ROLE OF E-CADHERIN EXPRESSION IN THE PROGNOSIS OF BREAST CARCINOMA

Yamuna Devi Rayapuri[1], Tiwari Sundari Devi[2]

[1]Blood Bank Medical Officer, Aarohi Blood Bank, Hyderabad, Telangana.
[2]Associate Professor, Department of Pathology, Government Medical College, Nalgonda, Telangana.

ABSTRACT

BACKGROUND

Breast cancer is 2nd most common cancer in women after cervical cancer in India and is associated with high mortality and morbidity. Several parameters have been investigated to predict the prognosis in the breast cancer. E-cadherin, a calcium dependent epithelial cell adhesion molecule is a novel prognostic indicator. Its loss differentiates intralobular carcinoma from invasive duct cell carcinoma (IDCC) and its reduced expression has been associated with metastasis.

The aim of the study is to assess the E-cadherin expression in breast cancer as a diagnostic marker in general and as a prognostic marker in metastasis of duct cell carcinoma.

The aim of the study was to evaluate E-cadherin as a diagnostic marker, to differentiate between IDCC and ILC and as a novel prognostic marker with a potential to predict invasion and metastasis.

MATERIALS AND METHODS

This was a cross-sectional study done for a duration of 2 years, with a total of 50 cases, in the department of pathology, Gandhi Medical College/Hospital. All the mastectomy specimens received were considered. All the samples were routinely processed, stained with H&E and IHC with E-cadherin done. The slides were analysed and interpreted.

RESULTS

Out of 50 cases 47 cases (94%) were invasive duct cells carcinomas of NOS type and 3 cases (6%) were invasive lobular carcinoma. The most common tumor size distribution observed was 4 – 5 cm. 42.5% of cases showed positive lymph nodes for metastasis while 57.5% of cases were negative. Majority (51%) of IDCC cases had grade -II while 34.5% cases had grade-I tumours. All ILCs showed loss of E-cadherin expression while 34.5% of IDCC cases showed strong membrane expression of E-cadherin and 65.5% cases of IDCC showed reduced membrane expression.

CONCLUSION

E-cadherin is a useful marker to differentiate between IDCC and ILC. Dynamic, reversible modulation of E-cadherin expression occurs during ductal carcinoma progression. Reduced E-Cadherin expression favours dissemination.

KEYWORDS

Breast Cancer, E-Cadherin, Metastasis, Mastectomy.

HOW TO CITE THIS ARTICLE: Rayapuri YD, Sundari Devi T. Role of e-cadherin expression in the prognosis of breast carcinoma. J. Evid. Based Med. Healthc. 2018; 5(42), 2960-2967. DOI: 10.18410/jebmh/2018/605

BACKGROUND

In India, cervical cancer is the most frequently diagnosed cancer followed by breast cancer in rural women, but in urban women, breast cancer is more common. The recent observed increase in the incidence of breast cancer in the Indian population is largely explained by westernization of lifestyles and changes in reproductive behaviour. Breast cancer accounts for 5-8% of all cancers in India and the incidence is on the rise. Locally advanced breast cancer accounts for 50% of all breast cancers.

Financial or Other, Competing Interest: None.
Submission 22-09-2018, Peer Review 26-09-2018,
Acceptance 07-10-2018, Published 15-10-2018.
Corresponding Author:
Dr. T. Sundari Devi,
H. No. 2-4-1000/2, Road No. 3A,
Samatapuri Colony, New Nagole,
Hyderabad- 500035, Telangana.
E-mail: ikomal21.kks@gmail.com
DOI: 10.18410/jebmh/2018/605

Certain specific cell-to-cell adhesion molecules have been found to be responsible for embryonic development. One such molecule is a family of Cadherins. It is a group of genetically related transmembrane glycoproteins, involved in calcium-dependent cell-to-cell adhesion mechanism and are sub-classified, based on their binding characteristics and tissue distribution like E-cadherin, P-cadherin, N-cadherins and others. At the structural level, E-cadherin has extracellular portion responsible for homophilic cellular interaction and an intracellular part provides link to actin cytoskeleton through an association with various catenins. Among these, β-catenin has significant role in cell adhesion and signal transduction.

A positive association between abnormal E-cadherin expression and occurrence of invasion and metastasis has been reported in cancers of stomach, breast and other organs.

Present study was undertaken to analyse E-cadherin expression in differentiating infiltrating lobular carcinomas (ILCs) from infiltrating duct cell carcinomas (IDCCs), in

uncertain histologic settings and in investigating its importance in predicting invasive potential of breast cancer.

Aims and Objectives

Aim

To assess the role of E-cadherin expression in prognosis of breast cancer.

Objectives

1) As a diagnostic marker, to differentiate between IDCC & ILC. 2) As a novel prognostic marker in the breast cancer with a potential to predict the invasion and metastasis. 3) In tumours with indeterminate histopathological features. 4) In relation to various histopathological grades of IDCC.

MATERIALS AND METHODS

The study was done in the Department of Pathology, Gandhi Hospital, Hyderabad from July 2015 to July 2017. Clinical data was retrieved from HPE records. The specimens were fixed in 10% buffered formalin, grossed and bits sampled from the representative sites. The bits were then processed in automated tissue processor and embedded in paraffin wax.

Inclusion Criteria for Selection of Cases

Diagnosis of invasive breast carcinoma, No prior treatment history, Adequate tumor tissue for analysis, Complete Clinicopathological data (age, sex, histopathological diagnosis).

Total specimens collected were 50, which were reported histopathologically as follows-

- Invasive ductal carcinomas No special type-47.
- Invasive lobular carcinoma-03.

Exclusion Criteria

- Improperly labelled samples, Unfixed specimens, Patients already on treatment.

Methods

Two micro sections of 4-5 micron thickness were prepared from the corresponding paraffin blocks, one on albumin coated slide for H&E staining and the other on poly-L-lysine coated slide for immune-histochemical staining.

Routine Haematoxylin and Eosin (H & E) Staining

Procedure

After clearing in Xylol, bring the section to water. Place in Harris haematoxylin for 5-6 minutes, wash in tap water for 3 minutes and differentiate in 1% acid alcohol- 3-5 quick dips. Then wash in running tap water for 5-10 minutes (blueing). Counter stain in 1% Eosin for 30 seconds. Wash in tap water, dehydrate in alcohol and mount with DPX.

RESULTS

- Nuclei - Blue, Cytoplasm-Pink.

Invasive breast Carcinoma histological typing and histological grading (I, II, and III) was done according to Elston using the scale assigned to three features: tubular formation (1 to 3), nuclear atypia (1 to 3), and mitoses (1 to 3).

The kits for E-cadherin immune-histochemical staining were obtained from DAKO company and staining was done according to the manufacturer's protocol, using peroxidise-antiperoxidase method.

Method of Immunohistochemical Staining

- 4 microns thin sections are taken on poly –L- lysine coated slides, deparaffinization done, followed by 3 changes of absolute alcohol for 5 min. Then washed under running tap water. Endogenous peroxidase activity is quenched by covering the slides with 3% H_2O_2 for 30 min.

  Again, washed under running tap water for 15 min. Antigen retrieval done by Pressure cooker (HIER, heat induced epitope retrieval) with Tris buffer (1.21 g of Tris Hydroxymethyl methylamine and 3.75 mg of EDTA in 1000 ml distilled water). Slides are washed with TBS buffer (9.6 g of Tris Hydroxymethyl methylamine and 8.6 g of NaCl in 1000 ml distilled water) pH 7.4-7.6.
- Incubated with Primary antibody (E-CADHERIN) which is ready to use, at room temperature in a humidifier chamber for 30 minutes. The sections were washed again with TBS buffer (9.6 g of Tris Hydroxymethyl methylamine and 8.6 g of NaCl in 1000 ml distilled water) pH 7.4-7.6, incubated with secondary antibody in a humidifier chamber for 30 minutes. The sections were again washed with TBS buffer. Chromogen DAB for 20 minutes used for detection of enzymatic activity. Counter staining done with Haematoxylin, dehydrated in alcohol and cleared in xylene. Mounted with DPX.

  The slides were then examined under microscope and E-Cadherin positivity is classified as strong, moderate and negative membrane staining.

Scoring and Evaluation

Scoring System-

The intensity was graded from 0 to +3.

1. 3+, strong complete membrane staining, comparable to benign ductal and lobular epithelial cells and >76-100% of tumour cells show positive reaction for E-cadherin.
2. 2+ moderate clear membrane staining and 51-75% of tumour cells show positive reaction for E-cadherin.
3. 1+ weak but still complete membrane staining and 26-50% of tumor cells show positive reaction for E-cadherin.
4. 0 or negative, for absent or incomplete membrane staining.

Evaluation

1) Strong membrane expression pattern was represented by 3+
2) Reduced E-cadherin expression patterns were represented by scores 2+ and 1+ staining
3) Negative membrane expression was represented by 0.

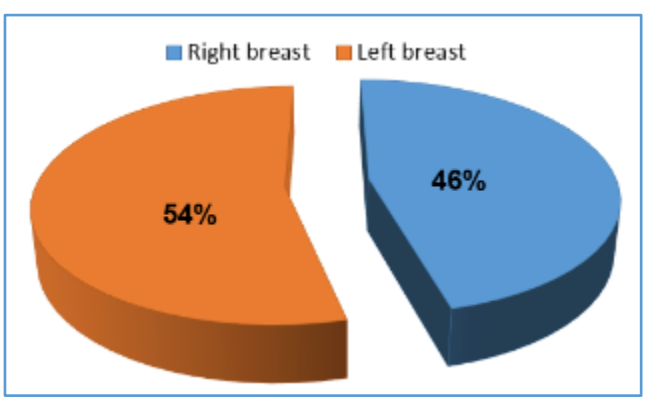
RESULTS

Out of 50 invasive breast carcinoma cases, 49(98%) were females and only 1(2%) was male.

The mean patient age was 50 years (range 30-70 years). Majority of cases were seen in 4th to 6th decade. Out of 50 cases 47 cases (94%) were invasive ductal carcinomas, No special type (No.s) and 3 Cases (6%) were invasive lobular carcinoma.

Age Group of Study	Female	Male	Total	Percent
30-40 Years	02	0	02	4%
41-50 Years	25	0	25	50%
51-60 Years	15	01	16	32%
61-70 Years	07	0	07	14%
Total	49	01	50	100%

Table 1. Showing Age and Sex Wise Distribution of Cases



Graph 1. Distribution of Lesions According to Laterality of Breast

There is slight preponderance to left side breast (54%).

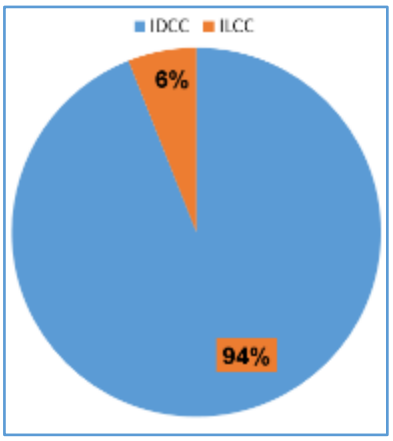
- The most common tumour size distribution in the present sample 4-5 cm.

Lymph Node Spread	Number	Percent
REACTIVE L.N	27	57.5%
METASTATIC L.N	20	42.5%
Total	**47**	**100%**

Table 2. Distribution of Lymph Node Metastasis in Study Subjects

Positive lymph nodes-42.5%, NEGATIVE nodes- 57.5% of cases.

Invasive breast carcinomas with IDCC type constitutes the major type (94%).



Graph 2. Distribution of Cases According to Diagnosis

Histological Grade	Number of Cases	Percent
GRADE-I	16	34.5%
GRADE-II	24	51%
GRADE-III	07	14.5%
Total Cases	47	100%

Table 3. Distribution of IDCC According to Histological Grade

Majority of the patients are categorized as grade-II i.e. 51% of cases and next is grade-I tumours i.e. 34.5% cases.

Histological Type	E-Cadherin Expression				P Value BY Chi-Square Test
	0	1+	2+	3+	
IDCC	0	7	24	16	<0.001
ILC	3	0	0	0	
Total Cases	3	7	24	16	

Table 4. Histological types vs. E-cadherin Expression

E-Cadherin Expression in Invasive Ductal Carcinomas

Expression of E-cadherin was examined in 47 cases of IDCCs that were grouped according to the histological grade. All IDCC cases retained at least some expression of E-cadherin.

- All the grade-I (16/47) tumours expressed strong membrane positivity given as 3+.
- Grade-II (24/47) tumours expressed moderate membrane positivity given as 2+.
- Grade-III (7/47) showed weak membrane positivity given as 1+.

In this study, E-cadherin strong membrane expression in IDCC was observed in 16/47 cases (34.5%) and reduced membrane expression was observed in 31/47 cases (65.5%).

E-Cadherin Expression in Invasive Lobular Carcinoma

ILCs are characterized in their classical form by the highly micro invasive, dispersed histological pattern. When ILCs were studied for E-cadherin expression, they were, in contrast to the IDCCs are all negative and given as 0. Entrapped normal ductal structures served as internal positive controls.

The complete loss of immunostaining correlated well with the histologic impression of lobular features and lack of tubule or lumen formation.

All the invasive lobular carcinomas 3/3 (100%) irrespective of their histological grades showed complete loss of E-cadherin expression.

Figure 1. Gross Specimen of Breast Carcinoma

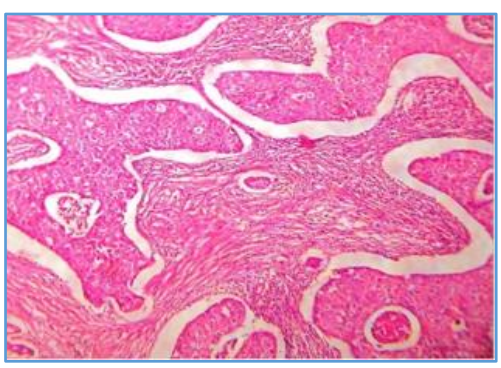


Figure 2. IDCC-Swell Differentiated (Grade-1) H & E 10X

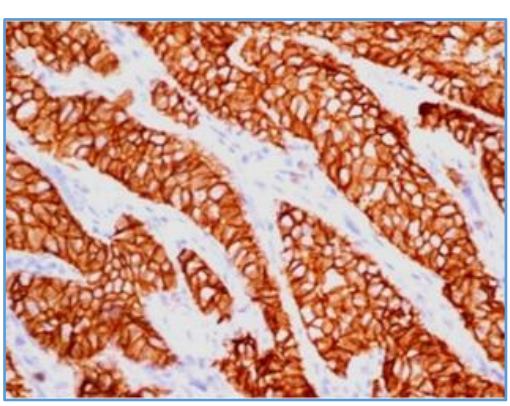


Figure 3. IDCC-Well differentiated (grade-I) E-cadherin expression 10x (strong membrane expression)

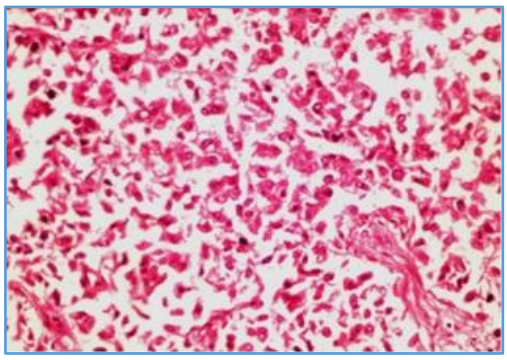


Figure 4. IDCC-Moderately Differentiated (Grade-II) H & E 40x

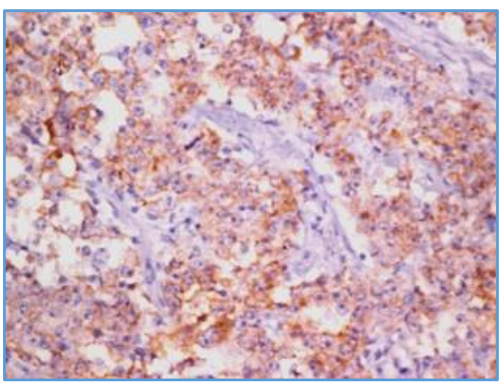


Figure 5. IDCC-Moderately Differentiated (Grade-II) E-Cadherin Expression-40x (Moderate Membrane Expression)

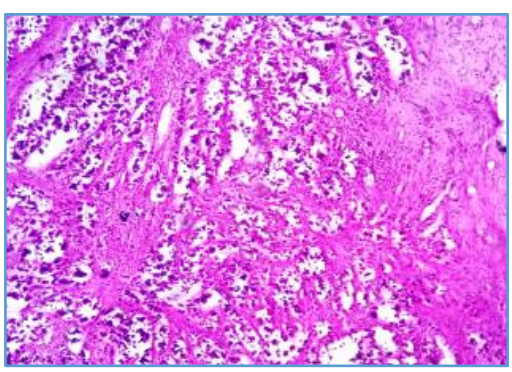


Figure 6. IDCC-Poorly Differentiated (Grade-III) H & E 40x

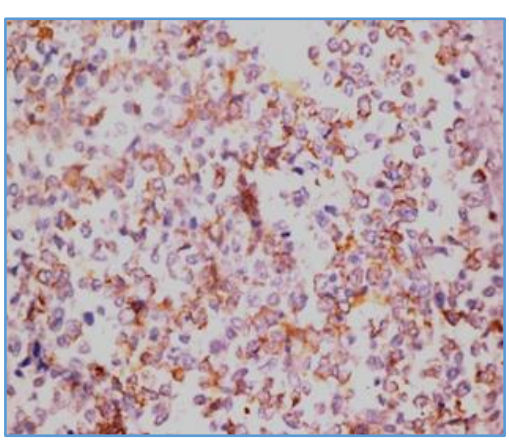


Figure 7. IDCC-Poorly Differentiated (Grade-III) E-Cadherin Expression 40x (weak membrane expression of e-cadherin with few tumour cells left unstained)

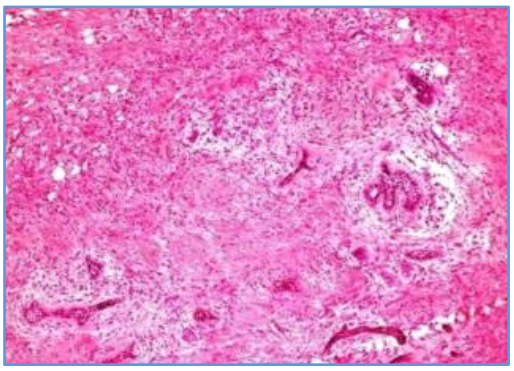


Figure 8. Invasive Lobular Carcinoma- H&E 10x

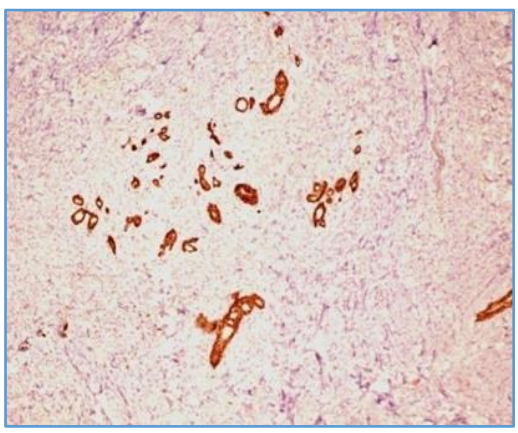


Figure 9. ILC E-Cadherin Expression 10X (Complete Loss of E-Cadherin Expression)

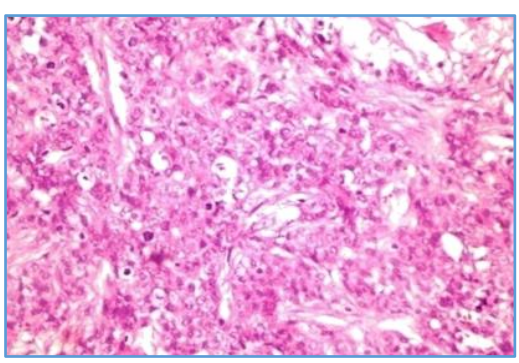


Figure 10. Lymph Node Metastasis of IDCC H&E 10x

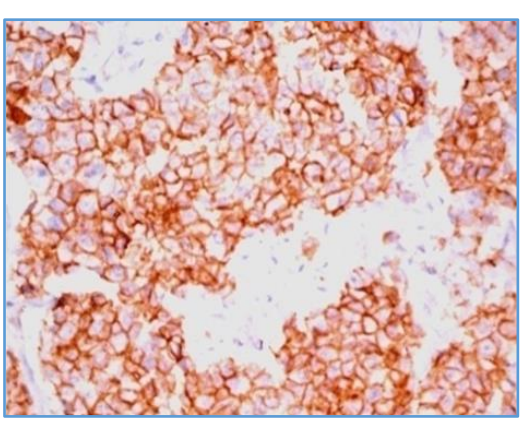


Figure 11. Lymph Node Metastasis of IDCC E-Cadherin Expression 10x (Moderate Membrane Expression of E-Cadherin)

DISCUSSION

In normal epithelial tissues, when the cell density reaches a certain value, the proliferation rate decrease, and this phenomenon is called contact inhibition.

Because of contact inhibition, normal epithelial cells control their own evolution and differentiates them from tumour cells. In tumour cells, contact inhibition is lost, which leads to aberrant, uncontrolled proliferation. Loss of contact inhibition is due to abnormal E-cadherin expression.

Adhesion molecules play a major role in tumour cell dissemination and development of metastasis.

E-cadherin is a glycoprotein with an extracellular domain that interacts with E- cadherin molecules on adjacent cells, thereby establishing adhesion between the epithelium.

Present study analysed the correlation between E-cadherin expression of Invasive ductal carcinoma and invasive lobular carcinoma and the following variables: size, tumour grade, lymph node status, and various other factors. A comparative study between present and other studies are elaborated in the following paragraphs.

Comparison of Patients Age in the Present Study with Other Studies

The commonly affected age group is 40-50 yrs. (40%) followed by 50-60 yrs. (33%) and 6th decades. The mean age of the sample is 55 years, the maximum and minimum age being 75 years and 40 years respectively.

Agarwal et al,[1] Forouzanfar M H et al,[2] observed that in Asia, breast cancer incidence peaks among women in their forties. In India incidence in pre-menopausal patients constitutes about 50% of all patients.

Study	Age
Fakeha. Rehman et al[3]	Mean age 60 years, age range 20-80 years
Reinholz MM et al[4]	Median age 56 years

Table 5. Comparison of Age of Present Study with Other Studies

Study	Right Breast	Left Breast
Present study	46%	54%
Ambroise M et al[5]	40.8%	59.2%
Azizunnisa et al[6]	43%	57%

Table 6. Comparison of Laterality of the Tumour with Other Studies

Carcinoma of breast more common in the left breast than in the right breast.

Comparison of tumour size in present study with other studies.

Most common tumour size is between 2-5 cms.

Suciu C et al[7] observed that the average tumour size was 2.5 cm and tumour size ranging in between 1 and 8.

Histological Type	Present Study	Indian Studies	Western Studies
IDCC	94%	85-95%	40-75%
ILC	06%	2-4%	5-15%

Table 7. Comparison of Histological Type of Tumour in the Present Study with Other

Invasive breast carcinoma with IDCC type more common in present study and also in the Indian and Westren studies.

Comparison of E-Cadherin Expression with Histological type of Tumour in Present Study with Other Studies

E-cadherin strong membrane expression in IDCC was observed in 16/47 cases (34.5%) and reduced membrane expression was observed in 31/47 cases (65.5%). All the invasive lobular carcinomas 3/3 (100%) irrespective of their histological grades showed complete loss of E-cadherin expression. Similar results were found in the following studies:

Kanthilatha Pai et al[8] found correlation of E- cadherin expression with the histological phenotype of the tumours. 26 of the 28 cases of IDCC showed a moderate to strong membrane (2+/3+) expression of E-cadherin, while only 1/28 cases of ILC showed a 2+ staining. All other cases of ILC were negative for the E-cadherin expression.

Lehr et al,[9] observed infiltrating duct cell carcinomas express E-cadherin in a similar peripheral-predominant Immunostaining pattern (33/33 cases), while all 15 lobular carcinomas were negative for E-cadherin expression.

In Contrast to the Present Study

James E. Korkola, Sandy DeVries, Jane Fridlyand, et al,[10] observed that out of 17 lobular tumours, 15 showed low levels of E-cadherin expression and remaining 2 lobular cases showed no E- cadherin immunostain.

Comparison of E-cadherin Expression with Different Grades of Infiltrating Duct Cell Carcinomas in Present Study with the Other Studies

Expression of E-cadherin was observed in 47 cases of IDCCs that were graded according to the Elston histological grade. All IDCC cases retained at least some expression of E-cadherin. All the invasive lobular carcinomas 2/2 (100%) irrespective of their histological grades showed complete loss of E-cadherin expression.

IDCC Grade	E-Cadherin Expression
Grade-I (34.5%)	Strong membrane expression
Grade-II (51%)	Moderate membrane expression
Grade-III (14.5%)	Weak membrane expression

Table 8. E-cadherin Expression in Histological Grades of IDCC in the Present Study

Gamallo et al,[11] studied the intensity of E-CADHERIN expression in 61 breast carcinomas and correlated with their histological type and grade and found, Grade 1 breast carcinomas (n = 10) showed greater immune-reactivity than grade 2 (n =25) and grade 3 (n = 19) carcinomas. None of the infiltrating lobular carcinomas expressed E-Cadherin in their infiltrating cells.

Kowalski et al,[12] studied the immuno-histochemical analysis of E-cadherin in tissues from 30 patients with primary invasive breast carcinoma. 55% of the primary invasive ductal carcinomas had normal E-cadherin expression and 45% had aberrant expression. One of eight (12%) primary invasive lobular carcinomas showed positive E-cadherin expression

Madhavan M et al,[13] observed that cadherins are Predictive Markers of Nodal Metastasis in Breast Cancer and E-cadherin expression is inversely correlated with the grade of the tumor.

Present study	Found that significant correlation between E-cadherin expression with histological grade of tumours.
Heimann R et al,[14] Asgeirsson et al,[15] Hunt NCA et al,[16] Oka H et al,[17] Siitonen SM et al,[18] Guriec N al[19]	In breast cancer, partial or total loss of E-cadherin expression correlates with increased tumour grade.
Moll et al,[20] Gamallo et al[11]	Reported reduced and heterogeneous E-cadherin immunostaining in poorly differentiated IDCC while preservation of E-cadherin expression in well and moderately differentiated carcinomas
Hashizume et al,[21] Charpin et al,[22] Gupta et al[23]	Studies have found correlations between reduced E-cadherin levels and high grade tumor

Table 9. Comparison of E-Cadherin Expression with Grades of Infiltrative Duct Cell Tumours in Present Study with Other Studies

In Contrast with Present Study

Md Isa Nurismah et al[24] studied E-cadherin expression in 32 cases of breast carcinomas comprising 16 IDCCs and 16 ILCs. There was no significant correlation between tumour grade and E-cadherin expression in IDCCs.

Present study showed highly significant correlation of E-cadherin membrane expression with the histologic grade of tumours. All Invasive Ductal Carcinoma cases showed moderate to strong membrane expression of E-cadherin, as seen in the non-neoplastic mammary epithelium.

Lymph Node	Onitilo AA et al	Zafrani B et al	Present Study
Positive	31%	37%	42.5%
Negative	69%	63%	57.5%

Table 10. Showing Lymph Node Status on Histopathological Examination in Comparison with Other Studies

In our study 42.5% cases showed node positivity, 57.5% cases showed node negativity, this is concordance with studies conducted by Zafrani B et al[25] (37%), Onitilo AA et al[26] (31%).

Summary

The present study has been conducted at Gandhi medical college from July 2015 to July 2017 in the department of Pathology. Out of total 50 cases studied, 94% (47 cases) were invasive ductal carcinoma, NOS type and 6% (3 cases) were invasive lobular carcinomas.

Routine processing and Haematoxylin and Eosin staining of the received specimens were done followed by immune-histochemical analysis with E-cadherin antibody.

Strong membranous expression of E-cadherin was found in (16/47) cases and reduced E-cadherin expression in (31/47) invasive ductal carcinomas and complete loss of E- cadherin expression in all invasive lobular carcinomas (3/3).

A statistically significant correlation was found between E-cadherin expression and histological phenotype of the tumor where all invasive ductal carcinoma retained at least some E-cadherin expression and all invasive lobular carcinomas showed complete loss of E-cadherin expression. Also reduced E-cadherin expression seen in higher grades of invasive ductal carcinomas. The selective loss of E-Cadherin can generate dedifferentiation and invasiveness in human Breast carcinomas, supporting a role for E-Cadherin as an invasion suppressor molecule.

CONCLUSION

E-cadherin is a useful marker to differentiate between IDCC and ILC where almost all lobular carcinomas are negative for E-cadherin expression.

The usefulness of E-cadherin expression as an independent prognostic indicator in ductal carcinomas of breast needs further investigation. Reduced E-cadherin expression favours dissemination.

The examination of the cell adhesion molecule E-cadherin might prove important not only for understanding the basic mechanisms involved in the progression of malignant epithelial tumours but might also be used as a histological marker for refinement of pathological diagnosis.

REFERENCES

[1] Agarwal G, Pradeep PV, Aggarwal V, et al. Spectrum of breast cancer in Asian women. World J Surg 2007;31(5):1031-1040.

[2] Forouzanfar MH, Foreman KJ, Delossantos AM, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 2011;378(9801):1461-1484.

[3] Rehman F, Nagi AH, Hussain M. Immunohistochemically expression and correlation of mammaglobin with the grading system of breast carcinoma. Indian J Pathol Microbiol 2010;53(4):619-623.

[4] Reinholz MM, Nibbe A, Jonart LM, et al. Evaluation of a panel of tumor markers for molecular detection of circulating cancer cells in women with suspected breast cancer. Clin Cancer Res 2005;11(10):3722-3732.

[5] Ambroise M, Ghosh M, Mallikarjuna VS, et al. Immunohistochemically profile of breast cancer patients at a tertiary care hospital in South India. Asian Pac J Cancer Prev 2011;12(3):625-629.

[6] Azizun-Nisa, Bhurgri Y, Raza F, et al. Comparison of ER, PR & Her-2/neu (c-erb B-2) reactivity pattern with histologic grade, tumor size and lymph node statues in breast cancer. Asian Pac J Cancer Prev 2008;9(4):553-556.

[7] Suciu C, Cîmpean AM, Mureşan AM, et al. E-cadherin expression in invasive breast cancer. Rom J Morphol Embryol 2008;49(4):517-523.

[8] Pai K, Baliga P, Shrestha BL. E-cadherin expression: diagnostic utility in differentiating breast carcinomas with ductal and lobular morphology. J Clin Diagn Res 2013;7(5):840-844.

[9] Lehr HA, Folpe A, Yaziji H, et al. Cytokeratin 8 immunostaining pattern and E-cadherin expression distinguish lobular from ductal breast carcinoma. Am J Clin Pathol 2000;114(2):190-196.

[10] Korkola JE, DeVries S, Fridlyand J, et al. Differentiation of lobular versus ductal breast carcinoma by expression microarray analysis. Cancer Res 2003;63(21):7167-7175.

[11] Gamallo C, Palacios J, Suarez A, et al. Correlation of E-cadherin expression with differentiation grade and histology type in breast carcinoma. Am J Pathol 1993;142(4):987-993.

[12] Kowalski PJ, Rubin MA, Kleer CG. E-catherin expression in primary carcinomas of the breast and its distant metastases. Breast Cancer Res 2003;5(6):R217-222.

[13] Madhavan M, Srinivas P, Abraham E, et al. Cadherins as predictive markers of nodal metastasis in breast cancer. Mod Pathol 2001;14(5):423-427.
[14] Heimann R, Lan F, McBride R, et al. Separating favorable from unfavorable prognostic markers in breast cancer: the role of E-cadherin. Cancer Res 2000;60(2):298-304.
[15] Asgeirsson KS, Jónasson JG, Tryggvadóttir L, et al. Altered expression of E-cadherin in breast cancer. Patterns, mechanisms and clinical significance. Eur J Cancer 2000;36(9):1098-1106.
[16] Hunt NC, Douglas-Jones AG, Jasani B, et al. Loss of E-cadherin expression associated with lymph node metastases in small breast carcinomas. Virchows Arch Int J Pathol 1997;430(4):285-289.
[17] Shiozaki H, Tahara H, Oka H, et al. Expression of immunoreactive E-cadherin adhesion molecules in human cancers. Am J Pathol 1991;139(1):17-23.
[18] Siitonen SM, Kononen JT, Helin HJ, et al. Reduced E-cadherin expression is associated with invasiveness and unfavorable prognosis in breast cancer. Am J Clin Pathol 1996;105(4):394-402.
[19] Guriec N, Marcellin L, Gairard B, et al. E-cadherin mRNA expression in breast carcinomas correlates with overall and disease-free survival. Invasion Metastasis 1996;16(1):19-26.
[20] Moll R, Mitze M, Frixen UH, et al. Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas. Am J Pathol 1993;143(6):1731-1742.
[21] Hashizume R, Koizumi H, Ihara A, et al. Expression of β-catenin in normal breast tissue and breast carcinoma: a comparative study with epithelial cadherin and α-catenin. Histopathology 1996;29(2):139-146.
[22] Charpin C, Garcia S, Bonnier P, et al. Reduced E-cadherin immunohistochemical expression in node-negative breast carcinomas correlates with 10-year survival. Am J Clin Pathol 1998;109(4):431-438.
[23] Gupta SK, Douglas-Jones AG, Jasani B, et al. E-cadherin (E-cad) expression in duct carcinoma in situ (DCIS) of the breast. Virchows Arch 1997;430(1):23-28.
[24] Nurismah MI, Noriah O, Suryati MY, et al. E-cadherin expression correlates with histologic type but not tumour grade in invasive breast cancer. Asian Pac J Cancer Prev 2008;9(4):699-702.
[25] Zafrani B, Gerbault-Seureau M, Mosseri V, et al. Cytogenetic study of breast cancer: clinicopathologic significance of homogeneously staining regions in 84 patients. Hum Pathol 1992;23(5):542-547.
[26] Onitilo AA, Engel JM, Greenlee RT, et al. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009;7(1-2):4-13.