Prognostic factors in patients with advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy: a cohort study

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Abstract

Purpose

Prognostic factors for the survival of patients with advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy remain controversial. The aim of this study was to identify the clinical factors that predict prognosis in patients with advanced HER2-positive gastric cancer.

Methods

We retrospectively reviewed the medical records of HER2-positive gastric cancer patients treated with trastuzumab-based chemotherapy at our institution. Clinical features and laboratory test results that considered prognostic factors were re-examined. Overall survival (OS) was estimated using the Kaplan-Meier method. Univariate analysis was performed with the log-rank test and multivariate analysis was performed using Cox's proportional hazard regression model.

Results

A total of 133 patients with advanced HER2-positive gastric cancer were enrolled. The median OS in this cohort was 18.7 months. Four prognostic factors: visceral metastasis (lung or liver), levels of haemoglobin (Hb) (< 11.6 g/dL), lactate dehydrogenase (LDH) (> 222 mg/dL), and C-reactive protein (CRP) (> 0.14 mg/dl) were identified as independent prognostic factors. The patients were placed into three groups according to their number of prognostic factors. These included low (0,1), moderate (2,3), and high (4) risk factors. The OS was separated into three categories with a median OS of 32.0, 18.7 and 10.1 months respectively. Compared to the low-risk group, hazard ratios for the moderate- and high-risk groups were 1.75 and 3.49, respectively.

Conclusion

Visceral metastasis and abnormal Hb, LDH, and CRP levels were associated with unfavorable OS. These findings may be beneficial for the management of advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy.

Background

Gastric cancer is currently the third-most common cause of cancer-related deaths and the fifth most commonly diagnosed cancer worldwide [1]. The standard of care for advanced gastric cancer includes systemic chemotherapy with fluoropyrimidine plus platinum. However, the prognosis of advanced gastric cancer remains poor. The global median overall survival (OS), excluding Japan and Korea, is less than 1 year. Regional differences between Asian and Western countries are well known in terms of gastric cancer

etiology and clinicopathological features. Gastroesophageal junction cancer is more common in Western countries. On the other hand, distal stomach cancer with intestinal metaplasia due to *Helicobacter pylori* infection is more common in East Asia. These two presentations of the disease are associated with their different molecular profiles [2]. In addition, second- or third-line treatments are more prevalent in East Asia. This suggests a lack of efficacy of the first-line option an may explain the difference in prognoses observed throughout the world.

Prognostic factors assist in the prediction of a patient's outcome. They are beneficial for developing a treatment strategy and follow-up schedule. They are also helpful for obtaining informed consent prior to initiating chemotherapy. Several gastric cancer prognostic factors have been previously proposed [3, 4, 5] and are included in the Royal Marsden Hospital (RMH) index, Glasgow Prognostic Score (GPS), and Japan Clinical Oncology Group (JCOG) prognostic index. However, their true prognostic value has not yet been clearly established. Asian and Western disparities in the prognosis of advanced gastric cancer may be attributed to inconsistencies in the prognostic indexes used in various studies.

Human epidermal growth factor receptor 2 (HER2) is a driver oncogene that promotes cell proliferation and inhibits apoptosis. This results in the progression and metastasis of cancer [6]. It is overexpressed in breast and gastric cancers. HER2 overexpression accounts for up to 21% of advanced gastric cancer cases in Japan [7, 8, 9]. It displays specific characteristics including predominant intestinal types and an absence of peritoneal and hepatic metastasis compared to HER2-negative gastric cancer [7]. Therefore, treatment regimens for HER2-positive gastric cancer differ from those used for treating HER2-negative gastric cancer. Furthermore, the addition of the anti-HER2 agent trastuzumab to standard chemotherapy results in an improved outcome [10, 11]. Consequently, trastuzumab in combination with chemotherapy has become the standard therapy.

Despite the abovementioned differences, no data focusing on the evaluation of specific prognostic factors in patients with advanced HER2-positive gastric cancer treated with trastuzumab are currently available. Thus, the application of pre-existing prognostic factors to define proper treatment options for HER2-positive gastric cancer seems contradictory. The aim of this study was to identify the clinical factors that predict the prognosis of patients with advanced HER2-positive gastric cancer who were treated with trastuzumab-based chemotherapy.

Methods

Patients and study design

In this retrospective observational study, we enrolled patients with advanced or metastatic HER2-positive gastric cancer. These patients received trastuzumab-based chemotherapy as first-line chemotherapy in our institution between March 2011 and June 2016. All patients were histologically confirmed to have HER2-positive gastric or gastroesophageal junction adenocarcinoma. The clinical data evaluated in this study were as follows: sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS),

measurability, extent of disease, number of metastatic organs, number of metastatic lesions, presence of visceral metastasis, pathological type of gastric cancer, HER2 status, previous adjuvant chemotherapy, previous gastrectomy, the neutrophil-to-lymphocyte ratio (N/L) [12, 13, 14], hemoglobin (Hb), serum albumin (Alb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), C-reactive protein (CRP) [4, 15, 16, 17], carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19 − 9. These parameters have been investigated as prognostic survival factors [18]. The reference range values used for the cut-off points of these laboratory data were previously defined in our institution. The exception was the N/L ratio, which was dichotomized according to the median of the collected data. Clinical data and treatment outcomes were collected from electronic medical records. This study was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (IRB number 2017 − 1044).

HER2 evaluation

Immunohistochemistry scoring (IHS) and fluorescent in situ hybridization (FISH) were used as criteria for HER2 expression, as reported by Hoffman et al. [19] IHC 3 + was defined as positive, corresponding to strong complete or basolateral membranous staining in ≥ 10% of the neoplastic cells in surgical specimens, or strong complete or basolateral membranous staining of at least five cohesive cells in a biopsy. A test for HER2 gene amplification by FISH was performed If IHC was equivocal (2+). This corresponded to moderate/weak complete or basolateral membranous staining in ≥ 10% of the neoplastic cells in surgical specimens, or moderate/weak complete or basolateral membranous staining of at least five cohesive cells in a biopsy. When FISH results were positive (HER2/CEP17 ≥ 2), the patient was considered to be eligible for trastuzumab-based chemotherapy.

Treatments and treatment outcomes

Trastuzumab-based chemotherapy regimens included capecitabine and cisplatin (XP, capecitabine 1000 mg/m^2 administered orally b.i.d. for 14 days, followed by 7 days of drug rest, and cisplatin 80 mg/m^2 intravenously infused on day 1), fluorouracil and cisplatin (FP, fluorouracil 800 mg/m^2 per day administered by continuous intravenous infusion on days 1 to 5 of each cycle, and intravenous cisplatin 80 mg/m^2 on day 1), S-1, tegafur/gimeracil/oteracil, and oxaliplatin (SOX, S-1 administered orally b.i.d. for 14 days followed by 7 days of drug rest, at a dose according to the body surface area: 80 mg/day for ≤ 1.25 m^2, 100 mg/day for 1.25–1.5 m^2, and 120 mg/day for ≥ 1.5 m^2, and oxaliplatin 100 mg/m^2 or 130 mg/m^2 administered intravenously on day 1). Trastuzumab was administered intravenously at a starting dose of 8 mg/kg on day 1, followed by 6 mg/kg every 3 weeks. Trastuzumab-based chemotherapy was administered on a 3-week cycle. Each type of chemotherapy was continued until disease progression, unacceptable toxicity, or patient's refusal. The exception was cisplatin, which was discontinued after a maximum of six cycles. Objective responses, according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), were assessed using computerized tomography (CT) or magnetic resonance imaging every 6 to 8 weeks.

Statistical analysis

The OS was used as the primary endpoint. OS was defined as the date of initial treatment until death from any cause. If patients did not meet the endpoint prior to May 31, 2017, they were censored at the time of last contact. OS was assessed using the Kaplan-Meier method. Univariate log-rank analysis was used to assess potential prognostic factors for OS. Independent significant factors were investigated using Cox's proportional hazard regression model. This included only those clinical factors with a *p*-value < 0.05 in the univariate analysis. For the multivariate analysis, Akaike's information criterion [20] was chosen as the best fit for the regression model. Statistical significance was set at $p < 0.1$ and were considered significant. All statistical analyses were conducted using R (version 3.3.3;2017-03-06).

Results

Patient's demographics and treatment regimen

A total of 133 patients treated with trastuzumab-based chemotherapy between March 2011 and June 2016 were enrolled in the study. The baseline characteristics of the patients are summarized in Table 1. The median age was 65 years (range: 21–86 years), 68% were ECOG PS 0 and more than 70% of the patients had their primary tumor in the stomach. Almost all patients (95%) presented with metastatic disease and 86% of the patients had 1–2 metastatic organs. We categorized lung and liver metastases as visceral metastases according to the ToGA study [10]. Using this criterion, 58% of the patients were determined to have visceral metastasis. Among the patients with visceral metastasis, 75% had liver metastases. Histopathological types of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (The 14th Edition). A total of 68% of the patients had differentiated types such as papillary adenocarcinoma and tubular adenocarcinoma. The remaining patients had undifferentiated types, such as poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Most (86%) were scored as 3 + on IHC for HER2 status. Forty-five patients (34%) had a previous gastrectomy. Among them, 26 patients received S-1 for one year as adjuvant chemotherapy.

Table 1
Baseline characteristics of patients (n = 133)

Characteristics	N = 133 (%)
Sex	
Male	92 (69)
Female	41 (31)
Age	
Median age (yr)	65 (range: 21–86)
< 65	62 (47)
≥ 65	71 (53)
ECOG performance status	
0	90 (68)
1	42 (32)
2	1 (1)
Primary tumour site	
Stomach	97 (73)
Gastro-oesophageal junction	36 (27)
Measurable tumour	116 (87)
Extent of disease	
Locally advanced	7 (5)
Metastatic	126 (95)
Number of metastatic sites	
1–2	114 (86)
> 2	19 (14)
Number of metastatic lesions	
1–4	38 (29)
> 4	95 (71)
Visceral metastasis (lung or liver)	
Yes	77 (58)

ECOG Eastern Cooperative Oncology Group, *IHC* immunohistochemistry

Characteristics	N = 133 (%)
No	56 (42)
Type of gastric cancer	
Differentiated	90 (68)
Undifferentiated	43 (32)
HER2 status	
IHC 3+	114 (86)
IHC 2+/FISH positive	19 (14)
Previous chemotherapy	26 (20)
Previous gastrectomy	45 (34)
ECOG Eastern Cooperative Oncology Group, *IHC* immunohistochemistry	

Treatment regimens combined with trastuzumab are shown in Table 2. Most patients (71%) received cisplatin-based chemotherapy. Twenty-one patients (16%) received the SOX regimen and 12 patients (9%) received single oral agents such as capecitabine or S-1.

Table 2
Chemotherapy regimens

Chemotherapy regimen	N = 133 (%)
FP	5 (4)
XP	95 (71)
SOX	21 (16)
Other	12 (9)
No. Trastuzumab cycles	Median 9.5 (range: 1–68)
Dose reduction	103 (77)
FP fluorouracil + cisplatin, *XP* capecitabine + cisplatin,	

SOX S-1 (tegafur/gimeracil/oteracil) + oxaliplatin

Treatment outcomes

The median number of trastuzumab treatment cycles was 9.5 (range: 1–68), (Table 2). The median follow-up period was 18.7 months (95% CI: 15.4–23.2) for all patients and 16.6 Â months (95% CI: 14.4–18.2) for censored patients. At the data cut-off date of June 2017, there were 89 (67%) deaths, while 15 (11%) patients continued to undergo trastuzumab-based chemotherapy. Among the 115 patients who

discontinued trastuzumab-based chemotherapy, 95 patients (83%) received post-treatment. This included systemic therapy in 85 patients (89%) and surgery as conversion therapy in 13 patients (14%). Three patients were lost to follow-up (Fig. 1). Paclitaxel with or without trastuzumab, ramucirumab, irinotecan, as well as other agents were administered to 85 patients who received salvage systemic therapy. Paclitaxel with trastuzumab therapy was administered to 15 patients. Paclitaxel with ramucirumab therapy was administered to 19 patients. There were no cases in which nivolumab was administered. Pembrolizumab was administered to three patients as part of a clinical trial.

The median OS in this cohort was 18.8 months (95% CI: 15.4–23.1), (Fig. 2). The objective response rates by the investigator are shown in Table 3. Among the enrolled patients, 120 had targeted lesions. Complete responses were observed in 3 patients (2%) and partial responses in 74 patients (56%). The response rate was 58% and the disease control rate was 81%.

Table 3
Objective response rate

Best overall response	**N = 133 (%)**
CR	3 (2)
PR	74 (56)
SD	24 (18)
PR	19 (14)
ORR	77 (58)
NE or NA	13 (10)

CR complete response, *PR* partial response, *SD* stable disease,

ORR overall response rate, *NE* not evaluable, *NA* not assessed

Prognostic factors

In the univariate analysis, metastatic lesions per patient (> 4), visceral metastasis, median N/L (> 3.2), and abnormal test results for Hb (< 11.6 g/dL), serum Alb (< 4.1 mg/dL), LDH (> 222 mg/dL), ALP (> 322 IU/L), and CRP (> 0.14 mg/dL) levels were significantly associated with shorter OS. The hazard ratios (HRs) are shown in Table 4. On multivariate analysis, visceral metastasis, Hb, LDH, and CRP levels were independent prognostic factors for OS, with HRs of 1.57 (95% CI: 0.98–2.50, $p = 0.059$), 1.51 (95% CI: 0.97–2.34, $p = 0.068$), 1.50 (95% CI: 0.96–2.34, $p = 0.072$), and 1.74 (95% CI: 1.01–2.99, $p = 0.044$), respectively. We categorized patients into three risk groups according to the number of OS-associated prognostic factors. Hence, patients with 0–1, 2–3, and 4 prognostic factors were categorized into low-, moderate-, and high-risk groups, respectively. The median OS of each group was 32.0, 18.7, and 10.1 months, respectively (Fig. 3). Compared to the low-risk group, the HRs of the moderate- and high-risk groups were 1.75 · (95% CI: 1.05 · –·2.93) and · 3.49 (95% CI: 1.81 · –·6.71), respectively (Table 5).

Table 4
Univariate and multivariate analysis of prognostic factors for overall survival

Prognostic factors	N= (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Male	92 (69)	1.07 (0.68–1.68)	0.77	-	-
≥ 65	71 (53)	1.13 (0.75–1.72)	0.56	-	-
PS (1–2)	43 (32)	1.53 (0.10–2.34)	0.052	-	-
Primary tumour site (stomach)	97 (73)	0.91 (0.57–1.45)	0.7	-	-
Measurable tumour	116 (87)	1.67 (0.83–3.32)	0.15	-	-
Extent of disease (metastatic)	126 (95)	2.28 (0.72–7.21)	0.15	-	-
Metastatic sites per patient (> 2)	19 (14)	1.22 (0.69–2.16)	0.5	-	-
Metastatic lesions per patient (> 4)	95 (71)	1.74 (1.05–2.89)	0.03*	-	-
Visceral metastasis (lung or liver)	77 (58)	1.69 (1.09–2.60)	0.017*	1.57 (0.98–2.50)	0.059**
Type of gastric cancer (por, sig)	42 (32)	1.50 (0.97–2.33)	0.068	-	-
HER2 status (IHC 3+)	114 (86)	0.68 (0.37–1.24)	0.21	-	-
Previous chemotherapy	26 (20)	0.95 (0.56–1.61)	0.85	-	-
Previous gastrectomy	45 (34)	0.89 (0.57–1.37)	0.59	-	-
N/L (median, > 3.2)	75 (56)	1.69 (1.10–2.61)	0.016*	-	-

HR, hazard ratio; CI, confidence interval; PS, performance status; *por* poorly differentiated adenocarcinoma; *sig* signet-ring cell carcinoma; *N/L* neutrophil/lymphocytes, *Hb* hemoglobin, *Alb* albumin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *CA 19 − 9* carbohydrate antigen 19 − 9

*$p < 0.05$

**$p < 0.1$

Prognostic factors	N= (%)	Univariate analysis		Multivariate analysis	
Hb level (< 11.6 g/dl)	67 (50)	1.67 (1.10–2.55)	0.016*	1.51 (0.97–2.34)	0.068**
Alb level (< 4.1 mg/dl)	99 (74)	2.0 (1.17–3.40)	0.0096*	-	-
LDH level (> 222 mg/dl)	53 (40)	1.84 (1.20–2.81)	0.0043*	1.50 (0.96–2.34)	0.072**
ALP level (> 322 IU/l)	53 (40)	2.06 (1.35–3.15)	< 0.001*	-	-
CRP level (> 0.14 mg/dl)	89 (67)	2.01 (1.24–3.27)	0.0041*	1.74 (1.01–2.99)	0.044*
CEA (> 5.0 ng/ml)	83 (62)	1.17 (0.76–1.79)	0.48	-	-
CA 19 − 9 (> 37.0 U/ml)	72 (55)	1.28 (0.84–1.96)	0.25	-	-
HR, hazard ratio; CI, confidence interval; PS, performance status; *por* poorly differentiated adenocarcinoma; *sig* signet-ring cell carcinoma; *N/L* neutrophil/lymphocytes, *Hb* hemoglobin, *Alb* albumin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *CA 19 − 9* carbohydrate antigen 19 − 9					
*$p < 0.05$					
**$p < 0.1$					

Table 5
Hazard ratios of moderate- and high-risk groups

	N = 133 (%)	Median OS (months)	HR (95% CI)
Low (0–1)	42 (32)	32.0	-
Moderate (2–3)	70 (53)	18.7	1.75 (1.05–2.93)
High (4)	21 (16)	10.1	3.49 (1.81–6.71)
OS overall survival			

Discussion

A enhanced understanding of the prognostic factors associated with OS is useful for preparing a treatment plan. Because HER2 positive gastric cancer has a distinct driver oncogene and a specific treatment regimen, prognostic factors in patients treated with trastuzumab should be investigated separately. In this study, visceral metastasis (lung or liver metastasis), and Hb, LDH, and CRP levels were identified as significant prognostic factors for OS. Moreover, after stratification by risk group (low, moderate, or high), survival curves were clearly separated. The median OS of each group was 32.0, 18.7,

and 10.1 months. The HRs of the moderate and high-risk groups, when compared to the low-risk group, were 1.75 (95% CI: 1.05–2.93) and 3.49 (95% CI: 1.81–6.71), respectively. Our data identified for the first time, prognostic factors associated with the survival of patients with advanced HER2-positive gastric cancer. These patients were treated with trastuzumab-based chemotherapy.

Various prognostic scores or indices have been suggested for classifying patients with advanced gastric cancer. The most well-known prognostic score is the GPS, which is based on serum biomarkers such as elevated CRP and hypoalbuminemia [21]. GPS has been validated in several types of cancers, including gastric cancer [21, 4, 22]. For upper gastrointestinal cancers such as locally advanced and metastatic esophagogastric cancer, Chau et al. proposed the use of the RMH index. This index was obtained using data from randomized phase III trials in the UK [4]. It consists of ECOG PS (≥ 2), liver metastases, peritoneal metastases, and serum ALP (≥ 100 U/L). Likewise, the JCOG index is based on randomized phase III trials conducted in Japan [17]. It uses ECOG PS ≥ 1, the number of metastatic sites ≥ 2, no prior gastrectomy, and elevated ALP levels as markers of a poor prognosis.

Takahari et al. showed how survival curves were clearly separated when patients were stratified by the JCOG prognostic index. This was opposed to what was observed when they were stratified by the RMH index [3]. The reasons for these inconsistent results could be explained by several disparities in the backgrounds, including clinicopathological features, molecular biology, and treatment strategies, between the UK and Japan studies. First, more than half of the patients had either lower esophageal (27.3%) or gastroesophageal junction cancer (23.0%) in the RMH index sample. However, these tumor locations were less prevalent (generally less than 10%) in Japan [23]. Second, recent data from The Cancer Genome Atlas (TCGA) demonstrated that gastric cancer consists of four molecular categories: Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN), and genomic stable (GS) type [24]. According to TCGA data, chromosomal unstable tumors are more prevalent in gastroesophageal junction/cardia cancer (65%) than in the gastric body or fundus. This suggests the existence of molecular disparity between the two studies. Third, the majority of patients were treated with an epirubicin, cisplatin, and 5-fluorouracil (ECF) regimen in the RMH index study. Although, all patients received fluoropyrimidine plus platinum in the JCOG prognostic index study. Finally, post-disease progression treatment is commonly applied in Japan, whereas the proportion of patients receiving post-disease progression treatment is low in Western countries [25]. Takashima et al. emphasized the importance of subsequent treatment to prolong OS by showing a positive correlation between the duration of post-progression survival and the proportion of patients receiving subsequent chemotherapy [26]. Indeed, in the AVAGAST trial, Japanese patients received subsequent chemotherapy with a higher frequency (77%). They had a longer median OS (14.1 months) than patients in the US or Western Europe (37%; median OS: 9.1 months) [7]. These regional differences in the treatment of gastric cancer may cause inconsistent results between the RMH index and JCOG index. This underscores the importance of considering regional differences when identifying prognostic factors.

Notably, this cohort was relatively homogeneous in terms of molecular status and treatment strategy compared with previous studies [4, 17]. HER2-positive gastric cancer, a specific tumor subtype, is

associated with intestinal histology, liver metastasis, and the absence of peritoneal metastasis [27]. Indeed, this cohort demonstrated a high incidence of differentiated histology (68%) and visceral metastasis (58%). In addition, according to TCGA, HER2-positive gastric cancer is classified as a chromosomally unstable tumor [24]. Moreover, all patients in our study were treated with trastuzumab-based chemotherapy. Their median OS was higher (18.8 months) than that obtained in previous studies. Under these circumstances, that is advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy, we identified four independent prognostic factors for OS. These include the presence of visceral metastases and levels of Hb, LDH, and CRP. Visceral metastasis, especially liver metastasis, is a well-known negative prognostic factor for gastrointestinal cancer. Conventionally, tumor burden is considered one of the reasons why liver metastasis is associated with a shorter survival [28]. However, recent data suggest that liver metastasis is associated with aggressive properties such as vascular invasion, angiogenesis, systemic immune tolerance. It is also associated with fewer infiltrating $CD8^+$ T-cells at the invasive margin in distant metastasis [29, 30]. Likewise, lower Hb levels could reflect not only the presence of a primary tumor, which can cause bleeding, but also exhaustion due to a prolonged illness.

Rapid proliferation and abnormal vasculature induce hypoxia within tumors [31]. Regardless of the available oxygen level, tumors mainly rely on the anaerobic glycolysis pathway. This is known as the Warburg effect [32]. Under this metabolic pathway, glucose changes to pyruvate, which is subsequently converted to lactate through catalysis by LDH. As a result, tumor cells take up more glucose and produce more LDH to obtain the energy needed for proliferation. In 18F-FDG-PET, a high maximum standardized uptake value (SUVmax) is recognized as a negative prognostic factor. SUVmax and LDH levels are positively correlated. Therefore, LDH levels could be an indicator of tumor activity [33]. Hypoxia also induces central necrosis in tumors. This results in cancer-related inflammation and increased CRP levels. Recent data suggest that vascular endothelial growth factor (VEGF) is induced by hypoxia. VEGF stimulates immunosuppressive cells such as regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressive cells in the tumor microenvironment [34]. Because one of the mechanisms of action of trastuzumab is antibody-dependent cellular cytotoxicity (ADCC) [35], trastuzumab might not show sufficient efficacy and anti-tumor effects under this immunosuppressive microenvironment. Therefore, our prognostic factors may reflect not only the tumor burden but also the tumor activity and immune status of the host.

In contrast to previous reports, PS was not significantly associated with OS in univariate analysis in our study as all except one of our patients had a PS of 0–1. In addition, there is a limitation in our study when assigning PS between 0 and 1 as it was a retrospective study. In previous studies, a high ALP level has been proposed as an independent risk factor. However, this was not reproduced in the multivariate analysis in this study. The exact reason why high ALP levels were not significantly associated with OS in this study is unclear. Considering the distinct molecular profile of the tumors and treatment strategy of patients with HER2-positive gastric cancer, the prognostic factors for survival may differ from those of patients with HER2-negative gastric cancer.

There are several limitations to this study that should be considered. First, this was a retrospective study conducted at a single institution. Second, the sample size was relatively small and no comorbidity data were available. Third, peritoneal metastasis, which has been indicated as a prognostic factor in several reports, was not evaluated. Finally, we do not have molecular data regarding the immune status and ADCC activity of trastuzumab under hypoxia. These limitations require further clinical validation using a larger prospective independent cohort and molecular correlative analysis. Nevertheless, considering the low incidence of HER2-positive gastric cancer, these data are valuable. Consequently, our simple and inexpensive scoring system, using laboratory and imaging tests, may prove useful in clinical practice. These factors can be used to assist in the treatment decision-making process for patients with advanced HER2-positive gastric cancer as they are based on the estimated prognosis.

Conclusion

We identified four independent prognostic factors for the survival of patients with HER2-positive gastric cancer treated with trastuzumab. They included the presence of visceral metastases, levels of Hb, LDH, and CRP. These factors can be useful prognostic markers for the management of HER2-positive gastric cancer.

Abbreviations

ADCC
antibody-dependent cell cytotoxicity
ALB
albumin
ALP
alkaline phosphatase
CA
carbohydrate antigen
CEA
carcinoembriogenic antigen
CIN
chromosomal instability
CRP
C-reactive protein
EBV
Epstein-Barr virus
ECF
epirubicin, cispaltin, 5-fluorouracil
ECOG
Eastern Cooperative Oncology Group

FDG-PET
fluorodeoxyglucose positron-emission tomography
FISH
fluorescent in situ hybridisation
FP
fluorouracil + cisplatin
GPS
Glasgow Prognostic score
HB
haemoglobin
HER2
Human epidermal growth factor receptor 2
HR
Hazard ratio
IHS
Immunohistochemistry scoring
JCOG
Japan Clinical Oncology Group
LDH
lactate dehydrogenase
MSI
microsatellite instability
OS
Overall survival
PS
performance status
RMH
Royal Marsden Hospital
SOX
S-1 (tegafur/gimeracil/oteracil) + oxaliplatin
TCGA
The Cancer Genome Atlas
VEGF
Vascular endothelial growth factor
XP
capecitabine + cisplatin

Declarations

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Compliance with Ethical Standards

Ethics approval and consent to participate:

This study was approved by the Cancer Institute Hospital of the Japanese Foundation for Cancer Research Institutional Review Board (2017-1044). The study followed the Declaration of Helsinki by the World Medical Association. Written informed consent was obtained from all study participants.

Disclosure of potential conflicts of interest

Shoko Marshall, Takeru Wakatsuki, Tomohiro Matsushima, Naoki Ishizuka, Izuma Nakayama, Hiroki Osumi, Mariko Ogura, Takashi Ichimura, Keisho Chin have no conflicts of interest to declare; Daisuke Takahari reports lectures related fees from Taiho, Eli Lilly, Bristol-Myers Squibb, Ono, Chugai outside the submitted work; Eiji Shinozaki reports lectures related fees from Chugai outside the submitted work; and Kensei Yamaguchi reports legal fees from Chugai outside the submitted work.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding

Author on reasonable request.

Authors' contributions

Shoko Marshall and Takeru Wakatsuki wrote the manuscript; Shoko Marshall and Tomohiro Matsushima collected data from medical records, Naoki Ishizuka contributed to statistical analysis, and all authors read and approved the final manuscript.

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Figures

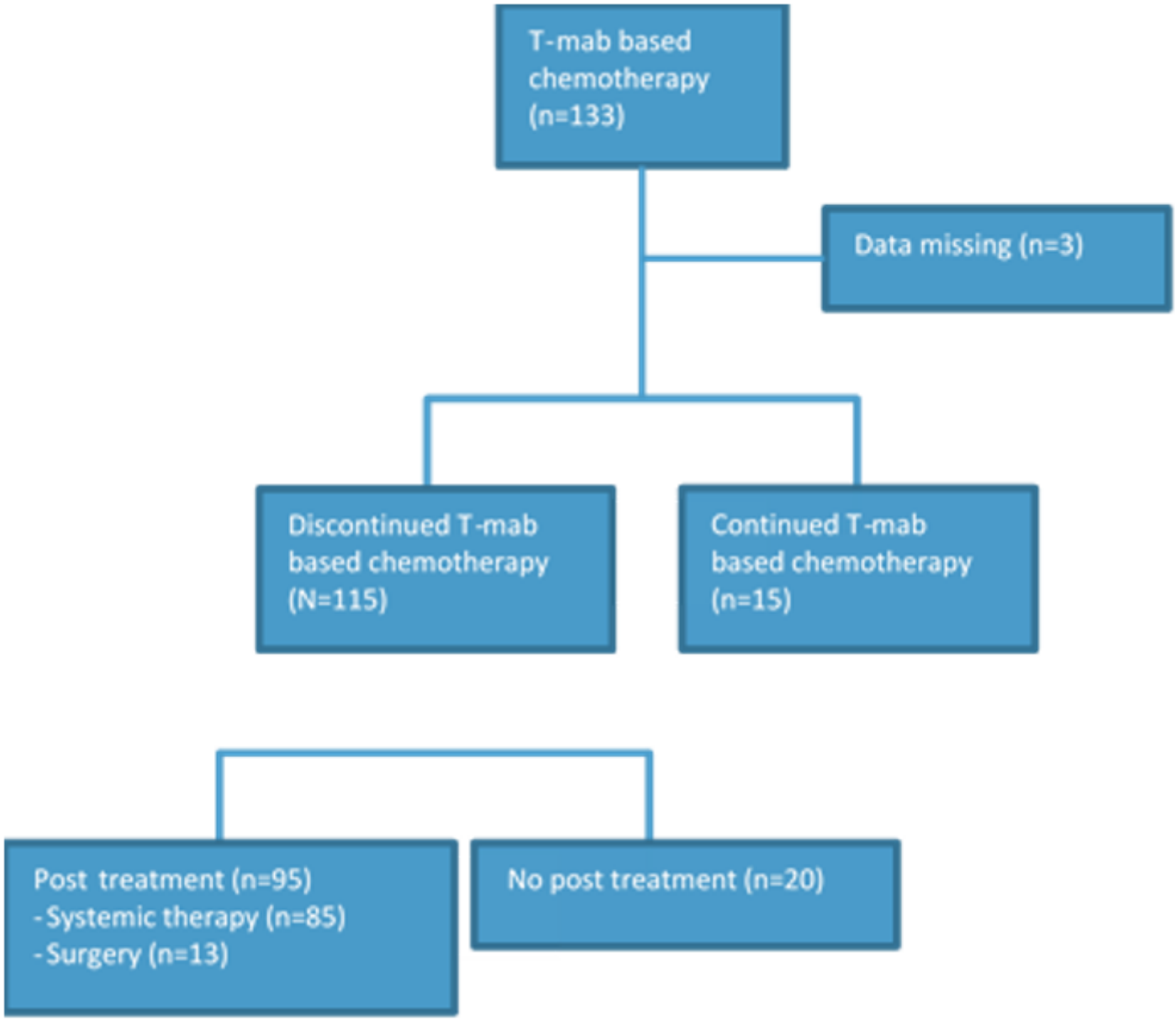

Figure 1

Study consort flow chart. Diagram of the number of patients who continued and discontinued trastuzumab (t-mab)-based chemotherapy, including those who received post treatment.

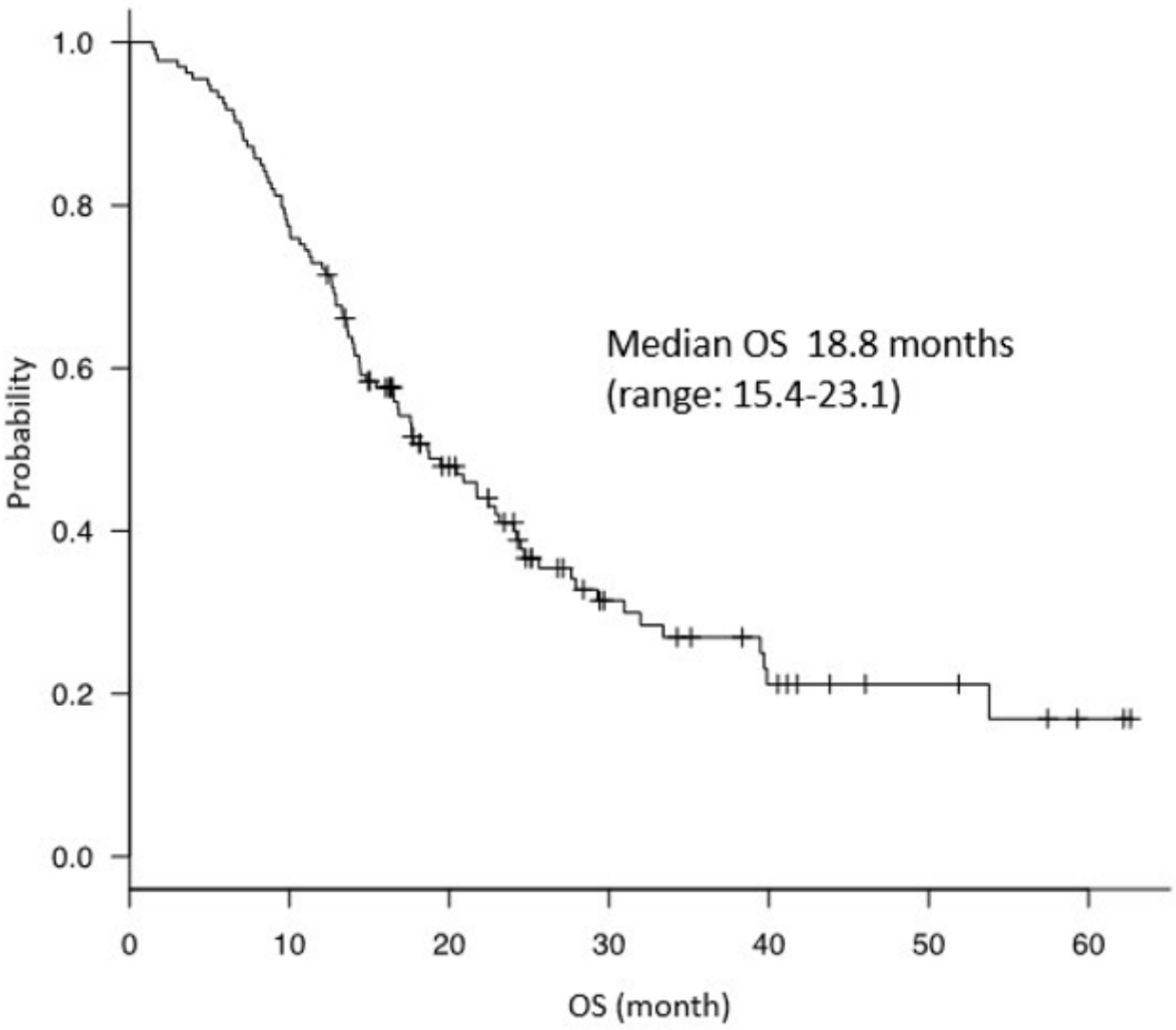

Figure 2

Overall survival (OS) curve. The median OS of the 133 patients enrolled in this study was 18.8 months (95% CI 15.4–23.1).

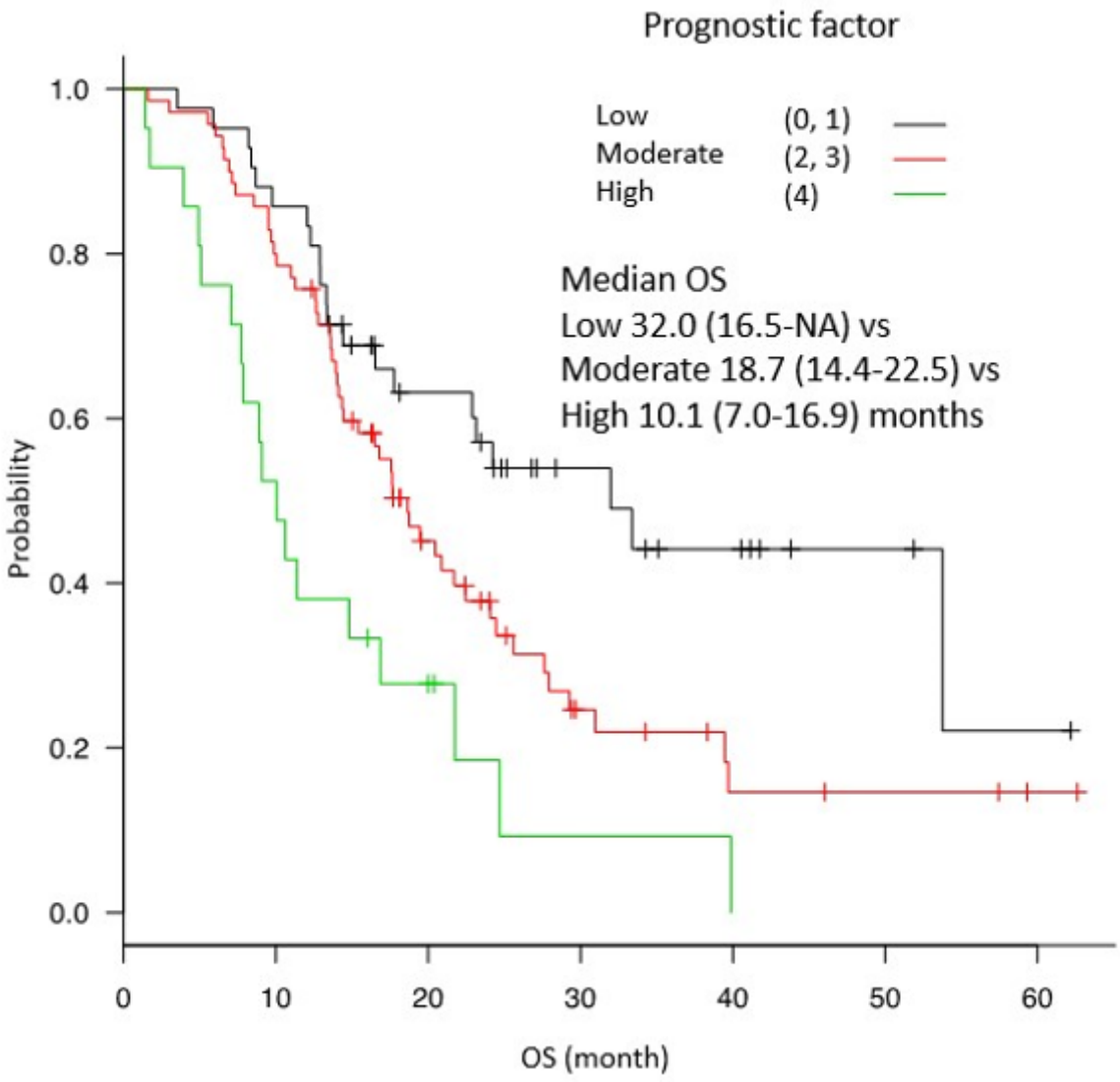

Figure 3

Overall survival (OS) according to risk group. Patients with 0–1, 2–3, and 4 prognostic factors were categorised in low- (black), moderate- (red), and high-risk (green) groups, respectively. Mean overall survival values for each group are indicated in the figure.