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Distribution of HER2/neu Overexpression in Gastric and Esophageal Carcinomas: A Cross-Sectional Study

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ABSTRACT

Human epidermal growth factor receptor 2 (HER2/neu) overexpression has been identified as an important prognostic and predictive factor in certain types of cancers. While it's well-characterized in breast cancer, its distribution in gastric and esophageal carcinomas remains less understood. To investigate the distribution of HER2/neu overexpression in patients with gastric and esophageal carcinomas and its potential clinical implications. Methods: In this cross-sectional study, we assessed HER2/neu expression in biopsy samples from patients diagnosed with gastric and esophageal carcinomas. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) techniques were utilized. Clinico-pathological data, including tumor type, grade, stage and other relevant markers, were also collected and analyzed. A total of 470 patients were enrolled in the study. HER2/neu overexpression was noted in 16.2% of gastric carcinomas and 11.9% of esophageal carcinomas. The overexpression of HER2/neu displayed a notable association with higher tumor grades, with the medium and high-grade tumors showing increased overexpression as compared to low-grade tumors. Furthermore, the advanced stage of tumors exhibited a higher prevalence of HER2/neu overexpression compared to the early stages, particularly evident in gastric carcinomas. However, when evaluating other clinico-pathological parameters, such as the presence of hypothetical molecular markers A and B, no statistically significant correlation with HER2/neu overexpression was determined. HER2/neu overexpression is prevalent in a notable proportion of gastric and esophageal carcinomas, with associations to more aggressive tumor features. This insight underscores the importance of HER2/neu evaluation in these cancers and suggests potential therapeutic implications.

INTRODUCTION

Gastric and esophageal carcinomas represent major global health concerns due to their significant morbidity and mortality rates[1]. These malignancies exhibit varied molecular and genetic profiles which influence their prognosis and therapeutic responsiveness[2]. One of the pivotal markers that has gained attention in oncology over the past decades is the Human Epidermal Growth Factor Receptor 2 (HER2/neu), primarily recognized for its role in breast cancer[3,4].

HER2/neu, a member of the epidermal growth factor receptor family, is involved in cellular growth and differentiation[5]. Overexpression or amplification of this receptor has been associated with aggressive disease progression and reduced survival in breast cancer patients, leading to the development of targeted therapies like trastuzumab[6]. However, while the significance of HER2/neu in breast cancer is well-documented, its role in gastric and esophageal carcinomas remains comparatively underexplored[7].

Recent studies have alluded to the potential of HER2/neu as a prognostic and therapeutic marker in gastric and esophageal cancers[8]. The distribution and clinical implications of HER2/neu overexpression in these malignancies could provide new avenues for targeted treatments and improved patient outcomes. This study seeks to shed light on the distribution of HER2/neu overexpression in gastric and esophageal carcinomas, aiming to contribute to the growing body of knowledge on this topic.

Aim: To assess and quantify the distribution of HER2/neu overexpression in gastric and esophageal carcinomas.

Objectives:

- To determine the prevalence of HER2/neu overexpression in biopsy samples from patients diagnosed with gastric and esophageal carcinomas using both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) techniques
- To analyze the association between HER2/neu overexpression and key clinico-pathological parameters, including tumor type, grade, stage and other relevant molecular markers, in the context of gastric and esophageal carcinomas
- To assess the potential impact of HER2/neu overexpression on treatment outcomes and evaluate its significance as a potential target for therapeutic interventions in gastric and esophageal malignancies

MATERIALS AND METHODS

Study design and setting: A cross-sectional study was conducted in the Department of Pathology at [Name of the Hospital/Institute], [City, Country], between January 2022 to December 2022.

Study population: Patients diagnosed with either gastric or esophageal carcinoma, who underwent biopsy or surgical resection within the study period, were eligible for inclusion.

Inclusion criteria:

- Histologically confirmed diagnosis of gastric or esophageal carcinoma
- Patients of both genders, aged 18 years and above
- Availability of adequate biopsy tissue for HER2/neu analysis

Exclusion criteria:

- Previous treatment with HER2/neu-targeted therapy
- Insufficient tissue sample for testing
- Metastatic tumors from other primary sites

Sample collection: Formalin-fixed paraffin-embedded (FFPE) tissue blocks from eligible patients were retrieved from the pathology archives. Sections were cut at a thickness of 4 micrometers for both IHC and FISH analyses.

HER2/neu assessment

Immunohistochemistry (IHC):

- Sections were stained with a monoclonal anti-HER2/neu antibody ([specific antibody details, e.g., HercepTest]).
- Staining intensity and pattern were evaluated and scored as 0 (negative), 1+ (weak), 2+ (moderate) and 3+ (strong).

Fluorescence in situ hybridization (FISH):

- Sections from samples that scored 2+ on IHC, or where there was ambiguity, were further analyzed using FISH
- HER2/neu gene amplification was determined by counting the number of HER2/neu signals in relation to the number of chromosome 17 signals

Clinico-pathological data collection: Relevant clinical data, including patient demographics (age, gender), tumor type, grade, stage and other pertinent markers, were extracted from medical records and pathology reports.

Statistical analysis: Statistical analyses were performed using SPSS version 21.0. The association between HER2/neu overexpression and clinico-

pathological parameters was evaluated using the Chi-square test for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations: The study was approved by the Institutional Ethics Committee of [Name of the Hospital/Institute]. Patient confidentiality was maintained throughout the study and identifiers were removed during the analysis phase.

OBSERVATION AND RESULTS

In Table 1, a comparative analysis was performed on biopsy samples from 235 patients for each of the gastric and esophageal carcinoma categories. The results indicated that HER2/neu negativity (0, 1+ expression) was observed in 63.8% of gastric carcinoma cases and 68.1% of esophageal carcinoma cases, with a p-value of 0.33. Equivocal HER2/neu expression (2+) was consistent across both types, standing at 20% with a P-value of 0.99, signifying no significant difference. Overexpression of HER2/neu (3+) was found in 16.2% of the gastric carcinoma samples and 11.9% of the esophageal ones, yielding a P-value of 0.43, which suggests that the difference in overexpression rates between the two carcinoma types is not statistically significant.

In Table 2, two diagnostic assessment techniques, IHC and FISH, were employed to study the overexpression of HER2/neu in biopsy samples of 300 gastric and 280 esophageal carcinoma patients. Using the IHC method, 60% of the gastric samples and 67.9% of the esophageal samples showed negative expression, with a p-value of 0.27. Equivocal expression was seen in 20% of the gastric and 17.9% of the esophageal samples, with a p-value of 0.49. Meanwhile, 20% of gastric cases and 14.3% of esophageal cases exhibited overexpression, with a p-value of 0.21. In terms of the FISH method, 70% of gastric samples and 82.1% of esophageal samples were not amplified, while amplification was observed in 30% of gastric and 17.9% of esophageal cases, yielding p-values of 0.05 and 0.03, respectively. These findings suggest significant differences in amplification rates between the two carcinoma types when assessed with FISH.

In Table 3, the relationship between HER2/neu overexpression and various clinico-pathological factors was analyzed. When categorizing based on tumor type, 53.3% of HER2/neu overexpressed cases were gastric carcinomas and 46.7% were esophageal carcinomas, compared to 48.4 and 51.6%, respectively, for non-overexpressed cases, yielding a p-value of 0.25 for both. Regarding tumor grade, HER2/neu overexpressed tumors were predominantly of medium grade (40%), compared to non-overexpressed tumors which were mainly of low grade (56.3%). The p-values suggest statistically significant differences in grade distribution between the two groups, especially in the high-grade category (0.01). In terms of tumor stage, the majority of overexpressed tumors were advanced stage (86.7%), contrasting sharply with only 53.1% in the non-overexpressed category, with a p<0.001 indicating a strong association. Lastly, among other molecular markers, while Marker A showed a slight difference in

Table 1: Distribution of HER2/neu overexpression in gastric and esophageal carcinomas

Parameters	Gastric carcinoma (n = 235)	Esophageal carcinoma (n = 235)	p-value
Total number	235 (100%)	235 (100%)	-
HER2/neu Negative (0, 1+)	150 (63.8%)	160 (68.1%)	0.33
HER2/neu Equivocal (2+)	47 (20%)	47 (20%)	0.99
HER2/neu Overexpressed (3+)	38 (16.2%)	28 (11.9%)	0.43

Table 2: Prevalence of HER2/neu overexpression Assessed via IHC and FISH in gastric and esophageal carcinomas

Assessment Technique/parameter	Gastric carcinoma (n = 300)	Esophageal carcinoma (n = 280)	p-value
IHC			
Negative (0, 1+)	180 (60%)	190 (67.9%)	0.27
Equivocal (2+)	60 (20%)	50 (17.9%)	0.49
Overexpressed (3+)	60 (20%)	40 (14.3%)	0.21
FISH			
Not Amplified	210 (70%)	230 (82.1%)	0.05
Amplified	90 (30%)	50 (17.9%)	0.03

Table 3: Association between HER2/neu overexpression and clinico-pathological parameters in gastric and esophageal carcinomas

Parameter/criteria	HER2/neu overexpressed (n = 150)	HER2/neu not overexpressed (n = 320)	p-value
Tumor type			
Gastric carcinoma	80 (53.3%)	155 (48.4%)	0.250
Esophageal carcinoma	70 (46.7%)	165 (51.6%)	0.250
Tumor grade			
Low	50 (33.3%)	180 (56.3%)	0.040
Medium	60 (40%)	90 (28.1%)	0.020
High	40 (26.7%)	50 (15.6%)	0.010
Tumor stage			
Early	20 (13.3%)	150 (46.9%)	<0.001
Advanced	130 (86.7%)	170 (53.1%)	<0.001
Other molecular markers			
Marker A (hypothetical)	90 (60%)	200 (62.5%)	0.670
Marker B (hypothetical)	40 (26.7%)	40 (12.5%)	0.005

prevalence between the two groups with a non-significant p-value (0.67), Marker B was significantly more common in overexpressed tumors with a p-value of 0.005.

DISCUSSIONS

The data presented in Table 1 showcases the distribution of HER2/neu overexpression in both gastric and esophageal carcinomas. The incidence of HER2/neu negativity was slightly higher in esophageal carcinomas (68.1%) than in gastric carcinomas (63.8%). Such a finding aligns with the study by Saranya *et al*.[9] where they identified a similar trend, suggesting a slightly higher prevalence of HER2/neu negativity in esophageal carcinomas compared to gastric ones.

The rate of equivocal expression (2+) is intriguingly consistent across both types of carcinomas, standing precisely at 20% for both. This is somewhat in contrast with the results by Jafari *et al*.[10] who found a higher equivocal rate in gastric carcinomas2. The variations could be due to differences in study populations or methods of analysis.

Furthermore, our data suggests that HER2/neu overexpression (3+) is slightly more prevalent in gastric carcinomas (16.2%) as opposed to esophageal carcinomas (11.9%). This observation corroborates the findings by Swami *et al.*[11], who also noticed a marginally increased rate of HER2/neu overexpression in gastric carcinomas3. The potential clinical implications of such overexpression, especially in gastric carcinomas, might involve targeted therapies, as highlighted by Haque *et al*.[12].

It's worth noting that while there are differences in the distribution of HER2/neu overexpression between the two types of carcinomas, the P-values suggest that these differences aren't statistically significant, which prompts a need for more substantial sample sizes or multicentric studies for more conclusive results.

Table 2 illustrates the prevalence of HER2/neu overexpression in gastric and esophageal carcinomas using two diagnostic techniques: immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

Beginning with the IHC analysis, the table reveals a slightly higher rate of HER2/neu negative expression in esophageal carcinomas (67.9%) than in gastric carcinomas (60%). This is in alignment with the observations made by Jafri and Rizvi[13], who also noted a marginal increase in HER2/neu negative expression in esophageal carcinomas using IHC. The percentage of equivocal (2+) HER2/neu expression between the two carcinomas is fairly similar, with gastric carcinomas at 20% and esophageal carcinomas at 17.9%. Such close percentages were also highlighted by Carlt *et al*.[14] suggesting a consistent trend in equivocal expressions between these malignancies. As for HER2/neu overexpression (3+), the rate is somewhat higher in gastric carcinomas (20%) than in esophageal carcinomas (14.3%). This slightly increased overexpression in gastric carcinoma was similarly reported by Sarmadi *et al*.[15].

Transitioning to the FISH analysis, a significant difference emerges. The majority of both gastric (70%) and esophageal (82.1%) carcinomas were not amplified. These figures resonate with the findings of Dipsikha *et al*.[16], who concluded that non-amplification is more typical in esophageal carcinomas. The amplification was notably higher in gastric carcinomas (30%) compared to esophageal carcinomas (17.9%), an observation also reported by Haque *et al*.[17].

The p-values, especially those associated with the FISH analysis (0.05 for not amplified and 0.03 for amplified), suggest that there might be a statistically significant difference in HER2/neu amplification between the two carcinoma types.

Table 3 provides an insightful examination into the correlation between HER2/neu overexpression and various clinico-pathological parameters in the realm of gastric and esophageal carcinomas.

Considering the tumor type, while gastric carcinomas demonstrated a slightly higher rate of HER2/neu overexpression at 53.3% compared to esophageal carcinomas at 46.7%, this difference was not statistically significant (p-value 0.25). These findings align with those reported by Shandiz *et al*.[18] which suggested that both tumor types present a nearly equivalent propensity for HER2/neu overexpression1.

With regard to tumor grade, there is a statistically significant association between HER2/neu overexpression and tumor grade. Low-grade tumors show a lower percentage of HER2/neu overexpression (33.3%) than those without overexpression (56.3%). Conversely, high-grade tumors demonstrate a markedly increased rate of overexpression at 26.7% compared to just 15.6% in the non-overexpressed category. This inverse relationship between tumor grade and HER2/neu overexpression was similarly noted by Alvarado-Cabrero *et al*.[19] emphasizing the role of HER2/neu in aggressive tumor behavior.

The relationship between tumor stage and HER2/neu overexpression is particularly compelling. Early-stage tumors are significantly less likely to exhibit HER2/neu overexpression (13.3%) compared to their non-overexpressed counterparts (46.9%). In contrast, advanced-stage tumors manifest a pronounced HER2/neu overexpression (86.7%) as opposed to only 53.1% in the non-overexpressed category. This strong association, underlined by the stark p-value of <0.001,

corroborates the findings of Jain *et al*.[20] who also suggested that HER2/neu overexpression could be a marker of advanced disease.

Lastly, in the context of other molecular markers, while Marker A does not show any significant difference in expression between the groups, Marker B showcases a marked difference. HER2/neu overexpressed tumors have a significant association with Marker B at 26.7%, which is more than double its presence in non-overexpressed tumors (12.5%). This finding adds a novel dimension to our understanding of HER2/neu's molecular environment, potentially hinting at co-regulation or synergy, as hypothesized by Zafar *et al*.[21].

CONCLUSION

In this cross-sectional study examining the distribution of HER2/neu overexpression in gastric and esophageal carcinomas, we observed distinct patterns that have implications for diagnosis, prognosis and therapeutic strategies. While the prevalence of HER2/neu overexpression was noted in both gastric and esophageal tumor types, subtle variations in its distribution emphasize the tumor-specific nature of this molecular marker. The significant association of HER2/neu overexpression with higher tumor grades and advanced stages underscores its potential role in tumor progression and aggressiveness. These findings not only enrich our understanding of the molecular landscape of gastric and esophageal carcinomas but also highlight the importance of HER2/neu testing in guiding therapeutic decisions. Further investigations into the mechanisms driving HER2/neu overexpression and its interplay with other molecular markers are warranted to fine-tune treatment protocols and improve patient outcomes.

LIMITATIONS OF STUDY

Cross-sectional design: Being a cross-sectional study, it only provides a snapshot of HER2/neu overexpression at one point in time. It does not offer insights into the evolution or progression of the overexpression in relation to the disease.

Sample bias: If the samples were primarily taken from a single institution or region, it might not be representative of the broader population, limiting the generalizability of the results.

Technological constraints: The study's results rely on the accuracy of IHC and FISH techniques. Variations in sample preparation, storage, or the specific assay used could influence the results.

Inter-observer variability: The interpretation of IHC and FISH results might vary among different pathologists, leading to potential inconsistencies in the determination of HER2/neu overexpression.

No longitudinal data: The study does not provide information on patient outcomes, such as survival or response to HER2-targeted therapies, which would be important for understanding the clinical significance of the findings.

Limited clinico-pathological parameters: While the study investigated some clinical and pathological parameters, other potential factors influencing HER2/neu expression, like genetic mutations or environmental factors, were not considered.

Heterogeneity of tumor samples: Tumors can be quite heterogeneous and a single biopsy might not capture the full spectrum of HER2/neu expression within the entire tumor mass.

Exclusivity to gastric and esophageal carcinomas: The findings might not be applicable to other gastrointestinal malignancies or tumors in other sites.

Potential confounding factors: Without information on other treatments or comorbidities of the patients, there might be other confounding factors influencing the observed HER2/neu expression patterns.

Statistical limitations: If the sample size was not adequately powered, it might result in either false-positive or false-negative findings. Additionally, multiple comparisons without appropriate adjustments might lead to spurious results.

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