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HER 2 positivity in gastrointestinal malignancies : A clinicopathological analysis in a prospective observational study.

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Abstract

Aim & Objectives: To know incidence of HER 2 positivity in gastrointestinal malignancies. **Primary Objectives:** To know the incidence of HER 2 positivity in different type of gastrointestinal malignancies in Indian patients. **Secondary objectives:** To evaluate whether HER2 expression correlated with the Clinicopathological parameters. ***Methodology:*** Samples were collected from Nizam's Institute of Medical Sciences (NIMS). The study was conducted after taking clearance from the Institutional Ethics Committee. Patient samples were collected following informed consent as per the modified Helsinki declaration of 2008 (http://www.wma.net/en/30publications/10policies/b3/) and samples collected from patients suffering from gastrointestinal tract cancer admitted to the Surgical Gastroenterology Department, Nizam's Institute of Medical Sciences. 102 samples were collected & analysed and out of which 67 samples were from gastrointestinal malignancies and 35 were hepatopancreaticobiliary malignancies. In the current study all the 67 samples from gastrointestinal tract were included. The samples were collected over a period of three years. ***Results:*** In this study of 67 patients, we used IHC markers to know the over expression of HER2 and considered positive for score 3+ and 2+ in specimen. Control sample of HER2 positive breast carcinoma used to assure quality of results. HER 2 positivity Seen in 9/67 (13.4%) of our patients. ***Conclusions:*** The incidence of HER2 positivity observed in our study is consistent with that reported in the current literature. Although our study is limited by a small sample size and did not demonstrate a statistically significant association between HER2 positivity and clinicopathological parameters such as age, gender, tumor site, differentiation, stage, nodal metastasis, lymphovascular invasion, and perineural invasion ($p > 0.05$) in gastrointestinal malignancies, the findings remain clinically relevant. HER2 status may still have important therapeutic implications at the individual patient level, particularly in guiding the selection of targeted therapies.

Keywords: HER2, Gastrointestinal malignancies, Lymphovascular invasion, Breast carcinoma.

INTRODUCTION

The human epidermal growth factor receptor (HER) family of receptors plays a central role in the pathogenesis of several human cancers. They regulate cell growth, survival, and differentiation via multiple signal transduction pathways and participate in cellular proliferation and differentiation.

HER2 Overexpression in Cancers

Most of the studies on HER2 have been carried out in breast cancer, after it was found to induce mammary carcinogenesis in vitro [1, 2] and in vivo [3]. Amplification or overexpression of the HER2 gene occurs in approximately 15–30% of breast cancers [4]. With increasing understanding of HER2 biology, it has now been recognized that HER2 overexpression occurs in other forms of cancers also such as stomach, ovary, uterine serous endometrial carcinoma, colon, bladder, lung, uterine cervix, head and neck, and esophagus [5, 6]. Apart from its role in development of various cancers, it has also been intensely evaluated as a therapeutic target.

Target

The anti-HER2 antibody trastuzumab represents an effective, targeted therapy with significant efficacy in treatment of HER2-positive breast and gastric cancer [7, 8]. Indeed, trastuzumab in combination with cisplatin and a fluoropyrimidine has been approved for the treatment of patients with HER2 overexpression metastatic gastric or Gastroesophageal (GE) junction adenocarcinoma, who have not received prior treatment for metastatic disease. The approval is based on a significant improvement in median overall survival (OS) of 2.5 months with trastuzumab plus chemotherapy treatment compared to chemotherapy alone, demonstrated in an international, multicenter, open-label, randomized clinical trial (ToGA trial) [7]

Indian data is not available regarding the HER2 positivity in GI tract malignancies and its prognostic significance (except cancers of stomach, GE junction and gall bladder). So, we planned to collect Indian data regarding HER2 positivity in GI tract malignancies.

AIMS AND OBJECTIVES

Aim

- To know incidence of HER 2 positivity in gastrointestinal malignancies

Primary Objectives

- To know the incidence HER 2 positivity in different type of gastrointestinal malignancies in Indian patients

Secondary objectives

- To evaluate whether HER2 expression correlated with the Clinicopathological parameters.

MATERIALS AND METHODS

Study design

- Single centre, prospective, nonrandomized observational study

Time frame

- June 2015 to May 2017

Setting

- All the patients included in this study were treated at Nizam's institute of medical sciences

Place of study

- Department of Surgical Gastroenterology and Pathology, Nizam's Institute of Medical Sciences (NIMS), Hyderabad.
- Data was collected prospectively from department of Surgical Gastroenterology and Pathology which included patient and disease characteristics, several preoperative, intraoperative and post-operative parameters.
- 102 samples were collected & analysed and out of which 67 samples were from gastrointestinal malignancies and 35 were hepatopancreaticobiliary malignancies. In the current study all the 67 samples from gastrointestinal tract were included. The samples were collected over a period of three years (2015 to 2017).
- For each patient, clinical and pathological data were collected prospectively from maintained data base in surgical gastroenterology and pathology departments which included patient and disease characteristics, several pre-operative, intra-operative and post-operative parameters.

Population/ participants:

- Samples were collected from Nizam's Institute of Medical Sciences (NIMS). The study was conducted after taking clearance from the Institutional Ethics Committee.
- Patient samples were collected following informed consent as per the modified Helsinki declaration of 2008 (http://www.wma.net/en/30publications/10policies/b3/) and samples collected from patients suffering from gastrointestinal tract cancer admitted to the Surgical Gastroenterology Department, Nizam's Institute of Medical Sciences.

Inclusion criteria:

1. Patients with gastrointestinal tumors operated at NIMS
2. Histologically confirmed gastrointestinal tumor patients
3. Adequate paraffin- embedded tumor tissue sample for pathologic and human epidermal growth factor receptor 2 (HER2) status analyses.

Exclusion criteria:

1. If histopathology blocks were not available due to inadequate tissue
2. Other malignancy within the last 5 years
3. < 18 years age

4. Complete pathological response

Methods: Processing of tissues and microscopy

- Subsequent to surgery, specimens were transferred to the Histology section in 10 % neutral buffer formalin.
- Samples were examined for gross features and paraffin blocks were prepared for subsequent staining and microscopy.
- Tissue sections, each measuring 3 to 4 µm in thickness were cut from the paraffin blocks and processed for H&E staining.
- Clinicopathological parameters were recorded including

i. Tumor type,
ii. Tumor grade (according to the World Health Organization (WHO) criteria as grade I (well differentiated), grade II (moderately differentiated) and grade III (poorly differentiated).
iii. Pathological staging of each cases were recorded as per the 7th edition of the American Joint Committee on Cancer Staging (stage I to stage IV)

Immunohistochemistry and scoring of HER-2/neu overexpression

- Sections were deparaffinized, dehydrated and antigen retrieval was performed.
- Sections were incubated with the mouse primary monoclonal antibody against Her- 2/neu (clone CB-11, dilution 1:65, Cellmarque) for 1 h in the moisturisation chamber.
- Secondary antibody (Hi-Def detection system) (Cellmarque) containing solution A as amplifier and solution B as polymer was used.
- Control sample of carcinoma breast taken along these samples
- HER-2/neu stained slides were independently evaluated by experienced pathologists.
- In order to quantify/Score HER-2/neu expression criteria given by College of American Pathologists used.

Outcome measures:

1. Primary outcome

i. HER 2 Positivity in gastrointestinal tract malignancies

2. Secondary outcome

i. Clinical correlation between HER 2 Positivity

Statistical analysis:

- Parameters were recorded and arranged on Microsoft Excel spreadsheet (Microsoft, Seattle, WA). Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0.
- Continuous variables were presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage.
- The comparison of normally distributed continuous variables between the groups was performed using Student's t test.
- Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. $P<0.05$ was considered statistically significant

RESULTS

Gastrointestinal tract malignancies are common problem over worldwide and carry major burden over the gastrointestinal surgeons. We designed our study to find out the percentage of HER2 positivity with their clinicopathological analysis. Total 67 patients were included in the study, out of which 48(71.6%) were male and 19(28.4%) were female.

Table 1 Showing Characteristics of study Group

		Value (%)
Age	Mean = 52 (Range 17-73)	
Gender	Male	48(71.6)
	Female	19(28.4)
Organ	Esophagogastric	23(34.3)
	Duodenal	5(7.4)
	SmallBowel	6(8.9)
	Appendix	3(4.4)
	Colorectal	30(44.7)

During the study period we have taken samples from all system. Cases from esophagogastric, duodenum, small bowel, appendix and colorectal were 34.3, 7.4, 8.9, 4.4 and 44.7 percentage.

Table 2: Organ wise HER2 Positivity

Organ	No of Patients (%)	No of HER2 + (%)
Esophagogastric	23(34.3)	4(17.3%)
Duodenal	5(7.4)	3(60%)
Small Bowel	6(8.9)	0(0%)
Appendix	3(4.4)	0(0%)
Colorectal	30(44.7)	2(6.7%)
Total	67	9(13.4%)

Gastroesophageal Cancer

Total 23 patients studied in this section. Only one case was of Type 1 GE junction growth having squamous histology and HER2 negative. 22 patients were of stomach cancer. The mean age of presentation is 52 years (Range 28-73 years). Male papulation is more than females (74% versus 26%).

Proximal and distal tumors are almost equally distributed in the study population. Our stomach tumors are more aggressive, having poor differentiation in 56% of the cases with high TNM Stage.

Nodal metastasis present in 52% of the patients. Lymphovascular and Perineural invasion present in 34% of the patients. HER2 positivity seen in 4 (17.3%) of the patients, out of which 3 have score 2+ and 1 have 3+ score. HER2 Positivity is not having significant association with the age, sex, site, tumor differentiation, stage, nodal metastasis, Lymphovacular and Perineural invasion ($p>0.05$)

Table 3: Clinicopathological Characteristics of Gastroesophageal Cancers

		HER2 Expression n%		P-value	
Variables					
		Total	Yes	No	
Age	≤ 50	9	0(0)	9(100)	0.54
	>50	14	4(30.76)	10(69.23)	
Gender	Male	17	3(17.64)	14(82.35)	0.95
	Female	6	1(16.6)	5(83.33)	
Site	Proximal	12	1(8.33)	11(91.66)	0.33
	Distal	11	3(27.27)	8(72.72)	
Differentiation	Well	4	1(25)	3(75)	0.073
	Moderate	6	2(33.33)	4(66.66)	
	Poor	13	1(9.09)	12(92.30)	
T Stage	T1	4	2(50)	2(50)	0.31
	T2	5	1(20)	4(80)	
	T3	11	1(9.09)	10(90.90)	
	T4	3	0(0)	3(100)	
TNM Stage	I	8	2(25)	6(75)	0.36
	II	9	2(22.22)	7(77.77)	
	III	4	0(0)	4(100)	
	IV	2	0(0)	2(100)	
	Present	12	3(25)	9(75)	0.33
Lymph node metastasis					
	Absent	11	1(9.09)	10(90.90)	
Lymphovascular Invasion	Present	8	0(0)	8(100)	0.11
	Absent	15	0(0)	15(100)	
Perineural infiltration	Present	8	0(0)	8(100)	0.12
	Absent	15	0(0)	15(100)	

Duodenal tumors

Total 5 patients studied in this group. Interestingly all of these cases were WDAC, low grade tumors. All patients underwent Whipple's procedure. The Lymph node metastasis, Lymphovascular and Perineural invasion present in 60, 40 and 40 % respectively.

HER2 positivity seen in 3 (60%) of the patients, out of which 2 was having score 2+ and 1 have 3+ score. HER2 Positivity is not having significant association with the age, sex, site, tumor differentiation, stage, nodal metastasis, Lymphovascular and Perineural invasion (p>0.05)

Table 4: Clinicopathological Characteristics of Duodenal Cancers

HER2 Expression n%					**P-value**
Variables					
		Total	**Yes**	**No**	
Age	≤ 50	3	2(66.66)	1(33.33)	0.78
	>50	3	1(33.33)	2(66.66)	
Gender	Male	2	1(50)	1(50)	0.78
	Female	3	2(66.66)	1(33.33)	
Differentiation	Well	5	3(60)	2(40)	1
	Moderate	0	0(0)	0(0)	
	Poor	0	0(0)	0(0)	
T Stage	T1	1	1(100)	0(0)	0.32
	T2	0	0(0)	0(0)	
	T3	1	1(100)	0(0)	
	T4	3	1(33.33)	2(66.66)	
TNM Stage	I	1	1(100)	0(0)	0.87
	II	1	0(0)	1(100)	
	III	3	2(66.66)	1(33.33)	Z
	IV	0	0(0)	0(0)	
Lymph node metastasis	Present	3	2(66.66)	1(33.33)	0.78
	Absent	2	1(50)	1(50)	
Lymphovascular Invasion	Present	3	2(66.66)	1(33.33)	0.78
	Absent	2	1(50)	1(50)	
Perineural infiltration	Present	2	2(100)	0(0)	0.21
	Absent	3	1(33.33)	2(66.66)	

Small Bowel Tumors

Total 6 patients evaluated in this category of patients. 3 were having GIST, 1 NET and 1 was having non hodgkin lymphoma of jejunum. None was stained positive for HER 2 receptor.

Appendicular Tumors

Total 3 patients evaluated in this category of patients and all were low grade mucinous neoplasm. None of these was stained positive for HER 2 receptor

Colorectal Tumors

Total 30 patients studied in this section. Colon cancer was present in 16 (53%) patients and rest 14(47%) were having rectal cancer. The mean age of presentation is 49 years (Range 16- 76 years). Male papulation is more than females (73% versus 27%).

Our colonic tumors are less aggressive, having well differentiation in 63% of the cases with highest T3 lesion.

Nodal metastasis present in 50% of the patients. Lymphovascular and Perineural invasion present in 10 and 20% of the patients. HER2 positivity seen in 2 (6.7%) patients, out of which 2 was having score of 2+ and none have 3+ score. HER2 Positivity is not having significant association with the age, sex, site, tumor differentiation, stage, nodal metastasis, Lymphovascular and Perineural invasion (p>0.05)

Table 5: Clinicopathological Characteristics of Colorectal Cancers

HER2 Expression n%	**P-value**				
Variables					
		Total	Yes	No	
Age	≤ 50	18	0(0)	18(100)	0.07
	>50	12	2(16.66)	10(83.33)	
Gender	Male	22	1(4.54)	21(95.45)	0.45
	Female	8	1(12.5)	7(87.5)	
Site	Colon	16	0(0)	16(100)	0.13
	Rectal	14	2(14.28)	12(85.71)	
Differentiation	Well	19	2(10.52)	17(89.47)	0.39
	Moderate	4	0(0)	4(100)	
	Poor	7	0(0)	7(100)	
T Stage	T1	0	0(0)	0(0)	0.22
	T2	6	1(16.66)	5(83.33)	
	T3	21	1(4.76)	20(95.23)	
	T4	3	0(0)	3(100)	
TNM Stage	I	5	1(20)	4(80)	0.11
	II	8	1(12.5)	7(87.5)	
	III	14	0(0)	14(100)	
	IV	3	0(0)	3(100)	
Lymphnode metastasis	Present	15	0(0)	15(100)	0.15
	Absent	15	0(0)	15(100)	
Lymphovascular Invasion	Present	6	0(0)	6(100)	0.48
	Absent	24	0(0)	24(100)	
Perineural infiltration	Present	3	0(0)	3(100)	0.63
	Absent	27	0(0)	27(100)	

DISCUSSION

HER2 is well recognized to be a key mediator of the carcinogenic process, and its dysregulation, mainly via protein over-expression and/or gene amplification, characterizes a substantial subgroup of patients affected by different tumor types. In this study we used IHC markers to find the expression of HER2 positivity in malignancies of gastrointestinal tract.

Min Yan et al (2015) had done largest study in literature. He studied 37,992 patient samples for HER2 expression in diverse groups of patients using immunohistochemistry. Over- expressed HER2 was detected predominantly in malignancies of epithelial origin [11].

Malignancies	**Percentage of HER2 positivity (%)**
Esophagus and GE junction	11.3
Stomach	4.7
Small intestine	0.9
Colorectal	1.8
GIST	0.0
Liver	0.4
Bile Duct	6.3
Gall bladder	9.8
Pancreas	0.7

Gastroesophageal Cancers

HER2 pathway which is upregulated in 12% to 14% of esophageal adenocarcinoma tumors and <1% of squamous tumors. In our study only one patient was having Type 1 GE junction squamous cell tumor and which was not expressing HER2. Aggregate expression of HER2 is found to be 17.3%.

Anuradha et al in 2012 published a paper regarding HER 2 Expression in gastric tumors form South India and found that HER2 overexpression in 23 of 52 (44.2 %) patients. Two patients had equivocal result by IHC (2+), one of whom was positive on analysis by FISH. There was no difference in HER2 overexpression (positivity) or negativity in relation to age, gender, tumor site, histological subtype, tumor differentiation, serosal involvement or lymph nodal status. HER2

overexpression rates were similar for intestinal type as compared to diffuse histological type (OR 1.84), as also for proximal as compared to distal gastric cancers (OR 0.81) [12].

Mallika Tewari et al. In 2015 published a paper from North India regarding HER 2 expression from gastroesophageal tumors. They found HER2 overexpression was found in 15 (21.4 %) samples, was significantly (p=0.006) more common in intestinal type (45 %), but it did not correlate with age, gender, stage, or grade of tumor and did not affect the 2-year disease-free survival [9].

The phase III ToGA study compared a cisplatin/fluoropyrimidine combination plus or minus trastuzumab as first-line therapy for metastatic gastric or GEJ adenocarcinoma overexpressing Her-2.320 In this pivotal trial, 22.1% of tumors were found to be Her-2/neu positive by IHC or FISH and 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n = 298; chemotherapy alone, n = 296), of whom 584 were included in the primary analysis (n = 294; n = 290). Median overall survival was 13.8 months (95% CI: 12, 16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months (95% CI: 10, 13) in those assigned to chemotherapy alone (hazard ratio 0.74, 95% CI:0.60, 0.91; P = 0.0046). Rates of overall grade 3 or 4 adverse events (201 [68%] vs 198 [68%]) and cardiac adverse events (17 [6%] vs 18 [6%]) did not differ between groups. The ToGA trial is the first positive phase III trial of a targeted agent in upper GI tumors. Unfortunately, only 15% to 20% of patients with esophageal or gastroesophageal tumors will have HER2 FISH- positive disease indicating that this strategy will be beneficial for only a limited number of patients [7].

In 2013, a Spanish, multicenter, phase II study called NEOHX was initially presented and the final results were updated in 2015 (NCT01130337). This study evaluated the efficacy and toxicity profile for perioperative XELOX-T (capecitabine, oxaliplatin, and trastuzumab) followed by 12 cycles of adjuvant trastuzumab in monotherapy for patients with HER2-positive locally advanced but resectable stomach or esophagogastric-junction adenocarcinoma. The primary end point was disease-free survival (DFS) at 18 months and secondary end points included pathologic complete response rate (pCR), R0 resection rate, overall response rate, toxicity of preoperative treatment, and biomarker expression. A total of 63 patients were included. Before surgery, five patients stopped treatment because of toxicity. The overall response rate was 39%. Surgery was performed in 31 patients and 28 (78%) had an R0 procedure. Three patients had pCR (8.3%). After surgical resection, postoperative XELOX-T was administered to 24 patients, 22 of whom underwent trastuzumab monotherapy. With a median follow-up of 24.1 months, the 18-month DFS was 71% (95% confidence interval [CI], 53%–83%), the 24-month DFS was 60%, and median DFS and OS had not been reached [13].

In the postoperative setting there is a Turkish phase II, single arm, open-label study called TOXAG evaluating the safety and efficacy of the combination oxaliplatin, capecitabine, trastuzumab, and radiation as adjuvant treatment of patients with curatively resected HER2- positive gastric or gastroesophageal junction cancer. Patients will receive concurrent chemotherapy with radiation. Trastuzumab will be continued after radiation for a total of 12 months. The expected completion date is May 2017.

Small Intestinal Tumors

Total 5 patients studied in this duodenal cancer group. Interestingly all of these cases were WDAC, low grade tumors. All patients underwent Whipple's procedure. The Lymph node metastasis, Lympho vascular and Perineural invasion present in 60, 40 and 40 % respectively.

HER2 positivity seen in 3 (60%) of the patients, out of which 2 was having score 2+ and 1 have 3+ score. HER2 Positivity is not having significant association with the age, sex, site, tumor differentiation, stage, nodal metastasis, Lympho vascular and Perineural invasion (p>0.05)Mi Jin Gu et al. (2013) analyzed the HER 2 expression in small intestinal cancers. Tumors distribution was in the duodenum in 105 cases (54.1 %), the jejunum in 59 cases (30.4%), and the ileum in 30 cases (15.5 %). HER2 protein overexpression/gene amplification was observed in 2.1 % of SIC. This finding indicates that HER2 overexpression or amplification does not play a major role in carcinogenesis in small intestine cancers [14].

Total 6 patients evaluated in this category tumors of ileum and jejunum. 3 were having GIST, 1 NET and 1 was having non hodgkin lymphoma of jejunum. None was stained positive for HER 2 receptor
Lisandro Ferreira Lopes 2008 analyzed the HER 2 expression in GIST and found no amplification of HER2 in 477 cases. They concluded that HER-2 may not have any role in GIST pathogenesis and that the neoplasm may not be suitable for treatment with trastuzumab [15].

Colorectal cancer

Overexpression of Her-2/ neu in colorectal cancer shows a wide range of variability between 0-84 percent in different studies [16].

In our study we have taken 30 patients in this colorectal group. Colon cancer was present in 16 (53%) patients and rest 14(47%) were having rectal cancer. The mean age of presentation is 49 years (Range 16-76 years). Male papulation is more than females (73% versus 27%).

HER2 positivity seen in 2 (6.7%) patients, out of which 2 was having score of 2+ and none have 3+ score. HER2 Positivity is not having significant association with the age, sex, site, tumor differentiation, stage, nodal metastasis, Lympho vascular and Perineural invasion (p>0.05).

B Ingold Heppner et al (2014).In this study we investigated the prevalence of HER2/neu overexpression and amplification in a cohort of 1645 primary CRC. We found a positive HER2/neu status in 1.6% of all cases, with a significant association with higher UICC stages and positive nodal status [17].
Chao LI et al (2014) did meta-analysis HER-2 overexpression and survival in colorectal cancer. They suggested that HER-2 overexpression probably had little impact on CRC survival [18].

LIMITATIONS OF STUDY

- Single centered, nonrandomized observational study
- No long-term follow-up
- No survival analysis
- Small sample size
- Multiple tumors taken in account simultaneously

Summary of Incidence of HER2 positivity in our study (Primary end point)

- Esophagogastric cancers: 17.3%
- Duodenal Adenocarcinoma: 60%
- Small bowel GIST and NET: 0%
- Appendicular mucinous tumor: 0%
- Colorectal: 6.7%.

CONCLUSION

The incidence of HER2 positivity observed in our study is consistent with that reported in the current literature.
Although our study is limited by a small sample size and did not demonstrate a statistically significant association between HER2 positivity and clinicopathological parameters such as age, gender, tumor site, differentiation, stage, nodal metastasis, lymphovascular invasion, and perineural invasion ($p > 0.05$) in gastrointestinal malignancies, the findings remain clinically relevant. HER2 status may still have important therapeutic implications at the individual patient level, particularly in guiding the selection of targeted therapies.

FUTURE PERSPECTIVES

- IHC study for detection of HER2 overexpression is enough for score of 3+ (positive) tumors but for score of 2+ (equivocal) the FISH is needed to confirm the results.
- Large Sample size needed to validate the results.
- Survival analysis and long-term follow-up is needed to see the real impact of HER2 overexpression on individual tumors.
- We have to start phase 2/3 study with monoclonal antibodies against the tumors expressing HER2.

REFERENCES

1. Fornaro L, Lucchesi M, Caparello C, Vasile E, Caponi S, Ginocchi L et al. Anti-HER agents in gastric cancer: from bench to bedside. Nat Rev Gastroenterol Hepatol. 2011 Jun 7; 8(7):369-83. Doi: 10.1038/nrgastro.2011.81.
2. Di Fiore PP, Pierce JH, Kraus MH, Segatto O, King CR, Aaronson SA. ErbB-2 is a potent oncogene when over expressed in NIH/3T3 cells. Science. 1987 Jul 10; 237(4811):178-82.
3. Muller WJ, Sinn E, Pattengale PK, Wallace R, Leder P. Single-step induction of mammary adenocarcinoma in transgenic mice bearing the activated c-neu oncogene. Cell. 1988 Jul 1; 54(1):105-15.
4. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med. 2005 Oct 20; 353(16):1652-4.
5. Fukushige S, Matsubara K, Yoshida M, Sasaki M, Suzuki T, Semba K et al. Localization of a novel v-ErbB-related gene, c-erbB-2, on human chromosome 17 and its amplification in a gastric cancer cell line. Mol Cell Biol.1986 Mar; 6(3):955-8.
6. Reichelt U, Duesedau P, TsourlakisMCh, Quaas A, Link BC, Schurr PG et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol. 2007 Jan; 20(1):120-9.
7. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A et.al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or

gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010 Aug 28;376(9742):687-97
8. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE,et.al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005 Oct 20; 353(16):1673-84.
9. CDER.Retrieved from http://www.fda.gov/AboutFDA/Centers Offices/Office of Medical Products and Tobacco/CDER/ ucm230418.htm (accessed).
10. Tewari M, Kumar A, Mishra R, Kumar M, Shukla HS. HER2 Expression in Gastric and Gastroesophageal Cancer: Report from a Tertiary Care Hospital in North India. The Indian Journal of Surgery. 2015; 77(Suppl 2):447-451. Doi: 10.1007/s12262-013-0871-y.
11. Sekaran A, Kandagaddala RS, Darisetty S, Lakhtakia S, Ayyagari S, Rao GV, Rebala P et al. HER2 expression in gastric cancer in Indian population--an immune histo chemistry and fluorescence in situ hybridization study. Indian J Gastroenterol. 2012 Jun; 31(3):106-10. Doi: 10.1007/s12664-012-0214-0.
12. An M, Schwaederle M, Arguello D, Millis SZ, and Gatalica Z, Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev. 2015 Mar; 34(1):157-64. Doi: 1007/s10555-015-9552-6.
13. Riese DJ 2nd, Stern DF. Specificity within the EGF family/ErbB receptor family signaling network. Bioessays. 1998 Jan; 20(1):41-8.
14. Van der Geer P, Hunter T, Lindberg RA. Receptor protein-tyrosine kinases and their signal transduction pathways. Annu Rev Cell Biol. 1994; 10:251-337.
15. Carpenter G, King L Jr, Cohen S. Epidermal growth factor stimulates phosphorylation in membrane preparations in vitro. Nature. 1978 Nov23; 276(5686):409-10.
16. Padhy LC, Shih C, Cowing D, Finkelstein R, Weinberg RA. Identification of a phosphoprotein specifically induced by the transforming DNA of rat neuroblastomas. Cell. 1982 Apr; 28(4):865-71.
17. Schechter AL, Stern DF, Vaidyanathan L, Decker SJ, Drebin JA, Greene MI et al. The neu oncogene: an Erb-B-related gene encoding an 185,000-Mr tumour antigen. Nature. 1984 Dec 6-12; 312(5994):513-6.
18. Brandt-Rauf PW, Pincus MR, Carney WP. The c-erbB-2 protein in oncogenesis: molecular structure to molecular epidemiology. Crit Rev Oncog. 1994; 5(2-3):313-29.