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The Her2/Neu Paradox: Overexpression and Its Clinicopathological Implications in Esophageal and Gastric Malignancies of Upper Gastrointestinal Biopsies

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Conflict of interest: Nil

Abstract

Introduction: HER2/neu is crucial in the development of Gastric and Esophageal carcinomas. The incidence of HER2/neu-positive tumors in Gastric and Esophageal cancers varies between 9-64% and 4.4-53.4%, respectively. Accurate determination of HER2/neu status is essential for identifying patients who may benefit from targeted HER2/neu molecular therapy.

Aim/Objectives: This study aims to investigate the correlation between HER2/neu overexpression and various clinicopathological factors, including age, sex, histological type, and tumor grade, in gastric and esophageal carcinoma cases diagnosed through upper gastrointestinal endoscopic biopsies.

Material and Method: Immunohistochemistry was employed to examine HER2/neu expression in 25 upper gastrointestinal biopsies of gastric and esophageal carcinomas received at our institution over a period of 18 months and was performed to investigate the correlation between HER2/neu expression and various clinicopathological parameters. A two-tailed p-value of <0.05 was considered statistically significant.

Result: Among the cases analyzed, spanning an age range of 18-80 years, no statistically significant correlations were observed between HER2/neu overexpression and age, sex, or tumor grade ($P > 0.05$). However, a significant correlation was found with the intestinal type of tumors ($P < 0.05$). HER2/neu overexpression was detected in: 40% of Esophageal Adenocarcinomas (n=2), 16.6% of Esophageal Squamous cell carcinomas (n=1) and 44.4% of Gastric Adenocarcinomas (n=4) predominantly of Intestinal Type(33.3%).

Conclusion: HER2/neu positivity emerged as a significant predictor of mortality in patients with gastric and esophageal carcinomas. Notably, amidst the rising incidence of upper gastrointestinal tract malignancies, HER2/neu overexpression was associated with a poorer overall survival rate compared to those without HER2/neu overexpression.

Keywords: Adenocarcinoma, Endoscopic biopsies, HER2/neu, Immunohistochemistry

Introduction

Gastric carcinoma ranks as the fourth most commonly diagnosed cancer globally and is the second leading cause of cancer-related death[1]. Meanwhile, esophageal carcinoma incidence has risen more rapidly than any other malignancy, with expectations of continued growth in the coming decades[2]. Unfortunately, over 50% of cases present at advanced, unresectable stages, rendering cure impossible. Gastric carcinomas exhibit varied morphological and histological types, which do not reliably correlate with prognosis[3].

Advances in endoscopy and biopsy techniques have enabled earlier diagnosis and intervention through upper gastrointestinal endoscopy. HER-2/neu has emerged as a potential prognostic tool for gastric cancer, with overexpression linked to poor outcomes and more aggressive disease.

HER2/neu (c-erb-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity, known as p185. This protein belongs to the epidermal growth factor receptor family and regulates various biological functions, including cell proliferation, differentiation, motility, and apoptosis[4]. Overexpression of HER2/neu has been observed in numerous types of cancer, such as breast, lung, salivary gland, ovary, colon, prostate, and pancreatic cancers[5,6]. Studies have shown that 10-38% of gastric cancer patients exhibit HER2/neu overexpression[7]. However, the correlation between HER2/neu expression and gastrointestinal cancer prognosis remains unclear, with varying levels of HER2/neu expression reported in different studies [8,9,10].

Trastuzumab is a fully humanized monoclonal antibody that targets the extracellular domain of the HER2 receptor, preventing its activation. Currently, Trastuzumab is used to treat HER2-positive breast cancer, improving survival rates in these patients[11]. Researchers are now investigating the antitumor activity of Trastuzumab in patients with HER2-positive gastrointestinal adenocarcinomas.

The incidence of HER-2 positive tumors in gastric and esophageal cancers ranges from 4% to 53%[12] and 9% to 64%,[13] respectively. However, observational studies have yielded inconsistent findings regarding its correlation with survival. The ToGA trial marked a significant breakthrough in targeted gastric cancer therapy[14,15].

Accurate characterization of HER-2/Neu status in gastric and esophageal cancer patients may enhance the efficacy of trastuzumab therapy while minimizing undesirable side effects. This cross-sectional study aimed to evaluate HER-2/neu expression in gastrointestinal cancer patients using immunohistochemistry and correlate overexpression with clinical, pathological, and disease-stage parameters[16].

Material and Method

In this study, we studied the expression of the HER-2/neu marker in Gastric and esophageal carcinoma and compared it with various clinicopathological parameters known to have prognostic significance.

This prospective study was conducted over 18 months, from April 2023 to September 2024, at the Department of Pathology, DR B R Ambedkar Medical College and

Hospital. The study included 25 upper gastrointestinal (UGI) endoscopic biopsies of gastric and esophageal carcinomas.

Inclusion criteria

- Cases received as only endoscopic biopsy specimens
- Histopathologically confirmed esophageal and gastric carcinoma cases

Exclusion criteria

- Cases with extensive tumor necrosis lack sufficient viable tumor cells for analysis.
- Patients who had received prior chemotherapy.

Ethical clearance was taken from the Institutional Ethical Committee before the commencement of the study.

Histopathology: Tissue samples were thoroughly examined, fixed in 10% buffered formalin, and processed according to standard protocols. Sections (3-5 μ thick) were stained with hematoxylin and eosin and evaluated for histopathological type and tumor grade.

After histopathological confirmation, paraffin blocks were processed for HER2/neu receptor IHC staining using HER2 (BioGenex, mouse Ig). The staining procedure included positive and negative control groups. A known HER2/Neu-positive (3+) breast cancer tissue served as the positive control, while normal gastric mucosal glands negative for HER2/neu served as the negative control.

Evaluation and Scoring

Experienced pathologists reviewed the HER2/Neu-stained slides and assigned scores (0-3+) based on membrane staining in at least 10% of tumor cells, following the criteria recommended by Hoffman et al (8) with scores as follows: 0, no reactivity or membranous reactivity in <10% of cells; 1+, faint/barely perceptible membranous reactivity in >10% of cells (cells are reactive only in part of their membrane); 2+, weak to moderate complete or basolateral membranous reactivity in >10% of tumor cells & 3+, moderate to strong complete or basolateral membranous reactivity in >10% of tumor cells. HER2/Neu-negative status was assigned to scores 0 and 1+, while scores 2+ required FISH analysis for confirmation, which was not feasible in this study due to economic constraints. The expression profile of HER2/neu among various subgroups of gastric carcinoma was evaluated using the chi-square test. The Chi-square test was performed to assess the association between clinicopathological parameters.

Statistical analysis

Statistical analyses were conducted using SPSS software version 25.0. A two-tailed p-value of <0.05 was considered statistically significant.

Results

This study included 25 biopsies diagnosed as malignant lesions based on histopathological examination. Of these, 15 were from male patients (60%) and 10 from female patients (40%) [Figure-1], yielding a male-to-female ratio of 1.5:1. The majority of cases were in the age range of 18 to 80 years, with gastric tumors being more prevalent in the 61-70 years age group, and a mean age of 68.5 years [Figure-2]. Gastric tumors were more common in males than females, with a male-to-female ratio of 1.2:1. Adenocarcinomas were the most frequent type of gastric cancer. Esophageal carcinoma was more common in the 71–80-year age group, with a mean age of 76.25 years [figure-2] and a male-to-female ratio of 1.4:1. Squamous cell carcinoma was the predominant type of esophageal cancer, followed by adenocarcinoma. Cases involving the gastroesophageal junction (GEJ) were relatively rare. Among the 2 cases, one was diagnosed as squamous cell

carcinoma, while the other was diagnosed as Adenosquamous cell carcinoma [Table-1].

Lauren's classification was applied to gastric adenocarcinomas that revealed a majority of cases to be diffuse types. [Figure-3]

IHC staining for HER-2/neu was conducted, as HER-2/neu is a cytoplasmic membrane marker. The staining pattern was compared with control slides from known HER-2/neu-positive breast cancer. HER-2/neu protein expression on the cell membrane was scored based on the criteria outlined by Hofmann and colleagues for biopsy specimens. The association between the age, sex, and grade of gastric and esophageal carcinomas with HER-2/neu status (positive or negative) was analyzed using the Chi-square test of independence. The p-value was not statistically significant (>0.05) [Table-2,3,4].

In our study, 9 cases were diagnosed as gastric adenocarcinoma, of which 4 cases (44.4%) showed overexpression of HER2/neu. HER2/neu overexpression was more prevalent in the intestinal type (3 cases)[Figure-4,5,6], followed by the diffuse type (1 case). The HER2/neu status was found to be significantly associated with the type of gastric adenocarcinoma (p-value <0.05) [Table-5].

HER-2/neu analysis was also performed on esophageal carcinomas. The frequency of HER-2/neu expression in these lesions was lower compared to gastric carcinomas [Table-6]. The majority of squamous cell carcinomas were scored 0, with only one case showing a 3+ score [Figure-7,8] Among esophageal adenocarcinomas, 2 out of 5 cases (40%) exhibited HER-2/neu positivity. The case diagnosed as undifferentiated adenocarcinoma shows negative expression for HER2/neu.

Gastroesophageal junction malignancies show negative expression of Her2/neu. [Figure-9,10]

HER2/neu status was found to be significantly associated with types of Gastric adenocarcinoma (p-value <0.05). No significant association was observed between HER2/neu status with age, sex, and degree of differentiation of gastric and esophageal carcinomas (p-value>0.05).

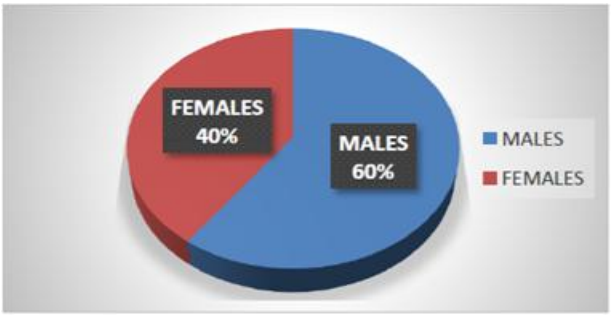

Figure 1: Sex-wise distribution of Esophageal and gastric carcinomas

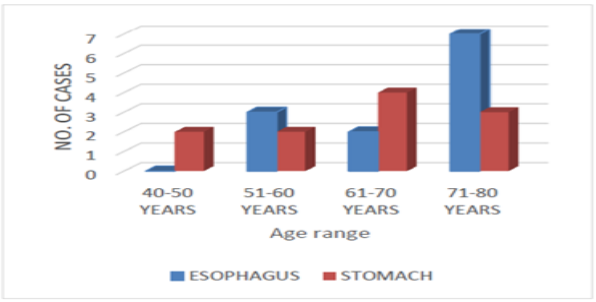

Figure 2: Age-wise distribution of Esophageal and gastric carcinomas

PARAMETERS(Total no. of cases)		HER2/neu expression		P value
		IHC score(0/+1)	IHC score (+2/+3)	
Age	<60 (7)	6	1	
	>60 (18)	12	6	0.34909
Gender	Male (15)	11	4	
	Female (10)	7	3	0.85570
Total no. of cases = 25				

Table 1: Association of HER2/neu expression of gastric carcinoma and esophageal carcinoma with clinical parameters (n=25)

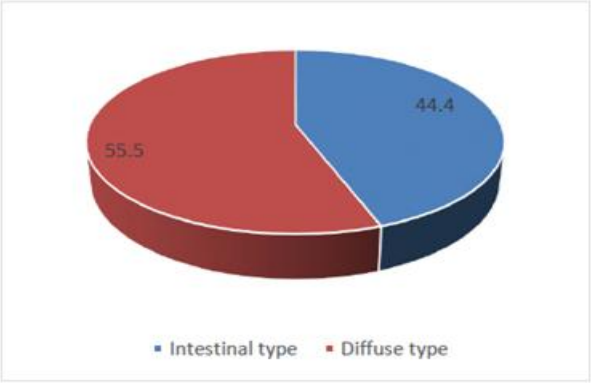

Figure 3: Distribution of Gastric adenocarcinoma cases according to Laurens Classification.

SITE (No. of cases)	Adenocarcinoma	Squamous cell Carcinoma	Undifferentiated carcinoma	Adenosquamous carcinoma
Esophagus (12)	5	6	1	0
Stomach(11)	9	1	1	0
Gastroesophageal junction(2)	0	1	0	1
Total number of cases = 25				

Table 2: Site-wise distribution of malignancies

Grade of Gastric carcinomas	HER2/neu expression		P value
	IHC score(0/+1)	IHC score (+2/+3)	
Well-differentiated (4)	3	1	0.2937
Moderately differentiated (5)	2	3	
Poorly differentiated (1)	0	1	
Undifferentiated carcinoma (1)	1	0	
Total	6	5	11

Table 3: Association of HER2/neu status with degree of differentiation of Gastric Carcinomas (n=11)

Grade of Esophageal carcinomas	HER2/neu expression		P value
	IHC score(0/+1)	IHC score (+2/+3)	
Well-differentiated (3)	3	0	0.77816
Moderately differentiated (7)	4	3	
Poorly differentiated (1)	1	0	
Undifferentiated carcinoma (1)	1	0	
Total	9	3	12

Table 4: Association of HER2/neu status with a degree of differentiation of Esophageal Carcinomas (n=12)

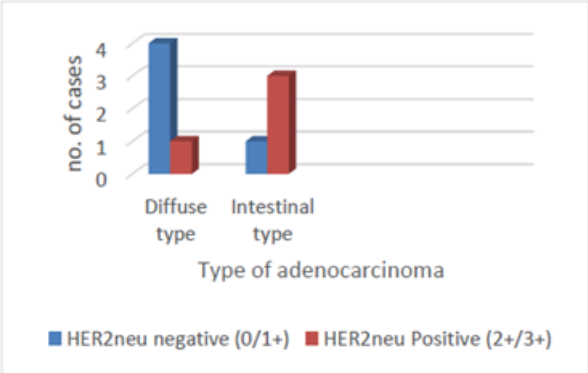

Figure 4: HER2/neu status versus types of Gastric adenocarcinoma (LAUREN's Classification).

Types of Adenocarcinoma (Lauren's classification)	HER2/neu expression		P value
	IHC score(0/+1)	IHC score (+2/+3)	
Intestinal Type (4)	1	3	0.0356
Diffuse Type (5)	4	1	
Total	5	4	9

Table 5: Association of HER2neu expression with histologic subtypes of Gastric carcinoma (Laurens classification) (n=9)

	IHC Score	No. of cases	Percentage
Squamous cell carcinoma (6)	0	5	83.3%
	3+	1	16.6%
Adenocarcinoma (5)	0	3	60%
	3+	2	40%
Undifferentiated carcinoma (1)	0	1	0
Total no. of cases =12			

Table 6: Frequency of HER2/NEU expression in Esophageal carcinomas (n=12)

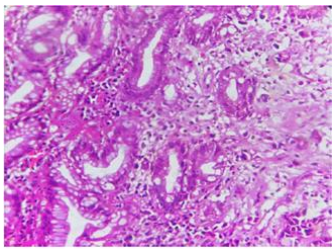

Figure 5: Intestinal-type adenocarcinoma- Stomach. (H&E, 400x)

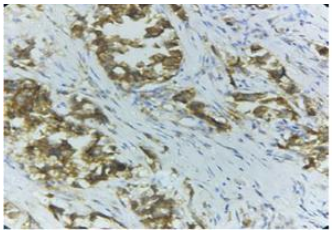

Figure 6: HER-2/ neu Score 3+ Intestinal-type adenocarcinoma- Stomach. (IHC, 400x)

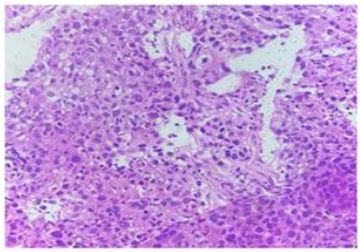

Figure 7: Moderately differentiated squamous cell carcinoma- Esophagus. (H&E, 400x)

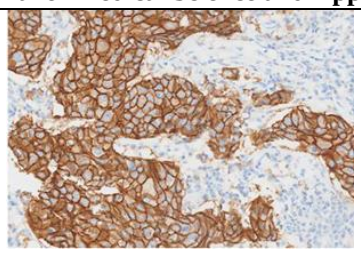

Figure 8: HER-2/ neu Score 3+ in Moderately differentiated squamous cell carcinoma- Esophagus. (IHC, 400x).

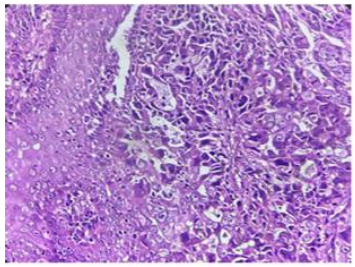

Figure 9: Adenosquamous cell carcinoma- GEJ (H&E,400x)

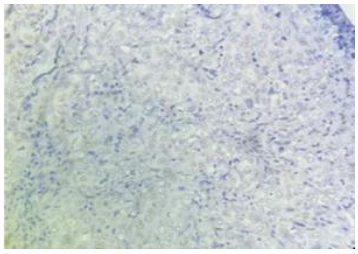

Figure 10: HER-2/ neu Score 0 in Adenosquamous cell carcinoma- GEJ (IHC, 400x)

Discussion

Endoscopic biopsy, followed by histopathological analysis, remains one of the most effective diagnostic tools for identifying gastrointestinal tract (GIT) lesions, both neoplastic and non-neoplastic. The critical insights obtained from biopsies play a vital role in aiding surgeons to strategize further management plans. In this prospective study, 25 endoscopic biopsies, confirmed as esophageal or gastric carcinoma through histopathology, were examined and analyzed.

The age distribution in the study was extensive, ranging from 18 to 80 years, with a mean age of 67.2 years. Most

cases fell within the 60 to 80-year age group, aligning with findings from studies conducted by Sunita Sharma et al.[17], Saurabh Sharma et al.[18], and Qiu et al.[19].

The majority of patients undergoing endoscopic biopsies were males, with a male-to-female ratio of 1.5:1. This male predominance was also reported in studies by Sandhya PG et al.[20], Katiyar et al.[21], and Qiu et al. The higher male prevalence might be attributed to greater exposure to risk factors, such as smoking, alcohol consumption, and dietary habits, compared to females.

In our study, the esophagus was the most common site for biopsies, followed by the stomach, aligning with the findings of Sunita Sharma et al.[17]. However, other studies, such as those by Jaynul Islam SM et al.[22] and Sandhya PG et al.[20], identified the stomach as the most frequently biopsied site. This difference could be attributed to the fact that esophageal cancer tends to present earlier with distinct signs and symptoms, whereas gastric cancer often manifests with vague, non-specific symptoms [23].

The frequency of HER2 overexpression in gastric and gastroesophageal cancers varies significantly across the literature, with inconsistent findings regarding its prognostic significance[24]. The introduction of trastuzumab for advanced gastric cancer has increased the clinical demand for HER2 assessment. However, HER2 testing in gastric cancer differs from breast cancer due to inherent differences in tumor biology, intratumoral heterogeneity of HER2 expression, and the incomplete membrane staining frequently observed in gastric tumors [25]. Therefore, the development of a standardized HER2/neu detection test is essential to identify eligible patients for trastuzumab therapy. The Hofmann scoring system, which aligns with the guidelines provided by EMA[26] and ToGA[27], was utilized in the present study

In the present study, HER-2/neu overexpression was observed in 4 cases (44.4%) of gastric carcinomas, with 3 cases belonging to the intestinal type and 1 case to the diffuse type. Among esophageal malignancies, HER-2/neu positivity was identified in 1 out of 6 (16.6%) squamous cell carcinomas and 3 out of 5 (40%) adenocarcinomas. These findings align with similar studies conducted by Schoppmann et al.[28] and Lynda et al[16].

HER-2/neu overexpression varies based on the carcinoma type, whether it is squamous cell carcinoma or adenocarcinoma. In the present study, it was more frequently associated with adenocarcinoma, consistent with findings by Schoppmann et al.[28] and Lynda et al. [16] . These variations in HER-2/neu expression across the histologies of adenocarcinoma and squamous cell carcinoma suggest that HER-2/neu may have distinct prognostic implications for the two types.

In the present study, HER2/neu overexpression was significantly associated with the types of gastric adenocarcinoma (p=0.003), with the highest expression observed in the intestinal type of gastric carcinoma, followed by the diffuse type. These findings are consistent with those of studies conducted by Rajagopal I. et al.[29] (2015), Gordon M.A. et al.[30] (2013), and Tewari M. et al.[31] (2013). The results of the present study align with the observations reported in previous research.

The aforementioned variation in HER-2/neu expression can be attributed to the distinct molecular pathways and genetic alterations that characterize intestinal and diffuse types of adenocarcinomas. These types also exhibit differing histological features. Notably, the lack of E-cadherin, which is inversely related to HER-2/neu expression, is more frequently observed in the intestinal type of adenocarcinoma[32].

In this study, HER-2/neu was found to be overexpressed in 16.6% of esophageal squamous cell carcinomas and 40% of esophageal adenocarcinomas. Dreilch et al.[33] concluded in their research that HER-2/neu overexpression serves as a poor prognostic factor for esophageal squamous cell carcinoma but does not influence the survival outcomes of patients with esophageal adenocarcinoma.

The prognostic significance of HER-2/neu overexpression in gastric and esophageal carcinomas remains a subject of debate. Furthermore, the association between HER-2/neu-positive gastric cancer and clinicopathological features has shown inconsistency. Similar to the findings reported by various authors [32, 33], the present study also observed no correlation between HER-2/neu overexpression and the gender or age of patients with gastric or esophageal carcinoma.

Dreilich et al.[33] demonstrated that a HER-2/neu 3+ score on IHC in esophageal squamous cell carcinoma is linked to poor survival, whereas no impact on survival was observed in patients with adenocarcinoma. Similarly, Schoppmann et al.[28] investigated HER-2/neu expression in esophageal carcinomas and concluded that there is no correlation between overall survival and either squamous cell carcinoma or adenocarcinoma.

In this study, moderately differentiated tumors were the most prevalent, accounting for 12% of cases, a finding consistent with the observations of Fondevila et al.[34]. However, no correlation was observed between the grade of differentiation and Her2neu expression in our study. Previous studies have reported higher Her2neu positivity rates in well-differentiated gastric cancers compared to poorly differentiated ones. The molecular mechanisms underlying Her2neu positivity in various grades of differentiation are intricate and warrant further investigation.

The role of Her2neu as a prognostic marker in the survival of gastrointestinal cancer patients remains highly debated due to inconsistent findings across various studies. In our study, Her2neu positivity emerged as an independent predictor of mortality in patients with gastric and esophageal carcinoma. Patients with Her2neu overexpression (Her2neu 2+ or 3+) exhibited significantly lower survival rates compared to those without Her2neu expression, demonstrating poorer outcomes for Her2neu-positive individuals.

Previous studies have similarly reported reduced overall survival rates in gastrointestinal cancer patients with Her2neu overexpression[35]. For instance, a Bulgarian study found that Her2neu positivity was linked to the worst outcomes post-surgical resection compared to Her2neu-negative patients[36]. Zhang et al., in their analysis of 102 gastric cancer cases, observed shorter survival durations among patients with Her2neu overexpression [37]. Conversely, a large-scale study by Yu et al., involving 1,143 gastric cancer patients, reported no correlation between survival time and Her2neu positivity[38]. Nonetheless, most publications have affirmed the association of Her2neu positivity with worse outcomes in gastric cancer, underscoring its potential role as a prognostic factor for patients with gastric carcinoma [39].

The primary limitation of our study was the relatively small sample size. However, the prospective design and the correlation of Her2neu expression with patient outcomes added considerable strength to our findings.

Conclusions

In conclusion, Her2neu plays a crucial role in tumor development and disease progression in gastric and esophageal carcinoma. HER-2/neu overexpression is

predominantly observed in adenocarcinomas, especially in the intestinal subtype, and is associated with poor patient survival. A small percentage of esophageal squamous cell carcinomas also demonstrate HER-2/neu oncoprotein expression. However, no correlation was found between HER-2/neu status and the tumor grade, age, or sex of the patient.

It is recommended that Her2neu testing be performed in all patients with early gastric cancer, and targeted therapy with trastuzumab may be considered following Her2neu status determination. Incorporating HER - 2/neu evaluation into the routine diagnostic workup for upper gastrointestinal carcinomas could prove beneficial. Immunohistochemistry (IHC) is suggested as the initial testing methodology.

One limitation of our study was the unavailability of FISH analysis for HER2/neu expression in 2+ positive cases, which warrants further evaluation for better correlation. Future research with larger sample sizes and extended follow-up periods is needed to better elucidate the significance of HER2/neu expression in predicting patient prognosis.

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