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Frequency Of Her2/Neu Expression In Colorectal Adenocarcinoma: Two Year Study In Tertiary Care Hospital Of Kashmir

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Abstract

Background: Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidences. It is the third most common cancer worldwide and the fourth most common cause of death. Overexpression of HER2/neu has been reported in many epithelial malignancies, including cancers affecting breast, lungs, prostate, bladder and pancreas and has been notably associated with increased cellular survival, increased proliferation and decreased apoptotic potential of cells leading to malignant transformation and maintenance of the associated malignancy. The role of HER2/neu directed therapy and its success in breast cancer patients has led to evaluation of protein overexpression, gene amplification, and anti-tumor activity of Herceptin in multiple tumor types, including colorectal and gastric adenocarcinomas.

Material and methods: This study was conducted in the department of Pathology, government medical college Srinagar, Kashmir which is a tertiary care referral hospital for a period of two years. Total number of 366 cases were collected and incorporated in the study followed by which HER2/neu expression was studied using immunohistochemistry.

Results: We observed that 3.1 % (11) cases of colorectal adenocarcinoma were positive for HER2/neu expression while 96.9% (355) were negative.

Conclusion: HER2neu expression is observed in a small percentage of colorectal adenocarcinomas and its value for the purpose of targeted therapy requires a clinical trial on the basis of which it can be determined whether HER2 directed Targeted therapy can be effective in HER2 mutated tumors.

Keywords: Colorectal adenocarcinoma, HER2/neu, Herceptin.

Introduction

Incidence

Colorectal cancer is a major cause of morbidity and mortality throughout the world.[1] It accounts for over 9% of all cancer incidence.[2,3] It is the third most common cancer worldwide and the fourth most common cause of death.[4] It affects men and women almost equally, In 2012, 614,000 women (9.2% of all new cancer cases) and 746,000 men (10.0% of new cancer cases) were diagnosed with colorectal cancer worldwide.[5] Colorectal cancer is, in general, a disease of older people with a peak incidence in the early 70s.[6] Carcinoma of the large bowel is common in northwest Europe, North America, and other Anglo-Saxon areas, but low in Africa, Asia, and some parts of South America.[7,8]

Aetiology

Exogenous factors: environmental effects

The colorectal epithelium acts as a functional barrier between the luminal colonic environment and the internal milieu. As such it is heavily exposed to the effects of the environment as transmitted by diet and other swallowed substances

Bile Acids

Recent molecular genetic studies have demonstrated that bile acids can produce DNA damage through oxidative stress and particular targets may include the KRAS gene [9].

High Meat And Fat Diets

There is much experimental and epidemiological evidence linking excess of red meat, processed meat and animal fat with colorectal carcinoma [10, 11, 12–17].

Fibre

Epidemiological studies of populations with diets rich in fibre have produced strong evidence for a protective effect of fibre against colorectal carcinoma [17, 18].

Obesity

The link between obesity and colon cancer risk is clearer for men than women and the association is strongest with adult weight gain rather than body mass index (BMI) before the age of 18 years [19].

Smoking And Alcohol

The association of colorectal cancer with alcohol consumption, particularly beer, is well founded [20]. It appears that the risk of colorectal cancer increases in a linear fashion as alcohol intake increases [21].

Vitamins, Calcium And Selenium

There have been numerous studies into the effects of vitamin deficiency on the risk of colorectal cancer. Vitamins B2, B6, B12, C and D may all be mildly protective [22–27]. Selenium reduces the development of intestinal cancers in experimental animals and, in mice, selenium-enriched dairy proteins can suppress the development of aberrant crypt foci and KRAS mutations [28–30].

8. Aspirin And Colorectal Carcinoma

The preventive effect of aspirin may be greatest in the proximal colon and is likely to be mediated through inhibition of the cyclo-oxygenase 2 (COX-2) enzyme, which is up regulated in colorectal adenomas and carcinoma [31, 32].

Endogenous Factors

Endocrine effects

Although adenomas are more common in males than in females, adenomas in females are likely to be larger [33–35]. It has been suggested that female sex hormones, or the expression of hormone receptors, might be important in adenoma progression and that adenomas in females are more likely to become malignant [36–38].

Genetic Factors

Classic Inherited Colorectal Cancer Syndromes

The APC gene is the tumour-suppressor gene implicated in the autosomal dominant disorder familial adenomatous polyposis (FAP) [39]. A second example is the inheritance of a mutated DNA mismatch repair (MMR) gene responsible for the autosomal dominant disorder HNPCC or Lynch syndrome [40].

Non-Classic Inherited Pathways

The APC I1307K mutation occurring in Ashkenazi Jews does not of itself cause classical FAP but creates a short hypermutable mononucleotide repeat in APC that is susceptible to further frameshift mutations that may inactivate APC function. The resulting phenotype is an increased frequency of adenomas and a roughly twofold increased risk of carcinoma in affected families [41, 42].

Site And Gross Features

Approximately 50% of all carcinomas occur in the recto sigmoid area [43].Right-sided tumors are associated with older age at presentation.[44] Multicentric carcinomas are found in 3%–6% of the cases.[45] Grossly, most colorectal carcinomas are either polypoid or ulcerative/infiltrating. The former presents as a bulky mass with well-defined, rolled margins, and a sharp dividing line with the normal bowel. The latter has a less elevated surface and is centrally ulcerated.

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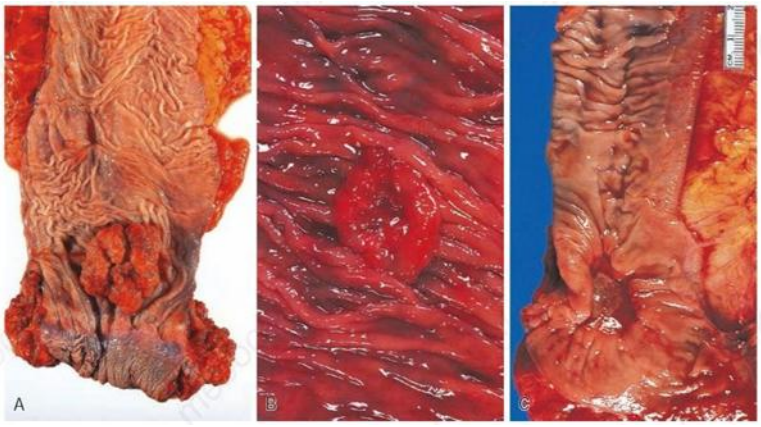
Figure: Various Gross Appearances of Colonic Adenocarcinoma. A.Polypoid pattern of growth in a rectal lesion. B.Cake-like configuration with central ulceration.C. penetrating and ulcerating Deeply tumor. Cooke, Courtesy of Dr. R.A. Brisbane, Australia, from Cooke RA, Stuart B. Colour Atlas of Anatomical Pathology. Edinburgh: Churchill Livingstone; 2004.

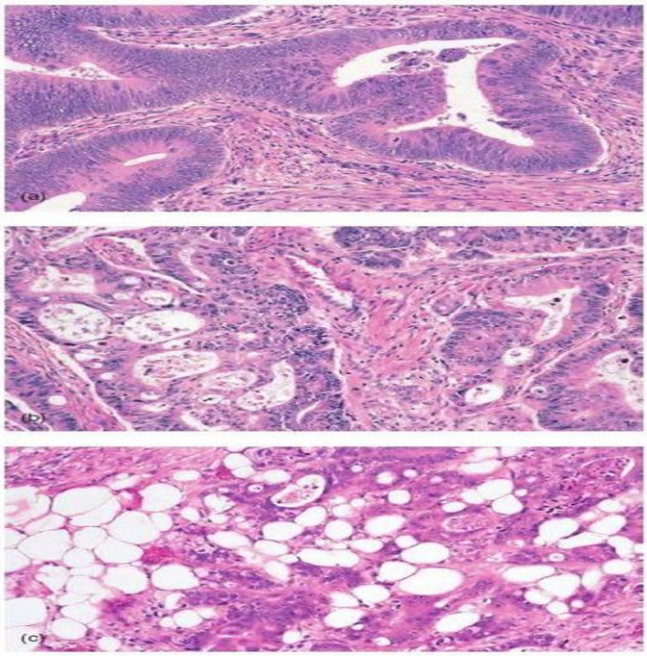


Microscopy

The usual malignant tumor of the large bowel is a well-to-moderately differentiated adenocarcinoma secreting variable amounts of mucin. The tumor cells represent a combination of columnar and goblet cells, with occasional participation of neuroendocrine cells and the exceptional occurrence of Paneth cells. The carcinoma consistently elicits an inflammatory and desmoplastic reaction, which is particularly prominent at the edge of the tumor. Most of the inflammatory cells are T lymphocytes, but B lymphocytes, plasma cells, histiocytes, and S-100 protein–positive dendritic cells may also be present. Occasionally there are numerous eosinophils, a feature thought to be due to interleukin-5 production.

Figure :

(a)Well differentiated (b) Moderately differentiated (c) Poorly differentiated adenocarcinoma of large bowel showing a progressive variance from normal epithelial morphology. (Morson and Dawsons Gastrointestinal Pathology, Fifth Edition page : 704)



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Her2/neu

Definition and Importance

HER2 is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. ERBB2, a proto-oncogene, is located at the long arm of human chromosome 17 (17q12).

Activation of HER2/neu leads to initiation of signaling pathways like MAPK/P13K/AKT, essential for cell proliferation and differentiation [46]. HER2 is the only member of the EGFR family that does not bind ligands; it is activated via heterodimerization with other ligand-bound receptors [47], with the strongest mitogenic signals created by HER2–HER3 heterodimers. HER2 overexpression, usually caused by gene amplification, allows HER2 activation even in the absence of ligand bound to the other partners [48]. Overexpression of HER2/neu has been reported in many epithelial malignancies, including cancers affecting breast, lungs, prostate, bladder and pancreas and has been notably associated with increased cellular survival, increased proliferation and decreased apoptotic potential of cells leading to malignant transformation and maintenance of the associated malignancy [49]. The role of HER2/neu directed therapy and its success in breast cancer patients has led to evaluation of protein overexpression, gene amplification, and anti-tumor activity of Herceptin in multiple tumor types, including colorectal and gastric adenocarcinomas [50,51].

Interpretation

Positive:

IHC 3+: (strong positive): tumor displays complete, intense circumferential membranous staining in

> 10% of tumor cells (*readily appreciated using a low power objective and observed within a homogenous and contiguous invasive cell population).

Equivocal:

IHC 2+: weak to moderate complete membrane staining observed in > 10% of invasive tumor cells. Negative:

IHC 1+: incomplete faint membrane staining and within > 10% of invasive tumor cells.

IHC 0: no staining observed or incomplete faint / barely perceptible membrane staining within ≤ 10% of invasive tumor cells.

Material and Methods

This study was conducted in the department of Pathology, government medical college Srinagar, Kashmir which is a tertiary care referral hospital for a period of two years. Total number of 366 cases were collected and incorporated in the study. Before taking up of cases complete history, clinical and radiological findings were taken into consideration. The tissue samples were Formalin-fixed paraffin- embedded (FFPE) followed by routine Hematoxylin and Eosin (H & E) staining and immune- histochemical staining for HER2/neu. Sections were thoroughly studied with proper clinico radiological context. Interpretation of HER2/neu expression was done using internationally accepted protocol.

Results

We observed that 3.1 % (11) cases of colorectal adenocarcinoma were positive for HER2/neu expression while 96.9% (355) were negative. (No staining at all or membrane staining in < 10% of tumor cells was given the score “0”. Faint staining in ≥ 10% of tumor cells was given the score “1+”, as well as in cells which were only stained in part of the membrane. Weak to moderate staining of the entire membrane in ≥ 10% of the tumor cells was given the score “2+”, and strong staining of the entire membrane in ≥ 10% tumor cells was given the score “3+”).

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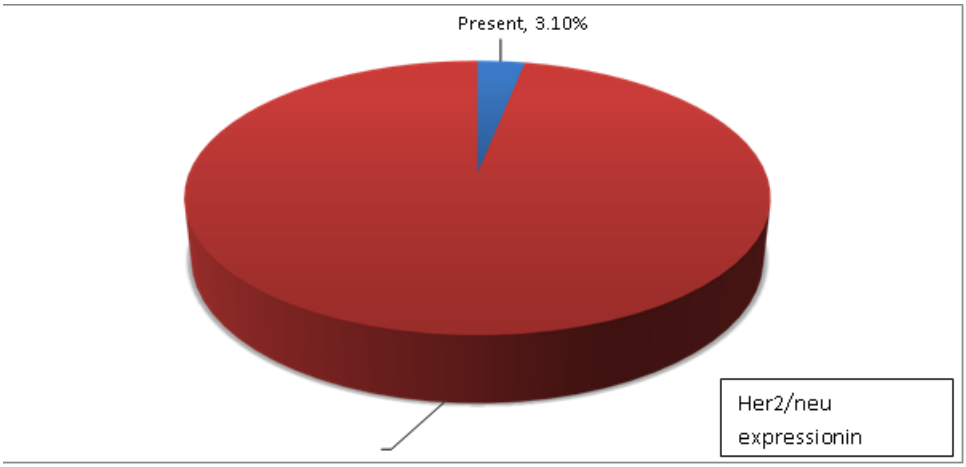
Table HER2/neu Expression in colorectum

			Colorectal	Total
HER2/neu	Present	Count	11	11
		% within Site1	3.1%	3.1%
	Absent	Count	355	355
		% within Site1	96.9%	96.9%
Total		Count	366	366
		% within Site1	100.0%	100.0%



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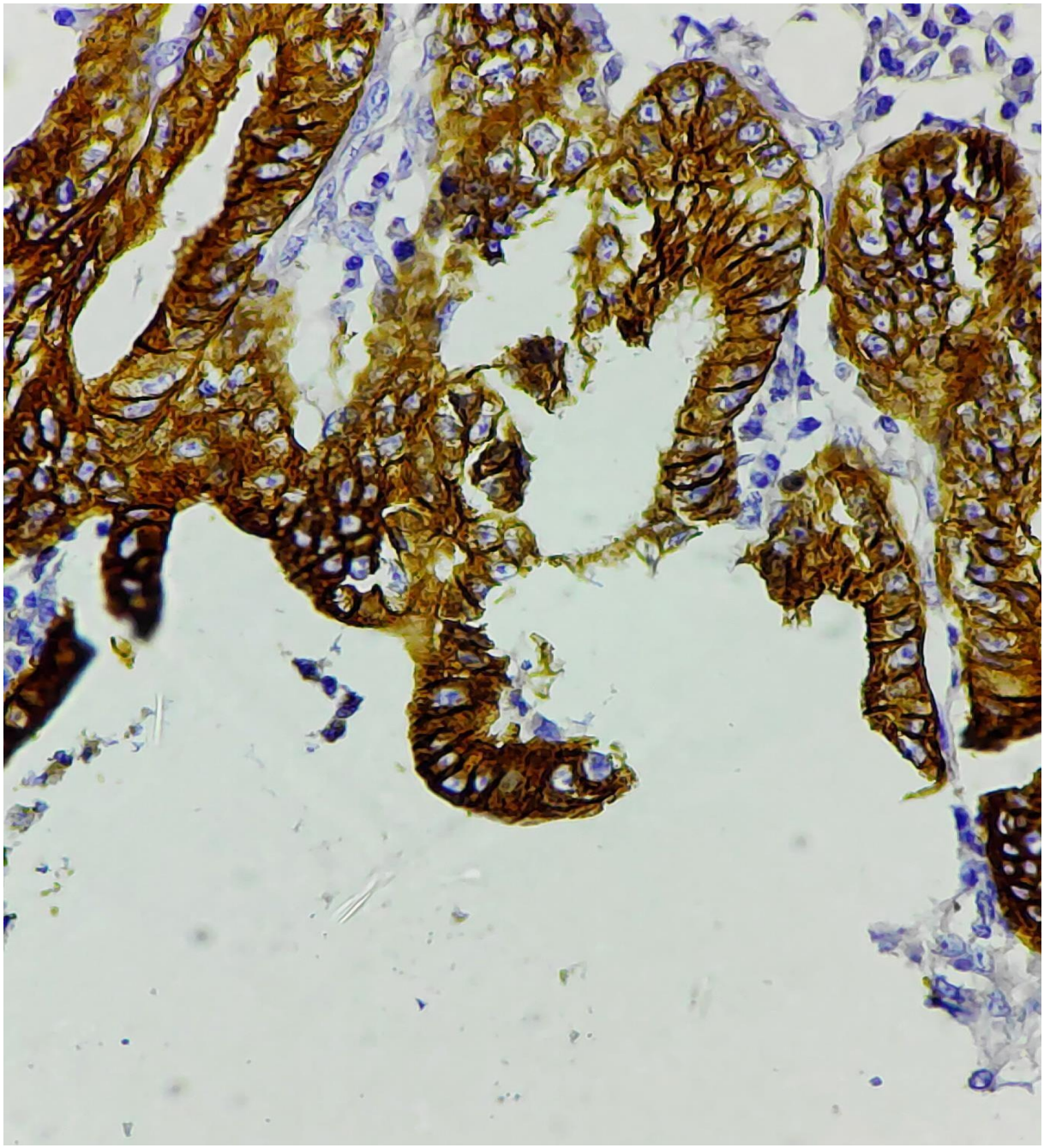
HER2/neu Positive Adenocarcinoma



Summary

The aim of this study was to report the expression of HER2/neu proto-oncogene in colorectal adenocarcinomas (CRC's) in the population of Kashmir and to compare findings with others international studies.

A small proportion of CRC's overexpress the HER2 oncogene and the effective targeting of this pathway in other malignancies such as breast and gastric cancer has led to efforts to determine if it can be exploited as a target in CRC. The HER2 receptor is a protein that is normally found on the surface of several different types of cells in the body but over expressed in multiple cancer types including ~1-6% of patients with colorectal cancer. The HER2 receptors span into the cell and are part a biologic pathway that is involved in cellular replication. Sometimes a gene that is responsible for the HER2 receptor becomes mutated, and too many receptors are produced. This, in turn, results in cells that divide and spread without their normal biologic controls.

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Cancer cells that have too many HER2 receptors are referred to as HER2-positive.

Herceptin (trastuzumab) and Tykerb (lapatinib) are two precision cancer medicines that bind along the HER pathway at different points, both producing anti-cancer effects in HER2+ breast cancer. To date, recently published and presented data has shown that HER2neu positivity is seen in a small number of cases of colorectal adenocarcinoma and we have observed similar results in our study.

B Ingold Heppner et al (2014)[52] found that 1.6% of the cases of colorectal adenocarcinoma were HER2/neu positive.

Zhila Torabizadeh et al (2016)[53] conducted a study on HER2/nue expression in colorectal adenocarcinoma and found that only 2% of the cases showed a score of +3.

Xin-Yu Wang et al (2019)[54] conducted a study on HER2/nue expression in colorectal adenocarcinoma and found that HER2 IHC scores of 3 + were observed in 2.6% of the cases.

Study	**HER2/neu + Expression**
B Ingold Heppner et al (2014)	1.6%
Zhila Torabizadeh et al (2016)	2%
Xin-Yu Wang et al (2019)	2.6%
Present Study	3.1%

Conclusion

Our study provides insight into expression of HER2/neu proto-oncogene in colorectal carcinomas (CRC's) in the population of Kashmir. HER2neu expression is observed in a small percentage of colorectal adenocarcinomas and its value for the purpose of targeted therapy requires a clinical trial on the basis of which it can be determined whether HER2 directed Targeted therapy can be effective in HER2 mutated tumors.

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