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HER-2 Status and Heterogeneity in Gastric Cancer: An Experience at a Community Hospital

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Abstract

Background: The efficacy of the trastuzumab therapy in breast cancer patients prompted studies to evaluate potential clinical benefit of the drug in patients with HER2 positive gastric cancer. Unlike in breast cancer, the studies, in gastric cancer to date have yielded inconsistent findings regarding the frequency of HER-2 status. Furthermore, few studies have shown that intratumoral heterogeneity can lead to false negative results. All studies were done at the large medical centers. At the community hospital, we wish to assay HER-2 status intratumoral heterogeneity in patients with gastric cancer, and compare the results with that of large medical centers.

Materials and Methods: We investigated 185 cases of gastric cancer specimens using immunohistochemistry (IHC) for HER2 status. The matched biopsy and resection specimen of 30 patients were also investigated for their correlation and the presence of intratumoral heterogeneity.

Results: The positive HRE2 status was 29.7% (n=55), falling between the published data .One of two neuroendocrine tumors was HER2 positive, which was never reported before.

We found the concordance rate of 83% in 30 matched biopsy and gastrectomy specimens; 57% of the gastrectomy specimens showed intratumoral heterogeneity.

Conclusion: Anti-HER2 targeted therapy has been approved by FDA, Japan, and European Medicine Agency, as a standard initial treatment in HER2 positive gastric cancer. Overall, both biopsy and resection specimens are appropriate for HER-2 testing. The wide range of HER-2 frequency giving in the literature indicated that some problems exist. We are hoping that future study will clarify those confusing problems and standardized HER-2 assay method will become available. It is crucial for accurate selection of patients who could really benefit from a targeted therapy.

Keywords: HER-2; Gastric cancer; Trastuzumab; Immunohistochemistry; Heterogeneity; Biopsy

Abbreviations

IHC: Immunohistochemistry, FISH: Fluorescence *In Situ* Hybridization, ToGA: Trastuzumab for Gastric Cancer

Introduction

The role of HER2 in tissue is to promote cell proliferation and suppress apoptosis, resulting in excessive cell growth gain malignant property to invasion metastasis and angiogenesis [1]. Overexpression/amplification of HER2 have been detected in various cancers, and most widely studied in breast cancer since the late1980 [2]. It was found that HER2 positive breast cancer was associated with very poor prognosis; as compared with HER2 negative cancer. Consequently, a monoclonal antibody, trastuzumab, was discovered. Many studies have confirmed treatment with this antibody to HER2 positive breast cancer patients conferring a survival benefit, and improved outcomes as compared with the established therapies using cytotoxic agents alone. Ever since, with increasing understanding of molecular biology of HER2, the treatment of HER2 positive breast cancer has revolutionized, and its outcomes significantly improved [3].

The efficacy of the trastuzumab therapy in breast cancer patients prompted studies to evaluate potential clinical benefit of the drug in patients with HER2 positive gastric cancer. Unlike in breast cancer, the studies, in gastric cancer to date have yielded inconsistent findings regarding the prognostic and treatment relevance of HER2 [4-8].

Immunohistochemistry (IHC) is the most widely used method to evaluate HER2 status as compared with fluorescence in situ hybridization (FISH). IHC is easier to perform and relatively inexpensive; therefore, it is used more often. In most cases, the biopsy specimen is used for IHC. Giving the published data of the HER2 status in positive gastric cancer varies considerably [9]. It may make one wonder whether the biopsy specimens are representative for HER2 status in patients with gastric cancer. Furthermore, few studies have shown that intratumoral heterogeneity can lead to false negative results. An accurate assessment of HER2 is crucial to select patients who will benefit most from the therapy.

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The aim of this study is to assess the frequency of HR2 status in gastric cancer in a community hospital. Meantime, we try to correlate HER2 status between matched biopsy and resection specimens of gastric carcinoma in order to determine whether the biopsy specimens are predictive of HER2 status in gastric cancer patients.

Materials and Methods

185 cases of gastric biopsy between January 2016 and December 2020 with diagnosis of gastric cancer were retrieved from our pathology data base for HER2 analysis. The original H and E stained sides were adequate to assess for histological type. In 30 patients, they underwent gastric resection, after biopsy was done confirming the diagnosis of gastric cancer. In these patients, matched biopsy and resection specimens were compared for the HER2 status.

Immunohistochemistry

Immunohistochemitry (IHC) for HER2 was performed on 185 diagnostic biopsy specimens and representative 30 blocks from patients who underwent gastrectomy.

In the biopsy series, the number of tissue fragments on the slide was 5.9 in average. In the surgical series, one of the most representative blocks was selected.

HER2 IHC was performed on formalin-fixed paraffin embedded tissue using Leica, Bondmax automated stainner with rabbit monoclonal antibody (Zeta: no Z2564RL Arcadia, CA, USA) applied at 1: 100 dilution. In each run, negative and positive controls were included. The gastrectomy and biopsy specimen were scored for HER2 overexpression according to Hofmann et al.'s criteria [10]. One pathologist interpreted the stained slides. When difficult cases were encountered, two pathologists used the double-headed microscope together to achieve the consensus interpretation of these cases.

Results

The demographic data and clinical features are noted in Table 1. It is worth mentioning that for the pathological subtype of gastric cancer, we used WHO classification, instead of Lauren classification. The majority were of intestinal type (n=178, 96.2%); diffuse type (n=4, 2.1%), mixed (n=1, 0.5%), neuroendocrine tumor (n=2, 0.2%). HER-2 positivity was phenotypically associated with differentiated histology.

When Hoffman et al.'s criteria [10] were followed; the results of HER2 analysis were shown in Figure 1. (IHC 3+ 29.7%; IHC 2+ 12.9%; IHC 1+ 35.1%; negative 13.5%). Our study showed highest HER-2 overexpression rate in intestinal type, followed by diffuse type and mixed type. HER-2 status was also related to good differentiation. One of two neuroendocrine tumors was HER2 positive (Figure 2), which was never reported before. The limitation of our study is that IHC 2+ cases were not further evaluated by fluorescence in situ hybridization method (FISH).

Matched biopsy and resection specimens

As shown in Table 2 and 3, concordance of IHC HER-2 status on biopsies and gastrectomy was seen in 83%. There was no definition of heterogeneity currently existing. In this study, we defined heterogeneity as detection of areas in tumor showing different HER2 staining score [11]. In Table 3, five cases were discordant; 4 were positive on resection only, and one was positive on biopsy only. The reasons for the 4 discordant cases were attributed to intratumoral heterogeneity. In case 3, HER-2 was IHC 2+ on biopsy, but was shown to be negative in the resection. A possible explanation for this discrepancy could be delayed fixation after the specimen was resected. Overall, the result of the heterogeneity in the 30 gastrectomy specimens was 57%.

Table 1: Demographic data of the patients (n=185).

Sex	
Male	108
Female	77
Age	
Male	
Range	55-94
Median	75
Female	
Range	54-95
Median	75
Gastric carcinoma subtype	
Intestinal	178
Diffuse	4
Mixedsw	1
Neuroendocrine CA	2
Histological grad	
Well differentiated	0
Moderately differentiated	79
Poorly differentiated	76
Site of biopsy	
Antrum	56
Body	72
Cardia	57

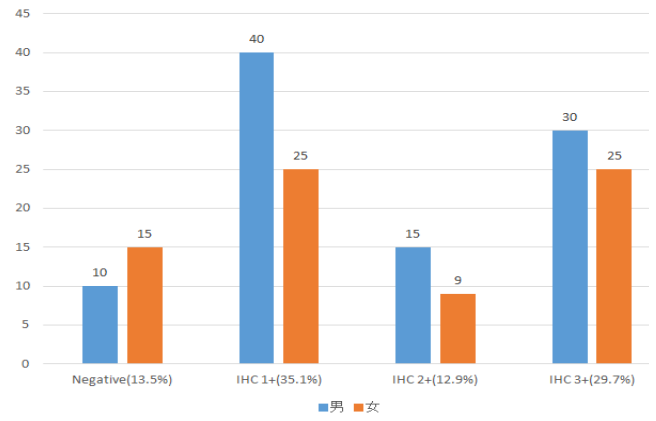

Figure 1: Results of HER-2 status of 185 biopsy specimens.

Discussion

The published data with regard to percentage of patients of HER2 positive gastric cancer seemed to be rather wide; 6.1-32.0%

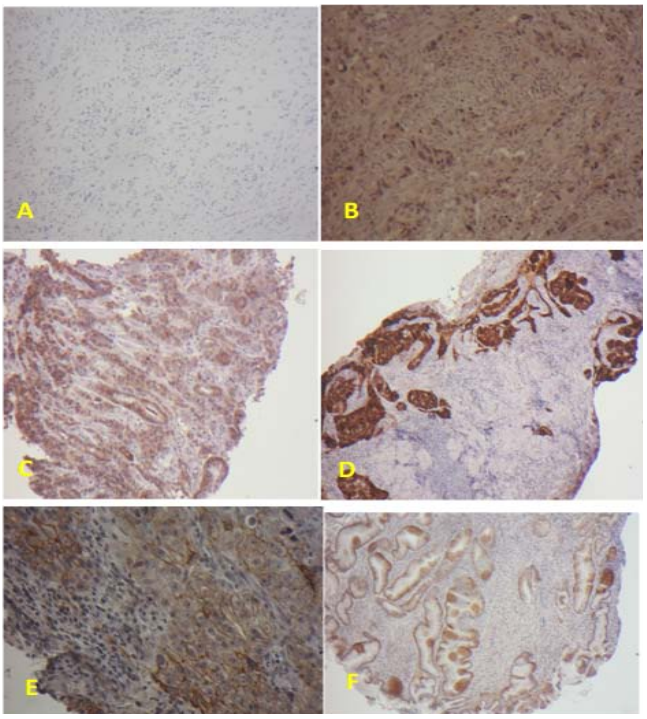

Figure 2: A: negative, no reactivity or membranous reactivity in <10% of cells. B: 1+, faint/barely perceptible membranous reactivity in>10% of cells. C: 2+, weak to moderate or basolateral membranous reactivity in >10% of tumor cells. D: 3+, moderate to strong complete or basolateral membranous reactivity in >10% of tumor cells. E: IHC 3+ of the patient with neuroendocrine tumor. F: IHC 2+ can be seen on the normal mucosal glands.

[9]. There are several possible reasons for this, including the use of different antibodies to assess HER2 status, the subjectivity of the pathologists' interpretations, and different scoring system being employed, etc. In our series, 1 of two cases of neuroendocrine tumor had HER2 3+, which has never been reported (Figure 2E). Our results of HER-2 positivity rate of 29.7 % fell in the range of IHC studies from a literature survey by Hoffman et al. [10], but on the high side above the mean of 17.6%. The wide range of HER-2 positive rate in the published data indicates that there is a need for standardization of HER-2 testing. Lee et al. [12], suggested the need to expand the IHC 2+ cases for further evaluation by FISH method. In the study by Pirelli et al. [13], there were two overexpressed cases that were not amplified. Similar results were in the series by Yang et al. [11], and in a small percentage of the ToGA trial series [14]. In gastric cancer, the gene amplification may not be the primary mechanism by which the protein is overexpressed. Therefore, IHC 2+ cases might not need for further evaluation by FISH.

There are relatively few studies performed thus far examining matched biopsy and resection specimens of gastric cancer. In our 30 patients, the concordance rate was 83%. as compared with other studies; 74.1%, 79% and 96.1% respectively [3,12,13].

The discordance was mostly due to intratumoral heterogeneity. Since there is no definition of heterogeneity currently existing, it was not possible to compare our results of 57% with that of others study; especially our cohort study was small in number. In view of the well-described problem of intratumoral heterogeneity in gastric cancer, it would be expected that examination of gastric biopsies alone might result in a proportion of false positive and/or false negative cases, since biopsy samples only represent a small part of the cancer. In this respect, Ruschoff et al. [15] recommended that ideally, at least 6-8 fragments of tumor should be present in biopsies for adequate assessment; in our series of biopsy specimens, there were average of 5.9 fragments on the slides. Validation of our definition of heterogeneity is required prior to clinical application with large cohort number.

Table 2: Concordance of HER2 in gastric cancer between biopsy and resection.

Case	Age/ Sex	No of fragments on sides	No with tumor	Lauren type	Grade	IHC Status	
						Biopsy	Resection
1	83/F	4	3	Intestinal	2	3+	3+
2	78/M	7	4	Diffuse	3	3+	3+
3	57/M	3	2	Intestinal	2	2+	2+
4	79/M	6	3	Intestinal	2	3+	3+
5	74/M	5	3	Intestinal	2	2+	2+
6	54/F	9	7	Intestinal	3	1+	1+
7	84/M	4	4	Intestinal	2	0	0
8	91/F	6	3	Intestinal	2	1+	1+
9	80/F	5	2	Diffuse	3	1+	1+
10	59/M	4	2	Diffuse	3	0	0
11	81/M	8	6	Intestinal	2	3+	3+
12	80/M	3	2	Intestinal	3	1+	1+
13	82/F	6	4	Intestinal	3	1+	1+
14	63/F	5	3	Intestinal	2	3+	3+
15	78/M	7	5	Intestinal	2	0	0
16	85/M	9	6	Intestinal	3	3+	3+
17	82/M	8	5	Intestinal	2	1+	1+
18	86/F	6	4	Intestinal	3	2+	2+
19	60/M	5	3	Mixed	3	1+	1+
20	71/M	7	4	Intestinal	2	3+	3+
21	59/M	7	5	Intestinal	3	1+	1+
22	75/M	3	3	Intestinal	2	3+	3+
23	70/F	6	4	Intestinal	2	2+	2+
24	75/M	8	6	Intestinal	2	3+	3+
25	74/F	5	3	Intestinal	3	1+	1+

Grade 1: Well differentiated; Grade 2: Moderately differentiated; Grade 3: Poorly differentiated.

Table 3: Characteristics of discordant cases.

Case	Age/ Sex	No of fragments on sides	No with tumor	Lauren type	Grade	IHC Status	
						Biopsy	Resection
1	79/M	9	7	Intestinal	2	1+	3+
2	62/M	7	5	Diffuse	3	1+	3+
3	76/M	3	2	Intestinal	2	2+	Negative
4	69/M	6	3	Intestinal	2	2+	3+
5	75/M	5	3	Intestinal	2	2+	3+

Grade 1: Well differentiated; Grade 2: Moderately differentiated; Grade 3: Poorly differentiated.

Conclusion

Anti-HER2 targeted therapy has been approved by FDA, Japan, and European Medicine Agency, as a standard initial treatment in HER2 positive gastric cancer. The trial for advanced gastric cancer or gastro-esophageal junction cancer (ToGA) [15] showed a statistically significant gain in overall survival in HER2 positive patients, who received the combined treatment of trastuzumab and chemotherapy compared to those treated with chemotherapy alone. We reported a case of gastric cancer with extensive liver metastasis [16], the patient was treated with trastuzumub with combined chemotherapy. Four years after therapy, the liver metastasis, as well as the primary tumor in the stomach has cleared up. He is healthy like a normal man. At a community hospital, we have started routinely performing HER2 analysis on patients with gastric cancer. We are hoping that future study will clarify those confusing problems, and standardized HER-2 assay method will become available for accurate selection of patients who could really benefit from the targeted therapy.

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