esophageal surgical group, while those with type II or III are treated by the gastric surgical group. In such facilities, there can be two separate databases.

In the present study, we examined databases for both esophageal and gastric cancer to clarify the distribution and clinical outcomes of AEG at a single cancer center hospital in Japan. The aims of this study are to evaluate clinicopathological features and oncological outcomes of AEGs according to Siewert's subtype, and to define predictive factors for prognosis.

PATIENTS AND METHODS

Patients

We retrospectively reviewed a database of 179 consecutive patients with AEG (Siewert's type I, II, and III) who underwent curative surgical resection at the National Cancer Center Hospital East between January 1993 and December 2008. Type III tumors were defined as subcardial cancers infiltrating the EGJ, whose epicenter is within the proximal 5 cm of the stomach; therefore, subcardial cancers not extending into the EGJ were excluded from this study. Follow-up periods ranged from 1.5 to 173 months (median 33 months). Overall survival analysis contained all deaths, including those due to an unrelated cause. Exclusion criteria included prior history of surgery for gastric cancer or gastric stump cancer.

Before surgery, all patients underwent chest radiographs, an abdominal ultrasonography, or a computed tomography (CT) scan for tumor staging. Upper gastrointestinal endoscopy was performed and barium swallows taken. From these findings, we determined preoperative Siewert's subtype and surgical approach. The choice of operation was based on preoperative diagnosis and estimated length of esophageal invasion. The intent was complete surgical resection.

All surgical specimens were delivered to the pathology department after the operations. We took photographs and sketched the appearance of each one and made a detailed record. Pathologists recorded the margin of the tumor, the esophagogastric junction (EGJ), and the tumor center. Based on the pathological and preoperative findings, we measured the distance from the EGJ to the tumor center, then to the oral top of the tumor. This was defined as the length of esophageal invasion. We then recorded the Siewert's type for all specimens.

Data were evaluated based on gender, age, tumor appearance, tumor size, length of esophageal invasion, operative methods, perioperative chemotherapy, tumor pathology and lymph node staging, histological grading, lymphovascular and venous invasion, and recurrence patterns. We also compared these data among the AEG subtypes.

The UICC 7th tumor-node-metastasis (TNM) classification of esophageal cancer was used to describe tumor progression and histopathological grading.[10] The macroscopic appearances of the tumors were divided according to Borrmann's classification.[11] Number of regional lymph node stations was categorized according to the Japanese classification of gastric carcinoma.[12]

Statistical Analyses

Statistical analyses were performed by chi-square test and *t*-test. Cumulative survival rates were generated by the Kaplan–Meier method. Survival curves were compared with the log-rank test. Significant factors were identified by univariate analysis, and further examined by multivariate analysis. Multivariate regression analysis was carried out using the Cox hazards model. All statistical analyses were performed using SPSS (SPSS Inc., Tokyo, Japan) for Windows. *p*-Value < 0.05 was considered statistically significant.

RESULTS

Patient Population and Tumor Characteristics

Ten of 179 patients had type I (5.6%) tumors, 107 had type II (59.8%), and 62 had type III (34.6%). The characteristics of the patients and surgical approaches are presented in Table 1. There were no significant differences in age and gender between the three subtypes. The superficial tumor type was observed in 40% of patients with type I cancer, whereas it was less common in types II (19.6%) and III (9.7%). In types II and III, Borrmann 3 was the most common macroscopic appearance (42.1% and 56.5%). Borrmann 4 was generally rare, but observed mainly in type III (11.3%).

Tumor size was significantly larger in type III (81.6 mm) than types I (55.1 mm) and II (45.2 mm).There was no significant difference between types II and III in the length of esophageal invasion. The longest esophageal invasion was 70 mm in type I. In types II and III, the longest invasions were 55 mm and 50 mm, respectively. Surgical approaches varied by tumor type. The transthoracic technique was used most often on type I (80%) tumors, which included 50% of right thoracic and 50% of left thoracoabdominal approaches. In contrast, the transhiatal approach was common in type III. In type II, 34.6% of operations were performed transthoracically and 65.4% transhiatally. In type I, subtotal esophagectomy (50%) and proximal gastrectomy with distal esophagectomy (40%) were common, whereas total gastrectomy with distal esophagectomy was common in types II (71.0%) and III (90.3%). We saw no significant difference in the rate of patients who received perioperative chemotherapy.

TABLE 1 Baseline characteristics of patients and surgical approaches ($n = 179$)

Classification	Type I ($n = 10$)	Type II ($n = 107$)	Type III ($n = 62$)	p-value
Age (years)	63.5 (48–83)	65 (30–86)	65.5 (31–62)	NS
Male:female	7:3	85:22	41:21	NS
Macroscopic type				
Superficial	4 (40%)	21 (19.6%)	6 (9.7%)	
Borrmann 1	2 (20%)	7 (6.5%)	3 (4.8%)	
Borrmann 2	2 (20%)	29 (27.1%)	11 (17.7%)	
Borrmann 3	1 (10%)	45 (42.1%)	35 (56.5%)	
Borrmann 4	0	1 (0.9%)	7 (11.3%)	
Unclassifiable	1 (10%)	4 (3.7%)	0	
Tumor size (mm)	45.2 ± 5.1	55.1 ± 2.6	81.6 ± 4.5	<0.001(II/III) 0.317 (I/II)
Esophageal invasion (mm)	46.3 ± 4.3	15.3 ± 1.1	13.6 ± 1.4	<0.001(II/III) 0.359 (II/II)
Approaches				
Transthoracic	8 (80%)	37 (34.6%)	10 (16.1%)	0.005 (I/II)
(Right:left)	(4:4)	(7:30)	(0:10)	0.010 (I/III)
Transhiatal	2 (20%)	70 (65.4%)	52 (83.9%)	
Subtotal esophagectomy	5 (50%)	8 (7.5%)	0	
Total gastrectomy with distal esophagectomy	1 (10%)	76 (71.0%)	56 (90.3%)	
Proximal gastrectomy with distal esophagectomy	4 (40%)	23 (21.5%)	6 (9.7%)	
Neoadjuvant chemotherapy	0	0	3 (4.8%)	NS
Adjuvant chemotherapy	1 (10%)	13 (12.1%)	17 (27.4%)	NS

NS not significant

The pathological characteristics of the patients are presented in Table 2. Patients with type III classification had significantly deeper tumors than those with types I and II. Additionally, the frequency of lymph node metastasis was significantly higher in those with type III rather than type II tumors. Similarly, higher tumor stage was observed in those in the type III class than types I and II. The incidence of mediastinal lymph node metastasis was significantly higher in type I patients than in types II and III. Histopathological grading was significantly poorer in type III than type II tumors.

Patterns of Lymph Node Metastasis

Table 3 presents the frequency of lymph node metastasis as well as 5-year survival for each lymph node station. Using these results, we computed the index of estimated benefit from lymph node dissection (IEBLD) using the formula: IEBLD = frequency of metastasis to each lymph node station (%) × 5-year survival rate of metastatic cases (%)/100.[13]

These values are shown in Table 3. The rate of metastasis was high in lymph node stations 1, 2, 3, and 7, and their IEBLDs were also high (7.0–21.0). The metastatic rate of mediastinal lymph nodes was 22.2% in total (40.0% in type I, 21.3% in type II, and 12.5% in type III), and the 5-year survival rate was 17.6%. The IEBLD of the mediastinal lymph node was 3.9, the same as that for the 16th station.

Survival Outcomes

The survival curves for each Siewert type are shown in Fig. 1. We observed no significant difference in overall survival by subtypes. Five-year survival rates were 51.4% in type I, 51.8% in type II, and 62.6% in type III. The median follow-up period of survivors was 33 months. We used Kaplan–Meier survival analysis to assess 11 prognostic factors: age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (type I or II versus III), depth of tumor (T1–2 versus T3–4), existence of lymph node metastasis, existence of mediastinal lymph node metastasis, length of esophageal invasion (<20 mm versus >20 mm), degree of venous and lymphovascular invasion, and histopathological grade (G1, 2 versus G3, 4) (Table 4).

Univariate analysis showed that the following seven factors were associated with survival: depth of tumor

TABLE 2 Pathological characteristics of patients ($n = 179$)

Classification	Type I ($n = 10$)	Type II ($n = 107$)	Type III ($n = 62$)	p-value
UICC 7th T category				
T1a	0	1 (0.9%)	1 (1.6%)	
T1b	4 (40%)	23 (21.5%)	2 (3.2%)	(T1/T2~)
T2	2 (20%)	14 (13.1%)	7 (11.2%)	0.213 (I/II)
T3	3 (30%)	32 (29.9%)	18 (29.0%)	<0.001 (I/III)
T4a	1 (10%)	34 (31.8%)	29 (46.8%)	0.003 (II/III)
T4b	0	3 (2.8%)	5 (8.1%)	
UICC 7th N category				
N0	2 (20%)	43 (40.2%)	12 (193%)	(N0/N1~)
N1	5 (50%)	23 (21.5%)	12 (193%)	0.210 (I/II)
N2	3 (30%)	9 (8.4%)	16 (253%)	0.960 (I/III)
N3	0	32 (29.9%)	22 (355%)	0.005 (II/III)
UICC 7th TNM stage				
IA	1 (10%)	20 (18.7%)	2 (32%)	
IB	1 (10%)	7 (65%)	0	
IIA	0	4 (3.7%)	2 (32%)	(Stage I, II/III, IV)
IIB	3 (30%)	13 (12.1%)	7 (113%)	0.586 (I/II)
IIIA	3 (30%)	14 (131%)	10 (161%)	0.023 (I/III)
IIIB	1 (10%)	4 (3.7%)	7 (113%)	0.002 (II/III)
IIIC	1 (10%)	32 (29.9%)	24 (38.7%)	
IV	0	13 (12.1%)	10 (161%)	
Histopathological grade				
G1/2	6 (60%)	71 (66.4%)	31 (50.0%)	0.685 (I/II)
G3/4	4 (40%)	36 (33.6%)	31 (50.0%)	0.557 (I/III)
				0.036 (II/III)

($p = 0.003$), lymph node metastasis ($p = 0.002$), mediastinal lymph node metastasis ($p = 0.001$), esophageal invasion >20 mm ($p = 0.023$), venous invasion ($p = 0.005$), lymphovascular invasion ($p = 0.022$), and histopathological grade 3/4 ($p = 0.042$). Subsequent multivariate analysis confirmed that only depth of tumor ($p = 0.001$) [95% confidential interval (CI), 1.62–6.16] and mediastinal lymph node metastasis ($p = 0.001$) (95% CI, 1.74–5.92) were significant and independent prognostic indicators after curative resection for AEG (Table 4).

We performed multivariate analysis of seven factors to determine the risk for mediastinal lymph node metastasis. These included age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (types I and II versus III), depth of tumor (T1–2 versus T3–4), length of esophageal invasion (<20 mm versus >20 mm), and histopathological grade (G1, 2 versus G3, 4). We found that esophageal invasion (>20 mm) ($p < 0.001$) (95% CI, 4.28–108.2) and histopathological grade 3/4 ($p = 0.035$) (95% CI, 1.10–15.40) were significant and independent risk factors for mediastinal node metastasis (Table 5).

TABLE 3 Frequency of lymph node metastasis as well as 5-year survival for each station

Lymph node station	Rate of lymph node metastasis (%)				5-Year survival rate (%)	IEBLD
	Type I	Type II	Type III	Total		
1	30.0	42.1	58.1	46.9	44.8	21.0
2	20.0	20.6	24.2	27.9	33.7	9.4
3	30.0	23.4	43.5	36.9	43.4	16.0
4sa	0.0	5.6	14.5	8.4	25.7	2.2
4sb	0.0	2.8	8.1	4.5	0.0	0.0
4d	0.0	1.2	10.2	4.9	0.0	0.0
5	0.0	3.5	3.5	3.5	0.0	0.0
6	0.0	2.6	3.6	3.0	0.0	0.0
7	40.0	22.4	14.5	21.8	32.3	7.0
8	0.0	6.7	13.6	9.3	30.4	2.8
9	0.0	13.3	8.6	10.8	13.8	1.5
10	0.0	3.9	12.3	7.4	30.0	2.2
11p	0.0	14.0	15.5	14.4	38.7	5.6
11d	0.0	6.3	7.1	6.5	0.0	0.0
12	0.0	0.0	3.3	1.5	0.0	0.0
16	0.0	12.2	20.7	15.1	22.7	3.4
Mediastinal	40.0	21.3	12.5	22.2	17.6	3.9

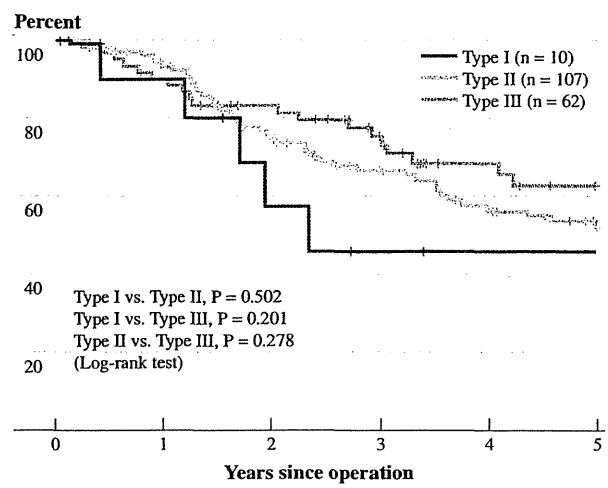

FIG. 1 Survival curves in each type of cancer (type I, II, or III). We saw no significant difference in overall survival by subtype

DISCUSSION

In this single-institution series of 179 AEGs in Japan, the proportions of types I, II, and III cancers were 5.6%, 59.8%, and 34.6%, respectively. After R0 resection, 5-year survival rates were 51.4% for type I, 51.8% for type II, and 62.6% for type III tumors. Mediastinal lymph node metastasis and a deeper tumor were significant and

TABLE 4 Univariate and multivariate predictors of overall survival

	No.	Univariate analysis *p*-value	Multivariate analysis *p*-value	Multivariate analysis Hazard ratio (95% CI)
Age (years)				
<65	93	0.826		
≥65	86			
Sex				
Male	133	0.685		
Female	46			
Tumor maximal size (mm)				
<60	89	0.113		
≥60	90			
Siewert type				
Type I, II	117	0.255		
Type III	62			
UICC 7th N category				
T1–2	54	0.003	0.001	3.16 (1.62–6.16)
T3–4	125			
UICC 7th N category				
N0	57	0.002	0.242	
N1–3	122			
Mediastinal nodes				
Negative	163	0.001	0.0001	3.21 (1.74–5.92)
Positive	16			
Para-aortic nodes				
Negative	168	0.018	0.066	
Positive	11			
Esophageal invasion (mm)				
<20	124	0.023	0.351	
≥20	55			
Venous invasion				
Negative	33	0.005	0.395	
Positive	146			
Lymphovascular invasion				
Negative	67	0.022	0.182	
Positive	112			
Histopathological grade				
G1/2	71	0.042	0.363	
G3/4	108			

TABLE 5 Multivariate analysis of mediastinal lymph node metastasis

	Hazard ratio (95% CI)	*p*-value
Esophageal invasion ≥20 mm	21.5 (4.28–108.2)	<0.001
Histopathological grade G3/4	4.12 (1.10–15.10)	0.035

independent factors for poor prognosis. In patients with mediastinal lymph node metastasis, recurrence rate was quite high (87.5%). Although curative surgery is the primary treatment modality for AEG, survival rates in patients with poor prognostic factors are unsatisfactory.

This study shows a significantly higher prevalence of types II and III AEGs in Japan compared with Western nations. Nonetheless, data indicate that the prevalence of AEG is rising in Western countries, but not in the East.[1–4] The distribution of the three types of AEGs also differs between West and East, with type I tumors less frequent in the latter.[3,6,7] Most papers from Japanese institutions have reported on types II and III; data on all three types are scant.[7–9]

To establish the prevalence and trend of types I, II, and III in Japan, we reviewed the database of gastric and esophageal cancers in our hospital. Of the three types, 5.6% were type I, 59.8% type II, and 34.6% type III. These findings are similar to reports from Hasegawa et al. in Japan, Bai et al. in China, and Fang et al. in Taiwan.[6,7,14] The lower frequency of type I AEGs in Eastern countries may be explained by a lower prevalence of gastroesophageal reflux, obesity, and *Helicobacter pylori* infection.

In the present study, we saw no significant differences in age and gender among the three types of cancers, but clinicopathological features differed. Type III cancers were more aggressive than types I and II. Tumors were larger and deeper, with a higher rate of lymph node metastasis. This trend has been reported by other groups. Conversely, we observed no significant difference in rates of tumor progression between types I and II cancers. This may indicate that type III tumors include cardia cancer centered 2–5 cm below the EGJ that enlarges, and then subsequently infiltrates the EGJ. It may also be more difficult to detect early cancer around the cardia than in the distal esophagus by screening endoscopy.

The UICC 6th TNM classification did not include integrated staging criteria for AEGs. They were staged according to criteria for esophageal or gastric cancer.[15] The UICC 7th TNM classification, however, defined AEG as a new disease category to be classified according to staging for esophageal cancer.[10] Here we classified and staged 179 AEGs according to the latest criteria. However, surgeons should note that most type II and III tumors have features of subcardial gastric cancer, which originates in the gastric mucosa. Type I cancer is closely associated with intestinal epithelial metaplasia (Barrett's epithelium). Type II cancer may arise from either Barrett's epithelium or junction epithelium. The etiology of type III relates to the gastric mucosa, in particular an association with *Helicobacter pylori* or atrophic gastritis.

In this study, Barrett's epithelium accounted for 90% (9/10) of type I adenocarcinomas, 10.3% (11/107) of type II, and 0% of type III cancers. These results are similar to those of Siewert and Stein (76.9%, 9.8%, and 2%).[5] Our data suggest that the origins of AEG tumors are somewhat alike in Western and Eastern countries. However, several studies out of Japan disagree. Yuasa et al. found that prevalence of Barrett's epithelium in type II cancer is lower in Japan than in Western countries.[9] Okabayashi et al. suggested that the occurrence of superficial carcinoma of the cardia had no relationship to Barrett's epithelium in Japan.[3]

In the present study, 5-year survival rates were similar among the three types of cancers: 51.4% for type I, and 51.8% and 62.6%, respectively, for types II and III. Although our series only included R0 resection, these outcomes seem better than those from prior reports. Data from Western countries indicate that type I has the best prognosis, followed by types II and III.[5] Conversely, reports from Asian countries show no obvious differences between subtypes. Fang et al. reported similar survival rates between types II and III (59.6% versus 63.5%).[6] The reasons for this discrepancy are unclear. One explanation may be that surgeons in Asian countries are more accustomed to surgery for gastric cancer or D2 dissection, leading to better outcomes in type III tumors.

We also evaluated the frequency of lymph node metastasis as well as 5-year survival for each positive station. To estimate the therapeutic value of lymph node dissection, we calculated IEBLD.[13] Our data show that lymph node stations 1, 2, 3, and 7 (around the cardia, the lesser curvature of the proximal stomach, and root of the left gastric artery) had high rates of metastasis. Nonetheless, patients had relatively good prognoses, suggesting that dissections of the abdominal lymph nodes are vital to AEG patients.

Our data also show that IEBLD were relatively low in dissection of numbers 8 and 9 lymph nodes (around the common hepatic and the celiac artery). However, they suggest benefit from D2 lymphadenectomy in patients with type II and III tumors. At the least, data suggest the need to remove the lymph nodes around the root of the left gastric surgery (no. 7). The rate of mediastinal lymph node metastasis was 22.2% in the present study, but its IEBLD was low, as was the 5-year survival rate of patients (17.6%). This figure is consistent with previous reports. The JCOG 9502 trial (phase III) clearly showed that a thoracoabdominal approach with radical mediastinal node resection did not improve survival in patients with type II or III adenocarcinomas. It did, however, increase surgical risk.[16] Our data may support the results of that trial.

Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators after R0 resection for AEG. In our series, 16 patients had mediastinal lymph node metastasis, and the recurrence rate for these patients was 87.5% (14/16), whereas it was 38% (62/163) in those without mediastinal lymph node metastasis. Recurrence patterns in these patients were seven nodal (five para-aortic, two cervical), three hematogenous (liver, bone, brain), three peritoneal, and one anastomotic. Mediastinal lymph node metastasis at operation indicates more systemic spread of cancer cells, and that dissection may not improve the survival rate.

Further multivariate analysis showed that esophageal invasion and histopathological grade were independent risk factors for mediastinal lymph node metastasis. Patients with swollen mediastinal lymph nodes detected by preoperative CT scan are likely to have poor prognosis. Even in patients without swollen mediastinal lymph nodes, those with relatively long esophageal invasion (>20 mm) or poorly differentiated histological type may also have poor prognosis.

Radical surgery is the primary modality in the treatment of AEG cancer. However, long-term outcome in patients with mediastinal lymph node metastasis is still unsatisfactory. For such patients, effective perioperative chemotherapy may improve their prognosis. Phase III trials of perioperative chemotherapy for gastric cancer have been conducted in Japan (ACTS-GC) and the UK (MAGIC trial); both demonstrated significant improvement in survival with perioperative chemotherapy.[17,18] However, only 26% of patients in the MAGIC trial had AEG, and numbers are not available in the ACTS-GC study. A phase III trial to evaluate perioperative chemotherapy in AEG patients is needed. Their poor prognosis creates an urgent need for this research. Therefore, future studies to evaluate the efficacy of perioperative chemotherapy should focus on treatment of AEGs.

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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

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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

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 sub-lesions, 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

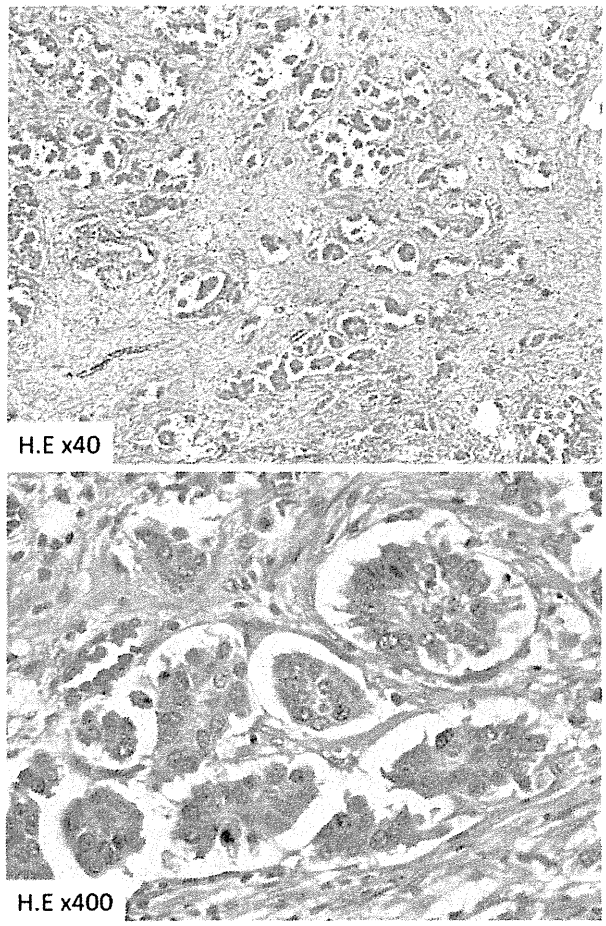

Fig. 1 Representative images of the regional invasive micropapillary component. There was no case of pure form of invasive micropapillary carcinoma in gastric cancer; however, 1.5% of cases contained a regional invasive micropapillary structure

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

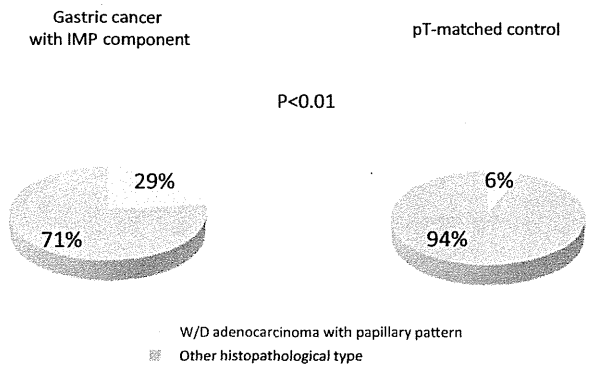

Fig. 2 Histopathological types of the primary lesions in patients with an invasive micropapillary component (IMP). In the patients with an invasive micropapillary component, 29% showed well-differentiated (*W/D*) adenocarcinoma with a papillary pattern as the co-existent histological component, whereas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

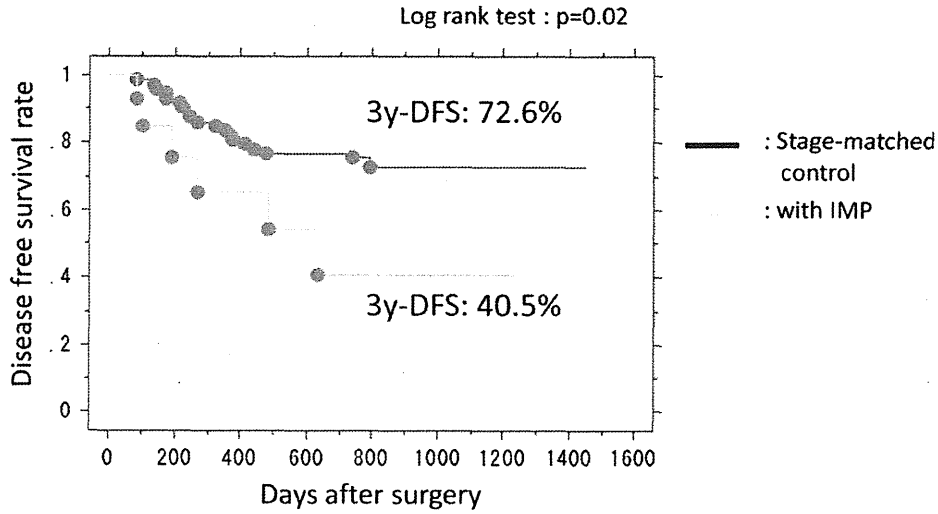

Fig. 3 Disease-free survival (*DFS*) of the patients with gastric cancer with a regional invasive micropapillary structure. The three-year (*3y*) DFS rate of the patients with an invasive micropapillary structure was significantly lower than that of the stage-matched controls (72.6 vs 40.5%, $p = 0.02$)

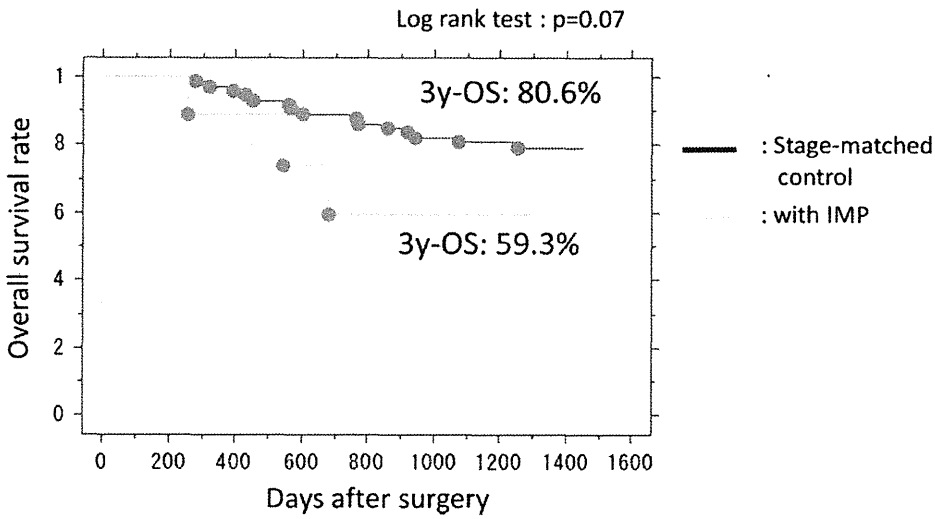

Fig. 4 Overall survival (*OS*) rate of the patients with gastric cancer with a regional invasive micropapillary structure. The 3-year survival rate of the patients with an invasive micropapillary structure was lower than that of the stage-matched controls (80.6 vs 59.3%, $p = 0.07$), although the difference 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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Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies

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We analyzed the correlation between primary tumor response within 6 months after radiation therapy (RT) including proton beam therapy (PBT) and progression free survival rate (PFS) in patients with nasal cavity and paranasal sinus malignancies to clarify the impact of early radiological evaluation of treatment response on prognosis. Sixty-five patients treated between January 1998 and December 2008, and whose follow-up duration was more than 2 years were included. The *Response Evaluation Criteria in Solid Tumors* (version 1.1) was used for the evaluation of treatment. Median age was 59 years (range 21–83 years). Olfactory neuroblastoma ($n = 20$, 30%) and squamous cell carcinoma ($n = 15$, 23%) were the major pathological tumor types. The median follow-up duration was 51.6 months. Radiological response evaluation within 6 months after treatment demonstrated that 15% of the patients achieved complete response (CR), and 3-year progression free survival rates of all patients was 49.2%. The 3-year PFS rates according to response for the treatment were 55.6% in the patients with CR and 46.4% in those with non-CR, respectively ($P = 0.643$). However, the 3-year PFS rates were 80.% in the patients with CR and 10.% in those with non-CR ($P = 0.051$) in the patients with squamous cell carcinoma (SCC) histology. Radiological response evaluation within 6 months did not have a significant impact on prognosis when analysis included all histology, although early radiological response within 6 months after RT had a borderline significant impact on treatment outcomes for the patients with nasal and paranasal SCC.

Keywords: response evaluation; nasal cavity; paranasal sinuses; radiation therapy; proton beam therapy

INTRODUCTION

Malignancies of the nasal cavity and paranasal sinuses are extremely rare, representing only 3–5% of all head and neck cancer and less than 1% of all malignancies [1–5]. Most cases are curatively treated by craniofacial surgery and postoperative radiation therapy, either alone or in combination [1–4, 6]. However, several problems with these treatment strategies remain. In cases where the disease has spread deeply into the intracranial region, surgical approaches are often complicated by the risk of serious functional deformity and a lack of satisfactory surgical clearance [7, 8]. Therefore, definitive radiation therapies (RTs) including 3D-conformal radiation therapy (3DCRT) or intensity modulated radiation

therapy (IMRT) and proton beam therapy (PBT) are often performed as an alternative treatment [2, 4, 9].

Generally, total tumor eradication is a fundamental efficacy measure for treatments and is often considered a surrogate for overall survival in the case of non-surgical approaches [10, 11]. However, Zenda *et al.* reported that patients with nasal or paranasal malignancies occasionally survive for long periods without complete response at the primary tumor site [9]. To our knowledge, however, there have been few reports that have examined response evaluation for nasal or paranasal sinus malignancies after non-surgical approaches. Here, we conducted a retrospective analysis examining the correlation between radiological tumor response and prognosis in patients with malignancies of the nasal cavity and paranasal sinuses to clarify the impact of early radiological evaluation of treatment response on prognosis.

MATERIALS AND METHODS

Patients

Patients fulfilling the following criteria were included: (i) malignancies of the nasal cavity or paranasal sinuses, (ii) received RT including PBT as a curative setting at the National Cancer Center Hospital East (NCCHE) between January 1998 and December 2008 and (iii) had sufficient radiographic information, such as that obtained by magnetic resonance imaging (MRI) and computed tomography (CT) for response evaluation.

Pretreatment evaluation

Pretreatment evaluation included a physical examination, a direct flexible fiberoptic endoscopic examination, MRI and CT.

Tumor staging in the present study was based on sections of the nasal cavity and paranasal sinuses in the TNM classification of the Union for International Cancer Control (UICC; 7th edition), regardless of histology type. For olfactory neuroblastoma (ONB), a system devised by Kadish *et al.* [12], which is based on anatomic extension, was used. During the preparation of this article, Kadish A, B, and C ONB were reclassified as T1, T2 and T4. Radiologists, head and neck surgeons, and medical oncologists at our institution reviewed radiological evaluation for tumor staging.

Radiation therapy

Proton beam therapy (PBT)

We used a 3D CT planning system to prepare the treatment planning. In this system, the proton beam was generated with a Cyclotron C235 (Sumitomo Heavy Industries, Ltd, Tokyo, Japan) with an energy of 235 MeV. Based on our preclinical experiments, relative biological effectiveness was defined as 1.1. Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Conventional radiation therapy

All photon beam RT was delivered using 6-MV X-rays and either 3D conformal techniques or IMRT, depending on the year of treatment and adjacent organs at risk.

Irradiation field

In general, primary tumors and metastatic lymph nodes were included in the irradiated field. Elective nodal irradiation was not performed. Gross tumor volume (GTV) was determined by pretreatment assessment with any or all of CT, MRI and Positron Emission Tomography-CT (PET-CT). Clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and the sinuses adjacent to the GTV. In cases involving brain invasion, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin for PBT and a 5–7-mm margin for RT, but was finely adjusted where necessary in consideration of organs at risk.

Imaging analysis

Response to treatment at the primary site was evaluated using the *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) [13]. Radiological response evaluation was carried out using CT/MRI performed within 6 months after treatment. At least two radiologists determined radiological evaluations for treatment response. In response evaluations within 6 months, patients who had achieved complete disappearance of all target lesions were defined as CR, while the remaining patients were classified as non-CR patients. Overall survival (OS) was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmation date if the patient was alive. Progression-free survival (PFS) was defined as from the day of initiation of treatment to the first day of confirmation of progressive disease or death by any cause.

Statistical analysis

The close-out date for survival analysis was 31 December 2010. Data were analyzed using StatView statistical software (Version 5.0, SAS Institute, Cary, NC, USA). Cumulative survival and tumor control rates were calculated using the Kaplan–Meier product-limit method. Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. P values of <0.05 were considered statistically significant.

RESULTS

Patient and treatment characteristics

A total of 75 patients with malignancies of nasal or paranasal sinuses were treated with RT including PBT at the

NCCHE between January 1998 and December 2008. Sixty-five patients met the inclusion criteria and were retrospectively analyzed in our study. Patient characteristics are listed in Table 1. The median age was 59 years (range, 21–83 years), with 39 male and 26 female patients. Most of the patients had T4 tumors ($n = 53$), and the majority of patients presented with a tumor of the nasal cavity ($n = 43$). Six patients presented with cervical lymph node metastasis at the time of diagnosis.

Medical records and pathological reports were reviewed to assess the histological examination results. ONB was the major histological type ($n = 20$), followed by squamous cell carcinoma (SCC, $n = 15$), melanoma ($n = 9$), adenoid cystic carcinoma (ACC, $n = 9$), undifferentiated carcinoma ($n = 6$), and others ($n = 6$) (Table 1).

RT was given to 13 patients. Three of the 13 patients received IMRT and the remaining 10 patients were administered 3DCRT. Median doses were 66 Gy (range, 66–70 Gy). Fifty-two patients received PBT, with median doses of 65 GyE (range, 60–70 GyE). A total of six patients had clinically positive cervical lymph nodes at the beginning of treatment. Three of six patients underwent a neck dissection and the remaining three patients received complete neck irradiation in the definitive setting.

Systemic chemotherapy

As the present data was compiled over a 10-year period, several treatment methods were used in our study. A total of 31 patients received chemotherapy in addition to radiation therapy. The chemotherapy regimens are listed in Table 2.

Treatment outcomes

Median interval between the end of treatment and radiological response evaluation was 9.5 weeks (range, 2–27 weeks). In the radiological response evaluation within 6 months, CR was achieved in 10 (15%) of the 65 patients. With a median follow-up period of 51.6 months (range, 25–125 months), the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively (Fig. 1). Loco-regional

Table 1. Patient characteristics (N = 65)

Characteristic		N
Age (range)		59 yrs (21-83 yrs)
Gender (male/female)		39/26
Primary site	Nasal cavity	43
	Ethmoidal sinus	11
	Maxillary sinus	5
	Sphenoid sinus	4
	Other site	2
Tumor type	ONB	20
	SCC	15
	ACC	9
	Melanoma	9
	Undifferentiated	6
	Others	6
T stage	T1 (Kadish A)	1
	T2 (Kadish B)	7
	T3	4
	T4 (Kadish C)	53
N stage	N0	59
	N1	3
	N2	3

Abbreviations: ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; SCC, squamous cell carcinoma; Undif, undifferentiated carcinoma

Table 2. Treatment methods and radiation schedules

Treatment			N
Chemotherapy	IC regimen	DOC + CDDP + TS-1	12
		CDDP + 5-FU	1
		CDDP + VP-16(+ADM)	2
		DOC + CPT-11	6
		none	44
	CRT regimen	CDDP	15
		CDDP + 5-FU	4
		5-FU	1
		DOC + CPT-11	1
		none	44
Radiotherapy	Modality	Proton	52
		Photon	12
		Electron	1
	RT dose schedule	60 GyE/15 fr	7
		65GyE/26fr	41
		66 GyE/33 fr	8
		70 GyE/28 fr	1
		70 Gy/33 fr	1
		70 GyE/35 fr	7

Abbreviations: ADM, doxorubicin; CPT-11, irinotecan; CRT, chemoradiotherapy; CDDP, cisplatin; DOC, docetaxel; 5-FU, 5-fluorouracil; IC, induction chemotherapy; TS-1, tegafur-gimeracil-oteracil; VP-16, etoposide

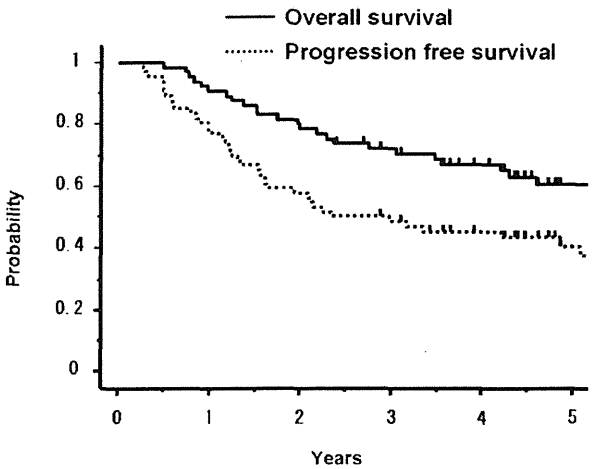

Fig. 1. PFS and OS curves of all patients. With a median follow-up period of 51.6 months, the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively.

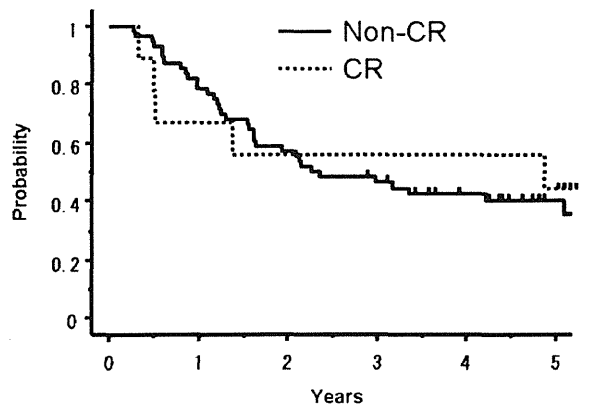

Fig. 2. PFS curves of all patients based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 55.6% in the patients whose response was CR and that of those whose response was non-CR was 46.4%, respectively ($P = 0.643$).

progression was observed in 52.3% of patients and distant metastasis was developed in 12.3% of patients. In the patients who achieved CR, the 3-year PFS rate was 55.6% and that of those whose responses were non-CR was 46.4%, respectively, which did not represent a statistically significant difference ($P = 0.643$) (Fig. 2).

In the patients whose histology was SCC, the 3-year PFS rate was 80.0% in the patients who achieved CR ($n = 6$) and 10.0% in those whose responses were non-CR ($n = 9$). The difference between patients with CR and those with non-CR was borderline significant ($n = 0.051$) (Fig. 3).

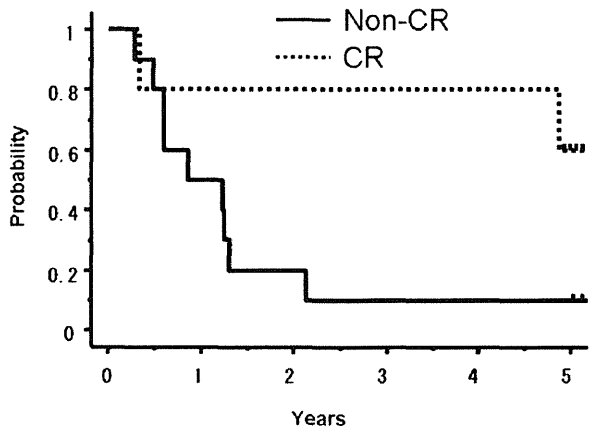

Fig. 3. PFS curves of the patients whose histology was SCC based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 80.0% in the patients who achieved CR and 10.0% in those whose responses were non-CR. The difference between patients with CR and those with non-CR was borderline significant ($P = 0.051$).

DISCUSSION

In the present retrospective study, we demonstrated that radiological response evaluation within 6 months after radiation therapy with or without chemotherapy in patients with malignancies of the nasal cavity or paranasal sinuses did not have a significant impact on prognosis such as PFS when we analyzed all patients included whose histologies were SCC and non-SCC. However, the results of this study demonstrated that the difference in the 3-year PFS of the SCC patients between those with CR and those with non-CR was borderline significant (80% vs 10%). This raised the possibility that early radiological response might serve as a surrogate for treatment outcomes (PFS) especially in patients with SCC histology.

The optimal treatment of malignancies in the nasal cavity and paranasal sinuses is controversial. Existence of risk organs such as brain nerves and extension to skull base often makes it difficult to remove tumors totally, indicating that RT would be an effective approach for nasal cavity and paranasal sinus malignancies. The 5-year OS rate after RT with or without surgery ranged from 15% to 55% [1–6]. Regarding the clinical outcomes after PBT, several studies including a study from our institution demonstrated that 5-year OS ranged from 70–80%, although the histological types of patients analyzed were not homogenous. These results indicated that clinical outcomes were slightly better than those after conventional radiation therapy [9, 14, 15, 16]. The main advantages of radiation therapy for nasal cavity and paranasal malignancies are to preserve organs and their functions by delivering enough total dose to the tumors while sparing excessive doses to the adjacent

critical normal structures such as the brain, brainstem and the optic structures. Among radiotherapeutic approaches, PBT can provide higher doses to tumors compared with 3DCRT or IMRT because of the unique physical properties of PBT. The physical properties of protons are rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth and delivery [6, 15, 16].

The objective evaluation of tumor shrinkage is often considered a surrogate for survival [10, 17]. In esophageal cancer, endoscopic findings 4 or 6 weeks after concurrent chemoradiotherapy or RT alone have been used as a surrogate for survival [18, 19], while disease control rate and CR/partial response (PR) 8 weeks after registration are associated with longer survival in advanced non-small-cell lung cancer [17]. Initial loco-regional response is also important in radiotherapeutic outcomes of patients with head and neck SCC. However, the treatment response of nasal cavity or paranasal sinus malignancies, with the exception of SCC, appears to differ from those of other malignancies. The results of this study indicate that salvage treatment should be carefully considered in patients whose histologies are non-SCC, even if the patient does not achieve CR at the time of radiological response evaluation within 6 months. This raises the possibility that radiological response evaluation within 6 months after radiation therapy might not be optimal, especially in patients whose histologies are non-SCC, e.g. ONB, ACC or melanoma. However, early radiological response in patients whose histology was SCC would be important, similar to other SCCs of the head and neck cancer, such as hypopharyngeal cancer. There are a few reports regarding the optimal timing of radiological evaluation using CT or MRI after radiotherapy. Hermans *et al.* suggested using follow-up CT at 8–12 weeks after completion of radiotherapy with larynx and hypo pharynx [20]. In addition, response evaluation at eight weeks after the completion of treatment was often adopted in clinical trials for head and neck cancer [21, 22]. This might suggest that the optimal timing of radiological response evaluation in patients with nasal and paranasal sinus malignancies appears to be different according to the histological type, although the number of patients analyzed in this study is still not enough to draw a definite conclusion. There is a limit to the ability of morphological images, such as CT or MRI, to evaluate tumor shrinkage after radiotherapy of the nasal cavity or paranasal sinus malignancies without SCC; it is necessary to evaluate with dynamic images such as PET-CT.

Recently, there have been many studies that have demonstrated the clinical usefulness of new imaging modalities, particularly PET-CT in response evaluation for RT with or without chemotherapy [17, 23]. In our clinical practice, the changes in positivity of PET-CT before and after RT provided helpful information regarding the decisions for salvage treatment. In the present study, however, we could not evaluate local response using PET-CT in addition to CT and MRI, because PET-CT before and after treatment was only available in a limited number of patients. Hence, investigation regarding the clinical usefulness of PET-CT including other new imaging modalities in response evaluation for nasal and paranasal malignancies other than SCC is warranted in future prospective trials.

Limitations of our study are as follows. First, the number of patients according to histological type was small, resulting in insufficient statistical differences between each group, and second, the optimal response evaluation of lymph nodes metastases could not be sufficiently discussed.

In conclusion, the results of this study demonstrated that radiological response evaluation within 6 months did not provide significant impact on prognosis when analysis included all histology such as ONB, although early radiological response within 6 months after radiation therapy had a borderline significant impact on treatment outcomes (PFS) for nasal and paranasal malignancies in patients with SCC histology. Hence, further study is warranted to ensure the impact of histological type on the outcomes of early radiological response evaluation.

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