

## Evaluation of e-cadherin expression in gastric cancer as a prognostic marker

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### Abstract

**Introduction:** Carcinoma of stomach is a common malignancy and globally stands at fourth position frequency-wise. E-cadherin, is a major cell adhesion molecule, the loss of which gives rise to invasive and metastatic properties to the cancer cells.

**Aim of the Study:** To study the E-cadherin expression in gastric carcinomas by immuno-histochemistry and to correlate its pattern of staining with tumor differentiation, invasion, histological variants, and lymph node status.

**Materials and Methods:** A two year prospective study was done from September 2011 to August 2013 at Kakatiya Medical College and MGM Hospital, Warangal. The resected specimens of stomach and endoscopic biopsy specimens taken from carcinoma stomach in this study period were considered. Routine histopathology and immunohistochemistry for E-cadherin were done on the sections.

**Results:** 60 cases were studied of which 26 were gastric biopsies and 34 were gastrectomy specimens. The patient age ranged from 41-72 years and the male to female ratio was 1.6:1. There were 70% and 30% cases that showed intestinal type and diffuse type morphology respectively. Preserved E-cadherin was mainly seen in intestinal type tumors 14/42 (33.33%) with grade 3 staining, while majority of diffuse adenocarcinomas 8/18 (44.44%) were negative for E-cadherin staining. Higher stage tumors and poorly differentiated adenocarcinomas showed reduced E-cadherin staining. Cases with positive lymph nodes 22/29(75.86%) had diminished / absent E-cadherin staining.

**Conclusion:** Normal gastric mucosa on IHC shows strong membranous E-cadherin positivity. There is a gradual decrease in intensity and percentage, and the pattern changes towards cytoplasmic staining in gastric carcinomas.

**Keywords:** Gastric carcinoma, E-Cadherin expression, Prognostic markers, Immunohistochemistry.

### Introduction

Gastric cancer is a common malignancy. It is at fourth position incidence-wise and holds second place for deaths due to cancer. The disease usually has a poor prognosis and Western literature reports 30% five year survival rates.<sup>1,2</sup>

Based on Lauren's system, the cancers of stomach have been divided histologically into intestinal and diffuse type tumors. The AJCC (American Joint Committee on Cancer) accepts this classification system as it offers correlation between histomorphological types and epidemiological data.<sup>3,4</sup>

Carcinoma of the stomach is attributable to genetic factors in the patient, his environmental factors, patient susceptibility to environmental factors and the interaction between the two. Also *Helicobacter pylori* infection has come out as a high risk factor for gastric carcinomas.<sup>5</sup>

Infection with *Helicobacter pylori* causes complete or partial loss of E-cadherin and is thought to be associated with early events in stomach cancer.<sup>6,7</sup>

E-cadherin which is an important cell adhesion molecule is a glycoprotein situated in the cell membranes and is regarded as a tumor suppressor gene. It is thought to have a role in suppression of invasion by gastric carcinoma.<sup>8,9</sup>

Many different cancers including gastric cancers have aberrant E-cadherin expression. As the E-cadherin expression reduces, the tumor cell cohesiveness also reduces, thereby favouring metastasis.<sup>10-12</sup>

As per recent studies, E-cadherin in carcinogenesis has a role in invasion and metastasis. It is involved in modulation of intracellular signalling, and thus promotes tumor growth. Some of the cases with familial gastric carcinomas have demonstrated mutations of E-cadherin gene. This indicates towards role of E-cadherin in earlier stages of tumor development and also its role as a tumor suppressor gene.<sup>13,14</sup>

Altered E-cadherin expression due to genetic mutations is commonly seen in diffuse type gastric carcinomas and emphasizes the significance of E-cadherin in early diffuse type tumors.<sup>15,16</sup>

The loss of CDH1 gene that is responsible for E-cadherin expression is seen often in diffuse-type gastric cancers many of which are hereditary.<sup>17-19</sup>

### Aims and Objectives

1. To study the expression of E-cadherin in gastric adenocarcinomas by immuno-histochemistry.
2. To correlate the staining pattern of E-cadherin with tumor differentiation, invasion, histological types, and lymph node status.

### Materials and Methods

No ethical issues were involved in the study. This was a prospective study done for duration of two years from September 2011 to August 2013 in department of Pathology at Kakatiya Medical College and MGM Hospital, Warangal, Telangana.

Gastrectomy specimens and endoscopic gastric biopsies done in cases of gastric cancers submitted to the department of Pathology were considered.

**Inclusion Criteria**

1. Tissue with light microscopic diagnosis of definite adenocarcinomas were included.

**Exclusion Criteria**

1. Congenital lesions and gastritis cases were excluded.
2. Biopsy specimens from which representative archival tissue could not be recovered were excluded.
3. Non-representative samples were excluded.

**Specimen Handling**

The tissue specimens were fixed in 10% neutral buffered formalin and were submitted for routine histopathological processing. Basic demographic details of each case were noted including the surgical biopsy number, age of the patient, clinical presentation, nature of specimen and the type of adenocarcinoma.

Tissue sections were made from the paraffin block. A 4-5 micron thick section was stained with routine hematoxylin and eosin stains.

Next, for the IHC study, two sections of 3-5-micron thickness were taken on poly-L-lysine coated slides that were subjected to E-cadherin IHC staining.

E-cadherin immunostaining with monoclonal mouse anti-human e-cadherin clone NCH-38 (DAKO) was used.

The slides were examined and the interpretation was recorded for each case.

**Interpretation**

A positive reaction was taken as crisp golden brown membranous and cytoplasmic staining. Intensity of staining was graded as Jawhari scores:

**Abnormal**

- Score 0: faint or absent staining.
- Score 1: reduced cytoplasmic staining.
- Score 2: membranous and cytoplasmic staining. (Heterogenous)

**Normal**

- Score 3: strong membranous staining.
- Statistical analysis of the data was performed using t-test. P-value of <0.05 was taken as statistically significant.

**Results and Observations**

We evaluated 60 cases which had 26 gastric biopsies and 34 gastrectomy specimens. The patient age ranged from 41-72 years and the male to female ratio was 1.6:1. There were 37 (61.66%) males and 23 (38.33%) female patients.

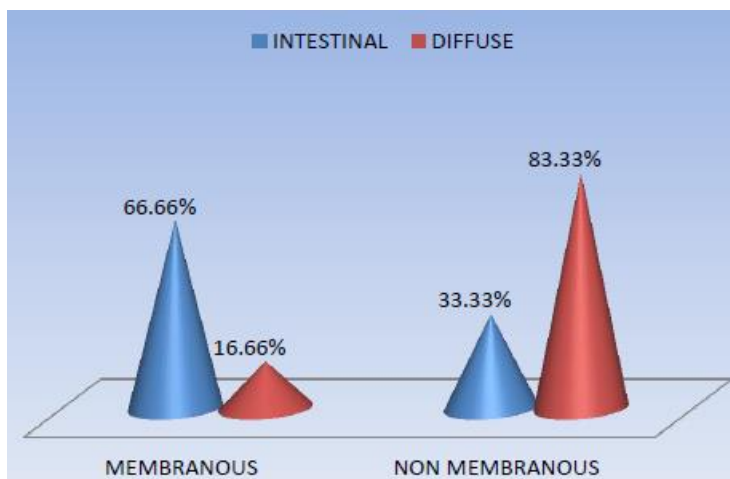
**Age distribution:** Out of 60 cases majority of the cases 24 (40%) were seen between 50 – 59 years and least number of cases 02(3.33%) were seen in >70 years of age.

**Table 1: E-cadherin expression (by score) in gastric cancer according to histological types**

E cadherin score	Intestinal	Diffuse	P value <0.05
3	14(33.33%)	0	
2	14(33.33%)	3(16.66%)	
1	10(23.8%)	7(38.88%)	
0	4(9.52%)	8(44.44%)	
Total	42(100%)	18(100%)	

Tumors were subtypes based on Lauren’s classification. Out of 60 gastric carcinoma cases, 42 (70%) showed intestinal type morphology and 18 (30%) showed diffuse type morphology of adenocarcinomas. Most of the intestinal

type tumors 14/42 (33.33%) showed grade 3 E-cadherin positivity, while majority of diffuse adenocarcinomas 8/18 (44.44%) were negative for E-cadherin staining.



**Fig. 1: E-cadherin expression (membranous versus non-membranous) in gastric cancer according to histological types**

Out of total 42 intestinal type adenocarcinomas, membranous staining ie, grade 3 and grade 2 positivity was seen in 28 (66.6%) cases and 14 (33.3%) cases showed non-

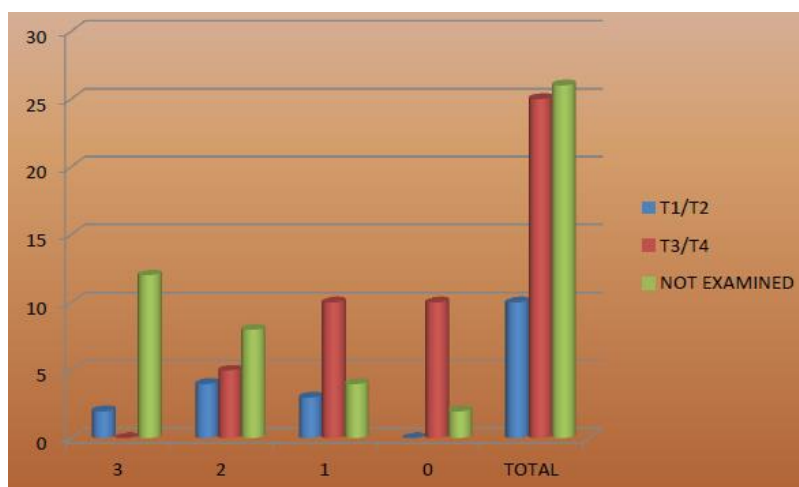
membranous or absent staining. Out of 18 cases of diffuse type adenocarcinomas, 15/18 (83.33%) showed grade 1 and grade 0 staining. The p value was <0.05.

**Table 2: E-cadherin expression according to tumor differentiation**

Score	Well differentiated	Moderately differentiated	Poorly differentiated	P value<0.05
3	13(48.14%)	1(10%)	0	
2	8 (29.62%)	5(50%)	4(17.39%)	
1	5 (18.51%)	4(40%)	8(34.78%)	
0	1 (3.70%)	0	11(47.82%)	
Total	27	10	23	

The well and moderately differentiated carcinomas showed good E cadherin positivity. Whereas, the poorly

differentiated tumors 11/23 (47.82%) did not show any E cadherin positivity.

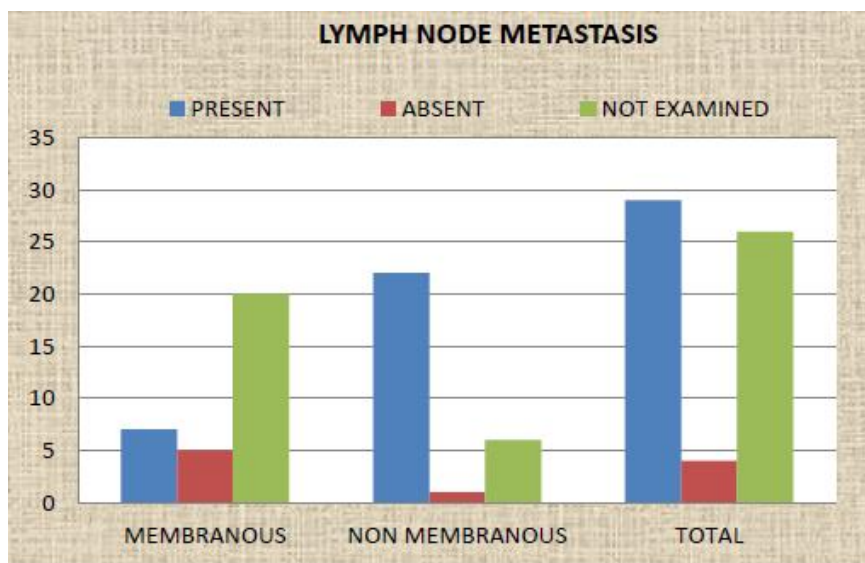


**Fig. 2: E-cadherin expression according to tumor stage**

There were 9 cases in T1/T2 group and 25 cases in T3/T4 group. For 26 cases staging could not be done as these were endoscopic biopsy tissue bits. In the T1/T2 group, the E-cadherin score of 3, 2, 1 and 0 were seen in 2(22.22%), 4(44.44%), 3(33.33%) and 0 cases respectively. In the T2/T3 group, the E-cadherin score of 3, 2, 1 and 0 were seen in 0, 5(20%), 10(40%) and 10(40%) cases respectively. In the tumor stage not examined group, the E-cadherin score of 3, 2, 1 and 0 were seen in 12(46.15%), 8(30.76%), 4(15.38%) and 2(7.69%) cases respectively. The p value was <0.05.

Most of the T3 and T4 stage tumors 10/25 (40%) did not show E-cadherin expression. However, for 26 cases tumor staging could not be done.

**Tumor histological grade and stage:** Of the 9 cases in T1/T2 group, there were 5 cases of moderately differentiated and 4 cases of well differentiated carcinomas. Poorly differentiated carcinoma was not seen in the T1/T2 stage. In the T3/T4 group, there were 25 cases of which 22 showed poorly differentiated morphology, 2 cases had moderate and only 1 case showed well-differentiated morphology.

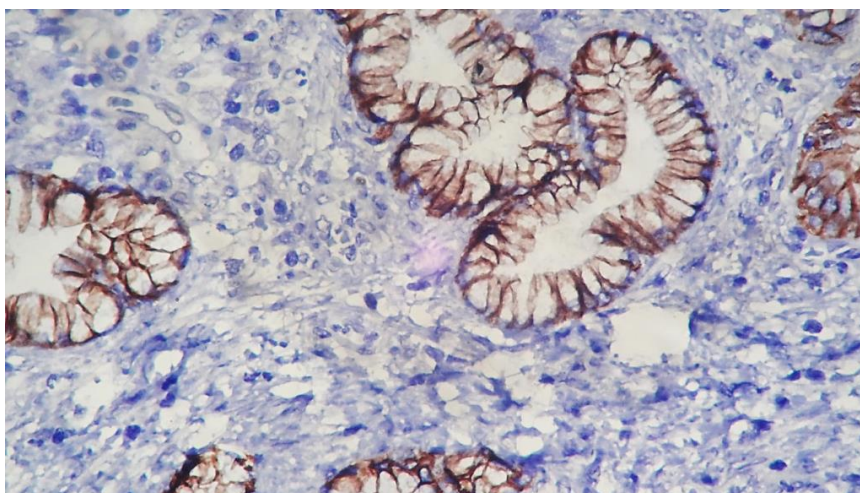


**Fig. 3: E-cadherin expression in gastric cancer with lymph node metastasis**

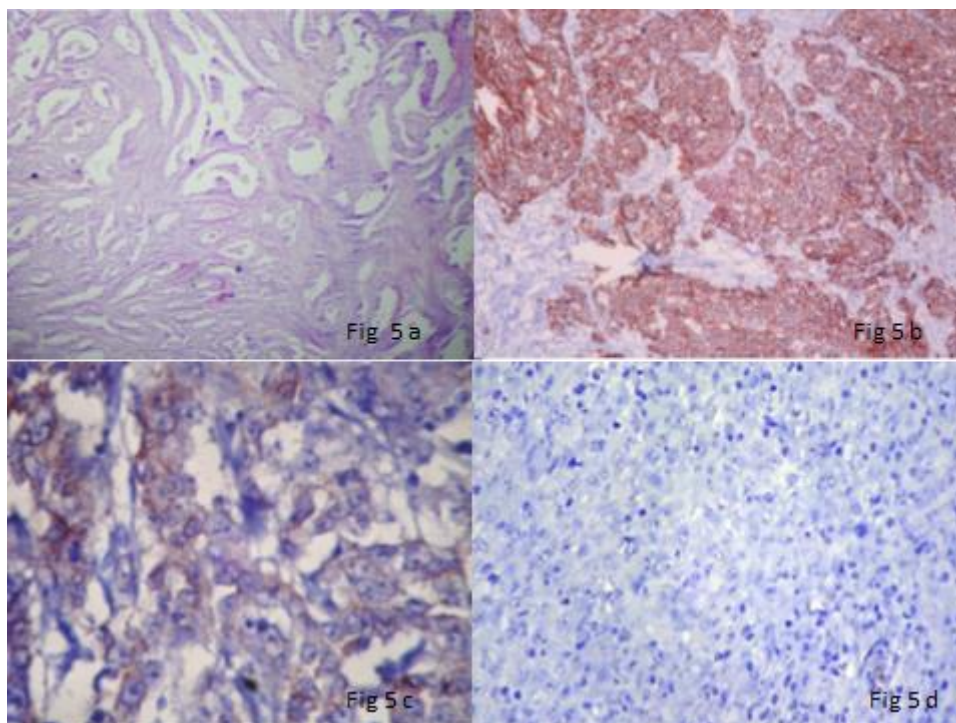
In our study, 29/60 cases showed positive metastatic deposits in the lymph node, whereas, 5 cases showed only reactive changes and were negative for metastasis. In 26 cases the lymph nodes could not be examined. Majority of lymph node positive cases 22/29 (75.86%) showed diminished / absent cytoplasmic E-cadherin, ie non-membranous pattern and 7(24.13%) cases showed preserved membranous pattern. In the 5 node negative cases, 4(80%) showed preserved membranous pattern and 1(20%) showed non-membranous pattern. Of the 26 nodes not examined

group, 20 (76.92%) cases showed membranous and 6 (23.07%) showed non-membranous staining for E-cadherin. The p value was <0.05.

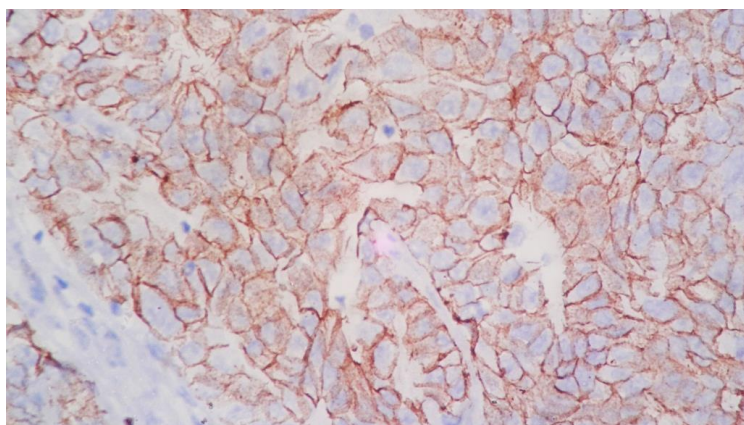
**Tumor histology and Lymph node metastasis:** Majority of lymph node positive cases 22/29 (75.86%) had poorly differentiated morphology. Moderately and well differentiated morphology was seen in 6 cases and 1 case respectively. There were 5 node negative cases in which 4 cases had well differentiated morphology and 1 case had moderately differentiated morphology.



**Fig. 4: Positive control - normal gastric mucosa showing strong membranous positivity for E-cadherin immunostaining. (Immunohistochemistry 40X)**



**Fig. 5:** a: Intestinal type of gastric adenocarcinoma-well differentiated (Hematoxylin and eosin 40X); b: Shows immunohistochemistry with strong membranous positivity for E-cadherin immunostaining, Score: 3; c: Shows reduced cytoplasmic staining, Score: 1; d: Shows diffuse type adenocarcinoma with absent staining for E-cadherin, Score: 0



**Fig. 6:** Intestinal type of gastric adenocarcinoma-moderately differentiated, on immunohistochemistry showing membranous and cytoplasmic staining (Score: 2)

## Discussion

The cadherins are different type of molecules that mediate cell to cell adhesion and binding between same type of cells. E- cadherin, is one such molecule having a weight of 123 –kD and is found on all epithelial cell membranes. Whenever the expression of E- cadherin is reduced or absent it causes dissociation of the cells by loosening of cell junctions and in a way acts as a tumor suppressor.<sup>20</sup>

Literature has reported on the association between diminished E- cadherin expression and increased invasiveness in gastric carcinomas.<sup>21</sup> We undertook the present study to look at this association in our local population.

Various workers have worked on tumor cells that have been cultured. The E-cadherin molecular complex that was lost in these tumor cells was again inserted and was made to function normally. They found that the invasiveness of the tumor got reverted to non-invasive phenotype with the onset of E-cadherin expression.<sup>22,23</sup>

Various in-vitro and in-vivo studies have shown the inverse and direct correlation between tumor metastasis and the level of E- cadherin expression respectively.<sup>24,25</sup>

All these studies demonstrate that E- cadherin loss leads to increased cell dissociation thereby favouring cancer invasion and enhanced metastatic ability.

The Jawhari scoring system is a good qualitative approach to evaluate E-cadherin expression. The location of

E-cadherin expression is very important. It is normally present in cell membranes and gives a score of 2 or 3. Reduced or absent expression in cell membranes is scored as 0 or 1.

In our study, good correlation was seen in the better differentiated tumors of intestinal histotype (66.66%) that

showed preserved E-cadherin expression, whereas, absent E-cadherin expression was more commonly seen in the diffuse histotype (83.33%) and this difference was statistically significant. Our findings compare well with the observations of Philip et al<sup>26</sup> Stanculescu et al<sup>27</sup> and Wu et al.<sup>28</sup>

**Table 3: E-cadherin expression in gastric cancer histological types in various studies**

E-cadherin staining	Daniela et al <sup>29</sup> n =55		Wu et al <sup>28</sup> n =30		Philip et al <sup>26</sup> [2002] n = 143		Present study n =60	
	IGC	DGC	IGC	DGC	IGC	DGC	IGC	DGC
Membranous (%)	26 (92.87)	3 (17.64)	9 (81.8)	7 (36.8)	60 (69)	25 (45)	28 (66.66)	3 (16.66)
Non-membranous (%)	12 (42.85)	14 (82.35)	2 (18.2)	12 (63.2)	27 (31)	31 (55)	14 (33.33)	15 (83.33)
Total	38	17	11	19	87	56	42	18

IGC: Intestinal gastric carcinoma, DGC: Diffuse gastric carcinoma

**Table 4: Expression of E-cadherin (by score) in gastric cancer histological types-comparison with other study**

E-cadherin score	Present study n =60		Sundaram et al <sup>[30]</sup> n =20	
	Intestinal (42 cases)	Diffuse (18 cases)	Intestinal (10 cases)	Diffuse (10 cases)
3	14(33.33%)	0	0	0
2	14(33.33%)	3(16.66%)	4(40%)	0
1	10(23.8%)	7(38.88%)	4(40%)	3(30%)
0	4(9.52%)	8(44.44%)	2(20%)	7(70%)

In our study, the poorly differentiated tumors 11/23(47.82%) showed loss of E-cadherin expression.

Lazar et al<sup>29</sup> and Mayer et al<sup>31</sup> also reported that decreased E-cadherin expression was related to cellular differentiation. It is felt that expression of E-cadherin on

tumor cells is related to the glandular differentiation and histotype in gastric carcinomas.

Wu et al<sup>28</sup> analysed E-cadherin expression in gastric cancers in 30 cases. They observed significant correlation between poor differentiation of tumors and loss of E-cadherin molecules.

**Table 5: Histological grade and E-cadherin expression in gastric adenocarcinoma, comparison with other study**

E-cadherin staining	Wu et al <sup>28</sup> n = 30		Present study n = 60	
	WD and MD 13 Cases	PD 17 cases	WD and MD 37 cases	PD 23 cases
Membranous	11 (84.61%)	5 (29.41%)	27 (87.09%)	4 (17.39%)
Non membranous	2 (15.38%)	12 (70.58%)	10 (27.02%)	19 (82.60%)

WD: Well differentiated, MD: Moderately differentiated, PD: poorly differentiated

Similar to Mayer et al<sup>31</sup> even we observed a statistically significant correlation between E-cadherin expression and depth of tumour invasion. Most of the higher stage tumors such as T3 and T4 had loss of E-cadherin expression, although for most of the cases tumor stage was not examined. Wu et al<sup>[28]</sup> and Sundaram et al<sup>30</sup> found no significant association between tumor stage and E-cadherin expression.

In our study, we observed significant correlation between E-cadherin expression and presence of lymph node metastasis. Out of 60 cases studied, 29 cases were positive for nodal metastatic disease. Majority of lymph node

positive cases 22/29 (75.86%) showed reduced cytoplasmic and absent staining for E-cadherin. Our results compared well with the observations of Wu et al.<sup>28</sup>

Our results are contrary to those of Lazar et al<sup>29</sup> Sundaram et al<sup>30</sup> where they found no correlation between E-cadherin expression; tumor invasion and lymph node metastasis.

Normal gastric epithelium shows strong E-cadherin expression that is membranous in location. In carcinomas where the cells are neoplastic the E-cadherin expression is less intense, expressed in less number of cells and also the location becomes altered ie it expresses in the cytoplasm

instead of cell membranes. In our study, there was good correlation between E-cadherin expression and tumour differentiation. Poorly differentiated and diffuse type tumors showed loss of E-cadherin expression. Our observations are in concurrence with other studies.<sup>32</sup>

The loss of E-cadherin from the membranes promotes the notion that loss of this adhesion molecule promotes tumor disaggregation and dissemination.

In gastric carcinomas, the prognosis depends on the size of the primary tumor, the presence of nodal involvement, tumor stage, degree of differentiation and histologic type. In addition to the above factors E-cadherin can also serve as a prognostic marker to assess the tumor invasiveness and

metastatic potential. This may help in assessing the patient survival.

**Pitfalls in E-cadherin IHC interpretation:** Many workers<sup>29,30</sup> found no correlation between E-cadherin expression with tumor invasion and lymph node metastasis. Also Huiping et al<sup>33</sup> in their study observed that in gastric cancers though there is aberrant expression of E-cadherin and beta-catenin, it does not give information on the fact that whether e-cadherin loss acts as an initiator or promoter of the cancer. An interesting point about E-cadherin is that its expression reappears in cells at metastatic sites so as to prevent apoptosis and establish metastasis firmly.<sup>34</sup>

**Table 6: Association of E-cadherin expression with lymph node metastasis in gastric cancer**

E-cadherin staining pattern						
Wu et al <sup>28</sup> n = 30				Present study n = 60		
Lymph node metastasis	Total	Membranous (%)	Non-membranous (%)	Total	Membranous (%)	Non-membranous (%)
Present	18	6 (33.33%)	12 (66.7%)	29	7 (24.13%)	22 (75.86%)
Absent	12	10 (83.3%)	2 (16.7%)	5	4 (80%)	1 (20%)
Not examined	0	0	0	26	20 (76.92%)	6

## Conclusion

1. E-cadherin expression by immunohistochemistry showed strong membranous positivity in normal gastric mucosa, whereas, in gastric carcinomas the expression gradually decreased in intensity and percentage, and the location of staining changed to cytoplasmic from membranous staining.
2. Staining pattern varied with histological type, differentiation, tumor stage and lymph node metastasis.
3. Majority of poorly differentiated tumors showed non-membranous staining as compared to better differentiated tumors.
4. E-cadherin expression was lost in tumors with higher clinical stage and in those with positive nodes.
5. A clinico-histological study combined with study for E-cadherin expression will be helpful to predict the metastatic potential in gastric cancers and will provide useful information for prognosis, recurrence and survival.

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