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# Study of HER2/neu Overexpression in Colorectal Carcinoma at a Tertiary Care Centre in Rajasthan, India

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## ABSTRACT

**Introductio**n: Colorectal cancer remains one of the major leading causes of death worldwide. The therapeutic implications of Human Epidermal Growth Factor (HER2/neu) in certain cancers like breast cancer and gastric cancer has already established. The prognostic significance of molecular marker HER2/neu in colorectal cancer is unclear and studies have shown wide range of positivity, 0%-83%. This study was undertaken to study overexpression of HER2/neu in colorectal cancer, hence opening doors to new modalities of treatment.

**Material and Methods:** The study included 77 cases with a histological diagnosis of colorectal cancers received in pathology department of our medical college and hospital during a period of 49 months from September 2013 to September 2017. Immunohistochemical staining for Her-2/neu receptor using enzyme linked polymer based detection method was done in each and every case of colorectal carcinoma and scoring for Her-2/neu was done according to ASCO/CAP Guidelines Update 2013. Poorly fixed/unfixed specimens and patients with past history of breast cancer were excluded.

**Results:** Among the 77 cases studied, age of patients ranged from 21-80 years with male predominance. Most common age group involve was 51-60 years. The commonest histopathological finding was moderately differentiated adenocarcinoma. HER2/neu immunohistochemistry score of "3+" was taken as positive, which constituted 3.89%.

**Conclusion:** Her-2/neu might potentially serve as a promising marker in colorectal cancer and also seems to be a valuable prognostic marker within the multimodal treatment of advanced colorectal cancer.

**Keywords:** Colorectal carcinoma, HER2/neu overexpression, Immunohistochemistry.

## INTRODUCTION

Colorectal cancer remains one of the major leading cause of death worldwide, despite of advances in surgical techniques and adjuvant chemotherapeutic regimens.[1] HER2/neu is a protooncogene and located on chromosome 17q21, encodes a transmembrane protein having tyrosine kinase activity. HER2/neu gene importance is proved in breast cancer but in colorectal cancer its prevalence and significance have been poorly documented.[2] Overexpression of HER2/neu in colorectal cancer correlates with poor prognosis and tumors which express it would require a different therapeutic approach, as these cases could respond to transtuzumab (Herceptine) therapy.[3] Different studies of molecular marker HER2/neu expression in colorectal cancer have shown wide range of positivity 0% to 83%.[2] This study was undertaken to study overexpression of HER2/neu in colorectal carcinoma, hence opening doors to newer modalities of treatment.

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## MATERIALS AND METHOD

The present study was undertaken during a period of 49 month from September 2013 to September 2017. 77 cases of colorectal carcinoma received in pathology department of Mahatma Gandhi medical college and hospital were included in this study.

The surgical specimen and colonoscopic biopsies were fixed in formalin and processed and paraffin blocks were made. The blocks were cut in 3-5 micron thickness and stained with Haematoxylin and Eosin. Detailed microscopic examination of tumor with lymph node status was done to arrive at a histopathological diagnosis. As needed, diagnosed colorectal carcinoma cases subjected to immunohistochemical staining for detection of Her-2/ neu expression.

In immunohistochemistry, antigen retrieved by Heat Induced Epitope Retrieval (HIER) method. Pre diluted antibodies are used for staining Her-2/neu antigens and cromogen diamino benzoic acid (DAB) is used for Her-2/neu. Immunohistochemical stain HER-2/neu imparts dark brown precipitate of variable intensity to the cell membrane with or without cytoplasmic staining.

**IHC scoring**: For Her-2/neu (ASCO/CAP Guidelines Update 2013)[4]
**Score 0:** No stain or faint incomplete membrane stain in not more than 10% within the cells.
**Score 1+:** Weak and incomplete membrane staining in more than 10% of the tumor surface.
**Score 2+:** Complete intense membrane staining in not more than 10% of the invasive tumor cells or weak/moderate heterogeneous incomplete staining in more than 10% of the invasive tumor cells.
**Score 3+:** Strong complete homogenous membrane staining in more than 10% of the invasive tumor cells.

HER2/neu immunohistochemistry score of "3+" was taken as positive. Poorly fixed/unfixed specimens and patients with past history of breast cancer were excluded.

## RESULTS

A total of 77 colonoscopic biopsies and surgical specimen were studied. Among the 77 cases studied, age of patients ranged from 21-80 years with male predominance. Most common age group involve was 51-60 years. Left sided colorectal cancers were predominant over right sided. The commonest histopathological finding was moderately differentiated adenocarcinoma. HER2/neu immunohistochemistry score of "3+" was taken as positive. (Image 1 and 2)

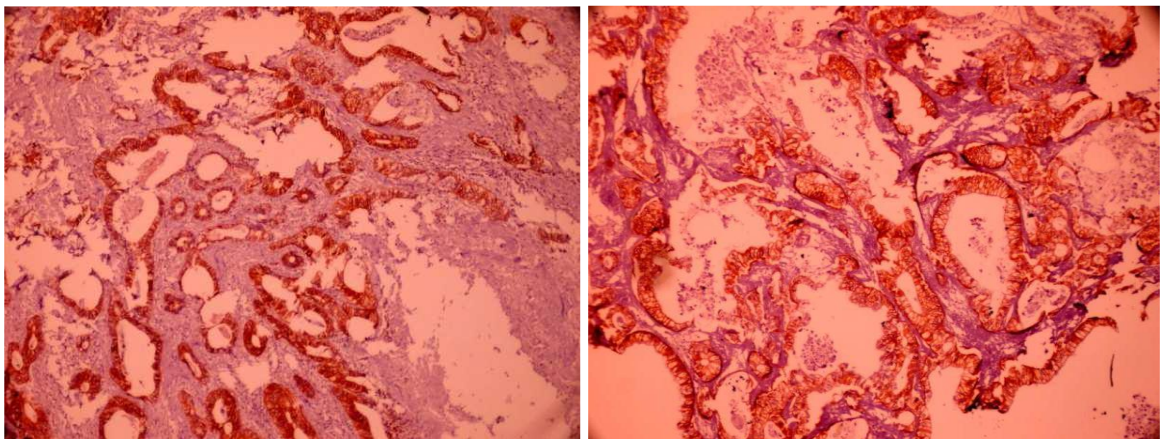

**Image 1 and 2: Her-2/neu Staining 3+ on IHC (10X magnification)**

**Table 1: Her-2/neu score in colorectal carcinoma**

| Score | Number | Percentage |
|---|---|---|
| 0+ | 49 | 63.64% |
| 1+ | 20 | 25.97% |
| 2+ | 5 | 6.49% |

| | | |
|---|---|---|
| 3+ | 3 | 3.89% |

Maximum number of cases showed Score of "0"- 49 cases (63.64%). Score of "3+" was taken as positive, which constituted only 3 cases (3.89%). In the present study we have found that 2 cases Her-2/neu positive in low grade colorectal carcinoma patients and 1 case Her-2/neu positive case in high grade colorectal carcinoma. In the present study, no correlation was found between the Her-2/neu score and lymph node status. P-value was statistically insignificant (0.95).

## DISCUSSION

Her2/neu is a transmembrane receptor tyrosine kinase, located on chromosome 17q21. Activation of Her2/neu plays an important role in cell proliferation, cell differentiation, inhibition of apoptosis and tumor progression. It initiates signal cascades including the MAPK (Mitogen activated protein kinase) and PI3K/AKT (3-kinase) pathways that are essential for cell proliferation and differentiation.

The importance of Her-2/neu in breast carcinoma pathology has been proven and the obvious survival benefit from the use of trastuzumab therapy has led to evaluation of Her-2/neu expression in various tumor types. The expression of Her-2/neu has been studied in prostate, ovarian and lung cancers as well as in several forms of gastrointestinal malignancies, including colorectal cancer.

Conflicting data exist about prevalence of Her-2/neu over expression in colorectal cancer which ranges from 0%-83%.[2] This broad range of Her-2/neu overexpression might be due to:
• Varying patterns of staining (cytoplasmic/membranous/ both) by which overexpression was defined.
• Difference in fixation of tumor tissues.
• Diversity of the antibody and IHC procedure which was used. There was lack of standardization of the detection system.[2]

Data regarding its prognostic value also remains inconclusive.[5] In the present study we have taken the 77 cases of colorectal carcinoma and maximum number of cases showed Score of "0"- 49 cases (63.64%). Score of "3+" was taken as positive, which constituted only 3 cases (3.89%).

**Table 2: Comparison of study in the over expression of Her-2/neu with the similar studies**

| **Author** | **Study** | **Conclusions** |
|---|---|---|
| Scheull et al [6] | 77 CRC cases | 3% showed positivity |
| Nathanson et al[7] | 139 CRC cases | Overexpression in 4% |
| Kavanagh et al[8] | 132 CRC cases | 2% positivity |
| Park et al[9] | 137 CRC cases | 47.4% over expressed Her-2/neu |
| Ghaffarzadegan et al[10] | 69 cases | 59.4% showed over expression |
| Tavangar et al[11] | 55 cases | Overexpression in 22% cases |
| Present study | 77 cases | Overexpression in 3.89% cases |

Table No. 21 shows the variability in the Her-2/neu over expression in Colorectal carcinomas. The present study is in accordance with the study of Nathanson et al79 which showed over expression in 4% cases. Present study showed Her-2/neu positivity in 3.89% of cases.

In the present study we have found the 2 cases Her-2/neu positive in low grade colorectal carcinoma patients and 1 case Her-2/neu positive case in high grade colorectal carcinoma. Since the p value is >0.05, the results were insignificant for this present study so there is no correlation is found between Her-2/neu staining and grade of tumor which is accordance with study of Nathanson et al**.**[7]

In the present study, no correlation was found between the Her-2/neu score and lymph node status. P-value was statistically insignificant (0.95). This finding is in accordance with the study

conducted by McKay et al, where they did not find any correlation between Her-2/neu staining and lymph node metastases.[12]

## CONCLUSION

Colorectal carcinoma was diagnosed especially in people over 50 years, affecting male population more than females. Our study showed Her-2/neu overexpression in 3.89% cases of colorectal carcinoma, this would create a new treatment strategy with transtuzumab in patients who overexpress HER2/neu. There were no correlations found between Her-2/neu overexpression with grade of tumor and lymph node status.

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