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ORIGINAL ARTICLE

Clinicopathological features of stomach cancer with invasive micropapillary component

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Abstract

Background Invasive micropapillary carcinoma has been recognized as a rare disease entity with aggressive tumor behavior. However, few reports have described invasive micropapillary carcinoma in the gastrointestinal tract, particularly its involvement in gastric cancer.

Methods We retrospectively analyzed 930 patients diagnosed with gastric cancer who underwent gastrectomy, and we then histopathologically evaluated the existence of a regional invasive micropapillary component. Clinicopathological features were investigated in patients with an invasive micropapillary component and compared with such features in 100 patients with gastric adenocarcinoma, selected as stage-matched controls, who underwent gastrectomy during the same period.

Results Of the 930 patients, 14 were histopathologically diagnosed with gastric cancer with a regional invasive micropapillary component. There were no significant differences in age, gender, tumor location, macroscopic type, or type of surgery between patients with an invasive micropapillary component and the pT-matched controls. Histopathologically, significant differences were observed in lymphatic infiltration, venous invasion, the percentage of cases with lymph node metastasis, and the median number of metastatic lymph nodes. The three-year disease-free and overall survival rates of patients with an invasive micropapillary component were 40.5 and 59.3%, respectively, compared with those for the stage-matched controls, which were 72.6 and 80.6%, respectively ($p = 0.02$ and 0.07).

Conclusions Patients with gastric cancer with a regional invasive micropapillary component showed marked cancer infiltration in the lymphatic pathway and poor prognosis after gastrectomy.

Keywords Gastric cancer · Invasive micropapillary carcinoma · Prognosis

Introduction

Invasive micropapillary (IMP) carcinoma was first reported as a rare subtype of invasive ductal carcinoma of the breast [1], defined as a carcinoma composed of small clusters of tumor cells lying within clear spaces simulating vascular channels. This rare histological type frequently shows aggressive tumor behavior with marked lymph-vascular invasion, resulting in poor prognosis [2, 3]. Recently, carcinomas demonstrating histological findings similar to IMP carcinoma of the breast have been reported to occur in various organs, including the urinary bladder [4], ureter [5], lung [6], and parotid gland [7]. However, few reports have discussed such cancers originating from the gastrointestinal tract [8–10]. In particular, study of the IMP component in cancer of the stomach has

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been limited and has not been well addressed [8]. Previous investigation of primary IMP carcinoma of the stomach showed downregulation of E-cadherin expression [8], implying that the presence of an IMP component in stomach cancer is a poor prognostic factor, as with other organs. Nevertheless, because previous study has been confined to the immunohistochemical analysis of a single case of IMP carcinoma, the clinical behavior of gastric cancer with an IMP component has not been clarified. Moreover, it is unclear whether gastric cancer with an IMP component shares common features with IMP carcinoma of the breast, such as aggressive behavior with marked lymph-vascular invasion.

Therefore, in the present study, to reveal the clinical features of gastric cancer with an IMP component, we compared such cases of gastric adenocarcinoma with randomly assigned stage-matched controls who underwent gastrectomy during the same period, and here we discuss the prognosis of this unique histopathological entity.

Patients and methods

Patients

Patients who underwent surgery for gastric cancer from January 2005 to July 2009 were identified from the Division of Pathology database at the National Cancer Center Hospital East; their data were retrospectively analyzed following approval from The Investigational Review Board at the National Cancer Center. Preoperative diagnosis was based on preoperative imaging studies, including upper gastrointestinal studies, endoscopy, and conventional cross-sectional imaging studies (computed tomography). Histological evaluation of endoscope-guided biopsy specimens was performed in all cases. The patients' medical records were reviewed to determine the preclinical stage of the disease, surgical procedures employed, histopathological findings of the lesions, and the outcomes.

In all cases, gastrectomy was performed in the usual manner under the direction of the regular attending surgeons. In distal gastrectomy, resection of about 2/3 of the stomach with D2 regional lymph node dissection was performed, regardless of the size of the tumor. In total gastrectomy, resection of the whole stomach with D2 regional lymph node dissection was performed. Splenectomy was performed in cases where the tumor invasion was found to extend further than the subserosal layer of the stomach, and when the tumor was located on the greater curvature of the stomach. Reconstruction of the stomach was performed mostly using the Billroth 1 procedure for distal gastrectomy and the Roux-en-Y procedure for total gastrectomy.

Histopathological and immunohistochemical analyses

The surgically resected stomachs were processed in the usual manner. In brief, the resected stomachs were opened along the greater curvature, placed on a wooden board with the mucosa facing up, and fixed with a 10% formalin solution for at least 24 h. Several portions, including the distal and proximal stump, as well as both main and sublesions, were sliced to a thickness of 5 mm and histologically examined. For the histopathological evaluation, at least 2 pathologists who specialized in the field of gastrointestinal tract evaluated all stained slides of the lesions. An IMP component was determined to exist if the component was found to be present in a macroscopic regional manner. In brief, we confirmed the micropapillary component by immunohistochemical staining for epithelial membrane antigen (EMA), and if the component was present in more than 10% of each tumor the diagnosis was gastric cancer with an IMP component.

The gastric cancers were evaluated according to the Japanese Gastric Cancer Association, Japanese classification of gastric carcinoma [11]. The macroscopic pattern of early gastric cancers was classified according to the Japanese Society for Gastroenterology endoscopic criteria as type 0-I (protruded), type 0-IIa (elevated), type 0-IIb (flat), type 0-IIc (depressed), type 0-III (excavated), and type 1-4 (Bormann 1-4). Histological grading of the gastric cancers was divided into 3 types; well, moderately, and poorly differentiated adenocarcinoma [12]. The IMP component was diagnosed by at least two pathologists who specialized in the field of gastrointestinal tract. To rule out adenocarcinoma with extensive lymphatic infiltration, or mucinous carcinoma (which could potentially mimic the IMP component), histopathological examination was performed using D2-40 and periodic acid-Schiff (PAS) stain.

Statistical analysis

Statistically significant differences were analyzed using the χ^2 test and the Mann–Whitney U-test. Univariate analysis and multivariate analysis with the Cox proportional hazards model were performed to evaluate the significance of the clinical and histopathological parameters. A value of $p < 0.05$ was considered statistically significant.

Results

Incidence and clinical manifestations of gastric cancers with an IMP component

From January 2005 to July 2009, 930 patients with gastric cancers underwent gastrectomy at the National

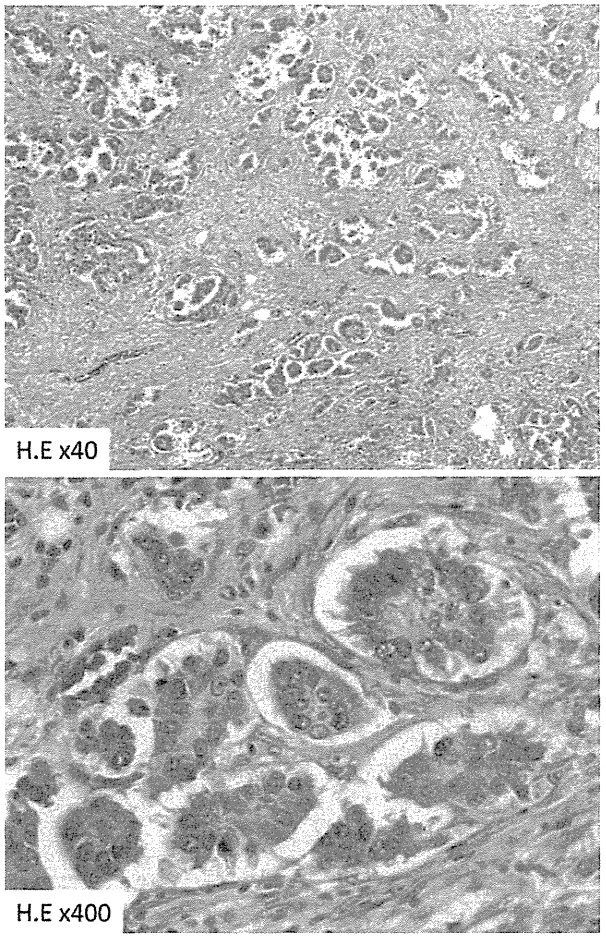

Fig. 1 Representative images of the regional invasive micropapillary component. There was no case of pure form of invasive micropapillary carcinoma in gastric cancer; however, 1.5% of cases contained a regional invasive micropapillary structure

Cancer Center Hospital East. Of these, 14 patients (1.5%) histologically showed a regional IMP component. Representative images of the IMP component are shown in Fig. 1; no patients showed a pure form of IMP carcinoma.

In order to evaluate the biological characteristics of the tumor itself in patients with gastric cancer with an IMP component, the clinical manifestations of these 14 patients were compared with those of randomly assigned pT factor-matched controls (pT-matched controls) whose data were extracted from the data of the initial 930 patients and who had gastrectomies during the same period as the study subjects (see Table 1). The median ages of the patients with gastric cancer with an IMP component and the pT-matched controls were 62.1 years (range 43–75 years) and 60.4 years (range 38–82 years), respectively ($p = 0.37$). No significant difference was found in the gender distribution (IMP component, M:F = 2.5:1; pT-matched controls, M:F = 1.7:1), in the distribution of tumor location in the stomach (upper third of the stomach:middle third of the stomach:lower third of the stomach—IMP component 21:50:28.5%, pT-matched controls 14:37:49%), or in the macroscopic type of the lesion (IMP component, type 0-IIc:type 1:type 2 or 3 = 21.4:7.1:71.4%; pT-matched controls, type 0-IIc:type 1:type 2 or 3 = 24:7:69%).

Histopathological manifestations of gastric cancers with an IMP component

The percentages of well-differentiated adenocarcinoma with a papillary pattern are shown in Fig. 2. Well-differentiated adenocarcinoma with a papillary pattern was

Table 1 Patient characteristics of gastric cancer with IMP component

Variables	With IMP structure ($n = 14$)	Without IMP structure (pT-matched control) ($n = 100$)	p value
Age, years, median (range)	62.1 (43–75)	60.4 (38–82)	0.37
Gender (M:F)			0.80
Male	10 (71.4%)	64 (64.0%)	
Female	4 (28.5%)	36 (36.0%)	
Location of tumor			0.59
Upper third of stomach	3 (21.4%)	14 (14.0%)	
Middle third of stomach	7 (50.0%)	37 (37.0%)	
Lower third of stomach	4 (28.5%)	49 (49.0%)	
Macroscopic type			0.86
Type 0-IIc	3 (21.4%)	24 (24.0%)	
Type 1	1 (7.1%)	7 (7.0%)	
Type 2 or 3	10 (71.4%)	69 (69.0%)	
Type of surgery			0.80
Distal gastrectomy	9 (64.2%)	65 (65.0%)	
Total gastrectomy	5 (35.7%)	35 (35.0%)	

IMP invasive micropapillary component, *Type0-IIc* depressed type of early gastric cancer

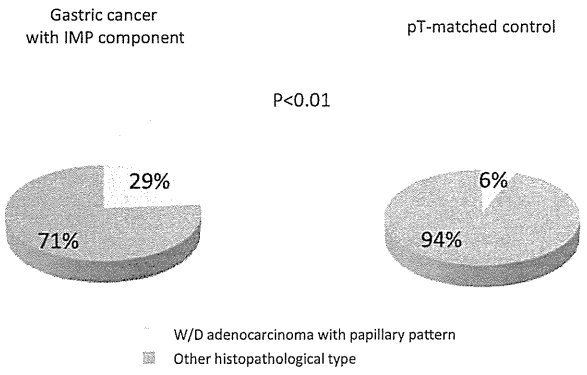

Fig. 2 Histopathological types of the primary lesions in patients with an invasive micropapillary component (IMP). In the patients with an invasive micropapillary component, 29% showed well-differentiated (*W/D*) adenocarcinoma with a papillary pattern as the co-existent histological component, whereas only 6% of the pT-matched controls showed well-differentiated adenocarcinoma with a papillary pattern ($p < 0.01$)

found in 29% of cases with gastric cancer with an IMP component, whereas 6% of the pT-matched controls showed well-differentiated adenocarcinoma with a papillary pattern ($p < 0.01$). There were no differences in the distribution of moderately differentiated adenocarcinoma orpoorly differentiated adenocarcinoma between the groups ($p = 0.83$) (Table 2).

The histopathological manifestations in patients with an IMP component compared with those in the pT-matched controls are shown in Table 2. Between patients with gastric cancer with an IMP component and pT-matched controls, no significant differences were found in the size of the primary lesion (median size 61.5 vs 56.2 mm: $p = 0.23$), in the depth of invasion of the tumor (mucosa-muscular layer 42.8%, subserosal-serosal layer 57.1% vs mucosa-muscular layer 43.0%, subserosal-serosal layer 57.0%: $p = 0.96$), in the dominant histological grade of the lesion (percentage of well-differentiated adenocarcinoma

Table 2 Histopathological features of gastric cancer with IMP component

Variables	With IMP structure ($n = 14$)	Without IMP structure (pT-matched control) ($n = 100$)	p value
Size of tumor, median, mm (range)	61.5 (42–89.5)	56.2 (2.5–85)	0.23
Invasion of tumor			0.96
Mucosa-muscular layer	6 (42.8%)	43 (43.0%)	
Subserosa-serosal layer	8 (57.1%)	57 (57.0%)	
Invasion to adjacent organ	0 (0%)	0 (0%)	
Histological type			0.83
Well-differentiated adenocarcinoma	6 (42.8%)	28 (28.0%)	
Moderately differentiated adenocarcinoma	7 (50.0%)	56 (56.0%)	
Poorly differentiated adenocarcinoma	1 (7.1%)	14 (14.0%)	
Other histological type	0 (0%)	2 (2.0%)	
Lymphatic infiltration			<0.01
ly0 or ly1	3 (21.4%)	68 (68.0%)	
ly2 or ly3	11 (78.5%)	32 (32.0%)	
Venous invasion			0.02
v0 or v1	5 (35.7%)	70 (70.0%)	
v2 or v3	9 (62.4%)	30 (30.0%)	
Perineural invasion			0.96
ne0 or ne1	10 (71.4%)	75 (75.0%)	
ne2 or ne3	4 (28.5%)	25 (25.0%)	
No. of metastatic lymph nodes, median, no. of cases (range)	16.3 (1–42)	3.2 (0–24)	<0.01
Lymph node metastasis			<0.01
pN(−)	0 (0%)	43 (43.0%)	
pN(+)	14 (100%)	57 (57.0%)	
p-Stage			0.08
Stage I or II	6 (42.8%)	70 (70.0%)	
Stage III or IV	8 (57.1%)	30 (30.0%)	

Table 3 Clinicopathological features of gastric cancer with IMP component in the comparison with those with stage-matched control

Variables	With IMP structure ($n = 14$)	Without IMP structure (stage-matched control) ($n = 100$)	p value
Age, years, median (range)	62.1 (43–75)	61.6 (38–89)	0.33
Gender (M:F)	10:4	68:32	0.96
Location of tumor			0.60
Upper third of stomach	3 (21.4%)	21 (21.0%)	
Middle third of stomach	7 (50.0%)	34 (34.0%)	
Lower third of stomach	4 (28.5%)	45 (45.0%)	
Type of surgery			0.80
Distal gastrectomy	9 (64.2%)	65 (65.0%)	
Total gastrectomy	5 (35.7%)	35 (35.0%)	
Size of tumor, median, mm (range)	61.5 (42–89.5)	58.2 (2.5–108)	0.26
Invasion of tumor			0.98
Mucosa-muscular layer	6 (42.8%)	37 (37.0%)	
Subserosa-serosal layer	8 (57.1%)	59 (59.0%)	
Invasion to adjacent organ	0 (0%)	4 (4.0)	
Histological type			0.75
Well-differentiated adenocarcinoma	6 (42.8%)	24 (24.0%)	
Moderately differentiated adenocarcinoma	7 (50.0%)	59 (59.0%)	
Poorly differentiated adenocarcinoma	1 (7.1%)	14 (14.0%)	
Other histological type	0 (0%)	3 (3.0%)	
Lymphatic infiltration			<0.01
ly0 or ly1	3 (21.4%)	71 (71.0%)	
ly2 or ly3	11 (78.5%)	29 (29.0%)	
Venous invasion			<0.01
v0 or v1	5 (35.7%)	73 (73.0%)	
v2 or v3	9 (62.4%)	27 (27.0%)	
Perineural invasion			0.76
ne0 or ne1	10 (71.4%)	79 (79.0%)	
ne2 or ne3	4 (28.5%)	21 (21.0%)	
Lymph node metastasis			<0.01
pN(−)	0 (0%)	58 (58.0%)	
pN(+)	14 (100%)	42 (42.0%)	
p-Stage			0.83
Stage I or II	6 (42.8%)	44 (44.0%)	
Stage III or IV	8 (57.1%)	56 (56.0%)	

42.8 vs 28.0%, moderately differentiated adenocarcinoma 50.0 vs 56.0%, poorly differentiated adenocarcinoma 7.1 vs 14.0%, other histological type 0 vs 2.0%: $p = 0.83$), in the perineural invasion of the tumor (percentage of ne2, 3; cases 28.5 vs controls; 25.0%: $p = 0.96$). On the other hand, statistically significant differences were observed in the degree of lymphatic infiltration (ly2 or 3; 78.5 vs 32.0%: $p < 0.01$), in the degree of venous invasion (incidence of v2 or 3; 62.4 vs 30.0%: $p = 0.02$), in the median number of metastatic lymph nodes (number/case; 16.3 vs 3.2: $p < 0.01$), and in the frequency of lymph node metastasis (percentage of cases; 100 vs 57.0%: $p < 0.01$). In particular, all patients with the IMP component showed marked lymph node metastasis.

Outcome for patients with an IMP component

The results of the present study indicate that patients with an IMP component frequently showed marked lymphatic infiltration and lymph node metastasis, which are clinicopathological characteristics similar to those of IMP carcinoma of the breast. Thus, in order to assess the outcome for patients with gastric cancer associated with an IMP component, we evaluated the survival rate in these patients and

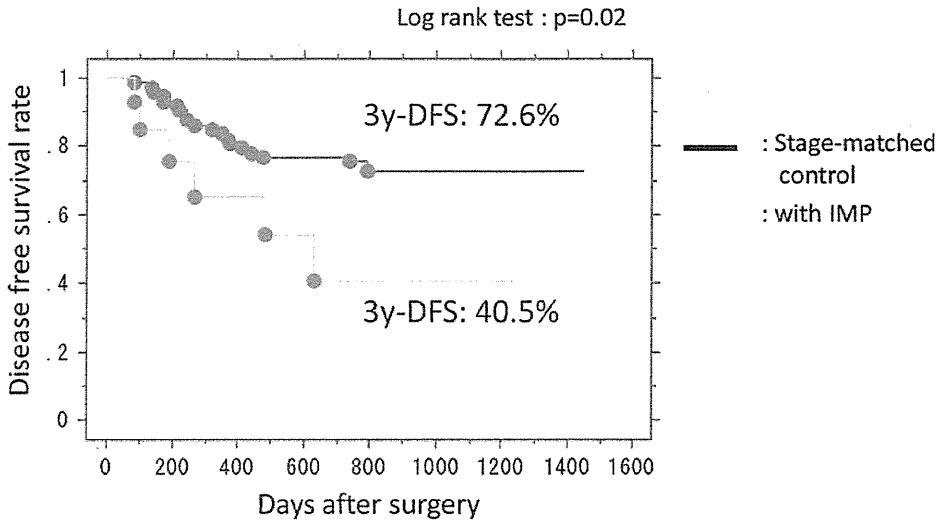

Fig. 3 Disease-free survival (*DFS*) of the patients with gastric cancer with a regional invasive micropapillary structure. The three-year (*3y*) DFS rate of the patients with an invasive micropapillary structure was significantly lower than that of the stage-matched controls (72.6 vs 40.5%, $p = 0.02$)

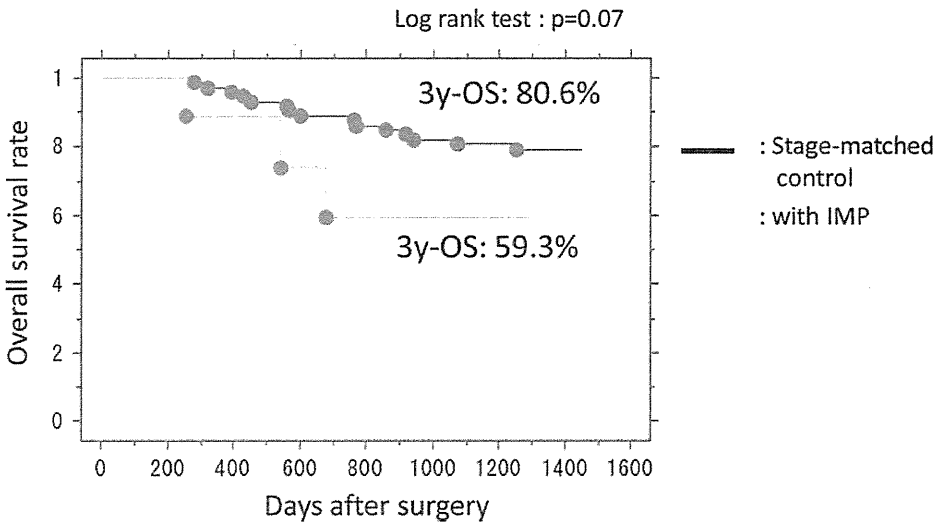

Fig. 4 Overall survival (*OS*) rate of the patients with gastric cancer with a regional invasive micropapillary structure. The 3-year survival rate of the patients with an invasive micropapillary structure was lower than that of the stage-matched controls (80.6 vs 59.3%, $p = 0.07$), although the difference was not significant

compared it with the survival rate in 100 stage-matched controls randomly assigned over the same period. The patients' demographic data and characteristics are shown in Table 3. Patients with an IMP component showed a significantly higher incidence of aggressive lymphatic infiltration ($p < 0.01$), venous invasion ($p < 0.01$), and lymph node metastasis ($p < 0.01$). As shown in Fig. 3, the 3-year disease-free survival rate of patients with an IMP component was 40.5%, whereas that of the stage-matched controls was 72.6% ($p = 0.02$). Further, as shown in Fig. 4, the 3-year overall survival rate of patients with an IMP component was 59.3%, whereas that of the stage-matched controls was 80.6% ($p = 0.07$).

Univariate analysis and multivariate analysis

To explore factors with potential prognostic significance, various pathological parameters were investigated in the 14 patients with the IMP component and in the 100 stage-matched controls (total 114 cases). The results of univariate analysis revealed that the following factors were significant indicators of survival in patients after the operation: IMP component ($p = 0.02$), depth of tumor invasion ($p < 0.01$), lymphatic infiltration ($p = 0.01$), venous invasion ($p = 0.04$), perineural invasion ($p = 0.03$), and lymph node metastasis ($p < 0.01$). To further evaluate the significance of these 6 factors, multivariate analysis was carried out. Results of the multivariate analysis with the Cox proportional hazard model showed that depth of tumor invasion [hazard ratio (HR) 4.28, 95% confidence interval (CI) 1.493–12.320, $p < 0.01$] and lymph node metastasis (HR 6.29, 95% CI 1.749–22.686, $p < 0.01$) were independent prognostic factors for disease-free survival, and the IMP component was not an independent prognostic factor for disease-free survival (Table 4).

Table 4 Univariate and multivariate analysis of prognostic factors of survival

Variables	Values (%)	Univariate analysis *p* value	Multivariate analysis *p* value
IMP component		0.02	0.35
With IMP component	14 (12.2)		
Without IMP component	100 (87.8)		
Invasion of tumor		<0.01	<0.01
Mucosa-muscular layer	43 (37.7)		
Subserosal or more	71 (62.3)		
Histological type		0.27	–
Well-differentiated adenocarcinoma	30 (26.3)		
Other histological type	84 (73.7)		
Lymphatic infiltration		0.01	0.28
ly0 or ly1	74 (64.9)		
ly2 or ly3	40 (35.1)		
Venous invasion		0.04	0.50
v0 or v1	78 (68.4)		
v2 or v3	36 (31.6)		
Perineural invasion		0.03	0.35
ne0 or ne1	89 (78.0)		
ne2 or ne3	25 (22.0)		
Lymph node metastasis		<0.01	<0.01
pN(−)	58 (50.8)		
pN(+)	66 (49.2)		

Discussion

The present study provides the first analysis of the clinicopathological features of IMP carcinoma of the stomach. Cancers with an IMP component have been reported not only in the breast but also in various other organs [3–7]. The accumulated evidence indicates that most breast cancers with an IMP component show marked tumor invasion of the lymphatic system, resulting in aggressive tumor behavior and a poor clinical course [3]. A similar IMP pattern has been reported in cancers originating from the gastrointestinal tract [8–10]. However, to the best of our knowledge, because the number of reports to date is limited, the clinical and histopathological features of this specific subtype of stomach cancer are largely unknown and are not being addressed in cases of IMP carcinoma of the stomach. Therefore, we first investigated the incidence of gastric cancer with an IMP component and found that there were no cases that exhibited the pure form of IMP carcinoma, which differs from the situation in breast cancer [13]. We found that, in the regional form of the invasive component, 1.5% (14/930) of cases showed an IMP pattern. Categorizing these cases as gastric cancer with a regional IMP component, we investigated the clinical and histopathological features of such cancers and found that all these cases shared common histopathological findings, such as a higher incidence of lymphatic infiltration and lymph node metastasis, which is consistent with the features of IMP carcinoma of the breast. In the present study, higher rate of papillary carcinoma was found in cancers with IMP component compared with those without IMP component. We have no definitive explanation to clarify the underlying mechanism why the high rate of papillary pattern is found in cancer of IMP component, and we cannot exclude a potential bias, because the number of gastric cancers with an IMP component was so small. In a recent report, however, differences in tumor grades were also demonstrated in colon cancer with an IMP component compared with colon cancer without an IMP component. Moreover, differences in the molecular background, such as differences in *p53* or *MMR* gene expression and microsatellite instability status, were reported in gastrointestinal cancers with an IMP component compared with those without the IMP component. Thus, it is not unreasonable that these differences in molecular background could be involved in the patterns of tumor growth.

The prognosis for patients with IMP carcinoma has not been clarified. Due to the peculiar proclivity for lymphatic infiltration and the high incidence of lymph node metastasis, a poorer prognosis for IMP carcinoma was shown than that for usual invasive ductal carcinoma of the breast [14]. However, other reports have observed no poorer survival rates in patients with IMP carcinoma of the breast when data were adjusted for stage of disease, reasoning that

a higher incidence of lymph node metastasis is usually categorized as advanced stage disease [15, 16]. In the present study, although the number of patients with an IMP component was small, we demonstrated a significant difference in disease-free survival rates in patients with IMP carcinoma of the stomach compared with stage-matched controls during the same period. Considering that lymph node metastasis is an important parameter for the determination of the stage of disease, the reasons for the poor prognosis in gastric cancer patients with the IMP component could also have been due to the aggressive tumor behavior in infiltration of the venous system.

The molecular background of IMP carcinoma has been examined in gastric cancer. Previous immunohistochemical analysis of this subtype have revealed the downregulation of E-cadherin compared with that in normal gastric epithelia [8]. Because *E-cadherin* is generally recognized as an invasion-suppressor gene [17, 18] and loss of E-cadherin expression has been demonstrated to be associated with tumor invasion in adenocarcinoma of the stomach [19], the aggressive tumor behavior of this subtype could be partly attributed to its molecular characteristics. Although there are conflicting data, several previous reports have demonstrated the molecular profile of IMP carcinoma in the breast. Estrogen receptor expression has been found in 25% [20] to 90% [21] of all pure IMP carcinoma cases, whereas HER2 protein overexpression has been observed in 36–100% [20, 22]. Other previous reports on breast cancer demonstrated that 72% of cases with IMP carcinoma expressed HER2 protein and 45% showed amplification of *HER2* gene levels [23]. Considering the usual incidence of overexpression of HER2 protein and amplification of the *HER2* gene, IMP carcinoma of the breast could have a higher incidence of overexpression of *HER2* status. Also, taking into consideration a recent report from a large clinical trial in patients with gastric cancer (ToGA study) [24], it appears that information based on an investigation of HER2 status would provide interesting insights into IMP carcinoma. The ToGA study demonstrated a significantly better survival rate in patients treated with additional administration of trastuzumab (a monoclonal antibody against HER2) [24]. Therefore, it is potentially of great importance to evaluate the HER2 level in this subtype of gastric cancer when considering the future treatment strategy for patients with gastric cancer with a regional IMP component.

The present study has several limitations. Due to the low incidence of patients diagnosed with a regional IMP component, the number of patients was too small to perform more rigorous statistical evaluations, and the clinicopathological investigation was possibly biased. Furthermore, the present study covered a period of almost 4 years, during which preoperative diagnostic accuracy and postoperative follow-up regimens differed slightly. However, the performance of histopathological explorations was consistent, and this consistency may be considered a strong point of the study.

In conclusion, the results of the present study indicate the following: (1) there were no significant differences among patients with gastric cancer with an IMP component compared with controls in terms of age or gender or the location or macroscopic type of the tumor. (2) In patients with gastric cancer with an IMP component, significantly higher incidences of lymphatic infiltration, venous invasion, and lymph node metastasis were apparent compared with controls. (3) Survival rates of patients with an IMP component did tend to be lower than those of the stage-matched controls. Further analysis including the molecular background of the lesions and investigations of a large number of cases in a prospective setting should provide more detailed clues for understanding the prognosis and clinicopathological features of gastric cancer with an IMP component.

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Conflict of interest There are no financial supports or relationships that may pose a conflict of interest.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Sentinel Node Mapping for Gastric Cancer: A Prospective Multicenter Trial in Japan

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ABSTRACT

Purpose
Complicated gastric lymphatic drainage potentially undermines the utility of sentinel node (SN) biopsy in patients with gastric cancer. Encouraged by several favorable single-institution reports, we conducted a multicenter, single-arm, phase II study of SN mapping that used a standardized dual tracer endoscopic injection technique.

Patients and Methods
Patients with previously untreated cT1 or cT2 gastric adenocarcinomas < 4 cm in gross diameter were eligible for inclusion in this study. SN mapping was performed by using a standardized dual tracer endoscopic injection technique. Following biopsy of the identified SNs, mandatory comprehensive D2 or modified D2 gastrectomy was performed according to current Japanese Gastric Cancer Association guidelines.

Results
Among 433 patients who gave preoperative consent, 397 were deemed eligible on the basis of surgical findings. SN biopsy was performed in all patients, and the SN detection rate was 97.5% (387 of 397). Of 57 patients with lymph node metastasis by conventional hematoxylin and eosin staining, 93% (53 of 57) had positive SNs, and the accuracy of nodal evaluation for metastasis was 99% (383 of 387). Only four false-negative SN biopsies were observed, and pathologic analysis revealed that three of those biopsies were pT2 or tumors > 4 cm. We observed no serious adverse effects related to endoscopic tracer injection or the SN mapping procedure.

Conclusion
The endoscopic dual tracer method for SN biopsy was confirmed as safe and effective when applied to the superficial, relatively small gastric adenocarcinomas included in this study.

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INTRODUCTION

Gastric cancer remains a major cause of cancer death throughout Asia. Although advances in multimodal approaches have significantly improved management of localized and resectable gastric cancer, gastrectomy with regional lymphadenectomy remains the mainstay of multimodal therapeutic strategies. Gastrectomy with D2 lymph node dissection (D2 gastrectomy) has become a standard surgical approach for resectable gastric cancer worldwide.[1-3] Although improved long-term results were reported after D2 gastrectomy in comparison with D1 gastrectomy, surgical morbidity after D2 gastrectomy remains significant, particularly in Western countries.[4] Furthermore, the incidence of regional lymph node metastasis is limited in patients with cT1 or T2N0 gastric cancer, whereas D2 gastrectomy seems to be an overly invasive surgery for patients with pN0 gastric cancer. Nevertheless, because of the limitations of the sensitivity of preoperative diagnostic imaging methods to detect pathologic metastasis in regional lymph nodes, D2 gastrectomy has become a standard procedure to ensure cure, even for clinically node-negative patients. Therefore, we hypothesized that sentinel node (SN) mapping offers a promising tool to resolve this issue.[5,6] SN mapping was applied to the upstaging of colorectal cancer as an initial clinical application in GI malignancies.[7]

Although there are controversial aspects regarding the application of SN mapping in gastric cancer, which has a relatively complicated lymphatic flow, several successful single-institution studies have been reported.[8-11] However, the indications and the procedures applied for SN mapping in these previous reports varied. Therefore, a prospective

multicenter trial with a fixed standard protocol was considered essential for establishing solid evidence that confirms the clinical significance of SN mapping in gastric cancer. A study group of the Japan Society of Sentinel Node Navigation Surgery analyzed the results of the previous studies and formulated an optimal procedure for SN mapping using the dual tracer method with technetium 99m–labeled tin colloid and 1% isosulfan blue dye (Lymphazurin, TycoHealth Care, Tokyo, Japan) in which the detection rate and sensitivity to detect metastasis by SN biopsy was relatively high.[5,10] Twelve institutions with established SN mapping protocols in place and experienced surgical staffs participated in this prospective study in which the validity of the SN concept and current optimal indications and procedures for gastric cancer treatment were evaluated.

PATIENTS AND METHODS

Patients

Patients with histologically confirmed clinical T1N0M0 or T2N0M0 adenocarcinoma of the stomach (International Union Against Cancer [UICC] TNM Classification, 6th edition) with single primary lesions (≤ 4 cm) without previous treatment, including endoscopic mucosal resection or endoscopic submucosal dissection, were preoperatively considered for inclusion in this study. Clinical staging was made by preoperative endoscopy and computed tomography. Endoscopic ultrasound was not routinely performed in the patients included in this study. Patients with apparent T3/T4 tumors, nodal or distant metastasis diagnosed intraoperatively, extensive abdominal adhesion, or poor general condition during surgery were excluded from the study. Patients with a history of drug-related allergy or active asthma were also excluded because of the potential risk of anaphylactic reaction after blue dye injection. All patients enrolled onto this study were preoperatively registered in a central data center.

All patients provided written informed consent. This study was approved by all local institutional review boards and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The 12 hospitals that participated in this multicenter prospective study had previous experience (> 30 patients each) with SN mapping for gastric cancer using the dual tracer method.

SN Mapping Procedure

The dual tracer method with radiolabeled tin colloid and blue dye was performed as previously described.[5] Briefly, the day before surgery, 20 mL of technetium 99m tin colloid solution (0.5 mL × 4 points; total 150 MBq; 0.3 mCi at the time of surgery) was injected in four quadrants of the submucosal layer of the primary lesion by using an endoscopic puncture needle. Intraoperatively, the gastrocolic ligament was divided to visualize all possible directions of lymphatic flow from the stomach. The 1% isosulfan blue dye was injected via intraoperative endoscopy in exactly the same manner as the preoperative injection of the radioactive tracer. Within 15 minutes, the lymphatic vessels and lymph nodes were dyed blue and imaged. Simultaneously, a handheld gamma probe was used to locate the radioactive SN. Lymph nodes with radioactivity > 10× background activity were defined as hot nodes. Hot and/or blue nodes were identified as the SNs in this study. In principle, the dual tracer technique was performed as an ideal SN mapping procedure in this study. However, the radioguided method alone was also permitted per our protocol in cases in which it was difficult to intraoperatively inject the blue dye.

Intraoperative Histologic Examination of SNs

Harvested SNs were subjected to intraoperative histologic examination by hematoxylin and eosin (HE) staining by using one representative cut surface of a frozen section of each SN. Intraoperative histologic examinations were optional and were performed on a case-by-case basis.

Surgical Procedure

After SN mapping, D2 or modified D2 gastrectomy was performed for all patients by using the therapeutic guidelines recommended by The Japan Gastric Cancer Association for standard care of this patient population.

Evaluation of SN Mapping for Gastric Cancer

The primary end point of the study was sensitivity to detect metastasis on the basis of SN status. Secondary end points included SN detection rate, number and distribution of identified SNs, and rate of adverse effects as a result of SN mapping. The pathologic status of SNs and all harvested non-SNs after D2 or modified D2 gastrectomy were examined by HE staining of one representative cut surface of a paraffin-embedded specimen.

Statistical Consideration

We reasoned that a sensitivity of 95% in patients with lymph node metastasis would indicate clinical usefulness, whereas a rate of 85% would be the lower limit of interest. On the basis of this assumption, we calculated that 89 patients were needed to provide a 90% power for a two-sided 0.05 level of a type I error. Taking ineligible patients into account, we planned to include 100 patients with lymph node metastasis. Assuming that approximately 20% of the patients in the study population had lymph node metastasis, the sample size was set at 500. Statistical analysis of the data was performed by using χ^2 and Fisher's exact tests.

RESULTS

Patients and Treatment

From July 2004 to March 2008, 433 patients were preoperatively enrolled onto this study. As shown in Figure 1, seven patients were

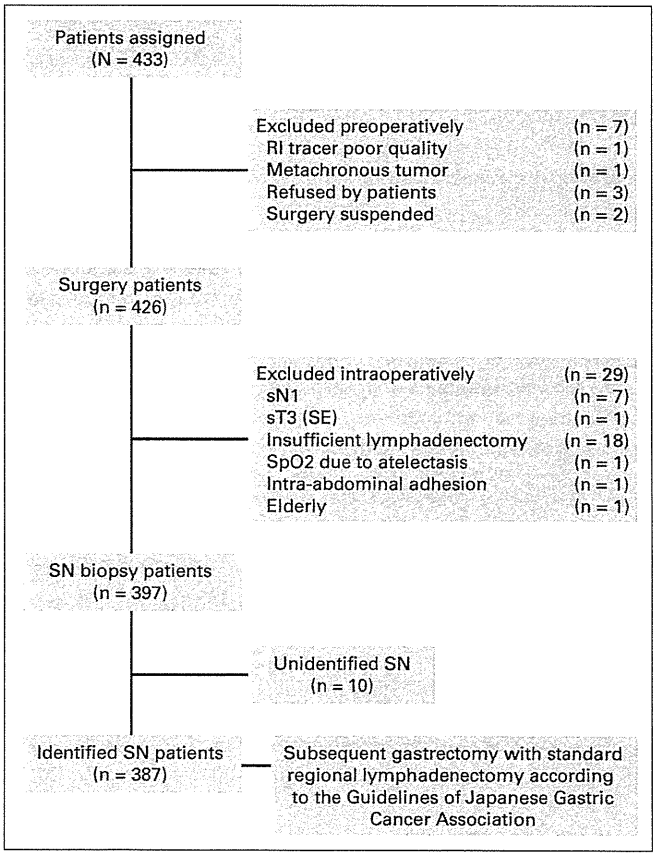

Fig 1. Flow of accrued patients. RI, radioisotope; SE, tumor penetration of serosa; SN, sentinel node; SpO_2, pulse oximeter oxygen saturation.

Table 1. Patient Characteristics (N = 397)

Characteristic	No.	%	G	A	L	P
Age, years						
Median	63					
Range	29-87					
Sex						
Male	264	66				
Female	133	34				
Location of tumor (in stomach)						
Upper third	76		5	6	41	24
Middle third	176		30	30	67	49
Lower third	145		31	22	63	29
cT factor						
T1	341	86				
T2	56	14				
Tumor size, cm (measured after gastrectomy)						
Median	3.0					
Range	0.6-10.0					

Abbreviations: A, anterior wall; G, greater curvature; L, lesser curvature; P, posterior wall.

Table 2. Adverse Effects (N = 397)

Adverse Effect	No.	%
Administration of the tracers		
Allergic reaction to the radioactive tracer	0	0
Allergic reaction to the dye tracer	0	0
Intraoperative remarkable findings		
Pigmentation (transient)	1	0.3
$SpO_2 \downarrow$ (transient)	3	0.8
Postoperative complications		
Pneumonia	2	0.5
Anastomotic leakage	1	0.3
Pancreatic leakage	2	0.5
Intra-abdominal abscess	5	1.3
Anastomotic stenosis	1	0.3
Small bowel obstruction	4	1.0
Bleeding	2	0.5
Thrombus/embolism	1	0.3

Abbreviation: SpO_2, pulse oximeter oxygen saturation.

preoperatively excluded and 29 others were excluded on the basis of intraoperative findings according to the protocol eligibility criteria. In 18 patients, the extent of lymphadenectomy was not sufficient for several reasons, including severe intra-abdominal adhesion, obesity, or the patients' and/or surgeon's desire for minimized gastrectomy, such as partial resection. Finally, 397 patients underwent SN biopsies (Table 1). We diagnosed 341 lesions (86%) as primary T1 lesions. In addition to the radioguided method, 363 patients (91%) underwent dye-guided SN mapping. Laparoscopy-assisted gastrectomy was performed in 161 patients (41%). Intraoperative histologic examinations were performed on frozen sections from 301 patients (76%).

Adverse Effects of SN Biopsy

No serious allergic reactions were observed after tracer injection, except for instances of transient pigmentation (0.3%) and decreased pulse oximeter oxygen saturation (0.8%), which might have been related to the intraoperative dye injection (Table 2). These reactions were observed intraoperatively and sufficiently controlled while the patient was under general anesthesia. As indicated in Table 2, there was no significant increase in the number of postoperative complications caused by the SN biopsy procedures or standard surgery.

Results of SN Biopsy

The SN detection rate determined by using the dual tracer method was 97.5% (387 of 397; Table 3). Three (30%) of the 10 patients with undetected SNs underwent radioguided mapping alone. Lymph node metastasis was diagnosed in 57 (14.7%) of 387 patients, and the incidence of lymph node metastasis was significantly higher in cT2 tumors than in cT1 tumors ($P < .001$). Of the 57 patients with lymph node metastasis, 53 (93.0%) showed positive SNs. The accuracy of metastatic status based on SN evaluation was 99.0% (383 of 387). In 32 (60.4%) of 53 patients with positive SNs, lymph node metastases were limited to only SNs. Of 21 SN-positive/non–SN-positive patients, 15 (71.4%) had metastatic non-SNs within SN basins and six (28.6%) had metastatic non-SNs located outside the SN basins but within the extent of the D2 lymph node dissection. Four patients had false-negative SN biopsy results of whom three had either pT2 or primary tumors > 4 cm or both (Fig 2A).

Diagnostic Accuracy of the Primary Tumor

We evaluated differences in clinical and pathologic tumor depth (UICC TNM Classification, 6th edition) and primary tumor diameter (Table 3). Notably, 314 (94.3%) of 333 cT1 (mucosa + submucosa) patients were diagnosed as pT1 (mucosa + submucosa), but only 26 (48.1%) of 54 cT2 (muscularis propria + subserosa) patients were diagnosed as pT2 (muscularis propria + subserosa). Regarding pT3 (tumor penetration of serosa), one (0.3%) cT1 and three (5.6%) cT2 patients (a total of four [1.0%] of 387 patients with cT1 or cT2) were diagnosed as pT3. Regarding tumor diameter, 78 (20.2%) of 387 tumors were > 4 cm.

Sensitivity of Intraoperative Pathologic Detection of Metastases in SNs Using Frozen Tissue Sections

Intraoperative examinations showed that nine patients were SN negative, but permanent tissue sections were SN positive. The sensitivity of metastatic SN detection that uses intraoperative frozen sections was 79% when based on patients and 70% when based on lymph nodes. In seven (78%) of these nine patients, metastatic spread was limited to the SNs. In the remaining two patients, metastases were limited to the area within the SN basins.

Distribution of SNs

The distribution of SNs is shown in Figures 2B to 2D. SNs were located outside the area of D2 lymph node dissection in 1% of patients with primary tumors in the upper third, 3% in the middle third, and 6% in the lower third of the stomach, respectively.

DISCUSSION

The results of this multicenter prospective trial demonstrated that SN mapping for gastric cancer with the dual tracer method is a feasible and safe procedure. The detection rate of SNs and the

Table 3. Results of SN Biopsy and Diagnostic Accuracy of Tumor Depth

Variable	All Patients (N = 397)		cT1 Patients (n = 341)		cT2 Patients (n = 56)		*P*
	No.	%	No.	%	No.	%	
SN identification							.64
Detected	387	97.5	333	97.7	54	96.4	
Undetected	10	2.5	8	2.3	2	3.6	
No. of identified SNs							.13
Mean	5.6		5.5		6.1		
± SD (per patient)	3.1		3.2		2.8		
pN factor	387		333		54		<.001
pN positive	57	14.7	32	9.6	25	46.3	
pN negative	330	85.3	301	90.4	29	53.7	
SN metastasis	57		32		25		.62
pSN positive	53	93.0	29	90.6	24	96.0	
pSN negative (false negative)	4	7.0	3	9.4	1	4.0	
SN/non-SN metastatic status	387		333		54		< .001
SN positive/non–SN negative	32	8.3	21	6.3	11	20.4	
SN positive/non–SN positive	21	5.4	8	2.4	13	24.1	
SN negative /non–SN negative	330	85.3	301	90.4	29	53.7	
SN negative/non–SN positive	4	1.0	3	0.9	1	1.9	
Pathologic T factor	387		333		54		< .001
T1 (M + SM)	339	87.6	314	94.3	25	46.3	
T2 (MP + SS)	44	11.4	18	5.4	26	48.1	
T3 (SE)	4	1.0	1	0.3	3	5.6	
T4 (SI)	0		0		0		

Abbreviations: M, mucosa; MP, muscularis propria; SD, standard deviation; SE, tumor penetration of serosa; SI, tumor invasion to adjacent structures; SM, submucosa; SN, sentinel node; SS, subserosa.

sensitivity of detection of regional lymph node metastasis by SN biopsy were comparable to previously reported data regarding breast cancer and melanoma.[13,14]

Regarding indications for SN mapping, patients with clinically evident lymph node metastasis were excluded because the purpose of this technique was to identify clinically undetectable lymph node involvement. T3 or T4 tumors in which the anatomically natural lymphatic drainage routes might be obstructed or altered were also considered as not within the evaluation range of this study. Previous single-institution studies suggested that cT1 tumors would be the most suitable indication for this procedure. To confirm the proper indications of SN biopsy in terms of the depth of the primary lesions, patients with clinically T1 or T2 tumors with a primary lesion diameter of ≤ 4 cm were enrolled onto this prospective study. We concluded that SN mapping is indicated in cT1 lesions because the false-negative rate was significantly higher in cT2 tumors than in cT1 tumors in this study.

Our results also suggested that meticulous attention to an accurate preoperative diagnosis of the T factor is necessary to optimize SN mapping. Notably, the diagnostic accuracy of cT2 is not currently sufficient; therefore, the clinical application of SN mapping should be limited to cT1 tumors. Furthermore, if the primary tumor is diagnosed as cT1, but pT2 or deeper in patients who undergo function-preserving gastrectomy based on SN mapping, additional treatment, including surgery or chemoradiotherapy, should be considered.

The SN hypothesis is applied to patients at risk of lymph node metastasis, which is diagnosed by the characteristics of the primary tumor, but having clinically undetectable regional metastatic nodes, as confirmed by preoperative diagnostic imaging. Therefore, patients indicated for endoscopic treatment such as endoscopic mucosal resection and endoscopic submucosal dissection were excluded from the selection criteria for SN biopsy (additional detail is provided in the Appendix, online only).[15,16] Although an SN biopsy is technically feasible for lesions > 4 cm, the volume and injection points for the tracers must be considered in each case. Furthermore, tumors > 4 cm are not practical targets for minimally invasive and modified surgery based on SN status. We could not identify additional exclusion criteria such as the histologic type in this trial because of the limited number of patients with false-negative SN biopsy results. Furthermore, we found no clinical issues to account for the failure to identify SNs in the 10 patients with undetected SNs. Nonetheless, our results suggested that the dual tracer method might have been responsible for the higher SN detection rate compared with the radio-guided method alone.

At this time, radio-guided SN mapping combined with dye-guided real-time visualization of lymphatic vessels and SNs is recommended as a reliable SN detection method in gastric cancer. Although there remain several controversial points regarding performance of the actual procedure, such as the type of dye, the injection route (submucosal or subserosal), the volume of tracer, and the observation timing,[17] the multicenter study group of the Japan Society of Sentinel Node Navigation Surgery has adopted an optimal procedure for SN mapping of gastric cancer from a previous single-institution experience. We chose to use technetium 99m tin colloid, which has a relatively large particle size. In our experience, tin colloid migrates into the SNs within 2 hours and remains there for > 20 hours until it is phagocytized by macrophages. Endoscopic injection enables us to accurately inject the tracer, even laparoscopically, compared with

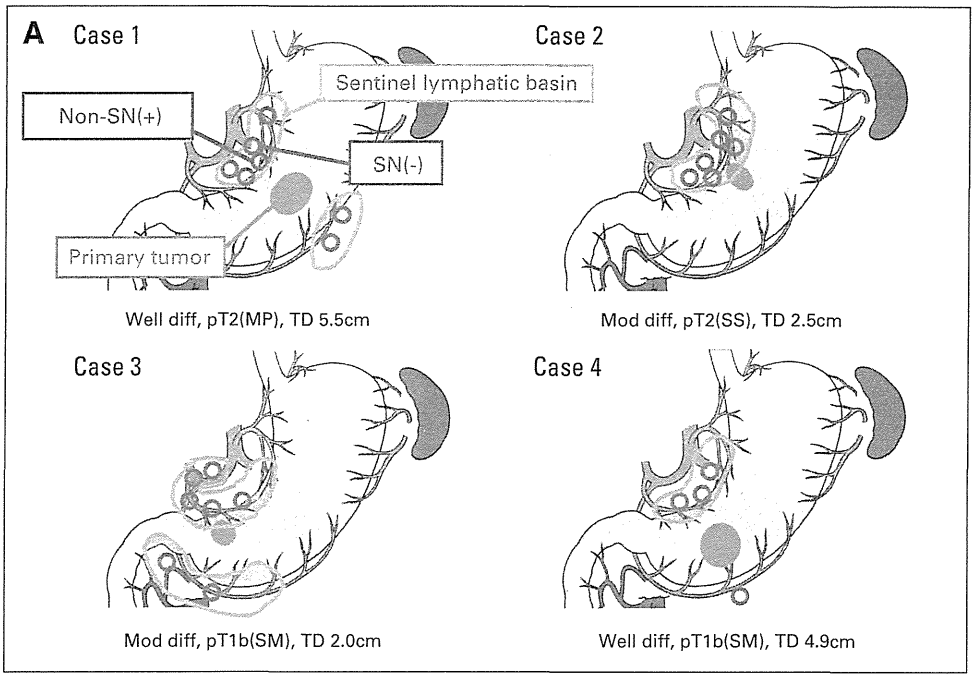

Fig 2. Distribution of identified sentinel nodes (SNs). (A) False-negative cases. Pink region, primary tumor; red circles, SNs (no metastasis); blue circles, nonsentinel nodes (metastatic); gold regions, sentinel node basins. Mod diff, moderately differentiated adenocarcinoma; MP, muscularis propria; 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

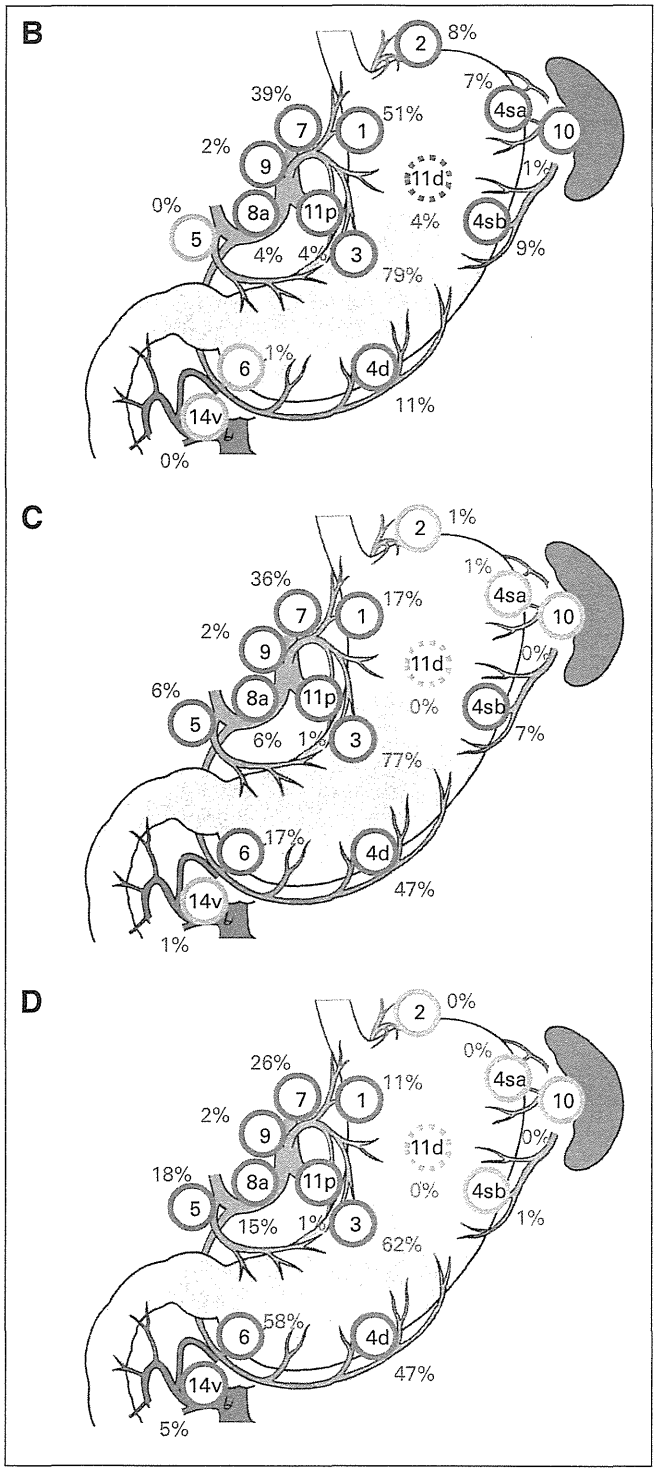

Fig 2. (Continued).

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