ISSN: 0975-3583, 0976-2833 VOL14, ISSUE12, 2023

Expression of HER-2 in colorectal carcinomas and its correlation with histological grades

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ABSTRACT

Background and objective: The study was carried out to check the expression of HER-2 in colorectal carcinoma and to correlate the findings with the histological grades. Colorectal cancer is the third most common malignancy worldwide, and is the second leading cause of cancer related deaths. HER-2 is a useful antigenic marker in the immunological studies of colorectal cancer and it can be used for predicting the prognosis and treatment.

Materials and methods: The present study was conducted for a period of 2 years from January 2021 to December 2022 on 33 histopathologically diagnosed cases of colorectal carcinoma in RIMS, Imphal, India. Immunohistochemistry was done to study the expression of HER-2 (Clone: EP3/PathnSitu biotechnologies). HER-2 expression was quantified according to staining pattern, staining intensity, percentage of tumor cells stained and statistical correlation was performed with its values and histopathological grades.

Results: HER-2 was positive in 72.7% of the cases of colorectal carcinoma. It was expressed in 60% of the well differentiated, 82.6% of the moderately differentiated and 40% of the poorly differentiated colorectal carcinomas. Majority of the HER-2 positive cases showed isolated cytoplasmic staining (83.33%) and weak staining intensity (75%). A statistically significant correlation was noted among histologic type of CRC with HER-2 scoring (p= 0.016) and also among histologic grade with pattern of HER-2 staining (p=0.043).

Conclusion: It was concluded that HER-2 is frequently expressed in colorectal carcinomas in Indian population and can be used as a reliable biomarker for cancer prognostication. However, further large-scale studies on Indian population are warranted for validating pre-existing information.

Keywords: Colorectal carcinoma, immunohistochemistry, HER-2 expression

1. INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy (after breast and lung carcinoma) worldwide, and the second leading cause of cancer deaths (after lung cancer) in 2020.[1] It has become a global burden in relation to its complications, mortality, side effects of treatment, utilization of health care services, and medical costs.[2] The incidence and mortality

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE12, 2023

of CRC among various countries of the world varies widely.[3] A recent study by Arnold et al[4] reported that its incidence in countries with a very high human development index (HDI) were 6 times higher than that in countries with a low HDI, and a similar correlation was observed for mortality as well. Although the results from studies assessing colorectal cancer risk and single foods or nutrients have tended to be inconsistent[5], the revised World Cancer Research Fund/American Institute for Cancer Research reports evidence that processed meat, alcohol drinks, and body fatness increase risk, whereas physical activity is protective.[6] A diet high in the consumption of red or processed meats has been associated with an increased risk of colon cancer.[7]

Recently many Asian countries have observed an increase of 2-4 times in the incidence of colorectal cancer. The incidence and mortality from CRC is more in wealthy than in poorer societies and differs substantially among ethnic groups. Although changes in dietary habits and lifestyle are believed to be the reasons underlying the increase, the interaction between these factors and genetic characteristics of the Asian populations might also have a pivotal role.[8]

Carcinoma of the colon and rectum is a less common malignancy in India when compared with the western world; however, its incidence is increasing. According to GLOBOCAN 2020 report[1], number of new colorectal cancer cases in males in India was estimated to be 40,408 (6.3%) and in females 24,950 (3.7%). Colorectal cancer ranks as fourth most frequent cancer in men (after lip and oral cavity, lung and stomach cancer) and fifth in women (after cancer of breast, cervix and uterus, ovary, lip and oral cavity). An estimated 1.9 million new cases of colorectal cancer occurred worldwide in 2020, representing about 10% of all new cancers. An estimated 935,173 deaths occurred worldwide in 2020 due to colorectal cancer, representing 9.4% of all cancers. A 60% increase in the global burden of CRC with more than 2.2 million new cases and 1.1 million deaths is predicted by 2030.

As per the latest report from National Cancer Registry Programme in India[9], the age adjusted rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100,000 respectively. The AAR for colon cancer in women is 3.9 per 100,000. In Manipur, the incidence of cancer in colon and rectum in men was 3.1 and 3.4 per 100,000 respectively. The age adjusted incidence rates of colorectal cancer in male and female of Manipur state was 3.9 and 3.4 per 100,000 respectively.

The incidence of colorectal carcinoma is still low in Manipur. However, with changes of lifestyle, dietary habits and existing risk factors it may increase like other Asian countries. According to a study done by Laishram et al[10] it was found that CRC occurs earlier in Manipur which might be due to hidden risk factors for colon cancer and further extensive studies on it was recommended.

Growth factors are the protein products of genes called proto-oncogenes, which are fundamentally important for normal cells. The HER (Human epidermal growth factor receptor) is a family of four membrane-bound receptors namely HER1 (EGFR), HER-2 (Her2/neu or ErbB-2), HER3 and HER4. The G-protein receptors, when activated, drive multiple signal transduction pathways which regulate the cellular growth.[11]

HER-2 is located on chromosome 17q21 and it encodes a 185kD transmembrane protein that lacks a natural ligand. HER-2 activation initiates signal cascades including the MAPK (Mitogen activated protein kinase) and PI3K/AKT (3-kinase) pathways that are essential for cell proliferation and differentiation.[12] In tumor model systems, the overexpression of HER-2 gene correlates with mitogenesis, malignant transformation, increased cell motility, invasion and metastasis.[13] Overexpression of HER-2 has been reported in many other epithelial

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malignancies, including cancers of the lung, prostate, bladder, pancreas and esophagus and in sarcomas.[11]
In recent past, HER-2 has emerged as a potential prognostic factor for colorectal cancer. In addition, it can also be a therapeutic option with monoclonal antibodies such as trastuzumab. Data on HER-2 expression of colorectal carcinoma is limited, especially in this part of the country. Study of HER-2 expression might help in prognostication and targeted therapy of the patients with CRC. This study was being done to determine the level of expression of HER-2 in colorectal carcinomas and to correlate its level of expression with various histological grades of colorectal carcinoma.

2. MATERIALS AND METHODS

The present study was conducted in the department of Pathology, Regional Institute of Medical Sciences, Manipur, India for a period of 2 years from January 2021 to December 2022 on 33 cases of colorectal carcinoma which were received as surgically resected colorectal tissues. Ethical clearance was obtained from Research Ethics Board, RIMS, Imphal. Particulars of the patient, relevant clinical history and gross examination findings were recorded. The tissues were formalin fixed and paraffin embedded and sections of three microns were cut and stained with haematoxylin and eosin for histological typing and grading of the lesions. The sections were subjected to immunohistochemical staining for HER-2 for studying its expression.
Immunohistochemistry was performed on three to five micron thick sections which were made on poly-L-lysine coated slides. Antigen retrieval was performed by heating the sections in phosphate buffer at pH 7.2-7.6 by using a pressure cooker. HER-2 detection was done using rabbit monoclonal antibody, EP3 (PathnSitu biotechnologies).
Results and interpretation of the IHC staining:

- The positive control tissue showed a brown coloured end product for HER-2 at the site of target antigen in the cytoplasm and/or membrane of the cells.
- The negative control sections did not have any coloured product since there was no antigen antibody reaction.

Histological evaluation:
Tumors were classified according to the WHO classification and the pTNM stage was determined according to the eighth edition of the Union for International Cancer Control (UICC) guidelines.[14]
Immunohistochemical evaluation:
The tumor tissue with more than 10% tumor cells, which showed staining for HER-2 was considered as positive and those with no staining or less than 10% staining were considered as negative (scored as 0). Level of expression for HER-2 positive cases was quantified according to the following three criteria:

1. The staining pattern was observed as:
    a. Only cytoplasmic staining.
    b. Mixed cytoplasmic and membranous staining.
    c. Only membranous staining.
2. Intensity of staining was observed as:
    a. Weak staining.
    b. Moderate staining.
    c. Strong staining.

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3. Percentage of cells stained were scored as:
    a. 10-40% cells stained as score 1+
    b. 40-70% cells stained as score 2+
    c. >70% cells stained as score 3+

Statistics

Descriptive and inferential analysis was carried out in the study. Age in years was expressed as mean +/- SD and results on categorical data of sex, religion, types and stages of tumor and HER-2 expression are presented in frequency and percentage. The histopathological findings were correlated with IHC findings using Chi-square test. p value of <0.05 was considered statistically significant. Data was entered and analysed using SPSS version 21.

3. RESULTS

A total of 19 males and 14 females participated in our study. The present sample comprises of 57.6% of males and 42.4% females. 30.3% participants were below 50 years and 69.7% were more than 50 years. The mean age was 55.73 years with age ranging from 18 to 80 years. Peak incidence for colorectal carcinoma was observed in the 5^{th} and 6^{th} decade. Manipur is a Hindu dominated state and therefore highest percentage of participants (63.6%) belonged to Hinduism, followed by Christianity (21.2%) and Islam (15.2%). All the above findings are illustrated in **Table 1.**

Length of resected specimen was more than 20cm in majority of cases (12 cases, 54.5%), followed by 10-20 cm in 9 (40.91%) cases. In majority of cases, the tumor length in greatest dimension was in between 5-10 cm (13 cases, 59.09%) (**Fig 1a, 1b**). Lymph node was dissected in 21(63.6%) cases. All the findings are illustrated above in **Table 2.**

Adenocarcinoma NOS was the predominant histologic type comprising of 28 (84.85%) cases followed by mucinous carcinoma in 5 (15.15%) cases (**Fig 2a, 2b**). Majority of the cases were moderately differentiated carcinomas (23 cases, 69.7%) followed by well differentiated and poorly differentiated carcinomas with 5 cases each (15.15%). Tumor positive regional lymph nodes were detected in 13 (39.39%) cases. According to tumor staging, T3 stage was the most common with 15 (68.19%) cases whereas in lymph node staging, N0 was the most common stage with 8 (36.36%) cases followed by N2a seen in 4 (18.18%) cases. All the results are illustrated in **Table 3.**

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Table 1: Particulars of the patient (N= 33)

Variables		**No. of cases**	**Percentage (%)**
Age	<50 years	10	30.3
	>50years	23	69.7
Gender	Male	19	57.6
	Female	14	42.4
Religion	Hinduism	21	63.6
	Christianity	7	21.2
	Islam	5	15.2

Table 2: Gross specimen findings (N= 33)

Variables		**N (%)**
Length of resected specimen in cm (N= 22)	<10	01 (4.55)
	10-20	09 (40.91)
	>20	12 (54.54)
Tumor length in cm (N= 22)	<5	05 (22.73)
	5-10	13 (59.09)
	>10	04 (18.18)
Lymph node dissection	Yes	21 (63.60)
	No	12 (36.40)

Fig 1a: Photograph of a gross specimen of Carcinoma rectum (abdominoperineal resection) which involves the whole rectum and extends into the anal canal.

Fig 1b: Photograph of a cut section of APR specimen showing an infiltrative type of tumor originating from the rectum and involving circumferentially.

Table 3: Histopathological findings (N= 33)

Variables		**N (%)**
Histologic type	Adenocarcinoma, NOS	28 (84.85)
	Mucinous adenocarcinoma	05 (15.15)
Histologic grade	G1	05 (15.15)
	G2	23 (69.70)
	G3	05 (15.15)
Positive lymph nodes	Yes	13 (39.39)
	No	20 (60.61)

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Lymphovascular invasion (N=22)	Present	16 (72.70)
	Absent	06 (27.30)
T stage (N= 22)	T2	02 (9.09)
	T3	15 (68.19)
	T4a	04 (18.18)
	T4b	01 (4.54)
N stage (N=22)	N0	08 (36.36)
	N1a	03 (13.64)
	N1b	03 (13.64)
	N1c	01 (4.54)
	N2a	04 (18.18)
	N2b	02 (9.10)
	Nx	01 (4.54)

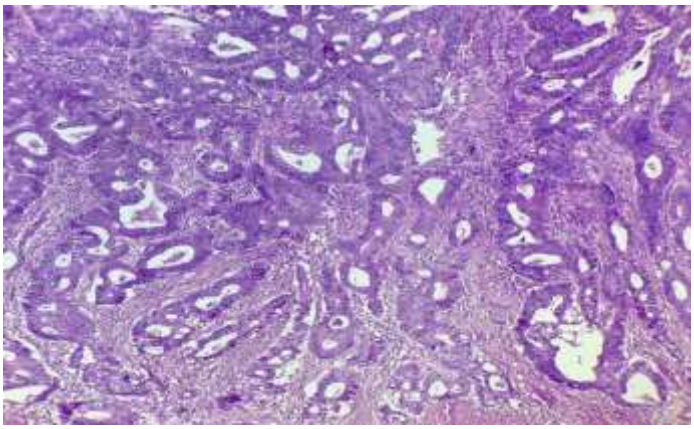

Fig 2a: Photomicrograph of an ascending colon with adenocarcinoma, NOS, moderately differentiated (Grade 2) showing malignant cells arranged in glandular pattern (H & E staining, 10X)

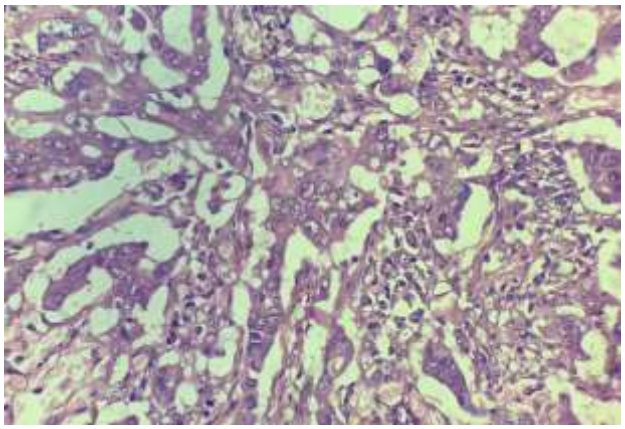

Fig 2b: Photomicrograph of rectum with adenocarcinoma, NOS, moderately differentiated (Grade 2) showing markedly pleomorphic malignant cells arranged in glandular pattern (H & E staining, 40X)

IHC findings:

HER-2 positivity: Total number of participants consisted of 33 cases, among which HER-2 positivity was seen in 24 (72.7%) cases. HER-2 was positive in 22 (78.57%) cases of adenocarcinoma NOS, and 2 (60%) cases of mucinous adenocarcinoma. (**Fig 3a, 3b).**

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HER-2 staining pattern: Among HER-2 positive CRCs which were having histological type Adenocarcinoma NOS, 18 (81.81%) cases showed isolated cytoplasmic staining and 04 (18.18%) cases showed mixed cytoplasmic and membranous staining. All the HER-2 positive cases of mucinous adenocarcinoma showed isolated cytoplasmic staining. However, none of the cases of CRCs, irrespective of typing showed isolated membranous staining.

Staining intensity: Among the adenocarcinoma NOS cases, 16 (72.7%) cases were weakly positive, 05 (22.8%) cases were moderately positive and only 01 (4.5%) case was strongly positive for HER-2 staining. All the HER-2 positive cases of mucinous adenocarcinoma showed weak positivity for HER-2 staining.

HER-2 score: Of the HER-2 positive Adenocarcinoma NOS cases, 03 (13.6%) cases had an IHC score of 1+, 17 (77.3%) cases had a score of 2+, while only 2 (9.1%) cases had a score of 3+. All the HER-2 positive mucinous adenocarcinoma cases had a score of 1+ for the marker.

A statistically significant correlation was observed between histological type and HER-2 score (p= 0.016) and also among histologic grade with pattern of HER-2 staining (p=0.043). However no statistically significant correlation was noted among histological type of colorectal carcinoma and other HER-2 parameters. All the results are illustrated in **Table 4.**

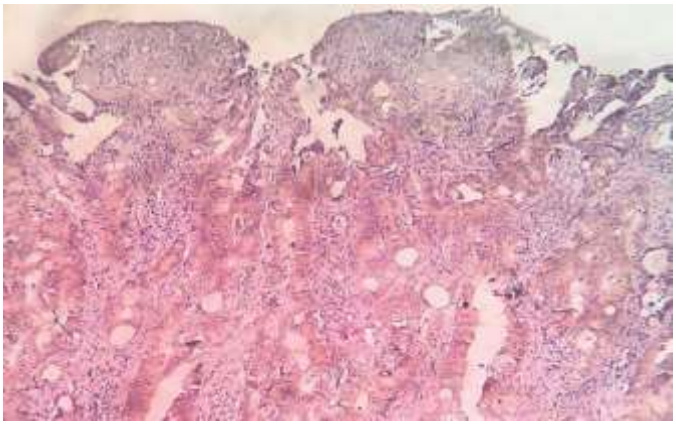

Fig 3a: Photomicrograph showing IHC staining positive for HER-2, moderately positive staining seen in more than 70% malignant cells with negative internal control (IHC staining for HER-2 marker, 10X)

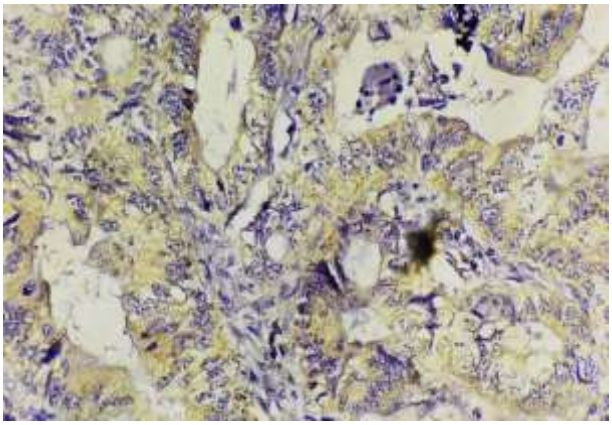

Fig 3b: Photomicrograph showing immunohistochemical stain positive for HER-2 marker, strongly HER-2 positive mixed cytoplasmic and membranous staining seen with negative internal controls (IHC staining for HER-2 marker, 40X)

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Table 4: Expression of HER-2 in colorectal carcinomas and comparison with histopathological grading (N= 33)

Immunohistochemistry features for HER-2		**Well differentiated CRC (n= 05)**	**Moderately differentiated CRC (n= 23)**	**Poorly differentiated CRC (n=05)**	**p-value**
HER-2 Positivity	YES	**03 (05)**	**19 (23)**	**02 (05)**	**0.120**
	NO	**02 (05)**	**04 (23)**	**03 (05)**	
HER-2 staining pattern (n= 22)	Cytoplasmic	**01 (03)**	**17 (19)**	**02 (02)**	**0.043**
	Membranous	**00 (03)**	**00 (19)**	**00 (02)**	
	Mixed cytoplasmic and membranous	**02 (03)**	**02 (19)**	**00 (02)**	
Intensity of HER-2 stain (n= 22)	Weak	**01 (03)**	**15 (19)**	**02 (02)**	**0.074**
	Moderate	**01 (03)**	**04 (19)**	**00 (02)**	
	Strong	**01 (03)**	**00 (19)**	**00 (02)**	
HER-2 score (n= 22)	1+	**00 (03)**	**04 (19)**	**01 (02)**	**0.376**
	2+	**02 (03)**	**14 (19)**	**01 (02)**	
	3+	**01 (03)**	**01 (19)**	**00 (02)**	

4. DISCUSSION

The incidence of colorectal cancer is increasing in many developing countries like India, with westernization of lifestyle.[15] Even though the absolute rates are still low; the rising rates pose a problem with increasing concern of morbidity.

Our study includes 19 (57.6%) male and 14 (42.6%) female participants with M: F ratio of 1.46:1 showing male preponderance for the disease which is in concordance with similar studies with some regional variations within India. It was 1.5:1 in another study conducted by Gill MK et al[16] in Punjab, 1.4:1 in study conducted by Velayutham P et al[17] in Tamil Nadu (South India) and 1.7:1 in a study from Rajasthan (West India).[18]

Mean age of patients in our study was found to be 55.73 years with peak incidence in the 5th decade. 30.3% of the CRC cases were detected in patients with age less than 50 years and 69.7% cases in patients above 50 years. Similar findings were observed in another study by Vishnukumar et al[19] in Tamil Nadu where mean age was 59.5 years. In studies from USA, 90% of the cases were in patients of more than 50 years.[20,21] Large regional variations in age distribution is seen in India with cases less than 50 years representing 20-50% of total cases.[17,18,22] Colorectal cancer in India thus appears to be more frequent in younger patients compared to the west.

Majority of the resected samples were more than 20 cm (54.54% cases) and tumor length in greatest dimension was 5-10 cm (59.09% cases). Similar studies conducted by Wu QB et al[23] and Li Q et al[24] shows tumor length predominantly less than 5 cm (65% cases).

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Lymph node dissection was performed in most of the cases (63.60%). However regional lymph node positivity was noted in a small number of cases (13 cases, 39.39%). Similar finding was observed in a study by Li Q et al[24].

Histological subtype of majority of the colorectal carcinoma cases were Adenocarcinoma NOS (28 cases, 84.85%). Similar finding was observed in a study conducted by Gill MK et al[16] (77.5% cases) and Sekhar G et al[25] (80% cases). Our present study shows the predominant histologic grade of CRC cases to be Grade 2 or moderately differentiated (23 cases, 69.7%) similar to the findings conducted in many other studies.[23,25,26,27,28] Contradicting findings are observed as well where well differentiated[11,16] or poorly differentiated[22] carcinomas are the predominant grades. These dissimilarities can be attributed to the variations within different study population.

Lymphovascular invasion was seen in 72.7% cases of CRC in our study. Similar finding was observed in a study conducted by Lee W et al[29] in China with LVI seen in 67% of the cases. However, study conducted by Khelwatty et al[30] in UK showed the lymphovascular invasion in 33% CRC cases only.

Predominant tumor stage in our study was T3 (68.19% cases) and that of lymph node stage was N0 (36.36% cases). Similar findings showing T3 as the most common tumor stage and N0 as the most common lymph node stage was also observed in other studies.[27,31]

In our study, there was a high percentage of positive HER-2 staining (24 cases, 72.7%), out of which 20 cases (83.3%) were isolated cytoplasmic staining and remaining 16.7% were cytoplasmic-membranous staining. No case showed a pure membranous staining. Similar findings were observed in a study conducted by Ghaffarzadegan et al[11] in Iran where positive HER-2 staining was seen in 59.4% cases, with cytoplasmic staining in 65.9% and membranous cytoplasmic staining in 34.1% of the cases. Similar study conducted by Gill Mk et al[16] show high percentage of HER-2 positive staining (65%), with 88.5% cases showing cytoplasmic and remaining 11.5% with membranous-cytoplasmic staining.

Our study shows a statistically significant correlation among histologic type of CRC with HER-2 scoring (p= 0.016) and also among histologic grade with pattern of HER-2 staining (p=0.043). No significant correlation was established among HER-2 positivity with histologic type or grade as such. Similar study conducted by Gill MK et al[16] also showed no correlation among HER-2 expression and histologic type of tumor although there was a significant increase of HER-2 positivity with increasing patient age. Ghaffarzadegan et al[11] also found no significant correlation among HER-2 expression and histologic type of CRC. However, Tavanagar et al[32] reported a statistically significant correlation between tumor grade and HER-2 expression in CRC.

One of the main limitations of our study was small sample size to investigate correlation between HER-2 staining pattern and histologic type and grade of colorectal carcinoma. Further studies with bigger sample size are needed for more authentications of our findings. However, considering overexpression of HER-2 in majority (72.7%) of CRC cases our results could be applied to the meta-analyses of the prevalence of HER-2 overexpression in colorectal cancer patients in this region and also for developing newer HER-2 targeting chemotherapeutic regimens.

5. CONCLUSION

HER-2 is frequently expressed in colorectal carcinomas in the study population. It can be reliably used as a biomarker in colorectal carcinoma patients for prognostication of the cases as well as selecting a subset of patients who can be benefitted from targeted treatment

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strategies using immunotherapy with anti-HER-2 antibodies. IHC is easily available and relatively inexpensive as a part of routine services in the department of pathology. Further research and large-scale studies in this field are required to validate these findings and develop India specific criteria.

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