

Immunohistochemical Expression of Her-2/Neu in Gastric and Gastroesophageal Junction Cancers in Anambra State, Southeast Nigeria: A Multicenter 10-Year Retrospective Review

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Article received: 11/01/2026, Article Revised: 09/02/2026, Article Accepted: 11/03/2026, Article Published: 18/04/2026
Article DOI: - <https://doi.org/10.55640/irjmsmc-v03i04-04>

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ABSTRACT

Background: Gastric and gastroesophageal carcinomas are amongst the leading contributors of cancer deaths globally. In Nigeria, late diagnosis is the norm for these malignancies resulting in major cancer related mortality. The role of targeted therapy in the management of advanced gastric and gastroesophageal carcinomas using anti-HER2 monoclonal antibody is being explored in various populations following studies revealing improved overall survival.

Materials and Methods: The relevant data were retrieved from four major histopathology laboratories in Anambra, Southeast Nigeria over a 10-year period. Haematoxylin & Eosin slides were made from the formalin fixed paraffin embedded blocks and were reviewed to confirm diagnosis and pathological parameters. HER-2 overexpression was assessed by staining with anti-HER-2 antibody

Results: HER-2 overexpression was found in 5.97% of gastric & GEJ carcinomas studied. All HER-2 positive tumours from this study were intestinal-type tumours, however this association is not statistically significant. No correlation was found between HER-2 overexpression and the variables; age, sex, tumour grade, tumour stage and tumour location.

Conclusion: HER-2 overexpression is seen in a small percentage of gastric and gastroesophageal carcinomas in Anambra state. This HER-2 overexpression has not shown any statistically significant associations with clinical and pathological parameters studied.

Keywords: HER-2 overexpression, Gastric carcinoma, Gastroesophageal junction carcinoma (GEJ carcinoma), Targeted therapy, Anti-HER2 monoclonal antibody

INTRODUCTION

Cancer is the second leading cause of death globally after cardiovascular diseases. Upper gastrointestinal cancers, including gastric and gastroesophageal junction carcinomas, are among the most common cancers. Despite the decline in gastric cancer rates in recent decades, it is still a major cause of cancer mortality. It has been shown that 6.8% of global cancer deaths are due to gastric cancer. It is estimated that in 2022, gastric cancer accounted for 768,793 deaths worldwide.¹

The incidence of gastric cancer and gastroesophageal junction cancers show wide geographical variation. The high-risk areas are East Asia and Eastern Europe. The low-risk areas are Southern Asia, North and East Africa, and North America. Gastric cancer has a low prevalence in sub-Saharan Africa with the lowest incidence rates in Western Africa.^{1,11,12} In Nigeria, gastric cancer accounts for 1.1-6.0% of all cancers and the mean age of diagnosis is 56 years.^{2-6,11}

HER-2 protein (ErbB-2) is an 18-kDa transmembrane receptor with tyrosine kinase activity and belongs to the epidermal growth factor receptor (EGFR) family. This family includes four members: HER1 (EGFR), HER-2, HER3 (ErbB-3), and HER4. These receptors share a

common structure consisting of an extracellular ligand-binding domain, a short transmembrane segment, and an intracellular domain with tyrosine kinase activity, except for HER3. Ligand binding to the extracellular domain triggers a cascade of signaling events that impact various aspects of tumor cell biology, such as proliferation, migration, and adhesion. While HER-2 does not directly bind any known ligands, it serves as the preferred partner for heterodimerization within the HER family.⁷

HER-2 overexpression and/or amplification have also been observed in breast, colon, ovarian, uterine cervix and gastric carcinomas.⁸ Amplification and/or overexpression of HER-2 has been reported in 4.4% to 53.4% of gastric and gastroesophageal junction cancer cases and has been correlated with poor outcomes in many studies.^{8,9,13-18} Targeting HER-2 with trastuzumab, a monoclonal antibody directed against HER-2, has been shown to inhibit tumour cell growth in gastric and gastroesophageal junction cancers.¹⁰

This study is aimed at using immunohistochemical staining to review HER-2 overexpression in gastric and gastroesophageal junction cancers' surgical pathology specimens seen in Anambra, south-east Nigeria, and their relationship with clinical and pathologic findings.

MATERIALS AND METHOD

This is a retrospective study of all gastric and gastroesophageal junction biopsies and gastrectomy specimens diagnosed as cancers at the four major histopathology laboratories in Anambra state. These are: histopathology laboratories of Nnamdi Azikiwe University Teaching Hospital Nnewi (NAUTH), Chukwuemeka Odumegwu Ojukwu University Teaching Hospital Awka, Pathocon Specialist Clinic and Research Institute Nnewi and Nkeoma Specialist Hospital Onitsha, over 10-years, from January 1st 2011 to December 31st 2020.

Inclusion and Exclusion Criteria

The study included well-preserved tissue blocks with sufficient accompanying data and adequate material for additional sectioning. Cases with incomplete biographical data or missing tissue blocks were excluded.

1. Collection of Biographical Data

Relevant patient information, such as age, sex, and tumor location, was extracted from the request forms. Patient

names were omitted to ensure confidentiality.

2. Histopathological Examination and WHO Classification

Histological slides, paraffin blocks, and biopsy specimens from gastric and gastroesophageal junction cancers diagnosed between January 2011 and December 2020 were retrieved from the archives of the facilities studied. Fresh sections were prepared and stained with hematoxylin and eosin for cases where slides were damaged, faded, or otherwise of poor quality. All slides were reviewed, classified, graded, and T-staged in accordance with the 2019 WHO Classification of Gastric Tumors for consistency.

3. Immunohistochemical Studies

Immunohistochemistry was conducted using the Streptavidin-Biotin immunoperoxidase technique on 4 µm sections from formalin-fixed, paraffin-embedded tissues. This method utilized the strong affinity between streptavidin, derived from *Streptomyces avidinii*, and biotin, a water-soluble vitamin. Tissue sections were deparaffinized in xylene, rehydrated with graded alcohol solutions, washed in PBS buffer, subjected to antigen retrieval by boiling in EDTA solution (pH 8.0, 100°C, 2.5 minutes), and cooled. Sections were stained using anti-HER-2 monoclonal antibody clone A0485 (Dako, Denmark).

Using Fischer method of sample size calculation:

$$\text{Sample size, } n^0 = \frac{Z^2 P(1-P)}{d^2}$$

$$\text{When sample size is corrected for finite population, } n = \frac{n^0}{1 + \frac{n^0 - 1}{N}}$$

Z = Z for level of confidence

P = expected prevalence or proportion

d = precision

N = population size

Z for the level of confidence at 95%, which is conventional, Z is 1.96

In determining the value P(expected proportion), the only Nigerian studies on HER2 overexpression in gastric cancers, Ogun et al and Onyekwelu et al revealed the proportions of HER2 positivity to be 11% and 13% respectively.^{14,15} Ogun et al discovered 4 positive cases in 36 cases studied while Onyekwelu found 7 positive cases from 54 cases. For this sample size calculation, the average proportion from both studies which is 12% will be used.

P = 0.12

d, precision at 5% = 0.05

N = The total population of gastric and gastroesophageal carcinomas in the records of the laboratories are as follows: Nnamdi Azikiwe University Teaching Hospital – 29, Pathocon Specialist Clinic and Research Institute Nnewi – 34, Nkeoma Specialist Hospital Onitsha – 18, Chukwuemeka Odumegwu Ojukwu University Teaching Hospital Awka – 14. The total number is 95.

N = 95

$$\text{Calculating } n^0 = \frac{Z^2 P(1-P)}{d^2} = \frac{1.96^2 \times 0.12(1-0.12)}{0.05^2} = 162$$

$$\text{When corrected for population } n = \frac{n^0}{1 + \frac{n^0 - 1}{N}} = \frac{162}{1 + \frac{162 - 1}{95}} = 60$$

n = sample size = 60

An attrition rate of 10% is to be assumed to account for anticipated dropout. The total sample size is calculated as sample size (60)/1-attrition rate. = 60/1-0.1= 60/0.9 = 67

The interpretation of HER-2 immunohistochemical staining followed the HER-2 scoring system for gastric cancer developed in the pre-ToGA study, as revised by Ruschoff et al. in 2010.¹⁹ (Table 1)

Table 1: Immunohistochemistry Interpretation Pattern.

Surgical specimen staining pattern	Biopsy specimen staining pattern	Classification/score
No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or no membranous reactivity in any tumour cell	Negative/0
Faint or barely perceptible membranous reactivity in $\geq 10\%$ of tumour cells; cells are reactive only in part of membrane barely perceptible	Tumour cell cluster with faint or membranous reactivity irrespective of percentage of tumour cells stained	Negative/1+
Weak to moderate complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal/2+
Strong complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive/3

Data was analyzed using simple descriptive statistics such as chi-square test, which was used to measure associations with level of significance p less than 0.05.

The above analysis was done using Statistical Package

for Social Sciences (SPSS version 25) ©IBMInc Chicago.

Ethical approval for the study was obtained from the ethics committee of NAUTH Nnewi.

RESULTS

Her-2 Status of Carcinomas

After immunohistochemical staining of the 67 gastric & GEJ carcinomas with HER-2 mouse monoclonal antibody, the HER-2 staining pattern revealed that 62 of 67 cases (92.54%) showed no staining at all, 1 case (1.49%) showed 1+ staining intensity, 4 cases (5.97%) showed 3+ staining intensity (Figs. 1 & 2). No case showed a 2+ staining intensity.

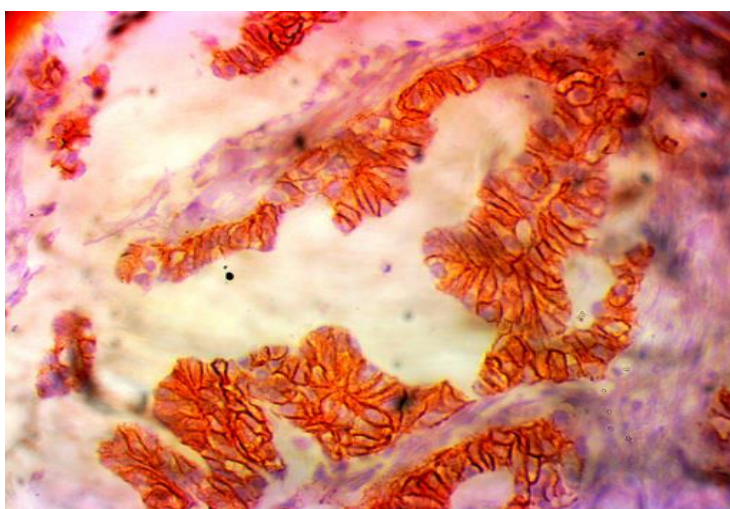


Fig 1: Papillary adenocarcinoma exhibiting branching papillae. HER-2 stain (3+) x400

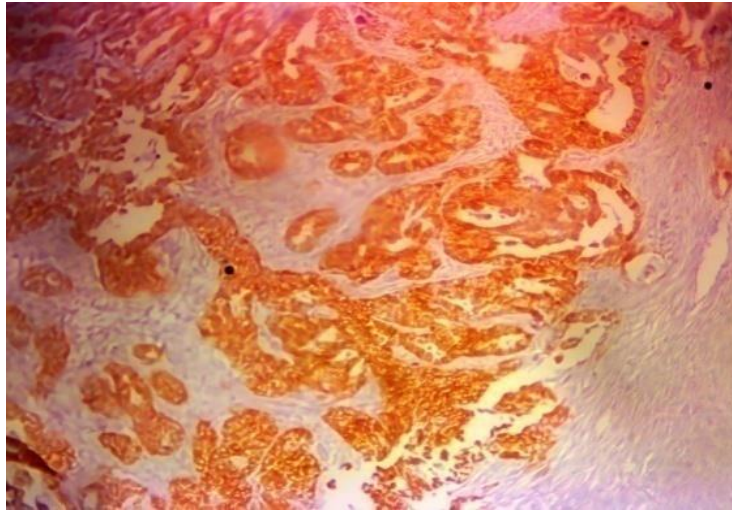


Fig 2: Tubular adenocarcinoma showing fused tubules forming cribriform structures. HER-2 Stain (3+) x200

There was no significant statistical association between HER-2 status and clinical variables such as age and gender. Two cases each were positive for the male and female genders.

A cross-tabulation of HER-2 status and age of the 67 patients is shown in Table 2.

Table 2: HER-2 Status and age of 67 gastric and GEJ carcinomas

		HER-2 Status of Carcinoma		
		Positive	Negative	Total
Age Range in years	<20	0	0	0
	20-29	0	0	0
	30-39	0	9	9
	40-49	1	9	10
	50-59	0	11	11
	60-69	3	19	22
	70-79	0	11	11
	>79	0	4	4
	Total	4	63	67

$P = 0.439$

All four HER-2 positive tumours are intestinal type carcinoma, but this association is not statistically significant ($P=0.175$). A cross-tabulation of HER-2 Status and carcinoma histological type (WHO Classification) is shown in Table 3. There was also no significant association between the two variables. ($P=0.193$).

Table 3: Cross-tabulation of HER-2 status and carcinoma histological type (WHO Classification)

		HER-2 Status of Carcinoma		
		Positive	Negative	Total
Carcinoma Histological Type (WHO Classification)	Tubular Adenocarcinoma	2	29	31
	Papillary Adenocarcinoma	1	1	2
	Poorly Cohesive Carcinoma; Signet Ring Cell Type	0	8	8
	Poorly Cohesive Carcinoma; Other Subtypes	0	13	13
	Mucinous Adenocarcinoma	1	1	2
	Mixed Adenocarcinoma	0	5	5
	Squamous Cell Carcinoma	0	4	4
	Other Histologic Subtypes	0	2	2
	Total	4	63	67

$P=0.193$

Thirty-three of the sixty-seven gastric and GEJ cases were tubular or papillary carcinomas, and these were classified as well- or poorly differentiated. Three cases of well differentiated carcinomas were positive, while 22 well differentiated tumours were negative. No poorly differentiated tumour tested positive. There was no significant association between HER-2 status and tumour grade ($P=0.176$).

There were 17 gastrectomy specimens amongst the 67 gastric and GEJ tumours studied. HER-2 staining revealed one stage T3 and T4 tumor stained positive each. The other 15 gastrectomies specimens stained negative. There was no significant association between HER-2 positivity and tumour stage ($P=0.573$).

Fifty-seven cases of the gastric and GEJ carcinomas have known tumour location. Three positive cases were located on the pylorus/antrum while one case was on the cardia/fundus area. There was no significant

association between the two variables ($P=0.409$).

DISCUSSION

This study sought to determine the frequency and clinicopathological correlates of HER-2/NEU immunopositivity in gastric and GEJ junction carcinomas in Anambra state, southeast Nigeria. The HER-2 status of the gastric and GEJ carcinomas studied was determined according to the validation study done by Ruschoff et al which considered only membrane staining as positive regardless of the nuclear and cytoplasmic staining. 4 of 67 (5.97%) cases of the gastric and GEJ in this study were positive. This HER-2 positivity rate of approximately 6% falls within the widely varied range of 4.4% to 53.4% reported internationally.^{8,9,13-17}

Two Nigerian studies were found in literature on this subject and these were by Ogun et al in Ibadan and

Onyekwelu et al in Lagos, both in Southwestern Nigeria.^{14,15} Ogun et al reported 11% (4 out of 36 cases) positivity while Onyekwelu et al reported 13% positivity (7 out of 54 cases). Other African studies found in literature are those of Nyaboga et al which reported a positivity rate of 7.6% and Simpong et al which reported 41%.^{20,9}

Globally, in a large trial in Asia, Yan et al studied HER-2 status in 37,992 diverse cancers and found 5% HER-2 positivity in gastric carcinomas. Kattan et al in Lebanon reported 6.4% positivity in 2022, Marx et al, 2009 in Germany reported 16.9% while Zhang et al in the same year, reported 18.6% in China.^{8,24,25,28}

These examples of HER-2 positivity are consistent with a wide variation of HER-2 positivity reports seen across the world. This seemingly wide variation is attributable to various factors including different populations of study, inter-observer variability, use of non-standardized assays and different scoring criteria.

This study used the scoring system first developed by Hofmann et al in 2008 and modified by Ruschoff et al in 2010.^{21,19} Some of the studies prior to the development of a validated scoring system, reported higher positivity rates. For example, Park et al in 2006 used a four-tiered scoring system for reporting HER-2 overexpression in breast cancer suggested by the manufacturer of the antibody they used. They reported 15.9% positivity.²²

Our study found no significant association between the HER-2 status of the gastric & GEJ carcinomas and the age and gender of the patients. This finding concurs with several other studies including those by Onyekwelu et al in Southwest Nigeria, Kattan et al in Lebanon and Ljubomir et al in Republic of Northern Macedonia, which found no significant association between the HER-2 status and those clinical features.^{15,22,26,28}

However, in contrast to these studies, larger multinational studies across European, North American and Asian continents by both Jianjigian et al and Kim et al found HER-2 positivity to be significantly more common in males than in females.^{27,30} Kataoka et al in Japan reported a significant association between HER-2 status and increasing age.²⁹

All four HER-2 positive cases from this study are intestinal-type adenocarcinomas. However, this

association is not statistically significant. Nigerian studies on same subject reported similar findings, Ogun et al reported all HER-2 positive cases in their study as intestinal-type adenocarcinomas while Onyekwelu et al found 6 in 7 positive tumours as intestinal-type tumours, but both studies reported no significant statistical association.

Globally, some studies that compared the two variables, HER-2 status and tumour histiotype found a statistical association between HER-2 positivity and intestinal-type adenocarcinoma.^{16,24,25,27,29,30} These studies have evidently larger sample sizes than the Nigerian studies, Kim et al studied 4949 cases while Janjigian studied 381 gastric cancers, both were multinational studies.

However, some other large international studies did not find any association between HER-2 status and tumour histological type.²⁸

Using the WHO Classification of gastric tumours, the HER-2 positive tumours in this study were 2 cases of tubular adenocarcinomas, and a positive case each of papillary adenocarcinoma and mucinous carcinoma. Kataoka et al reported most HER-2 positive gastric carcinomas to be tubular and papillary adenocarcinomas in Japan.²⁹

Akin to studies by Onyekwelu et al in Nigeria and Marx et al in Germany, data from this study did not reveal any statistically significant association between HER-2 positive gastric carcinomas and tumour grade.^{15,25} In contrast, some other studies like those by Ljubomir et al and Huemer et al in Europe reported that HER-2 positivity in gastric carcinoma is significantly associated with well-differentiated carcinomas.^{26,31} Chua et al carried out a systematic review article of 49 studies that compared HER-2 positivity and clinico-pathological findings in gastric cancers; they found a significant number of studies establishing both association and no association between HER-2 overexpression and tumour grade. They resolved that it is not possible to provide definitive conclusion from the literature on the association of HER-2 overexpression with tumour grade.³²

This study found no statistically significant association between HER-2 status of gastric and GEJ carcinomas and tumour stage. This finding is consistent with most other international studies which sort for association between HER-2 status and tumour stage.^{25,28-30} However

a few other studies reported significant association between stage III and V tumours and HER-2 positivity.^{16,22,24} The Nigerian study on the subject, Onyekewu et al found no association between HER-2 and tumour stage.¹⁶ As with HER-2 status association with tumour grade, there appear to be no consensus on tumour stage relationship with HER-2 status of gastric cancers in the literature.

This study also found no association between HER-2 status and tumour location. Three of the four HER-2 positive tumours were located at the pylorus/antrum but this was not statistically significant. None of the 11 gastroesophageal tumours were positive for HER-2 overexpression from this study. Several international studies which compared HER-2 overexpression of gastric carcinomas versus GEJ carcinomas found more HER-2 positive GEJ tumours compared to gastric tumours, with varying ratios. Kataoka et al found the HER-2 positivity ratio to be almost three times as high in the tumours invading the esophagus than in other gastric locations.²⁹ In a multinational study involving a large sampling of gastric and GEJ carcinomas, Kim et al reported significant more HER-2 positivity in GEJ vs gastric tumours.³⁰

Finally, Van Custem et al in a multinational review across Europe and Asia also found higher rate of HER-2 positivity amongst GEJ cancers versus gastric cancers (32% vs 21%). They opined that this higher rate in GEJ carcinomas could be explained by the dominant tumour histologic type in GEJ carcinomas which is the intestinal-type adenocarcinomas (gastric intestinal-type carcinomas have been reported to show significant higher association with HER-2 positivity than other histological type).³³ It appears larger multicenter studies involving many more cases is necessary to seek out the association between these two variables in Nigeria.

STUDY LIMITATIONS

A few factors limit the observations and values obtained from this study. The small-scale nature of cohort used. A larger cohort study would have been more revealing on some of the various observations noted in the study. The retrospective nature of the study precluded the possibility of controlling for pre-fixation factors such as cold ischemic time, which are known to affect HER-2 antigen retrieval.³⁴ This could lead to a deceptively lower HER-2 positivity rate as reported by this study. Some endoscopic biopsies lack specific pathologic information such as tumour location.

CONCLUSION

HER-2 overexpression was found in a minority of gastric & GEJ studied (5.97%). This value is comparable to the HER-2 positivity rates in gastric cancers reported in many local and international studies. All HER-2 positive tumours from this study were intestinal-type tumours. However, this association is not statistically significant. No correlation was found between HER-2 overexpression and other clinico-pathologic variables namely age, sex, tumour grade, tumour stage and tumour location.

AUTHOR CONTRIBUTION

All authors played a substantive role in shaping this study and developing the manuscript. K.G.I. conceptualised the work and designed the overall study framework. Data analysis, interpretation of data and validation of findings were carried out collaboratively, with each author contributing to the discussions that informed the final results. G.M.Y., C.E.E. and K.O.O. prepared the initial manuscript draft, covering the introduction, methods, results and discussion. Co-authors strengthened the analysis, offered detailed revisions and enhanced the clarity and coherence of the final document. Every author reviewed the complete manuscript, approved the final version and accepted responsibility for the integrity of the work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGEMENT

The authors acknowledge the management and technical staff of PENKUP Research Institute, Birmingham, UK, for their excellent assistance and for providing manuscript writing and editorial support in accordance with the Good Publication Practice (GPP3) guidelines.

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