Section: Pathology

Original Research Article

EXPRESSION OF E-CADHERIN AND BETA-CATENIN IN GASTRIC CARCINOMA IN A TERTIARY CARE HOSPITAL

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Abstract

Background: Worldwide, gastric carcinoma is the 4th most common malignancy and 2nd most common cause of death due to malignancy1. Annual incidence rate of gastric cancer in India is low compared to the western countries. Incidence of gastric carcinoma is relatively high in southern India, with increase in incidence also being reported in north-eastern India[2]. **Materials and Methods:** Study Design: Prospective Hospital based observational study. Study area: Department of Pathology (Histopathology laboratory), G S Medical College, Hapur, Uttar Pradesh. Study Period: January 2020 – December 2022. Study population: Surgically excised/biopsy specimens of Gastric carcinomas. Sample size: study consisted a total of 80 cases. Sampling method: Simple random method. Study tools and Data collection procedure: One micro section of 4-5µm thickness was prepared from the corresponding paraffin blocks, taken on an albumin coated slide for H&E staining. Gastric carcinomas were classified according to Lauren's classification as intestinal and diffuse. Representative areas of gastric carcinoma were marked on the slides and the blocks. Using a hollow needle, tissue cores with regions of interest are removed and inserted into a recipient paraffin block to prepare a tissue microarray for IHC staining. Cores of 5mm were used and 6 cores were arranged on each slide. The kits for E-cadherin and β-catenin Immunohistochemical staining were obtained from Biogenex Company. Staining was done according to manufacturer's protocol. Normal gastric mucosa included within the tissue sections were used as positive controls. The fibroblasts and lymphocytes in these samples were used as negative controls. Two micro sections of 4-5µm thickness were prepared from each of the tissue microarray paraffin blocks and taken on poly-L-lysine coated slides for immunostaining of E-cadherin and β-catenin. **Results:** In the present study, the four cases that were below the age of 30 years, showed aberrant expression of both E-cadherin and β-catenin. In the cases aged 31 to 40 years, 5 out of the 6 cases in males and 3 out of the 4 cases in females showed aberrant expression for E-cadherin and β-catenin. Of the 6 cases aged in between 71 to 80 years, two out of 6 showed aberrant expression for E-cadherin and one out of the 6 showed aberrant expression for β-catenin. **Conclusion:** Thus, the present study shows that E-cadherin and β-catenin are implied in the initiation and progression of gastric carcinomas as its expression is lost in advanced stages of the disease and high grade tumors. Diffuse carcinomas are associated with absence of membranous staining of E-cadherin and β-catenin and show absent or cytoplasmic staining for E-cadherin and nuclear and/or cytoplasmic staining for β-catenin.

INTRODUCTION

Worldwide, gastric carcinoma is the 4th most common malignancy and 2nd most common cause of death due to malignancy.[1] Annual incidence rate of gastric cancer in India is low compared to the western countries. Incidence of gastric carcinoma is relatively high in southern India, with increase in incidence also being reported in north-eastern India.[2] Geographic variability is because of the interaction of host genetic factors and socio-environmental factors.

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In India, approximately 34,000 new cases are reported every year which is expected to rise to 50,000 by the year 2025.There is a male preponderance in the incidence (male: female = 2:1).[3] Increase in incidence is due to Helicobacter pylori infection, diet and lifestyle modifications, tobacco, alcohol and genetic susceptibility. The signs and symptoms are often reported late, when the disease is in advanced stages.

Gastric cancer is mainly classified in to two histological subtypes: Intestinal and Diffuse. The Intestinal-type gastric cancer is more common in the older ages and in high incidence areas.[4] Diffuse-type of gastric cancer is common in the younger population, with an obvious hereditary form.

Gastric carcinogenesis is a multistep and multifactorial process. Numerous abnormalities of expression have been reported in molecules modulating growth and cell division such as tyrosine kinase growth factor receptors, p53, other apoptosis-related genes and genes controlling intercellular adhesion, such as E-cadherin. Experimental studies have suggested an important permissive role for loss of cadherin-catenin complex function in invasion and metastasis.[5,6]

E-cadherin gene is located on the long arm of chromosome 16 (q22.1) and produces E-cadherin transmembrane protein. It is considered as a tumor suppressor, invasion or metastatic suppressor gene as it suppresses proliferation, invasion, motility, and differentiation. E- Cadherin is a 120 k D transmembrane glycoprotein, which is expressed on the surface of epithelial cells, at the level of the intercellular junction and is important for establishing cell polarity, maintaining epithelial integrity and cellular differentiation.[7,8]

Decreased expression of E-cadherin leads to dissociation and dissemination of adenocarcinoma cells that lead to invasiveness and metastasis. Detection of loss of E-cadherin is useful for prognostication and selection of patients for targeted chemotherapy with demethylating agents. Hence the present study was undertaken to assess E-cadherin expression using immunohistochemistry in gastric carcinoma.

Objectives

1. To evaluate E-CADHERIN expression in Gastric Carcinoma.
2. To evaluate BETA-CATENIN expression in Gastric Carcinoma.

MATERIALS AND METHODS

Study Design Prospective Hospital based observational study.

Study area Department of Pathology (Histopathology laboratory), G S Medical College, Hapur, Uttar Pradesh.

Study Period January 2020 – December 2022.

Study population Surgically excised/biopsy specimens of Gastric carcinomas.

Sample size study consisted a total of 80 cases.

Sampling method Simple random method.

Inclusion Criteria

1. Surgically excised/biopsy specimens of Gastric carcinomas.
2. Adequate tumor tissue for analysis.

Exclusion Criteria

1. Benign lesions of the stomach.
2. Inadequate tumor tissue.

Ethics committe consideration: Institutional Ethics committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure

One micro section of 4-5µm thickness was prepared from the corresponding paraffin blocks, taken on an albumin coated slide for H&E staining.

Gastric carcinomas were classified according to Lauren's classification as intestinal and diffuse. Representative areas of gastric carcinoma were marked on the slides and the blocks. Using a hollow needle, tissue cores with regions of interest are removed and inserted into a recipient paraffin block to prepare a tissue microarray for IHC staining. Cores of 5mm were used and 6 cores were arranged on each slide.

The kits for E-cadherin and β-catenin Immunohistochemical staining were obtained from Biogenex Company. Staining was done according to manufacturer's protocol. Normal gastric mucosa included within the tissue sections were used as positive controls. The fibroblasts and lymphocytes in these samples were used as negative controls. Two micro sections of 4-5µm thickness were prepared from each of the tissue microarray paraffin blocks and taken on poly-L-lysine coated slides for immunostaining of E-cadherin and β-catenin.

Method of Immunohistochemical Staining

Immunohistochemical staining of E-cadherin and β-catenin protein was done using peroxidase-antiperoxidase method, protocol described by Biogenex.

- 4µm thin sections are taken on poly-L-lysine coated slides
- De-paraffinization is done by dipping the slides in 3 changes of xylene 10 min each, followed by 3 changes of absolute alcohol for 5 min each.
- The slides are washed under running tap water for 15 mins.
- Endogenous peroxidase activity is quenched by covering the slides with 3% H2O2 for 30 minutes.
- Wash under running tap water for 15 mins.
- Antigen retrieval is done by Pressure cooker (11IER, heat induced epitope retrieval) with Tris buffer (1.21 g of Tris Hydroxymethyl Methylamine and 3.75 g of EDTA in 1000ml distilled water).
- Slides are washed with TBS buffer (9.6 g of Tris Hydroxymethyl Methylamine and 8.6 g of NaCl in 1000ml distilled water). pH 7.4 – 7.6.
- Incubate with Primary antibody [E-cadherin antibody (clone EP6- Biogenex) for E- cadherin

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immunostaining and β-catenin antibody (clone EP35- Biogenex) for β- catenin immunostaining] which is ready to use, at room temperature in humidifier chamber for 30 mins.

- Slides are again washed with TBS buffer (9.6 g of Tris Hydroxymethyl Methylamine and 8.6 g of NaCl in 1000ml distilled water). pH 7.4 – 7. 6.
- Incubate with secondary antibody in a humidifier chamber for 30 minutes. The sections are again washed with TBS buffer.
- Chromogen (DAB) is placed on the tissue for 10-15 min.
- Counter staining is done with Harris Haematoxylin.
- Dehydrate in Alcohol and Xylene
- Slides are dried and mounted with DPX.
- The slides are then examined under microscope and E-cadherin scoring was given.

Scoring and Evaluation

Scoring of E-cadherin immunohistochemical staining was done according to the system of Jawhari10:

0- No staining.

1. Cytoplasmic staining without membranous staining.
2. Cytoplasmic and membranous staining in the same case.
3. Normal membranous immunoexpression.

- Abnormal patterns were represented by scores 0, 1 and 2
- Normal pattern were represented by score of 3.

Scoring of β-catenin immunohistochemical staining was done according to the system of Sergio et al.11 where membranous expression of β-catenin was quantitatively scored:

0- No or weak dot like membranous staining.

1- Membranous staining in <25% of tumor cells.

2- Membranous staining in 25-75% of tumor cells. 3- Membranous staining in >75% of tumor cells.

- Abnormal patterns were represented by scores 0,1 and 2.
- Normal pattern were represented by score of 3.

Statistical Analysis

Once all the observations had been recorded, the data collected was transferred to a master chart and analyzed. Data analyzed by using SPSS version 20. Correlation between E- cadherin expression, β-catenin expression and clinicopathological factors was evaluated using Chi square test. p-values <0.05 were considered to be statistically significant.

RESULTS

Table 1: Showing sex distribution, mean and median age in patients of gastric carcinoma

	MALES	FEMALES
No. Of cases	56	24
Mean age	55.82	58
Median age	58	55

In the present study, ages of the patients ranged from 18 to 80 years with majority of cases seen in 6th and 7th decade. The mean of the ages was 53.89 and the median was 57.5. Male to female ratio was 2.3:1 with 56 males and 24 females.

Table 2: Showing distribution of cases according to anatomic location

SITE	NO.OFCASES	PERCENTAGE
CARDIA	5	6.25%
FUNDUS	7	8.75%
BODY	20	25%
PYLORUSANDANTRUM	48	60%

Table 3: Distribution according to Laurens' classification

TYPE	NUMBER	PERCENTAGE
INTESTINAL	40	50%
DIFFUSE	39	48.75%
MIXED	01	1.25%

Most commonly, Laurens' classification is used to classify gastric carcinomas into intestinal type, diffuse type and mixed type. Of the 80 cases included in the present study, 40 were of the intestinal type, 39 were of the diffuse type and 1 was of the mixed type.

Table 4: Distribution of cases according to grade of tumor

GRADE	NUMBER	PERCENTAGE
WELLDIFFERENTIATED	27	33.75%
MODERATELYDIFFEENTIATED	14	17.5%
POORLYDIFFERENTIATED	39	48.75%

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Table 5: E-cadherin scores according to Laurens' classification

E-CADHERIN SCORE	INTESTINALTYPE (n=40)	%	DIFFUSETYPE (n=39)	%	MIXED(n=1)	%
0	2	5%	7	17.95%	-	-
1	1	2.5%	6	15.38%	1	100%
2	17	42.5%	21	53.85%	-	-
3	20	50%	5	12.82%	-	-

Table 6: β-catenin scores according to Laurens' classification

B-CATENINSCORE	INTESTINAL TYPE(n=40)	%	DIFFUSE TYPE(n=39)	%	MIXED TYPE(n=1)	%
0	1	2.5%	2	5.13%	1	100%
1	6	15%	6	15.38%	-	
2	12	30%	22	56.41%	-	-
3	21	52.5%	9	23.08%	-	-

Table 7: Cases showing co-expression of E-cadherin and β-catenin with p-value

	E-cadherin aberrant expression	E-cadherin normal expression	p-value
β-catenin aberrant expression	42	8	0.000145 significant
β-catenin normal expression	13	17	

Table 8: Comparison of E-Cadherin Expression in Different Variables

		E-CADHERIN EXPRESSION		p-VALUE
		ABERRANT	NORMAL	
SEX	MALES (n=56)	37	19	0.429795(p>0.05)
	FEMALES(n=24)	18	6	INSIGNIFICANT
AGE (mean)	(n=80)	56.72	52.93	
LOCATION	CARDIA	4	1	0.072(p>0.05)NOT
	FUNDUS	7	0	
	BODY	17	3	SIGNIFICANT
	PYLORIC ANTRUM	27	21	
GRADE	WELL DIFFERENTIATED	15	12	
	MODERATELYDIFFEED	7	7	0.004449(p<0.05)SIGNIFICANT
	POORLYDIFFERENTIATED	34	5	
LAURENS	INTESTINAL	20	20	0.000382(p<0.05)SIGNIFICANT
	DIFFUSE	34	5	
	MIXED	1	-	

Table 9: Comparison of β-catenin expression in different variables

		B-CATENINSCORE		p-VALUE
		ABERRANT	NORMAL	
SEX	MALES (n=56)	35	21	1(p>0.05)NOT
	FEMALES (n=24)	15	9	SIGNIFICANT
AGE (mean)	(n=80)	55.8	53.1	
LOCATION	CARDIA	3	2	0.9415(p>0.05)NOT
	FUNDUS	5	2	
	BODY	13	7	SIGNIFICANT
	PYLORIC ANTRUM	29	19	
GRADE	WELL DIFFERENTIATED	12	15	
	MODERATELY DIFFERENTIATED	8	6	0.024866(p<0.05)SIGNIFICANT
	POORLY DIFFERENTIATED	30	9	
LAURENS'	INTESTINAL	19	21	0.007059(p<0.05)SIGNIFICANT
	DIFFUSE	30	9	
	MIXED	1	-	

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DISCUSSION

The present study was done in the Department of Pathology. Staining patterns of E-cadherin and β-catenin were evaluated in gastric carcinomas. E-cadherin and β-catenin are involved in cell-to-cell adhesion and loss of expression is associated with invasion and metastasis.[12]

In recent studies, E-cadherin has been shown also to be involved in modulating intracellular growth signalling and thus promotes tumor growth. Mutations of E-cadherin found in familial gastric cancers suggests its involvement in early stages of tumor genesis and its role as a tumor suppressor gene.[13]

β-catenin apart from its involvement in cell adhesion, also plays an important role in Wnt signalling pathway. Dysregulation of β-catenin leads to uncontrolled activation of Wnt signalling pathway, uncontrolled proliferation of target cells and contributes to development of malignancy.[14]

In the present study, ages of the patients ranged from 18 to 80 years with majority of cases seen in 6th and 7th decade. The mean of the ages was 53.89 and the median was 57.5. Male to female ratio was 2.3:1 with 56 males and 24 females.

The range of the ages was comparable to the studies done by Guo-Yang Sun et al.[15], In Mok Jung et al[14], Byung Joo Song et al.[16], Yong-Ning-Zhou et al[12] and Young- Eun Joo et al.[17] The ages in various studies ranged from 18-94 years. The median ages were also comparable to these studies. In the present study, the number of cases occurring below 20 years of age were just 1 and below 30 years of age were 4 cases. In the compared studies, no case was below the age of 18 years and the minimum age of the patients in these studies ranged from 26 to 31 years. Majority of the cases occurred after the age of 50. The mean age in patients showing aberrant expression of E-cadherin was 56.72 and in those showing aberrant expression β-catenin was 55.8. There was no statistical significance between the age, mean age, median age and the aberrant expression of E-cadherin and β-catenin. Even in the studies comparing the ages of the patients, no statistical significance was established between the age and aberrant expression for E-cadherin and β-catenin.

In the present study, the four cases that were below the age of 30 years, showed aberrant expression of both E-cadherin and β-catenin. In the cases aged 31 to 40 years, 5 out of the 6 cases in males and 3 out of the 4 cases in females showed aberrant expression for E-cadherin and β-catenin. Of the 6 cases aged in between 71 to 80 years, two out of 6 showed aberrant expression for E-cadherin and one out of the 6 showed aberrant expression for β-catenin. Thus aberrant expression is seen more commonly in the younger ages in the present study.

In the comparison of different studies, all showed male preponderance in the occurrence of gastric carcinomas. In the present study, though there was male preponderance seen in the incidence of gastric carcinomas, the percentage of cases showing aberrant expression of E-cadherin was more in females. The percentage of cases showing aberrant expression of β-catenin were equal in males and females. More females in the extremes of ages showed aberrant expression of E-cadherin and β-catenin when compared to males in the same age groups.

Most commonly, Laurens' classification is used to classify gastric carcinomas into intestinal type, diffuse type and mixed type. Of the 80 cases included in the present study,40 were of the intestinal type, 39 were of the diffuse type and 1 was of the mixed type. In the intestinal types of the gastric carcinomas, half of the cases showed aberrant expression for E-cadherin and slightly less than half of the cases showed aberrant expression for β-catenin. In the diffuse type of gastric carcinomas, 34 cases out of 39 (87.2%) showed aberrant expression of E-cadherin and 30 out of 39 (76.9%) showed aberrant expression of β-catenin. Mixed type of gastric carcinoma in the present study, diagnosed as Mixed Adeno-neuroendocrine Carcinoma (MANEC), showed aberrant expression of both E-cadherin and β-catenin. Aberrant expression of E-cadherin and β-catenin can be seen in a number of human cancers. E-cadherin and β-catenin are necessary for maintaining cell-cell adhesion and loss of expression of E-cadherin and β-catenin is associated with progression of many Carcinomas.[18] Compared to the normal mucosa, there was reduced membranous expression of E-cadherin and β-catenin in the tumor tissue in the present study. E-cadherin is part of "invasion suppressor system" and its loss has been reported to increase frequency of lymph node metastasis and distant metastasis compared to those with preserved expression.[5,6]

Study by Elena Fricke et al.[19] have shown mutation in the gene encoding E-cadherin in up to 66% of diffuse gastric carcinomas. E-cadherin mutations were analysed using IHC and mutation sequence analysis using RT PCR. The relationship between loss of expression of E-cadherin and β-catenin and classification of tumors by Laurens' classification has been controversial. In the present study, there was a statistical correlation between Laurens' classification and loss of expression of E-cadherin and β-catenin. It was in concordance with studies done by Yong-Ning-Zhou et al.[12] and Yaw Ohene et al.[20] Studies done by In Mok Jung et al.[14], Dorra Ben et al.[21] and Jolanta et al.[22] have also shown that the correlation between Laurens' classification and loss of expression of E-cadherin and β-catenin is Insignificant.

In the study by Yong-Ning-Zhou et al.[12], expression of E-cadherin and β-catenin in gastric carcinomas was compared to the clinical pathological features and patient survival. A total of 163 cases of gastric carcinoma were studied, which according to Laurens' classification was divided into 108 cases of intestinal type, 40 cases of diffuse type and 15 cases of mixed type. Aberrant expression of E-cadherin and β-

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catenin were seen in majority of cases belonging to diffuse type of gastric carcinomas and the values were statistically significant and is also in concordance with the present study.

In the study by Yaw Ohene et al.[20], expression of E-cadherin and β-catenin was compared with the macroscopic and histological types of gastric carcinoma. Also, the expression of α and γ-catenins was compared. Of the 41 cases included in the study, 40 showed aberrant expression of at least one of the markers used in the study.

Study by Jolanta et al.[26] though showed increased abnormal expression of E-cadherin and β-catenin in gastric carcinomas, it could not establish a statistical significance between their aberrant expression and histological subtypes. Similarly, in the study by Dorra Ben et al.[21], in spite of higher rate of abnormal expression in diffuse carcinomas, it could not establish a statistical significance between the aberrant expression of E-cadherin and β-catenin and histological subtypes.

In the study by Young-Eun Joo et al.[17], expression of E-cadherin and β-catenin was done 65 cases of gastric carcinomas. The number of cases, median age of the patients and the male to female ratio were comparable and in concordance with the present study.

CONCLUSION

Thus, the present study shows that E-cadherin and β-catenin are implied in the initiation and progression of gastric carcinomas as its expression is lost in advanced stages of the disease and high grade tumors. Diffuse carcinomas are associated with absence of membranous staining of E-cadherin and β-catenin and show absent or cytoplasmic staining for E-cadherin and nuclear and/or cytoplasmic staining for β-catenin. Absence of membranous expression of E-cadherin and β-catenin is associated with invasion, metastasis and thus with poor prognosis.

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