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HER2 Expression in Carcinomas of the True Cardia (Siewert Type II Esophagogastric Junction Carcinoma)

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Abstract
Objectives To evaluate the HER2 status in patients with Siewert type II esophagogastric junction carcinoma.
Background Trastuzumab is now approved for use in the treatment of human epidermal growth factor receptor 2 (HER2)-positive unresectable metastatic gastric or esophagogastric junction (EGJ) carcinoma. Several studies have evaluated HER2 status in EGJ carcinoma, but none has addressed the implication of HER2 positivity in patients with Siewert type II EGJ carcinoma.
Methods We retrospectively evaluated the frequency of HER2 positivity in a large single-center cohort of 208 patients with Siewert type II tumors. The relations between HER2 expression and the outcomes and other clinicopathologic features were examined.
Results Overall, 18.2 % (38/208) of patients in our cohort had HER2-positive tumors. HER2 positivity was associated only with differentiated carcinomas. The 5-year overall survival (OS) rate was 58.7 %. The 5-year OS rates in the patient groups with HER2-negative and HER2-positive tumors were 61.2 and 48.5 %, respectively. There was no significant difference between the groups. Recurrence in the liver was observed in 23.7 % patients of the HER2-positive group and 7.6 % patients of the HER2-negative group. Multivariate analysis to identify the risk factors for liver recurrence revealed only HER2 positivity ($p = 0.0155$) as an independent predictive factor.
Conclusions HER2 positivity is a powerful predictor of liver recurrence in patients with Siewert type II EGJ carcinoma. Use of trastuzumab in combination with chemotherapy in an adjuvant setting can be a potentially useful therapeutic strategy to prevent hepatic recurrence in patients with resectable EGJ adenocarcinoma showing HER2 overexpression.

Introduction

Based on recent evidence provided by the Trastuzumab for Gastric Cancer (ToGA) study, trastuzumab is now approved for use in treating human epidermal growth factor receptor 2 (HER2)-positive unresectable metastatic gastric or esophagogastric junction (EGJ) carcinoma [1]. EGJ carcinoma—which involves the anatomic junction between the esophagus and the stomach—has attracted considerable attention recently because of a marked increase in its incidence [2, 3]. EGJ tumors have been classified based on their epicenters according to the Siewert system [4]. Siewert type II cancer is a true carcinoma of the cardia.

Several studies have evaluated the HER2 status in EGJ carcinomas. They reported that the HER2 positivity rates were higher in the EGJ carcinomas than in gastric carcinomas [5–8]. However, the role of HER2 as a prognostic factor in patients with this cancer remains controversial [5, 7, 9, 10] as none of the reports specifically addressed the implication of HER2 positivity in Siewert type II EGJ carcinoma.

The purpose of this study was to evaluate the frequency of HER2 positivity in Siewert type II cancers. The relations between HER2 expression and the prognosis and other clinicopathologic features were examined.

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Patients and methods

Patient population and staging

Between January 1980 and January 2010, a total of 11,647 patients with gastric carcinoma underwent surgery at the Gastric Surgery Division, National Cancer Center Hospital, Tokyo. Trastuzumab was not administered to patients during this period. Of these patients, 299 were diagnosed as having Siewert type II EGJ carcinoma. We defined Siewert type II EGJ carcinoma based on a definition of this type of carcinoma described previously [3]. In brief, the epicenter of the tumor was taken as the point midway between the proximal and distal extent of the gross tumor mapped on a photograph of the resected specimen. A lesion was considered a Siewert type II EGJ carcinoma if its epicenter was within 1 cm proximal and 2 cm distal to the anatomic EGJ. It has been routine clinical practice in this hospital since 1962 to obtain detailed clinical photographs of all postoperative specimens. Each specimen is sectioned at 5-mm intervals, and the location of each cut and the tumor are mapped onto these photographs by the pathologist. Because these pathology reports with photographs were made precisely, the tumors are classified precisely.

Of the 229 patients, 225 underwent an R0/R1 operation. Of these 225 patients, 208 in whom testing for HER2 was successfully conducted by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) were enrolled in this study. All of the specimens were routinely fixed in 10 % formalin and were embedded in paraffin. Using a representative whole section, tumors were tested for the HER2 status with IHC (HercepTest; Dako, Copenhagen, Denmark) and FISH (PathVysion; Abbott, Abbott Park IL, USA) (HER2/CEP17 ratio was $\geq$2). Tumor samples were scored as IHC 3+ or 2+ if $\geq$10 % cells anywhere in the tumor tissue showed strong or equivocal membrane staining, respectively. Samples with <10 % of cells showing strong membrane staining were scored as IHC 2+. Cases with IHC 3+ and IHC2+/FISH-positive were judged as being HER2-positve [11].

We conducted the tumor staging according to the International Union Against Cancer (UICC) TNM staging system for EGJ cancer [12]. Well-differentiated and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as differentiated-type carcinomas. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma were classified as undifferentiated-type carcinomas. Postoperative information was obtained from the follow-up records of the patients and the city registry office.

Table 1 Correlation of HER2 scores with clinicopathologic variables

Variable	HER2 scores		*p*
	Scores 0, 1+, and 2+ with FISH− $n = 170$	Score 2+ with FISH+; HER2 score 3+ $n = 38$	
Age (years)			
<65	87	18	0.7217
≧65	83	20	
Sex			
Male	139	35	0.1484
Female	31	3	
Tumor size			
<5 cm	67	10	0.1419
≧5 cm	103	28	
Tumor histology			
Differentiated	110	33	0.0068
Undifferentiated	60	5	
pTNM stage[a]			
I	37	5	0.2458
II	34	8	
III	82	24	
IV	17	1	
Lymphatic invasion			
Negative	59	10	0.3482
Positive	111	28	
Vascular invasion			
Negative	98	20	0.5913
Positive	72	18	
Lymph node metastasis			
Negative	64	11	0.3545
Positive	106	27	
pT			
T1	37	7	0.1807
T2	18	2	
T3	65	22	
T4	50	7	

χ^2 test using two-sided Fisher's exact test

HER-2 human epidermal growth factor receptor 2, *FISH* fluorescence in situ hybridization

[a] Union Internationale Contre le Cancer (UICC), 7th edition

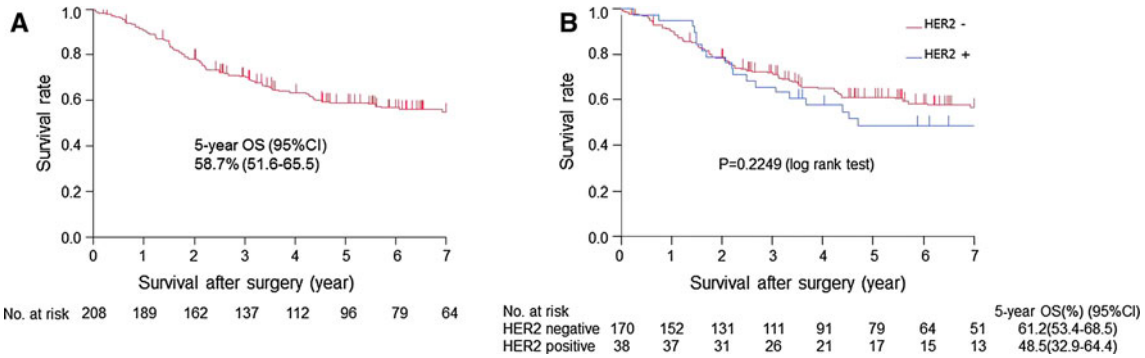

Fig. 1 OS following resection of type II EGJ carcinoma. **a** All cases. **b** HER2 positivity. *95 %CI* 95 % confidence interval

Statistical analysis

This retrospective study was designed to evaluate the frequency of HER2 positivity in patients with Siewert type II cancer. The relations between HER2 expression and the outcomes and other clinicopathologic features were examined.

Statistical analysis was carried out using JMP 8.0.1 (SAS Institute, Cary, NC, USA). The overall survival (OS) rate was calculated from the date of the operation to the date of death from any cause. Patient survival data were obtained from the patient medical records and census registries. We constructed Kaplan–Meier survival curves to estimate the impact of HER2 positivity on survival. We used the log-rank test for comparisons.

Fisher's exact test was applied to assess the univariate relations between clinicopathologic variables and HER2 positivity and to assess the correlation of the HER2 status with the initial site of recurrence. Values of $p < 0.05$ were considered to indicate statistical significance.

A multivariate logistic regression analysis was performed to identify the independent risk factors associated with liver recurrence among the variables: HER2 status, sex, age, presence/absence of lymphatic invasion and venous invasion, tumor size, tumor histology, pT, and pN.

Results

Patient demographics and baseline characteristics

Overall, 18.2 % (38/208) of patients had HER2-positive tumors in our study cohort. The relations between HER2 positivity and various clinicopathologic variables were investigated (Table 1). The results revealed that HER2 positivity was associated only with a differentiated type of tumor histology.

Table 2 Correlation of HER2 scores with initial site of recurrence

Site of recurrence	HER2 scores Scores 0, 1+, and 2+ with FISH− ($n = 170$)	HER2 score Score 2+ with FISH+; HER1 score 3+ ($n = 38$)	*p*
Liver	13 (7.6 %)	9 (23.7 %)	0.0075
Peritoneal	11 (6.5 %)	2 (5.3 %)	1.0
Lymph node	20 (11.8 %)	5 (13.2 %)	0.7855
Local	5 (2.9 %)	2 (5.3 %)	0.6139
Others	19 (11.2 %)	3 (7.9 %)	0.7719

χ^2 test using two-sided Fisher's exact test

Survival

The median OS was 9.5 years for the entire cohort (208 patients). The median duration of follow-up of the survivors was 6.4 years (range 0.2–20.7 years). In all, 101 patients died during follow-up: 65 deaths were due to recurrence and the remaining 36 to other causes. The 5-year OS rate of the entire cohort with Siewert type II EGJ carcinoma was 58.7 %. The 5-year OS rates in the patient groups with HER2-negative and HER2-positive tumors were 61.2 and 48.5 %, respectively. There is no significant difference between the groups (Fig. 1).

Mode of recurrence

The initial sites of recurrence are shown in Table 2. The most frequent site of recurrence was the liver in the HER2-positive group (23.7 %), followed by the lymph nodes (13.2 %). In the HER2-negative group, the most frequent initial site of recurrence was the lymph nodes (11.8 %), followed by the liver (7.6 %) and peritoneal cavity (6.5 %). There was a statistically significant difference between the two groups regarding the incidence of the initial recurrence in the liver.

Table 3 Multivariate logistic regression analysis to identify independent risk factors associated with liver recurrence

Variable	OR	95 % CI	*p*
HER2 (∓)	3.85	1.30–11.62	0.0155
Sex (M/F)	0.71	0.10–2.98	0.6612
Age (<65/≧65 years)	0.79	0.29–2.13	0.6448
Lymphatic invasion (∓)	2.57	0.58–18.30	0.2274
Venous invasion (∓)	1.41	0.50–4.15	0.5199
Tumor size (<50/≧50 mm)	0.80	0.26–2.60	0.6936
Histology (diff/undiff)	0.56	0.17–1.66	0.3065
pT (1–3/4)	2.81	0.97–8.59	0.0582
pN (0/1–3)	3.05	0.66–22.20	0.1606

OR odds ratio, *CI* confidence interval, *diff* differentiated, *undiff* undifferentiated

The relevance of HER2 for liver recurrence was assessed by multivariate logistic regression analysis after adjustments for the following factors: HER2 status, sex, age, presence/absence of lymphatic invasion and venous invasion, tumor size, tumor histology, pT, and pN (Table 3). Multivariate analysis to identify the independent risk factors for liver recurrence revealed that only HER2 positivity ($p = 0.0155$) was an independent predictive factor for liver recurrence.

Discussion

There was an 18.2 % incidence of HER2-positive tumors in our study cohort. Reported rates of HER2 positivity in gastric or EGJ carcinomas from previous series using different HER2 scoring systems varied from 4 to 53 % [13]. The series from Japan and Korea using the same scoring system as in the present study reported an HER2 positivity rate of 8–13 % [6, 14, 15]. The prevalence of HER2 positivity in the present study fell beyond the upper limit of this range.

Several authors have reported a strong correlation between HER2 expression and differentiated tumor histology [1, 5, 7, 9, 14, 16, 17]. This correlation was confirmed for Siewert type II tumors in the current study.

In our previous article [3], a multivariate Cox regression analysis revealed that the patient's age, pN category (pN0/1/2/3), and residual tumor classification (R0/1) were independently associated with outcome. This study showed that HER2 status was not associated with the OS [14, 17, 18]. The role of HER2 as a prognostic factor in gastric cancer remains controversial [5, 7, 9, 10]. HER2-positive tumors are expected to have more aggressive characteristics than HER2-negative tumors because one of the main functions of HER2 is to promote cell growth, differentiation, and survival [19, 20]. In several series of patients with resected disease [14, 17, 18], however, the HER2 status did not influence the outcomes after operation. Although our patient cohort was small, the present results suggest that HER2 status might not influence the outcomes after gastrectomy.

The analysis using the logistic regression model identified only HER2 positivity as a strong predictor of recurrence in the liver as the initial site of recurrence. Janjigian et al. [5] also found that HER2 positivity was associated with a high risk of liver metastasis in gastric cancer patients. The predominant site of recurrence after gastrectomy for differentiated advanced adenocarcinoma is reported to be the liver [21]. We previously also reported vascular invasion as a risk factor for liver recurrence [22].

It is noteworthy that HER2 positivity was identified as the only predictor of liver recurrence in patients with Siewert type II cancer, although we included both vascular invasion and histology as candidate risk factors for liver recurrence in our model for the multivariate analysis. Therefore, we need to bear in mind that HER2 positivity is a powerful predictor of liver recurrence in patients with Siewert type II esophagogastric carcinoma.

From this point of view, although HER2 may not be a negative prognostic factor for survival in Siewert type II EGJ carcinoma after gastrectomy with curative intent, it does not negate its value as a predictive marker. Although control of liver recurrence is beyond the hands of the surgeon, the ToGA study demonstrated the usefulness of trastuzumab administered in combination with chemotherapy for HER2-positive advanced gastric or EGJ cancer. Use of trastuzumab in combination with chemotherapy in an adjuvant setting can be a potentially useful therapeutic strategy to prevent hepatic recurrence in patients with resectable EGJ adenocarcinoma displaying HER2 overexpression.

Conflict of interest The authors have no conflicts of interest to declare.

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