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Oncology

# CORRELATION OF HER 2 AND E-CADHERIN EXPRESSION WITH CLINICOPATHOLOGICAL FEATURES IN GASTRIC CANCER

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**ABSTRACT** HER2 and E-cadherin are two predictive biomarkers in gastric cancer. This study was proposed to establish the expression of HER2 and E-cadherin in gastric adenocarcinoma and to find its correlation with different histopathological features. A total of 65 patients with gastric adenocarcinoma were included in the study. Histopathological examination and IHC studies were done on gastrectomy specimens received in Department of Patholgy, Medical College, Thrissur Kerala. The intestinal variant of gastric cancer was the most common among the samples (37; 56.92%) and most of the patients had moderately differentiated (26, 40%) adenocarcinoma. Overall, 4 (6.15%) patients had tumors that were scored as HER 3+, and 9 (13.85%) patients had tumors that were scored as E-cadherin +3. None of the clinicopathological features had a significant association with HER 2 or E-cadherin expression. Larger studies with standardized testing and scoring are required before using these biomarkers in targeted therapy.

**KEYWORDS :** gastric cancer, HER2, E-cadherin

## Introduction

Gastric cancer is one of the most common adenocarcinomas in Indian population (Shrikhande et al, 2014). Prognosis of this cancer is very poor and the standard therapy seems to be having unsatisfactory clinical outcomes (Patel & Kooby, 2011). Oncological treatment now has a paradigm shift to customized therapies using biomarkers. Predictive biomarkers can be used to identify subpopulations of patients who are most likely to respond to a treatment (Italiano, 2011).
HER2 is one of the four members of the human EGFR family of receptor tyrosine kinases and is expressed in both normal and cancerous cells. Overexpression of HER2 results in cell proliferation, growth and cell survival (Gravalos & Jimeno, 2008). Prognostic and predictive value of this biomarker is well studied and established in breast cancer, but its value is yet to be confirmed in gastric cancer. The rate of HER 2 overexpression in different studies ranges from as low as 2% to as high as 91% (Grabsch, Sivakumar, Gray, Gabbert, & Müller 2010; Allgayer et al., 2000).

E-cadherin gene produces the E-cadherin transmembrane glycoprotein that plays an important role in epithelial cell adhesion and differentiation (Devita, Vincent, Hellman, & Rosenberg, 2012). Mutation in this gene is found to be associated with various epithelial cancers. In some studies, level of E-cadherin expression was directly linked to sensitivity of tumor cells to chemotherapy (Wang et al., 2009). Information on E-cadherin expression and its association with various clinicopathological factors are heterogenous and conflicting.
There is a paucity of information on the expression of these biomarkers in gastric cancer and their correlation with clinicopathological features from India. Considering the prospects of a targeted therapy with these biomarkers, it is important to have adequate information on the expression profile of HER2 and E-cadherin in gastric cancer. This study was proposed with the objective of establishing the expression of HER2 and E-cadherin in resectable gastric adenocarcinoma and to find its correlation with different clinicopathological features.

## Materials and Methods

This study was conducted for a period of 1.5 years from 2015 to 2017 at Department of Pathology, Govt Medical College, Thrissur, Kerala. A total of 65 patients with diagnosed cases of resectable gastric adenocarcinoma was included in the study. Gross appearance and microscopic features of gastrectomy specimens received in pathology department were studied in detail. Immunohistochemical staining was done on selected paraffin blocks of tumor tissues. Haematoxylin and eosin stained sections were examined. Immunohistochemically stained sections were used for scoring. IHC was done using Poly Excel HRP /DAB detection system.

Expression of the biomarkers were noted and correlated with different clinicopathological factors of the tumor. Correlation of different factors was analyzed using Chi-square test. All statistics were performed using 2-sided analysis, with a significance level of $p<0.05$.

## Result

The study population consisted of 65 patients with 52 males (80%) and 13 females (20%). The mean age of the patients in the study was 59.84 ± 10.18 years of which 37 (56.93%) were above 60 years while 28 (43.07%) patients were below 60 years. Fifty six patients out of the total 65 had tumor of pT4 according to the TNM classification. The intestinal variant of gastric cancer was the most common among the samples (37; 56.92%), followed by diffuse variant (23; 35.38%) and mixed (5; 7.69%; **Figure 1**). Most of the patients had moderately differentiated (26, 40%) adenocarcinoma, while 24 (36.92%) had poorly differentiated and 15 (23.07%) well differentiated adenocarcinoma.

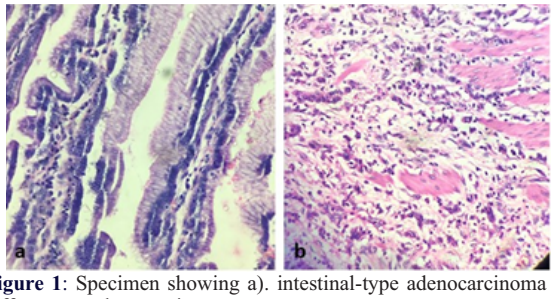
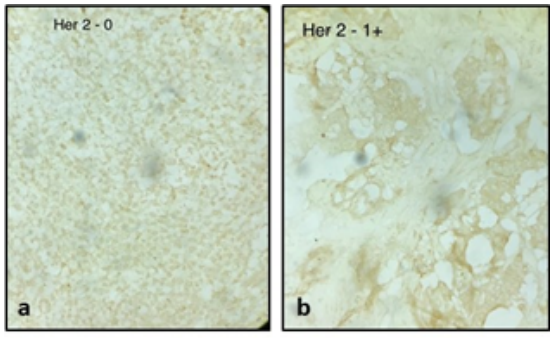



**Figure 1**: Specimen showing a). intestinal-type adenocarcinoma b) diffuse-type adenocarcinoma

## Expression of HER2

Overall, 4 (6.15%) patients had tumors that were scored as HER 3+, 10 (15.38%) were 2+, 34 (52.3%) were 1+ and the remaining 17 (26.15%) were negative with respect to expression of HER2 (**Figure 2**). There was no significant association between HER 2 expression and many of the histopathological features including tumor location, grade, T-stage, or lymphatic invasion (**Table 1**). The size of the tumors were not significantly correlated ($p=0.6941$) with the expression of this biomarker.



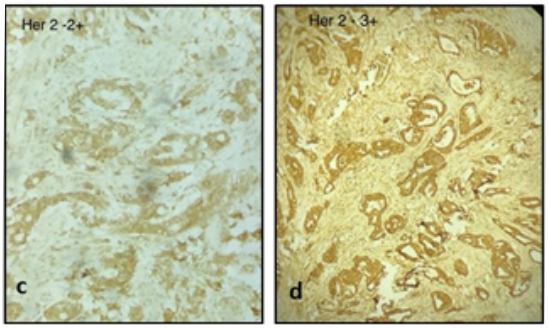


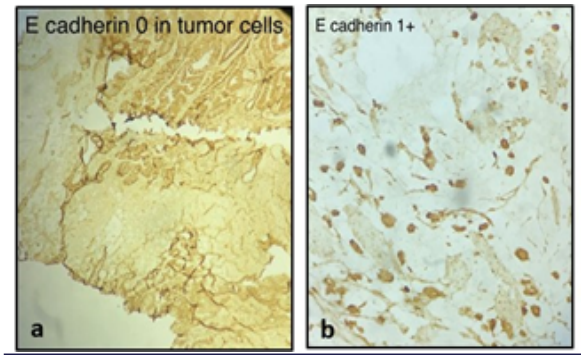

**Figure 2:** HER 2 expression. Tumors showing expression of score (a) 0 (b) 1+ (c) 2+ and (d) 3+

**Table 1: Correlation of HER 2 expression with histopathological features.**

| Characteristic | Patients n(%) | HER 2 expression | | | | p-value |
|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | |
| **Age (Years )** | | | | | | |
| <60 | 28(43.07) | 5 | 16 | 5 | 0 | 0.892 |
| >60 | 37(56.93) | 12 | 18 | 5 | 2 | |
| **Gender** | | | | | | |
| Male | 52 (80) | 13 | 27 | 9 | 3 | 0.8391 |
| Female | 13 (20) | 4 | 7 | 1 | 1 | |
| **Tumor location** | | | | | | |
| Body | 26 | 5 | 15 | 4 | 2 | 0.987 |
| Fundus | 12 | 4 | 6 | 2 | 0 | |
| Pylorus | 38 | 10 | 21 | 5 | 2 | |
| **Classification** | | | | | | |
| Diffuse | 23 (35.38) | 5 | 15 | 3 | 0 | 0.999 |
| Intestinal | 37 (56.92) | 9 | 17 | 7 | 4 | |
| Mixed | 5 (7.69) | 3 | 2 | 0 | 0 | |
| **Differentiation** | | | | | | |
| Well-differentiated | 15 (23.07) | 5 | 6 | 2 | 2 | 0.999 |
| Moderately-differentiated | 26 (40) | 6 | 11 | 7 | 2 | |
| Poorly-differentiated | 24 (36.92) | 6 | 17 | 1 | 0 | |
| **T-stage** | | | | | | |
| T1 | 3 (4.62) | 1 | 2 | 0 | 0 | 0.999 |
| T2 | 4 (6.15) | 1 | 1 | 1 | 1 | |
| T3 | 3 (4.62) | 1 | 0 | 1 | 0 | |
| T4 | 56 (86.15) | 14 | 31 | 8 | 3 | |
| **Lymphatic invasion** | | | | | | |
| Present | 54 (83.08) | 13 | 29 | 10 | 2 | 0.989 |
| Absent | 11 (16.92) | 4 | 5 | 0 | 2 | |

### Expression of E-cadherin

Overall, 9 (13.85%) patients had tumors that were scored as E-cadherin 3+, 19 (29.23%) were 2+, 19 (29.23%) were 1+ and the remaining 18 (27.69%) were negative with respect to expression of E-cadherin (Figure 3). There was no significant association between E-cadherin expression and many of the histopathological features including tumor location, grade, T-stage, or lymphatic invasion (Table 2). The size of the tumors were not significantly correlated (p=0.051) with the expression of this biomarker.



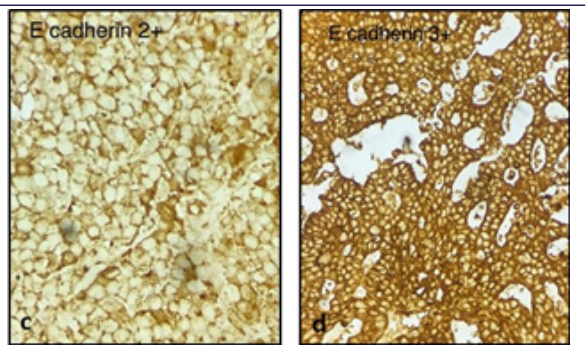




**Figure 3: E-cadherin expression. Tumors showing expression of score (a) 0 (b) 1+ (c) 2+ and (d) 3+**

**Table 2: Correlation of E-cadherin expression with histopathological features**

| Characteristic | Patients n(%) | E-cadherin expression | | | | p-value |
|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | |
| **Age (Years )** | | | | | | |
| <60 | 28(43.07) | 5 | 6 | 7 | 10 | 0.943 |
| >60 | 37(56.93) | 4 | 13 | 12 | 8 | |
| **Gender** | | | | | | |
| Male | 52 (80) | 6 | 14 | 16 | 16 | 0.927 |
| Female | 13 (20) | 3 | 5 | 3 | 2 | |
| **Tumor location** | | | | | | |
| Body | 26 | 7 | 10 | 3 | 6 | 0.999 |
| Fundus | 12 | 2 | 2 | 7 | 1 | |
| Pylorus | 38 | 6 | 12 | 9 | 11 | |
| **Classification** | | | | | | |
| Diffuse | 23 (35.38) | 8 | 12 | 3 | 0 | 0.354 |
| Intestinal | 37 (56.92) | 1 | 7 | 14 | 15 | |
| Mixed | 5 (7.69) | 3 | 2 | 0 | 0 | |
| **Differentiation** | | | | | | |
| Well-differentiated | 15 (23.07) | 0 | 2 | 5 | 8 | 1 |
| Moderately-differentiated | 26 (40) | 0 | 2 | 5 | 8 | |
| Poorly-differentiated | 24 (36.92) | 8 | 10 | 6 | 0 | |
| **T-stage** | | | | | | |
| T1 | 3 (4.62) | 0 | 0 | 2 | 1 | 0.999 |
| T2 | 4 (6.15) | 0 | 0 | 2 | 2 | |
| T3 | 3 (4.62) | 1 | 0 | 1 | 0 | |
| T4 | 56 (86.15) | 9 | 18 | 15 | 14 | |
| **Lymphatic invasion** | | | | | | |
| Present | 54 (83.08) | 9 | 16 | 15 | 14 | 0.921 |
| Absent | 11 (16.92) | 0 | 3 | 4 | 4 | |

### Discussion

HER2 and E-cadherin are two most important biomarkers in gastric cancer with prognostic and predictive values (Baniak et al., 2016). HER 2 expression is presently used as an important biomarker for identifying patients for trastuzumab treatment (Bang et al., 2010).

### Expression of HER2

Overexpression of HER2 in gastric cancer was reported as early as 1986 (Fukushige et al., 1986; Sakai et al., 1986). Among the studies that assessed HER 2 as a prognostic factor, some of them reported a significant correlation between its expression and prognosis, while others failed to find a direct correlation (Yano et al., 2006; McCulloch et al., 1997; Begnami et al., 2011). The present study showed no significant correlation between HER2 expression and any of the clinicopathological features like tumor size, stage, invasion, site or differentiation (**Table 1**). Prognostic implications of HER2 expression, and correlation of this biomarker with many clinicopathological features are still ambiguous (Baniak et al., 2016). While some studies do show a correlation, others fail to show any significant relationship between HER2-positive tumors and these features (Grabsch et al., 2010).

A number of factors can be attributed to this variability, including sample size, study specimen, methodology, and scoring. Differences in in-situ hybridization techniques give different advantages, with better interpretation by silver-enhanced ISH (SISH; Rüschoff et al., 2012). Majority of the specimens in the present study (93.84%) showed weak or basolateral membranous reactivity (+1 or +2 score), and should have been considered for FISH evaluation to classify them as positive or negative for expression of HER 2 (Hoffmann et al., 2008). Unavailability of FISH and SISH for confirmation is a limitation in the study. Many of the above scores may turn positive for HER2 overexpression with FISH evaluation, as reported in one of the studies (Shan, Ying, & Lu, 2013). Lack of a standardized HER2 test and scoring criteria add to the ambiguity and lack of consensus in the reported results.

Only 4 (6.15%) of the patients in the study showed a positive HER2 expression (+3 score). This is lower than what is reported from other studies (Jørgensen & Hersom, 2012). This difference in HER 2 overexpression may be associated with the ethnic heterogeneity of aberrations that cause solid tumors (Johansson, Mentens, & Miteiman 1991). There are very few studies on HER 2 expression from Indian population for comparison at a larger scale.

**Expression of E-cadherin**

E-cadherin gene mutation is reported in several epithelial cancers. In the present study 18 (27.69%) of the adenocarcinomas showed abnormal expression of E-cadherin. The values are similar to a study conducted in Army Hospital, Delhi (Dewan, Madan, & Sengupta, 2016). Reduced E-cadherin expression was noted in gastric adenocarcinoma in many other studies (Xing et al., 2013). As in HER2, reports on prognostic impact of E-cadherin expression in gastric cancers are heterogenous and controversial. A meta-analysis of studies correlating E-cadherin expression and different histopathological features showed a significant association in gastric cancer (Xing et al., 2013). But in some other studies no significant association was reported between E-cadherin down regulation and other characteristics including grade, histological type, depth of invasion, and lymph node involvement (Schizas et al., 2017). A study in invasive lobular breast carcinomas showed reoccurrence of E-cadherin in metastatic cells, suggesting prevention of apoptosis by re-establishment of cellular contact (Bukholm, Nesland, & Boressen, 2000). Earlier in 1991, study conducted by Shimoyama and Hirohasht (1991) had reported that abnormal expression of E-cadherin is not significantly associated with lymph node metastasis. The sample size of the present study is small to generalize and conclude this aspect.

Some studies show a positive correlation between E-cadherin downregulation and more aggressive gastric tumors (Anbiaee, Sheibani, Torbati, & Jaam, 2013). While another study shows a direct relationship between increased serum concentration of E-cadherin and intestinal type of gastric cancer, particularly in the advanced stages (Juhasz et al., 2009). This shows a dual role for E-cadherin in the development of metastatic gastric adenocarcinoma, indicating that levels of E-cadherin can be interpreted only with the type of gastric cancer. Further, concentration of soluble E-cadherin increase with aging and hence the serum levels can be considered only in age-matched populations (Pedrazzani et al., 2008). Literature is still equivocal regarding this association and larger studies with similar methodologies, especially in Indian population, are needed to fully elucidate the predictive role of this biomarker.

**Conclusions**

The present study did not show a correlation between HER2 and E-cadherin expression with any of the histopathological features. Although studies do show that HER 2 and E-cadherin expressions serve as predictive biomarkers in gastric cancer, there is no consensus regarding the same. Larger studies with standardized testing and scoring are required before using these biomarkers in targeted therapy.

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