Table I. Demographic and clinicopathological data.

Clinicopathological data	Total	Completed	Discontinued	P-value
Number of patients	58	34	24	
Age (years)	63.4±8.0	61.4±83.4	66.3±6.5	0.02
Gender				
Male	43 (74.1%)	24 (70.6%)	19 (79.2%)	0.42
Female	15 (25.9%)	10 (29.4%)	5 (20.8%)	
Histological classification				
Intestinal	23 (39.7%)	12 (35.3%)	11 (45.8%)	0.52
Diffuse	32 (55.2%)	19 (55.9%)	13 (54.2%)	
Adenosquamous	2 (3.4%)	2 (5.9%)	0 (0.0%)	
Tumor depth				
T2	24 (41.4%)	15 (44.1%)	9 (37.5%)	0.83
T3	32 (55.2%)	18 (52.9%)	14 (58.3%)	
T4	2 (3.4%)	1 (2.9%)	1 (4.2%)	
Lymph node metastasis				
N0	10 (17.2%)	6 (17.6%)	4 (16.7%)	0.85
N1	27 (46.6%)	15 (44.1%)	12 (50.0%)	
N2	21 (36.2%)	13 (38.2%)	8 (33.3%)	
Stage				
II	25 (43.1%)	15 (44.1%)	10 (41.7%)	0.18
IIIA	18 (31.0%)	8 (23.5%)	10 (41.7%)	
IIIB	15 (25.9%)	11 (32.4%)	4 (16.7%)	
Type of gastrectomy				
Total	30 (51.7%)	20 (58.8%)	10 (41.7%)	0.24
Distal	28 (48.3%)	14 (41.2%)	14 (58.3%)	
Reconstruction				
Billroth I	22 (37.9%)	11 (32.4%)	11 (45.8%)	0.48
Billroth II	3 (5.2%)	2 (5.9%)	1 (4.2%)	
Roux en Y	33 (56.9%)	21 (61.8%)	12 (50.0%)	
Cholecystectomy				
Yes	24 (41.4%)	14 (41.2%)	10 (41.7%)	0.95
No	34 (58.6%)	19 (55.9%)	14 (58.3%)	
Splenectomy				
Yes	20 (34.5%)	12 (35.3%)	8 (33.3%)	0.81
No	38 (65.5%)	22 (64.7%)	16 (66.7%)	
Doctor in charge				
Junior (≤15 yrs)	25 (43.1%)	11 (32.4%)	14 (58.3%)	0.04
Senior (>15 yrs)	33 (56.9%)	23 (67.6%)	10 (41.7%)	
Total amount of S-1 (mg)	16495.4±8851.9	23146.7±3335.6	7350.0±4954.9	<0.0001

principle, if patients had hematological toxic effects of grade 3 or 4 or non-hematological toxic effects of ≥ grade 2, their daily dose was reduced and/or their schedule was changed from a 4-week administration followed by a 2-week rest, to a 2-week administration followed by a 1-week rest.

Measures. If no gross residual disease was evident at the time of surgery and the resection margins were tumor-free on histological examination, surgery was considered curative. Pathological findings in gastric cancer patients were described on the basis of the JCGC (6). Adverse reactions were evaluated according to the common toxicity criteria of the National Cancer Institute, version 3.0 (http://ctep.cancer.gov).

OS was measured from the date of resection to the date of mortality from any cause. Relapse-free survival was measured from the date of resection to the date when relapse was evident by computed tomography, gastrointestinal endoscopic examination, abdominal ultrasonography, upper gastrointestinal series and/or positron emission tomography. Data for the patients who survived were censored in our survival analyses.

Table II. Adverse reactions to adjuvant therapy with S-1 among the 58 patients included in this study.

	No. of patients				Percentage (%)	
Adverse reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3 or 4
Leukopenia	5	3	3	-	14.0	5.3
Anemia	26	3	-	-	50.9	0
Elevated t-bil level	4	2	-	-	10.5	0
Stomatitis	5	2	-	-	12.3	0
Anorexia	20	1	1	-	36.8	1.8
Nausea	6	2	-	-	14.0	0
Diarrhea	8	6	1	-	24.1	1.8
Skin lesions	8	1	-	-	15.5	0
Fatigue	8	3	-	-	19.3	0
Watering or dry eye	7	6	-	-	22.8	0

t-bil, total bilirubin.

The medication completion rate was measured from the date of treatment commencement to the date of treatment discontinuation. Data for patients in whom S-1 treatment was discontinued due to tumor recurrence or mortality were censored in this analysis. All patients were observed at our hospital or outpatient clinic at 2- to 4-week intervals up to 12 months after surgery, 3- to 4-month intervals during the 2 years of the study and every 6 or 12 months thereafter for 3 years.

Statistical analysis. Statistical calculations were performed using StatView version 5.0 (SAS Institute, Inc., Cary, NC, USA). Data are expressed as the means ± SEM. Statistical analyses were performed using the Mann-Whitney U test or Chi-square test with Fisher's exact test, as appropriate. Survival and medication completion rates were calculated using the Kaplan-Meier method and the significance of the difference was determined by a log-rank test. $P<0.05$ was considered to indicate a statistically significant result.

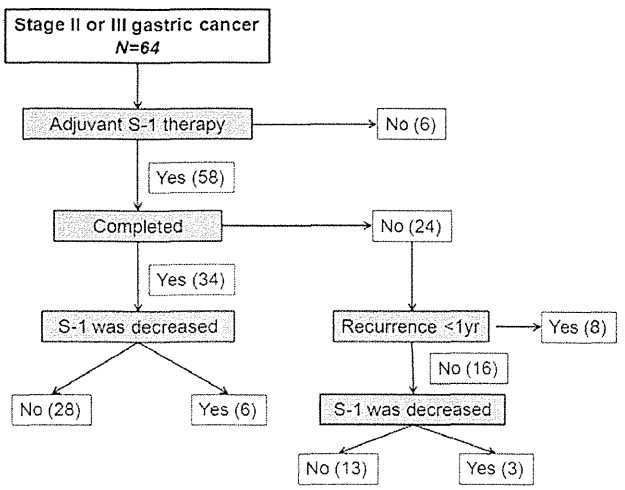

Figure 1. Flowchart of the treatment outcomes of adjuvant therapy with S-1.

Results

Of the 64 patients included in the study, 6 refused adjuvant therapy with S-1 due to age (n=4) or financial concerns (n=2). The remaining 58 patients received S-1 within 8 weeks of surgery (Fig. 1). Twenty-four patients (41.3%) discontinued treatment within 12 months as a result of disease relapse (n=8) and intolerable adverse events (n=16). The S-1 dose was decreased in 9 of the 58 patients (15.5%). Of the 34 patients who underwent treatment for 12 months, the S-1 dose was decreased in 6 (17.6%), and of the 24 patients who discontinued treatment, the S-1 dose was decreased in 3 (12.5%). Among the 58 patients who received S-1 therapy, treatment was continued for at least 3 months in 49 patients (84.5%), at least 6 months in 45 patients (77.6%), at least 9 months in 37 patients (63.8%) and 12 months in 34 patients (58.6%).

Demographic and clinicopathological data of patients are shown in Table I. Patients who discontinued S-1 treatment within 12 months were older than those who completed 12 months of adjuvant therapy. However, no differences were observed in tumor stage and surgery type (gastrectomy, reconstruction or resection of other organs) between the two groups. Patients who completed 12 months of adjuvant therapy with S-1 were more frequently treated by senior doctors (>15 years of experience). More favorable outcomes in OS and relapse-free survival were observed in these patients than in those who discontinued treatment (Fig. 2).

Table II summarizes the data concerning the adverse reactions observed among the 58 patients in this study. No patient had ≥ grade 4 adverse events; however, 3 patients had grade 3 leukopenia. In terms of non-hematological adverse events, grade 3 anorexia was observed in 1 patient and grade 3 diarrhea was observed in 1 patient. The most frequent cause of S-1 treatment discontinuation was tumor recurrence. Non-hematological adverse events such as diarrhea and nausea were also associated with treatment discontinuation (Table III). Fig. 3 shows the medication completion rates. S-1 treatment time was significantly shorter in patients who

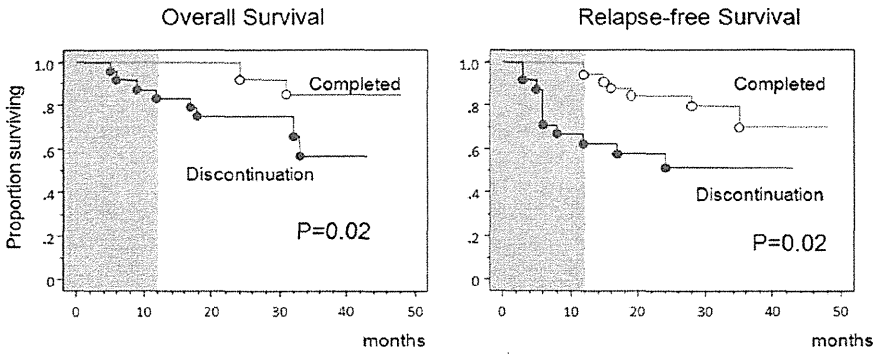

Figure 2. Overall and relapse-free survival rates following curative D2 gastric dissection. Completed, patients who completed 12 months of adjuvant therapy with S-1; Discontinuation, patients who discontinued treatment before 12 months.

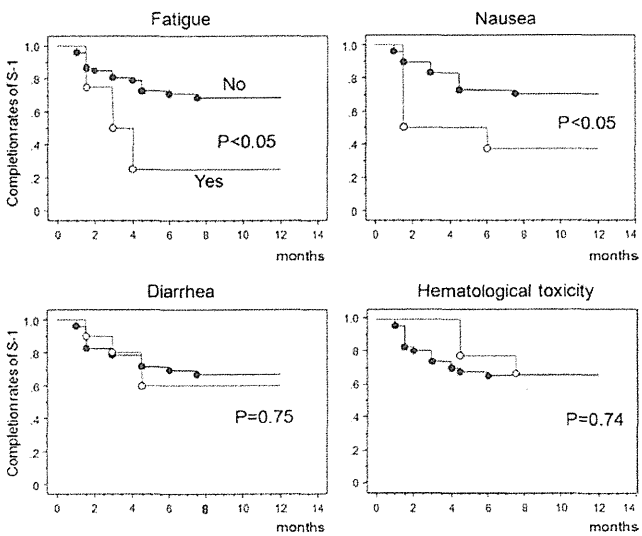

Figure 3. Medication completion rates of adjuvant therapy with S-1 calculated by the Kaplan-Meier method. Discontinuation of S-1 administration due to adverse events was considered as an event.

Table III. Chief causes of S-1 treatment discontinuation.

Adverse reaction	No. of patients	Percentage (%)
Recurrence	8	33.3
Diarrhea	3	12.5
Nausea	3	12.5
Elevated t-bil level	2	8.3
Intestinal obstruction	2	8.3
Fatigue	2	8.3
Neutropenia	1	4.2
Ascites	1	4.2
Stroke	1	4.2
Death of another cause	1	4.2
Total	24	100.0

t-bil, total bilirubin.

experienced fatigue or nausea as an adverse event, whereas diarrhea and hematological toxicity did not significantly affect the period of treatment.

Discussion

This study demonstrated that patients who completed 12 months of adjuvant therapy with S-1 were younger and more frequently treated by doctors with >15 years of experience than those who did not. Non-hematological adverse events such as nausea and fatigue were frequent causes of S-1 treatment discontinuation. Adverse events of ≥ grade 3 were significant causes of treatment discontinuation in a small number of patients.

In a postmarketing survey of S-1 (9), including 3,294 patients with advanced or recurrent gastric cancer, the incidence of adverse reactions following administration of the drug at the usual dose level according to the patient body surface area was 74.1%, which was approximately equal to that obtained in premarketing trials. The major reasons for drug discontinuation during the first and second course of therapy were exacerbation of symptoms (43%) and adverse drug reactions (33%). Therefore, to facilitate S-1 administration for prolonged time periods, the incidence of adverse reactions should be reduced. To accomplish this goal, several regimens have been established (10). Kimura *et al* developed a new S-1 dosing regimen in which S-1 is administered for a 2-week period separated by 1-week drug-free intervals, as adverse reactions due to S-1 therapy begin to appear 2-3 weeks after initial dosing (11). Sakuma *et al* also proposed alternate-day treatment with S-1 as a strategy for reducing toxicity, although the total dose of this regimen was 75% that of standard treatment (12). Both regimens decreased the incidence of adverse reactions and improved treatment compliance when compared with the conventional 4-week administration followed by a 2-week rest regimen.

In the ACTS-GC trial, 143 of 517 (27.7%) patients discontinued S-1 treatment due to adverse events, which was consistent with our results (27.6%). Only 5% patients in the ACTS-GC trial had metastasis or relapse of gastric cancer. Our study, which includes potentially more cases of advanced

stage disease than the ACTS-GC trial, involved relatively shorter time periods of the treatment than the ACTS-GC trial.

Patients who experienced fatigue or nausea as adverse events continued S-1 treatment for significantly shorter time periods. However, diarrhea and hematological toxicity did not significantly affect the treatment period. Following gastrectomy, fatigue and gastrointestinal symptoms such as nausea and appetite loss, even of ≤ grade 2, appeared to have a major impact on treatment compliance.

In conclusion, the completion rate of S-1 treatment did not depend on the type of surgical procedures, i.e., gastrectomy, reconstruction or resection of other organs. Fatigue and gastrointestinal symptoms affected the period of treatment continuation. In addition, patients who completed 12 months of adjuvant therapy with S-1 were more frequently treated by doctors with ≥15 years of experience. Thus, to facilitate the continuation of adjuvant therapy with S-1, patients and doctors must be made completely aware of the issues of toxicity, compliance and efficacy associated with this therapy.

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ORIGINAL ARTICLE

Lymph node metastasis from cancer of the esophagogastric junction, and determination of the appropriate nodal dissection

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Abstract
Purpose Both squamous cell carcinomas and adenocarcinomas can develop in the esophagogastric junction. To clarify the appropriate lymph node dissection range, lymph node metastases from cancers in the esophagogastric junction were investigated.
Methods The nodal metastases were analyzed in 64 patients with squamous cell carcinoma and 129 with adenocarcinoma according to Siewert's classification, which is based on topographic anatomical criteria for adenocarcinoma.
Results The squamous cell carcinomas located above the esophagocardial junction had more frequent metastasis to the lower and middle mediastinal lymph nodes in proportion to the depth of the tumor. Nodal metastasis was also often detected in the abdominal lymph nodes. In contrast, adenocarcinomas metastasized less frequently to the mediastinal lymph nodes, and the metastatic rates in the abdominal nodes were higher than those from squamous cell carcinoma.
Conclusion Esophagectomy with mediastinal and abdominal lymph node dissection is considered to be an appropriate approach for surgical resection of squamous cell carcinomas, whereas transhiatally extended gastrectomy with lower mediastinal and abdominal lymph node dissection is recommended for the treatment of adenocarcinomas.

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Keywords Esophagogastric junction · Squamous cell carcinoma · Adenocarcinoma · Lymph node metastasis

Introduction

Cancer in the esophagogastric junction is an important clinical entity, as pathologically different tumors arise in this border between the esophageal squamous epithelium and the gastric adenomatous epithelium. The correct diagnosis of malignancy in this area is essential for choosing the appropriate surgical approach and for performing a resection that will provide the best patient outcome. In 2008, 406,806 people died from esophageal cancer worldwide, and 738,069 died from gastric cancer, making these the sixth and the second highest mortalities from cancer in the world [1]. Esophageal cancer is also one of the most aggressive cancers, with a 5-year survival rate of 25.0 ± 0.6% [2].

The incidence of adenocarcinoma of the esophagus and esophagogastric junction is dramatically increasing in Western countries [3, 4]. However, there is no evidence indicating a similar increase of adenocarcinoma of the esophagogastric junction in Eastern countries [5, 6]. Given their different pathogenic processes, epidemiology, tumor biology, and prognosis, squamous cell carcinomas and adenocarcinomas should be analyzed and reported separately [7–9]. Stein et al. [10] investigated early esophageal cancer, and reported that the prevalence and pattern of lymphatic spread, as well as the long-term prognosis, differ markedly between early esophageal squamous cell and adenocarcinoma. They recommended limited resection techniques and individualized lymphadenectomy strategies for patients with early adenocarcinoma.

There have not been any recent clinical studies on the pattern of lymphatic spread between squamous cell carcinoma and adenocarcinoma in the esophagogastric junction. With regard to squamous cell carcinoma of the lower esophagus, adding cervical lymph node dissection (3-field dissection) has been reported to provide a better survival benefit for patients compared to 2-field dissection [11]. In addition, adenocarcinoma of the gastric cardia or the upper part of the stomach has been reported to have a poorer prognosis than carcinomas of the more distal stomach [12, 13].

To improve patient survival, surgical resection, including complete removal of the primary tumor, together with its lymphatic drainage, is the mainstay of treatment for esophagogastric junction tumors [14]. To establish a more effective surgical treatment, the incidence of nodal metastasis from squamous cell carcinoma or adenocarcinoma of the esophagogastric junction was investigated in this study.

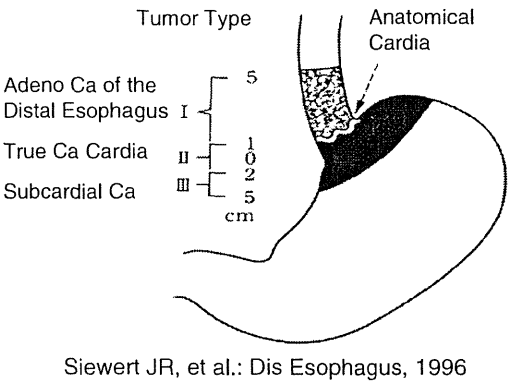


Fig. 1 The Siewert classification. Topographic-anatomic classification of adenocarcinomas of the esophago-gastric junction (AEG) based on their relationship to the endoscopic gastric cardia. *Type I* Adenocarcinoma of the distal esophagus, *Type II* true adenocarcinoma of the cardia, *Type III* subcardial gastric carcinoma infiltrating the esophagogastric junction

Patients and methods

A total of 193 patients with esophagogastric cancer who underwent surgery at the Department of Surgery and Science, Kyushu University Hospital and the Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka, Japan, from 1980 to 2005, were included in the study. Resected specimens were all examined pathologically and lymph node metastases were mapped.

The location of the primary cancer was classified using Siewert's classification, which is based on topographic anatomical criteria for adenocarcinoma [15]. Adenocarcinoma of the esophagogastric junction was defined as tumors whose center was within 5 cm oral and aboral of the anatomical esophagogastric junction. Type I disease was defined as a tumor in which the center was located 1–5 cm above the esophagogastric junction (EGJ), regardless of invasion to the EGJ; type II was defined as a tumor invading the EGJ, in which the center was located between 1 cm above and 2 cm below the EGJ; and type III was defined as a tumor invading the EGJ, in which the center was located 2–5 cm below the EGJ (Fig. 1). This classification has been introduced from a surgical viewpoint, and approved at the consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) [16]. Although this classification is for adenocarcinoma, we also applied it to squamous cell carcinoma in this study to clarify the relationship between the anatomical location of the tumor and nodal metastasis.

The surgical approaches and nodal dissections performed are listed in Table 1. All 64 squamous cell carcinoma patients underwent the thoracoabdominal approach with 59 two-field lymph node dissections (mediastinal and abdominal lymphadenectomy) and 5 three-field dissections (cervical, mediastinal, and abdominal lymphadenectomy) [17]. For adenocarcinoma, 30 patients underwent the thoracoabdominal approach, while 99 patients underwent the abdominal approach. The lymph node metastatic rates were calculated as the ratio between metastasis positive cases and the number of assessed cases in each numbered regional lymph node. The clinicopathological factors were evaluated according to the guidelines for clinical and pathologic studies on carcinoma of the esophagus [18, 19], and the Japanese classification of gastric carcinoma [20]. The recurrence pattern was investigated in 160 patients who underwent R0 resection, a microscopically margin-negative resection, in which no gross or microscopic tumor remained in the primary tumor bed. Survival data from 178 patients were analyzed by the Kaplan–Meier method.

Results

Of the 64 patients with squamous cell carcinoma, 41 patients had type I tumors and 23 patients had type II tumors. Of the 129 patients with adenocarcinoma, 6 patients had type I tumors, 60 patients had type II tumors, and 63 patients had type III tumors.

Squamous cell carcinoma

The metastatic rates in each lymph node are shown in Fig. 2. The rate of metastasis to Group 1 lymph nodes (1, 2, 3) was 16–28%. The metastatic rates to lower and middle mediastinal lymph nodes, which were Group 2 and 3 nodes, were 5–13 and 8%, respectively. Mediastinal lymph

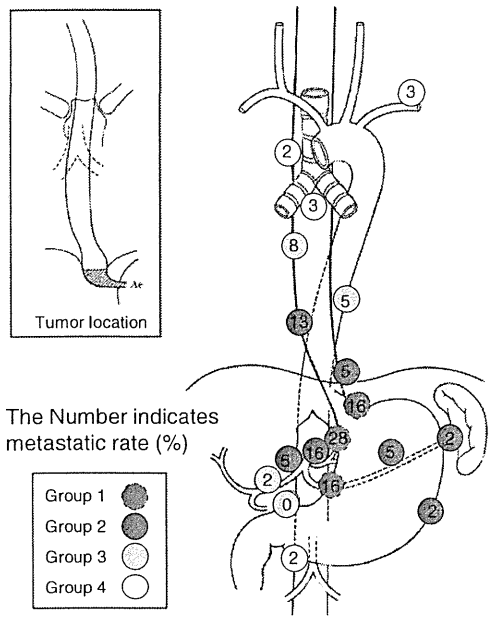
Table 1 Surgical approaches and nodal dissections performed

Histology	No. of pts.	Approach	Lymph node dissection	No. of pts
Squamous cell carcinoma	64	Thoracoabdominal	3-field dissection	5
			2-field dissection	59
Adenocarcinoma	129	Thoracoabdominal	3-field dissection	3
			2-field dissection	27
		Abdominal	1-field dissection	99

Fig. 2 Metastatic rates of lymph nodes from squamous cell carcinoma. Cervical lymph nodes: 101, 102, 103, 104; upper mediastinal nodes: 105, 106; middle mediastinal nodes: 107, 108, 109

Squamous cell carcinoma n=64

Lymph node	Metastatic rate (%)
cervical	3
upper mediastinal	2
middle mediastinal	8
110	13
111	5
112	5
1	28
2	16
3	16
4	2
5	0
6	2
7	16
8	2
9	5
10	2
11	5



nodes should therefore be dissected for patients with squamous cell carcinoma of the esophagogastric junction. Figure 3 shows the metastatic rates according to Siewert's classification. Compared to type I tumors, type II tumors had no upper mediastinal lymph node metastasis and more abdominal node metastasis. We experienced one type I and one type II tumor with cervical lymph node metastasis. These patients died 88 and 126 days postoperatively.

We also investigated the nodal metastatic rate in relation to the depth of tumor invasion (Table 2). Type I tumors, in which the tumor was located above the esophagocardial junction, had more metastasis to the lower and middle mediastinal lymph nodes in proportion to the depth of the tumor. Three pT1 tumors had no mediastinal node metastasis; however, one tumor had abdominal node metastasis. With regard to the type II tumors, which were located in the esophagocardial junction, mediastinal lymph node metastasis was not observed in pT1 and pT2 tumors, but was noted in patients with pT3 tumors. The nodal metastasis was often detected in the abdominal lymph nodes.

The recurrence pattern in relation to the depth of the tumor invasion is shown in Table 3. There was a higher incidence of recurrence in the patients who had more invasive tumors. Lymph node metastasis occurred most frequently, followed by distant metastasis and local recurrence. The patients' survival is shown in Fig. 4. The prognoses of the patients with invasion to the esophageal adventitia (pT3) or to the adjacent organs (pT4) were poor.

Adenocarcinoma

Figure 5 shows the nodal metastatic rates from adenocarcinomas. Limited metastasis was observed in the mediastinal lymph nodes, and the metastatic rates in the abdominal nodes were higher than those from patients with squamous cell carcinoma. Figure 6 shows the metastatic rates according to Siewert's classification. In the six type I tumors, only one tumor had mediastinal lymph node metastasis, with a poor prognosis of 214 postoperative days. The abdominal lymph node metastasis was localized around the primary tumor. Type II and III tumors had higher metastatic rates in the abdominal lymph nodes than type I tumors. Although the prognosis of the single case with cervical or upper mediastinal lymph node metastasis

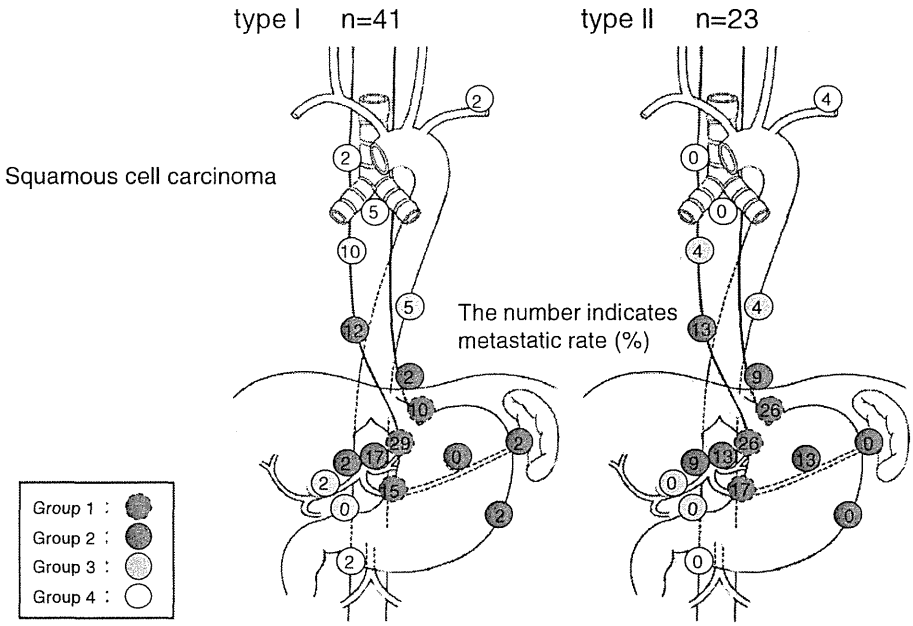


Fig. 3 The incidence of lymph node metastasis from squamous cell carcinoma according to the location of the tumor

Table 2 Lymph node metastasis from squamous cell carcinoma in relation to the depth of the tumor invasion

Depth of the tumor	Lymph node																			
	104	105	106	107	108	109	110	111	112	1	2	3	4	5	6	7	8	9	10	11
Type I																				
pT1 ($n = 3$)	0	0	0	0	0	0	0	0	0	0	0	33	33	0	33	33	0	0	0	0
pT2 ($n = 6$)	0	0	0	0	0	0	17	0	0	17	17	0	0	0	0	17	0	0	0	0
pT3 ($n = 27$)	4	4	0	4	8	0	11	0	8	33	11	15	0	0	0	11	4	4	0	0
pT4 ($n = 5$)	0	0	0	20	40	0	20	20	0	40	0	20	0	0	0	40	2	0	20	0
Type II																				
pT1 ($n = 1$)	0	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
pT2 ($n = 2$)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	50	0	0	0	0
pT3 ($n = 17$)	6	0	0	0	6	0	18	12	6	35	29	24	0	0	0	12	0	12	0	18
pT4 ($n = 3$)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The number shows the metastatic rate (%)

Table 3 The recurrence pattern of squamous cell carcinoma in relation to the depth of the invasion of the tumor

Location	Depth	Number of cases	Recurrence (%)	Site of recurrence			
				Lymph node metastasis	Distant metastasis	Local recurrence	Peritoneal dissemination
Type I: 1–5 cm above the EGJ	pT1	3	0 (0)	0	0	0	0
	pT2	6	2 (33)	0	2	0	0
	pT3	24	13 (54)	7	3	2	0
	pT4	5	5 (100)	1	3	2	0
Type II: Between 1 cm above and 2 cm below the EGJ	pT1	1	0 (0)	0	0	0	0
	pT2	2	0 (0)	0	0	0	0
	pT3	9	6 (67)	3	2	1	0
	pT4	3	2 (67)	1	0	0	1

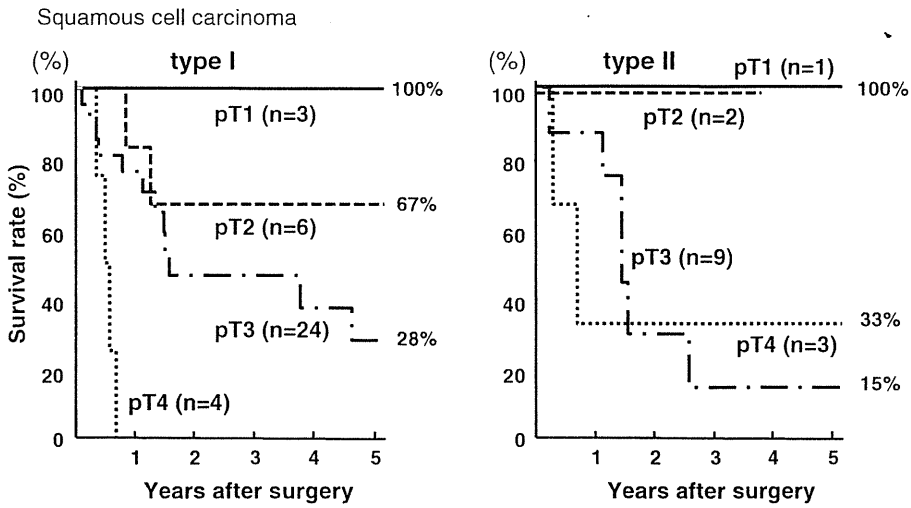


Fig. 4 The survival of patients with squamous cell carcinoma in relation to the depth of the tumor invasion

Adenocarcinoma n=129

Lymph node	Metastatic rate (%)
cervical	1
upper mediastinal	2
middle mediastinal	2
110	2
111	1
112	1
1	46
2	24
3	40
4	14
5	7
6	7
7	23
8	12
9	15
10	7
11	16
12	2
14	2
16	2

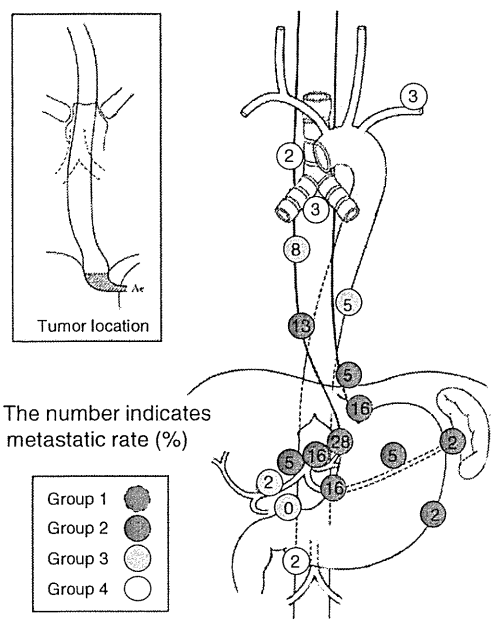


Fig. 5 The metastatic rates of lymph nodes from adenocarcinoma. Cervical lymph nodes: 101, 102, 103. 104; upper mediastinal nodes: 105, 106; middle mediastinal nodes: 107, 108, 109

was poor (270 postoperative days), the prognosis of some cases with middle or lower mediastinal nodes was favorable after lymph node dissection (960, 1,099, 1,528 postoperative days). However, the cases with metastasis in the lymph nodes around the abdominal aorta had a poor prognosis (35, 331, 204, 294 postoperative days).

Figure 7 shows the mediastinal lymph node metastasis from adenocarcinoma in relation to the extent of the esophageal invasion. These data were from 23 patients who all underwent thoracotomy. Invasion into the esophagus by more than 1 cm was related to an increased incidence of mediastinal node metastasis. However, we did not find any evidence suggesting that there was any increase in nodal metastasis associated with a deeper esophageal invasion. The cases with cervical lymph node metastasis (n4) had a poor prognosis, with the two patients dying on postoperative days 273 and 270. However, even the cases with more than 5 cm esophageal invasion survived for a relatively long time (960 and 1,528 postoperative days) after the combined resection of the lower esophagus and a mediastinal lymph node dissection.

The histology of the adenocarcinomas and lymph node metastases is shown in Table 4. Both differentiated and undifferentiated adenocarcinoma metastasized less frequently to the mediastinal lymph nodes than squamous cell carcinoma. With regard to the abdominal lymph nodes, undifferentiated adenocarcinomas metastasized more often than did the differentiated adenocarcinomas.

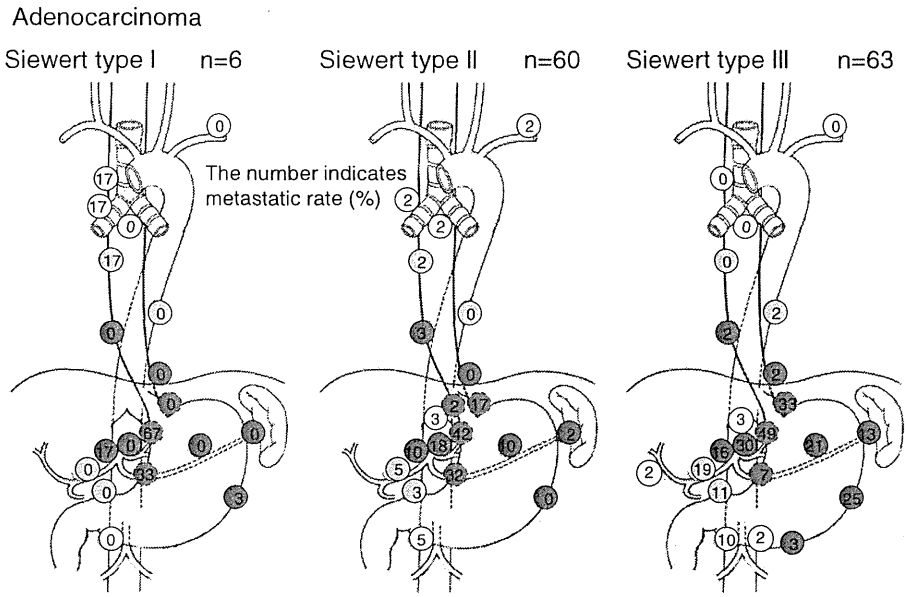


Fig. 6 The incidence of lymph node metastasis from adenocarcinoma according to the location of the tumor

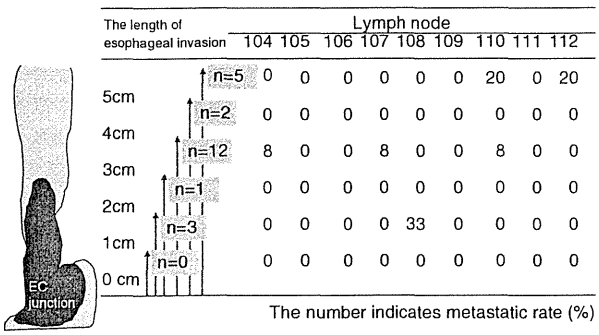


Fig. 7 The incidence of lymph node metastasis from adenocarcinoma according to the extent of the esophageal invasion

The recurrence pattern in relation to the depth of tumor invasion is shown in Table 5. We found similar patterns for adenocarcinomas as were observed for the squamous cell carcinomas, in that the deeper the tumor invaded, the higher the incidence of recurrence the patients had. However, the major recurrence pattern was shifted from lymph node metastasis in Siewert's type I cases to peritoneal dissemination in type III cases. Distant metastasis and local recurrence were also observed. The patients' survival is shown in Fig. 8. The prognoses of the patients with tumor penetration of the serosa (pT3) or tumor invasion to adjacent structures (pT4) were poor. In patients with Siewert type III tumors, the survival of the patients with tumor invasion of the muscularis propria or subserosa (pT2) was also poor.

Discussion

Because an increase of cancer in the esophagogastric junction has been observed, and is expected to continue increasing, the classifications of esophageal cancer and gastric cancer in this area have been harmonized in the East [21] and West [22]. In the Western world, most esophageal tumors are adenocarcinomas arising from the lower esophagus and the gastroesophageal junction [23]. In contrast, in Japan, squamous cell carcinoma represents more than 90% of all esophageal cancer cases [24].

The present study analyzed the incidence of lymph node metastases according to the location of the tumor. In patients with squamous cell carcinoma of the distal esophagus (Type I), the most common metastatic sites were the lower mediastinal and perigastric nodes. Although true cardia squamous cell carcinoma (Type II) tended to metastasize more frequently to the perigastric lymph nodes than Type I tumors did, it seemed to be appropriate to treat squamous cell carcinoma of the esophagogastric junction in accordance with the guidelines for thoracic esophageal cancer. The thoracoabdominal approach with two-field lymph node dissection is feasible for squamous cell carcinoma of the esophagogastric junction.

We seldom see cases of distal esophageal adenocarcinoma (Type I) in Japan, and the metastatic rates to the mediastinal lymph nodes of such patients were relatively low. Patients with true cardia adenocarcinomas (Type II) harbor metastases in lymph nodes of the paracardial region, lesser and greater curvatures, left gastric artery toward the celiac axis, splenic artery, superior border of the pancreas toward the splenic hilum, and the lower posterior mediastinum [13, 25]. Total gastrectomy with a transhiatal resection of the distal esophagus may be the best approach for these Type II tumors [10]. Subcardiac adenocarcinomas (Type III) more frequently metastasize to intraabdominal lymph nodes. Extended surgery, such as a retroperitoneal

Table 4 Lymph node metastasis from adenocarcinoma in relation to the histology

Histology	Mediastinal lymph node								
	104	105	106	107	108	109	110	111	112
Differentiated ($n = 83$)	1	1	0	1	2	0	2	0	0
Undifferentiated ($n = 44$)	0	0	0	0	0	0	2	2	2

Histology	Abdominal lymph node													
	1	2	3	4	5	6	7	8	9	10	11	12	14	16
Differentiated ($n = 83$)	43	20	36	8	4	5	22	7	11	4	13	1	0	1
Undifferentiated ($n = 44$)	50	34	48	25	14	11	27	20	23	14	20	5	7	5

The number shows the metastatic rate (%)

Table 5 The recurrence pattern of adenocarcinoma in relation to the depth of the tumor invasion

Siewert's classification location	Depth	Number of cases	Recurrence (%)	Site of recurrence			
				Lymph node metastasis	Distant metastasis	Local recurrence	Peritoneal dissemination
Type I: 1–5 cm above the EGJ	pT1	1	0 (0)	0	0	0	0
	pT2	2	1 (50)	1	0	0	0
	pT3	2	1 (50)	1	0	0	0
Type II: Between 1 cm above and 2 cm below the EGJ	pT1	9	0 (0)	0	0	0	0
	pT2	12	5 (42)	3	0	2	0
	pT3	29	20 (69)	4	8	5	6
	pT4	2	2 (100)	1	1	1	0
Type III: 2–5 cm below the EGJ	pT1	7	0 (0)	0	0	0	0
	pT2	12	6 (50)	4	3	0	2
	pT3	18	13 (72)	1	6	0	9
	pT4	13	9 (69)	0	0	1	9

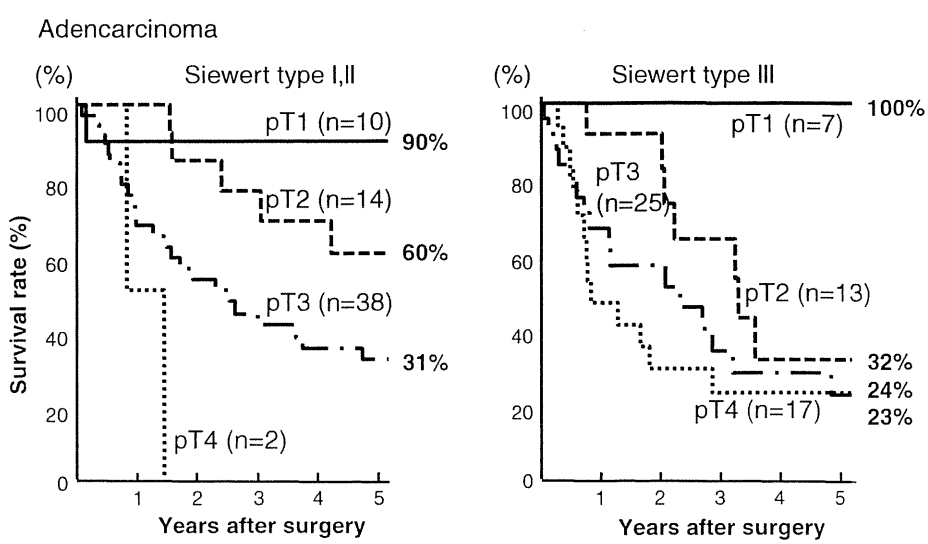


Fig. 8 The survival of patients with adenocarcinoma in relation to the depth of the tumor invasion

lymphadenectomy with left-sided pancreatic resection plus splenectomy, has not been recommended because of its negative side-effects [26, 27].

For patients with highly advanced pT3 or pT4 tumors, standard surgery alone does not exert an effect sufficient to improve the patient survival. Most of these cases had recurrences, distant metastasis, or peritoneal dissemination. It does not seem to be necessary to perform more extended resection or dissection for esophagogastric cancer [14]. In addition, the value of neoadjuvant chemotherapy has not been established as a standard therapy. Therefore, not only for patients with local lymphatic recurrence but also for patients with distant hematogenous recurrence, it is important to define the subset(s) of patients who might benefit from neoadjuvant chemotherapy. Accurately predicting chemosensitivity based on either the molecular characteristics or the use of diagnostic imaging devices should be therefore the focus of future studies.

In conclusion, based on the present data about squamous cell carcinoma, a transthoracic esophagectomy with two-field lymphadenectomy appears to be feasible, and for adenocarcinoma, a total gastrectomy with transhiatal distal esophagectomy is recommended unless lymph node metastases have been detected in the proximal part of the chest.

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ORIGINAL ARTICLE

Prognostic effects of oral anti-cancer drugs as adjuvant chemotherapy for 2 years after gastric cancer surgery

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Abstract
Purpose We conducted this retrospective study to evaluate the effectiveness of giving oral anti-cancer drugs for 2 years as postoperative adjuvant chemotherapy to gastric cancer patients.
Methods The subjects were 76 patients with stage II and III gastric cancer, who underwent curative surgery between 1989 and 2008. We divided the 20 years chronologically into the UFT term (1989–2003) and the S-1 term (2004–2008). The patients from each term were then divided into three groups according to the length of drug administration; namely, the surgery alone group, the 1-year group, and the 2-year group.
Results The survival time of the 2-year group was better than that of the surgery alone group, not only in the UFT term, but also in the S-1 term ($P = 0.0224$). Longer relapse-free survival was evident in the S-1 term, especially for the 2-year group ($P = 0.0110$). A multivariate analysis showed both the stage of the cancer and 2 years of postoperative adjuvant chemotherapy to be independent factors predictive of prolonged survival ($P = 0.0040$ and $P = 0.0022$, respectively).
Conclusions The 2-year administration of oral anti-cancer drugs as postoperative adjuvant chemotherapy might improve the outcome of stage II, III gastric cancer patients. Randomized control trials are warranted to prove the effectiveness of this 2-year regimen.

Keywords Gastric cancer · Adjuvant chemotherapy · Two years administration · Oral anti-cancer drugs

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Introduction

Postoperative adjuvant chemotherapy is commonly given after the curative resection of gastric cancer in both Eastern and Western countries [1–4]. Two recent randomized trials on postoperative adjuvant chemotherapy showed significant survival benefits of gastrectomy followed by UFT [5-fluorouracil (5-FU) analog, tegafur combined with uracil in a ratio of 1:4, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan], and S-1 (a new oral fluoropyrimidine containing tegafur, 5-chloro-2, 4-dihydropyrimidine and potassium oxonate, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) versus surgery alone [5, 6]. Several meta-analyses also support the effectiveness of adjuvant therapy [7–9].

These findings suggest the efficacy of adjuvant chemotherapy using a tegafur-based regimen for curatively resected gastric cancer with extensive lymph node dissection [10, 11]. However, the optimal length of time for which these drugs should be administered has not been established.

Several studies have evaluated the effects of giving chemotherapy for periods ranging from 6 to 12 months [12]; however, Kodama et al. [13] proposed a 2-year regimen of postoperative long-term combination chemotherapy (PLCC) for curatively resected gastric cancer after observing a better prognosis in these patients. Based on the strategy of PLCC, some patients at our institute have been treated with oral anti-cancer drugs for 2 years or longer postoperatively, and have been followed up long-term under close surveillance.

We conducted this study to compare the effectiveness of 1 versus 2 years of UFT or S-1 as postoperative adjuvant chemotherapy for stage II or III gastric cancer. The data were examined by both univariate and multivariate analyses.

Patients and methods

Patients

The subjects of this study were 76 patients with primary gastric cancer pathologically classified as stage II or III, who underwent surgery in Fukuoka City Hospital between 1989 and 2008. The patients were selected based on the following criteria: they were younger than 80 years old, they had no double cancer history, and the cause of death was limited to the original diseases. None of the patients had received neoadjuvant chemotherapy.

The mean age of the patients was 62.2 ± 11.1 years (range 33–79 years old) and there were 50 men and 26 women. The 76 patients were chronologically divided into the UFT term group (1989–2003, $n = 47$) and the S-1 term group (2004–2007, $n = 29$) according to the drugs administered postoperatively. The UFT group included those treated with conventional tegafur-based drugs, mainly UFT. After having taken the drugs for 1 year, the patients in each group were informed of the expected advantages and disadvantages of continuing to take the drugs for a second year. When the patients agreed to the concept of long-term adjuvant chemotherapy, the drugs were administered for an additional year. We compared the prognoses of patients treated with surgery alone, those treated with 1 year of adjuvant chemotherapy, and those treated with 2 years of adjuvant chemotherapy.

Clinicopathological investigation

We assessed the clinicopathological factors according to the Japanese Classification of Gastric Carcinoma outlined by the Japanese Gastric Cancer Association [14].

Follow-up

Patient follow-up continued until death and only those patients who died of gastric cancer were included in the analysis. The postoperative follow-up period ranged from 221 to 5760 days (mean 1581 ± 1293, median 1223.5 days).

Adverse effects of the drugs

Adverse reactions of the drugs in each regimen were monitored and evaluated at the outpatient clinic, based on the criteria of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical Analysis

Both univariate and multivariate analyses were conducted to establish the association between prognosis and age, sex, depth of tumor invasion, lymph node metastasis, and adjuvant chemotherapy in the 1- and 2-year UFT and S-1 groups. Statistical analyses were performed among the groups, using the Chi-square or non parametric Wilcoxon tests or the Cochran–Armitage trend test. Survival curves were generated by the Kaplan–Meier method and the log-rank test was used to analyze the equality of the survival curves. A Cox proportional hazard model was used for the multivariate analyses to determine the independent prognostic factors. A P value of less than 0.05 was considered to indicate significance.

Results

Profiles of the patients in each term

Table 1 shows the daily drug dosages and the length of their administration in the UFT group (1989–2003) and the S-1 group (2004–2008). Table 2 summarizes the clinical findings in the surgery alone, 1-year, and 2-year treatment groups within the UFT group. Although there were no

Table 1 Drug dosages and lengths of administration in each term

Term	UFT term ($n = 47$)			S-1 term ($n = 29$)		
Years	1989–2003			2004–2008		
Groups	Surgery alone ($n = 11$)	1-year UFT treatment ($n = 27$)	2-years UFT treatment ($n = 9$)	Surgery alone ($n = 10$)	1-year S1 treatment ($n = 6$)	2-years S-1 treatment ($n = 13$)
Dosage of drugs (mg/day)	–	361 ± 112	333 ± 132	–	92.0 ± 17.9	100 ± 14.8
Length of administration (months)	–	10.4 ± 3.0	23.1 ± 5.6	–	12.3 ± 3.7	25.2 ± 3.4

Table 2 Background of the patients in the UFT term (1989–2003)

Factors	Surgery alone ($n = 11$)	UFT 1 year ($n = 27$)	UFT 2 years ($n = 9$)	p value
Age[a]	67.8 ± 7.7	61.7 ± 12.8	60.6 ± 11.9	0.113
Male vs. female	7 vs. 4	18 vs. 9	5 vs. 4	0.744
Depth of tumor invasion				
t1,2	5 (45.5%)	14 (51.9%)	2 (22.2%)	0.355
t3,4	6 (54.5%)	13 (48.1%)	7 (77.8%)	
Extent of lymph node metastasis				
n0,1	2 (18.2%)	10 (37.0%)	7 (77.8%)	0.009
n2,3	9 (81.8%)	17 (63.0%)	2 (22.2%)	
Histological type				
Undifferentiated	4 (36.4%)	14 (51.9%)	6 (66.7%)	0.1756
Differentiated	7 (63.6%)	13 (48.1%)	3 (33.3%)	
Stage				
II	1 (9.1%)	6 (27.3%)	2 (22.2%)	0.669
IIIA	8 (72.3%)	15 (45.4%)	4 (44.4%)	
IIIB	2 (18.6%)	6 (27.3%)	3 (33.4%)	
Lymph node dissection				
D0,1	1 (9.1%)	3 (11.1%)	0 (%)	0.474
D2,3	10 (90.9%)	24 (88.9%)	10 (100%)	

[a] Mean ± standard deviation

Table 3 Background of the patients in the S-1 term (2004–2008)

Factors	Surgery alone ($n = 10$)	S-1, 1 year ($n = 6$)	S-1, 2 years ($n = 13$)	p value
Age[a]	63.6 ± 10.3	62.2 ± 5.4	58.0 ± 13.6	0.273
Male vs. female	5 vs. 5	5 vs. 1	10 vs. 3	0.196
Depth of tumor invasion				
t1,2	7 (70.0%)	2 (33.3%)	6 (46.2%)	0.303
t3,4	3 (30.0%)	4 (66.7%)	7 (54.8%)	
Extent of lymph node metastasis				
n0,1	8 (80.0%)	2 (33.3%)	6 (46.2%)	0.136
n2,3	2 (20.0%)	4 (66.7%)	7 (54.8%)	
Histological type				
Undifferentiated	6 (60.0%)	1 (16.7%)	6 (46.2%)	0.617
Differentiated	4 (40.0%)	5 (83.3%)	7 (54.8%)	
Stage				
II	6 (60.0%)	2 (33.3%)	4 (30.8%)	0.125
IIIA	3 (30.0%)	2 (33.3%)	5 (38.4%)	
IIIB	1 (10.0%)	2 (33.3%)	4 (30.8%)	
Lymph nodes dissection				
D0,1	0 (0%)	0 (0%)	0 (0%)	1.000
D2,3	14 (100%)	6 (100%)	13 (100%)	

[a] Mean ± standard deviation

significant differences in age, sex, depth of tumor invasion, stage, or lymph node dissection, there was a significantly lower incidence of extensive lymph node metastasis in the 2-year group than in the other two groups ($P = 0.009$). Table 3 summarizes the clinical findings of the patients in the S-1 group, which showed no significant difference in backgrounds.

Survival rates

There were no significant differences in 5-year survival rates between either of the UFT-treatment groups and the patients treated with surgery alone in this term ($P = 0.0617$, Fig. 1a). Conversely, the 5-year survival rate of all the patients treated with S-1 was significantly better than

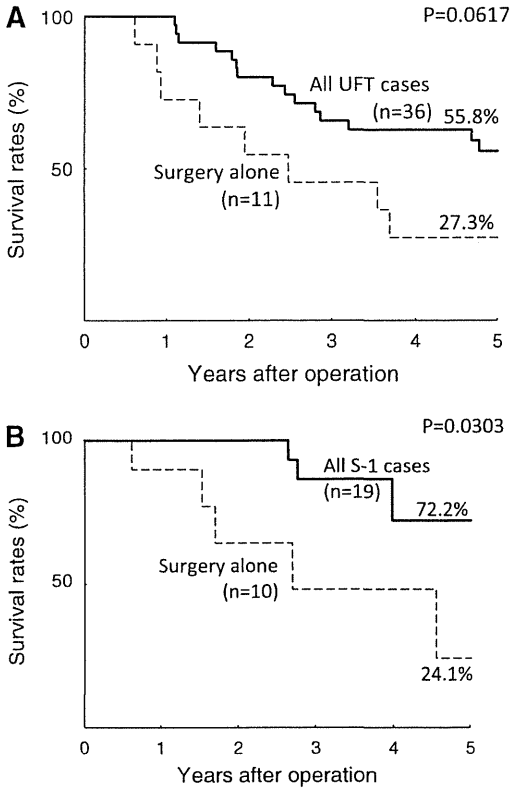

Fig. 1 Survival curves of the patients in the UFT (1989–2003) and S-1 (2004–2008) terms. **a** The *dotted line* represents the surgery alone group ($n = 11$) and the *heavy line* represents both the UFT groups ($n = 36$). There was no significant difference between the groups. **b** The *dotted line* represents the surgery alone group ($n = 10$) and the *heavy line* represents both the S-1 groups ($n = 19$). The P value was 0.0303, indicating significance

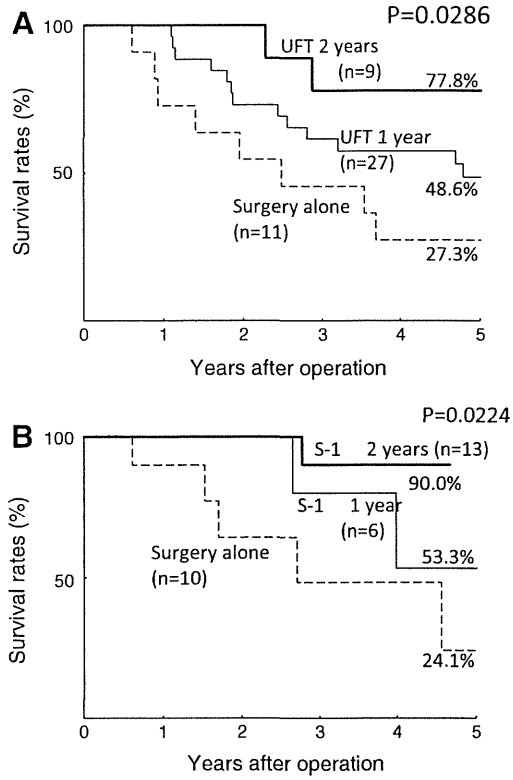

Fig. 2 Survival curves according to whether adjuvant therapy was given for 1 year or 2 years postoperatively. **a** The *dotted line* represents the surgery alone group ($n = 11$), the *light line* represents the 1-year UFT-treatment group ($n = 27$) and the *heavy line* represents the 2-year UFT-treatment group ($n = 9$). The P value was 0.0286, indicating significance. **b** The *dotted line* represents the surgery alone group ($n = 10$), the *light line* represents the 1-year S-1 treatment group ($n = 6$) and the *heavy* line represents the 2-year S-1 treatment group ($n = 13$). The P value was 0.0224, indicating significance

that of the patients treated with surgery alone in this term ($P = 0.0303$, Fig. 1b). Survival curves according to the time each drug administered for are shown in Fig. 2. Survival of the 2-year UFT-treated patients was significantly better than that of the surgery alone group in this term ($P = 0.0286$, Fig. 2a). Similarly, survival of the 2-year S-1-treated patients was significantly better than that of the surgery alone group in this term ($P = 0.0224$, Fig. 2b). Ultimately, S-1 administration resulted in significantly better relapse-free survival in all patients ($P = 0.0108$, Fig. 3a). There was a significant difference in relapse-free survival time between the surgery alone group and the 2-year S-1 treated group ($P = 0.0110$, Fig. 3b).

Univariate and multivariate analyses were conducted for each pathologic factor (Table 4). The multivariate analysis proved that stage and 2 years of postoperative adjuvant chemotherapy were independent factors for prolonged survival ($P = 0.0400$ and $P = 0.0022$, respectively).

Adverse reactions

Table 5 summarizes the adverse reactions observed during all treatment courses in the S-1 group according to CTCAE version 4.0. Two grade 2 cases were recognized in the 1-year S-1 group and one grade 2 case was recognized in the 2-year S-1 group. Myelosuppressive, mucositis, and gastrointestinal toxicities were generally mild and there was no treatment-related death. The dosage was decreased by 20% for one patient with grade 2 leukopenia. No adverse reactions of more than grade 3 toxicity occurred in any group.

Recurrence

Table 6 summarizes the sites of recurrence and the second-line chemotherapy in the S-1 group. The sites of recurrence were distributed in various organs of the hosts. Second-line

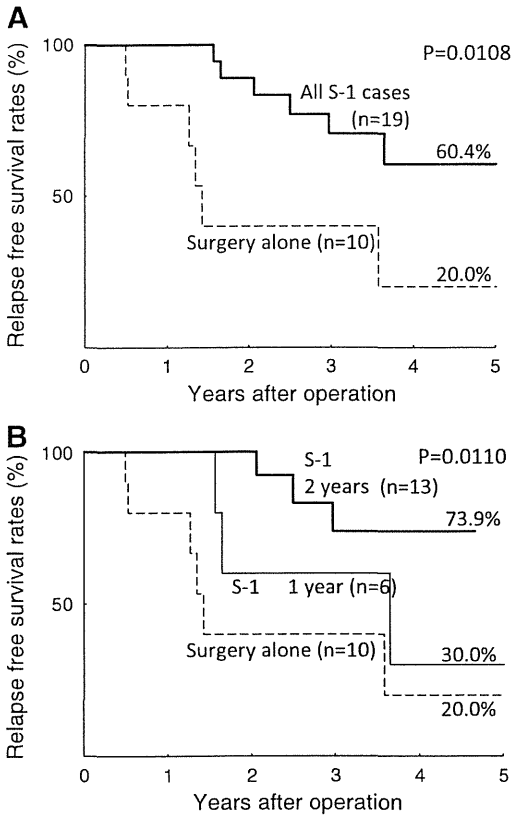

Fig. 3 Progression-free survival curves in the S-1 term. **a** The *dotted line* represents the surgery alone group ($n = 10$) and the *heavy line* represents both the UFT groups ($n = 19$). The P value was 0.0108, indicating significance. **b** The *dotted line* represents the surgery alone group ($n = 10$), the *light line* represents the 1-year UFT group ($n = 6$) and the *heavy line* represents the 2-year UFT group ($n = 13$). The P value was 0.0110, indicating significance

chemotherapy usually comprised either the single or combined use of taxane, cisplatin, and S-1.

Discussion

The purpose of adjuvant chemotherapy is to eradicate residual cancer cells in the peritoneal cavity after curative surgery [15]. The main mechanisms are recognized as better perfusion of blood, allowing access of the drug to small tumor cells; and better sensitivity to most anticancer drugs in cells with a higher rate of rapid proliferation in small tumors [16, 17].

The cytotoxicity of 5-FU is dose- and time-dependent with its accumulation in the blood [18]. Better survival rates are observed in patients given a higher dose of UFT after curative surgery for gastric cancer [19]. Kodama et al. [13] advocated the concept of the PLCC for resected gastric cancer, with a regimen of 2 years of oral mitomycin C, tegafur (oral 5-FU analog) and immunostimulator,

Table 4 Univariate and multivariate analyses of the prognostic factors over the whole study period

Factors	Univariate analysis	Multivariate analysis		
	p value	p value	Hazard ratio	95% CI
Age				
<65 vs. >65 years	0.3877	0.3871	1.3606	0.6771–2.7342
Sex				
Male vs. female	0.4347	0.4356	0.7425	0.3512–1.5696
Depth of tumor invasion				
t1,2 vs. t3,4	0.5556	0.5548	1.2417	0.6054–2.5468
Lymph node metastasis				
n0,1 vs. n2,3	0.1151	0.1200	1.8189	0.8557–3.8663
Histological type				
undifferentiated vs. differentiated	0.7315	0.7311	0.8831	0.4346–1.7944
Stage				
II vs. IIIA, IIIB	0.0320	0.0400	3.0544	1.0523–8.8712
Lymph nodes dissection				
D0,1 vs. D2,3	0.9332	0.9331	1.0633	0.2536–4.4583
Period of adjuvant chemotherapy				
none vs. 1 year	0.0769	0.0799	0.5168	0.2469–1.0818
none vs. 2 years	0.0004	0.0022	0.1397	0.0396–0.4928

CI confidence interval

Table 5 The adverse reactions observed during all treatment courses in the S-1 group according to CTCAEVer. 4.0

Toxicity	S-1 groups	
	1 year ($n = 6$)	2 years ($n = 13$)
Grade 2		
Leukopenia	0 (0%)	1 (7.7%)
Neutropenia	0 (0%)	0 (0%)
Anemia	0 (0%)	0 (0%)
Thrombocytopenia	0 (0%)	0 (0%)
Anorexia	1 (16.7%)	0 (0%)
Diarrhea	0 (0%)	0 (0%)
Nausea/vomiting	0 (0%)	0 (0%)
Mucositis	1 (16.7%)	0 (0%)
Pigmentation	0 (0%)	0 (0%)
Grade3	0 (0%)	0 (0%)

after observing that it achieved a better prognosis. Similar findings were observed in patients with stage IV gastric cancer and esophageal cancer after esophagectomy [20, 21].

Maehara et al. [22] reported that S-1 is the standard first-line postoperative adjuvant chemotherapy for resected

Table 6 Sites of recurrence and the second-line regimens in the S-1 group

Term	S-1 term ($n = 29$)		
Groups	Surgery alone ($n = 10$)	1 year ($n = 6$)	2 years ($n = 13$)
Cases of recurrence	6 (60.0%)	3 (50.0%)	2 (15.4%)
Recurrence site			
Liver	0	1	0
Anastomotic site	0	0	1
Peritoneum	2	1	1
Lymphnodes	3	0	0
Lung	0	1	0
Bone	1	0	0
Second-line regimen			
Taxane	1	1	1
LV + 5FU	0	1	0
S-1 + taxane	1	0	1
S-1 + cisplatin	1	0	0

LV leucovorin

gastric cancer, in accordance with the current recommendation of the 1-year administration of S-1 as the standard postoperative adjuvant chemotherapy regimen for stage II and III gastric cancer [6, 23]. In the present series, the oral anti-cancer dose- and time-dependent drugs, UFT and S-1, were administered for up to 2 years or longer, based on the PLCC strategy to improve prognosis. The patients were followed up carefully in the outpatient clinic under close surveillance for compliance and adverse reactions, because cytotoxic 5-FU could accumulate in their bodies [18].

Previous data reveal that PLCC courses are occasionally suspended following adverse effects, such as bone marrow suppression, serious gastrointestinal manifestations, and liver dysfunction, but recommenced thereafter on the completion of adequate treatments [13, 20]. The adverse effects after 2 years administration in the present series were also mild, demonstrating the feasibility of this 2-year adjuvant chemotherapy regimen.

This study found a favorable prognosis for increased overall survival in the 2-year UFT and S-1 groups and increased relapse-free survival in the 2-year S-1 group. Furthermore, multivariate analyses revealed the prognostic significance of giving the adjuvant therapy drugs for 2 versus 1 year. These findings are consistent with those of the previous PLCC studies [13, 20, 21], supporting the 2-year administration of these cancer drugs. The administration of S-1 might not be recommended for very elderly patients, because of the risk of severe adverse reactions. UFT might be preferred for older patients because of its mild toxicity [24].

In conclusion, the findings of the present study suggest that the 2-year administration of oral anti-cancer drugs as postoperative adjuvant chemotherapy may lead to a favorable outcome for stage II and III gastric cancer patients. However, no definitive conclusions can be drawn until randomized control trials are conducted to prove the effectiveness of this 2-year regimen.

Conflict of interest Toshiro Okuyama and his co-authors have no conflict of interest.

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ORIGINAL ARTICLE

A randomized phase-II trial comparing sequential and concurrent paclitaxel with oral or parenteral fluorinated pyrimidines for advanced or metastatic gastric cancer

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Abstract

Background The purpose of this study was twofold: (1) to compare S-1 with infusional 5-fluorouracil (FU) to determine which would be a better partner of paclitaxel (PTX), and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Methods The 161 eligible patients were randomized into four arms to receive the following regimens: A (sequential), intravenous 5-FU at 800 mg/m^2 for 5 days every 4 weeks followed by weekly PTX at 80 mg/m^2; B (sequential), S-1 at 80 mg/m^2 for 4 weeks and 2-week rest followed by PTX; C (concurrent), intravenous 5-FU at 600 mg/m^2 for 5 days and weekly PTX at 80 mg/m^2 every 4 weeks; and D (concurrent), S-1 for 14 days and PTX at 50 mg/m^2 on days 1 and 8 every 3 weeks. The primary endpoint was the overall survival (OS) rate at 10 months.

Results The ten-month OS rates in arms A, B, C, and D were 63, 65, 61, and 73%, respectively. The OS was best in the concurrent S-1/PTX arm, with a mean survival time of

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