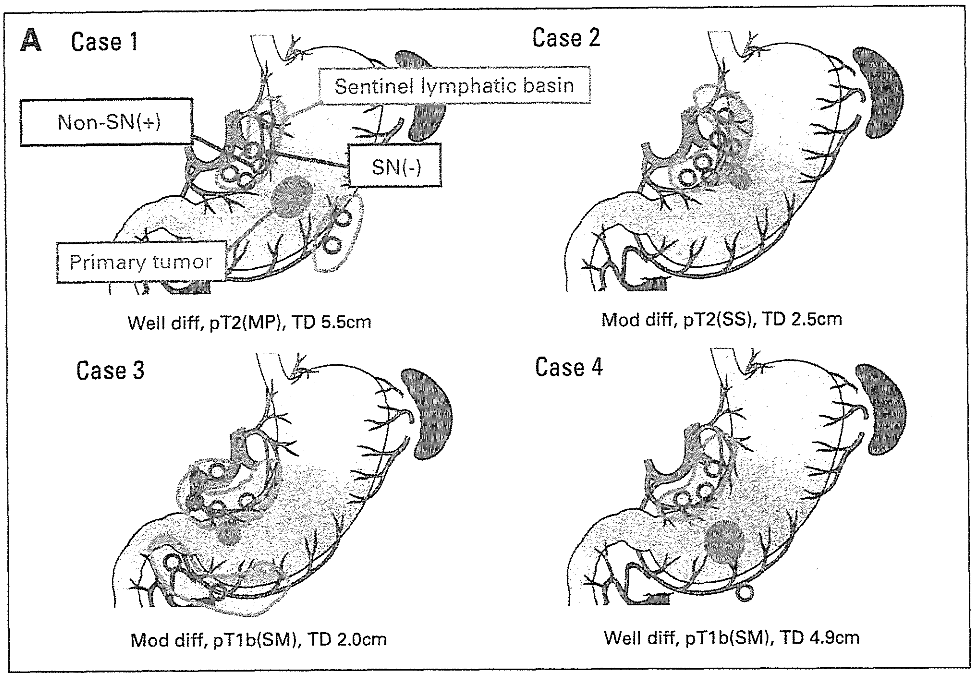

Fig 2. Distribution of identified sentinel nodes (SNs). (A) False-negative cases. Pink region, primary tumor; red circles, SNs (no metastasis); blue circles, nonsentinel nodes (metastatic); gold regions, sentinel node basins. Mod diff, moderately differentiated adenocarcinoma; MP, muscularis propria; SM, submucosa; SS, subserosa; TD, tumor diameter; Well diff, well differentiated adenocarcinoma. (B) Distribution and incidence of identified sentinel nodes: gastric cancer of the upper third of the stomach (n = 75). Blue circles, lymph nodes in the first compartment; red circles, lymph nodes in the second compartment; gold circles, lymph nodes in the third or other compartments. (C) Distribution and incidence of identified sentinel nodes: gastric cancer of the middle third of the stomach (n = 175). Blue circles, lymph nodes in the first compartment; red circles, lymph nodes in the second compartment; gold circles, lymph nodes in the third or other compartments. (D) Distribution and incidence of identified sentinel nodes: gastric cancer of the lower third of the stomach (n = 137). Blue circles, lymph nodes in the first compartment; red circles, lymph nodes in the second compartment; gold circles, lymph nodes in the third or other compartments. (B-D) The station number was described according to the Japanese Classification of Gastric Carcinoma12: (1) right cardiac lymph nodes, (2) left cardiac lymph nodes, (3), lymph nodes on lesser curvature, (4sa) lymph nodes along the short gastric vessels, (4sb) lymph nodes along the left gastroepiploic vessels, (4d) lymph nodes along the right gastroepiploic vessels, (5) suprapyloric lymph nodes, (6) intrapyloric lymph nodes, (7) lymph nodes along the root of left gastric artery, (8a) lymph nodes along the common hepatic artery, (9) lymph nodes along the celiac artery, (10) lymph nodes at the splenic hilum, (11p) lymph nodes along the proximal splenic artery, (11d) lymph nodes along the distal splenic artery, and (14v) lymph nodes along the superior mesenteric vein.

subserosal direct injection, although the latter might be easier during open surgery.

Intraoperative pathologic diagnosis was not mandatory in this study and was not available in 24% of the patients because of pathology policies in each institution. Intraoperative pathologic examinations are important for developing a future individualized function-preserving gastrectomy procedure on the basis of SN mapping. However, the main purpose of this multicenter trial was to verify the SN concept in gastric cancer surgery; therefore, we analyzed the histologic results of permanent tissue sections to assess the status of the SNs and other lymph nodes. Our results suggested that the sensitivity of intraoperative histologic diagnosis that uses an HE-stained section of one representative cut surface of a frozen section of a harvested SN is limited and may not be sufficient to provide reliable information for deciding the indications of limited lymph node dissection. Several reports described upstaging by more accurate and intensive examinations focused on SNs, which included step sections, immunohistochemical analysis, and molecular biologic techniques.[18-21] Molecular assessment of SNs may be a variable tool to complement histologic examination for gastric cancers. Recently, we established a highly sensitive real-time reverse transcriptase polymerase chain reaction system to detect messenger RNA of cytokeratin 19, cytokeratin 20, and carcinoembryonic antigen in SNs of patients with gastric cancer.[18] This system generated results within 80 minutes and might be available for intraoperative diagnosis in the future. Moreover, in all nine patients in this study with a false-negative intraoperative pathologic diagnosis, metastatic spread was limited to either the SNs or within the SN basins. We reasoned that SN basin dissection might be beneficial to future clinical applications of individualized minimally invasive gastrectomy based on intraoperative histologic diagnosis of SNs to amend the insufficiency of intraoperative pathologic diagnosis.

Generally, two types of SN sampling procedures for gastric cancer have been described. The pick-up method is a well-established and simple method that is currently used to assess breast cancer and melanoma. Miwa et al[22] proposed the concept of SN basin dissection on the basis of their own data, in which SN basins contained true-positive nodes, even in patients with a false-negative SN biopsy. This concept was also valid in this prospective multicenter trial with only one exception. SN basin dissection is considered a minimally focused lymphadenectomy method for early gastric cancer with a reasonable safety net to avoid recurrence after a false-negative SN biopsy.

In 2004, the Japan Clinical Oncology Group (JCOG) conducted a multicenter prospective clinical trial of SN biopsy for cT1N0 gastric cancer.[23] The JCOG 0302 study was designed to evaluate the feasibility and accuracy of diagnosis using SN biopsy by the dye-guided method with intraoperative subserosal direct injection of indocyanine green. This study was designed as a simple and practical procedure to evaluate the applications of modified

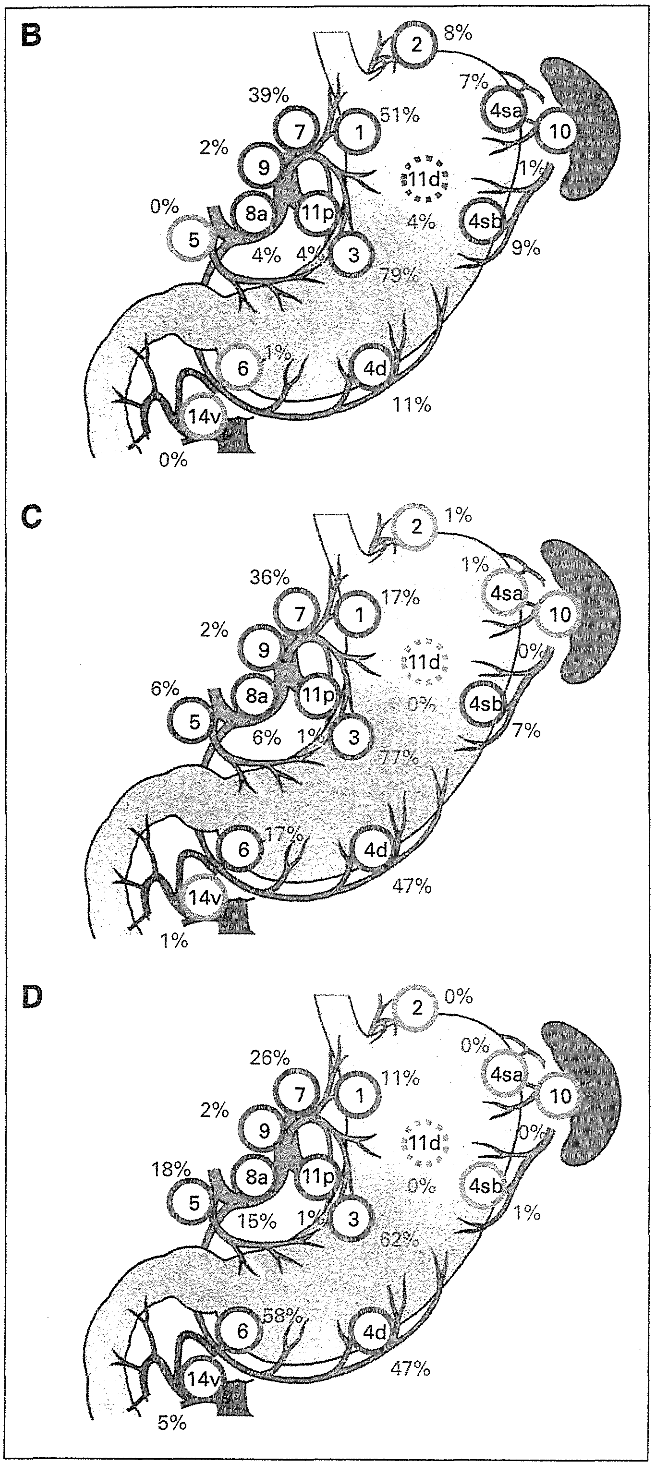

Fig 2. (Continued).

surgery without lymphadenectomy for SN-negative early gastric cancer. The details of the study have not yet been published since patient recruitment was terminated midway because of the unexpectedly high false-negative rate. Several factors were involved, including technical issues of the dye-guided method with direct injection of the tracer and limited sensitivity of intraoperative histologic diagnosis of SN status. One of the most critical limitations in the JCOG 0302 study could be the fact that there were only five initial cases for training in each institution. In this multicenter study, 30 cases were required as the minimum initial learning phase to participate, which was based on a previous multicenter report regarding SN biopsies for breast cancer.[24]

In future studies, appropriate indications for function-preserving gastrectomy, including proximal gastrectomy, segmental gastrectomy, pylorus-preserving gastrectomy, and partial resection for cT1N0 gastric cancer, should be individually determined on the basis of the SN mapping concept. Various types of laparoscopic function-preserving surgeries can be performed for patients with cancer who have negative SNs. Earlier recovery after surgery and preservation of quality of life in the late disease phases can be achieved by limited laparoscopic gastrectomy with SN navigation. Meanwhile, unexpected anatomic skip metastases might be accounted for by aberrant drainage routes from the primary lesion. As shown in this study, D2 gastrectomy was not always an effective method for harvesting the first draining nodes from a primary lesion. The distribution of sentinel lymphatic basins and SN status would be useful information for deciding on the extent of gastric resection.

On the basis of the findings in this prospective study, we designed our next randomized controlled trial to compare individualized gastrectomy based on intraoperative SN biopsy data with conventional distal/total gastrectomy (for further detail, see the Appendix). We believe that our next trial will demonstrate similar oncologic outcomes and superiority in postoperative quality of life for patients who have individualized gastrectomy, and it will further validate the clinical utility of SN mapping with SN basin dissection for early gastric cancer to achieve the goal of minimizing unnecessarily extensive surgery. Although there are several unresolved issues, SN navigation surgery presents a novel individualized, minimally invasive approach for early gastric cancer, both in terms of degree of incisional access and extent of function preservation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Appendix

Indication of Endoscopic Treatments

The indications of endoscopic treatments such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) were limited to the following: (1) mucosal tumors, (2) histologically differentiated-type adenocarcinomas, (3) tumors with diameters < 2 cm, and (4) no sign of ulceration of the lesion. If the primary tumor characteristics met these criteria, then lymph node metastasis was considered absent.[15] Recently, Gotoda et al[16] proposed an expansion of the ESD criteria to identify early gastric cancer without lymph node metastasis. According to the new criteria, a differentiated-type mucosal carcinoma of any size without ulceration or ulcer scarring and differentiated-type mucosal tumors < 3 cm with ulceration or ulcer scarring can be curatively resected endoscopically. Regarding the undifferentiated-type, the expanded criteria have been carefully revised to account for patients with a relatively high risk of lymph node metastasis. Sentinel node (SN) biopsy can be performed in patients with cT1N0M0 gastric cancer beyond these EMR/ESD criteria.

Our Next Trial

On the basis of the findings in this prospective study, we designed our next randomized controlled trial to compare individualized gastrectomy based on intraoperative SN biopsy data with conventional distal/total gastrectomy. In the next trial, the patients will be limited to those with cT1N0M0 gastric cancers, characterized by single lesions < 4 cm in size, who received no previous endoscopic treatment. In the individualized surgery group, according to the intraoperative pathologic examination results, minimized gastrectomy with SN basin dissection is indicated for patients with no SN metastases or standard gastrectomy with D2 lymph node dissection for patients with SN metastases. The 5-year recurrence-free survival rate will be the primary end point to compare the individualized gastrectomy group and the conventional distal/total gastrectomy group, and the 3-year recurrence-free survival, 3- to 5-year overall survival, diagnostic accuracy of SNs, and postoperative quality of life were chosen as secondary end points. SN basin dissection is considered a minimally focused lymphadenectomy method for early gastric cancer and a reasonable safety net to ameliorate an intraoperative pathologic misdiagnosis to avoid recurrence after a false-negative SN biopsy.

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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].

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.

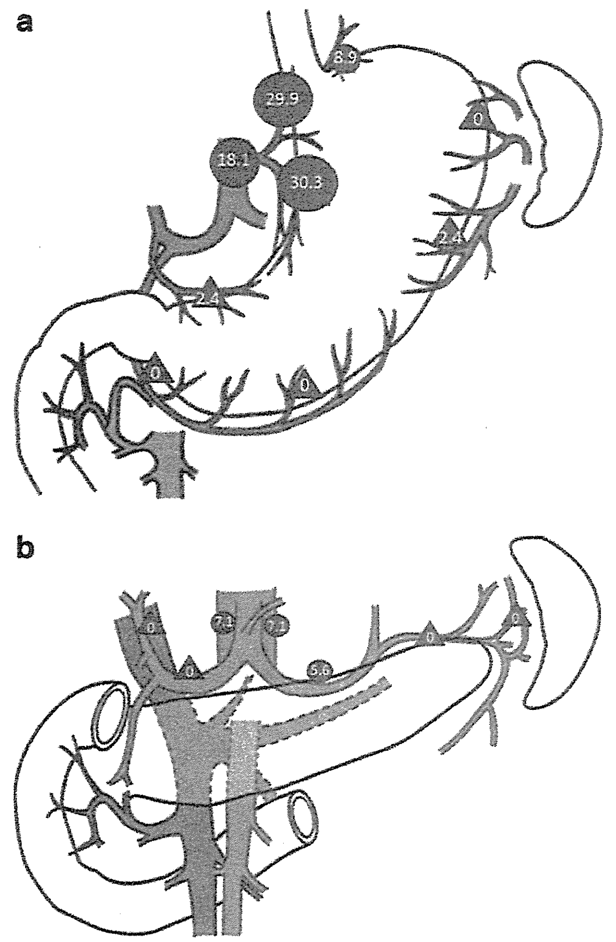

Fig. 1 Index of estimated benefit from lymph node dissection (IEBLD) for each lymph node station. *Circles*, IEBLD greater than 5; *triangles*, IEBLD less than 5

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	

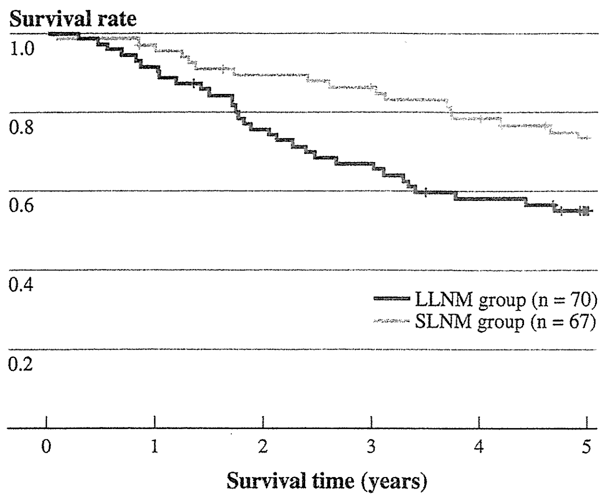

FIG. 1 Overall survival curves of patients in the LLNM group ($n = 70$) and SLNM group ($n = 67$). The 5-year overall survival rate is significantly worse in the LLNM group (55 %) than in the SLNM group (73.2 %; $P = 0.008$)

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 %; $P = 0.035$)

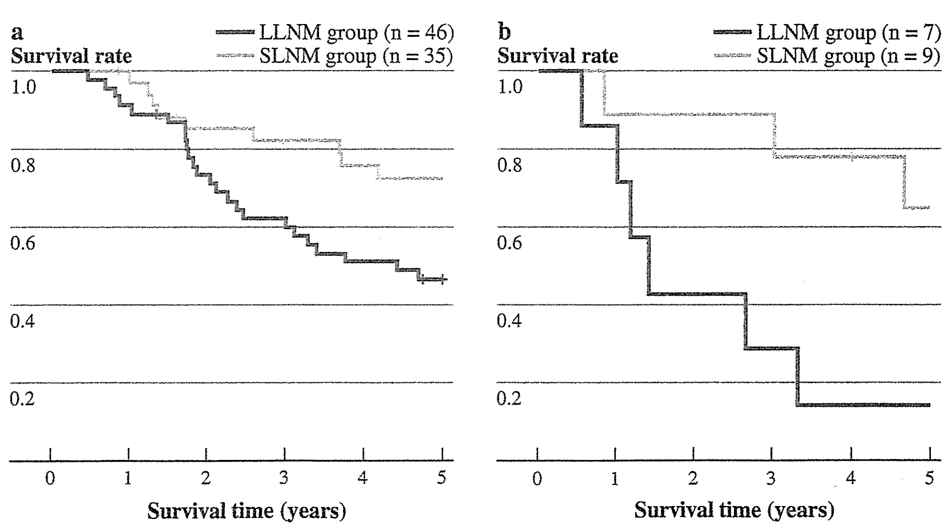

TABLE 3 Results of multivariate analysis

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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Poor Survival Rate in Patients with Postoperative Intra-Abdominal Infectious Complications Following Curative Gastrectomy for Gastric Cancer

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ABSTRACT

Background. The impact of postoperative complications on recurrence rate and long-term outcome has been reported in patients with colorectal and esophageal cancer, but not in patients with gastric cancer. This study evaluated the impact of postoperative intra-abdominal infectious complications on long-term survival following curative gastrectomy.

Methods. This study included 765 patients who underwent curative gastrectomy for gastric cancer between 2002 and 2006. Patients were divided into 2 groups: with (C-group, $n = 81$) or without (NC-group, $n = 684$) intra-abdominal infectious complications. Survival curves were compared between the groups, and multivariate analysis was conducted to identify independent prognostic factors.

Results. Male patients were dominant, and total gastrectomy was frequently performed in the C-group. The pathological stage was more advanced and D2 lymph node dissection and splenectomy were preferred in the C-group. The 5-year overall survival (OS) rate was better in the NC-group (86.8 %) than in the C-group (66.4 %; $P < .001$). The 5-year relapse-free survival (RFS) rate was also better in the NC-group (84.5 %) than in the C-group (64.9 %; $P < .001$). This trend was still observed in stage II and III patients after stratification by pathological stage. Multivariate analysis identified intra-abdominal infectious complication as an independent prognostic factor for OS (hazard ratio, 2.448; 95 % confidence interval [95 % CI], 1.475–4.060) and RFS (hazard ratio, 2.219; 95 % CI, 1.330–3.409) in patients with advanced disease.

Conclusions. Postoperative intra-abdominal infectious complications adversely affect OS and RFS. Meticulous surgery is needed to decrease the complication rate and improve the long-term outcome of patients following curative gastrectomy.

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Gastrectomy with R0 resection is inevitable to cure patients with gastric cancer.[1,2] However, even after R0 resection, a significant number of patients suffer from recurrence, particularly after surgery for advanced gastric cancer.[3–5] Tumor depth and lymph node status are well-known prognostic factors, and patient age and performance status have also been reported as having an impact on the long-term outcome of patients.[1,2, 6,7]

In Japan, gastrectomy with D2 lymph node dissection has been the standard treatment for advanced gastric cancer.[8–11] However, Western randomized trials have failed to prove the efficacy of D2 lymph node dissection, presumably because of the increased incidence of postoperative morbidity, which results in increased in-hospital deaths following D2 lymph node dissection.[12–14] Moreover, postoperative morbidity may adversely affect long-term, as well as short-term outcomes in patients.

Previously, the impact of postoperative complications on recurrence rate and long-term outcome has been reported in patients with colorectal cancer and esophageal or esophagogastric junction cancer.[15–23] In the case of colorectal cancer, anastomotic leakage is generally associated with a high local recurrence rate, as well as a poor long-term survival rate.[15–18] Additionally, a strong correlation between postoperative complications and poor long-term outcome has been reported for esophageal and esophagogastric junction cancer.[19,21,23] However, contradictory studies have also been published. Branagan and Finnis [15] reported that anastomotic leakage does not result in poor survival following colorectal surgery. After esophagogastrectomy, Junemann-Ramirez et al.[22] reported that anastomotic leakage does not correlate with poor survival, and Ancona et al.[20] reported that surgical complications themselves do not affect patients' long-term outcomes although survival of patients with both surgical and medical complications was poor.

In patients with gastric cancer, there have been limited reports assessing the relationship between postoperative complications and long-term outcome. Sierzega et al.[7] reported that anastomotic leakage as well as deeper tumor depth, lymph node metastasis, distant metastasis, and poor performance status were found to be independent prognostic factors following total gastrectomy for gastric adenocarcinoma. Their study included 690 patients from 7 university surgical centers in Poland. However, the impact of other postoperative complications on long-term outcome was not investigated, and their study included patients whose surgery was not curative. Moreover, it is unclear whether their results can be adopted by East-Asian countries where the incidence of gastric cancer is high and the reported incidence of postoperative complications is low compared with Western countries.[13,24–26]

The aim of the present study was to clarify the impact of postoperative intra-abdominal infectious complications on the long-term survival rate of patients undergoing curative gastrectomy in one of the highest-volume centers in Japan.

PATIENTS AND METHODS

A total of 765 patients who underwent curative gastrectomy (R0 resection) for gastric cancer at the Shizuoka Cancer Center between September 2002 and October 2006 were included in the present study. Patients who received neoadjuvant or adjuvant chemotherapy, patients who had other cancers and patients who underwent surgery for gastric stump carcinoma were excluded. Patients were also excluded if the histology of the primary lesion was not adenocarcinoma.

The patients' characteristics and pathological and surgical findings were collected from our database records and individual patient electronic medical records. The postoperative clinical course of each patient, including the incidence and severity of intra-abdominal infectious complications, was collected from individual electronic medical records. The data collection and analysis were 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, Seventh edition.[27]

Histological type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system, in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.[28]

Definition of Postoperative Intra-abdominal Complications

In this study, the Clavien–Dindo (CD) classification was adopted to classify each patient's postoperative intra-abdominal complication.[29,30] According to the CD classification, patients were classified as having grade II complications if antibiotics were administered. They were classified as grade IIIa or IIIb if surgical intervention was indicated. If patients required admission to the intensive care unit, they were regarded as having grade IVa or IVb complications. Postoperative mortality was defined as a grade V complication. If multiple complications occurred in a single patient, the highest grade was used.

Comparison Between Patients With and Without Complications

Clinicopathological characteristics were compared between patients with postoperative intra-abdominal infectious complications (C-group, $n = 81$) and those without complications (NC-group, $n = 684$). Overall survival time and relapse-free survival time were also compared between the groups.

Statistical Analyses

All continuous variables are presented as the median (range). Statistical analyses were performed using the Fisher exact test, t test, and Mann–Whitney test. The 5-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 the analysis, each patient's age, sex, histology, type of surgery, degree of lymph node dissection, intraoperative blood loss, operation time, pathological stage, and postoperative intra-abdominal infectious complication were included as covariates. $P < .05$ was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

RESULTS

The clinicopathological characteristics of all the patients are shown in Table 1. There was no difference in age between the C-group and NC-group. Male patients

TABLE 1 Clinicopathological characteristics of patients in both groups

	C-group	NC-group	*P* value
Sex (*n*)			.001
Male	68	452	
Female	13	232	
Age (years)			.061
Median	66	64	
Range	31–83	24–88	
Performance status (ECOG)			.545
0 or 1	80	678	
2 or 3	1	6	
Hemoglobin (g/dL)			.577
Median	13.7	13.7	
Range	7.5–16.4	6.3–17.5	
Albumin (g/dL)			.090
Median	4.3	4.3	
Range	2.4–5.0	1.8–5.3	
Lymphocyte count[a]			.352
Median	1920	1700	
Range	870–3450	620–3960	
Surgical procedure (*n*)			<.001
Total gastrectomy	44	142	
Partial gastrectomy	37	542	
Splenectomy (*n*)			<.001
Performed	38	67	
Not performed	43	617	
Lymph node dissection			<.001
<D2	25	431	
≥D2	56	253	
Operation time (min)			<.001
Median	244	186	
Range	125–733	50–725	
Intraoperative blood loss (mg)			<.001
Median	454	250	
Range	50–2650	0–1800	
Postoperative hospital stay (days)			<.001
Median	23	11	
Range	12–308	7–56	
Histology (*n*)			.347
Differentiated	47	355	
Undifferentiated	34	329	
Tumor depth (*n*)			<.001
T1	29	430	
T2	10	70	
T3	29	150	
T4a	11	31	
T4b	2	3	
Lymph node status (*n*)			.004
N0	39	449	
N1	10	88	
N2	17	77	
N3	15	70	
Pathological stage (*n*)			<.001
I	29	440	
II	27	120	
III	21	115	
IV	4	9	

ECOG Eastern Cooperative Oncology Group

[a] Lymphocyte count was measured in 27 patients in the C-group and 189 patients in the NC-group

predominated in both groups and total gastrectomy was frequently performed in the C-group. Preoperative serum albumin level, hemoglobin level, and lymphocyte count were not different between the groups. D2 lymph node dissection and splenectomy were also preferred in the C-group. Operation time was longer and intraoperative blood loss was higher in the C-group than in the NC-group ($P < .001$). More advanced gastric cancer was observed in the C-group than in the NC-group ($P < .001$).

The type and severity of complications are shown in Table 2. Intra-abdominal infectious complications were observed in 11 % (81 of 765) of patients. Pancreas-related infections were the most frequently observed intra-abdominal infectious complication, followed by intra-abdominal abscess and anastomotic leakage. We found 33 % of patients recovered well with medication (grade II), and surgical intervention with local or general anesthesia was required in 62 and 1 % of patients, respectively. One patient died following deterioration of a postoperative intra-abdominal infectious complication. In every pathological stage, grade IIIa complications were the most frequently observed, followed by grade II complications.

We also investigated the number of patients who required readmission because of postgastrectomy syndromes, which included bowel obstruction, cholecystitis, and insufficient oral intake. If patients had a recurrence, admission after the recurrence was not counted. In the C-group, 7 of 81 patients (9 %) required readmission because of a postgastrectomy syndrome. In the NC-group, readmission was required in 32 of 684 patients (5 %; $P = .174$). The most frequent reason for readmission was bowel obstruction in both groups (4 patients in the C-group, and 20 patients in the NC-group; $P = .308$). We investigated serum albumin levels of patients without recurrence 1 year after the surgery to assess nutritional status. There was no difference in the serum albumin level change between the groups ($P = .330$).

Details of the initial recurrence site following gastrectomy are listed in Table 3. Recurrence was observed in 21 of 81 patients (26 %) in the C-group, and 83 of 684 patients (12 %) in the NC-group ($P = .002$). In the NC-group, peritoneal metastasis was the most frequent recurrence pattern followed by lymph node metastasis and liver metastasis. In the C-group, lymph node metastasis was the most frequently observed site of recurrence. Locoregional recurrence was not observed in any of the patients in the C-group even after anastomotic leakage. The pattern of recurrence was not different between the 2 groups ($P = .401$).

In the median follow-up period of survivors of 63 months, the 5-years overall survival rate was better in the NC-group (86.8 %) than in the C-group (66.4 %; $P < .001$). The 5-years relapse-free survival rate was also better in the NC-group (84.5 %) than in the C-group (64.9 %; $P < .001$).

Overall and relapse-free survival curves stratified by pathological stage were compared between the groups (Figs. 1a, b, 2a, b). In patients with stage I early gastric cancer, there were no differences between the groups. Conversely, in patients with stage II and III gastric cancer, overall and relapse-free survival rates were significantly better in the NC-group than in the C-group, except for relapse-free survival time in patients with stage III gastric cancer. In patients with stage III gastric cancer, the 5-years relapse-free survival rate still tended to be better in the NC-group (55.1 %) than in the C-group (41.3 %); however, the difference did not reach significance ($P = .11$).

Table 4 shows the results of the Cox-proportional hazards model used to identify independent prognostic factors for overall survival. In this analysis, only patients with stage II or more advanced disease were included because the survival analysis did not show a survival difference between the 2 groups in patients with pathological stage I disease. Pathological stage (hazard ratio [HR], 2.564; 95 % CI, 1.681–3.912) and intra-abdominal infectious complications (HR, 2.448; 95 % CI, 1.475–4.060) were found to be independent prognostic factors. The same independent prognostic factors were identified for relapse-free survival (pathological stage [HR, 2.657; 95 % CI, 1.782–3.962], and intra-abdominal infectious complications [HR, 2.219; 95 % CI, 1.330–3.409], Table 5).

Figure 3 shows hazard ratio for death among subgroups. The overall survival was analyzed according to sex, age, type of surgery, splenectomy, degree of lymph node dissection, intraoperative blood loss, operation time, histology, pathological tumor depth, and pathological nodal status.

TABLE 2 Details of postoperative intra-abdominal complications

	Grade of CD classification						Total
	II	IIIa	IIIb	IVa	IVb	V	
Type of complication							
Pancreas-related complication	15	27	0	0	0	0	42
Anastomotic leakage	1	14	1	1	1	0	18
Intra-abdominal abscess	11	9	0	0	0	1	21
Pathological stage							
I	11	17	0	1	0	0	29
II	10	17	0	0	0	0	27
III	6	12	1	0	1	1	21
IV	0	4	0	0	0	0	4
Total	27	50	1	1	1	1	81

CD Clavien–Dindo

TABLE 3 Site of initial recurrence after surgery

	C-group			C-group total	NC-group
	Pancreas-related infection	Anastomotic leakage	Intra-abdominal abscess		
Peritoneal metastasis	4	1	1	6	35
Liver metastasis	5	0	1	6	19
Locoregional recurrence	0	0	0	0	5
Lymph node metastasis	8	1	4	13	31
Lung	1	1	0	2	6
Bone	0	0	0	0	5
Other	0	0	0	0	3
Unknown	0	0	0	0	1
Number of cases with recurrence[a]	12	3	6	21	83

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

DISCUSSION

The present study revealed that postoperative complications were strongly associated with poor overall survival time and relapse-free survival time. This trend was also observed even after stratification by pathological stage.

To investigate the prognostic value of postoperative complications, appropriate assessment of the incidence and severity of complications is mandatory. In 2004, Clavien and Dindo proposed the CD classification, which is a treatment-oriented, objective criteria for postoperative complications.[29,30] Recently, a number of reports, including those concerning postgastrectomy morbidities, have