Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i8.7330

FREQUENCY OF HER2 OVEREXPRESSION IN METASTATIC GASTRIC AND GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

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ABSTRACT

Objectives: To assess the frequency of her2 overexpression in metastatic gastric and gastroesophageal junction adenocarcinoma
Study Design: Cross Sectional survey
Place & Duration of Study: Kuwait Teaching Hospital, Peshawar, from May 2023 to December 2023.
Methodology: Total of 200 patients diagnosed with gastric adenocarcinoma and gastroesophageal junction adenocarcinoma and metastatic disease were included in this study. Biopsy samples were taken and Her2 expression was assessed.
Results: - Out of the total 200 patients included, the average age of enrolled patients was 51.07 ±11.85 years. There were 93 (46.5%) males and 107 (53.5%) females. Out of 200 cases, 96 (48.0%) had gastric adenocarcinoma while 104 (52.0%) had gastroesophageal junction adenocarcinoma. Out of 200 patients, her2 expression was positive in 49 (24.5%) cases.
Conclusion: The conclusion of this study is that patients with metastatic gastric and gastroesophageal junction adenocarcinoma, the presence of her2 expression is a common finding.

Key Words: her2 overexpression, metastatic disease, gastric adenocarcinoma, gastroesophageal junction adenocarcinoma

INTRODUCTION

Gastric and gastroesophageal junction cancer is a prevalent kind of malignancy that is widespread around the globe. In cases of unresectable or metastatic illness, the prognosis is unfavorable and often has a life expectancy of less than one year.[1] stomach cancer is a significant global health issue and ranks as the fifth most prevalent disease globally. In 2012, there were 952,000 newly diagnosed instances of stomach cancer. Each year, 0.7 million individuals succumb to gastric cancer, accounting for 8.8% of all cancer-related deaths.[2, 3] In Asia, gastric malignancies rank as 2nd most

prevalent malignancy among males and 3rd in females. Additionally, it is the second leading cause of cancer-related fatalities in India.[4, 5] In the last 10 years, the methods of therapy before and after surgery for individuals with esophageal or gastric cancer that might possibly be cured have become better.[6]

Patients diagnosed with stomach cancer that might possibly be cured undergo a treatment plan that includes receiving chemotherapy before and after surgery to remove the tumor. Although these treatment methods have led to increased overall survival rates, the outlook for patients with gastric or esophageal cancer remains bleak primarily because of the high occurrence of local recurrence and distant spread of the disease. Furthermore, at the time of diagnosis, about 50% patients with gastro-esophageal malignancy had metastasized disease.[7] Timely detection of metastases is crucial to prevent ineffective locoregional therapy. The time period, site, and extent of metastatic illness exhibit significant diversity. To enhance the assessment of patients before therapy and to guarantee proper monitoring, it is crucial to get more knowledge on the metastatic pattern seen in this particular group of patients.[8, 9]

Gastric and esophageal adenocarcinomas are a kind of cancer that is characterized by a wide range of biological variations. The discovery of "human epidermal growth factor receptor 2 (HER2)" overexpression in the early 1980s was a significant breakthrough in understanding the molecular complexity of this illness. This overexpression is seen in 12 to 20% of patients. As a result, anti-HER2 therapies were developed, with trastuzumab being the first to show improved response rate and survival when used alongside cisplatin and 5FU/capecitabine chemotherapy in the initial treatment of patients with metastatic, HER2-positive gastroesophageal adenocarcinomas. [10]

HER2 is the trans-membrane tyrosine kinase receptor, belonging to HER2 family. It has a molecular weight of 185 kilodaltons and is encoded by the erb2 gene located on chromosome 17. HER2 is a proto-oncogene. The amplification of the HER2 gene and the overexpression of its protein are significant factors in the growth, cell death, attachment, blood vessel formation, and aggressiveness of several types of solid tumors. HER2 expression, which was first linked to breast cancer, has since been shown to be involved in several types of cancer, such as colon, bladder, ovarian, uterine cervix, gastric, and gastroesophageal junction cancers.[11, 12] HER2 overexpression is becoming more well acknowledged as the common molecular aberration in gastroesophageal malignancies. Given the recent implementation of HER2-molecular-targeted treatment in individuals with advanced stage gastric malignancies, it is essential to determine the HER2 status to identify patients who might potentially benefit from this treatment.[13]

Thus, this research has been designed to determine the magnitude of the issue among the local community in order to facilitate the development of risk classification and management strategies.

METHODOLOGY

This descriptive cross-sectional study was conducted from May 2023 to December 2023 at the outpatient department after obtaining approval from ethical review board. Sampling was done via non probability consecutive sampling. Sample size of 200 was estimated using 95% confidence level, 7% margin of error & previously reported prevalence of HER2 positivity i.e. 56% in patients with gastric carcinoma.[14]

Inclusion criteria: Patients aged above 30 years, either gender, fulfilled the criteria for diagnosis of gastric & gastroesophageal adenocarcinoma were included. Patients undergoing for biopsy for with metastatic disease were enrolled in the study.

Exclusion criteria: Patients already received or receiving chemotherapy or receiving radiotherapy were not enrolled in the study. In adequate samples or samples not stored or handled carefully were also excluded from sample.

Informed written consent was taken from the patients after ensuring them about confidentiality of their record. Their age, gender, duration of cancer, marital status, diet history, life style, family history of cancer, occupation, residence and socioeconomic status were recorded. Then biopsy

samples were collected. The samples were sent to the pathology department after storing them carefully in sterile container to prevent contamination. In pathology department, HER2 immunohistochemistry were tested and final report was collected. Reports were assessed and disused with histopathologist and expression of her2 was noted. A pre-designed proforma was used to collect the information.

Data analysis: Statistical Package for Social Sciences SPSS version 25 was used to analyze data. Gender, marital status, diet history, life style, family history of cancer, occupation, residence and socioeconomic status and her2 expression were presented as frequency & percentage. Age and duration of cancer were presented as mean ± Standard Deviation.

RESULTS

Out of the total 200 patients included, the average age of enrolled patients was 51.07 ±11.85 years (ranged from 30 – 70). Out of 200, 93 (46.5%) were male while 107 (53.5%) were female. Out of 200 patients, 16 (8.0%) were unmarried, 157 (78.5%) were married and 27 (13.5%) were separated, divorced or widow. Out of 200 patients, 22 (11%) were doing business, 50 (25%) were doing jobs, 119 (59.5%) females were housewives and 9 (4.5%) males were retired. The mean duration of cancer was 3.37 ± 1.68 months. Diet history was also taken and 54 (27.0%) had history of home-made food consumption, 55 (27.5%) mostly take fast-food, 47 (23.5%) were fond of street-food and 44 (22.0%) were following diet plan before diagnosis of cancer. There were 106 (53.0%) patients who had active life style while 94 (47.0%) had sedentary life style. About 54 (27.0%) came from rural area, 71 (35.5%) were living in urban areas and 75 (37.5%) were living in semi urban areas. Out of 200 patients, 67 (33.5%) had low socioeconomic status, 68 (34.0%) belonged to middle class and 65 (32.5%) belonged to high socioeconomic class. Family history of gastric cancer was positive in 16 (8%) cases. Out of 200 cases, 96 (48.0%) had gastric adenocarcinoma while 104 (52.0%) had gastroesophageal junction adenocarcinoma. Table: 1

Out of 200 patients, her2 expression was positive in 49 (24.5%) cases while negative in 151 (75.5%) cases. Fig: 1

Stratification analysis was performed and observed that rate of positive her2 expression was insignificant for age, gender, duration of disease, and other effect modifiers as shown in Table: 2.

Table: 1 Basic information of patient enrolled in the study (n = 200)

		Mean ± SD
Age (Years)		51.07 ±11.85
Gender	**Males**	93 (46.5%)
	Females	107 (53.5%)
Marital Status	**Unmarried**	16 (8.0%)
	Married	157 (78.5%)
	Separated / divorce / widow	27 (13.5%)
Occupation	**Business**	22 (11.0%)
	Job	50 (25.0%)
	Housewife	119 (59.5%)
	Retired	9 (4.5%)
Duration of cancer		3.37 ± 1.68
Diet history	**Home-made**	54 (27.0%)
	Fast-food	55 (27.5%)
	Street-food	47 (23.5%)
	Diet plan	44 (22.0%)
Life style	**Active**	106 (53.0%)
	Sedentary	94 (47.0%)
Residence	**Rural**	54 (27.0%)
	Urban	71 (35.5%)
	Semi-urban	75 (37.5%)

Socioeconomic status	**Low**	67 (33.5%)
	Middle	68 (34.0%)
	High	65 (32.5%)
Family history of gastric cancer		16 (8.0%)
Type of adenocarcinoma	**Gastric adenocarcinoma**	96 (48.0%)
	Gastroesophageal junction adenocarcinoma	104 (52.0%)

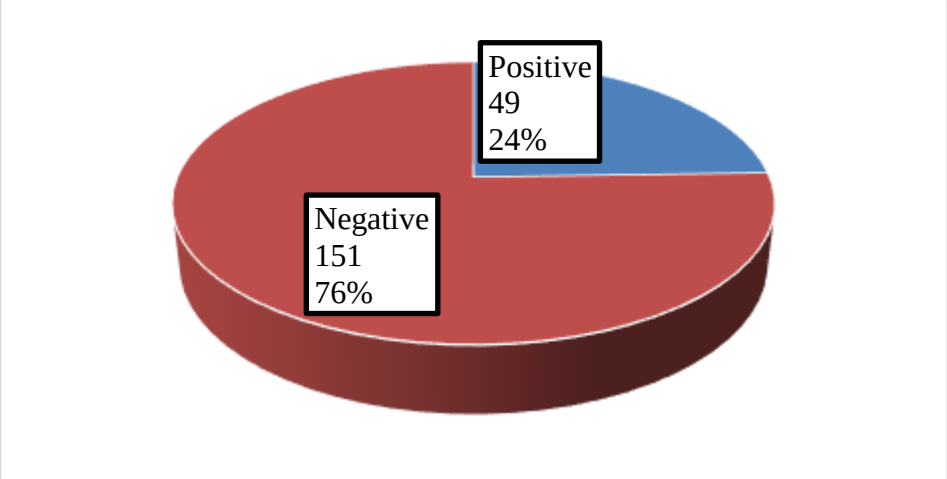

Fig 1: Frequency of her2 expression (n = 200)

Table: 2 Comparison of her2 expression in different groups

	Cutoff	**Her2 expression**		P-Value
		Positive	**Negative**	
		n = 49	**n = 151**	
Age groups (Years)	**30-50**	22 (24.7%)	67 (75.3%)	0.949
	50-70	27 (24.3%)	84 (75.7%)	
Gender	**Male**	20 (21.5%)	73 (78.5%)	0.359
	Female	29 (27.1%)	78 (72.9%)	
Duration of cancer	**≤3 months**	3 (27.5%)	79 (72.5%)	0.277
	>3 months	19 (20.9%)	72 (79.1%)	
Marital status	**Unmarried**	5 (31.3%)	11 (68.8%)	0.780
	Married	37 (23.6%)	120 (76.4%)	
	Separated / divorced / widow	7 (25.9%)	20 (74.1%)	
Diet history	**Home-made**	12 (22.2%)	42 (77.8%)	0.088
	Fast-food	11 (20.0%)	44 (80.0%)	
	Street-food	118 (38.3%)	29 (61.7%)	
	Diet plan	8 (18.2%)	36 (81.8%)	
Life style	**Active**	25 (23.6%)	81 (76.4%)	0.749
	Sedentary	24 (25.5%)	70 (74.5%)	
Family history of cancer	**Positive**	3 (18.8%)	13 (81.3%)	0.577
	Negative	46 (25.0%)	138 (75.0%)	
Occupation	**Business**	5 (2.7%)	17 (77.3%)	0.943
	Job	11 (22.0%)	39 (78.0%)	
	Housewife	31 (26.1%)	88 (73.9%)	
	Retired	2 (22.2%)	7 (77.8%)	

Residence	**Rural**	17 (31.5%)	37 (68.5%)	0.369
	Urban	15 (21.1%)	56 (78.9%)	
	Semi-urban	17 (22.7%)	58 (77.3%)	
Socioeconomic status	**Low**	22 (32.8%)	45 (67.2%)	0.066
	Middle	17 (25.0%)	51 (75.0%)	
	High	10 (15.4%)	55 (84.6%)	
Type of carcinoma	**Gastric adenocarcinoma**	18 (18.8%)	78 (81.3%)	0.069
	Gastroesophageal junction adenocarcinoma	31 (29.8%)	73 (70.2%)	

DISCUSSION

HER2, encrypts the trans-membrane proteins by tyrosine-kinase activity and belongs to HER-receptor family. HER2 plays a role in the signal transduction pathways, which regulates the cell growth and its differentiation.[15, 16] Excessive expression of HER2 in gastroesophageal malignancy. The first description of IHC occurred in 1986. [14] A multitude of research conducted in the Western world have extensively examined the correlation between HER2 positive and significant clinic-pathological parameters as well as survival rates in gastric malignancy. The prevalence of HER2 positive in malignancy varies from 4% to 53%.[17-19] In this research, we found that 24.5% of cases exhibited positive her2 expression. Specifically, 18.8% of gastric adenocarcinoma cases and 29.8% of gastroesophageal junction adenocarcinoma cases showed positive her2 expression.

A literature study was conducted on a large sample of over 8000 patients, revealing a median HER2 positive rate of 20.2%.[20] Asians may have a greater rate of HER2 expression compared to Europeans.[21] The prevalence of positive HER2/neu has been reported as high (nearly in 54% cases) in a cohort of 76 Egyptian patients with resectable gastric cancer.[22]

The prevalence of HER2 positive was higher in gastroesophageal junction adenocarcinomas (32.2%) compared to gastric carcinoma (21.4%), and it was also higher in intestinal tumors (31.8%) compared to diffuse tumors (6.1%).[23] According to the latest worldwide data, the occurrence of HER2 overexpression in patients with gastric cancer ranged from around 7.3% to 20.2% of all cases. The incidence of HER2 expression differed depending on the nation.[19] A retrospective analysis of 726 cases of gastric carcinoma that underwent operative resection in China revealed a HER2-positivity rate as 13%. Similarly, a multicenter study involving 734 patients with gastric carcinoma or gastroesophageal junction adenocarcinomas at eleven hospitals found that about 12% of the cases had HER2-positivity.[24, 25]

Moreover, there is ongoing debate on the correlation between HER2 overexpression and the prognosis of individuals with gastric cancer. A prospective study revealed an unfavorable prognosis in patients diagnosed with gastric carcinoma that overexpresses the HER2 protein. Similarly, a multicenter study conducted in Japan, involving 1148 gastric carcinoma patients, demonstrated a correlation between HER2 overexpression and prognosis.[26, 27] Contrarily, Sarah B Fisher et al. conducted an analysis on 111 patients with gastric cancer / gastroesophageal junction adenocarcinoma to determine the HER2 status. Their findings indicated that HER2-overexpression or amplification did not correlate with a worse prediction. Likewise, Shen et al., could not discover a correlation between the levels of HER2 expression and the prognosis of 1562 patients with stomach cancer in China.[28, 29]

CONCLUSION

The conclusion of this study is that patients having metastatic gastric & gastroesophageal-junction adenocarcinoma, the presence of her2 expression is a common finding. In patients of metastatic gastroesophageal-junction adenocarcinoma, the chances of her2 expression are more common.

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