E-CADHERIN EXPRESSION IN GASTRIC ADENOCARCINOMA

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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.


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 membrane.”
- 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 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 40 - 49 years and 7 cases (15.2%) to 70 - 79 years, and 1 case (2.2%) to 30 - 39 years.

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.

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.
Gender Distribution of Gastric Adenocarcinoma Cases
Among 46 cases studied, 37 cases (80%) were males and 9 cases (20%) were females.

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.

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.

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

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.

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.

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.
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.

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

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.

E-cadherin Expression among Gross Types of Gastric Adenocarcinoma
Aberrent expression was commonly seen in all gross type.
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)

<table>
<thead>
<tr>
<th>Size</th>
<th>Loss/Aberrant Expression</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 cm</td>
<td>21 (45%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>&gt; 6 cm</td>
<td>19 (41%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Loss/Aberrant Expression</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>16 (34%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>5 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse</td>
<td>17 (17%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Depth of Tumour</th>
<th>Aberrant/ Loss</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 and T2</td>
<td>3 (6.5%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>T3 and T4</td>
<td>37 (80%)</td>
<td>5 (10.8%)</td>
</tr>
</tbody>
</table>

Relation between Lymph Node Status and E-Cadherin Expression

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

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

<table>
<thead>
<tr>
<th>Lymph Node Status</th>
<th>E-cadherin Negative</th>
<th>E-cadherin Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph Node Negative</td>
<td>11 (23%)</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>Lymph Node Positive</td>
<td>2 (4.4%)</td>
<td>4 (8.6%)</td>
</tr>
</tbody>
</table>

Chi-square- 0.088, P value = .767 (Not Significant).
E-cadherin Expression with Distant Metastasis

<table>
<thead>
<tr>
<th></th>
<th>Aberrant/Loss</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mets Negative</td>
<td>39 (84.7%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Mets Positive</td>
<td>1 (2.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>40</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

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

Gross Photographs

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

**Figure 21. Gross Picture of Ulcerative Type of Gastric Adenocarcinoma**

**Figure 22. Gross Picture of Infiltrative Type of Gastric Adenocarcinoma**

**Figure 23. Gross Picture of Polypoidal type of Gastric Adenocarcinoma**

Microscopy Photographs

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

**Figure 25. Photomicrograph showing Normal Expression (Strong Membrane Staining) of E-cadherin (10x)**
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. 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. Male: female ratio in the study was 3.08:1. In study conducted by Ramesh et al 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.

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. Sandhya Sundaram 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.
In our 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. Sandhya sundaram 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 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 Sandhya sundaram et al had 5 nodes negative cases, of which 3 showed absent staining and 6 out 15 showed absent staining in node positive cases.

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

<table>
<thead>
<tr>
<th>Intestinal Type</th>
<th>Diffuse Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberrant/ Normal</td>
<td>Aberrant/ Normal</td>
</tr>
<tr>
<td>Present study</td>
<td>23 6 17 0</td>
</tr>
<tr>
<td>Robabanbiaee et al</td>
<td>9 30 20 18</td>
</tr>
<tr>
<td>Ze-yy wu et al</td>
<td>9 2 12 7</td>
</tr>
<tr>
<td>Sandhya sundaram et al</td>
<td>10 0 10 0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Lymph Node Status</th>
<th>Aberrant/ Loss</th>
<th>Normal</th>
<th>Aberrant/ Loss</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>29 4</td>
<td>11 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandyha sundaram et al</td>
<td>15 0</td>
<td>5 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ze-yy wu et al</td>
<td>12 6</td>
<td>2 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yonemura et al</td>
<td>47 14</td>
<td>19 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramesh et al</td>
<td>26 5</td>
<td>4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>T1 and T2</th>
<th>T3 and T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberrant/ Normal</td>
<td>Aberrant/ Normal</td>
</tr>
<tr>
<td>Present study</td>
<td>3 1 37 5</td>
</tr>
<tr>
<td>Sandyha sundaram et al</td>
<td>5 0 15 0</td>
</tr>
<tr>
<td>Robabanbiaee et al</td>
<td>28 15 34 18</td>
</tr>
</tbody>
</table>

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.
REFERENCES


