

E-CADHERIN EXPRESSION IN GASTRIC ADENOCARCINOMAChristopher Udayan C¹, Prabhalakshmy K. K², S. Sankar³¹Junior Resident, Department of Pathology, GMC, Kottayam, Kerala.²Associate Professor, Department of Pathology, GMC, Kottayam, Kerala.³Professor and HOD, Department of Pathology, GMC, Kottayam, Kerala.**ABSTRACT****BACKGROUND**

Gastric adenocarcinoma is one of the most common cancers in the world and 2nd most common cause of cancer deaths. It develops due to genetic and environmental factors. Histologically, Lauren's classified Gastric adenocarcinoma is classified into intestinal and diffuse types. Intestinal type can be of well differentiated, moderately differentiated or poorly differentiated. E-cadherin is a protein that helps in cell to cell adhesion.

This study is conducted to find out relation between E-cadherin expression and tumour infiltration and lymph node status.

MATERIALS AND METHODS

A descriptive study was conducted to assess E-cadherin expression in gastric adenocarcinoma specimens received in the Department of Pathology, Govt. Medical College, Kottayam during a period of 15 months (March 2016 - June 2017).

RESULTS

Among 46 cases studied, 40 (80%) cases showed aberrant/ loss of E-cadherin expression. Among these 16 (72%) cases were well differentiated type, 5 (100%) cases were moderately differentiated, 2 (100%) cases were poorly differentiated and 17 (100%) cases were diffuse type. Aberrant/ loss of expression is seen in 29 (87%) cases of lymph node positivity. Aberrant/ loss of expression is seen in 37 (88%) cases of T3/T4 stage.

CONCLUSION

In the study aberrant E-cadherin expression was seen in 74% cases, loss of expression in 13% cases and normal expression in 13% cases. A negative correlation was seen between E-cadherin expression and lymph node status. Level of tumour invasion also had a negative correlation with E-cadherin expression.

KEYWORDS

E-Cadherin, Gastric Cancer, Tumour Differentiation.

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BACKGROUND

Gastric adenocarcinoma is one of the most common cancers in the world and 2nd most common cause of cancer deaths.¹ It develops due to genetic and environmental factors. According to Borrmann's classification, stomach cancers are classified into polypoidal, fungating, ulcerative and infiltrative.² Histologically, Lauren classified gastric adenocarcinoma into intestinal and diffuse types. Intestinal type can be of well differentiated, moderately differentiated or poorly differentiated.³

E-cadherin is a protein that helps in cell to cell adhesion. This 120-kilodalton transmembrane glycoprotein, predominantly localised to the lateral cell border and associated with the contractile cytoskeleton, mediates homotypic adhesion and plays a key role in the organisation and maintenance of tissue structure.⁴ Loss of E-cadherin is associated with metastasis. Thus, blockage or down-regulation of E-cadherin encoding gene (CDH1) can be helpful in providing early detection and better prognosis.

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E-cadherin expression or function is associated with changes in cellular phenotype and with the development of invasive behaviour of tumour cells, effects which can be reversed by transfection of E-cadherin-encoding cDNA.⁵ Evidence that down-regulation of E-cadherin can occur during tumourigenesis has been obtained in carcinogen-induced skin tumours in mice.⁶ Potentially, reversing methylation at E-cadherin in the gastric epithelium in patients with H. pylori infection may halt the process of future development of gastric cancer.⁷ An understanding of how E-cadherin expression is regulated in normal and malignant cells is therefore a critical point in understanding tumour progression of gastric adenocarcinoma.⁸ This study aims in finding relation between loss of E-cadherin and gastric adenocarcinoma.

Objectives of this Study are-

1. To describe the loss/ aberrant expression of E-cadherin in gastric adenocarcinoma.
2. To describe the E-cadherin expression in various histological types of gastric adenocarcinoma.
3. To correlate between E-cadherin expression and lymph node status/ level of invasion.

MATERIALS AND METHODS

This descriptive study included first 46 cases of gastric adenocarcinoma received in Department of Pathology, Govt. Medical College, Kottayam during a period of 15 months from

March 2016 to June 2017. The age, gender and investigation reports were collected from the clinical data sent along with the gastrectomy specimen. Cases that are proved to be gastric adenocarcinoma by histopathology report only was included for the study. Cases with differential diagnosis, small biopsy specimens was excluded. Clinical and pathological details of each cases was recorded as in the proforma.

All specimens were fixed in 10% buffered formalin. Tissue sections were taken from tumour site, processed and tissue embedded in paraffin. Sections were taken from tumour paraffin embedded blocks and stained with H and E for routine examination. IHC was performed using monoclonal mouse anti-human E-cadherin on representative gastric sections and was evaluated. Slides with normal gastric mucosa was used as positive control. Furthermore, positive E-cadherin staining in the adjacent non-involved gastric mucosa also served as an internal positive control. Immunohistochemical results were correlated with lymph node status, presence or absence of distant metastasis, size of tumour, histological type and gross type. Clinical staging for each gastric carcinoma was evaluated according to the TNM staging system indicating the extent of tumour spread. Gross appearance of the tumours was described according to the Borrmann's classification. Histomorphological tissue architecture of the tumour samples, expressed according to the Lauren's classification. E-cadherin staining was examined under a light microscope and classified according to the pattern of staining-

- E-cadherin was considered as normal when the pattern of staining was "strong and membranous."
- E-cadherin expression was considered aberrant when the pattern of staining was "Membranous and Cytoplasmic." This type of staining is also called heterogeneous. "Membranous and Faint" - this is also called homogeneous.

The E-cadherin expression is considered absent when the staining pattern was "absent." The following Statistical Methods were used to arrive at the Conclusion-

1. Ratio and proportion for age, gender, gross type, histological type and size.
2. Chi-square test for correlation of-
 - Lymph node status and E-cadherin expression.
 - Depth of tumour and E-cadherin expression.

For correlation purpose, the loss of E-cadherin expression and aberrant expression were together taken as aberrant. Lymph node status was divided into lymph node positive and lymph node negative. Tumour invasion, T1 and T2 stages were clubbed together and T3 and T4 stages were clubbed together.

RESULTS

The present study was conducted on 46 cases of gastric adenocarcinoma in gastrectomy specimens received in Department of Pathology, Govt. Medical College, Kottayam between March 2016 and June 2017.

Age Distribution of Cases

Among the 46 cases of gastric adenocarcinoma 16 cases (34.8%) belonged to 50 - 59 years' age group, 12 cases (26.1%) to 60 - 69 years, 10 cases (21.7%) to 40 - 49 years and 7 cases (15.2%) to 70 - 79 years, and 1 case (2.2%) to 30 - 39 years.

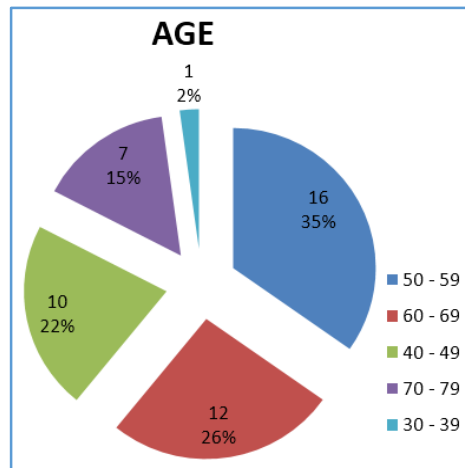


Figure 1. The Proportion of Gastric Adenocarcinoma among various Age Groups

The Distribution of Gross Types of Gastric Adenocarcinoma among various Age Groups

In all age groups, ulcerative type was predominant except in 30 - 39 age group were only one case present which was early gastric carcinoma.

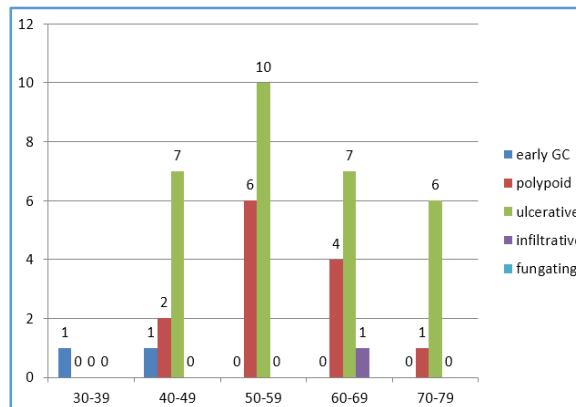


Figure 2. Distribution of Gross Types among various Age Groups

The Distribution of Histological Variants of Gastric Adenocarcinoma among various Age Groups

In the age groups 40 - 49 and 50 - 59, well differentiated adenocarcinoma predominates all other age group shows predominance of diffuse type.

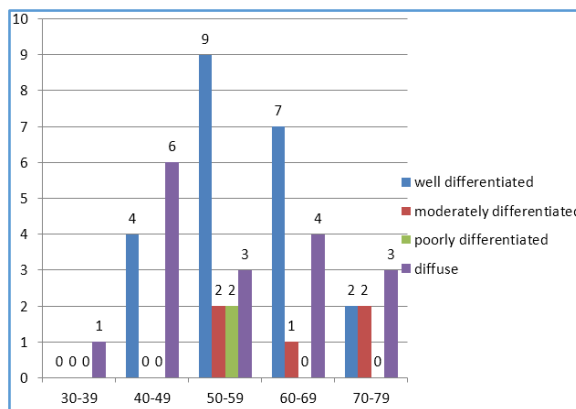


Figure 3. Distribution of Histological Types among various Age Groups

Gender Distribution of Gastric Adenocarcinoma Cases

Among 46 cases studied, 37 cases (80%) were males and 9 cases (20%) were females.

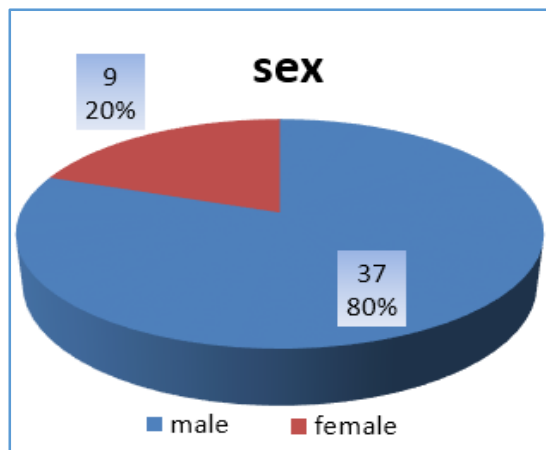


Figure 4. Gender Distribution of Cases

The Distribution of Gross Types of Gastric Adenocarcinoma among Males and Females

Among 46 cases studied, ulcerative type was predominant in both males and females.

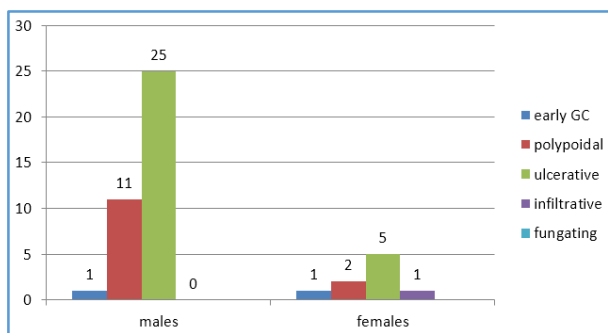


Figure 5. The Distribution of Gross Types of Gastric Adenocarcinoma among Males and Females

The Distribution of Histological Variants of Gastric Adenocarcinoma among Males and Females

In males, well-differentiated adenocarcinoma was predominant and in females diffuse type was predominant.

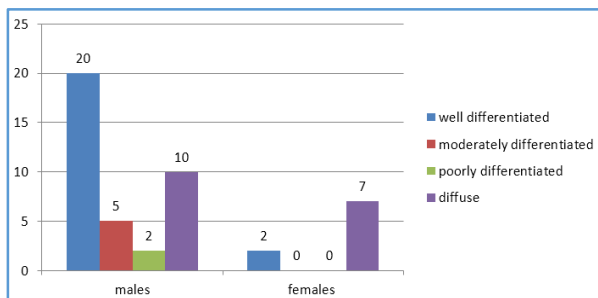


Figure 6. The Distribution of Histological Variants of Gastric Adenocarcinoma among Males and Females

Gross

Among the 46 cases collected 30 (67%) cases were ulcerative type, 13 (30%) cases were polypoidal type and 1 (2.2) case was infiltrative type and 2 (5%) cases were early gastric carcinoma.

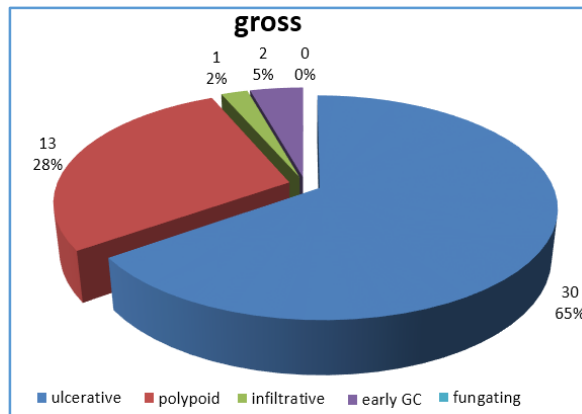


Figure 7. Distribution of Cases based on Gross Type

Distribution of Study Sample Based on Size

In the present study, 27 (59%) cases were less than 6 cm and 19 (41%) cases were greater than 6 cm.

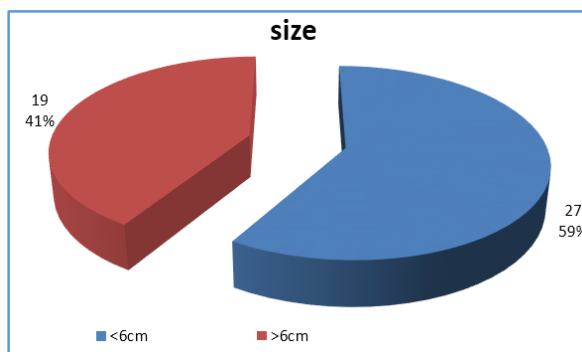


Figure 8. Distribution of Study Sample based on Size

Microscopy

Among 46 cases studied 29 (63%) were intestinal type adenocarcinoma, of these 22 (47.8%) were well differentiated adenocarcinoma, 5 (10.9%) cases were moderately differentiated and 2 cases were poorly differentiated. 17 (37%) were diffuse type.

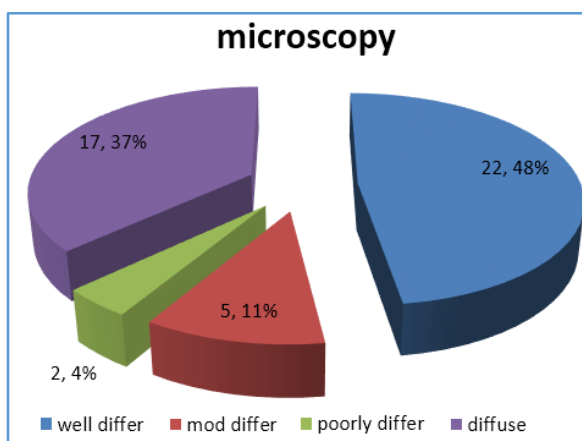


Figure 9. Distribution of Cases based on Microscopic Types

Involvement of Tumour

Among 46 cases studied, 22 (47.8%) cases have involvement upto adjacent perigastric tissue, 20 (43.5%) cases have involvement upto serosa, 2 (4.4%) cases each for submucosa and muscularis propria involvement.

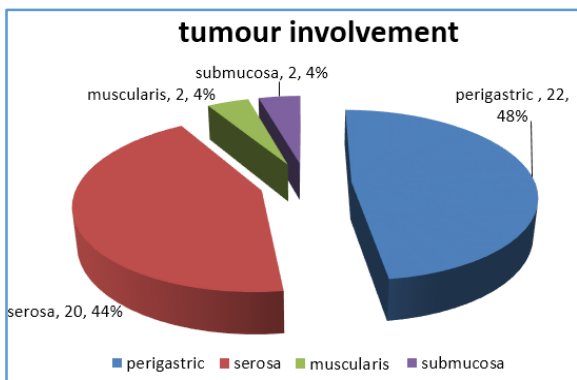


Figure 10. Distribution of Cases based on Depth of Tumour Involvement

Lymph Node Status

Among 46 cases studied 23 (50%) cases had lymph nodes between 1 - 6 nodes, 8 (17.4%) cases have lymph nodes between 7 - 15 and 2 (4.3%) cases have more than 15 nodes and 13 (28.3%) cases were node negative.

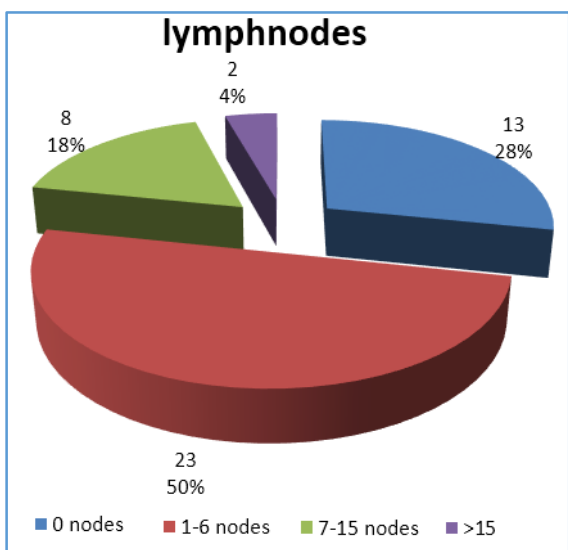


Figure 11. Distribution of Cases based on Lymph Node Status

Metastasis

Among 46 cases studied, only one case (2%) had metastasis.

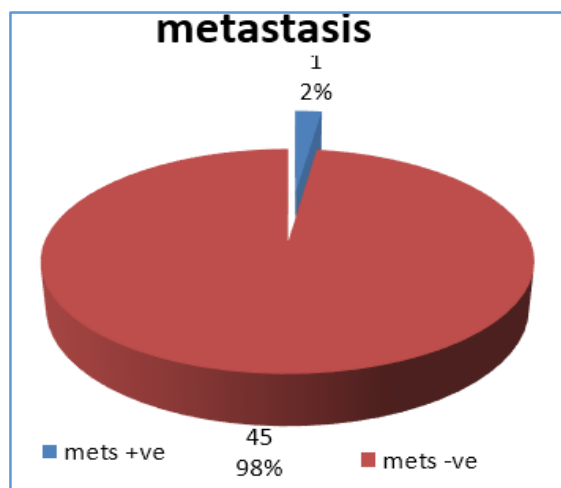


Figure 12. Distribution of Cases based on Metastasis

Stage of Tumour

Among 46 cases studied 21 (45.7%) cases were stage 4, 13 (28.3%) cases were stage 3a, 6 (13%) cases were stage 2 and there were 2 (4.4%) cases of stage 1a, 1b and 3b each.

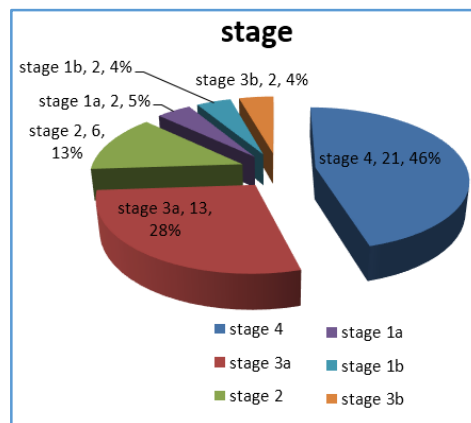


Figure 13. Distribution of Cases based on Stage of Tumour

IHC

Among 46 cases studied 34 (73.9%) cases showed aberrant expression, 6 (13%) cases showed absent expression and 6 (13%) cases showed normal expression.

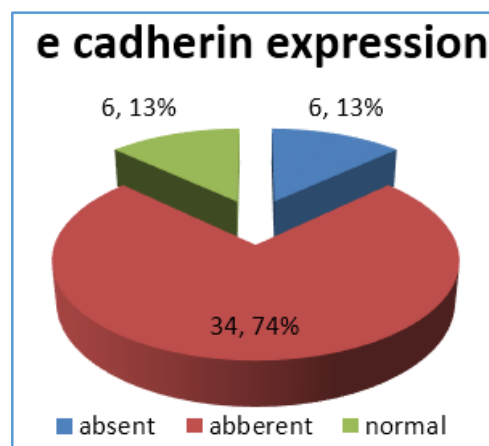


Figure 14. Distribution of Cases based on E-cadherin Expression

E-cadherin Expression among Gross Types of Gastric Adenocarcinoma

Aberrant expression was commonly seen in all gross type.

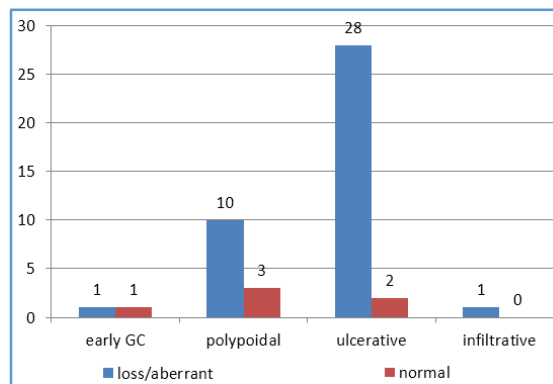


Table 15. Distribution of Study Sample based on Gross and IHC

E-cadherin Expression Distribution based on Size

Aberrant expression was predominantly seen in all groups.

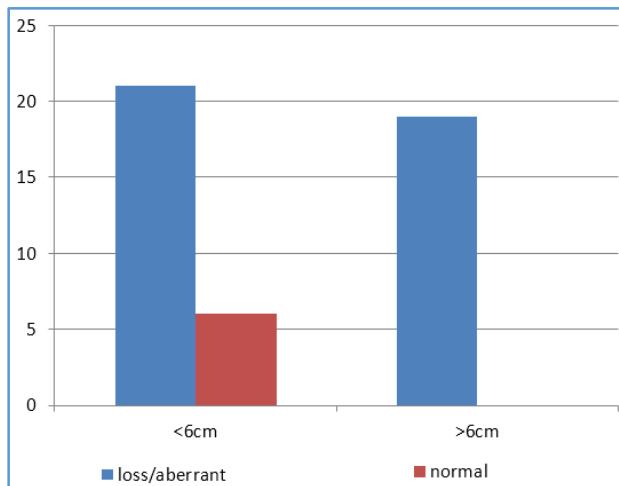


Table 16. Distribution of Study Sample based on Size and IHC Chi-Square: 4.85, P value= 0.028 (Significant)

	Loss/Aberrant Expression	Normal
< 6 cm	21 (45%)	6 (13%)
> 6 cm	19 (41%)	0

Table 1. Comparison of E-cadherin Expression with Tumour Size

E-cadherin Expression among Histologic Types of Gastric Adenocarcinoma

Aberrant expression was commonly seen in all histologic type of gastric carcinoma.

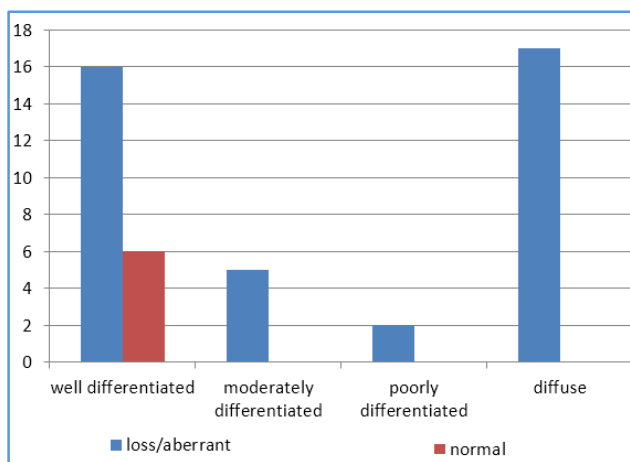


Figure 17. Distribution of Study Sample based on Microscopic Features and IHC

	Loss/ Aberrant Expression	Normal Expression
Well differentiated	16 (34%)	6 (13%)
Moderately differentiated	5 (11%)	0
Poorly differentiated	2 (4%)	0
Diffuse	17 (17%)	0

Table 2. Comparison of E-cadherin Expression with Histological Type

E-cadherin Expressions Based on Depth of Tumour Invasion of Gastric Adenocarcinoma

Aberrant expression was seen commonly in all groups.

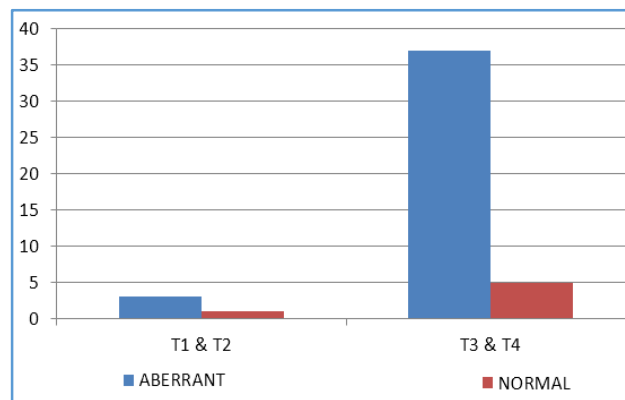


Figure 18. Distribution of Study Sample based on Depth and IHC

	Aberrant/ Loss	Normal
T1 and T2	3 (6.5%)	1 (2.3%)
T3 and T4	37 (80%)	5 (10.8%)

Table 3. Comparison of E-cadherin Expression with Depth of Tumour

Chi-square value- 0.552, P value- 0.457 (Not Significant).

Relation between Lymph Node Status and E-Cadherin Expression

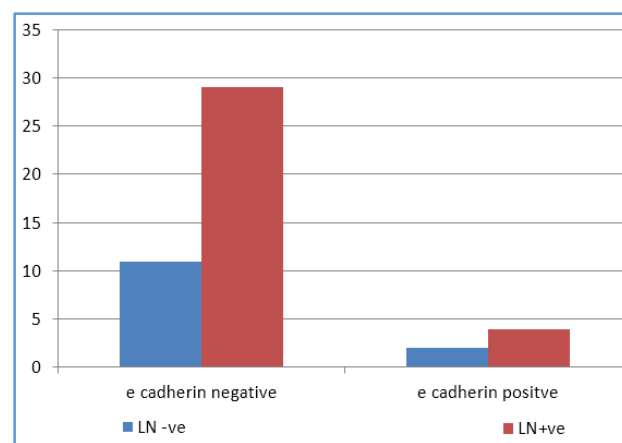


Figure 19. Distribution of Study Sample based on Lymph Node Status and IHC

Chi-square- 0.088, P value= .767 (Not Significant).

	Lymph Node Negative	Lymph Node Positive
E-cadherin Negative	11 (23%)	29 (63%)
E-cadherin Positive	2 (4.4%)	4 (8.6%)

Table 4. Comparison of E-cadherin Expression with Lymph Node Status

E-cadherin Expression with Distant Metastasis

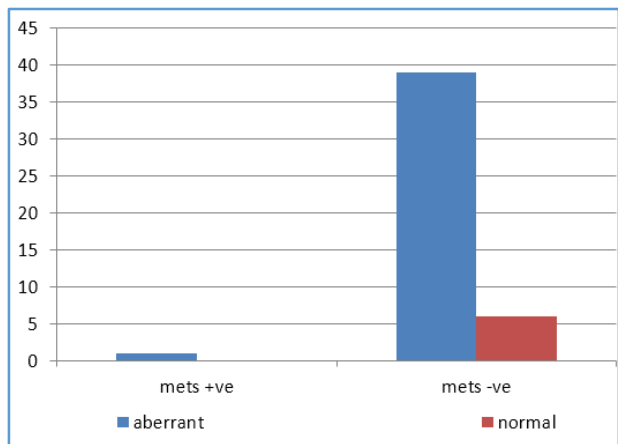


Figure 20. Distribution of Study Sample based on Mets and IHC



Figure 23. Gross Picture of Polypoidal type of Gastric Adenocarcinoma

	Aberrant/ Loss	Normal
Mets Negative	39 (84.7%)	6 (13%)
Mets Positive	1 (2.3%)	0
Total	40	6

Table 5. Comparison of E-cadherin Expression with Distant Metastasis

Microscopy Photographs

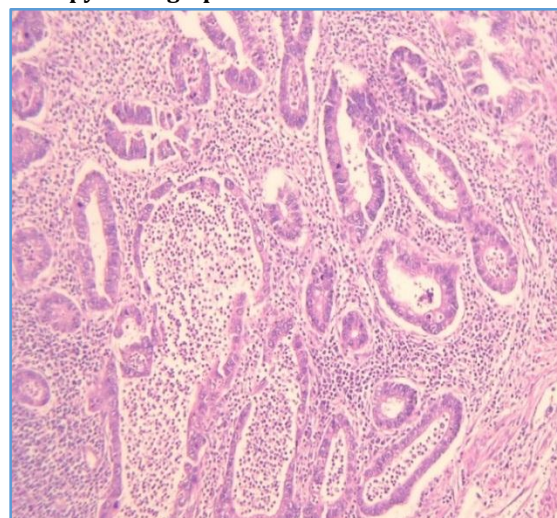


Figure 24. Photomicrograph showing Well Differentiated Gastric Adenocarcinoma (H and E, 10x)

Gross Photographs



Figure 21. Gross Picture of Ulcerative Type of Gastric Adenocarcinoma



Figure 22. Gross Picture of Infiltrative Type of Gastric Adenocarcinoma

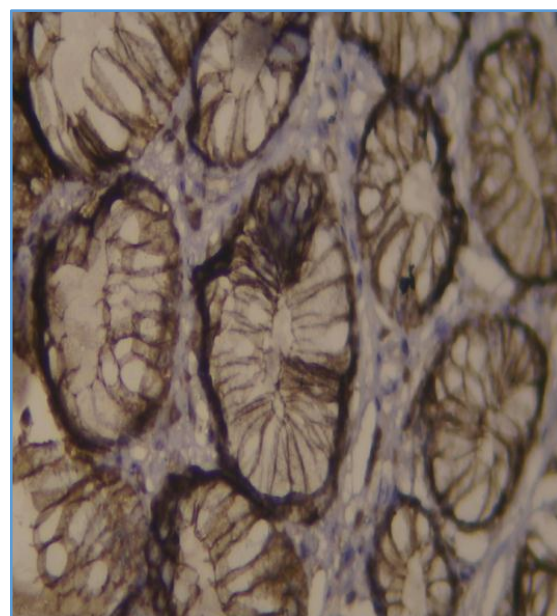


Figure 25. Photomicrograph showing Normal Expression (Strong Membrane Staining) of E-cadherin (10x)

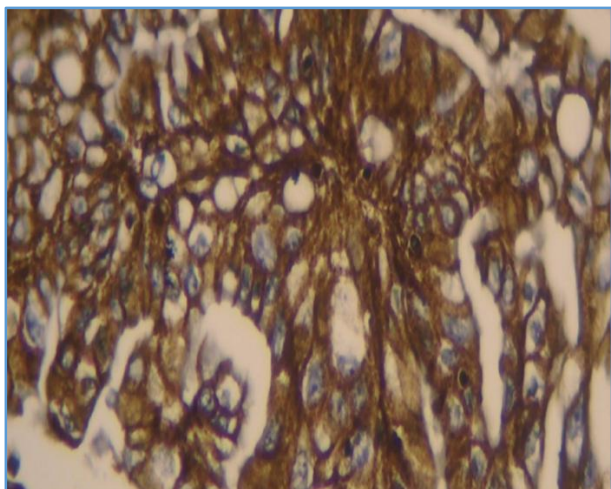


Figure 26. Photomicrograph showing Aberrant Expression (Membrane and Cytoplasmic) of E-cadherin (40x)

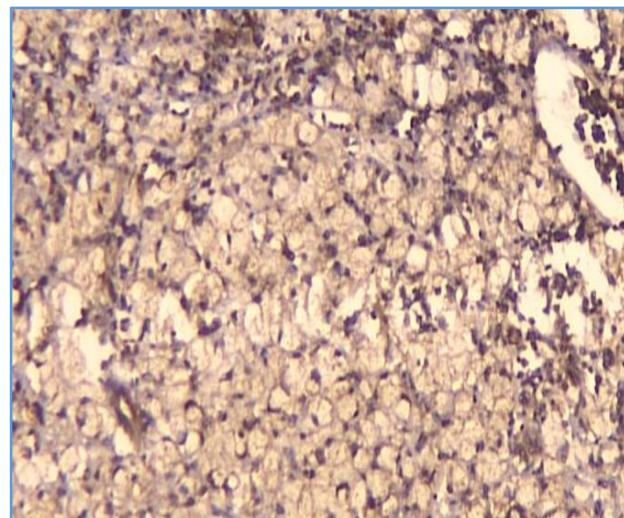


Figure 29. Photomicrograph showing Aberrant (Membrane and Cytoplasmic) Expression of E-cadherin (40x) in Diffuse Type

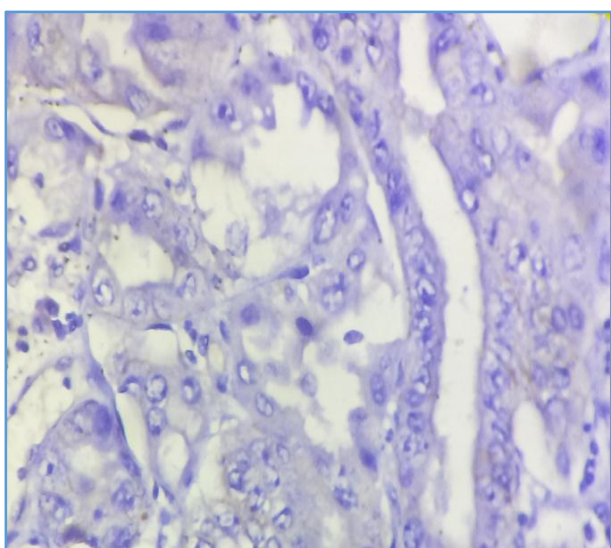


Figure 27. Photomicrograph of Loss of E-cadherin Expression in Gastric Adenocarcinoma (40x)

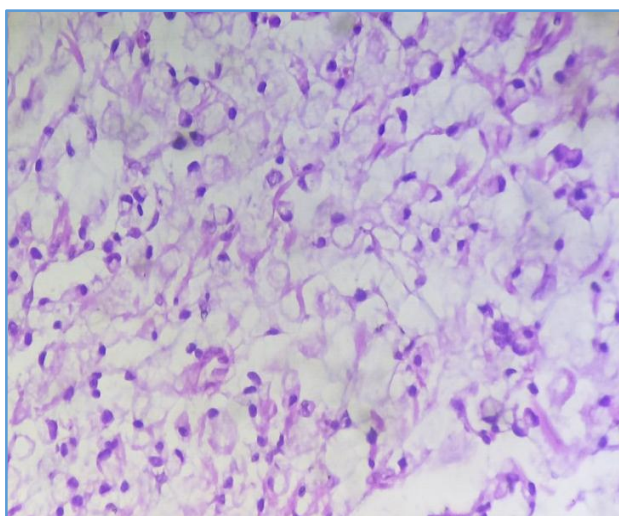


Figure 28. Photomicrograph of Diffuse Type of Gastric Adenocarcinoma (H and E, 40x)

DISCUSSION

The present study was conducted on 46 cases of gastric adenocarcinoma specimens received in Department of Pathology, Govt. Medical College, Kottayam between March 2016 and July 2017. In the present study, the age group was ranging from 39 years to 78 years and the mean age was 56.3 years. In study conducted by Ze-yu et al, the age group was ranging from 26 years to 82 years and the mean age was 56.8 years.⁹ Male-to-female ratio was 4: 1 in the present study and in study conducted by Ze-yu wu et al, the male: female ratio was 1.5: 1. In study conducted by Yong Ning Zhou et al, the age group was ranging from 28 years to 77 years and the mean age was 54.5 years.² Male: female ratio in the study was 3.08: 1. In study conducted by Ramesh et al¹⁰ at Department of Pathology and Surgery, Liverpool University, UK the mean age was 68 years and age range was 57 years to 87 years. Male: female ratio was 3.5: 1. In study of 95 cases conducted by Robab Anbiaee et al, mean age was 62 years with range 19 to 85 years.¹¹ Male-to-female ratio is 2.5: 1.

In the present study among 46 cases 27 cases were having size less than 6 cms, 19 cases were having size greater than 6 cms. All the 19 cases greater than 6 cm showed aberrant/ loss of expression. There was a positive correlation between the tumour size and aberrant/ loss of expression (p value- 0.028). In the study of Robab Anbiaee et al, 46 cases were less than 5 cm and of that 18 showed abnormal E-cadherin expression. 48 cases were more than 5 cm and 33 showed loss of E-cadherin expression. In study conducted by Ze-yu wu et al, 17 cases were below 5 cm and 13 cases were above 5 cm. 7 cases from each group showed loss of E-cadherin expression.

Out of the 46 cases of gastric adenocarcinoma studied 29 (63%) intestinal type, of that 22 (48%) were well differentiated, 5 (11%) were moderately differentiated and 2 (4%) were poorly differentiated type. In the present study, 17 (37%) were diffuse type. Sandhyasundaram et al studied 20 cases of gastric adenocarcinoma at SRM College, Chennai where 10 (50%) cases were intestinal type, in that 2 (10%) cases were well differentiated, 4 (20%) cases were moderately differentiated and 4 (20%) cases were poorly differentiated and 10 (50%) cases were diffuse type.³

Meyer et al studied 60 cases of gastric adenocarcinoma in University of Munich, 30 (50%) cases were intestinal type and 21 (35%) were diffuse type.⁴ Ze-yu wu et al studied 30 cases, of which 11 cases were intestinal type and 19 cases diffuse type. Ramesh et al studied 28 (70%) cases of intestinal type and 12 (30%) cases of diffuse type. Of the 28 cases of intestinal type 1 (2.5%) was well differentiated, 19 (47.5%) were moderately differentiated and 8 (20%) cases were poorly differentiated. In study conducted by Robab Anbiaee et al 39 (41%) cases were and 48 (59%) cases were diffuse type.

	Intestinal Type	Diffuse Type
Present study	29 (63%)	17 (37%)
Sandhyasundaram et al	10 (50%)	10 (50%)
Meyer et al	30 (50%)	21 (35%)
Ze-yu wu et al	11 (36%)	19 (64%)
Ramesh et al	28 (70%)	12 (30%)
Robabanbiaee et al	39 (41%)	48 (59%)

Table 6. Comparison of Histological variants of Gastric Adenocarcinoma Studied with other Studies

In all the studies including present study, intestinal type of adenocarcinoma was predominant type except in study by Ze-yu wu et al where 64% cases was diffuse.

In the present study, all of the diffuse type showed aberrant E-cadherin expression. This is in agreement with the study by Sandhyasundaram et al. Only 6 out of 29 cases in intestinal type showed normal E-cadherin expression. In study conducted by Robab Anbiaee et al, 20 out of 48 diffuse type showed aberrant E-cadherin expression. 9 out of 39 intestinal type showed aberrant expression. In study done by Ze-yu wu et al, 2 out of 11 intestinal type showed aberrant expression and 12 out of 17 diffuse type showed aberrant E-cadherin expression. In study by Sandhyasundaram et al 10 out of 10 diffuse type cases showed absent E-cadherin expression. 10 out of 10 intestinal type also showed aberrant expression.

	Intestinal Type		Diffuse Type	
	Aberrant	Normal	Aberrant	Normal
Present study	23	6	17	0
Robabanbiaee et al	9	30	20	18
Ze-yu wu et al	9	2	12	7
Sandhyasundaram et al	10	0	10	0

Table 7. Comparison of E-cadherin Expression and Histological Types with various Other Studies

In our present study 13 (28.3%) cases were node negative, 23 (50%) cases were in pN1 stage, 8 (17.4%) cases were pN2 stage and 2 (4.3%) cases were pN3 stage. Sandhyasundaram et al studied 20 cases of which 5 (25%) cases were node negative, 5 (25%) cases were in pN1 stage, 10 (40%) cases were pN2 stage and 4 (10%) cases pN3 stage.

In our study out of 13 node negative cases 11 cases showed aberrant staining, 2 cases showed normal membrane staining and no cases had absent staining. 6 out of 33 showed absent staining in node positive cases and 23 out of 33 showed aberrant staining. 4 out of 33 showed normal staining. This is not statistically significant. Study by Sandhyasundaram et al had 5 nodes negative cases, of which 3 showed absent staining and 6 out 15 showed absent staining in node positive cases.

	Lymph Node Positive		Lymph Node Negative Case	
	Aberrant/Loss	Normal	Aberrant/Loss	Normal
Present study	29	4	11	2
Sandhya-Sundaram et al	15	0	5	0
Ze-yu wu et al	12	6	2	10
Yonemura et al	47	14	19	12
Ramesh et al	26	5	4	5

Table 8. Comparison of E-cadherin Expression with Lymph Node Status in various Studies

Our study is in agreement with the studies of Ze-yu wu et al, Yonemura et al¹² and Ramesh et al.

Study by Sandhyasundaram et al showed total loss of expression in lymph node positive cases.

In our study 22 cases out of 46 were in T4 stage, 20 cases in T3 stage, 2 cases each were in T1 and T2 stages. 37 cases out of 41 cases in T3 and T4 stage showed aberrant staining and 3 out of 4 cases in T1 and T2 stage showed aberrant staining. There was no correlation between E-cadherin expression and depth of tumour invasion (p value- 0.457).

In study done by Sandhyasundaram et al, 15 cases were in T3 and T4 stage and 5 cases were in T1 and T2 stage. All cases showed aberrant staining. In study conducted by Robabanbiaee et al, 34 out of 52 cases in T3 and T4 stage showed aberrant staining.

Our study is in agreement with the study by Robab Anbiaee et al.

	T1 and T2		T3 and T4	
	Aberrant	Normal	Aberrant	Normal
Present study	3	1	37	5
Sandhyasundaram et al	5	0	15	0
Robabanbiaee et al	28	15	34	18

Table 9. Comparison of E-cadherin Expression with Tumour Depth in various Studies

Limitation of this Study

Small sample size and short duration of the study are the limitations. Multivariate analysis with a larger sample size and long-term follow-up of the cases only can assess the utility of E-cadherin expression loss in predicting the outcome of the disease.

CONCLUSION

The present study was done on 46 cases of gastric adenocarcinoma. Aberrant E-cadherin expression was seen in 74% cases, loss of expression in 13% cases and normal expression in 13% cases.

Among 29 cases of intestinal type aberrant/ loss of expression is seen in 72.7% of well differentiated type, 100% cases of moderately differentiated and 100% cases of poorly differentiated type. Normal expression was seen in 27.3% cases of well differentiated type. 100% cases of diffuse type also showed aberrant/ loss of expression.

In this study, a negative correlation was seen between E-cadherin expression and lymph node status. Level of tumour invasion also had a negative correlation with E-cadherin expression.

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