Article published online: 2023-09-27

Expression of Her2-Neu in Primary Gastric and Gastroesophageal Adenocarcinoma: An Experience from a Tertiary Center in South India

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South Asian J Cancer

Abstract

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Gastric cancer is one of the most commonly occurring cancers worldwide, often presenting at an advanced stage. Combining targeted therapy with chemotherapeutic agents can enhance and extend the survival of these patients. This 4-year retrospective study aims to assess the prognostic role of Her2-Neu expression in gastric and gastroesophageal (GE) cancer. Clinicopathological features, histological type (Lauren classification) of adenocarcinoma, and Her2 immunohistochemical expression were correlated with disease-free and overall survival in 114 patients. A Her2 score of 0 and 1+ indicated negativity, while 3+ marked positivity. For cases with a 2+ score, fluorescent in situ hybridization (FISH) was conducted for definitive categorization. Statistical analysis employed IBM SPSS version 20.0 software. Among 114 patients, 13 displayed strong Her2-Neu immunopositivity (3+), 9 scored 2+, and 92 were negative (0 [89] and 1+ [3]). FISH classified 4 and 5 cases as positive and negative, respectively. Most (64.7%) Her2-Neu-positive tumors occurred in the proximal stomach/GE junction (GEJ) and exhibited intestinal morphology (94.1%) with moderate differentiation (p-value < 0.05). Notably, 76.5% of Her2-Neu-positive patients exhibited advanced-stage disease with nodal/distant metastasis. The average disease-free survival was 15.4 months (standard error: 3.55) for positive Her2-Neu expression and 22.07 months (standard error: 1.364) for negative expression. The mean overall survival was 21.14 months (standard error: 3.702) for positive expression and 23.91 months (standard error: 1.474) for negative expression. Her2-Neu expression in gastric/GEJ adenocarcinomas correlates with reduced survival. Evaluating HER2-NEU in proximal gastric/GEJ cancers displaying low-grade intestinal morphology serves as both a predictive and prognostic indicator.

Keywords

- gastric cancer
- gastroesophageal adenocarcinoma
- Her2-Neu
- targeted therapy
- trastuzumab

DOI https://doi.org/10.1055/s-0043-1774290 ISSN 2278-330X

How to cite this article: Damle A, Paulose RR, Saikumar D, et al. Expression of Her2-Neu in Primary Gastric and Gastroesophageal Adenocarcinoma: An Experience from a Tertiary Center in South India. South Asian J Cancer 2023;00(00):00–00

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Gastric/gastroesophageal (GE) carcinoma is one of the common causes for cancer-related mortality in India and worldwide. The Global Burden of Disease Study 1990–2016 observed that gastric cancer is one of the top 10 common cancers in India and accounts for 9% of the total cancers disability-adjusted life years.[1–4] The incidence of gastric cancer is higher in South India[5] and often presents at advanced stages. The mainstay of treatment is surgery with perioperative chemotherapy.

The role of various cell surface antigens/transmembrane proteins/growth factor receptors like CDH1, MCT1, and MCT4[6,7] have been studied in gastric cancer. Her2-Neu oncogene is a member of the erbB-like oncogene family which are physiologically involved in signal transmission and are constituted by family of four cell surface receptors—HER1, HER2, HER3, and HER4, which exist as monomers and heterodimerize with her2 on ligand binding, in turn generating strong intracellular signals controlling normal cell proliferation.[8,9] Hence, Her2 overexpression in neoplastic cells causes uncontrolled cancer cell proliferation.[8]

The role of expression of Her2-Neu in gastric/GE junction (GEJ) cancers have gained interest after witnessing improved outcome on targeted therapy with trastuzumab (recombinant human anti-her2 monoclonal antibody).[9–11]

Despite being a poor prognosticator, it has been proved promising in early gastric cancers when used in combination with other chemotherapeutic agents.[10,12–16]

The immunohistochemical expression of Her2-Neu in gastric/GEJ cancers displays heterogeneity and also varies geographically.[17,18]

As there is paucity of Indian data on this, we conducted this study to evaluate the role of expression of Her2-Neu in gastric/GE cancer as a prognostic marker.

Materials and Methods

This is a 4-year (January 2011–December 2014) retrospective study followed by 7 years of follow-up (i.e., 2015–2021) of patients who underwent surgical resection for primary gastric or GEJ adenocarcinoma, at a tertiary center in South India. Institutional ethics committee approval was obtained for the study.

Details regarding patient demographics, tumor site and stage, and treatment including neoadjuvant/adjuvant therapy were obtained from the hospital information system. All cases were histologically categorized as per Lauren's classification into intestinal or diffuse and staged as per TNM 8th Edition. Immunohistochemistry (IHC) with Her2-Neu monoclonal primary antibody (polyclonal rabbit anti-human c-erbB-2 oncoprotein [DAKO] with a dilution of 1:600) was performed on 3-µm thick deparaffinized sections of tumor tissue using the two-step Super Sensitive Polymer HRP IHC detection kit including positive and negative controls in each run. Her2-Neu expression in the neoplastic cells was evaluated using previously validated scoring system adapted from Hofmann et al[19] and Rüschoff et al.[14] Score of 0 and 1+ was considered as negative, while 3+ was considered as positive. Score 2+ was considered as equivocal/borderline and further assessed by fluorescent in situ hybridization (FISH) for definitive categorization.

Follow-up period: The median follow-up period was 2 years (range 1–7 years). Information regarding disease progression/overall survival was obtained from hospital case notes and/or telephonic contact/cancer registry data.

Statistical analysis was performed using IBM SPSS version 20.0 software program (SPSS Inc., Chicago, Illinois, United States). Pearson's chi-square test was used to analyze the association of Her2-Neu expression with clinical details, type, and differentiation of adenocarcinoma and pathological stage of the tumor. To find the probability of overall survival and disease-free survival, Kaplan–Meier analysis was done and followed by log rank test for the comparison. A p-value of < 0.05 was considered to be statistically significant.

Results

A total 114 patients of histologically proven gastric/GE adenocarcinoma was considered in the study with a mean age of 61.75 ± 12.07. There were 90 males (78.95%) and 24 females (21.05%); male-to-female ratio was 3.75:1. The median age of the patients was 64.5 years (range 22–80 years). Eighty-two percent of gastric cancer patients were older than 50 years of age. The most common location of the tumor was the gastric cardia and GEJ (42.9%). The predominant histological type of adenocarcinoma was intestinal subtype (83.3%). Fifty-two percent of the tumor was of poor histological differentiation (grade 3). Majority (79%) of the patients had advanced stage of disease with metastases (►Table 1).

Her2-Neu expression profile: Only 13 patients were found to have positive staining for Her2-Neu (Score 3 +) (►Fig. 1). Four patients with equivocal IHC results (2 +) were confirmed to be Her2 overexpressed by FISH (►Table 2).

1. 1. Tumors with Her2-Neu positivity ($n = 17$)

The tumors with positive Her2-Neu expression were more frequently located in the proximal stomach (cardia) and GEJ (64.7%), with a predominant intestinal morphology (94.1%) and well/moderate differentiation (grade 1 and 2; 82.35%). The comparison of histological differentiation with Her2-Neu expression was found to be statistically significant (p-value 0.005) (►Fig. 2). Diffuse morphology was seen in only one patient. Seventy-five percent of patients had advanced stage of disease with distant/nodal metastases.

1. 2. *Tumors showing Her2-Neu negative* ($n = 97$) had no specific site location, histology, grade, or stage bias. In univariate analysis there were found to be no statistically significant association for tumor attributes with Her2-Neu expression status (►Table 3).

Follow-Up

The mean and median follow-up period was 2.6 and 3 years, respectively. Eight patients with Her2-Neu positive (2) and Her2-Neu negative (6) were lost to follow-up. Fifty-six

Table 1 Site, histological characteristics, and staging of tumors in the study population (total $n = 114$)

Characteristics	*n*	Percentage (%)
Site		
Gastric cardia and gastroesophageal junction	49	42.9
Gastric body/fundus	37	32.45
Distal gastric tumor (antrum/pylorus)	28	24.56
Histological type (Lauren's classification)		
Intestinal type	95	83.33
Diffuse type	19	16.66
Grade/histological differentiation		
Grade I (well differentiation)	16	14.03
Grade II (moderate differentiation)	39	34.2
Grade III (poor differentiation)	59	51.75
Tumor staging (as per AJCC TNM 8th edition)		
Lower tumor stage (pT1 and pT2)	24	21.06
Advanced tumor stage (pT3 and pT4)	90	78.94
Metastatic disease Including nodal metastasis and distant metastasis		
Present	82	71.93
Absent	32	28.07

Abbreviations: AJCC, American Joint Committee on Cancer; TNM, tumor, nodes, and metastases.

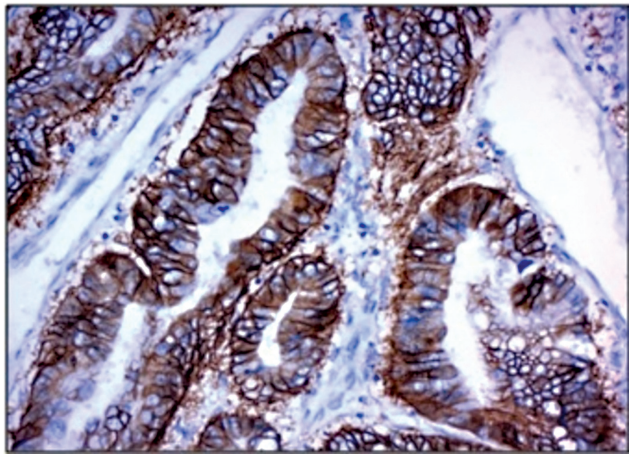

Fig. 1 Immunohistochemistry (IHC) for Her2-Neu positive staining (3+).

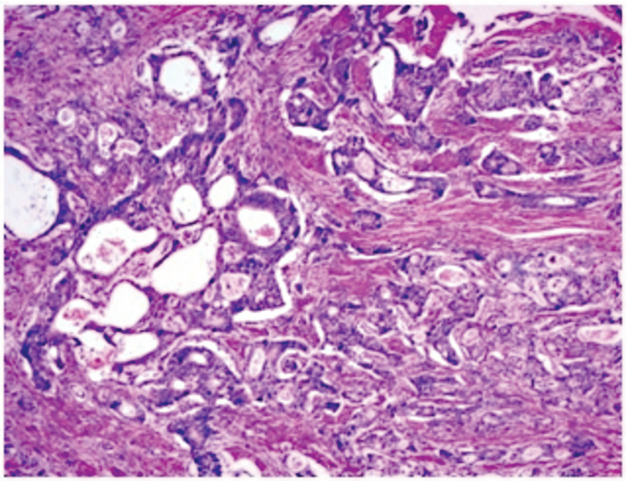

Fig. 2 Intestinal type adenocarcinoma morphology.

Table 2 Expression profile of Her2-Neu ($N = 114$)

IHC scoring for Her2-Neu	*N* (frequency)	Interpretation/ result
0	89	Negative
1+	3	Negative
2+	9	Negative
2+ FISH negative	5	**Negative**
2+ FISH positive	4	Positive
3+	13	**Positive**

Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry.

patients among 106 (52.8%) in our study population had disease recurrence and 51 (51%) died of the disease.

Eleven Her2-Neu positive patients (73.3%) had disease recurrence and 9 (69.23%) died of the disease. In comparison, with negative expression for Her2-Neu protein, 45 (49.5%) had disease recurrence and 42 (48.28%) died of the disease (►**Fig. 3**). The comparison of mortality and recurrence status was not found to be statistically significant (*p*-value 0.086 and 0.159, respectively).

The overall mean disease-free survival for our study population was 21.15 months with standard error of 1.498 (95% confidence interval [CI]: 18.216–24.087). The overall mean disease-free survival for the patients showing positive

Table 3 Multivariate table showing comparison of tumor attributes/characteristics with Her2-Neu expression status

Variable		HER2-NEU positive (total 17)		HER2-NEU negative (total 97)		*p*-Value
		N	%	*N*	%	
Age at diagnosis years	> 50	15	88.24	79	81.44	0.57
	< 50	2	11.76	18	18.56	
Gender	Male	14	82.35	76	78.35	0.95
	Female	3	17.65	21	21.65	
Site of tumor	GEJ	11	64.71	38	39.18	0.08
	Gastric body/fundus	2	11.76	35	36.08	
	Distal stomach	4	23.53	24	24.74	
Histological subtype	Intestinal type	16	94.12	79	81.44	0.34
	Diffuse type	1	5.88	18	18.56	
Differentiation	Well/moderate	14	82.35	41	42.27	0.005
	Poor	3	17.65	56	57.73	
Tumor stage	T1/T2	4	23.53	20	20.62	1.00
	T3/T4 (advanced stage)	13	76.47	77	79.38	
Node/distant metastasis	Present	13	76.47	69	71.13	0.8
	Absent	4	23.53	28	28.87	

Abbreviation: GEJ, gastroesophageal junction.

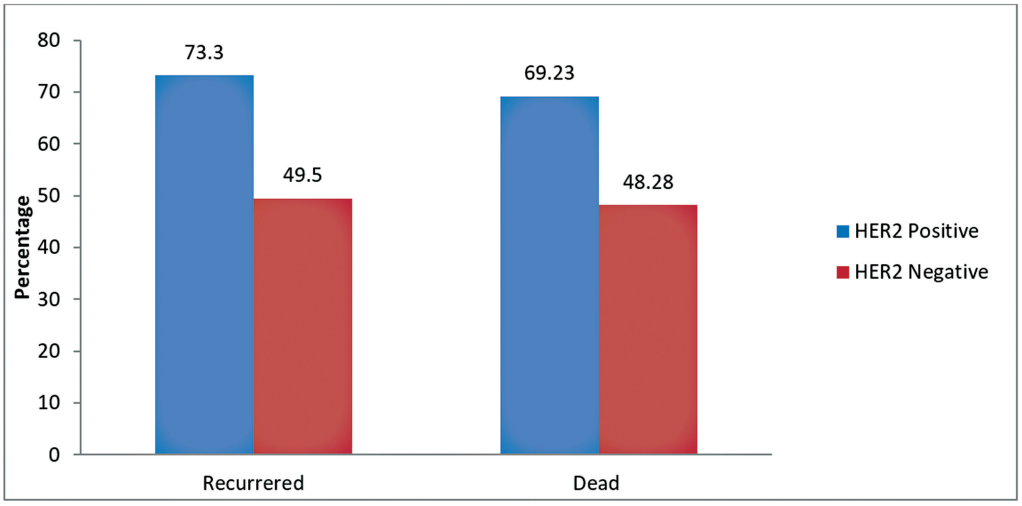

Fig. 3 Frequency of disease recurrence in relation to Her2-Neu expression.

Her2-Neu expression was 15.4 months with standard error of 3.55 and for patients with negative Her2-Neu expression was 22.07 months with standard error of 1.364 (*p*-value 0.08) (►**Fig. 4**).

The mean overall survival for our study population was 23.51 months with standard error of 1.364 (95% CI: 20.841–26.189). The mean overall survival for the patients showing positive Her2-Neu expression was 21.14 months with standard error of 3.702 and for patients with negative Her2-Neu expression was 23.91 months with standard error of 1.474 (*p*-value 0.245) (►**Fig. 5**). As the number of patients with Her2 positive disease were low, multivariate analysis was not feasible.

Discussion

The incidence of gastric cancer in India is relatively low compared with other countries. However, a regional variation has been observed in India with the highest incidence recorded from Southern and Eastern India.[20] There is paucity of data from these regions and hence this study was undertaken to understand the clinicopathological characteristics and survival outcome of patients with gastric and GEJ adenocarcinoma in relation to the expression of Her2-Neu, a potential oncological target. Concordant with other Indian studies,[21,22] this study found a male gender preponderance

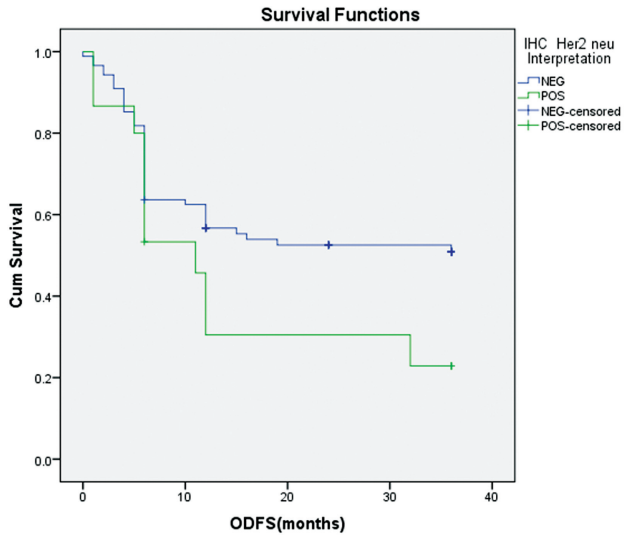

Fig. 4 Kaplan–Meyer curve depicting comparison of overall disease-free survival between Her2-Neu positive and negative groups.

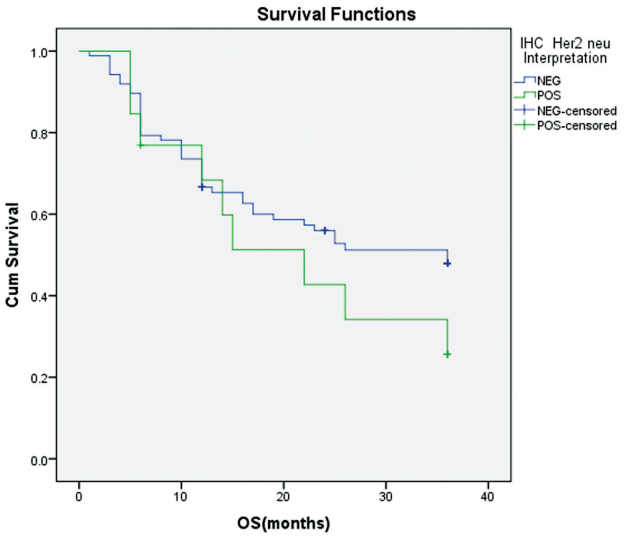

Fig. 5 Kaplan–Meyer curve depicting comparison of overall survival between Her2-Neu positive and negative groups.

for gastric cancer with male-to-female ratio of 2:1, 2.3:1, and 3.75:1, respectively. Other studies including a meta-analysis[15,23,24] have also reported similarly.

Gastric antrum has been observed to be the most common site of involvement as seen in studies from India and other Asian countries like Japan and Korea.[24,25] However, Devesa et al,[26] Harikumar et al,[27] and Abdi-Rad et al[24] have mentioned a paradigm shift of gastric cancer to cardia/proximal stomach in the West and in an Indian state Kerala. This was observed in this present study also and can be attributed to changing colonization of *Helicobacter pylori* with atrophic gastritis, dietary habits, lifestyle, obesity, and GE reflux.[28]

Frequency of positivity for Her2-Neu in gastric/GEJ cancers has been found variable across continents. Lei et al[15] in their meta-analysis have stated a slightly higher rate of positivity in Asian countries, that is, 19.52% in comparison to the European countries which is 16.91%. This heterogeneous expression has been observed between Asian countries and even within the Indian subcontinent. Shan et al[29] in a Chinese study demonstrated a frequency of 9.8%, while Matsusaka et al[30] in a Japanese multicenter observational study demonstrated 15.6% frequency of high Her2-Neu expression. Among the Indian studies, a geographic variation has been observed with Sukanya et al[22] from Tamil Nadu reporting a 12% frequency, Patil et al[31] in their multicentric clinical trial showed 7% frequency and a systematic review of 41 studies reported a median of 15%,[32] Gupta et al[21] from Delhi showed 24.5%frequency, Panda et al[33] from the state of Orissa showed 18.7% frequency, and the frequency in the present study done in a tertiary care institute of Kerala was 15%.

Significant association between Her2-Neu expression and proximal gastric/GEJ tumor site has been observed in studies done by Roy et al,[23] Shan et al,[29] and Lei et al[15] and in the present study. Although Sukanya et al[22] demonstrated higher expression of Her2-Neu in distal gastric cancers, the number of GEJ tumors was low in their comparatively smaller study population (4 out of total 70). A significant association of Her2-Neu expression with well/moderately differentiated (grade 1 and 2) intestinal type adenocarcinoma is there in the present study and in those conducted by Gupta et al,[21] Panda et al,[33] Lei et al,[15] and Shan et al.[29]

GEJ tumors are more aggressive and with advanced stage of disease.[24] In the present study, both Her2-Neu positive and Her2-Neu negative groups showed distant/nodal metastasis with only a borderline difference between them, not statistically significant. Lei et al[15] and Panda et al[33] in their meta-analysis and study, respectively, have demonstrated a statistical correlation between Her2-Neu positive tumor status and advanced tumor staging.

There is limited Indian data on survival/outcome of patients with Her2-Neu expression on gastric cancer; hence, this index study seems to be one of its kind. The mean overall disease-free survival and overall survival for the patients showing positive Her2-Neu expression in tumor was lower in comparison to those with negative Her2-Neu tumor expression in the present study; despite administration of neoadjuvant therapy (to 35 and 42% patients with Her2-Neu positive and negative expression in tumor, respectively) and adjuvant chemotherapy (to 70% patients from each group). Trastuzumab was not given to any of the patients in the present study at our center, due to the high cost of the drug in the given period of study. Chua and Merrett[32] in their review of 49 studies comprising 11,337 patients found that in patients with positive Her2-Neu expression the median 3-year disease-free survival was 58% (range: 50–88%) and in those with negative Her2-Neu expression the median 3-year disease-free survival was 86% (range: 62–97%); the median overall survival and 5-year survival rate was 21 (42%) and 33 months (52%) in Her2-Neu positive and Her2-Neu negative groups, respectively.

The fact that Her2-Neu positive tumors demonstrate advanced disease with lower survival rates despite giving neoadjuvant and adjuvant chemotherapy, targeted interventions are a ray of hope.

Few large-scale studies like the ToGA trial have not only indicated the poor prognostic value of Her2-Neu expression in gastric/GEJ cancers, but also had underlined the improved survival by using trastuzumab in combination with chemotherapy as new standard option for patients with Her2-Neu positive primary/advanced or recurrent gastric and GEJ cancers.[16] Kim et al in their study conducted in a single institution, investigated the outcomes of trastuzumab-based chemotherapy administrated to 47 Her2-Neu positive patients with recurrent or primary metastatic gastric cancer. The outcomes were comparable to that of the ToGA trial, and also concluded that the consideration of conversion surgery in fit patients can be done with R0 resection.[34] After observing significantly improved survival on the use of dual-targeted anti-Her2-Neu therapy in breast cancer, Tabernero et al had designed a study—JACOB—to assess the efficacy and safety of pertuzumab plus trastuzumab and chemotherapy in patients with previously untreated Her2-positive metastatic gastric/GEJ cancers. The primary results showed that the addition of pertuzumab did not significantly improve overall survival at $\geq$ 24.4 months' median follow-up, possibly due to increased complexity of gastric cancer and multifactorial disease progression.[35] However, descriptive end-of-study results showed some but limited evidence of treatment activity and acceptable toxicity profile for the use of above combination.[36]

Conclusion

Expression of Her2-Neu in gastric/GEJ adenocarcinomas though low in our population, was associated with lower survival and found to be a poor prognosticator.

Note

National conference as oral presentation and included in list of oral abstracts: APCON 2019: List of Oral Abstracts 2019. Indian J Pathol Microbiol 2019;62, suppl S1:2–5. Journal ID number (OP No.): OP37.

Availability of Data and Material

The authors confirm that the data supporting the findings of this study are available within the article in form of tables.

Ethics Approval

Obtained.

Authors' Contribution

The study's conception and design saw significant input from R.R.P., A.D., and V.J. A.D., D.A., and D.S. were responsible for data acquisition. Data analysis and interpretation were carried out by A.D., R.R.P., N.K., and R.B. A.D., R.R.P., and W.J. were involved in drafting and revising the article for substantial intellectual content. The final version approval for publication rests with R.R.P.

Funding

Funding was provided by the Amrita Institute of Medical Sciences, Kochi for performing Immunohistochemistry and FISH on the cases.

Conflict of Interest

None declared.

Acknowledgment

The authors thank the technical staff – Pathology Department, Amrita Institute of Medical Sciences, Kochi.

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