Original Article

Trastuzumab in combination with chemotherapy for HER2-positive metastatic gastric cancer patients underwent conversion therapy

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Background: Conversion surgery is a treatment that aims for R0 resection of primary advanced gastric cancers (GCs) that have responded well to systemic chemotherapy. We investigated the role of conversion therapy in initially unresectable metastatic cancer with positive HER2 status that responded to chemotherapy plus trastuzumab.

Methods: A total of 32 metastatic GC patients who underwent systemic chemotherapy plus trastuzumab sequenced by conversion surgery at Zhejiang Cancer Hospital between 2015 and 2020 were retrospectively reviewed.

Results: The observed overall survival (OS) and progression-free survival (PFS) for all the patients were 30.2 and 25.1 months, respectively. The 1-year survival rate was 81.25%, and the 1-year PFS rate was 78.13%. Univariate and multivariate analyses demonstrated that liver metastasis (P=0.021), peritoneal metastasis (P=0.047), para-aortic lymph node metastasis (16a1/b2) (P=0.048), macroscopic type 4 (P=0.027), number of noncurative factors (P=0.011), Yoshida *et al.* category (P=0.021), and inductive chemotherapy cycles (P=0.025) were independent prognostic factors for OS.

Conclusions: HER2-positive patients with potentially resectable disease had a remarkably good prognosis after conversion gastrectomy following trastuzumab treatment. Adequate selection of metastatic GC patients for conversion surgery is recommended.

Keywords: Gastric cancer; HER2-positive; conversion therapy

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Introduction

Gastric cancer (GC) is the fifth most common cancer and the fourth most common cause of cancer mortality globally (1). For patients with stage IV GC, the prognosis is very poor, with palliative chemotherapy remaining the principle therapeutic option (2,3). However, even with treatment, the overall survival (OS) time for patients with advanced GC is only 13–17 months (4,5).

In the REGATTA clinical trial, patients with stage IV GC with a single incurable factor, were randomized to receive chemotherapy alone or initial gastrectomy followed by chemotherapy. Patients underwent gastrectomy and subsequent systemic chemotherapy did not have any survival benefit compared with chemotherapy alone (6). Therefore, the REGATTA trial did not indicate the best treatment option for patients who have non-curable factors.

Several retrospective researches have explored the role of resection of the primary tumor and/or metastases in patients with stage IV GC and suggested that surgery might be associated with prolonged survival in select patients that responded well to systemic preoperative chemotherapy (7). Yamaguchi *et al.* reported the long-term survival of patients with advanced GC who underwent conversion therapy, with mean survival times of 28.3, 30.5, 31.0 and 24.7 months for categories 1, 2, 3, and 4, respectively, according to the new classification of advanced GC proposed by Yoshida *et al.* (8,9).

Newly developed combination regimens that include a HER2-targeted monoclonal antibody have demonstrated a promising response rate with moderate toxicity. Approximately 30% of intestinal-type GCs overexpress HER2, whereas 15% of mixed-type tumors, and 5% of diffuse-type tumors express HER2 (10). The phase III ToGA trial demonstrated that trastuzumab on the base of fluoropyrimidine plus cisplatin chemotherapy doublet regimen significantly improved the overall response rate (ORR) from 35% to 47% (P=0.0017) (10). Hence, the feasibility and survival benefit of conversion surgery for patients who respond to chemotherapy plus trastuzumab should be urgently addressed (11). Some case reports have shown that trastuzumab has a beneficial effect on tumor regression, R0 resection rate, and long-term survival (12,13). Nevertheless, any role of trastuzumab played in the context of conversion surgery have not been reported on a larger scale.

Metastatic GC is a heterogeneous disease with various extents of tumor load and is disseminated through diverse metastatic routes (14,15). Patients with different initial noncurative factors can obtain diverse survival benefits from chemotherapy and subsequent curative surgery. In some cases, inductive treatment results in a good response of the primary and metastatic lesions in these patients.

Here, we performed a retrospective analysis on the feasibility and efficacy of conversion surgery after preoperative anti-HER2 treatment, with a particular focus on selection of patients who might benefit from conversion therapy. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2886/rc).

Methods

Study population

Our study identified patients with histologically confirmed GC or esophagogastric junction cancer who received conversion treatment prior to surgical resection at Zhejiang Cancer Hospital from May 2015 to May 2020. Cases that satisfied all of the following criteria were included: (I) newly diagnosed as stage IV disease by imaging analysis; (II) HER2-positive, histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction cancer. We defined HER2 positivity as being IHC 3+ or IHC 2+ and *in situ* hybridization (ISH)-positive. (III) Received at least two cycles of chemotherapy plus trastuzumab as a conversion therapy (*Figure 1*).

Medical information, including demographic characteristics, tumor characteristics, treatment regimens, treatment responses, and survival, was retrieved from the patients' health records. A total of 32 patients that satisfied the inclusion terms were classified into four categories according to the classification by Yoshida *et al.* (9). Written informed consent was obtained from all patients. The ethical approval was waived by the Ethics Committee of Zhejiang Cancer Hospital due to the retrospective and non-interventional nature of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment regimens

First-line preoperative chemotherapies such as capecitabine plus oxaliplatin (referred to as the XELOX strategy), S-1 plus oxaliplatin (SOX strategy), S-1 (S-1 strategy), and S-1

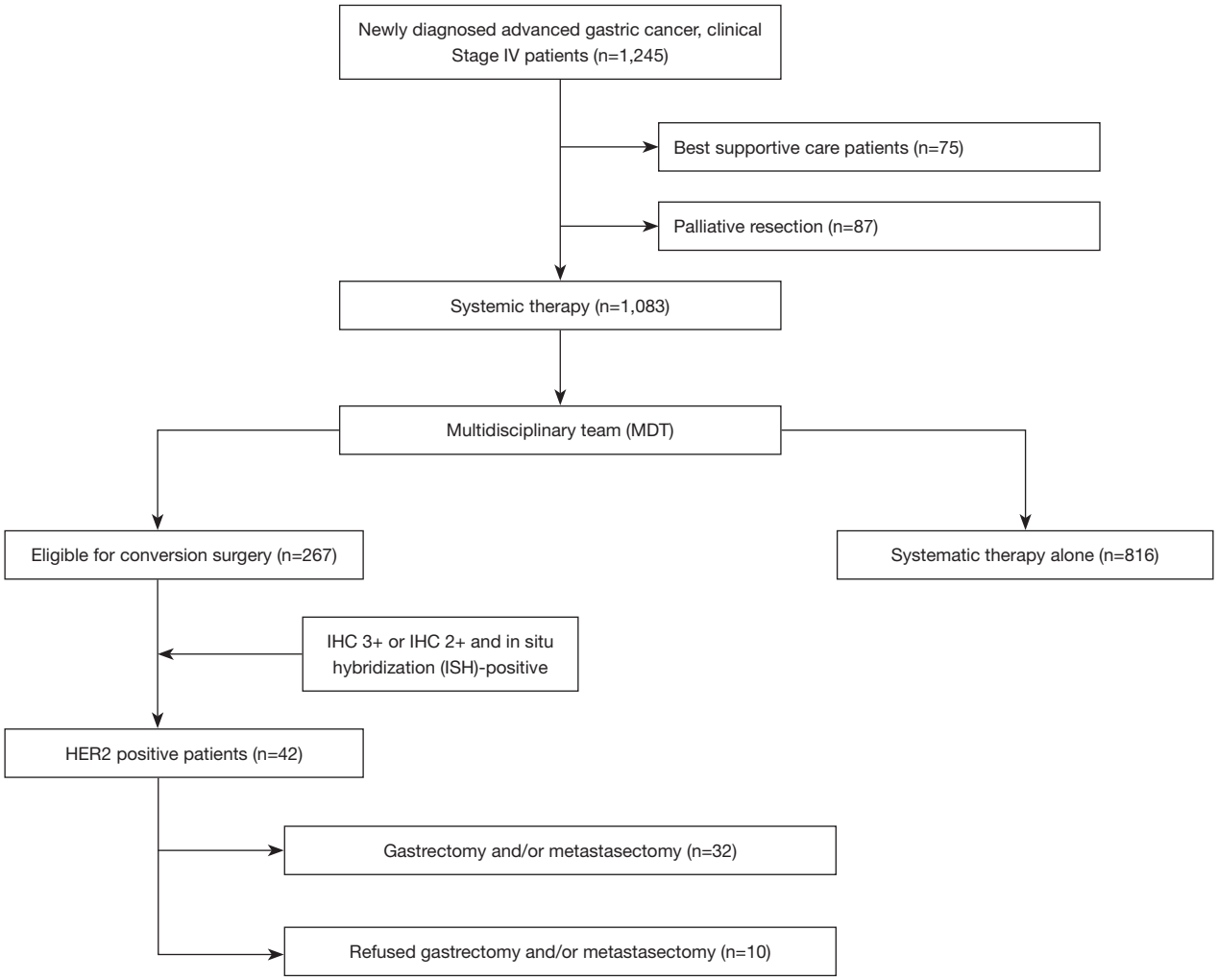

Figure 1 Flow chart. HER2, human epidermal growth factor receptor 2. IHC, immunohistochemistry.

plus docetaxel and cisplatin (DCS strategy) were delivered to GC patients, as decided by clinicians (16,17). A proficient multidisciplinary team (MDT), including radiologist, pathologist, surgeon, medical oncologist, and radiation oncologist, was responsible for evaluating operability. Therefore, conversion surgery is defined as a surgical treatment with the goal of curative resection of both primary and metastatic tumor in initially unresectable GC patients after response to chemotherapy.

Evaluation of the response to chemotherapy

The clinical response was assessed after 2–3 cycles of preoperative treatment based on contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis or magnetic resonance imaging (MRI). Radiographic tumour response was quantified by using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). All resected specimens were re-examined by the same pathology team to assess the extent of residual disease in accordance with the Japanese Classification of Gastric Carcinoma 3rd edition criteria, HER2 status, disease stage, and effect of preoperative therapy. We used the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) to evaluate the severity of adverse events associated with anticancer therapies. The Clavien-Dindo Classification of Surgical Classifications was used throughout surgery to grade adverse events (i.e., complications) that occurred as a result of surgical procedures. We only described complications above grade 3 and morbidity/mortality was

measured during surgical hospitalization.

Statistical analysis

Clinical data, including survival outcomes and disease status were followed up by telephone every 2 months or by record review. All analyses were performed by using the SPSS software. Comparisons of categorical variables between the groups were performed using the Fishers exact Chi-square test. Differences between the means of groups were compared using an independent sample *t*-test. Progression-free survival (PFS) was defined as the time from diagnosis of stage IV disease to progression or death. OS was defined as the time from diagnosis of stage IV disease to death due to any cause. Survival curves are estimated using the Kaplan-Meier method. All tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Figure 1 shows a flowchart of the study. A total of 32 HER2-positive primary advanced gastric adenocarcinoma patients who underwent preoperative trastuzumab plus chemotherapy and conversion surgery were included. The patient characteristics are shown in *Table 1*. By the date of the final follow-up, August 24, 2021, 17 deaths (53.1%) had occurred. The most frequent non-curable factor was para-aortic lymph node metastasis (16a1/b2) in 18 (56.3%) of the 32 patients.

Efficacy of pre-operative therapy and pathological outcomes

Efficacy of pre-operative therapy is summarized in *Table 2*. As the result showed, ORR was 65.6%, this treatment approach also resulted in a disease control rate (DCR) of 100.0%. Microscopically, 21.9% of patients presented with a pathological complete response.

Survival outcome

After a median follow-up of 25.4 (5.57–53.6) months, 19 patients relapsed, 17 patients died. The median OS and PFS were 30.2 and 25.1 months, respectively (*Figure 2*). The 1-year PFS rate and the 1-year survival rate were 78.13% and 81.25%, respectively.

Univariate and multivariate analysis demonstrated that liver metastasis (P=0.021), peritoneal metastasis (P=0.047), para-aortic lymph node metastasis (16a1/b2) (P=0.048), macroscopic type 4 (P=0.027), number of noncurative factors (P=0.011), Yoshida category (P=0.021), and induction chemotherapy cycles (P=0.025) were independent prognostic factors of OS (*Table 3*).

Table 4 shows the adverse events associated with chemotherapy in this study. Grade 3 or worse adverse events included neutropenia (6.3%), anemia (3.1%), thrombocytopenia (6.3%), anorexia (9.4%), nausea (9.4%), and fatigue (6.3%). No patients discontinued treatment due to severe AEs. No treatment-related deaths were reported in this study.

Postoperative complications, including wound infections (one case) and pulmonary infections (two cases) are shown in *Table 5*. No cases of postoperative death occurred in this study.

Among the 32 trastuzumab-treated patients, we checked the HER2 status in the primary specimen, 20 patients maintained HER2 positivity and seven patients achieved a complete pathological response (TRG 0), and their HER2 status were not available for re-evaluation (*Table 6*). Five patients lost HER2 positivity.

Notably, one patient who was diagnosed with bilateral multiple pulmonary metastasis on November 28, 2018 and received 6 cycles of S-1+ oxaliplatin + trastuzumab before conversion surgery (*Figure 3*). Metastatic pulmonary nodes disappeared after two cycles of induction therapy and remained undetectable. The patient was healthy throughout the follow up period, and there was no evidence of disease in his body.

Discussion

In the present investigation, conversion surgery after inductive therapy was performed in 32 patients with HER2-positive metastatic GC. Initially, we depicted the role of inductive therapy in this specific population. Then, data of ORR, OS, and PFS were greatly improved compared to those of conventional therapy.

The ToGA trial demonstrated that trastuzumab + chemotherapy prolonged OS by 2.7 months in patients with HER-2 positive gastric/gastroesophageal junction cancer compared with chemotherapy alone and improved the ORR (10). In our study the ORR was 65.6% and the median PFS and OS were 25.1 and 30.2 months, respectively. The difference in ORR may be due to the application of the DCS-T quadruplet regimen. This

Table 1 Baseline characteristics of the patients

Variable	Cases	Percentage (%)
Age (years)		
≥65	9	28.1
<65	23	71.9
Sex		
Male	20	62.5
Female	12	37.5
PS		
0	13	40.6
1	19	59.4
Metastasis sites		
Liver (H1)	5	15.6
Peritoneum	6	18.8
Para-aortic lymph node (16a1/b2)	18	56.3
Lung	1	3.1
Supraclavicular lymph nodes	2	6.3
Portal vein tumor thrombosis	2	6.3
Ascites	1	3.1
Location of primary tumor		
Upper third	4	12.5
Middle third	12	37.5
Lower third	16	50.0
Clinical tumor stage		
T2	2	6.3
T3	6	18.8
T4	24	75.0
Clinical nodal stage		
N0–1	5	15.6
N2–3	27	84.4
Histological type		
Intestinal	20	62.5
Diffuse	6	18.8
Mixed	6	18.8
Macroscopic type		
0–3 or 5	29	90.6
4	3	9.4
Historic classification		
Moderate-well differentiation	9	28.1
Low differentiation	23	71.9
Signet-ring cell component		
Yes	5	15.6
No	27	84.4
No. of noncurative factors		
1	17	53.1
≥2	15	46.9
HER2 status		
3+	16	50.0
2+/FISH+	16	50.0
Yoshida category[#]		
1	8	25.0
2	18	56.3
3	4	12.5
4	2	6.3
No. of cycles of induction chemotherapy		
1–2	5	15.6
3–5	21	65.6
≥6	6	18.8
Chemotherapeutic regimens		
XELOX/SOX	28	87.5
DCS	4	12.5
No. of cycles of postoperative chemotherapy		
0–2	0	0.0
3–5	26	81.3
≥6	6	18.8

[#], Yoshida category: Category 1 is defined as metastatic gastric cancer without visible peritoneal metastasis and surgical resection of metastasis is technically feasible. Category 2 is defined as metastatic GC without visible peritoneal metastasis and potentially resectable of metastasis. Category 3 includes peritoneal metastasis that is only cytologically positive and metastasis is potentially unresectable. Category 4 includes non-curable of metastasis. PS, performance status; HER2, human epidermal growth factor receptor 2; GC, gastric cancer.

regimen did not increase the incidence of severe AEs. Additionally, conversion surgery remarkably improved survival time in these patients. Intriguingly, combination therapy with trastuzumab seems to improve the pathological complete response rate.

Table 2 Treatment efficacy of the patients

Clinical and pathological response	Cases (%)
Clinical response	
Stable disease	11 (34.4)
Progressive disease	0
Partial response	21 (65.6)
Surgical procedure	
Proximal gastrectomy	2 (6.3)
Distal gastrectomy	23 (71.9)
Total gastrectomy	7 (21.9)
Residual tumor classification	
R0	30 (93.8)
R1/2	2 (6.3)
Extent of lymphadenectomy	
D0–1	2 (6.3)
D2	12 (37.5)
D2+PAND	18 (56.3)
TRG	
0	7 (21.9)
1	13 (40.6)
2	5 (15.6)
3	7 (21.9)

PAND, para-aortic lymph node dissection; TRG, tumor regression grade.

We found that loss of HER2-positivity occurred in 15.6% HER2-positive patients after anti-HER2 treatment. In addition, HER2-positivity loss was not associated with ORR, PFS, or OS. As shown in metastatic breast cancer, the loss of HER2 over-expression can also be observed in GC patients under the selective pressure of treatments (18-20). This phenomenon presumably was one of the biological reasons for the failure of anti-HER2 second-line strategies in initially HER2-positive diseases (21-23). The loss of the target is especially frequent in HER2-positive tumors classified as IHC2+/FISH positive (20). In the study by Wang *et al.*, the HER2 copy number decreased after anti-HER2 treatment, this phenomenon indicated HER2 amplification could be changed during the treatment process (24). In our study, five patients that were IHC2+ and FISH+ lost their HER2-positivity. Re-evaluation of HER2 status when diseases recur or progress is warranted because several new drugs such as trastuzumab deruxtecan (T-DXd) (DS-8201a) have been established for later line use as an anti-HER2 treatment (25,26).

Although the number of patients enrolled in this study was relatively small, most patients with measurable lesions achieved a major pathological response. In the retrospective study by Chen *et al.*, 2.1% of patients who received chemotherapy as preoperative treatment experienced complete remission (27). Our high pCR rate may partly be explained by the limited sample size, but the addition of trastuzumab should also be noted.

There was a patient with a severe case of multiple lateral lung metastasis who achieved a long remission after conversion surgery. The indications and optimal timing of surgery after palliative chemotherapy remains unclear, and should be further investigated.

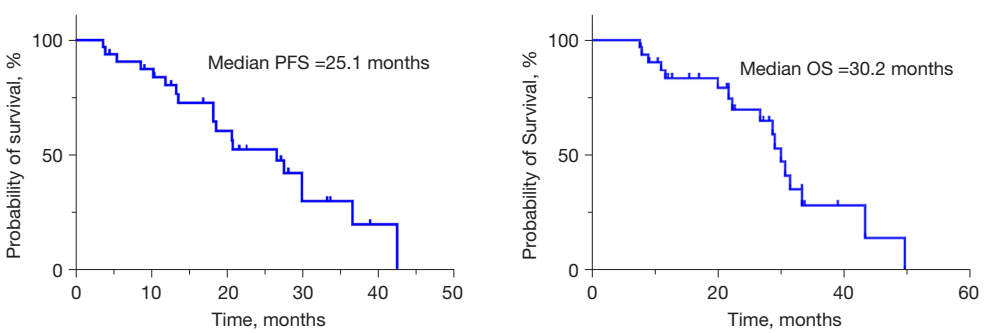

Figure 2 PFS and OS of the patients. PFS, Progression-free survival; OS, overall survival.

Table 3 Univariable and multivariable analysis of prognostic factors associated with overall survival of patients with conversion surgery and chemotherapy

Variable	Number	Univariable analysis		Multivariable analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (years)			0.425		
≥65	9	Reference			
<65	23	0.831 (0.733–1.165)			
Sex			0.132		
Male	20	Reference			
Female	12	1.176 (0.814–1.389)			
PS			0.210		
0	13	Reference			
1	19	1.134 (0.945–1.424)			
Liver metastasis (H1)			0.004		0.021
Yes	5	Reference		Reference	
No	27	0.614 (0.479–0.873)		0.657 (0.491–0.903)	
Peritoneal metastasis			0.023		0.047
Yes	6	Reference		Reference	
No	26	0.816 (0.745–0.956)		0.854 (0.791–0.992)	
Para-aortic lymph node metastasis (16a1/b2)			0.025		0.048
Yes	18	Reference		Reference	
No	14	2.852 (2.127–3.761)		2.467 (1.895–3.463)	
Location of primary tumor			0.153		
Upper third	3	Reference			
Middle third	18	1.154 (0.832–1.712)			
Lower third	11	1.011 (0.880–1.383)			
Clinical tumor stage			0.320		
T2	2	Reference			
T3	6	0.841 (0.549–1.112)			
T4	24	0.944 (0.747–1.143)			
Clinical nodal stage			0.067		
N0–1	5	Reference			
N2–3	27	0.741 (0.524–1.040)			
Histological type			0.135		
Intestinal	20	Reference			
Diffuse	6	1.124(0.867–1.414)			
Mixed	6	1.054 (0.878–1.372)			

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Number	Univariable analysis		Multivariable analysis	
		HR (95% CI)	P	HR (95% CI)	P
Macroscopic type					0.027
0–3 or 5	29	Reference	0.012	Reference	
4	3	2.145 (1.413–3.235)		1.988 (1.212–3.005)	
Historic classification			0.021		0.056
Moderate-well differentiation	9	Reference		Reference	
Low differentiation	23	1.326 (1.013–1.851)		1.267 (0.947–1.732)	
Signet-ring cell component			0.035		0.063
Yes	5	Reference		Reference	
No	27	0.873 (0.578–0.919)		0.913 (0.621–1.019)	
No. of noncurative factors			0.001		0.011
1	17	Reference		Reference	
≥2	15	2.784 (2.015–4.213)		2.285 (1.781–3.492)	
HER2 status			0.086		
3+	16	Reference			
2+/FISH+	16	0.842 (0.524–1.178)			
Yoshida category			0.007		0.021
1	8	Reference		Reference	
2	18	1.646 (1.518–2.504)			
3	4	2.150 (1.763–3.125)			
4	2	3.180 (2.549–4.655)			
No. of cycles of induction chemotherapy			0.012		0.025
1–2	5	Reference		Reference	
3–5	21	0.715 (0.513–0.947)		0.763 (0.581–0.969)	
≥6	6	0.602 (0.424–0.840)		0.635 (0.452–0.885)	
Chemotherapeutic regimens			0.346		
Two-drug regimen	28	Reference			
Three-drug regimen	4	1.037 (0.883–1.271)			
No. of cycles of postoperative chemotherapy			0.541		
0–2	0				
3–5	26	Reference			
≥6	6	1.015 (0.832–1.326)			

PS, performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

Table 4 Adverse events associated with pre-operative treatment

Adverse events	Grade 1–2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	16 (50.0)	2 (6.3)	2 (6.3)
Anemia	7 (21.9)	1 (3.1)	0
Thrombocytopenia	18 (56.3)	2 (6.3)	0
Febrile neutropenia	0	0	0
Anorexia	12 (37.5)	3 (9.4)	0
Nausea	12 (37.5)	3 (9.4)	0
Fatigue	14 (43.8)	2 (6.3)	0
Vomiting	13 (40.6)	0	0
Diarrhea	3 (9.4)	0	0
Stomatitis	5 (15.6)	0	0
Hand-foot syndrome	7 (21.9)	0	0
Increased creatinine	2 (6.3)	0	0
Hyponatremia	4 (12.5)	0	0
Sensory neuropathy	5 (15.6)	0	0

Table 5 Major postoperative complications of the surgery

Complication	Case (%)
Wound infections	1 (3.1)
Pulmonary infections	2 (6.3)
Anastomotic bleeding	0
Ileus	0
Abdominal infections	0
Acute pancreatitis	0
Death	0

Table 6 Changes in HER2 status after conversion therapy

Change in HER2 status	Conversion therapy, n=32 (%)
Loss of HER2 positivity	5 (15.6)
Maintained HER2 positivity	20 (62.5)
Complete pathological response	7 (21.9)

HER2, human epidermal growth factor receptor 2.

Until the DESTINY-Gastric01 study of T-DXd, there were no other globally approved HER2-targeted therapies for HER2-expressing GC, except for trastuzumab (10,26,28). T-DXd is an antibody-drug conjugate comprised a humanized anti- antibody against HER2, a novel linker and a topoisomerase I inhibitor. The randomized phase 2 trial DESTINY-Gastric01 assessed T-DXd compared with chemotherapy in pre-treated patients with HER2-expression advanced gastric or gastroesophageal junction adenocarcinoma (NCT03329690) (28).

Our study had some limitations. Foremost, this study was conducted in a single center, and the sample size was small, as the incidence of HER2-positive GC was relatively low. Next, the retrospective nature of the study is a limitation.

In conclusion, among the 32 patients with metastatic GC who underwent conversion surgery in this retrospective study, there were long-term survivors. With anti-HER2 treatment and adequate selection of stage IV GC patients, more benefit will derive from the conversion therapy.

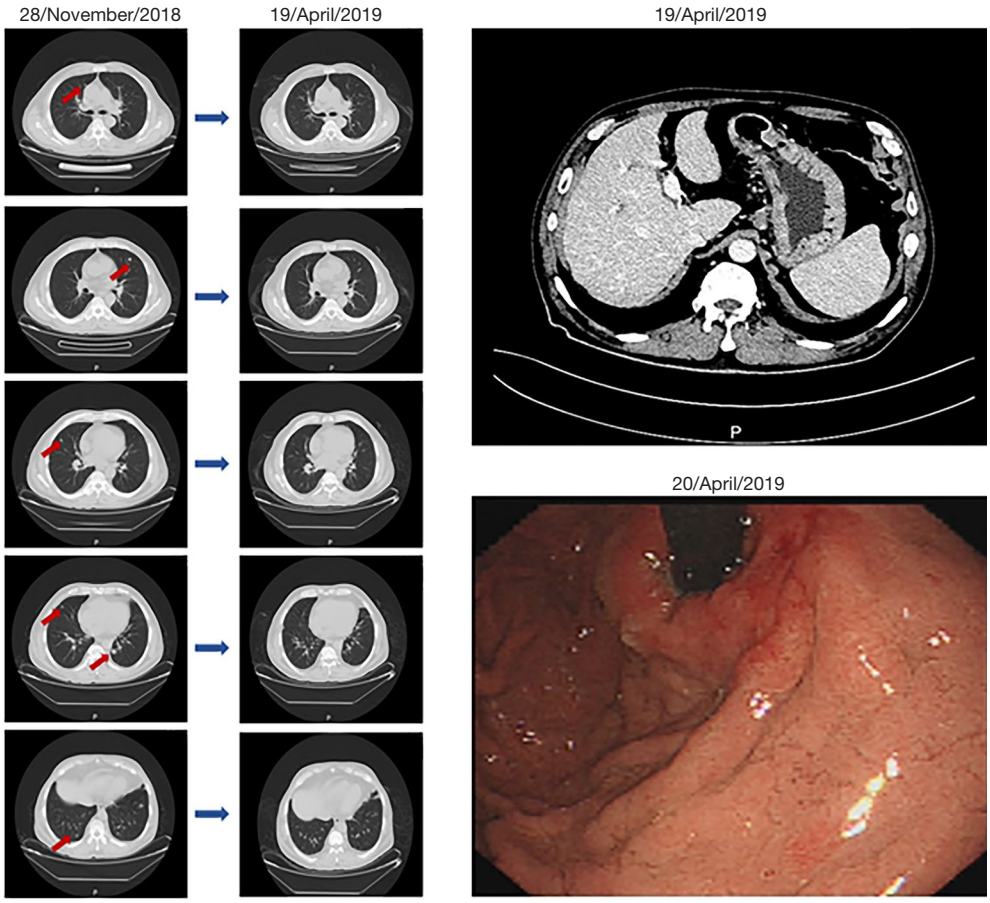

Figure 3 Representative images of a patient who got long survival time. The red arrows indicate lung metastasis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2886/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2886/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2886/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethical approval was waived by the Ethics Committee of Zhejiang Cancer Hospital due to the retrospective and non-interventional nature of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients.

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