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ORIGINAL ARTICLE

Associations between early tumor shrinkage and depth of response and clinical outcomes in patients treated with 1st-line chemotherapy for advanced gastric cancer

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Abstract
Background Although early tumor shrinkage (ETS) predictions of the efficacy and depth of response (DpR) reflects clinical outcomes in chemotherapy with epidermal growth factor receptor inhibitor regimens to treat metastatic colorectal cancer, their value in assessing treatments for advanced gastric cancer (AGC) is unclear. Here we evaluated relationships between ETS and DpR and clinical outcomes in AGC patients treated with first-line chemotherapy.
Methods We retrospectively enrolled 612 consecutive patients treated with first-line chemotherapy for AGC between January 2010 and June 2016. ETS and DpR were defined as changes from baseline in summed longest diameters in target lesions at 8 (±4) weeks for ETS and at the smallest observed volume for DpR.
Results Eligible patients were sorted into $HER2^+$ ($n = 100$) and $HER2^-$ ($n = 186$) groups. Median follow-up was 14.8 months. The overall response rate and disease control rates were 64 and 87% in the $HER2^+$ group and 53.2 and 86.0% in the $HER2^-$ group. Respective median PFS and OS were $HER2^+$: 7.9 and 20.8 months and $HER2^-$: 6.6 and 13.8 months. The respective ETS rate and median DpR were $HER2^+$: 70 and 44% and $HER2^-$: 57.5 and 24%. Clinical outcomes and ETS/DpR were correlated, especially in the $HER2^+$ group (OS: $P < 0.0001$; PFS: $P < 0.0001$). In multivariate analysis, ETS was an independent predictor for OS in the $HER2^+$ group and for PFS in both groups.
Conclusion These results indicate that ETS may be an early-on treatment predictor of the efficacy of $HER2^+$ advanced gastric cancer treated with first-line chemotherapy that includes trastuzumab.

Keywords Early tumor shrinkage · Depth of response · Advanced gastric cancer

Introduction

About 50,000 people per year die from gastric cancer. It is the second leading cause of cancer deaths. Although the mortality rate of gastric cancer has decreased in Japan over recent decades [1], its prevalence is increasing for both men and women in Japan [2]. Worldwide, it is the fifth most prevalent cancer and the third leading cause of cancer death [3].

In Japan, strategies to treat advanced gastric cancer (AGC) depend on the tumor's human epidermal growth factor receptor-2 (HER2) status [4]. This well-established target, HER2, is a member of the epidermal growth factor receptor (EGFR) family and is associated with tumor cell proliferation, apoptosis, adhesion, migration and differentiation [5]. HER2 is an important biomarker and key driver of tumorigenesis in gastric cancer. Patients with $HER2^+$ AGC are usually treated with fluoropyrimidine, platinum-based chemotherapy and trastuzumab as first-line chemotherapy, whereas patients with $HER2^-$ AGC usually receive fluoropyrimidine plus platinum-based chemotherapy only as first-line chemotherapy, according to Japanese gastric cancer treatment guidelines [4]. Bang et al. showed that 15–20% of all AGC was $HER2^+$, and the overall

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tumor response rate, time to progression and response duration were significantly improved in patients with HER2$^+$ AGC who received trastuzumab plus chemotherapy compared with those who received chemotherapy only [6].

Early tumor shrinkage (ETS) indicates decreased tumor load measured compared with that seen at the first imaging after the start of treatment [7]. Depth of response (DpR) is defined as the percentage of tumor shrinkage, based on the longest diameters or reconstructed volume at the smallest observed volume compared with baseline [8]. DpR quantifies the actual extent of tumor response and, unlike ETS (which is taken at a specific time point), is a continuous measure. Post hoc analyses of the CRYSTAL and OPUS trials indicated that a 20% reduction in sums of the longest diameters of target lesions after 8 weeks from initial treatment was the optimal cutoff to discriminate between early and non-early responders [8, 9], whereas post hoc analyses of the FIRE-3, PEAK and TRIBE trials indicated that DpR greater than the median value was associated with longer post-progression survival, PFS and OS [10–12]. Therefore, ETS is considered to predict treatment outcomes and DpR may reflect clinical outcomes in patients with metastatic colorectal cancer (mCRC) who are treated with chemotherapy and molecularly targeted drugs (MTD), such as EGFR inhibitors. As EGFR is in the HER family, we considered ETS might predict of efficacy and DpR might reflect clinical outcomes in the treatment of HER2$^+$ AGC. However, no reports have evaluated the relationships between ETS/DpR and clinical outcomes in AGC. This study evaluated whether clinical outcomes were related to ETS or DpR in patients with AGC who received first-line chemotherapy.

Patients and methods

Patients

We retrospectively enrolled 612 patients with histopathologically confirmed AGC who were treated with first-line chemotherapy in our institute between January 2010 and June 2016. We then excluded patients with peritoneal metastasis and/or those with bone metastasis with no target region. This study was performed in accordance with the Declaration of Helsinki. The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Institutional Review Board, approved this study (Registry No. 2016-1873).

Data collection

All data were identified by reviewing medical records and/or imaging. We confirmed age, sex, performance status (PS), location of the primary tumor, pathology of the primary tumor, metastatic sites, previous gastrostomy, CEA (cutoff: 5.0 ng/ml) and CA19-9 (cutoff: 37.0 U/ml) levels, HER2 status and ETS/DpR. Primary tumor sites were sorted into upper, middle or lower sites, in accordance with the Japanese Classification of Gastric Carcinoma [13]. Tumors were tested for HER2 status using immunohistochemistry (HercepTest®, Dako, Denmark) and fluorescence in situ hybridization (FISH; HER2 FISH pharmDx®, Dako) [6]. Patients were considered HER2$^+$ if their tumor samples were scored as 3+ on immunohistochemistry (IHC) or had a CEP17 ratio ≥2 when tested by FISH (if the HER2 score was 2+ in IHC). ETS was defined as the relative change in the sum of the longest diameters at week 8 (±4 weeks) compared to baseline (cutoff: 20%). DpR was calculated as the percentage change from baseline to nadir in patients who had tumor shrinkage (cutoff: median value). We adopted both definitions according to previous studies of mCRC [8, 9, 12]. Tumor response was assessed by computed tomography imaging, using RECIST 1.1. In this case series, antitumor efficacy was evaluated every 2 months (according to the standard practice at our institution), which corresponded to two or three treatment cycles. Both ETS and DpR were re-evaluated independently by three medical oncologists (HO, DT and ES). Progression-free survival (PFS) was defined as the time from the 1st day of treatment to either the first objective evidence of disease progression or death from any cause. In case of a discrepancy between the reevaluated RECIST-PD and physician's judgment concerning progressive disease (PD), PD by re-evaluation was adopted as an event for PFS if it was earlier than that by the physician's evaluation, and PD judged by the physician was adopted as censored on the day of the physician's judgment concerning PD if the treatment was discontinued before PD by re-evaluation. If

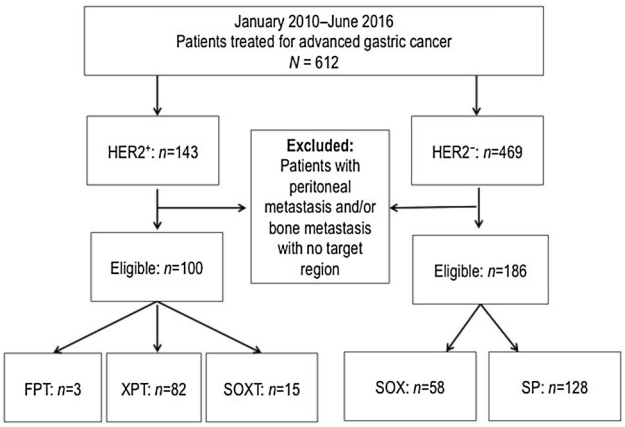

Fig. 1 CONSORT diagram of patient selection for this study. *FPT* 5-fluorouracil, cisplatin, trastuzumab; *SOX* S-1, oxaliplatin; *SOXT* S-1, oxaliplatin, trastuzumab; *SP* S-1, cisplatin; *XPT* capecitabine, cisplatin, trastuzumab

Table 1 Baseline demographics and disease characteristics of patients with advanced gastric cancer by HER2 status

	Overall, $n = 286$	HER2$^+$, $n = 100$	HER2$^-$, $n = 186$	P
Sex n (% male)	185 (64.6)	67 (67)	118 (63.4)	0.6
Median age in years (range)	67 (21–82)	64 (21–82)	68 (30–82)	0.007
ECOG PS 0/1/2	220/67/1	65/34/1	155/33/0	0.18
Location: upper/middle/lower	94/92/100	42/35/23	52/57/77	0.004
Type of gastric cancer (intestinal/diffuse)	152/144	70/30	82/114	<0.001
Locally advanced/metastatic	51/235	11/89	40/146	0.034
Metastatic sites per patient (1–2/>2)	268/18	88/12	180/6	0.008
Previous gastrectomy (yes/no)	65/221	28/72	37/149	0.13
HER2 status per FISH: IHC2$^+$/IHC3$^+$	–	11/89	–	
Chemotherapy regimen of HER2 positive patients (FPT/XPT/SOXT)	–	3/82/15	–	
Chemotherapy regimen of HER2 negative patients (CS/SOX)	–	–	128/58	

HER2 human epidermal growth factor receptor-2; *PS* performance status; *FISH* fluorescence in situ hybridization; *IHC* immunohistochemistry; *FPT* 5-fluorouracil, cisplatin and trastuzumab; *XPT* capecitabine, cisplatin and trastuzumab; *SOXT* S-1, oxaliplatin and trastuzumab; *CS* S-1 plus cisplatin; *SOX* S-1 plus oxaliplatin

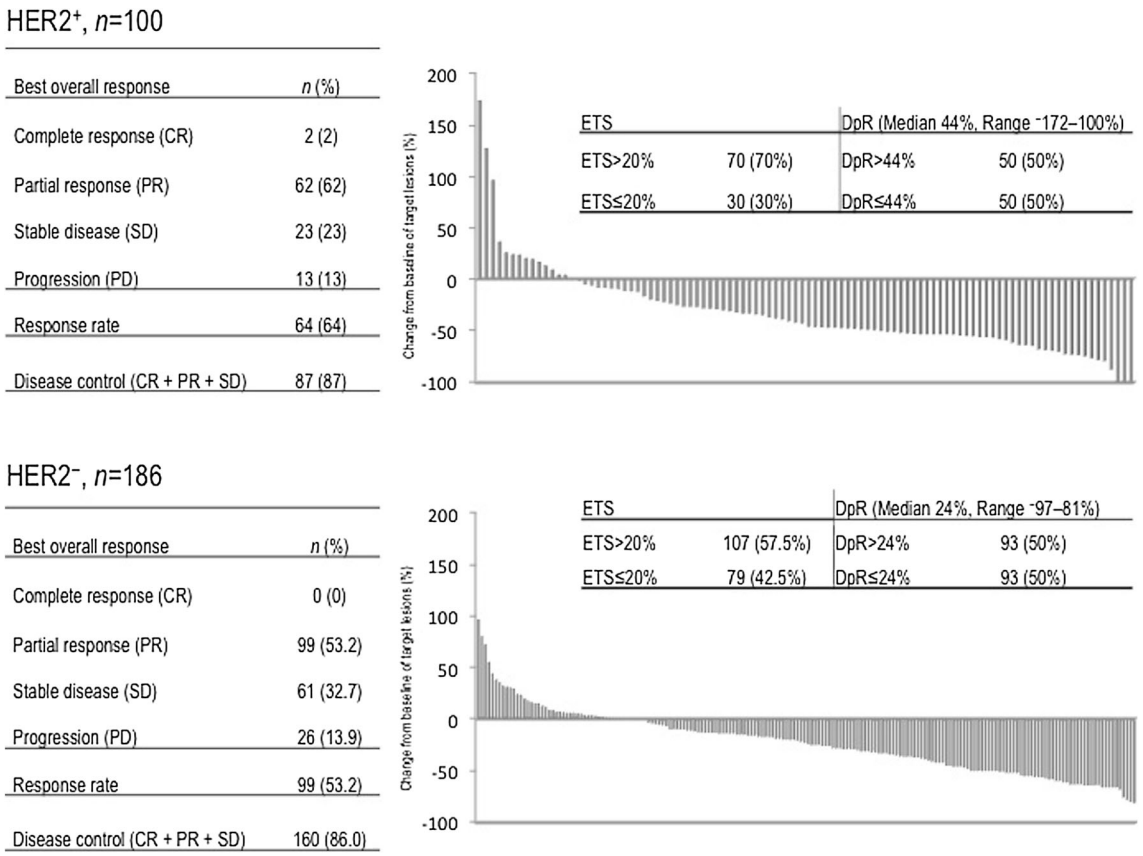

Fig. 2 Comparisons of overall response rate, waterfall plot of the tumor shrinkage, early tumor shrinkage rate and depth of response in patients with advanced HER2$^+$ and HER2$^-$ gastric cancers

tumor shrinkage had not reached DpR at the time of re-evaluation PD, maximum tumor shrinkage before re-evaluation PD was adopted as DpR. Overall survival (OS) was defined as the time from diagnosis of metastatic disease until the time of death.

Treatment

The details of chemotherapy regimens were as follows: HER2$^+$ disease: (1) capecitabine, cisplatin and trastuzumab: capecitabine 1000 mg/m was given orally twice a

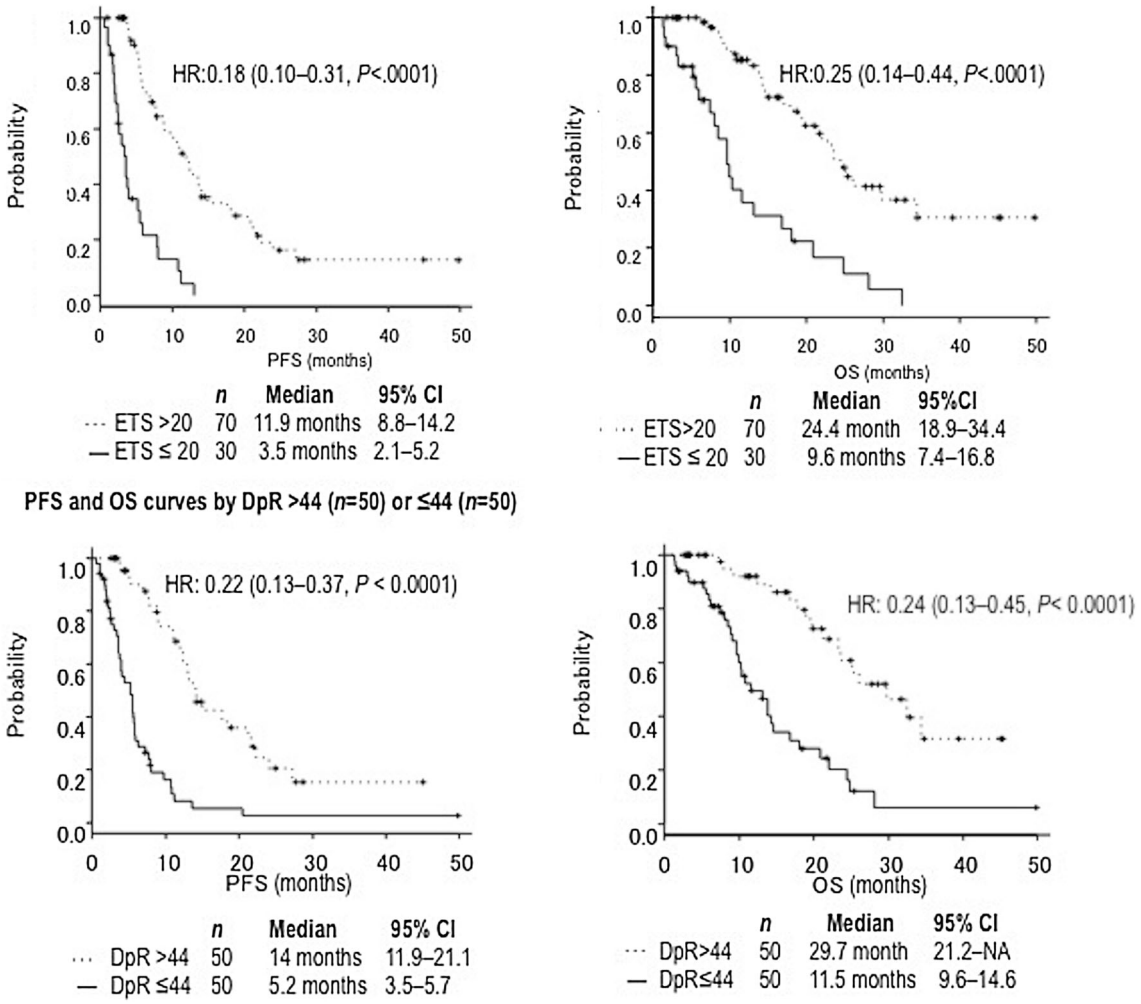

Fig. 3 PFS and OS curves by early tumor shrinkage >20 ($n = 70$) or ≤20 ($n = 30$) and by depth of response >44 ($n = 50$) or ≤44 ($n = 50$) in advanced HER2$^+$ gastric cancer

day for 14 days followed by a 1-week rest. Cisplatin 80 mg/m on day 1 was given by intravenous infusion. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. (2) 5-Fluorouracil, cisplatin and trastuzumab: fluorouracil 800 mg/m per day were given by continuous intravenous infusion on days 1–5 of each cycle. Cisplatin 80 mg/m on day 1 was given by intravenous infusion. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. (3) S-1, oxaliplatin and trastuzumab: S-1 [the dose was 80 mg/day for body surface area (BSA) <1.25 m^2, 100 mg/day for BSA ≥1.25 to <1.5 m^2 and 120 mg/day for BSA ≥1.5 m^2] was given orally, twice daily for 2 consecutive weeks, and oxaliplatin at 130 mg/m^2 was given intravenously on day 1. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks.

HER2$^-$ disease: (1) S-1 plus cisplatin: S-1 was given orally, twice daily for 3 consecutive weeks, and cisplatin at 60 mg/m^2 was given intravenously on day 8. (2) S-1 plus oxaliplatin: S-1 was given orally, twice daily for 2 consecutive weeks, and oxaliplatin at 100 mg/m^2 was given intravenously on day 1.

Doses were modified according to the standard practice at our institute at this time.

Statistical analysis

OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. All reported P values were the result of two-sided tests; $P < 0.05$ was considered significant. Prognostic factors for which $P < 0.2$ in univariate analysis were included in the multivariate analysis using backward elimination method. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Japan), which is

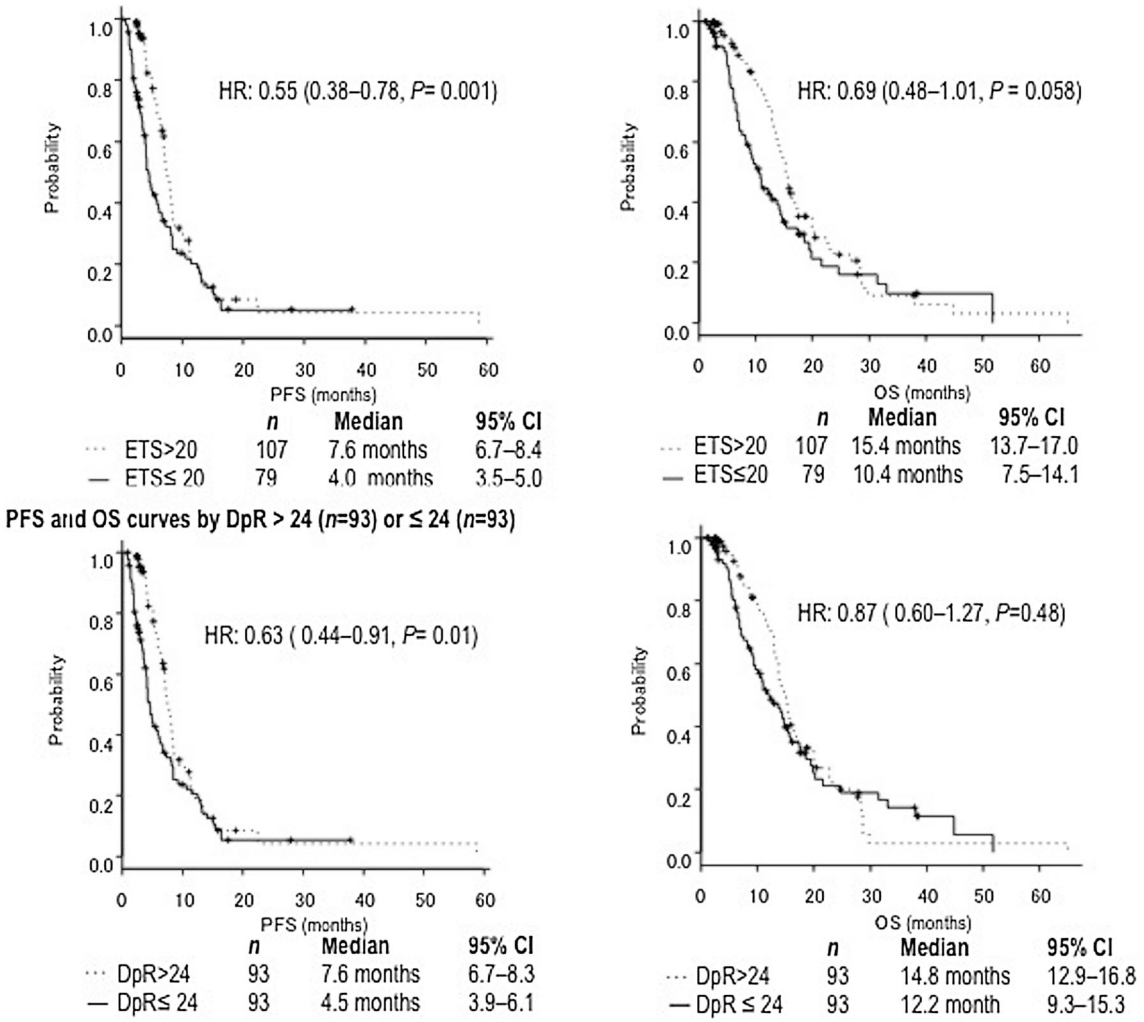

Fig. 4 PFS and OS curves by early tumor shrinkage >20 ($n = 107$) or ≤20 ($n = 79$) and by depth of response >44 ($n = 93$) or ≤44 ($n = 93$) in advanced HER2$^-$ gastric cancer

a graphical user interface for R (The R Foundation for Statistical Computing).

Results

Clinical characteristics

Our study cohort included 286 patients with AGC for whom a treatment response evaluation according to RECIST criteria version 1.1 was available (Fig. 1, CONSORT diagram), including 100 HER2$^+$ patients and 186 HER2$^-$ patients (Table 1). The HER2$^+$ group was younger and had higher percentages of lesions in the upper gastric region, differentiated type pathology and multiple metastases (>2) than did the HER2$^-$ group, whereas the HER2$^-$ group had a higher percentage of locally advanced cases. Median follow-up period at the time of the analysis was 14.8 months (range 1–65 months).

Correlations between ETS/DpR and clinical outcome

In the HER2$^+$ group, the overall response rate (ORR) was 64%. The disease control rate was 87%, including complete response (CR): 2%, partial response (PR): 62%; stable disease (SD): 23%; progressive disease (PD): 13%. Median PFS was 7.9 months (range 5.8–11 months); median OS was 20.8 months (range 14.3–24.8 months). The ETS rate was 70%. Median DpR was 44% (range −172 to 100%; Fig. 2) after a median period of 9.5 weeks (range 4.2–42 weeks). ETS ≥20% was associated with significantly longer OS and PFS than ETS <20% (ETS ≥20 vs. <20%—OS: 24.4 vs. 9.6 months, HR: 0.25,

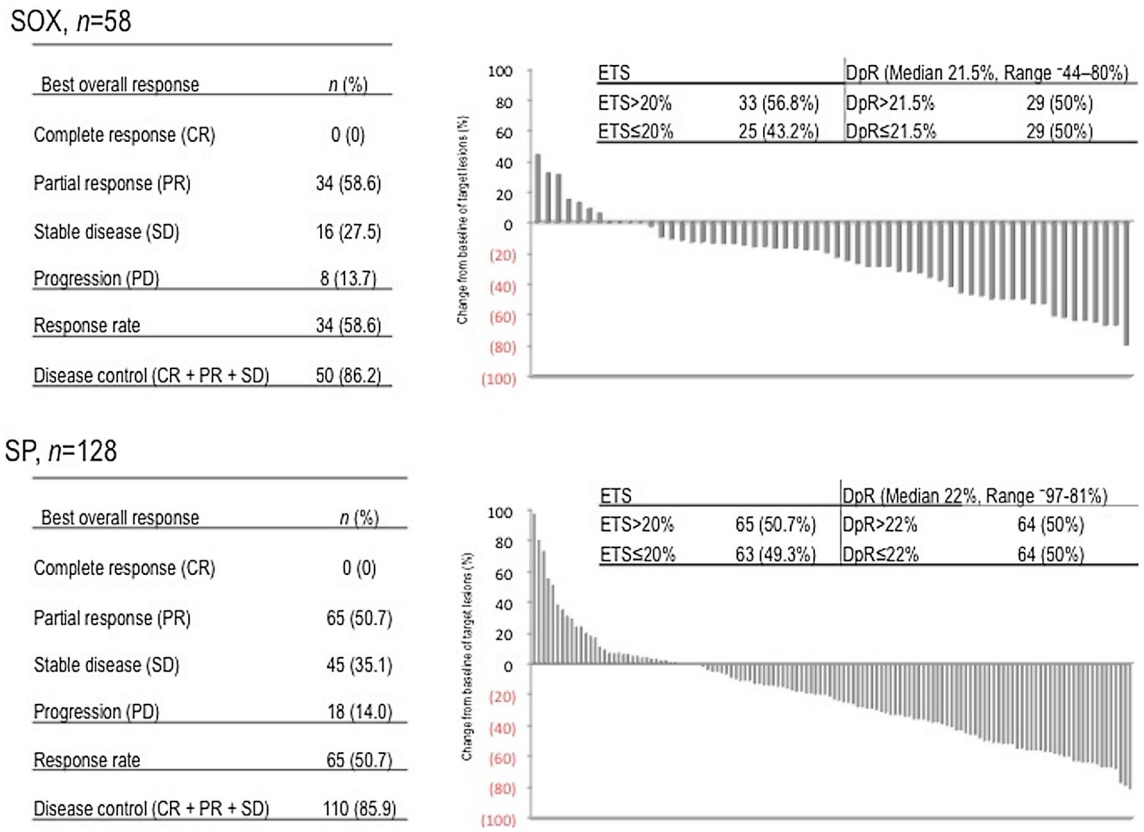

Fig. 5 Comparisons of overall response rate, waterfall plot of the tumor shrinkage, early tumor shrinkage rate and depth of response between the SOX group ($n = 58$) and the SP group ($n = 128$) among patients with advanced HER2$^-$ gastric cancer

$P < 0.0001$; PFS: 11.9 vs. 3.5 months, HR: 0.18, $P < 0.0001$). DpR ≥44% (i.e., the median value) was also associated with significantly longer OS and PFS than DpR <44% (DpR ≥44 vs. <44%—OS: 29.7 vs. 11.5 months, HR: 0.24, $P < 0.0001$; PFS: 14 vs. 5.2 months, HR: 0.22, $P < 0.0001$; Fig. 3).

For the HER2$^-$ group, ORR was 53.2%. The disease control rate was 86.0% (CR: 0%; PR: 53.2%; SD: 32.7%; PD: 13.9%). Median PFS was 6.6 months (range 5.2–7.4 months). Median OS was 13.8 months (range 12.2–15.3 months). The ETS rate was 57.5%. Median DpR was 24% (range −97 to 81%; Fig. 2) after a median period of 9.2 weeks (range 3.4–46 weeks). ETS >20% was associated with longer PFS than ETS ≤20% (ETS >20 vs. ≤20%: OS—15.4 vs. 10.4 months, HR: 0.69, $P = 0.059$, PFS—7.6 vs. 4.0 months, HR: 0.55, $P = 0.001$). DpR >24% (the median value) was also associated with significantly longer PFS than DpR ≤24% (DpR ≥24 vs. <24%: OS—14.8 vs. 12.2 months, HR 0.87 $P = 0.48$; PFS—7.6 vs. 4.5 months, HR 0.63, $P = 0.01$; Fig. 4). We performed the subgroup analysis of comparison between SOX ($n = 58$) and SP ($n = 128$) in the HER2$^-$ group. In the SOX group ($n = 58$), ORR was 58.6%. The disease control rate was 86.0% (CR: 0%; PR: 58.6%; SD: 27.5%; PD: 13.7%). The ETS rate was 56.8%. Median DpR was 21.5% (range −44 to 80%; Fig. 5) after a median period of 14 weeks (range 3.4–31 weeks). For the SP group, ORR was 53.2%. The disease control rate was 86.0% (CR: 0%; PR: 50.7%; SD: 35.1%; PD: 14.0%). The ETS rate was 50.7%. Median DpR was 22% (range −97–81%; Fig. 5) after a median period of 9.2 weeks (range 3.4–46 weeks).

Univariate and multivariate analyses of predictors of clinical outcome (Table 2)

In the univariate analysis, ETS was a predictive factor for PFS and pathology, CA19-9, ETS and HER2 status were predictive factors of OS. In the multivariate analysis, ETS was a predictive factor of PFS, and pathology, ETS and HER2 status were predictive factors of OS in HER2-positive patients. On the other hand, in the univariate analysis, age, PS, CEA and ETS were predictive factors for PFS, and age, PS, pathology and CEA were predictive factors of OS. In the multivariate analysis, age, PS and ETS were predictive factors for PFS, and age and PS were predictive factors of OS in HER2-negative patients.

Table 2 Factors that affected progression-free and overall survival in patients with advanced gastric cancer by HER2 status

HER2+	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
PFS						
Age (<65 vs. 65≤ years)	0.67	0.39–1.12	0.12	0.82	0.48–1.41	0.49
Sex (female vs. male)	1.2	0.72–2.0	0.47			
PS (0 vs. 1, 2)	3.8	0.52–28.7	0.18	1.27	0.16–10.9	0.81
Primary site (upper vs. middle, lower)	0.64	0.39–1.06	0.08	0.78	0.46–1.33	0.37
Pathology (intestinal/diffuse)	1.31	0.79–2.1	0.28			
Metastatic sites (1–2 vs. 2≤)	1.3	0.71–2.5	0.35			
Previous gastrectomy (yes vs. no)	1.2	0.72–1.98	0.47			
CEA (<5 vs. 5≤)	1.3	0.79–2.1	0.29			
CA19-9 (<37 vs. 37≤)	1.52	0.93–2.4	0.09	1.04	0.61–1.77	0.86
ETS (>20 vs. ≤20)	0.18	0.10–0.31	<0.0001	0.19	0.11–0.35	<0.0001
HER2 $IHC3^+$ vs. $IHC2^+$ (per FISH)	1.47	0.58–3.69	0.41			
OS						
Age (<65 vs. 65≤ years)	0.71	0.39–1.29	0.26			
Sex (female vs. male)	0.88	0.49–1.57	0.66			
PS (0 vs. 1 or 2)	3.3	0.44–24.9	0.23			
Primary site (upper vs. middle, lower)	0.86	0.44–1.46	0.47			
Pathology (intestinal/diffuse)	1.8	0.99–3.2	0.05	2.1	1.12–4.0	0.02
Metastatic sites (1–2 vs. 2≤)	1.28	0.61–2.4	0.57			
Previous gastrectomy (yes vs. no)	1.93	0.99–3.7	0.052	1.56	0.78–3.1	0.2
CEA (<5 vs. 5≤)	1.56	0.84–2.89	0.15	1.61	0.83–3.1	0.15
CA19-9 (<37 vs. 37≤)	1.76	1.1–3.7	0.02	1.76	0.89–3.4	0.09
ETS (>20 vs. ≤20)	0.25	0.14–0.44	<0.0001	0.26	0.14–0.48	<0.0001
HER2 $IHC3^+$ vs. $IHC2^+$ (per FISH)	3.1	1.19–8.0	0.02	3.59	1.25–10.31	0.01
HER2−	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
PFS						
Age (<65 vs. 65≤ years)	0.56	0.39–0.81	0.002	0.48	0.30–0.77	0.002
Sex (female vs. male)	1.1	0.76–1.59	0.58			
PS (0 vs. 1, 2)	2.5	1.6–4.0	<0.0001	2.32	1.33–4.04	0.002
Primary site (upper vs. middle, lower)	0.87	0.61–1.26	0.48			
Pathology (intestinal/diffuse)	1.29	0.83–2.0	0.25			
Metastatic sites (1–2 vs. 2≤)	1.14	0.42–3.1	0.78			
Previous gastrectomy (yes vs. no)	0.87	0.57–1.3	0.54			
CEA (<5 vs. 5≤)	1.64	1.14–2.3	0.007	1.23	0.78–1.92	0.35
CA19-9 (<37 vs. 37≤)	1.12	0.78–1.6	0.53			
ETS (>20 vs. ≤20)	0.55	0.38–0.78	0.001	0.46	0.29–0.73	0.001
OS						
Age (<65 vs. 65≤ years)	0.59	0.40–0.87	0.007	0.57	0.35–0.92	0.02
Sex (female vs. male)	1.1	0.76–1.59	0.58			
PS (0 vs. 1 or 2)	2.4	1.4–4.0	0.0008	2.26	1.19–4.29	0.01
Primary site (upper vs. middle, lower)	0.94	0.65–1.38	0.78			
Pathology (intestinal/diffuse)	1.7	1.09–2.81	0.01	1.45	0.88–2.38	0.13
Metastatic sites (1–2 vs. 2≤)	1.11	0.45–2.7	0.8			
Previous gastrectomy (yes vs. no)	0.99	0.63–1.55	0.97			
CEA (<5 vs. 5≤)	1.5	1.03–2.2	0.03	1.3	0.80–2.11	0.28

Table 2 continued

HER2−	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
CA19-9 (<37 vs. 37≤)	1.3	0.89–1.9	0.16	1.3	0.82–2.07	0.25
ETS (>20 vs. ≤20)	0.69	0.48–1.01	0.059	0.76	0.47–1.23	0.27

PFS progression-free survival; *OS* overall survival; *HER2* human epidermal growth factor receptor 2; *PS* performance status; *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9; *ETS* early tumor shrinkage; *IHC* immunohistochemistry; *FISH* fluorescence in situ hybridization; *HR* hazard ratio; *CI* confidence interval

Discussion

To our knowledge, this is the first study to evaluate the relationship between ETS/DpR and clinical outcomes in AGC. Our results show that ETS was a significant independent predictor of longer PFS in both groups and of longer OS in the $HER2^+$ group. ETS/DpR were better correlated as clinical outcomes in the $HER2^+$ group than in the $HER2^-$ group.

The present study shows, for the first time, a positive relationship between ETS/DpR and clinical outcomes in $HER2^+$ AGC. The percentage of the $HER2^+$ AGC patients who showed ETS was similar to results for mCRC patients treated with first-line chemotherapy plus EGFR inhibitors [14]. In other cancers treated by tyrosine kinase inhibitors (such as renal cell adenocarcinoma), ETS also identified patients who were likely to benefit from treatment with antitumor agents [15]. Grünwald et al. reported that patients who reached 10% ETS had significantly longer OS (HR: 0.615, $P < 0.0001$, median 28.5 vs. 16.0 months) and PFS (HR: 0.628, $P < 0.0001$, median 10.5 vs. 5.3 months) than did patients without ETS (Cox proportional hazards models). These reports indicate a strong correlation between ETS and clinical outcomes in patients treated with MTDs in which good tumor shrinkage is expected, regardless of cancer type.

The $HER2^-$ group showed a weak relationship between ETS/DpR and clinical outcomes.

We evaluated the difference of ETS/DpR between each regimen of chemotherapy at first. In a phase III study that compared oxaliplatin + S-1 (SOX) to cisplatin + S-1 (SP) in patients with AGC, response rates were similar in both groups (SOX: 55.7% vs. SP: 52.2%). However ETS was not mentioned [16]. In this study, subgroup analysis in $HER2^-$ AGC showed similar ETS/DpR in the SOX ($n = 58$) and SP groups ($n = 128$) (SOX: median DpR 21.5%, range −44 to 80%; SP: median DpR 22%, range −97 to 80%; $P = 0.16$; Fig. 5). ETS percentages were SOX: 56.8%; SP: 50.7% ($P = 0.52$). Therefore, there were no significant differences between SOX and SP for both ETS and DpR. One possible explanation was that evaluation of tumor growth at 8 weeks might be too late in the $HER2^-$ subgroup because median progression-free survival and overall survival were observed in the early period. In this study, ETS was defined as tumor shrinkage at week 8 compared to baseline, and the cutoff value was 20%. This was because this definition was used in several reports about metastatic colorectal cancer who were treated with anti-EGFR inhibitor. In these patients, median progression-free survival and overall survival are about 10 months and over 30 months, longer than for HER2-negative gastric cancer. Therefore, ETS assessment before 8 weeks after the start of chemotherapy may be able to better classify ETS and non-ETS groups for HER2-negative AGC. Both the optimal time of evaluation (6–8 weeks) and the cutoff values (10–30%) set for the optimal differentiation of ETS and non-ETS, even in the metastatic colorectal cancer, are controversial. In this study, the actual measurement range of ETS was from 7 to 12 weeks. In subset analysis, ETS using data for 8 ± 2 weeks (range 7–10) showed better separation between responders and non-responders than 8 ± 4 weeks (range 7–12) in HER2-positive patients (range 7–10, $n = 39$, OS: HR 0.18, 95% CI 0.06–0.50, $P < 0.001$, PFS: HR 0.11, 95% CI 0.04–0.31, $P < 0.001$; range 7–12, $n = 100$, OS: HR 0.25, 95% CI 0.14–0.44, $P < 0.001$, PFS: HR 0.18, 95% CI 0.10–0.31, $P < 0.001$). On the other hand, ETS using data during 8 ± 2 weeks did not show any difference compared to 8 ± 4 weeks in HER2-negative patients (range 7–10, $n = 148$, OS: HR 0.68, 95% CI 0.44–1.03, $P = 0.07$, PFS: HR 0.55, 95% CI 0.37–0.83, $P = 0.004$; range 7–12, $n = 186$, OS: HR 0.69, 95% CI 0.48–1.01, $P = 0.059$, PFS: HR 0.55, 95% CI 0.38–0.78, $P = 0.001$). Therefore, although ETS using data within 8 ± 2 weeks might be optimal for predicting clinical outcomes, optimization of the time at which ETS in AGC should be measured would require several time points using computed tomography, especially in the prospective study that fixed the interval of evaluation.

The present study has some limitations. It was a retrospective study with a small study cohort. The cutoff value for DpR was the median value in this study, which inevitably depends on the time of tumor assessment; thus, the exact smallest volume is unknown. A further large-scale

prospective study is necessary to validate the clinical significance and the productiveness of ETS and DpR in this context.

Conclusion

These results indicate that, as with mCRC treated with chemotherapy plus EGFR inhibitor, ETS may be an early-on treatment predictor of the efficacy of $HER2^+$ advanced gastric cancer treated with first-line chemotherapy that includes trastuzumab.

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Compliance with ethical standards

Conflict of interest Eiji Shinozaki, Honoria from Merck Serono Co.,Ltd, Takeda Co., Ltd, Taiho Co.,Ltd, Chugai Co., Ltd, Ono Co, Ltd. Yakult Honsha Co., Ltd. Bayer Yakuhin Co., Ltd, Eli Lilly Japan K.K. The remaining authors declare that they have no competing interests.

Ethics The present study was performed in accordance with the Declaration of Helsinki, approved by our institutional review board (Registry No. 2016-1873) and involved human participants.

Informed consent We obtained comprehensive written informed consent for the study before chemotherapy was performed.

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