcinomas of each phenotype have distinct clinicopathological characteristics.[26–29] Koseki *et al.* in a study of adenocarcinomas of the distal stomach, reported that adenocarcinoma with a gastric phenotype frequently had lymph node metastasis and undifferentiated components.[28] In the present study, AEGJ without IM was significantly correlated with a gastric phenotype, undifferentiated components and lymph node metastasis. Also, AEGJ with a gastric phenotype was significantly correlated with the presence of undifferentiated components. In contrast, AEGJ associated with IM was seen more frequently in older patients and had an intestinal phenotype. These findings are comparable to previous data for adenocarcinoma of the distal stomach,[28] and it has been shown that IM at the EGJ frequently develops with aging.[19] It is possible that a gastric phenotype causes an increased potential for malignancy including lymph node metastasis in patients with AEGJ unassociated with IM, and that AEGJ may arise more frequently via the pathway related to IM in aged patients.

In the present series, AEGJ with IM was predominantly of the intestinal phenotype, whereas that without IM tended to have the gastric phenotype. This tendency was more recognized in the incidence of the intramucosal phenotype. The positivity rates for both of the gastric phenotype markers, MUC5AC and MUC6, were higher in AEGJ without IM, whereas, those for all the intestinal phenotype markers, including MUC2, CD10, and Cdx2, were elevated in AEGJ with IM. In particular, there were significant differences in the positivity rates for MUC5AC and Cdx2 between AEGJ with and without IM. In the cases of undifferentiated components, the phenotype in the undifferentiated components did follow the phenotype in almost all of the cases. So, this difference between the gastric and intestinal phenotype of AEGJ may reflect the differentiation status of the surrounding mucosa, taking undifferentiation or deeper invasion of the tumor into consideration.

In summary, the present study of a series of small AEGJ in Japanese patients found a lower incidence of associated IM in comparison with Western series. Although Western reports have suggested that virtually all AEGJ might develop in a background of IM, we found that a proportion of AEGJ would arise from mucosa without IM. AEGJ with or without IM in the background mucosa was found to differ in several clinicopathological features including phenotypic expression, lymph node metastasis and the presence of undifferentiated components. Our findings suggest that there are two distinct pathways of AEGJ tumorigenesis: an IM-related pathway and an IM-unrelated pathway.

ACKNOWLEDGMENTS

This research was supported in part by a Grant-in-Aid for the Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan. We thank Ms Sekine for technical assistance.

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Jpn J Clin Oncol 2007;37(6)429–433
doi:10.1093/jjco/hym067

Risk Factors for Para-aortic Lymph Node Metastasis of Gastric Cancer from a Randomized Controlled Trial of JCOG9501

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Received May 24, 2006; accepted January 29, 2007

Background: No risk factor has been confirmed for para-aortic lymph node (PAN) metastasis from gastric cancer. To identify the risk factors and the most frequent route of metastasis to PAN, we analyzed the prospective data from a phase III trial.
Methods: In JCOG9501 comparing D2 and D2 + PAN dissection, 260 patients with T2(SS)-T4 gastric cancer underwent radical gastrectomy with PAN dissection. The association between various clinicopathological factors and PAN metastasis was examined.
Results: Macroscopic N stage and tumor size $\geq$5 cm were significant risk factors for PAN metastasis after adjusting for other factors. The proportion of PAN metastasis was clearly different between the N0–1 group and the N2–4 group (2.8% versus 20.5%). In the additional multivariate analysis including 17 regional lymph node stations, station No. 7 was the only station with statistical significance ($P = 0.002$, odds ratio = 41.0).
Conclusion: Macroscopic N stage and tumor size were associated with PAN metastasis, and the lymphatics along the left gastric artery seemed to be the most frequent route to the nodes surrounding the aorta. These findings may be useful in predicting PAN metastasis.

Key words: gastric cancer – para-aortic lymph node metastasis – risk factors – randomized controlled trial

INTRODUCTION

Most of the lymphatic flow from the stomach runs into the para-aortic lymph nodes (PAN), which are located above and below the left renal vein, before it flows into the cisterna chyli lying posterior to the aorta (1,2). Although the lymphatic flow is thought to reach the PAN through several routes (3,4), it is unclear which route is the most frequent access to PAN. In addition, the clinicopathological risk factors to predict metastasis to PAN have been unknown due to selection bias and contamination in surgically PAN positive patients in the majority of retrospective analyses.

In Japan, the regional lymph nodes of the stomach are generally classified into stations numbered as in Fig. 1 (5). According to the 12th Edition of the Japanese General Rules for the Gastric Cancer Study (GRGCS) (6), the lymph node metastasis of gastric cancer was classified into four categories (N1, N2, N3 and N4) (Table 1, Fig. 1). Metastasis to PAN belonged to N4, while it is grouped into distant metastasis (M1) in the TNM classification (7). In Japan, the extended lymphadenectomy including N1 and N2 categories, known as D2, has been accepted as a

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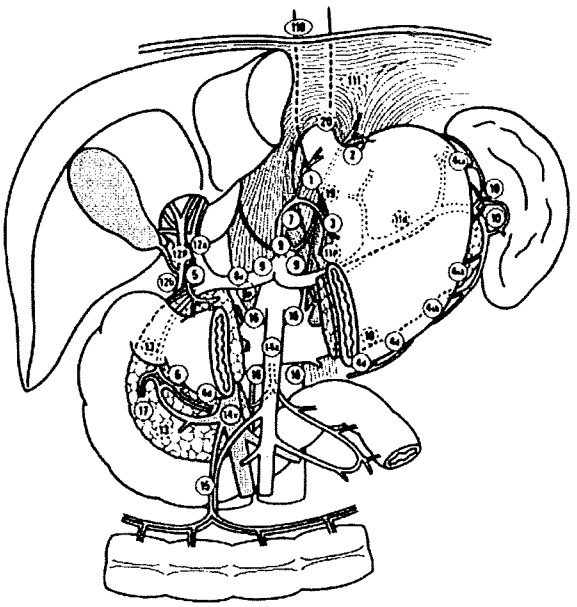

Figure 1. Schema of the location of the gastric regional lymph node stations (by Japanese Classification (5)) (please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org).

standard surgical procedure for gastric cancer (8,9), and more radical surgery with extended para-aortic lymph node dissection (PAND) has been practiced to improve the survival for advanced gastric cancer in some specialized centers (10–13). Because PAND was controversial, a randomized controlled trial, the Japan Clinical Oncology Group Study 9501, was launched in 1995 to explore the potential survival benefit of D2 plus PAND over D2 dissection.

In the present study, we focused on 260 gastric cancer patients in the experimental treatment arm of JCOG9501 who underwent curative gastrectomy with D2 plus PAND, to identify the risk factors for PAN metastasis and the most likely route of metastasis to PAN.

PATIENTS AND METHODS

We used data obtained from the JCOG9501 study. The details of this phase III trial have been described elsewhere (14). Briefly, the eligibility criteria were histologically proven adenocarcinoma of the stomach, T2(subserosa)-T4, M0, no macroscopic metastasis to the PAN, negative lavage cytology, adequate organ function, and age $\leq$75 years. Linitis plastica ('Bormann type 4') was excluded. All of the patients gave written informed consent to the study. Randomization and data handling were performed by the JCOG Data Center, a government-sponsored organization to perform multicenter clinical trials. Approval of the institutional review board was obtained at all participating institutions. The 24 institutions belonging to the Gastric Cancer Surgical Study Group of the JCOG participated in the trial.

From June 1995 to April 2001, 523 gastric cancer patients were randomized, and 260 patients were assigned to an experimental treatment arm and underwent D2 plus PAND surgery. In this group, PAN were dissected from the level of the celiac trunk down to the root of the inferior mesenteric artery (stations No. 16a2 and No. 16b1).

All the data were recorded according to the 12th Edition of the GRGCS (6) which was available at the start of the study. Although the 13th Edition (1998) with new nodal classification (N1–N3) is currently available (5), we used the original data description in the present study.

The clinicopathological parameters that could be identified pre- or intra-operatively to decide the indication for PAND were compared between patients with and without PAN metastasis. The Fisher's exact test or χ^2 test were used to assess the differences in proportion. To assess the association of various factors with PAN metastasis, multivariate logistic regression analysis was used with backward elimination procedure for variable selection with $\alpha = 0.20$. Next, the association between the histological status of 17 regional lymph node stations and the proportion of PAN metastatis were evaluated with odds ratio. In addition, to assess the relative strength of the association between lymph nodes and the PAN metastasis, all the 17 nodal stations were included in the multivariate logistic regression with backward elimination procedure for variable selection with $\alpha = 0.20$.

Table 1. Categories of the gastric regional lymph nodes divided by the location

Category*	Tumor location			
	Lower third	Middle third	Upper third	Whole stomach
N1	3, 4sa, 4sb, 4d, 5, 6	1, 3, 4sa, 4sb, 4d, 5, 6	1, 2, 3, 4sa, 4sb	1, 2, 3, 4sa, 4sb, 4d, 5, 6
N2	1, 7, 8a, 9	2, 7, 8a, 9, 10, 11	4d, 5, 6, 7, 8a, 9, 10, 11, 20	7, 8a, 9, 10, 11
N3	2, 8p, 10, 11, 12, 13, 14v, 17, 18	8p, 12, 13, 14v, 17, 18	8p, 12, 13, 14v, 17, 18, 19, 110, 111	8p, 12, 13, 14v, 17, 18, 20, 110, 111
N4	14a, 15, 16, 19, 20	14a, 15, 16, 19, 20	14a, 15, 16	14a, 15, 16, 19

*Categories of the regional lymph nodes were classified according to the 12th Edition of the Japanese General Rules for Gastric Cancer Study (6).

Table 2. Association between clinicopathological factors and histological metastasis of para-aortic lymph nodes (PAN)

Factors	Category	Proportion of PAN metastasis (%)	Univariate		Multivariate	
			Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex	Male	9.9% (18/182)	2.0 (0.7–6.2)	0.24	2.4 (0.7–7.7)	0.16
	Female	5.1% (4/78)				
Body mass index	<25	9.0% (20/221)	1.8 (0.4–8.2)	0.55	–	–
	25	5.1% (2/39)				
Macroscopic type	3, 5	9.9% (15/151)	1.6 (0.6–4.1)	0.37	–	–
	0, 1, 2	6.4% (7/109)				
Tumor location	Lower	10.9% (12/110)	5.6 (0.7–45.5)	0.19	–	–
	Middle	8.7% (9/103)	1.3 (0.5–3.2)		–	
	Upper	2.1% (1/47)				
Tumor size	5 cm	12.7% (21/165)	13.7 (1.8–103.6)	<0.001	8.2 (1.1–64.5)	0.045
	<5 cm	1.1% (1/95)				
Histological type	Undifferentiated	11.7% (18/154)	3.4 (1.1–10.3)	0.025	2.7 (0.8–8.8)	0.093
	Differentiated	3.8% (4/106)				
T stage	T3, T4	10.8% (18/167)	2.7 (0.9–8.2)	0.10	–	–
	T2(SS)	4.3% (4/93)				
N stage*	N2, N3, N4	20.5% (17/83)	8.9 (3.1–25.0)	<0.001	6.9 (2.4–20.0)	<0.001
	N0, N1	2.8% (5/177)				

*Macroscopic N stage was classified according to the 12th Edition of the Japanese General Rules for Gastric Cancer Study (6).

Two-sided *P* values were calculated and are presented. Statistical analysis was performed using SAS version 8.12 software (SA5 Institute, Tokyo, Japan).

In order to validate reproducibility of the predictive factors detected in this prospective study, we analyzed a retrospectively collected data set consisting of 158 patients who had undergone gastrectomy with PAND at Osaka Medical College between 1978 and 1999.

RESULTS

The patients ranged in age from 27 to 75 years (mean age, 61.0 years) and included 182 men and 78 women. In 47 of the 260 patients, the tumor was located in the upper third of the stomach, while it was in the middle third in 103 and the lower third in 110. Total gastrectomy was performed in 97 patients, distal gastrectomy in 160, and proximal gastrectomy in three.

PAN metastasis was histologically found in 22 (8.3%) of 260 patients. The association between the possible risk factors and PAN metastasis is shown in Table 2. Tumor size $\geq$ 5 cm, undifferentiated type of histology, and macroscopic N2–4 stage at surgery showed significant association in univariate analysis. After adjustment of other variables, macroscopic N stage and tumor size showed statistically significant association. The proportion of PAN metastasis stratified with macroscopic N stage is shown in Table 3. There were no significant associations in sex, body mass index, macroscopic tumor type, tumor location or macroscopic T stage.

In the independent data set from Osaka Medical College, the above results were reproduced; in macroscopically N0/N1 cases, PAN metastasis was found in 1.6% (1/64), while in macroscopically N2 or N3/4, PAN metastasis was found in 9.8% (6/61) and 42.4% (14/33), respectively (Table 3).

We next examined the associations between the histological status of 17 regional lymph node stations and PAN metastasis (Table 4). Most nodal stations except for those along the greater curvature of the stomach (No. 2, 4sa, 4sb, 10) and No. 13, had significant association with PAN

Table 3. Proportion of histological metastasis of para-aortic lymph nodes (PAN) stratified with macroscopic N stages

N stage*	Proportion of PAN metastasis (%)	
	JCOG9501	Osaka Medical College
N0	1/42 (2.4)	0/13 (0)
N1	4/135 (3.0)	1/51 (2.0)
N2	12/72 (16.7)	6/61 (9.8)
N3–4	5/11 (45.5)	14/33 (42.4)

*Macroscopic N stage was classified according to the 12th Edition of the Japanese General Rules for Gastric Cancer Study (6).

Table 4. Association between histological metastasis of 17 regional lymph node stations and that of para-aortic lymph nodes (PAN)

Lymph node station	Histological metastasis	Proportion of PAN metastasis (%)	Odds ratio (95% CI)	*P* value
1	+	27.5% (11/40)	7.2 (2.9–18.1)	<0.001
	−	5.0% (11/220)		
2	+	20.0% (2/10)	1.9 (0.4–10.0)	0.61
	−	11.7% (12/103)		
3	+	18.0% (21/117)	31.1 (4.1–234.8)	<0.001
	−	0.7% (1/143)		
4sa	+	20.0% (2/10)	2.2 (0.4–11.5)	0.31
	−	10.4% (11/106)		
4sb	+	13.3% (2/15)	1.7 (0.4–8.2)	0.37
	−	8.2% (20/245)		
4d	+	16.0% (12/75)	3.3 (1.4–8.0)	0.012
	−	5.4% (10/184)		
5	+	24.2% (8/33)	4.8 (1.8–12.6)	0.003
	−	6.2% (14/225)		
6	+	21.8% (17/78)	9.8 (3.5–27.6)	<0.001
	−	2.8% (5/180)		
7	+	45.5% (15/33)	26.2 (9.5–72.5)	<0.001
	−	3.1% (7/227)		
8a	+	28.6% (12/42)	8.3 (3.3–20.9)	<0.001
	−	4.6% (10/218)		
8p	+	40.0% (4/10)	8.5 (2.2–32.9)	0.006
	−	7.3% (17/233)		
9	+	35.3% (6/17)	7.7 (2.5–23.6)	0.001
	−	6.6% (16/243)		
10	+	25.0% (2/8)	3.3 (0.6–18.6)	0.20
	−	9.3% (9/97)		
11	+	33.3% (8/24)	7.9 (2.9–21.7)	<0.001
	−	5.9% (14/236)		
12	+	50.0% (3/6)	11.9 (2.2–63.5)	0.010
	−	7.7% (18/233)		
13	+	40.0% (2/5)	6.4 (1.0–40.7)	0.084
	−	9.5% (17/179)		
14v	+	37.5% (3/8)	6.6 (1.4–29.9)	0.030
	−	8.4% (17/203)		

metastasis ($P < 0.05$). Among those 12 stations, No. 3 and No. 7 showed much higher odds ratios than others. When we entered the histological status of all N1 or N2 stations to the multivariate logistic regression model, any stations except No. 7 were removed owing to the variable selection with $\alpha = 0.20$. Station No. 7 was shown to be statistically significant ($P = 0.002$) with the odds ratio of 41.0 (95% confidence interval (CI), 4.0–425.3). When we used the histological status of station No. 7 as the diagnostic factor of PAN metastasis, the sensitivity and specificity were calculated at 68.2 and 92.4%, respectively.

DISCUSSION

In the present study, the incidence of PAN metastasis was significantly higher in patients with undifferentiated tumor, large tumor and tumor with macroscopic N2–4. Similar results have been reported in retrospective studies by other researchers (15,16). Among these factors, macroscopic N stage ($P < 0.001$) and tumor size ≥ 5 cm ($P < 0.045$) were significant risk factors for PAN metastasis after adjusting for other variables. Only one tumor smaller than 5 cm had PAN metastasis, while 12.5% of larger tumors had metastasis.

The incidence of PAN metastasis was clearly different between the N0–1 group and the N2–4 group (2.8% versus 20.5%), and its odds ratio was 8.6 (95% CI, 3.1–24.2). The results were reproduced in an independent validation dataset.

As for the regional lymph node status, most of them were associated with PAN metastasis but station No. 7 was the only significant indicator to PAN metastasis after adjusting for other variables. The diagnostic sensitivity and specificity of station No. 7 for PAN metastasis were as high as clinically useful and this may be a convenient diagnostic indicator for PAN metastatis. Although station No. 9 around the celiac artery is located between station No. 7 and PAN, the histological status of station No. 9 did not show statistical significance in this multivariate analysis. It might be due to the high correlation between No. 7 and No. 9 status. Actually, all six cases with metastases in both station No. 9 and PAN were also positive in No. 7 station. This result indicated that the pathological status of No. 7 was considered to be the confounding factor between No. 9 and PAN status. Another explanation is that metastatic cancer cells that left No. 7 nodes enters PAN through the celiac route but sometimes without being trapped by No. 9 nodes. Or else, while the No. 7 lymph nodes along the left gastric artery can easily be identified during surgery, metastatic nodes at No. 9 station may be missed or misclassified at post-operative nodal retrieval.

This finding also helps us to study the pattern of lymphatic flow to the nodes surrounding the abdominal aorta. Lymphatic flow is thought to reach the para-aortic nodes via the following possible routes: (i) directly from the left para-cardial lymph nodes, (ii) from the lymph nodes along the splenic artery, (iii) from the lymph nodes around the celiac artery, (iv) from the lymph nodes along the superior mesenteric artery, and (v) from the lymph nodes on the posterior surface of the pancreatic head and the nodes along the posterior common hepatic artery (3,4). In this study, 15 of the 22 patients with PAN metastasis had involvement of lymph node No. 7, which is located by the celiac trunk. This suggests that the most likely route for PAN metastasis is from the left gastric artery nodes passing by the celiac artery.

JCOG9501 had superior quality control of surgical procedures and should provide more reliable data than previous retrospective studies. This also provides us with reliable information about metastasis to PAN, although the number of patients with PAN metastasis was not large ($n = 22$). The possible survival impact of PAND should be clarified in further analyses.

In conclusion, this study indicated that macrosocpic N staging and tumor size ≥ 5 cm were important and independent risk factors for PAN metastasis, and that the lymphatics accompanying the celiac artery seem to be the most frequent route for metastasis to PAN. Station No. 7 was the most diagnostic lymph node for indicating the status of PAN.

Acknowledgment

This study was supported by the Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare and the Second Term Comprehensive 10 year Strategy for Cancer Control by the Ministry of Health and Welfare, Japan.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine

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ABSTRACT

BACKGROUND

Advanced gastric cancer can respond to S-1, an oral fluoropyrimidine. We tested S-1 as adjuvant chemotherapy in patients with curatively resected gastric cancer.

METHODS

Patients in Japan with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph-node dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the S-1 group, administration of S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg of oral S-1 per square meter of body-surface area per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. The primary end point was overall survival.

RESULTS

We randomly assigned 529 patients to the S-1 group and 530 patients to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of the independent data and safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the S-1 group had a higher rate of overall survival than the surgery-only group ($P=0.002$). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.68 (95% confidence interval, 0.52 to 0.87; $P=0.003$). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute) that were relatively common in the S-1 group were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%).

CONCLUSIONS

S-1 is an effective adjuvant treatment for East Asian patients who have undergone a D2 dissection for locally advanced gastric cancer. (ClinicalTrials.gov number, NCT00152217.)

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N Engl J Med 2007;357:1810-20.

META-ANALYSES HAVE SHOWN THAT ADjuvant chemotherapy is effective in treating gastric cancer.[1-6] However, the effectiveness of specific regimens has not been verified in large clinical trials. In 2001, the Intergroup-0116 (INT-0116) study investigators reported that postoperative chemoradiotherapy was effective in treating adenocarcinoma of the stomach or gastroesophageal junction.[7] Subsequently, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[8] showed the efficacy of perioperative chemotherapy. Both studies assessed the benefits of adjuvant therapy after only limited surgery, but the type of surgical procedure for gastric cancer can influence the results of postoperative chemotherapy.[9,10] In Japan, gastrectomy with extended (D2) lymph-node dissection alone is considered standard treatment.[11]

S-1 (TS-1, Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1.[12,13] The rate of response to treatment with S-1 alone exceeded 40% in two late phase 2 trials involving patients with advanced or recurrent gastric cancer.[14,15] The pharmacokinetics of the fluorouracil that is derived from S-1 is not influenced by gastrectomy,[16] and for this reason, S-1 is suitable for the postoperative adjuvant setting. In a pilot study,[17] we examined the feasibility of using S-1 postoperatively in patients with gastric cancer. We report the results of a large-scale trial — the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) — involving patients with stage II or III gastric cancer who underwent D2 surgery.

METHODS

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by the institutional review board of each participating hospital. Written informed consent was obtained from all patients.

All members of the steering committee and the sponsor jointly designed the trial and collected the data, which were held by the independent ACTS-GC Data Center. The data were analyzed by the independent data and safety monitoring committee. All academic members of the steering committee vouch for the validity and completeness of the data and the analysis. All of the authors reviewed and approved the final version of the manuscript before submission.

ELIGIBILITY CRITERIA

The criteria for eligibility were histologically proven gastric cancer of stage II (excluding T1 cases), IIIA, or IIIB; D2 or more extensive lymph-node dissection with R0 surgery (with the result of no residual tumor[18]); no hepatic, peritoneal, or distant metastasis; no tumor cells in peritoneal fluid on cytologic analysis; an age of 20 to 80 years; no previous treatment for cancer except for the initial gastric resection for the primary lesion; and adequate organ function (a leukocyte count of at least 4000 per cubic millimeter or the lower limit of the normal range; a platelet count of at least 100,000 per cubic millimeter; a total bilirubin level of no more than 1.5 mg per deciliter [25.7 μmol per liter], aspartate aminotransferase and alanine aminotransferase levels no more than 2.5 times the upper limit of the normal range; and a serum creatinine level no greater than the upper limit of the normal range). Stage classification and the evaluation of resected specimens were performed in accordance with the guidelines of the Japanese Gastric Cancer Association.[18]

STUDY DESIGN AND TREATMENT

The primary end point was overall survival; secondary end points were relapse-free survival and the degree of safety of S-1. Patients were enrolled, within 6 weeks after surgery, over the telephone or by fax by staff at the ACTS-GC data center. Patients were randomly assigned to either the S-1 group or the surgery-only group, with the assignments made at the ACTS-GC data center by means of the minimization method and according to the cancer stage (II, IIIA, or IIIB). Zelen's adjustment[19] was applied to balance the numbers of patients between each group at each participating hospital.

Patients assigned to the S-1 group received two oral doses of 40 mg of S-1 per square meter of body-surface area per day, for 4 weeks, followed by 2 weeks of no chemotherapy. Specifically, during the treatment weeks, patients with a body-surface

Table 1. Baseline Characteristics of the Patients.

Characteristic	S-1 (N=529)	Surgery Only (N=530)	P Value*
Sex — no. (%)			0.98
Male	367 (69.4)	369 (69.6)	
Female	162 (30.6)	161 (30.4)	
Age			0.86
<60 yr — no. (%)	199 (37.6)	195 (36.8)	
60–69 yr — no. (%)	193 (36.5)	215 (40.6)	
70–80 yr — no. (%)	137 (25.9)	120 (22.6)	
Median — yr	63	63	
Range — yr	27–80	33–80	
Tumor stage — no. (%)			0.81
T1	1 (0.2)	0	
T2	289 (54.6)	286 (54.0)	
T3	225 (42.5)	232 (43.8)	
T4	14 (2.6)	12 (2.3)	
Nodal stage, Japanese classification — no. (%)†			0.72
N0	51 (9.6)	64 (12.1)	
N1	296 (56.0)	281 (53.0)	
N2	182 (34.4)	185 (34.9)	
N3	0	0	
No. of lymph-node metastases — no. (%)			0.37
0	51 (9.6)	64 (12.1)	
1–6	331 (62.6)	325 (61.3)	
7–15	117 (22.1)	113 (21.3)	
≥16	30 (5.7)	28 (5.3)	

area of less than 1.25 m^2 received 80 mg daily; those with a body-surface area of 1.25 m^2 or more but less than 1.5 m^2 received 100 mg daily; and those with a body-surface area of 1.5 m^2 or more received 120 mg daily. This 6-week cycle was repeated during the first year after surgery. If patients had hematologic toxic effects of grade 3 or grade 4 (highest possible grade) or nonhematologic toxic effects of grade 2, grade 3, or grade 4, their daily dose was reduced, from 120 mg to 100 mg, 100 mg to 80 mg, or 80 mg to 50 mg. The surgery-only group received no anticancer treatment after surgery, unless there was a confirmed relapse.

Patients in both groups were to be followed up for 5 years postoperatively. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0).

FOLLOW-UP

Patients in the S-1 group underwent hematologic tests and assessments of clinical symptoms every 2 weeks. Patients in the surgery-only group underwent similar examinations at least every 3 months. Evaluation for adverse events was performed every 3 months for 1 year after surgery.

The presence of a relapse was determined by means of imaging studies, including ultrasonography, computed tomography (CT), gastrointestinal radiography series, and endoscopy. Patients underwent at least one type of imaging study, usually CT, at 6-month intervals during the first 2 years after surgery and at 1-year intervals thereafter until year 5 after surgery. Case-report forms, which included the results of these tests and evaluations and the survival status of patients, were submitted 1 year, 1.5 years, 2 years, 3 years, 4 years,

Table 1. (Continued.)

Characteristic	S-1 (N=529)	Surgery Only (N=530)	P Value*
Cancer stage, Japanese classification — no. (%)‡			0.78
II	236 (44.6)	238 (44.9)	
IIIA	202 (38.2)	207 (39.1)	
IIIB	90 (17.0)	85 (16.0)	
IV	1 (0.2)	0	
Cancer stage, TNM classification — no. (%)			0.37
IB	1 (0.2)	0	
II	264 (49.9)	282 (53.2)	
IIIA	170 (32.1)	157 (29.6)	
IIIB	54 (10.2)	56 (10.6)	
IV	40 (7.6)	35 (6.6)	
Type of lymph-node dissection — no. (%)			0.69
D1	0	1 (0.2)	
D2	501 (94.7)	497 (93.8)	
D3	28 (5.3)	32 (6.0)	
Type of gastrectomy — no. (%)			0.26
Total	220 (41.6)	201 (37.9)	
Distal	301 (56.9)	316 (59.6)	
Proximal	4 (0.8)	11 (2.1)	
Other	4 (0.8)	2 (0.4)	

* P values for sex and type of gastrectomy were calculated with the use of the chi-square test. P values for age, tumor stage, nodal stage, number of lymph-node metastases, cancer stage (Japanese and tumor–node–metastasis [TNM] classifications), and type of lymph-node dissection were calculated with the use of the Wilcoxon test.

† Nodal stages according to the Japanese classification were defined as follows: N0, no evidence of lymph-node metastasis; N1, metastasis to group 1 lymph nodes; N2, metastasis to group 2 lymph nodes; and N3, metastasis to group 3 lymph nodes. Groups 1, 2, and 3 are regional lymph-node classifications defined according to the location of the primary tumor and based on the results of studies of lymphatic flow at various tumor sites and the observed survival associated with metastasis at each nodal station (i.e., position in relation to primary node).

‡ Cancer stages according to the Japanese classification were defined as follows: stage IA, T1N0; stage IB, T1N1 or T2N0; stage II, T1N2, T2N1, or T3N0; stage IIIA, T2N2, T3N1, or T4N0; stage IIIB, T3N2 or T4N1; and stage IV, T4N2, any T stage with N3, or distant metastasis.

and 5 years after surgery. Patients, their physicians, endoscopists, and radiologists were aware of the group assignment after surgery, and no placebo was used. However, relapses and other events were evaluated by members of the steering committee, who were unaware of the group assignments.

STATISTICAL ANALYSIS

The results of a previous study conducted in Japan[20] served as the basis for determining the required numbers of patients.[21] The 5-year overall survival rate in the surgery-only group was assumed to be 70%. We calculated that a total enrollment of 1000 patients was needed for a hazard ratio for death of 0.70 in the S-1 group as compared with the surgery-only group, with the use of the log-rank test, a two-sided alpha of 5%, and a statistical power of 80%, assuming 3 years of recruitment and an additional 5 years of follow-up.

Efficacy was to be evaluated in two interim analyses performed by an independent data and safety monitoring committee 1 year and 3 years after the completion of enrollment. Significance was evaluated with the use of the method of Lan and DeMets[22] and the O'Brien–Fleming boundary. Person-years were used to estimate information fractions for use in interim analyses. When calculating information fractions, we assumed that patients who had not completed the study before the interim analysis were continuously observed until the final analysis.

Data for all randomly assigned patients, whether eligible or not, were included in efficacy analyses. Data for eligible patients were also analyzed to evaluate the robustness of the results. Overall survival was defined as the period between randomization and death. All deaths, including those from other diseases, were considered to be events. Relapse-free survival was defined as the period between randomization and the occurrence of an event — relapse or death — whichever came first. Data for patients who had not had an event were censored as of the date of the final observation.

The median time from surgery to randomization was 28 days (range, 7 to 42) in the S-1 group and 28 days (range, 6 to 42) in the surgery-only group. Because the number of days from surgery to randomization varied among patients, we also calculated the overall survival from the date of surgery. In the first interim analysis, overall survival was also measured from the date of surgery. The Kaplan–Meier method was used to estimate the cumulative survival. The primary confirmatory analysis was performed with the use of the stratified log-rank test, with the cancer stage — which was used in the random assignment of patients at enrollment — as a stratification factor. The Cox proportional-hazards model was used to calculate the hazard ratios. All P values calculated in the subgroup analysis were two-sided and were not adjusted for multiple testing. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF PATIENTS

We enrolled and randomly assigned 1059 patients — 529 to the S-1 group and 530 to the surgery-only group — at 109 centers between October 2001 and December 2004. After randomization, 25 patients (14 in the S-1 group and 11 in the surgery-only group) were found to be ineligible. The reasons for ineligibility were as follows: the absence of cytologic examination of the peritoneal fluid (nine patients), cancers other than gastric cancer (five), previous treatment for gastric cancer (four), laboratory test values at enrollment that did not meet the protocol requirements (four), limited (D1) surgery (one), stage IV cancer (one), and T1 cancer (one). The main analyses were based on data from all randomly assigned patients, including those who were ineligible. The two groups were well balanced with regard to baseline clinical characteristics, surgical procedures, and pathological findings (Table 1).

INTERIM ANALYSIS

The first interim analysis was based on data derived from case-report forms submitted by December 2005, 1 year after enrollment of the last patient. This analysis (median follow-up, 2.0 years) was conducted by the independent data and safety monitoring committee in June 2006. In this interim analysis, both overall survival and relapse-free survival differed between the two groups, both for all randomly assigned patients (overall survival, $P=0.002$; relapse-free survival, $P<0.001$) and for all eligible patients (overall survival, $P<0.001$; relapse-free survival, $P<0.001$). The significance level of the differences was close to the predetermined threshold for the interim analysis, $P=0.001$. Given these results, the data and safety monitoring committee recommended discontinuation of the trial and publication of the results based on updated data (from follow-up surveys as of June 30, 2006).

ADVERSE EVENTS AND TREATMENT COMPLIANCE

Data on 517 patients in the S-1 group and 526 in the surgery-only group were analyzed for adverse events. Data from the remaining 12 patients in the S-1 group, who did not receive S-1, and from the remaining 4 patients in the surgery-only group, who requested that their treatment assignment be changed after randomization, were not included in the safety analysis. Adverse events of grade 1, 2, 3, or 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0) — including leukopenia, anemia, thrombocytopenia, elevated total serum bilirubin levels, and nonhematologic toxic effects — were more frequent in the S-1 group than in the surgery-only group. The adverse events of grade 3 or 4 that were more frequent in the S-1 group were anorexia, nausea, diarrhea, leukopenia, anemia, elevated total serum bilirubin level, stomatitis, and rash (Table 2).

Among the 517 patients in the safety population who received S-1, treatment was continued for at least 3 months in 452 patients (87.4%), at least 6 months in 403 patients (77.9%), at least 9 months in 366 patients (70.8%), and 12 months in 340 patients (65.8%). The reasons for withdrawal of treatment included refusal of the patient to continue treatment because of adverse events

Table 2. Adverse Events, According to Treatment Group.*

Event	S-1 (N=517)					Surgery Only (N=526)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4
	no. of patients				%	*no. of patients*				%
Leukopenia	157	144	6	0	1.2	93	32	2	0	0.4
Anemia	293	167	6	0	1.2	311	64	3	1	0.8
Thrombocytopenia	123	10	1	0	0.2	32	2	2	0	0.4
Elevated AST level	193	30	9	0	1.7	177	30	17	1	3.4
Elevated ALT level	192	26	6	0	1.2	182	27	16	1	3.2
Elevated total serum bilirubin level	155	75	7	1	1.5	40	13	5	1	1.1
Elevated creatinine level	25	2	0	0	0.0	24	2	1	1	0.4
Stomatitis	139	26	1	0	0.2	16	2	0	0	0.0
Anorexia	213	72	30	1	6.0	63	9	8	3	2.1
Nausea	146	37	19	—	3.7	40	7	6	—	1.1
Vomiting	88	23	6	0	1.2	42	6	7	3	1.9
Diarrhea	227	66	16	0	3.1	85	11	1	0	0.2
Rash	111	52	5	0	1.0	6	4	2	0	0.4
Pigmentation	204	37	—	—	—	2	0	—	—	—
Fatigue	242	60	3	0	0.6	88	4	3	0	0.6

* Grades of adverse events were defined according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0). AST denotes aspartate aminotransferase, and ALT alanine aminotransferase; dashes indicate not available.

or other factors (71 patients), the decision of the investigators to terminate treatment because of adverse events or complications (72), the detection of metastasis or relapse (25), the presence of cancers other than gastric cancer (2), post-enrollment ineligibility (5), and transfer to another hospital (2). The dose of S-1 was decreased in 219 of the 517 patients (42.4%) who received S-1. Of the 340 patients who received treatment for 12 months, the dose was decreased in 158 patients (46.5%).

OVERALL SURVIVAL AND RELAPSE-FREE SURVIVAL

On the basis of follow-up data updated on June 30, 2006, the median time from randomization to follow-up was 2.9 years in both the S-1 group and the surgery-only group. Seven patients in the S-1 group and six patients in the surgery-only group were lost to follow-up. A total of 102 patients died in the S-1 group, and 140 patients died in the surgery-only group. The causes of death in the S-1 and surgery-only groups were as follows: relapse (in 96 and 124 patients, respectively), other cancer (1 and 2), a cause other than cancer (4 and 7), and unknown causes (1 and 7). The number of patients who had recurrent metastasis was 133 in the S-1 group and 188 in the surgery-only group.

The hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.68 (95% confidence interval [CI], 0.52 to 0.87; P=0.003). The 3-year overall survival rate was 80.1% in the S-1 group (95% CI, 76.1 to 84.0) and 70.1% in the surgery-only group (95% CI, 65.5 to 74.6) (Fig. 1A). The hazard ratio for relapse in the S-1 group, as compared with the surgery-only group, was 0.62 (95% CI, 0.50 to 0.77; P<0.001). The rate of relapse-free survival at 3 years was 72.2% in the S-1 group (95% CI, 67.9 to 76.4) and 59.6% in the surgery-only group (95% CI, 54.9 to 64.3) (Fig. 1B). Among eligible patients, the hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.66 (95% CI, 0.51 to 0.86; P=0.002). The results for all randomly assigned patients were similar.

SITE OF FIRST RELAPSE

Common sites of first relapse were the peritoneum, hematogenous sites, and lymph nodes (Table 3). Local relapse occurred in 7 patients in the

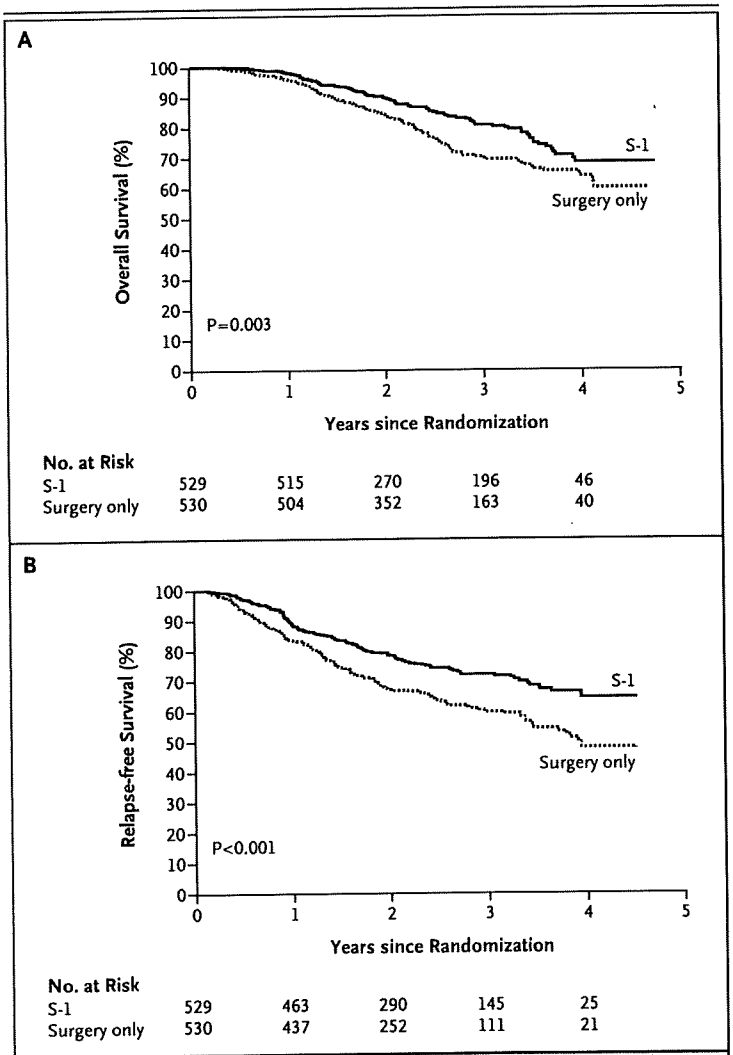

Figure 1. Kaplan–Meier Estimates of Overall Survival and Relapse-free Survival.

Three years after randomization, the rate of overall survival was 80.1% in the S-1 group and 70.1% in the surgery-only group (Panel A), and the rate of relapse-free survival was 72.2% in the S-1 group and 59.6% in the surgery-only group (Panel B). The hazard ratio for death in the S-1 group as compared with the surgery-only group was 0.68 (95% confidence interval, 0.52 to 0.87; P=0.003). The hazard ratio for relapse in the S-1 group was 0.62 (95% confidence interval, 0.50 to 0.77; P<0.001). P values were calculated with the use of the stratified log-rank test.

S-1 group (1.3%) and in 15 patients in the surgery-only group (2.8%). Postoperative treatment with S-1 reduced the frequencies of peritoneal and lymph-node relapses. In the surgery-only group, 84 patients (15.8%) had peritoneal relapse, and 46 patients (8.7%) had lymph-node relapse. In the S-1 group, 59 patients (11.2%) had peritoneal relapse, and 27 (5.1%) had lymph-node relapse.

SUBGROUP ANALYSIS

The overall survival of eligible patients was analyzed according to sex, age, cancer stage (Japanese classification and tumor–node–metastasis [TNM] classification), tumor stage, nodal stage (Japanese classification[18] and TNM classification), and histologic type (Fig. 2). A total of 25 ineligible patients (14 in the S-1 group and 11 in the surgery-only group), including those who had stage IV disease, were excluded. There was no significant interaction between the treatment group and any of the variables studied.

DISCUSSION

Few large-scale trials (those with >500 patients) have compared postoperative adjuvant therapy with surgery alone among patients with gastric cancer. Such large trials have been performed by Nakajima et al. (the JCOG [Japan Clinical Oncology Group] 8801 study),[20] Macdonald et al. (the INT-0116 study),[7] and Cunningham et al. (the MAGIC trial).[8] The JCOG 8801 study in Japan failed to demonstrate therapeutic benefits of adjuvant chemotherapy. The authors suggested that surgery probably resulted in a cure only in patients with T1 tumors, who accounted for nearly one third of all patients in the study, possibly masking differences in overall survival. The INT-0116 study, performed in the United States, showed that adjuvant chemoradiotherapy prolonged overall survival and relapse-free survival. Most patients in the INT-0116 study underwent either D0 or D1 surgery, with only 10% undergoing D2 surgery. The characteristics of patients in the INT-0116 study differed from those in the JCOG 8801 study and those in our trial. An analysis of benefit according to the type of lymph-node dissection showed no effect of adjuvant chemoradiotherapy among patients who underwent D2 surgery. In the MAGIC trial, conducted mainly in the United Kingdom, perioperative and postoperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil significantly prolonged overall survival and relapse-free survival. In that study, D2 surgery was not performed as a standard procedure.

In addition to the JCOG 8801 study, the JCOG