ABSTRACT

Background & Objectives: Gastric cancer is one of the leading causes of death and the fourth most prevalent cancer in the world. Most cases of gastric carcinoma are detected in advanced stages and are associated with high mortality and bad prognosis. For such advanced diseases, treatment options are limited. Trastuzumab has been approved for metastatic or locally advanced carcinomas arising in the stomach or the gastro esophageal junction in patients with HER2-positive tumours. The multicentre TOGA trial proved that targeted therapy could prolong patient lives by 2.7 months when compared to the standard treatment. There is limited data on the prevalence and behavior of HER2-positive cases among Indian patients. The current study aims to,

1. Compare HER2 expression between matched diagnostic biopsies and surgical specimens of patients with gastric adenocarcinoma in India.

2. Correlate HER2 expression with important prognostic pathological parameters and to determine the effect of non-Trastuzumab containing neo adjuvant chemotherapy (NAC) on this expression.

3. To study tumour heterogeneity among the HER2 positive Gastric adenocarcinomas

Type of study: prospective observational study.
**Materials and Methods:** Matched primary gastrectomy sections with corresponding diagnostic biopsies of 72 patients reported from June 1, 2016, to July 30, 2017 were used from the archives of the Department of Pathology. The immunohistochemical study was conducted using MILD CC 1 protocol perform with anti-HER 2/neu (4B5) Rabbit Monoclonal Primary Antibody, and the Ventana Pathway using automated slide stainer Ventana Bench mark XT. We stained whole-tissue sections with their matching diagnostic mucosal biopsies on the same slide. We compared HER2 expression status with all pathological parameters to assess statistically significant associations by the Chi-square test. HER-2 overexpression (HER2+) was defined by a score 3+ on IHC according to the standardized and validated scoring system of Hoffmann et al. used in most international trials including the TOGA trial.

**Results:** Paired HER2 status was determined for 72 patients (100%). HER2+ rates were 8.33% on biopsy (6/72) and 9.72% on resection (7/72). The overall HER2 positivity rate was 11.11% (8/72). There was an association between HER2 expression and WHO mixed adeno carcinoma histological subtype (P = 0.009) and presence of lymphovascular invasion (P = 0.045). No association was found between HER2 status and all other pathological parameters. When we independently analyzed the cases, 14/58 cases were NAC treated cases, and 3 cases showed HER 2 positivity. In non-NAC patients 4/5 (80%) HER 2 positive cases showed concordance between the biopsy and resection. The remaining 1/5 case showed discordance with a positive shift. In the NAC group 3/3 (100%) HER 2 positive cases showed discordance with 2/3 showing negative
shift and 1/3 with the positive shift. All 3/5 (60%) treated patients showed tumour heterogeneity and all three were mixed type. The remaining 2/5(40%) showed homogeneous staining pattern and were of the WHO tubular variant.

**Conclusion:** To our best knowledge this is the first study to analyse HER 2 expression in 72 matched biopsies with the corresponding resections in India and this largest study group compared with other similar studies published in India. Differences between biopsy and resection HER2 expression could be explained by intratumoral heterogeneity and by decreased HER2 expression in surgical sections after NAC in responding patients possibly due to a higher chemo sensitivity of HER2-positive clones. Combining the analysis of biopsy and resections could optimize the selection of Trastuzumab-eligible patients in case of advanced gastric adenocarcinoma particularly in previously NAC-responding patients having a mixed histological type of tumour with lymphovascular invasion.

Keywords: Her2, gastric cancer, neoadjuvant chemotherapy, Immunohistochemistry.