Single-institute comparison of the efficacy of systemic chemotherapy for oesophagogastric junction adenocarcinoma and stomach adenocarscinoma in a metastatic setting

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ABSTRACT

Background Different approaches are used to treat resectable tumours in patients having adenocarcinoma at the oesophagogastrointestinal junction (EGJ) or in the stomach. However, there is limited information about treatment efficacy for patients at metastatic stage. A recent molecular analysis of upper gastrointestinal tract adenocarcinoma revealed that the anatomical location can influence the molecular backgrounds of tumours. This study sought to elucidate whether different therapeutic approaches should be used for EGJ tumours relative to those in the stomach.
Methods This retrospective cohort study was conducted at a single institute in Japan. Patients having metastatic or recurrent adenocarcinoma in the EGJ or stomach who underwent platinum doublet chemotherapy between January 2007 and August 2014 were enrolled. Patients in the EGJ tumour group had tumours having an epicentre within 2 cm proximal or 5 cm distal to the estimated anatomical EGJ and cardia.
Results Among 378 consecutively enrolled patients, 61 were grouped into the EGJ group and the remainder comprised the stomach group. The EGJ group had more men and lower incidence of diffuse type and Borrmann type IV tumours and peritoneum metastasis compared with the stomach group. The median overall survival of patients in the EGJ and stomach groups was similar (17.3 months (95% CI 13.5 to 23.2) vs 14.5 months (95% CI 13.3 to 16.4)). No statistically significant difference was observed in progression-free survival. Although the overall postprogression survival differed significantly between the EGJ and stomach groups (8.2 months (95% CI 5.7 to 12.7) vs 7.1 months (95% CI 6.1 to 7.8)), on grouping patients by histological type, the two groups exhibited similar postprogression survival. Multivariate analysis demonstrated that diffuse-type histology, higher serum CA19-9 levels and neutrophil to lymphocyte ratios were independent poor prognostic factors.
Conclusions Different clinicopathological features of EGJ adenocarcinoma were not associated with clinical outcomes of platinum doublet chemotherapy. Histological subtype rather than anatomical location has more significance for treatment decisions for advanced gastric cancers.

Key questions

What is already known about this subject?

► Due to technical and anatomical factors, different treatment approaches using endoscopic or surgical resections have been used for oesophagogastrointestinal junction (EGJ) and stomach adenocarcinoma. However, there are limited data to indicate whether these different treatments approaches are needed.
► A recent comprehensive molecular analysis of upper gastrointestinal tract adenocarcinoma conducted by The Cancer Genome Atlas revealed that the anatomical location could, to some extent, reflect differences in the molecular background of the tumour.
► In metastatic colorectal cancers, the location of the primary tumour is considered to be a useful biomarker for choosing the optimal molecular target agent for initial treatment. However, for advanced gastric cancers, the significance of tumour location for treatment type remains unclear.

What does this study add?

► Despite several disparities in clinicopathological features of EGJ and stomach adenocarcinoma, no differences in clinical outcome were observed in this study cohort.
► This retrospective study using actual patient data demonstrated that standard chemotherapy for stomach adenocarcinoma had a similar efficacy for EGJ adenocarcinoma in a metastatic setting.
► Multivariate analysis showed that patients having a diffuse-type histology had a significantly poorer prognosis in treatment of advanced gastric cancers compared with patients having other histology types.

INTRODUCTION

Gastric carcinoma (GC) is estimated to be the fifth most common malignancy and the third leading cause of cancer death worldwide.[1] Over the past decade, because of the *Helicobacter pylori* (HP) infection rate decrease,

Key questions

How might this impact clinical practice?
► This study provides data concerning metastatic EGJ adenocarcinoma that could provide valuable insights into effective treatments.
► The present study concluded that histological features rather than anatomical location should be considered when selecting therapies for advanced gastric cancers.

eradication therapy for HP and environmental change such as the spread of refrigerator and water and sewer services, a shift in the incidence trend from the distal gastric towards the proximal site was reported.[2] The incidence of oesophagogastrointestinal junction (EGJ) adenocarcinoma has been increasing gradually not only in Western countries but also in Japan.[3–5] Moreover, since EGJ adenocarcinoma is associated with lifestyle habits, the incidence of EGJ adenocarcinoma would be expected to increase in other Eastern countries. The development of a therapeutic strategy for EGJ adenocarcinoma is one of the important issues being actively discussed among experts.

Due to anatomical reasons, some technically different approaches, such as an intrathoracic approach for lymphadenectomy, have been adapted for surgically resectable stage adenocarcinomas, depending on whether they involve the EGJ or the stomach. In addition, several trials using multimodal treatments such as perioperative chemotherapy or chemoradiotherapy were performed to develop the optimal therapeutic strategy for EGJ adenocarcinoma in the locally advanced stage.[6–8] In a metastatic setting, the impact of primary tumour origin (oesophageal, EGJ or stomach adenocarcinoma) was assessed using combined data from four randomised controlled trials conducted in Western countries. These data showed that there were no significant differences in overall survival (OS) and response rate of patients with EGJ adenocarcinoma compared with patients having either oesophageal or stomach adenocarcinomas.[9] However, as is already known, there are several differences in aetiology, clinicopathological features and therapeutic treatment of GC between Western and Eastern countries.[10] There are few available data to indicate whether a different treatment should be developed for EGJ adenocarcinoma compared with stomach adenocarcinoma in Eastern countries, including Japan.

Moreover, a recent comprehensive molecular analysis of upper gastrointestinal tract adenocarcinoma revealed that, to some extent, the anatomical location could reflect the differences in the molecular background.[11] Additionally, tumour location is recognised as a useful biomarker in treatment selection because it can act as a surrogate for a molecular profile in the treatment of the colorectal cancers. Therefore, recent treatment guidelines of metastatic colorectal cancer suggest that the sidedness of the primary tumour should be considered when choosing the initial treatment.[12 13]

Herein, we evaluated the efficacy of standard chemotherapy for stomach adenocarcinoma to treat patients with EGJ adenocarcinoma to elucidate whether these disease types require different therapeutic strategies.

METHODS
Patients
This was a retrospective study conducted at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan. We reviewed the medical records of patients treated at our institution between January 2007 and August 2014. Based on endoscopic findings, the distal end of the oesophageal palisade vessels was regarded as the estimated anatomical site of the EGJ. We classified tumours having an epicentre within 2 cm proximal or 5 cm distal to the estimated anatomical EGJ and cardia into the EGJ tumour group, consistent with the Japanese Gastric Cancer Association definition.[14] Patients meeting all of the following criteria were enrolled in the present study: (1) patients with histologically proven unresectable advanced or recurrent EGJ and stomach adenocarcinoma, (2) patients who underwent platinum doublet chemotherapy, (3) patients who underwent no prior systemic chemotherapy or radiotherapy for the metastatic setting, and (4) patients who provided written informed consent. We excluded patients who had only cytology positive (CY+) but not other distant metastasis, underwent R0 metastasectomy, had other types of advanced tumours diagnosed within the prior 5 years, and had early recurrence within 6 months after neoadjuvant or adjuvant chemotherapy. Medical records were reviewed to obtain clinical data about age, sex, histological appearance (Lauren and WHO classification), primary tumour site, laboratory data, surgery, macroscopic type, TNM stage, progression and survival outcomes. Clinical staging was conducted per the Japanese Classification of Gastric Carcinoma, the third English edition.

Treatment
The standard regimen for first-line treatment of GC in Japan has changed over time. After the conclusion of the SPIRITS (S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer) trial in 2007, S-1 plus cisplatin (SP) was the standard first-line treatment regimen for patients with GC.[15] In 2011, the ToGA (Trastuzumab for Gastric Cancer) trial demonstrated the efficacy of trastuzumab for treating human epidermal growth factor receptor type 2 (HER2)-positive GC. Since then, trastuzumab with capecitabine plus cisplatin has been administered to patients with HER2-positive GC.[16] Recently, oxaliplatin has been approved for the treatment of unresectable advanced or recurrent GC in Japan. Since 2014, S-1 plus oxaliplatin (SOX) has commonly been used to treat patients with HER2-negative GC at our institution.[17] The treatment schedule and dose are the same as those reported in pivotal clinical trials.

Statistical analysis

OS was defined as the time from the start of chemotherapy to the time of death or latest follow-up. Progression-free survival (PFS) was defined as the time from the start of chemotherapy to death or the first day of disease progression as determined by imaging or clinical examination. Postprogression survival (PPS) time was defined as the time from disease progression to the time of death or latest follow-up. In patients having measurable lesions, the overall response rate (ORR) and disease control rate (DCR) were calculated according to the Response Evaluation Criteria in Solid Tumors or RECIST V.1.1. The cut-off day was 30 April 2019. We used Kaplan-Meier survival curves to calculate the OS, PFS and PPS, and used the log-rank test to compare the clinical outcomes of systemic chemotherapy (EGJ vs stomach). Multivariate analysis was conducted using a Cox regression model to assess the significance of the primary tumour location. Covariates with a p value of <0.05 in the univariate analysis and primary tumour location were included in the multivariate analysis. We compared categorical characteristics using two-sided Fisher's exact tests. For all analyses, p values of <0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism V.7.03 for Windows (GraphPad Software, San Diego, California, USA).[18]

RESULTS

Patient characteristics

Between January 2007 and August 2014, 447 patients with unresectable advanced EGJ or stomach adenocarcinoma were administered platinum doublet chemotherapy in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan. In 14 patients, CY+ was the only factor indicating incurable disease. Seventeen patients had undergone R0 metastasectomy; 5 patients had prior radiotherapy or systemic chemotherapy; 5 patients had early tumour recurrence within 6 months after adjuvant chemotherapy; and 9 patients had other types of advanced tumours. Seventeen patients started treatment or underwent most of their treatment at another hospital, and thus we could not obtain sufficient clinical data. Therefore, we excluded these patients from the analysis. Moreover, because of lack of information about the primary tumour site, two patients were excluded. Ultimately, 378 consecutive patients were
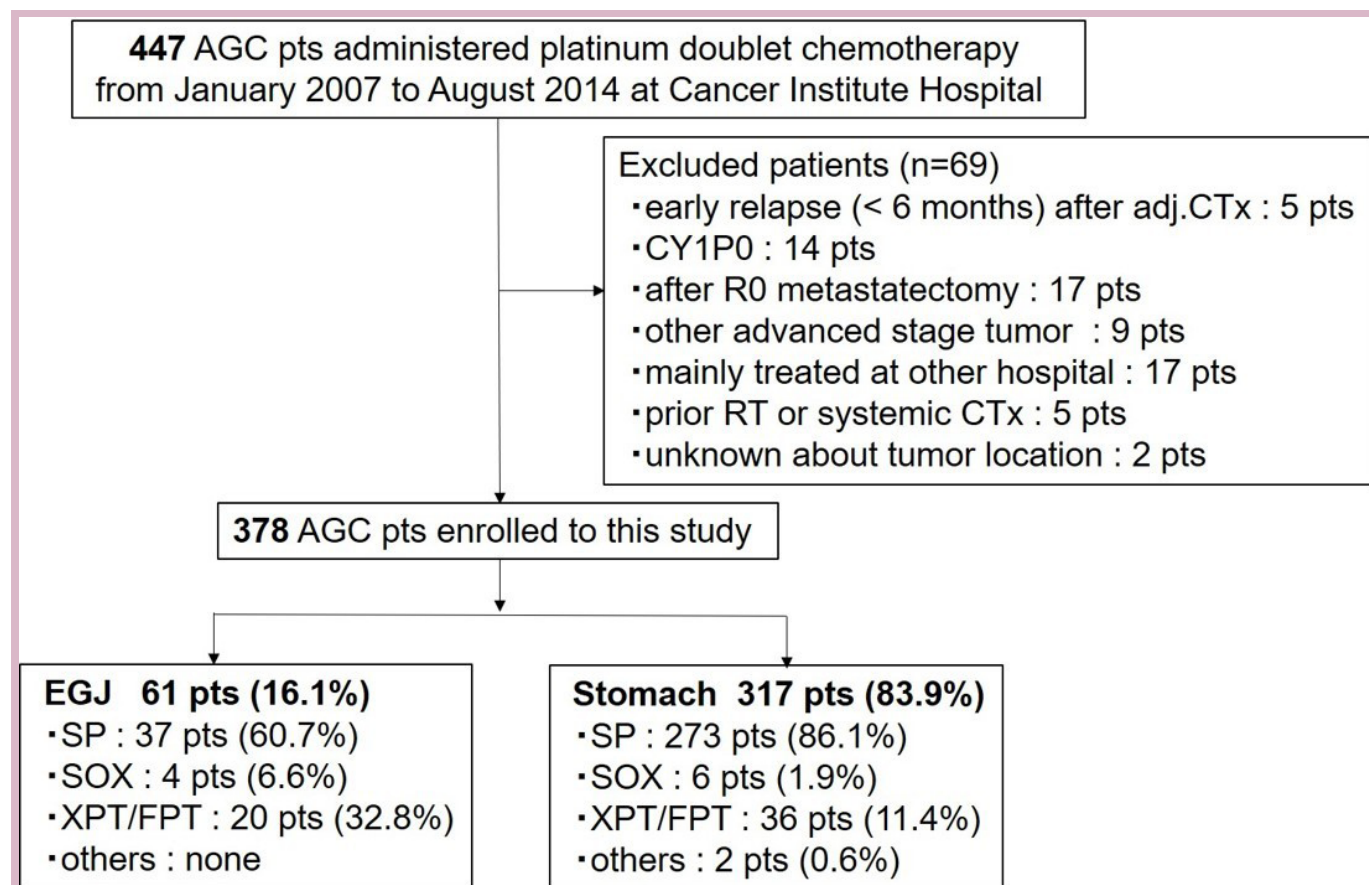

Figure 1 Figure 1Study schema of the patient selection. AGC, advanced gastric cancer; CTx, chemotherapy; RT, radiation therapy; pts; patients; EGJ, esophagogastric junction; SP, S-1 plus cisplatin; SOX, S-1 plus oxaliplatin; XPT, Capecitabine, cisplatin plus trastuzumab; FPT, fluorouracil, cisplatin plus trastuzumab .

enrolled in this study (figure 1). The patient characteristics are listed in table 1. Among these patients, 61 (16.1%) were assigned to the EGJ tumour group and the remaining 317 (83.9%) were assigned to the stomach group. Several disparities in clinicopathological features were observed between the groups. The EGJ group of patients had a higher proportion of men (83.6% vs 61.5%) and fewer diffuse-type tumours (47.5% vs 64.8%), Borrmann type IV tumours (4.9% vs 26.5%) and peritoneum metastases (18.0% vs 42.3%) compared with patients in the stomach group. Among the 217 patients who underwent HER2 testing, 22 (36.1%) tested positive in the EGJ group and 48 (15.1%) in the stomach group, and the difference was statistically significant. In addition, Eastern Cooperative Oncology Group performance status and number of metastatic lesions were also statistically significantly different between the EGJ and stomach groups.

Clinical outcomes (OS, progression-free survival, PPS time and objective response rate)

All treatment follow-ups were completed by 28 February 2019. The median follow-up time of the surviving patients by the cut-off date was 61.7 months, and except for three patients, all were followed up for more than 18 months after enrolment. At the date of analysis, 351 patients (92.9%) had died and 14 (3.7%) were alive without disease progression. The median OS rates in the EGJ and stomach groups were 17.3 months (95% CI 13.5 to 23.2) and 14.5 months (95% CI 13.3 to 16.4), respectively. A statistically significant difference in OS was not observed between the EGJ and stomach group (figure 2A). Among the 374 patients who discontinued their first-line treatment, 323 (86.4%) had disease progression at the cut-off date. There were no statistically significant differences in PFS between the EGJ (median: 7.4 months, 95% CI 6.3 to 10.1) and the stomach (median: 7.3 months, 95% CI 6.2 to 8.2) groups, respectively (figure 2B). The ORR of the EGJ tumour group (61.2%, 95% CI 46.2% to 74.8%) was greater than that of the stomach group (52.6%, 95% CI 44.9% to 60.3%), but a statistically significant difference was not observed (table 2). In terms of the prognosis after disease progression, there was a statistically significant difference between the EGJ and stomach groups. The median PPS of the EGJ group (n=54) was 8.2 (95% CI 5.7 to 12.7) months, and that of the stomach group was 7.1 (95% CI 6.1 to 7.8) months (figure 3A).

Univariate and multivariate analyses for OS

The results of univariate and multivariate analyses are summarised in table 3. Univariate analysis revealed that younger age (<60 years old), diffuse-type histology, no prior gastrectomy, trastuzumab administration, multiple metastases (≥2), liver metastases, elevated serum alkaline phosphatase level (>upper limit of normal (ULN)), elevated serum CA19-9 level (>ULN), elevated serum CA125 level (>ULN) and higher neutrophil to lymphocyte ratio (NLR) level (≥3.0) were associated with a significantly poorer prognosis (table 3). Multivariate analysis

demonstrated that diffuse-type histology, elevated serum CA19-9 level (>ULN) and higher NLR level (≥3.0) had independent prognostic values for shorter survival (table 3). Neither the location of the primary tumour (EGJ or stomach) nor delivery of trastuzumab for advanced HER2-positive GC had a significant association with prognosis.

Subsequent treatment

By the cut-off date, all patients (n=61) in the EGJ group and 308 of 317 patients (97.2%) in the stomach group had discontinued their first-line chemotherapy. Disease progression was the main reason for discontinuation in 54 patients in the EGJ group (88.5%) and 269 in the stomach group (87.3%), respectively. Fifty-one (83.6%) in the EGJ group and 225 (73.1%) in the stomach group underwent subsequent therapy. Although the proportions of patients undergoing subsequent therapy were similar between the EGJ (75.9%) and the stomach (70.7%) groups among those with diffuse-type histology, a larger difference, trending towards statistical significance (p=0.065), was observed between the EGJ (90.6%) and the stomach (77.8%) groups among those with intestinal-type histology. Additionally, there were no statistically significant differences in PPS between the EGJ and stomach groups among the patients with the same histological subtype (figure 3B). Twenty-four patients underwent gastrectomy after systemic chemotherapy, and only 9 patients underwent conversion surgery because of good response to the chemotherapy. Among the 268 patients who underwent second-line chemotherapy, 30 (61.2%) in the EGJ group and 141 (64.4%) in the stomach group were administered taxane-based chemotherapy. Twenty-one patients received anti-HER2 therapy in the second-line setting.

DISCUSSION

In the present study, there were several differences in the clinicopathological features of patients having adenocarcinoma in the EGJ and those with stomach adenocarcinoma. Patients with EGJ adenocarcinoma were more likely to be male, more likely to be positive for HER2, and less likely to have diffuse-type histology or have metastasis to the peritoneum relative to patients with stomach adenocarcinoma. These features were consistent with previous reports on EGJ adenocarcinoma.[4 19] Despite these differences, the efficacy of platinum doublet chemotherapy in the first-line treatment setting was similar for patients with EGJ and stomach adenocarcinoma as evidenced by the similar median OS (17.3 months (95% CI 13.5 to 23.2) vs 14.5 months (95% CI 13.3 to 16.4)). The OS survival time seen for the present study was comparable with those of phase III Japanese trials conducted during the same period as our study. In particular, the JCOG1013 trial reported a median OS of 15.3 months for the SP group (n=371).[20] Moreover, the median OS for patients with differentiated-type disease reached 17.5 months in

Table 1 Patient characteristics of EGJ and stomach adenocarcinoma (N=378)

	EGJ	Stomach	
	(n=61)	**(n=317)**	**P value**
Age (years)			
Median (range)	61 (38–77)	62 (16–79)	
Sex, n (%)			
Male	51 (83.6)	195 (61.5)	**0.001**
Female	10 (16.4)	122 (38.5)	
ECOG, n (%)			
PS 0	39 (67.2)	252 (80.1)	**0.014**
PS 1	18 (29.5)	59 (18.6)	
PS 2	1 (1.6)	3 (9.5)	
Unknown	3 (4.9)	3 (9.5)	
Lauren classification, n (%)			
Intestinal	32 (52.5)	111 (35.2)	**0.014**
Diffuse	29 (47.5)	204 (64.8)	
Unknown	0 (0.0)	2 (0.6)	
Borrmann type IV, n (%)			
Yes	3 (4.9)	84 (26.5)	**<0.001**
No	58 (95.1)	233 (73.5)	
HER2 status, n (%)			
Positive	22 (36.1)	48 (15.1)	**0.012**
Negative	23 (37.7)	124 (39.1)	
Unknown	16 (26.2)	145 (45.7)	
Extent of disease, n (%)			
Metastatic	47 (77)	274 (86.4)	0.077
Recurrent	14 (23)	43 (13.5)	
Prior gastrectomy, n (%)			0.549
Yes	17 (27.9)	103 (32.5)	
No	44 (72.1)	214 (67.5)	
Measurable lesion, n (%)			**0.002**
Yes	48 (78.7)	180 (56.8)	
No	13 (21.3)	137 (43.2)	
Metastatic site, n (%)			
Liver	20 (32.8)	87 (27.4)	0.439
Distant LN	25 (41)	94 (29.5)	0.097
Peritoneum/ovary	11 (18)	134 (42.3)	**<0.001**
Lung	8 (13.1)	14 (4.4)	**0.015**
Number of mestastases, n (%)			
2>	9 (58.1)	226 (71.2)	**<0.001**
≥2	52 (41.9)	91 (28.7)	
Treatment regimen, n (%)			**<0.001**
SP	37 (60.7)	273 (86.1)	
SOX	4 (6.6)	6 (1.9)	
XPT/FPT	20 (32.8)	36 (11.4)	
Others	0 0	2 (0.6)	

boldfaced P value means significant (<0.05)
ECOG, Eastern Cooperative Oncology Group; EGJ, oesophagogastrointestinal junction; FPT, fluorouracil, cisplatin plus trastuzumab; HER2, human epidermal growh factor type 2; LN, lymph node; PS, performance status; SOX, S-1 plus oxaliplatin; SP, S-1 plus cisplatin; XPT, capecitabine, cisplatin plus trastuzumab.
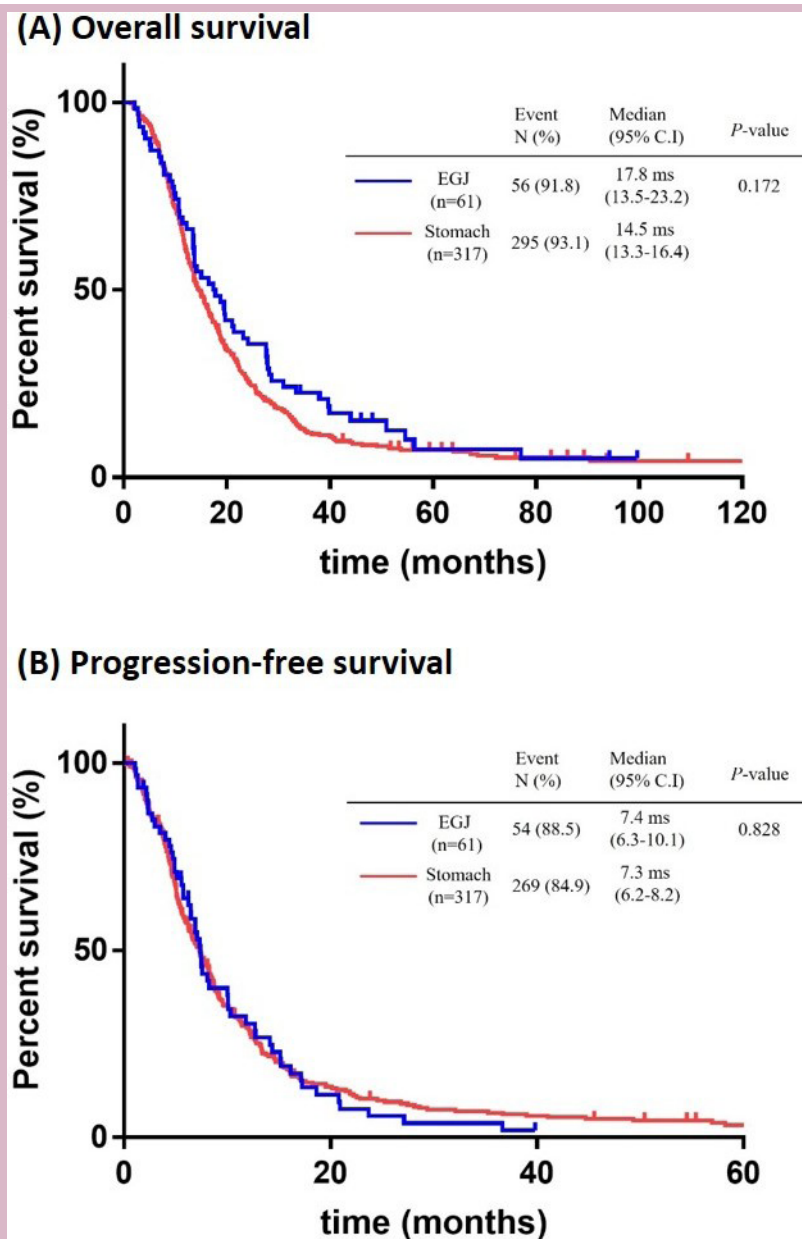
Figure 2 Figure2 (A) Comparison of OS drawn by Kaplan-Meier between EGJ (blue line) and stomach (red line) (B) Comparison of PFS drawn by Kaplan-Meier between EGJ (blue line) and stomach (red line). OS' overall survival; PFS, progression-free survival; EGJ, esophagogastric junction.

the doublet group. Based on these findings, the survival data of the present study are reproducible and not due to selection bias at our institute.

In terms of the molecular characteristics, the EGJ group included more patients with HER2-positive tumours, which has been reported elsewhere.[21] Our study confirmed that EGJ adenocarcinoma has different clinicopathological features from those of stomach adenocarcinoma in metastatic or recurrent GCs. In this study, the Kaplan-Meier curves of PFS were almost identical when comparing the EGJ and stomach groups. Moreover, both ORR and DCR were similar between the two groups, as was OS. The subgroup analyses of previous trials had demonstrated no interaction of the primary tumour

location with the efficacy of platinum doublet chemotherapies between the EGJ and stomach adenocarcinoma in spite of HER2 status.[16 22 23] These findings could support our results. Thus, the present study confirmed that the standard chemotherapy for stomach adenocarcinoma had similar efficacy for EGJ adenocarcinoma in the Japanese patient population.

A different treatment outcome was observed in PPS between the EGJ and stomach adenocarcinoma groups. However, this difference can be explained mainly by disparity in the histological subtype rather than the anatomical location. The difference of PPS between the EGJ and stomach groups was no longer significant when patients with the same histological subtype were

Table 2 Response rate and DCR

	Oesophagogastro intestinal junction (n=49)	Stomach (n=171)	
	n (%)	n (%)	P value
Complete response	1 (2.0)	4 (2.3)	
Partial response	29 (59.2)	86 (50.3)	
Stable disease	10 (20.4)	42 (24.6)	
Progressive disease	7 (14.3)	29 (17)	
Not evaluable	2 (4.1)	10 (5.8)	
Overall response rate (95% CI)	61.20% (46.2 to 74.8)	52.60% (44.9 to 60.3)	0.33
DCR (95% CI)	81.60% (68.0 to 91.2)	77.20% (70.2 to 83.3)	0.562

DCR, disease control rate.

compared (figure 3B). Furthermore, multivariate analysis including primary tumour location identified diffuse-type histology as one of the independent prognostic factors in this cohort. Therefore, histological subtype should be weighed more heavily than anatomical location in treatment development for metastatic or recurrent advanced GCs. For locally advanced-stage EGJ tumours, intensive treatments, such as triplet regimen or chemoradiation therapy, have been developed for the further improvement of clinical outcomes.[7 8] The docetaxel, oxaliplatin and fluorouracil/leucovorin or FLOT regimen is established as the standard treatment of locally advanced EGJ and stomach adenocarcinomas in Western countries.[24] However, in the JCOG1013 trial, the addition of docetaxel to cisplatin and S-1 did not increase OS in Japanese patients with advanced gastric cancer.[20] The doublet regimen has good safety and efficacy, and there are now several treatment options for subsequent treatments.

Therapeutic development of more intensive therapy is not to be recommended in metastatic or recurrent EGJ adenocarcinoma.

Additionally, recent molecular analyses revealed that there are distinct molecular changes underlying these differences.[11] The Cancer Genome Atlas (TCGA) suggests four molecular subtypes of stomach adenocarcinoma based on their comprehensive molecular analyses: tumours positive for Epstein-Barr virus, microsatellite instability (MSI), genomically stable and chromosomal instability (CIN). Among these subtypes, CIN was characterised by a higher somatic copy number alteration, especially focal amplification of the receptor tyrosine kinase genes. More tumours of the CIN subtype were found in the vicinity of the EGJ than of the distal stomach. On the other hand, MSI-H tumours, which often have deficiency of mismatch repair and are expected to be highly sensitive to the immune checkpoint inhibitors, were
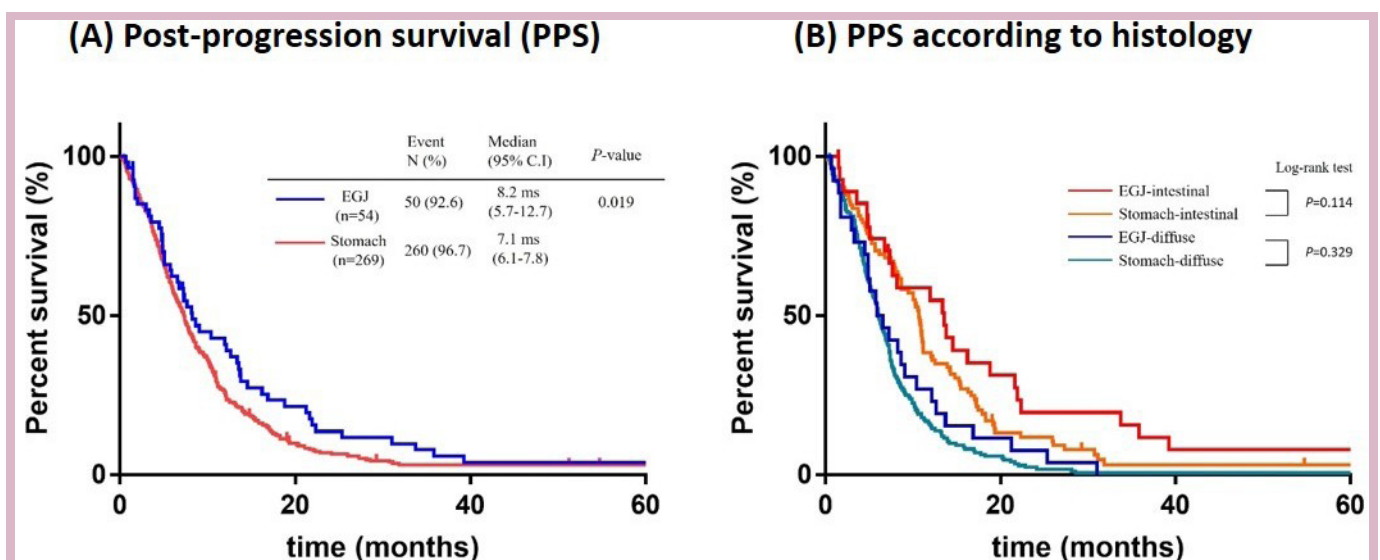

Figure 3 (A) Comparison of PPS drawn by Kaplan-Meier between EGJ (blue line) and stomach (red line). (B) Comparison of PPS drawn by Kaplan-Meier between EGJ and stomach according to the histological subtype. EGJ-intestinal (red line), EGJ-diffuse (blue-line), stomach-intestinal (orange line) and stomach-diffuse (light green line). PPS, post-progression survival; EGJ, esophagogastric junction.

Table 3 Univariate and multivariate analysis for survival

Variant	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR 95% CI	P value
Age (years): <60 versus ≤60	1.0 versus 0.79 (0.64 to 0.99)	0.038	1.0 versus 0.81 (0.54 to 1.21)	0.308
ECOG PS: 0 versus 1 or 2	1.0 versus 1.23 (0.96 to 1.59)	0.105		
Sex: male versus female	1.0 versus 0.90 (0.72 to 1.12)	0.351		
Histology: intestinal versus diffuse	1.0 versus 1.61 (1.29 to 2.01)	**<0.001**	1.0 versus 1.68 (1.12 to 2.51)	**0.038**
Location: stomach versus EGJ	1.0 versus 0.80 (0.60 to 1.07)	0.14	1.0 versus 0.89 (0.47 to 1.66)	0.704
Borrmann: no type IV versus type IV	1.0 versus 1.19 (0.93 to 1.53)	0.16		
HER2 status: negative versus positive	1.0 versus 0.77 (0.57 to 1.04)	0.092		
Distant of disease: metastatic versus recurrent	1.0 versus 0.78 (0.57 to 1.05)	0.098		
Prior gastrectomy: no versus yes	1.0 versus 0.77 (0.61 to 0.97)	**0.023**	1.0 versus 0.71 (0.43 to 1.15)	0.164
Trastuzumab (first): no versus yes	1.0 versus 0.66 (0.48 to 0.90)	**0.008**	1.0 versus 0.65 (0.08 to 5.11)	0.68
Measurable lesion: no versus yes	1.0 versus 1.02 (0.82 to 1.27)	0.839		
Number of metastatic sites: <2 versus ≤2	1.0 versus 1.48 (1.15 to 1.89)	**<0.001**	1.0 versus 1.00 (0,66 to 1.54)	0.981
Metastatic site				
Liver: no versus yes	1.0 versus 1.47 (1.17 to 1.86)	**0.001**	1.0 versus 1.49 (0.93 to 2.38)	0.1
Lung: no versus yes	1.0 versus 0.97 (0.63 to 1.51)	0.904		
Distant LN: no versus yes	1.0 versus 1.10 (0.87 to 1.38)	0.43		
Peritoneum/ovary: no versus yes	1.0 versus 1.15 (0.93 to 1.42)	0.209		
Serum ALP: ≤ULN versus <ULN	1.0 versus 1.55 (1.20 to 2.00)	**<0.001**	1.0 versus 0.75 (0.48 to 1.17)	0.211
Serum LDH: ≤ULN versus <ULN	1.0 versus 1.27 (0.98 to 1.64)	0.073		
Serum CEA: ≤ULN versus <ULN	1.0 versus 1.24 (1.00 to 1.55)	0.054		
Serum CA19-9: ≤ULN versus <ULN	1.0 versus 1.46 (1.17 to 1.82)	**<0.001**	1.0 versus 1.94 (1.31 to 2.87)	**<0.001**
Serum CA125: ≤ULN versus <ULN	1.0 versus 1.41 (1.03 to 1.92)	**0.03**	1.0 versus 1.36 (0.91 to 2.05)	0.138
NLR: <3.0 versus ≤3.0	1.0 versus 1.58 (1.27 to 1.95)	**<0.001**	1.0 versus 1.55 (1.05 to 2.32)	**0.023**

ALP, alkaline phosphatase; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; EGJ, oesophagogastrointestinal junction; HER2, human epidermal growth factor type 2; LDH, lactate dehydrogenase; LN, lymph node; NLR, neutrophil to lymphocyte ratio; PFS, progression-free survival; PS, performance status; SP, S-1 plus cisplatin; ULN, upper limit of normal.

more prevalent at the distal side.[25 26] After the release of positive results for the Attraction-2 trial in 2017,[27] monotherapy with the anti-PD1 inhibitor nivolumab was used after second-line treatment in Japanese clinical practice. However, patients enrolled in the present study underwent the first-line treatment between 2007 and 2015, and quite a few in this cohort underwent immunotherapy. Actually, by 2017, only 12 patients in our study cohort were confirmed to be alive, and of these, only one patient could have received nivolumab as the third-line treatment. The

location of the primary tumour could have some associations with the clinicopathological and molecular characterisations. Recently, nivolumab combined with SOX/CapeOX has shown encouraging results as a first-line treatment for unresectable advanced or recurrent HER2-negative gastric cancer.[28] In the near immune-oncology era, differences in primary tumour location could indeed affect clinical outcomes.

In other cancers such as ovarian or breast cancer, tumours harbouring a mutation in genes involved in

homologous recombination repair deficiency (HRD) had an increased sensitivity to platinum-containing chemotherapy.[29 30] According to the molecular classification by TCGA, a putative BRCA (Breast Cancer Susceptibility Gene) mutational signature was relatively common in the CIN subtype, which is the most prevalent among EGJ tumours.[25] However, there is still controversy about whether patients with GC involving genetic alteration of HRD have higher platinum sensitivity.[31 32] In this study, patients in the EGJ group did not show increased sensitivity for platinum in terms of PFS or ORR compared with patients in the stomach group. These tumours with a high level of genomic scarring have been known to be a good target for poly (ADP-ribose) polymerase (PARP) inhibitors.[33] At the moment, because of the negative result in the GOLD (Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy) trial, PARP inhibitors are not approved for the treatment of advanced GCs. However, notably, the GOLD trial showed improvement of clinical outcomes in some patients with DNA damage repair deficiency even in GC.[34] Moreover, associations of HRD-related genes with GC have been reported in several studies, and this has received attention as a significant genomic alteration in these cancers.[35 36] Future precision medicine could show the value of the tumour location as a predictive marker in advanced GC.

This study has several limitations. First, more than two-thirds of the patients had not undergone gastrectomy prior to their chemotherapy. Thus, we had to define the tumour epicentre based on only endoscopic findings. It is very difficult to measure precisely the distance to the centre of the primary EGJ tumour by endoscopy. However, the classifications into the EGJ and stomach groups were based on the evaluations of at least two physicians who had similar findings. Second, patients enrolled in this study had been treated between 2007 and 2014 in our institute. During this period, there were two major practice-changing events: the approval of trastuzumab for HER2-positive GC and emerging evidence supporting late-line chemotherapy. As mentioned previously, the proportion of patients with HER2-positive GC is higher among patients with EGJ adenocarcinoma compared with patients with stomach adenocarcinoma. Pivotal clinical trials have demonstrated that the OS of patients treated with trastuzumab was numerically longer than that of patients without trastuzumab. However, in this study, significant differences were not observed according to HER2 status (positive vs negative) or timing of chemotherapy induction (before 2011 or after 2011). Third, nearly all patients had no major trouble with oral intake, and they were administered an S-1 or capecitabine-based regimen. Compared with pyloric stenosis, stenosis or obstruction caused by an EGJ tumour would interfere with treatment to a greater degree. Bypass surgery is more invasive, and the endoscopic stenting procedure, which limits the chemotherapy regimen, is more frequently performed for EGJ tumours than for distal GCs. This selection bias potentially affected the results. However, these patients would be a very limited population.

In conclusion, there were several disparities in clinicopathological features between EGJ and stomach adenocarcinomas, but these differences did not appear related to the clinical outcomes. Current data would suggest that histological subtype rather than anatomical location has more significance in the development of treatment for advanced GCs.

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