in order to investigate LN metastasis. Furthermore, there is difficulty in determining accurate histopathological diagnoses of mixed type tumors, such as distinguishing between moderately differentiated type and poorly differentiated type lesions. In the present study, all cases were reviewed and diagnosed by at least two pathologists specializing in gastrointestinal pathology.

In conclusion, histologically mixed-type EGC with a predominantly differentiated component might be clinically managed the same way as a differentiated type EGC. However, the rates of lymphovascular invasion and LN metastasis in MD-type tumors were non-significantly higher than that of PD type lesions. Data suggest that MU-type tumors might have greater malignant potential than PU type tumors. Further investigation is warranted to confirm these findings.

Conflict of interest None.

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ORIGINAL ARTICLE

Value of splenectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction

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Abstract
Background The incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increasing recently in both Western and Eastern countries. However, an optimal treatment strategy for Siewert type II AEG is still unclear. The aim of this study was to clarify the value of splenectomy in patients with Siewert type II AEG.
Methods From September 2002 to November 2011, 42 patients underwent total gastrectomy with D2 lymph node dissection for Siewert type II AEG and were included in this study. We used the index of estimated benefit from lymph node dissection (IEBLD) to assess the efficacy of lymph node dissection of each station. Surgical complications were graded by the Clavien–Dindo classification.
Results The overall 5-year survival rate of the 42 patients was 57.5 %. The incidence of splenic hilar lymph node metastasis was 4.8 % and the 5-year survival rate of patients with splenic hilar lymph node involvement was zero. Consequently, the IEBLD of splenic hilar lymph nodes was zero. Postoperative morbidities occurred in 25 patients (59.5 %). Pancreas-related complications were the most frequently observed (28.5 %), followed by intraabdominal abscess (14.3 %) and anastomotic leakage (9.5 %).
Conclusions Splenic hilar lymph node dissection may be omitted without decreasing curability in patients with Siewert type II AEG, although a prospective study is necessary for more conclusive results.

Keywords Gastric cancer · Adenocarcinoma of esophagogastric junction · Siewert type II · Splenectomy

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Introduction

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increasing recently in both Western and Eastern countries [1]. In the East, the westernized lifestyle habit and the increased incidence of gastroesophageal reflux disease are thought to be possible reasons, with the incidence of AEG likely to increase further [2]. Siewert et al. [3] classified AEG into three subgroups according to the location of the tumor epicenter. Siewert type I AEG, which is frequently observed in Western countries, is generally treated as an esophageal cancer. Siewert type III AEG, which is frequently observed in Eastern countries, is mostly treated as a gastric cancer. An optimal treatment strategy for Siewert type II AEG is still unclear, and it is under debate whether Siewert type II AEG should be regarded and treated as an esophageal cancer or a gastric cancer [4, 5].

The latest European Society for Medical Oncology clinical practice guideline recommends D2 gastrectomy for curable gastric cancer. However, splenectomy is not recommended unless the tumor is directly infiltrating the spleen [6, 7]. In contrast, Japanese guidelines include splenectomy in D2 total gastrectomy. Consequently, splenectomy is mandatory in patients with type II AEG undergoing total gastrectomy in Japan [8, 9]. However, recent reports from the East have raised the question of whether splenectomy is valuable in these patients [10, 11].

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Reported are an increased incidence of pancreas-related complications following splenectomy and a low incidence of splenic hilar nodal involvement in patients with AEG [10–12]. However, these reports included a variety of patients, such as those with Siewert type I or III AEG and patients undergoing noncurative surgery [10, 11]; thus, the therapeutic value of splenectomy in patients with Siewert type II AEG undergoing curative gastrectomy remains unclear.

The aim of this study was to clarify the value of splenectomy in patients with Siewert type II AEG. We investigated the clinicopathological characteristics and long-term outcome of patients with Siewert type II AEG who underwent total gastrectomy with D2 lymph node dissection.

Materials and methods

Patients

From September 2002 to November 2011, 2,995 patients with gastric cancer underwent gastrectomy at the Shizuoka Cancer Center, Japan. Of these, 64 patients underwent total gastrectomy with D2 lymph node dissection for Siewert type II AEG. Patients with early gastric cancer (13 patients), those who received neoadjuvant chemotherapy (3 patients), and those who underwent noncurative gastrectomy (R1 or R2, 6 patients) were excluded, and the remaining 42 patients were included in the present study.

The International Union Against Cancer (UICC) TNM staging system for esophageal cancer was used for tumor staging [4]. The lymph node stations were numbered according to the definition of the Japanese Gastric Cancer Association (JGCA) [13].

Tumor histology was evaluated according to the JGCA classification [13]. Well- and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as differentiated-type carcinomas. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma were classified as undifferentiated-type carcinomas.

Patient characteristics and pathological and surgical findings were collected from our database records and individual patient electronic medical records. The data collection and analysis were approved by the institutional review board of the Shizuoka Cancer Center.

Surgery

Total gastrectomy with D2 lymphadenectomy was carried out in all patients included in the present study. All perigastric nodes and extraperigastric nodes, defined as second-compartment lymph nodes according to the JGCA classification, were retrieved (2nd English edition of JGCA). To completely remove the splenic hilar lymph nodes, all patients underwent splenectomy. The surgical complications were assessed by the Clavien–Dindo classification [14]. We defined any complication categorized as grade II or higher as a postoperative morbidity.

Evaluation of the therapeutic value of intraabdominal lymph node dissection

In the present study, we adopted the index of estimated benefit from lymph node dissection (IEBLD), a concept proposed by Sasako et al. [15] to assess the efficacy of lymph node dissection of each station. This index is calculated by multiplying the frequency of lymph node metastasis to each station by the 5-year survival rate of patients with positive lymph nodes at each station. The incidence of metastasis and the 5-year survival rate of patients with positive nodes were calculated independently for each lymph node, without any reference to the overall pathological nodal stage.

Statistics

Statistical analysis was carried out using SPSS version 19 for Windows. The Kaplan–Meier method was used to estimate survival curves. All continuous variables are presented as the median (range).

Results

Patient characteristics

The characteristics of the patients are described in Table 1. There were 26 male patients (62 %) and 16 female patients (38 %). Type 3 tumor was the most frequently observed macroscopic type (17 patients, 40.5 %). The transabdominal approach was the most preferred surgical approach used in this study (37 patients, 88.1 %). The reconstruction was performed by Roux-en-Y in all cases, and esophagojejunostomy was performed using a circular stapler. Lymph node metastases were observed in 32 patients (76.2 %: N1, 11 patients; N2, 7 patients; N3, 14 patients). Consequently, tumor stage was determined as IB in 6 patients, IIA in 4, IIB in 2, IIIA in 8, IIIB in 3, and IIIC in the remaining 19 patients. Adjuvant chemotherapy by S-1 was given to 15 patients.

Postoperative morbidities

The details of postoperative morbidities are described in Table 2. Grade II or higher postoperative complications

Table 1 Demographics of 42 patients with Siewert type II adenocarcinoma of the esophagogastric junction

Parameters	*N*
Age median (range), years	67 (30–79)
Sex	
Male	26
Female	16
Tumor size median (range), mm	57 (20–145)
Macroscopic type	
Type 0	9
Type 1	5
Type 2	11
Type 3	17
Circumferential distribution	
Lesser curvature	20
Greater curvature	1
Anterior wall	4
Posterior wall	8
Circular	9
Histological type	
Differentiated	21
Undifferentiated	21
Type of surgery	
TG + S	40
TG + PS	2
Approach	
Abdominal	37
Left thoracoabdominal	5
Tumor depth (histological)	
MP(T2)	8
SS(T3)	22
SE(T4)	12
Node stage (histological)	
N0	10
N1	11
N2	7
N3	14
Stage	
IA	0
IB	6
IIA	4
IIB	2
IIIA	8
IIIB	3
IIIC	19
IV	0
Adjuvant chemotherapy (S-1)	
+	15
−	27

PS pancreaticosplenectomy, *S* splenectomy, *TG* total gastrectomy, *MP* muscularis propria, *SS* subserosa, *SE* exposed beyond the serosa

Table 2 Postoperative complications in 42 patients after total gastrectomy with D2 lymphadenectomy

Complications	*n*	%
Complication, grade II or higher[a]	25	59.5
Pancreas-related complication	12	28.5
Intraabdominal abscess	6	14.3
Anastomotic leakage	4	9.5
Pneumonia	4	9.5
Pleural fluid	4	9.5
Bleeding	2	4.8
Cholecystitis	1	2.4
Wound complication	1	2.4

[a] Based on the Clavien–Dindo classification [14]

occurred in 25 patients (59.5 %). Pancreas-related complications were the most frequently observed morbidity (28.5 %), followed by intraabdominal abscess (14.3 %) and anastomotic leakage (9.5 %).

Survival outcomes

The 5-year survival rate of the 42 patients in this study was 57.5 %. Table 3 presents the frequency of metastasis of each regional lymph node, the 5-year survival rate of patients with nodal involvement, and the IEBLD for each station.

Lymph node involvement was observed in more than 10 % of patients (range 16.7–59.5 %) in stations 1, 2, 3, 7, 9, and 11p, and the IEBLDs of these stations ranged from 5.6 to 30.3. The incidence of metastasis was lower than 10 % (range 0–9.5 %) in the other stations, and the IEBLD was low (0–4.8). Lymph node metastasis was not found in stations 4d and 12a. In addition, the 5-year survival rate was zero if station 4sa, 4d, 6, 8a, 10, 11d, or 12a was involved.

Consequently, the IEBLDs of stations that were located far from the esophagogastric junction, such as stations 4d, 6 (along the right gastroepiploic artery), 8a (along the common hepatic artery), and 12a (along the proper hepatic artery), were zero. In addition, the IEBLDs of stations 10 and 11d, where splenectomy is necessary for complete retrieval of these nodes, were also zero (Fig. 1).

Discussion

The present study shows the IEBLD of regional lymph nodes in patients with Siewert type II AEG ranged from 0 to 30.3. It is plausible that dissection of some of these stations could be omitted even in advanced cases.

In the present study, the IEBLD of stations 1, 2, 3, 7, 9, and 11p were higher than the other stations. Previous

Table 3 Frequency of lymph node metastasis and 5-year survival for each lymph node station

Lymph node station	Number of patients with metastatic nodes	Number of patients in whom the station was dissected	Incidence of lymph node metastasis (%)	Five-year survival rate of patients with metastatic nodes (%)	IEBLD
1	25	42	59.5	50.3	29.9
2	8	42	19.0	46.9	8.9
3	24	42	57.1	53.0	30.3
4sa	1	42	2.4	0	0
4sb	2	42	4.8	50.0	2.4
4d	0	42	0	0	0
5	1	42	2.4	100	2.4
6	1	42	2.4	0	0
7	13	42	30.9	58.4	18.1
8a	1	42	2.4	0	0
9	10	42	23.8	30.0	7.1
10	2	42	4.8	0	0
11p	7	42	16.7	33.3	5.6
11d	2	42	4.8	0	0
12a	0	14	0	0	0
19	4	42	9.5	50.0	4.8
20	2	42	4.8	50.0	2.4

IEBLD index of estimated benefit from lymph node dissection

studies also reported a high IEBLD in these stations in patients with AEG [10, 11]. Investigation of lymphatic flow showed that these stations were sentinel nodes for the upper part of the stomach [16]. We consider complete retrieval of these stations would be of value and should not be omitted during curative surgery for Siewert type II AEG.

The IEBLDs of the remaining stations were lower than that of station 1, 2, 3, 7, 9, and 11p, and was zero in stations 4sa, 4d, 6, 8a, 10, and 11d; thus, lymph node dissection of some of these stations could be omitted. If we omit the supra- and infrapyloric lymph nodes, then the distal part of the stomach might be preserved [17]. In addition, the spleen could be preserved if the station 10 lymph node dissection was omitted, even in cases with advanced disease.

Previously, the therapeutic value of removing station 10 lymph nodes in AEG was investigated, and similar results, a low IEBLD for station 10 (0–2.2), were reported [5, 10, 11]. Yamashita et al. investigated IEBLD of 225 patients with Siewert type II AEG, and reported that of station 10 was 0.7. In addition, Hosokawa et al. reported IEBLD for station 10 in patients with AEG was 2.2. However, these previous studies included patients underwent non-curative gastrectomy or those with Siewert type I or III AEG. Therefore, to the best of our knowledge, our study is the first study to investigate the IEBLD of station 10 in patients with Siewert type II AEG underwent curative surgery.

The circumferential distribution is a possible reason why IEBLD of station 10 was zero in this study. Of 42 patients with circumferentially localized AEGs, the AEG was located along the lesser curvature in 20 patients. In contrast, it was located along the greater curvature in only one patient, the resulting tumor location being far away from the spleen, and there was a low incidence of station 10 lymph node involvement in this series. The same trend was also reported by Suh et al. [5] previously.

It would be advantageous to avoid splenectomy, a procedure necessary for the complete removal of the splenic hilar lymph node, as it has been reported that splenectomy increases pancreas-related complications and disturbs immune functions [12, 18, 19]. In fact, pancreas-related complications were the most frequently observed complication (28.5 %) in our study, and it was higher than that after spleen-preserving total gastrectomy in our institute (2.5 %; data not shown). Even in Japan, where splenectomy is mandatory for D2 gastrectomy, some studies have reported a lack of survival benefit and increased postoperative morbidities in patients undergoing splenectomy [12, 20–22]. In the West, although the current standard treatment for curable gastric cancer is a D2 gastrectomy, splenectomy is not a mandatory procedure, presumably because of increased postoperative pancreas-related complications and a lack of evidence that supports the feasibility of splenectomy [23–26]. Thus, splenectomy itself increases postoperative morbidities. Therefore, it would be of value if we could avoid splenectomy without worsening the long-term outcome of patients.

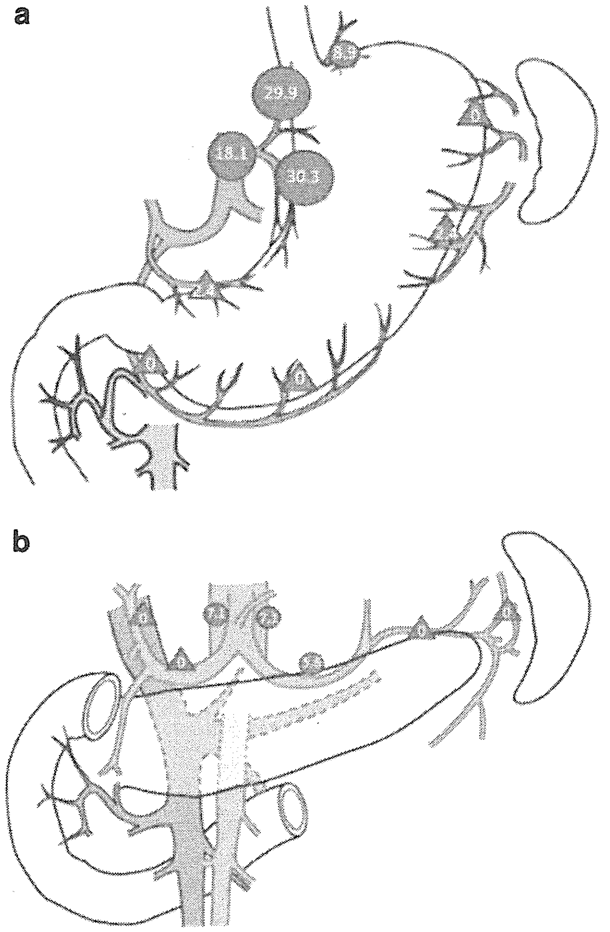

Fig. 1 Index of estimated benefit from lymph node dissection (IEBLD) for each lymph node station. *Circles*, IEBLD greater than 5; *triangles*, IEBLD less than 5

The present retrospective study has limitations, which include the small number of patients investigated in the study. Even though the number of patients with Siewert type II AEG has been increasing in Japan, the number of patients at each institute is still limited. Second, mediastinal lymph node dissection was not performed routinely, particularly in the early period of this study. Consequently, the value of mediastinal lymph node dissection cannot be assessed. The latest JGCA guidelines recommend mediastinal lymph node dissection for patients with AEG; thus, we currently perform lower mediastinal lymph node dissection for these patients (14th JGCA guidelines). We will be able to assess the value of lower mediastinal lymph node dissection in the near future.

In conclusion, the IEBLD of the splenic hilar lymph nodes was zero in the present study. Splenic hilar lymph node dissection may be omitted without decreasing curability in patients with Siewert type II AEG, although a prospective study is necessary for more conclusive results.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

The Impact of Preoperative Lymph Node Size on Long-Term Outcome Following Curative Gastrectomy for Gastric Cancer

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ABSTRACT

Background. Multidetector-row computed tomography (MDCT) is widely used to predict pathological nodal status. However, an appropriate nodal size cutoff value to predict pathological nodal status has not been determined, and the impact of preoperative lymph node size on long-term outcomes is unclear.

Methods. This study included 137 gastric cancer patients with nodal involvement who underwent R0 gastrectomy between September 2002 and December 2006. Lymph nodes with a short-axis diameter of 10 mm or more as measured by MDCT were regarded as metastasized. An appropriate cutoff value with a high positive predictive value (PPV) and high specificity also was identified, and the subsequent clinicopathological characteristics and long-term outcomes were investigated.

Results. A cutoff value of 15 mm was found to be appropriate for grouping patients into large (≥15 mm) and small (<15 mm) lymph node metastasis (LLNM and SLNM) groups, with a high PPV (98.6 %) and specificity (99.8 %). There were no differences in clinicopathological characteristics between the groups except for pathological nodal status. In the LLNM group, the 5-year survival rate was 55 %, which was significantly lower than in the SLNM group (73.2 %; $P = 0.008$). After stratification by tumor depth, the same trend was observed in patients with pT3 disease (46.8 % vs. 72.7 %; $P = 0.015$) and those with pT4 disease (14.3 % vs. 64.8 %; $P = 0.035$).

Conclusions. Gastric cancer patients with lymph nodes measuring 15 mm or more preoperatively have worse long-term outcomes. These patients would therefore be suitable candidates for future clinical trials investigating the efficacy of neoadjuvant chemotherapies.

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Gastric cancer is frequently diagnosed in east Asian countries. Early gastric cancer accounts for more than 50 % of cases in Japan and Korea, and favorable long-term outcomes have been reported following curative surgery.[1,2] Conversely, the long-term outcomes of patients with advanced gastric cancer remain poor, even after curative surgery.[1,2] In western countries, perioperative chemotherapy with or without radiation is a standard treatment for advanced gastric cancer.[3,4] In contrast, the standard treatment for advanced gastric cancer in east Asian countries is curative gastrectomy followed by adjuvant chemotherapy. The feasibility of utilizing neoadjuvant chemotherapy also is under investigation.[5–9]

Before neoadjuvant chemotherapy can become more widely used, it is necessary to determine the tumor stage before treatment begins. It is useful to identify patients who have a poor long-term outcome. Staging laparoscopy would be useful for detecting small peritoneal metastases for accurate staging[10]; however, this procedure is unable to assess nodal status accurately. Currently, multidetector-row computed tomography (MDCT) is widely used to predict pathological nodal status. However, an appropriate nodal size cutoff value to predict the pathological nodal status has not been determined, and the impact of preoperative lymph node size on long-term outcomes remains unclear despite a number of studies.[11–18]

In the present study, we investigated the clinicopathological characteristics of patients with lymph nodes longer than 10 mm in the short-axis diameter, as measured by preoperative MDCT. In addition, the long-term outcomes of patients with large lymph nodes (≥15 mm) were compared to those with smaller lymph nodes (<15 mm). The purpose of the present study was to clarify the impact of

TABLE 1 Accuracy of predicting pathological lymph node status for each cutoff value

Cutoff value (mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
10	39.1 (120/307)	96.9 (528/545)	87.6 (120/137)	73.8 (528/715)	76.1 (648/852)
15	22.5 (69/307)	99.8 (544/545)	98.6 (69/70)	69.6 (544/782)	71.9 (613/852)
20	14.0 (43/307)	100.0 (545/545)	100.0 (43/43)	67.4 (545/809)	69.0 (588/852)
30	2.0 (6/307)	100.0 (545/545)	100.0 (6/6)	64.6 (545/846)	64.8 (552/852)

PPV positive predictive value, *NPV* negative predictive value

preoperative lymph node size on clinicopathological characteristics and long-term outcomes.

PATIENTS AND METHODS

The present study included 137 gastric cancer patients with clinically diagnosed nodal involvement who underwent R0 gastrectomy between September 2002 and December 2006 at the Shizuoka Cancer Center in Japan. Patients who received neoadjuvant or adjuvant chemotherapy, patients who had other cancers simultaneously, or patients who underwent surgery for gastric stump carcinoma were excluded. Patients also were excluded if the primary lesion was not identified as an adenocarcinoma by histology.

Patient characteristics and the pathological and surgical findings were collected from our database records and individual patient electronic medical records. Data collection and analysis was approved by the institutional review board of the Shizuoka Cancer Center.

Pathological tumor depth, nodal status, and curability of surgery were assigned according to the International Union Against Cancer (UICC) classification system.[19] Histological type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system,[20] in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, whereas poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.

Preoperative Examinations

Enhanced MDCT scans were performed on all patients before surgery. If patients had severe renal dysfunction or an allergy to the contrast media, a plain MDCT scan was performed instead. The patients were examined in a supine position with their arms stretched above their heads at the end of inspiration using a CT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan). Parameters for scanning were: tube voltage, 120 kVp; scan time, 0.5 s; and reconstruction slice thickness, 2 mm. The tube current was automatically determined by the CT automatic exposure control system. The diameter of each lymph node was measured using transverse MDCT images. Lymph nodes with a short-axis diameter of 10 mm or more were regarded as clinically metastasized lymph nodes. Multiplanar reformation (MPR) images were not used in the present study, and the longitudinal diameter of each node was not taken into account.

A second cutoff value was also applied for further classification of the patients. Short-axis diameter cutoff values of 15 mm, 20 mm, and 30 mm were tested. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of each cutoff value were investigated (Table 1). To calculate the sensitivity and specificity of each cutoff value, 715 clinically node-negative patients (patients who had lymph nodes with a short-axis diameter less than 10 mm as measured by MDCT) who underwent curative gastrectomy during the same study period were recruited. Of these 715 patients, 187 patients were found to have pathologically positive lymph nodes.

Statistical Analyses

All continuous variables are presented as the median (range). Statistical analyses were performed by using Fisher's exact test, the Student's *t* test, and the Mann-Whitney test. Five-year survival rates were calculated by using the Kaplan-Meier method and the log-rank test was used to compare the groups. Independent prognostic factors were identified using the Cox proportional hazards model. In this analysis, each patient's age, sex, histology, type of surgery, tumor depth, and lymph node size measured by MDCT were included as covariates. $P < 0.05$ was considered significant. All statistical analyses were conducted using the R version 2.13.1 statistical package.

RESULTS

Table 1 shows the sensitivity, specificity, accuracy, PPV, and NPV of each cutoff value tested. Both clinically node-positive patients ($n = 137$) and clinically node-negative patients ($n = 715$) were included in these calculations. Specificity and PPV reached a plateau when a cutoff value of 15 mm was used. The specificity and PPV did not increase when higher cutoff values were adopted; however, the sensitivity, NPV, and accuracy decreased. Therefore, a cutoff value of 15 mm was considered suitable for dividing the patients into further groups. Patients who had lymph nodes with a short-axis diameter measuring 15 mm or more were placed into the large lymph node metastasis (LLNM) group. The remaining patients were placed into the small lymph node metastasis (SLNM) group. The clinicopathological characteristics and long-term outcomes were compared between the two groups.

Table 2 shows the clinicopathological characteristics of the patients. There were no differences in sex, age, surgical procedures, degree of lymph node dissection, operation times, intraoperative blood loss, length of postoperative hospital stay, histology, or number of retrieved lymph nodes between the two groups. The pathological nodal status was different between the two groups. In the LLNM group, 98.6 % of patients had pathologically positive lymph nodes, whereas in the SLNM group, 76.1 % of patients had pathologically positive lymph nodes. Consistent with these results, the positive predictive value (PPV) was 98.6 % (69/70) when a short-axis diameter of 15 mm was used as the cutoff value and 87.6 % (120/137) when a short-axis diameter of 10 mm was used as the cutoff value. In addition, the number of patients with N3 disease was higher in the LLNM group than in the SLNM group ($P < 0.001$).

Figure 1 illustrates the survival curves of all patients. The median follow-up period of survivors was 70 months. In the LLNM group, the 5-year survival rate was 55 %, which was significantly lower than that of the SLNM group (73.2 %; $P = 0.008$). Survival curves were stratified by the tumor depth and were not significantly different between the two groups in patients with pT1 ($P = 0.765$) and pT2 ($P = 0.548$) disease. Conversely, the survival rate was significantly worse in the LLNM group than in the SLNM group in patients with pT3 and pT4 disease. The 5-year survival rate for patients with pT3 disease was 46.8 % in the LLNM group and 72.7 % in the SLNM group (Fig. 2a; $P = 0.015$), and for patients with pT4 disease it was 14.3 % in the LLNM group and 64.8 % in the SLNM group (Fig. 2b; $P = 0.035$).

Table 3 shows the results of multivariate analysis. Tumor depth (hazard ratio [HR], 6.570; 95 % confidence interval [CI], 1.585–27.238) and lymph node size (HR, 1.879; 95 % CI, 1.068–3.304) were found to be independent prognostic factors of survival.

Table 4 describes the sites of initial recurrence after curative gastrectomy. Lymph node metastasis was the most frequently observed recurrence pattern in the LLNM group and accounted for 67 % of recurrences. In the SLNM group, blood-borne metastasis (56 %) was the most frequently observed recurrence pattern followed by lymph node metastasis (44 %) and peritoneal metastasis (44 %). There were no significant differences between the two groups in the initial recurrence site.

TABLE 2 Patient characteristics

Characteristics	LLNM group	SLNM group	*P* value
Sex, *n*			
Male	55	46	0.244
Female	15	21	
Age, years			
Median	68.5	66	0.446
Range	38–85	30–86	
Surgical procedure, *n*			
Total gastrectomy	37	29	0.306
Partial gastrectomy	33	38	
Lymph node dissection			
<D2	13	16	0.532
≥D2	57	51	
Operation time, min			
Median	224	211	0.153
Range	99–607	107–562	
Intraoperative blood loss, mg			
Median	447	363	0.238
Range	49–2267	20–2613	
Postoperative hospital stay, days			
Median	14.5	14	0.593
Range	7–78	7–308	
Histology, *n*			
Differentiated	35	31	0.733
Undifferentiated	35	36	
Number of retrieved lymph nodes, *n*			
Median	41.5	41	0.436
Range	16–98	4–75	
Tumor depth, *n*			
T1	11	11	0.437
T2	6	12	
T3	46	35	
T4a	5	7	
T4b	2	2	
Lymph node status, *n*			
N0	1	16	<0.001
N1	12	12	
N2	27	21	
N3	30	18	
Pathological stage, *n*			
I	4	10	0.075
II	17	23	
III	43	32	
IV	6	2	

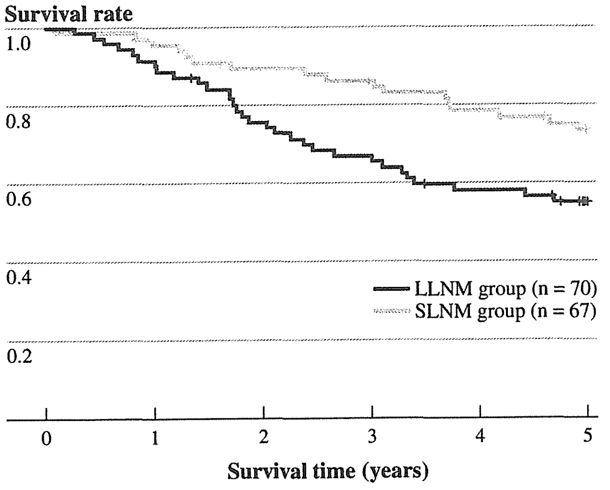

FIG. 1 Overall survival curves of patients in the LLNM group ($n = 70$) and SLNM group ($n = 67$). The 5-year overall survival rate is significantly worse in the LLNM group (55 %) than in the SLNM group (73.2 %; $P = 0.008$)

DISCUSSION

The present study showed that a high positive predictive value (87.6 %) for pathologically positive lymph nodes could be obtained by MDCT if a short-axis diameter of 10 mm was used as the nodal size cutoff value. This study also showed that the positive predictive value increased to 98.6 % if the short-axis diameter cutoff value was increased to 15 mm. In addition, survival analysis revealed that patients in the LLNM group had a worse overall survival rate than those in the SLNM group. Finally, multivariate analysis revealed that clinically measured lymph node size was an independent prognostic factor of survival.

The current standard treatment for advanced gastric cancer in western countries involves perioperative chemotherapy with or without radiation.[3,4] In contrast, curative gastrectomy followed by adjuvant chemotherapy is the standard treatment used in Japan and Korea.[6,8] Recently, the feasibility of neoadjuvant chemotherapy also has been investigated in east Asian countries, particularly for patients with advanced disease.[5,7] However, solid criteria for neoadjuvant chemotherapy do not exist, presumably due to the difficulty in accurate preoperative staging. If candidates can be selected for neoadjuvant chemotherapy appropriately, then the efficacy of neoadjuvant and adjuvant chemotherapy treatments in suitable candidates could be compared in future clinical trials.

There are a number of different criteria and ways to assess nodal status; therefore, no solid criteria exist for detecting metastasized lymph nodes appropriately. The ability of MDCT to detect lymph node metastasis preoperatively is limited, with a reported sensitivity of 62.5–91.9 % and specificity of 50–87.9 %.[21] The definition of metastasized lymph nodes differs between studies using MDCT and various cutoff values have been applied.[11,12,15–17,22] Ahn et al.[18] defined metastasized lymph nodes as having a short-axis diameter of ≥8 mm, and Yan et al.[12] defined regional lymph nodes as metastatic when the short-axis diameter was ≥6 mm, whereas extraperigastric lymph nodes were defined as metastatic when the short-axis diameter was ≥8 mm. In addition, the superiority of multiplanar reformation (MPR) images to transverse images in assessing tumor depth has been reported, although its feasibility for preoperative nodal staging remains controversial.[14,15]

Kim et al.[16] and Yang et al.[17] reported that the sensitivity and specificity of MDCT for gastric cancer staging differed according to the cutoff value used: the nodal size criteria were proportional to the specificity and inversely

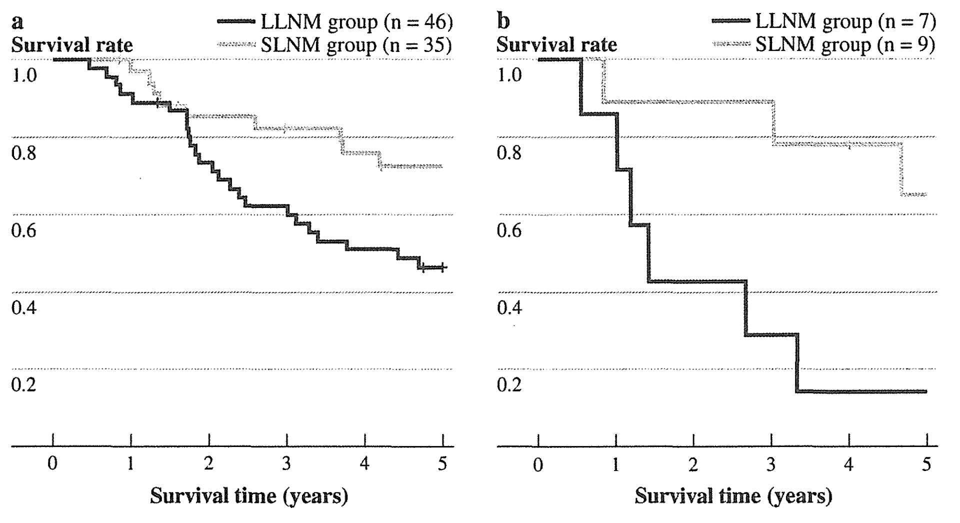

FIG. 2 **a** Overall survival curves of 81 patients with pT3 disease. The 5-year overall survival rate is significantly worse in the LLNM group (46.8 %) than in the SLNM group (72.7 %; $P = 0.015$). **b** Overall survival curves of 16 patients with pT4 disease. The 5-year overall survival rate is significantly worse in the LLNM group (14.3 %) than in the SLNM group (64.8 %; $P = 0.035$)

TABLE 3 Results of multivariate analysis

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥65 year vs. <65 year)	0.191	1.317	0.871–1.990
Sex (male vs. female)	0.405	1.322	0.686–2.546
Surgery (total gastrectomy vs. partial gastrectomy)	0.635	1.139	0.665–1.951
Histology (undifferentiated vs. differentiated)	0.155	1.488	0.860–2.576
pT (pT2–4 vs. pT1)	0.009	6.570	1.585–27.238
Lymph node size (LLNM vs. SLNM)	0.029	1.879	1.068–3.304

LLNM large lymph node metastasis, lymph node with a short-axis diameter measuring 15 mm or more; *SLNM* small lymph node metastasis, lymph node with a short-axis diameter measuring 10–14 mm

TABLE 4 Site of initial recurrence after surgery

Recurrence site	LLNM group	SLNM group
Peritoneal metastasis	8	7
Locoregional recurrence	3	0
Lymph node metastasis	22	7
Blood-borne metastasis	12	9
Number of cases with recurrence[a]	33	16

[a] Patients with multiple recurrence sites are included at each recurrence site

proportional to the sensitivity of nodal involvement. We believe that high specificity is more important than high sensitivity when selecting candidates for neoadjuvant chemotherapy if the administration of unnecessary toxic regimens to patients with early stage disease is to be avoided. In the present study, a sensitivity and specificity of 39.1 and 96.9 %, respectively, was achieved with a short-axis diameter cutoff value of 10 mm. When the short-axis diameter cutoff value was increased to 15 mm, a sensitivity of 22.5 % and specificity of 99.8 % was achieved. The specificity increased when higher cutoff values were adopted, which is consistent with the results of previous studies.

In the present study, the highest accuracy was obtained using a cutoff value of 10 mm; however, the PPV (87.6 %) was not high enough, meaning that 12.4 % of patients may receive excessive treatment if a cutoff value of 10 mm was adopted. Therefore, other cutoff values were tested, each of which yielded a higher PPV. Of these, a cutoff value of 15 mm yielded a higher sensitivity, NPV, and accuracy than the other cutoff values tested. Therefore, a second cutoff value of 15 mm was adopted. In addition, according to the new response evaluation criteria in solid tumors (RECIST version 1.1), lymph nodes with a short axis of 15 mm are considered measurable and assessable as target lesions.[23]

In this study, the long-term survival rate between the two groups also was compared. Previously, Dhar et al.[24,25] reported that the size of the lymph node, measured from the pathological specimen, was one of the independent prognostic factors following colorectal surgery and esophageal surgery. Dhar et al.[22] reported that this result was also applicable to patients with gastric cancer. Cheong et al.[26] reported that metastatic lymph nodes larger than 20 mm were an independent predictor of poor prognosis. However, in their study, lymph node diameters were measured by using pathologically resected specimens. In contrast, lymph node diameters in the current study were measured preoperatively using MDCT. Thus, the size of the lymph nodes was known before treatment, and this information could be used to select the relevant treatment strategy. By adopting a short-axis diameter cutoff value of 15 mm, node-positive patients could be identified with extremely high specificity. The survival outcome of patients in the LLNM group was poor; thus, these patients would be suitable candidates for much stronger multimodality treatment.

The present study has several limitations. First, the diameter of each node was measured retrospectively, and interobserver differences were not assessed. However, lymph nodes that are 15 mm in diameter were large enough for every investigator to find and assess. Therefore, any interobserver differences would be small compared with previous studies adopting cutoff values less than 10 mm.[15–17] Second, the results of the present study would be less meaningful in western countries where perioperative chemotherapy is already a standard treatment for advanced gastric cancer. However, even in western countries, patients with poor long-term outcomes could be identified with a cutoff value of 15 mm. A much stronger treatment regimen could then be indicated for these patients. Third, although a cutoff value of 15 mm yielded a high specificity (99.8 %) and PPV (98.6 %), the low sensitivity (22.5 %) and NPV (69.6 %) values were lower than desired. However, as stated previously, we believe high specificity is important if the administration of unnecessary toxic regimens is to be avoided if perioperative chemotherapy is planned. Lastly, transverse MDCT images were used to measure the diameter of each node instead of reconstructed MPR images, which were not routinely used during the study period. Although the superiority of MPR images over transverse images in the preoperative assessment of lymph nodes is under debate, these images would enable us to measure the longitudinal diameter of lymph nodes in future trials.[14,15]

CONCLUSIONS

By using a short-axis diameter cutoff value of 15 mm, MDCT was able to predict nodal status with high specificity (99.8 %) and achieve a high positive predictive value. Gastric cancer patients with enlarged lymph nodes, which have a short-axis diameter measuring 15 mm or more preoperatively, were found to have worse long-term outcomes than patients with lymph nodes smaller than 15 mm. These patients would therefore be suitable candidates for future clinical trials investigating the efficacy of neoadjuvant chemotherapies.

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Clinical Trial Note

A Phase III Study of Laparoscopy-Assisted Versus Open Distal Gastrectomy with Nodal Dissection for Clinical Stage IA/IB Gastric Cancer (JCOG0912)

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A Phase III study was started in Japan to evaluate the non-inferiority of overall survival of laparoscopy-assisted distal gastrectomy with open distal gastrectomy in patients with clinical IA (T1N0) or IB [T1N1 or T2(MP)N0] gastric cancer. This study followed the previous Phase II study to confirm the safety of laparoscopy-assisted distal gastrectomy (JCOG0703) and began in March 2010. A total of 920 patients will be accrued from 33 institutions within 5 years. The primary endpoint is overall survival. The secondary endpoints are relapse-free survival, proportion of laparoscopy-assisted distal gastrectomy completion, proportion of conversion to open surgery, adverse events, short-term clinical outcomes, postoperative quality of life. Only a credentialed surgeon can be responsible for both open distal gastrectomy and laparoscopy-assisted distal gastrectomy.

Key words: gastric cancer – laparoscopic surgery – gastrectomy – clinical trial – Phase III

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INTRODUCTION

The proportion of early gastric cancer accounts for only 15% in the western countries (1) while it does for more than 50% in Japan (2). In terms of the prognosis, the 5-year survivals of Stage IA and IB gastric cancer were reportedly as good as 93 and 87% (3). Especially for clinical stage IA gastric cancer which has no or only a few nodal metastases, less invasive procedure such as endoscopic mucosal resection or limited nodal dissection is recommended in the third version of Gastric Cancer Treatment Guideline in Japan (4). Laparoscopy-assisted gastrectomy (LADG) is another approach to reduce surgical invasion.

Since Kitano et al. (5) reported the first LADG in 1994, the number of patients who were treated by a laparoscopic technique has increased. However, laparoscopic surgery is still regarded as an investigational procedure in this guideline because the safety and feasibility was not well verified in a multi-institutional setting and there is no confirmatory randomized controlled trial to compare laparoscopy-assisted gastrectomy with open gastrectomy with a sufficient sample

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size. Thus, ODG is a standard procedure when tumors are located at distal stomach.

In our previous multi-institutional Phase II trial, we evaluated the safety of LADG with nodal dissection for clinical stage IA and IB gastric cancer (JCOG0703) (6). In this Phase II study, the proportion of patients with either anastomotic leakage or pancreatic fistula, the primary endpoint, was only 1.7% (3/173), which was much less than the pre-specified threshold (8%). In addition, the overall proportion of in-hospital grade 3 or 4 adverse events was as low as 5.1%. We concluded that the safety of LADG was confirmed in this Phase II study, and now have launched a randomized controlled trial to compare the efficacy of LADG and ODG for clinical IA/IB gastric cancer.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved this protocol in February 2010 and the patient enrollment was started in March 2010. The approval by the institutional review board was obtained before starting patient recruitment in each institution. This trial was registered at the UMIN Clinical Trials Registry as UMIN000003319 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE JCOG0912

Objectives

The aim of this study is to confirm the non-inferiority of overall survival of LADG with nodal dissection with ODG for clinical stage IA (T1N0) or IB [T1N1 or T2(MP)N0] gastric cancer.

Study Setting

A multi-institutional randomized Phase III study.

Endpoints

The primary endpoint is overall survival in all eligible patients. Overall survival is defined as days from randomization to death from any cause, and it is censored at the last day when the patient was alive. The secondary endpoints are relapse-free survival, proportion of LADG completion, proportion of conversion to open surgery, adverse events, short-term clinical outcomes and postoperative quality of life (QOL).

Relapse-free survival is defined as days from randomization to relapse or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of relapse. The proportion of LADG completion is defined as that of patients with whom LADG is completed without conversion to open surgery among all operated patients in the LADG arm. The proportion of conversion to open surgery is defined as the proportion of patients with conversion among the patients who are diagnosed before gastrectomy as clinical stage IA or IB. The short-term clinical outcomes consist of (i) the time from the end of surgery until the first episode of flatus, (ii) the proportion of patients requesting an analgesic on postoperative Days 5–10, (iii) the highest body temperatures during the first 3 days after the surgery and (iv) the highest body temperatures during hospitalization. Postoperative QOL is evaluated using EORTC QLQ-C30 and STO22. This QOL evaluation is performed only in four principal institutions due to the lack of resources in the other institutions. Primary analysis of QOL is performed using the global health status from EORTC QLQ-C30 in the 90th postoperative day.

Eligibility Criteria

Inclusion Criteria

(i) Histologically proven gastric adenocarcinoma.
(ii) Clinical stage IA (T1N0) or IB [T1N1, T2(MP)N0] according to the Japanese Classification of Gastric Carcinoma, Second English edition (7).
(iii) In case without preceding endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), either 'cN1' or 'cN0 and no indication of EMR' is eligible.
(iv) In case with preceding EMR or ESD, the following conditions are fulfilled: (i) pathological findings require additional gastrectomy, (ii) within 91 days from EMR, (iii) no perforation by EMR and (iv) resection margin of EMR did not reach to the upper third of the stomach.
(v) Tumor located in the middle or lower third of the stomach, and curative resection is expected to be achievable by distal gastrectomy.
(vi) No invasion to duodenum.
(vii) Aged 20–80 years.
(viii) PS (ECOG) of 0 or 1.
(ix) A body mass index of <30.
(x) No history of upper abdominal surgery and no history of intestinal resection.
(xi) No prior treatment of chemotherapy or radiation therapy against any other malignancies.
(xii) Sufficient organ functions.
(xiii) Written informed consent.

Exclusion criteria

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma *in situ*.
(ii) Infectious disease with a systemic therapy indicated.
(iii) Body temperature of 38°C or more.
(iv) Women during pregnancy or breast-feeding.
(v) Severe mental disease.
(vi) Continuous systemic steroid therapy.
(vii) Unstable angina pectoris or history of myocardial infarction within 6 months.
(viii) Uncontrollable hypertension.
(ix) Uncontrollable diabetes mellitus or administration of insulin.

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(x) Severe respiratory disease requiring continuous oxygen therapy.

Randomization

After the confirmation of the eligibility criteria, registration is made by telephone, fax or web-based system to the JCOG Data Center. Patients are randomized to either the ODG arm or the LADG arm by minimization method balancing the arms with institution and clinical stage (IA/IB).

Treatment Methods

The ODG or the LADG is performed in respective arms. All procedures are same except for the surgical approach. The extent of nodal dissection is decided according to the surgical T and N stage which is based on the third version of the Gastric Cancer Treatment Guideline in Japan (4). D1 or more dissection is applied for clinical stage IA tumor and D2 dissection is applied for clinical stage IB tumor. For clinical T1 gastric cancer having 4 cm or more margin from the pylorus, pylorus-preserving distal gastrectomy is allowed. Bursectomy is not allowed but preservation of omentum and/or vagus nerve is discretionary. The reconstruction method is not specified in this study.

In the LADG arm, >6 cm of the mini-laparotomy incision is not allowed. If the intraoperative findings reveal a tumor stage of II or greater, the LADG is converted to an open surgery.

Only the surgeons credentialed by the study chair can be responsible for both LADG and ODG. In the ODG arm, the experience of 60 or more open gastrectomies is needed to be certified as a credentialed surgeon. In the LADG arm, the experience of 30 or more LADGs and the certification or its equivalent by the Japan Society for Endoscopic Surgery are needed. All the LADG procedures are centrally reviewed by photographs.

Follow-Up

Adjuvant chemotherapy with S-1 for 1 year is recommended for patients with curative resection and pathological stage II, IIIA or IIIB tumors.

All randomized patients are followed up for at least 5 years. Tumor markers, chest X-ray, upper gastrointestinal endoscopy and enhanced chest computed tomography is evaluated at least every year for the duration of the follow-up.

Study Design and Statistical Analysis

This randomized trial is designed to demonstrate that LADG is non-inferior to ODG in terms of overall survival. Some endpoints are adopted to evaluate the less invasiveness of LADG over ODG, but those endpoints are all considered to be exploratory. Thus, as long as the non-inferiority of LADG is confirmed, LADG will be concluded as one of the options of the standard treatments for clinical stage IA/IB gastric cancer.

According to the Schoenfeld and Richter's method (8), the planned sample size is 920 patients, with 460 patients per arm. We anticipate 5 years of follow-up after 5 years of accrual, ensuring at least 80% power with a one-sided alpha of 5% and a non-inferiority margin of 5% in terms of 5-year survival. This assumes an expected 5-year overall survival of 90% in each arm.

The patients who are randomized to the LADG arm and are converted to ODG are included in the LADG population for the efficacy analyses based on the intention-to-treat principle. In the safety analyses, they are also regarded as the LADG population if the surgery starts as LADG but changes to ODG in the middle of the surgery, while they are included in the ODG population if the surgery starts as ODG from the beginning.

Interim Analysis and Monitoring

We plan to conduct two interim analyses, taking multiplicity into account using the Lan-DeMets method with the O'Brien and Fleming type alpha spending function. The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by JCOG Data Center to evaluate and improve the progress and quality of the study.

Participating Institutions (From North to South)

Hakodate Goryoukaku Hospital, Iwate Medical University, National Hospital Organization Sendai Medical Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Toranomon Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama City University Medical Center, Toyama Prefectural Central Hospital, Ishikawa Prefectual Central Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Fujita Health University, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Medical College, Kansai Medical University Hirakata Hospital, Hyogo Cancer Center, Wakayama Medical University School of Medicine, Shimane University School of Medicine, Hiroshima City Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Oita University Faculty of Medicine.

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Conflict of interest statement

None declared.

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Impact of Esophageal Invasion on Clinicopathological Characteristics and Long-Term Outcome of Adenocarcinoma of the Subcardia

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Backgrounds and Objectives: A different classification system was used in the 7th edition of the TNM classification for adenocarcinoma of the subcardia either with or without esophageal invasion. The aim of this study was to clarify the clinicopathological and survival impact of esophageal invasion.
Methods: The present study included 351 patients who underwent gastrectomy for adenocarcinoma located within 5 cm of the esophagogastric junction. The clinicopathological characteristics and survival curves were compared between patients with esophageal invasion [E (+) group, n = 125] and without esophageal invasion [E (−) group, n = 226].
Results: Patients in the E (+) group had more advanced disease. The 5-year survival rate following macroscopic curative resection was significantly better in the E (−) group (80.8%) than in the E (+) (48.7%, $P < 0.001$), even after stratification by the pathological stage and nodal status. Multivariate analysis identified esophageal invasion (hazard ratio; 3.323, 95% confidential interval; 1.815–6.082) as one of the independent prognostic factors.
Conclusions: Esophageal invasion affected the clinicopathological characteristics and long-term outcome of patients. Further study is necessary to clarify whether patients with esophageal invasion should be classified using the system for esophageal cancer or by another method.
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KEY WORDS: **TNM classification; gastric cancer; esophageal cancer; Siewert classification**

INTRODUCTION

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increasing in both Eastern and Western countries [1,2]. The classification of AEG as either an esophageal or a gastric cancer is controversial because of its anatomical characteristics [3]. Adenocarcinomas with an epicenter within 5 cm of the esophagogastric junction (EGJ) and characterized by esophageal invasion are classified as esophageal cancer according to the 7th edition of TNM classification [4]. However, adenocarcinomas of the subcardia without esophageal invasion are classified as gastric cancer, even if their epicenters are identical to those with esophageal invasion [4]. Accordingly, patients are classified into different stages despite having the same tumor depth and nodal status.

Esophageal invasion is generally associated with advanced disease and adversely affects the long-term outcome in patients with upper-third gastric carcinoma [5–7]. In fact, upper-third gastric cancer with esophageal invasion is not identical to Siewert type II or III AEG and the impact of esophageal invasion in adenocarcinoma with an epicenter within 5 cm of the EGJ remains unclear. We assume that the presence of esophageal invasion adversely affects long-term outcomes even in patients who have adenocarcinoma with identical epicenters to Siewert type II or III AEGs. These adverse effects may arise from the difficulty in surgical procedures and the complex lymphatic flow associated with esophageal invasion.

In this study, we retrospectively analyzed patients with adenocarcinoma that had an epicenter located within 5 cm of the EGJ. Our aim was to clarify the impact of esophageal invasion on clinicopathological characteristics and long-term outcomes.

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PATIENTS AND METHODS

Patients

The present study included 351 patients who underwent gastrectomy for adenocarcinoma with an epicenter within 5 cm of the EGJ. The procedures were performed at the Shizuoka Cancer Center between September 2002 and December 2010. Patients with gastric stump carcinoma and those who had received chemotherapy prior to the surgery were excluded. Patients were also excluded if the histology of the primary lesion did not identify it as adenocarcinoma. Data on the characteristics of the patients as well as their pathological and surgical findings were collected from our prospectively recorded database and from each patient's electronic medical record. The data collection and analysis were approved by the Institutional Review Board of the Shizuoka Cancer Center.

The macroscopic tumor type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system [8]. The histological tumor type was also classified according to the JGCA classification system, in which tubular and papillary

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adenocarcinomas are defined as differentiated adenocarcinomas, whereas poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinomas.

The TNM 7th edition was used to classify the tumor depth, lymph node status, pathological stage, and curability of the patients. In those patients with positive peritoneal lavage cytology, the surgery was regarded as R1 resection as long as the patients did not have other incurable factors. In the TNM 7th edition, adenocarcinomas with esophageal invasion were classified using the system for esophageal cancer, while those without esophageal invasion were classified using the system for gastric cancer [4]. However, in this study, we tentatively adopted classifications systems for gastric cancer because it was necessary to compare pathological characteristic and survival curves between patients using the same classification system.

Comparison Between Patients With and Without Esophageal Infiltration

Clinicopathological characteristics were compared between patients with esophageal invasion [E (+) group, n = 125] and those without esophageal invasion [E (−) group, n = 226]. The pictures of resected specimens fixed with formalin for a few days were evaluated macroscopically to assess esophageal invasion and to determine the epicenter of the tumor.

TABLE I. Characteristics of Patients in Both Groups

	E(+) group	E (−) group	*P*-value
Sex, n			
Male	99	166	0.246
Female	26	60	
Age, year			
Median	68	69	0.616
Range	27–86	29–90	
Location of the epicenter			
Within 20 mm of the EGJ	75	42	<0.001
20–50 mm from the EGJ	50	184	
Histology, n			
Differentiated	77	149	0.418
Undifferentiated	48	77	
Macroscopic type			
0	25	161	
1	18	9	
2	27	30	
3	53	22	
4	2	2	
5	0	1	<0.001
Tumor diameter			
Median	60	40	<0.001
Range	2–225	3–125	
Tumor depth, n			
T1	19	139	
T2	12	20	
T3	54	46	
T4a	30	19	
T4b	10	2	
Lymph node status, n			
N0	30	140	<0.001
N1	24	46	
N2	25	23	
N3	46	17	
Pathological stage (GC), n			
I	22	143	<0.001
II	32	46	
III	44	28	
IV	27	9	
Cytology			
Positive	20	9	<0.001
Negative	105	217	

EGJ, esophagogastric junction.

Surgical Approach for Subcardial Cancer With and Without Esophageal Infiltration

In our institute, trans-abdominal approach was selected in patients with subcardial cancer even in those with esophageal infiltration as long as obvious lower mediastinal lymph node metastases were not present and the length of esophageal invasion was shorter than 30 mm. In patients with esophageal infiltration, lower mediastinal lymph nodes were retrieved as many as possible by trans-hiatal approach.

If preoperative examinations revealed lower mediastinal lymph node metastases or the length of esophageal infiltration was longer than 30 mm, left thoraco-abdominal approach was selected in principle.

Statistical Analyses

All continuous variables are presented as the median (range). Statistical analyses were performed using the Fisher's exact test, Student's *t*-test, and Mann–Whitney test. Five-year survival rates were calculated using the Kaplan–Meier method and the log-rank test was used to compare the groups. Independent prognostic factors were identified using the Cox proportional hazards model. In these analyses, each patient's age, sex, histology, type of surgery, tumor diameter, esophageal invasion, location of tumor epicenter, tumor

TABLE II. Details of Treatment Provided and Early Surgical Outcomes

	E(+) group	E (−) group	*P*-value
Type of surgery			
Total gastrectomy	108	139	<0.001
Proximal gastrectomy	17	87	
Approach			
Rt thoracoacdominal approach	0	0	<0.001
Lt thoracoacdominal approach	8	1	
Transabdominal approach	117	225	
Splenectomy			
Performed	71	56	<0.001
Not performed	54	170	
Operation time (min)			
Median	247	213	<0.001
Range	130–675	104–702	
Intra-operative blood loss (ml)			
Median	528	331	<0.001
Range	100–2,106	18–1,924	
Number of resected lymph nodes			<0.001
Median	38.0	33.5	
Range	9–112	7–109	
Curability[a]			
R0	100	217	<0.001
R1	8	5	
R2	17	4	
Postoperative hospital stay			
Median	16	12	<0.001
Range	8–308	8–98	
Morbidity			
Yes	74	67	<0.001
No	51	159	
Mortality (n)	0	0	—

[a]Surgery was regarded as R1 resection if positive lavage cytology was the only incurable factor.

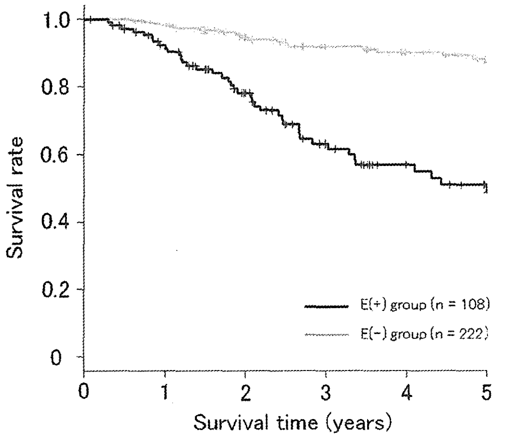

Fig. 1. Overall survival curves of patients. The 5-year overall survival rate is significantly better in the group of patients without esophageal invasion [E (−) group, 86.8%] than in the group with esophageal invasion [E (+) group, 48.7%, $P < 0.001$].

depth, nodal status, and splenectomy were included as covariates. $P < 0.05$ was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

RESULTS

There were no differences in sex, age, and histology between the groups of patients in this study (Table I). The tumor diameter was larger and epicenter of the tumor was closer to the EGJ in the E (+) group than in the E (−) group. Disease was more advanced in the E (+) group than in the E (−) group, and peritoneal lavage cytology was positive more frequently in the E (+) group (16%) than in the E (−) group (4%, $P < 0.001$).

The details of treatments provided and early surgical outcomes are shown in Table II. A total of 6% of patients in the E (+) group required the thoracoabdominal approach and total gastrectomy and splenectomy were more frequently performed in the E (+) group than in the E (−) group. R0 resection rate was 96% in the E (−) group, whereas it was 80% in the E (+) group ($P < 0.001$). Prolonged operation time, increased blood loss, and longer duration of postoperative hospital stay were observed in the E (+) group. The incidence of postoperative morbidity was higher in the E (+) group (59%) than in the E (−) group (30%) although postoperative mortality was not observed in either group.

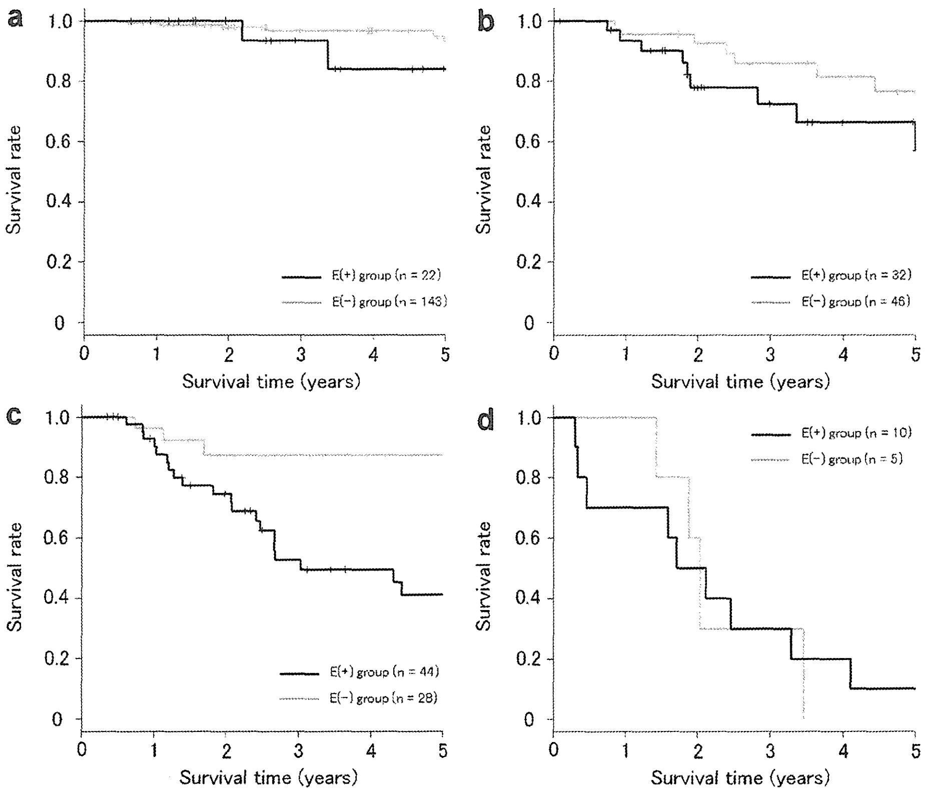

Fig. 2. Overall survival curves of patients stratified by pathological stage according to the classification system for gastric cancer. **a**: Overall survival curves of stage I patients. The 5-year overall survival rate is 84.0% in patients with esophageal invasion and 93.1% in those without esophageal infiltration ($P = 0.213$). **b**: Overall survival curves of stage II patients. The 5-year overall survival rate is 56.9% in patients with esophageal infiltration and 63.9% in those without esophageal infiltration ($P = 0.196$). **c**: Overall survival curves of stage III patients. The 5-year overall survival rate is 41.1% in patients with esophageal infiltration and 87.2% in those without esophageal infiltration ($P = 0.0139$). **d**: Overall survival curves of stage IV patients. The 5-year overall survival rate is 9.5% in patients with esophageal infiltration and 0% in those without esophageal infiltration ($P = 0.968$).