ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 03 | March - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF HER-2 OVEREXPRESSION IN GASTROINTESTINAL TUMORS

Pathology

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ABSTRACT

Introduction: HER-2 is emerging as a promising target for therapy across a variety of gastrointestinal tumors. HER-2 prevalence in patients with gastric cancer has been reported as 30%, in gastro-esophageal junction 35%, and 3% in metastatic colon cancer. Ki-67 is used as a marker of tumor aggressiveness. **Methods:** A descriptive cross-sectional study was done at a tertiary health care center for 18 months. 70 histopathologically proven malignant biopsies/surgically resected specimens of the gastrointestinal tract included. **Results:** In 70 cases studied, the stomach and esophagus were the most common sites. Out of 28 HER-2 positive cases, 12 had a score of 3+ on IHC. There was a significant association between HER-2 and Ki-67 levels among the poorly differentiated tumors. **Conclusion:** Routine testing of HER-2 in gastrointestinal tumors is recommended for therapeutic advantage.

KEYWORDS

Human epidermal growth factor receptor-2 (HER-2), Gastrointestinal tumors, Ki-67, Gastric cancer.

INTRODUCTION

Clinical applications of genomic medicine and molecular diagnostics based on the testing of tissues are becoming a reality in clinical practice, with a significant impact on personalized therapies for cancer patients. Increased understanding of the specific molecular pathways and driver mutations critical to cancer cell growth has allowed the development of these advanced therapeutics. Advances in targeted therapies for gastrointestinal tract cancers have recently emerged and are rapidly moving targets.

HER-2(ERBB2) is emerging as a promising target for genomically-informed therapy across various tumor types with the introduction of next-generation sequencing in clinical practice. Epidermal growth factor receptors and HER2/neu pathways now play a major role in the management of gastrointestinal cancers in addition to other solid malignancies. HER-2 prevalence in patients with gastric cancer has been reported as 30%, [1] in gastro-esophageal junction is 35% [1], and 3% in metastatic colon cancer. [2] For HER-2, gene amplification (increased copy number) is by far the most common genomic alteration and is associated with protein overexpression. [3-5] HER-2 overexpression drives tumorigenesis through the creation of spontaneous receptor homodimers or heterodimers with other ERBB family members resulting in activated oncogenic downstream signaling, such as PI3K/Akt/mTOR and MAPK, promoting cellular proliferation, survival and angiogenesis. [6-8]

Due to rapidly increasing number of new therapeutics targeting HER-2, accurate assessment of HER-2 status is therefore essential to determine which patients might benefit from it. With this background, present study was conducted to know the prevalence of HER-2 overexpression in gastrointestinal tumors. As Ki67 has a tight correlation with the degree of tumor differentiation, HER-2 and Ki-67 expression was compared for aggressive behavior in patients with gastrointestinal tumors.

MATERIAL AND METHODS

A descriptive cross-sectional study was carried out at a tertiary health care center over 18 months after obtaining approval of the ethics committee. 70 histopathologically proven malignant biopsies and/or surgically resected specimens of the gastrointestinal tract were included. Biopsy and surgical specimens negative or suspicious for malignancy on histology were excluded. After fixing and processing the tissue samples from the primary tumor, routine sections were stained with Hematoxylin and Eosin & were graded on histology.

Immunohistochemical staining with HER-2/neu and Ki67 was performed for each case. Grading of HER-2 was assessed by 2 different pathologists based on ASCO/CAP guidelines of 2018.

Strong, complete membranous staining on IHC in >10% tumor cells was scored as 3+ for HER-2. Weak to moderate complete membranous staining was scored as 2+. Faint or barely perceptible staining was scored as 1+ and no reactivity or reactivity in <10% of tumor cells was scored as 0. A score of 3+ was considered as positive, 2+ as equivocal while 1+ and 0 were negative for HER-2.

Ki-67 score was expressed as the percentage of the number of immuno-stained nuclei among the total number of nuclei of tumor cells regardless of the immunostaining intensity.

RESULTS

Out of 70 cases, 44(62.86%) were biopsy specimens and 26(37.14%) surgical specimens. We found male preponderance with a male-to-female ratio of 1.12:1 in the present study. The mean age of the study subjects was 56.30 years with a majority of people lying in the 51-60 years age group.

The stomach and esophagus were the most common sites, followed by the rectum and colon. Caecum and duodenum were the least common sites. Based on the histopathological diagnosis, the majority (71.43%) were adenocarcinoma followed by squamous cell carcinoma (17.14%). Out of a total of 70 cases, 28 (40%) were HER-2 positive and 42 (60%) HER-2 negative. According to ASCO/CAP guidelines of HER-2 grading on IHC, 12 cases (17.14%) with a score of 3+ & 16 cases (22.8%) with a score of 2+ were seen in the present study. None of the positive cases showed a score of 1+. The majority of the HER-2-positive cases were from the stomach, followed by the rectum and esophagus.

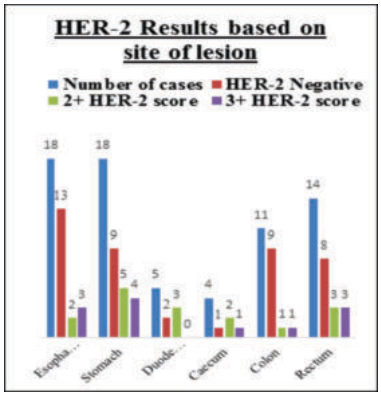

Figure 1: Compound bar chart demonstrating HER-2 results based on site of lesion.

Table 1: Distribution of study subjects based on the HER-2 and Ki 67 expression.

HER-2	Ki 67				Total		P value
	>30%		<30%				
	No.	%	No.	%	No.	%	
Positive	25	59.52	3	10.71	28	40	<0.001
Negative	17	40.48	25	89.29	42	60	
Total	42	100	28	100	70	100	

Overall, amongst the cases with a Ki67 index of >30%, 59.52% were positive for HER-2 and 40.48% were negative for HER-2 with a significant association between HER-2 and Ki67 seen in the present study with a p-value of <0.001.

Table 2: Distribution of study subjects based on the HER-2 and Ki 67 expression in poorly differentiated tumors.

HER-2	Ki 67				Total		P value
	>30%		<30%				
	No.	%	No.	%	No.	%	
Positive	13	68.42	2	15.38	15	46.88	0.0031
Negative	6	31.58	11	84.62	17	53.13	
Total	19	100	13	100	32	100	

A Significant association between HER-2 and Ki67 was seen in the poorly differentiated tumors with a p-value of 0.0031.

Table 3: Distribution of study subjects based on the HER-2 and Ki 67 expression in moderately differentiated tumors.

HER-2	Ki 67				Total		P value
	>30%		<30%				
	No.	%	No.	%	No.	%	
Positive	8	66.67	1	12.5	9	45.0	0.0124
Negative	4	33.33	7	87.5	11	55.0	
Total	12	100	8	100	20	100	

A Significant association between HER-2 and Ki67 was seen in the moderately differentiated tumors with a p-value of 0.0124.

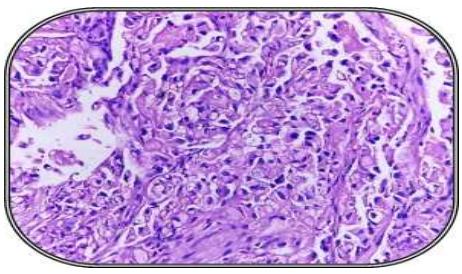

Fig-1: H&E,400x: Gastric adenocarcinoma on biopsy

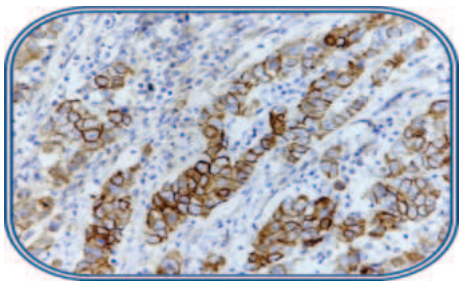

Fig.2: IHC,400x: HER-2 Score 3+

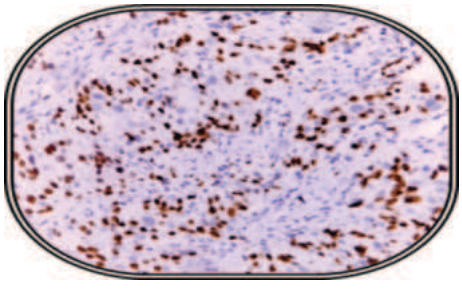

Fig.3: IHC,400x: Ki67>30%

DISCUSSION

Over the last decade, many studies have been conducted to evaluate the protein expression level of HER-2 using immunohistochemistry in breast & gastric cancers.

Gupta P et al [9] (2016), Thakur V et al [10] (2017), and Matsusaka S et al [11] (2016), conducted separate studies to determine the frequency of HER-2 expression in gastric carcinoma by IHC. However, Matsusaka S et al further performed FISH testing in HER-2 equivocal and positive cases. The overall HER-2 positivity rate (IHC score 3+ and FISH positive) was 21.2%. In the present study, out of 18 cases of gastric cancer, 22.22% were 3+ on IHC for HER-2(showing concordance with Gupta P et al which had 24.5% of cases as 3+), 27.78% of cases 2+ and 50% HER-2 negative. As further FISH testing was not carried out on equivocal cases, some positive cases of HER-2 might have been missed.

Very few studies have been conducted to determine the frequency of HER-2 overexpression in colorectal cancer patients. Karaca H et al [12] (2012) study and Tu J et al [13] (2015) study are among them. Tu J et al (2015) conducted a study to evaluate the protein over-expression level of HER-2 using IHC in colorectal cancers. It had a total of 102 cases (11.6%) out of the 878 demonstrating HER-2 positivity by IHC. In our study, a 3+ score for HER-2 was seen in 9.09% of cases of colon carcinoma, 25% of cases of caecum carcinoma, and 21.43% of rectal carcinoma.

Al-Momani H et al [14] (2012) conducted a study to determine the incidence of human epidermal growth factor receptor 2(HER-2) overexpression in esophageal cancers. 25 of the cases showed evidence of HER-2 overexpression. In the present study, 16.67% of cases of esophageal cancer were 3+ 11.12% were 2+ and the rest were negative.

CONCLUSION

Our study highlights the importance of HER-2 and Ki-67 testing among gastrointestinal tumors at tertiary health care centers. Routine testing of gastrointestinal tumors for HER-2 overexpression is recommended to provide a therapeutic advantage in Indian patients. In conclusion, increasing awareness of the HER-2 status of patients can enhance the incorporation of HER-2 targeted therapies in the multidisciplinary approach to gastrointestinal tumors.

Limitations of the study

The number of malignant cases of gastrointestinal tract included in the present study was less and also further FISH testing was not performed for cases with equivocal expression for HER-2 on IHC, i.e. cases with HER-2 score of 2+.

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