RESEARCH ARTICLE

E-CADHERIN AS A PROGNOSTIC AND PREDICTIVE BIOMARKER IN INVASIVE BREAST CARCINOMA, A CLINICO-PATHOLOGICAL STUDY.

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Manuscript Info	*Abstract*

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Background: Breast cancer continues to be a major cause of morbidity and mortality in Egypt. The behavior of breast cancer varies widely. Several parameters have been investigated to predict the prognosis in breast cancer. But still there is no single parameter that can predict prognosis in an individual patient.

E-cadherin is a novel prognostic marker; a calcium-dependent epithelial cell adhesion molecule. Its loss has been associated with metastases, thereby providing evidence for its role as an invasion suppressor.

Aim: The objective of the present study was to assess the prognostic value of E-cadherin expression in breast cancer cases, and its correlations with the other studied prognostic parameters, especially the lymph node status.

Materials and methods: the immunohistochemical expression of E-cadherin was studied in 70 cases of invasive breast cancer; ten of them are of the lobular subtype.

Results: E-cadherin expression was positive in 44 cases (62.9%) and negative in 26 cases (37.1%). It was positive in 42 cases of the 58 cases of invasive ductal type, while it was negative in all the lobular breast cancer cases and it was positive in both the mucinous and papillary carcinoma. There was a statistically significant difference between E-cadherin positive and E-cadherin negative cases as regard tumor grade and stage, lymph node status, Her2μ receptor status and conservative surgery rates while there was no statistically significant difference between E-cadherin+ /- as regard tumor size, Estrogen and Progesterone status.

Conclusion: A significant correlation was found between strong E-cadherin expression and node negative cases indicating that E-cadherin can be used as a prognostic and predictive marker.

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Introduction:-
Worldwide, Breast cancer is the most common cancer in women. It is the second most common cancer overall. It accounts for 12% of all new cancer cases and 25% of new cancer cases in women.[1]

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According to WHO incidence of breast cancer in North Africa among females reaches up to 42%.[2,3] Based upon results of Egyptian National Cancer Registry Program (NCRP), the highest incidence of cancer among females is breast cancer representing (32.0%) followed by liver cancer (13.5%).[4]

E-Cadherin is a calcium-dependent epithelial cell adhesion molecule expressed at adherens junctions. It is one of the most important molecules in cell-cell adhesion.[5,6]

E-cadherin tumor suppressor genes are active area of research in tumor genesis.[7] The calcium-dependent interactions among E-cadherin molecules are critical for the formation and maintenance of adherent junctions in areas of epithelial cell-cell contact. Loss of E-cadherin-mediated-adhesion characterizes the transition from benign lesions to invasive, metastatic cancer. [7-9] Furthermore, there is evidence that E-cadherin may also play a role in the *wnt* signal transduction pathway, together with other key molecules involved in it.[10]

Down-regulation or complete shutdown of E-cadherin expression, mutation of the E-cadherin gene, or other mechanisms that interfere with the integrity of the adherens junctions, are observed in carcinoma cells. In human tumors, the loss of E-cadherin-mediated cell adhesion correlates with the loss of the epithelial morphology and with the acquisition of metastatic potential by the carcinoma cells.[13-15] Thus, a tumor invasion/suppressor role has been assigned to this gene.[11,12]

It has been reported that inactivating mutations of E-cadherin gene are highly frequent in infiltrating lobular breast carcinomas, metastasizing ductal breast cancer and diffuse gastric carcinomas.[16,17]

Studies showed that E-cadherin is associated with aggressive behavior. This data indicates that E-cadherin can provide an accurate determination of the aggressiveness of cancer. This information can be used to identify breast cancer patients who will benefit by more aggressive treatment, thus increasing chances of survival.[16-18]

Aim Of The Work:-
The present work aimed at studying of E-cadherin in invasive breast cancer and its correlation with lymph node status and other clinicopathological parameters to identify it's utility as a novel prognostic marker of breast cancer, and a potential to predict which patients will experience more aggressive forms of the disease and so receive aggressive surgery and treatment.

Material And Methods:-
Materials:-
The present study constituted of seventy cases of invasive breast cancer admitted to the Medical Research Institute hospital, Alexandria University which were classified as follows: fifty eight cases of invasive ductal carcinoma, ten invasive lobular carcinoma, One case of mucinous carcinoma and One case of papillary carcinoma

The standard therapy for breast cancer was surgical resection, either Modified Radical Mastectomy (MRM) or conservative breast cancer with sentinel lymph node biopsy / axillary dissection.

Cases were collected between May 2015 and June 2016 (age ranged from 25 to 76 years), and for which ER, PR Her2 statuses were available from the archive of the Pathology Department of Medical Research Institute Alexandria University, Egypt. All cases had been diagnosed by two doctors at the department of pathology.

Methods:-
E-cadherin immunohistochemical staining and interpretation:-
Immunohistochemical staining was performed on paraffin block sections using E-cadherin antibody; the antibody used, antigen retrieval and dilution are illustrated in the following table.

Table 1:-E-cadherin antibody formations.

Antigen	Antibody	Clone	Laboratory	Antigen Retrieval	Dilution
E-cadherin	Monoclonal mouse	NCH-38	Dako	Citrate,PH6	1:100

Serial 5 um thick paraffin sections were subjected to immunohistochemical staining for E-cadherin as follows:
1. Sections were deparaffinized in xylene and rehydrated in graded ethanol (100% to 70%).
2. Slides were then washed 2 times in phosphate-buffered saline (PBS) each for 5 minutes.
3. Slides were incubated in Hydrogen Peroxide Block for 10-15 minutes, to block endogenous peroxidase activity in order to reduce non-specific background staining.
4. The slides were washed 4 times in PBS each for 5 minutes.
5. Antigen retrieval was performed by heating in a microwave oven in citrate buffer (0.01M Na citrate monohydrate, PH 6.0) for 15 minutes in thermo resistant container; slides were allowed to cool down in buffer to room temperature.
6. Sections were then washed in PBS 4 times each for 5 minutes.
7. Primary antibodies were then applied and incubated overnight.
8. Sections were washed 4 times in PBS each for 4 minutes.
9. The slides were incubated with biotinylated goat antipolyvalent for 10 minutes then washed 4 times each for 5 minutes.
10. Then the sections were incubated with streptavidin peroxidase for 10 minutes.
11. The slides were washed 4 times each for 5 minutes.
12. DAB was used as a chromogen applied to the slides for 15 minutes in the dark at room temperature to detect reaction product.
13. Slides were then washed 4 times in water. Slides were counterstained with Meyer's hematoxyline and microscopically examined by a light microscope.

E-cadherin immunohistochemical staining interpretation:-
E-cadherin positive immuohistochemical staining was accepted if membranous and/or cytoplasmic brown staining takes place.

The staining of E-cadherin was scored as the product of the staining intensity and the percentage of cells stained on a scale of 0-3 as follows: No staining=0, weak staining and less than 10% of the tumor cells show positive reaction=1+, moderate staining and more than 10% show positive reaction for E-cadherin =2+, strong staining in most of the tumor cells =3+.[19]

According to the score we divided cases into negative one (having a score of 0 or 1+) and positive one (having a score 2+ or 3+).

Positive membranous and or cytoplasmic staining of luminal cells was used as an internal positive control.

Statistical analysis of the data[20]:-
Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp)[21] Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

The used tests were
1. **Chi-square test:** For categorical variables, to compare between different groups.
2. **Fisher's Exact or Monte Carlo correction:** Correction for chi-square when more than 20% of the cells have expected count less than 5.
3. **Student t-test:** For normally distributed quantitative variables, to compare between two studied groups.
4. **Mann Whitney test:** For abnormally distributed quantitative variables, to compare between two studied groups.

Results:-
**Clinicopathologic characteristics of the studied cases of breast cancer:-**
These characteristics are demonstrated in table 2.

Table 2:-Distribution of cases according to the studied clinicopathological parameters.

Clinicopathological characteristics	N0	%
Tumor size		
T1(<2cm)	10	14.3
T2(2-5cm)	54	77.1
T3(>5cm)	6	8.6
Histologic subtypes		
Ductal carcinoma	58	82.9
Lobular carcinoma	10	14.3
Mucinous carcinoma	1	1.4
Papillary carcinoma	1	1.4
Histologic grades		
< grade3	54	22.9
>grade3	16	77.1
Lymphatic vascular invasion		
Negative	37	52.9
Positive	33	47.1
Lymph node status		
No	29	41.4
N1 (1-3)	13	18.6
N2(4-9)	19	27.1
N3 (>9)	9	12.9
Extranodal extension		
Negative	44	62.9
Positive	26	37.1
Disease stage		
Low stage(1,2)	40	57.1
High stage(3,4)	30	42.9
ER		
Negative	21	30.0
Positive	49	70.0
PR		
Negative	28	40.0
Positive	42	60.0
HER2		
Negative	55	55.0
Positive	15	15.0
Type of surgery		
Conservative surgery	34	48.6
Modified Radical Mastectomy	36	51.4

Relation between E-cadherin expression and the studied clinicopathological characteristics:-
Representative sections were stained with the monoclonal antibody against E-cadherin antigen. Positive internal control is shown in figure (1). E-cadherin expression was positive in 44 cases (62.9%) and negative in 26 cases (37.1%).
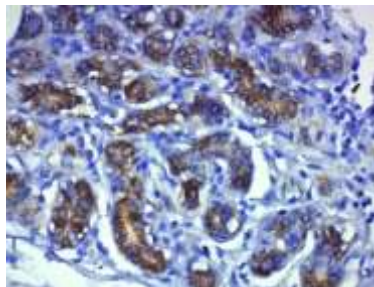
Figure 1:-Strong membranous and/or cytoplasmic staining of luminal cells (positive internal control)

There was no statistically significant differences between E-cadherin + and E-cadherin – cases as regards the tumor size. The E-cadherin staining characteristics varied with respect to percentage of tumor cells involved and intensity. Significant positive staining in higher grades of invasive carcinoma was demonstrated. There was a statistically significant association between E-cadherin expression and LVI with more positive staining in cases without lymphovascular invasion. There is a statistically significant association between E-cadherin expression and the lymph node status with strong positive staining in node negative cases. Extranodal extension shows a statistically significant association with E-cadherin negative staining. table 3.

Table 3:-Comparison between E-cadherin positive and negative according to tumor size, histological subtype, tumor grade, lymphatic involvement (n= 70)

| | Total (n= 70) | | E-cadherin | | | | χ^2 | P |
| | | | Negative (n= 26) | | Positive (n= 44) | | | |
	No.	%	No.	%	No.	%		
Tumor Size								
T1	10	14.3	4	15.4	6	13.6	0.201	FEp=
T2	54	77.1	20	76.9	34	77.3		1.000
T3	6	8.6	2	7.7	4	9.1		
Histological Subtype	10	14.3					19.744*	<0.001*
Lobular carcinoma	58	82.9	10	38.7	0	0.0		
Ductal carcinoma	1	1.4	16	61.6	42	95.5		
Mucinous arcinoma	1	1.4	0	0	1	2.3		
Papillary carcinoma			00	00	1	2.3		
Grade								
Grade I-II	54	77.1	26	100.0	28	63.6	12.256	<0.001*
Grade III	16	22.9	0	0.0	16	36.4		
Lymphovascular Invasion								
Negative								
Positive	37	52.9	10	38.5	27	61.4	4.440	0.049*
	33	47.1	16	61.5	17	38.6		
Lymph nodes status	29	41.4					18.803	<0.001*
No	13	18.6	6	23.1	23	52.3		
N1	19	27.1	4	15.4	9	20.5		
N2	9	12.9	7	26.9	12	27.3		
N3			9	34.6	0	0.0		
Extranodal extensions							10.554	0.001*
Negative	44	62.9	10	38.5	34	77.3		
Positive	26	37.1	16	61.5	10	22.7		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

There was no statistically significant differences between E-cadherin + and E-cadherin – cases as regards the ER or PR states.There is a statistically significant association between E-cadherin expression and Her2 status. Table 4

Table 4:-Relation between E-cadherin and ER, PR and Her-2 Scoring (n= 70

| | Total (n= 70) | | E-cadherin | | | | χ^2 | P |
| | | | Negative (n= 26) | | Positive (n= 44) | | | |
	No.	%	No.	%	No.	%		
ER scoring								
Negative	21	30.0	8	30.8	13	29.5	0.012	0.914
Positive	49	70.0	18	69.2	31	70.5		
PR scoring								
Negative	28	60	7	26.9	21	47.7	2.947	0.086
Positive	42	40	19	72.1	23	52.3		

Her2µ scoring								
Negative	55	78.6	25	96.2	30	68.2	7.595	0.006*
Positive	15	21.4	1	3.8	14	31.8		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups
*: Statistically significant at p ≤ 0.05

There is a statistically significant association between E-cadherin expression and the disease stage at diagnosis with negative expression in higher stages. There was also statistically significant association between E-cadherin expression and type of surgery with more breast conservation rates in cases with positive staining. Table 5

Table 5:-Relation between E-cadherin and type of surgery (n= 70)

	Total (n= 70)		E-cadherin				χ^2	p
			Negative (n= 26)		Positive (n= 44)			
	No.	%	No.	%	No.	%		
Stage at diagnosis							8.636	0.013*
I	15	21.4	3	11.5	12	27.3		
II	25	35.7	6	23.1	19	43.2		
III	30	42.9	17	65.4	13	29.5		
Type of surgery								
Conservative	34	48.6	5	19.2	29	65.9	14.255*	<0.001*
MRM	36	51.4	21	80.8	15	34.1		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups
*: Statistically significant at p ≤ 0.05

Discussion:-

Breast cancer is the most common malignancy in women, and it is complex in terms of disease heterogeneity associated with different morphologies, molecular characteristics, clinical behavior, and response to therapeutics. Prognostis in breast cancer has relied on the clinicopathological parameters such as age and tumor grade, and individual molecular markers such as hormone receptor, human epidermal growth factor status (HER2) and Ki67. Axillary lymph node status is the single most important prognostic variable in the management of patients with primary breast cancer. Yet, it is not known whether metastasis to the axillary nodes is a time-dependent variable or is a marker for a more aggressive tumor phenotype.

Therefore, there is still need for new biomarkers that can predict the tumor prognosis and aggressiveness which would serve for targeted treatment.

E-cadherin, a calcium-dependent epithelial cell adhesion molecule, is a potential prognostic marker as its loss has been associated with metastases, thereby providing evidence for its role as an invasion suppressor.

In this study, we performed an immunohistochemical based study to evaluate the expression of E-cadherin in invasive breast cancer and it's correlation with variable clinicopathologic parameters among which is the lymph node status and type of surgery used for management.

Our Cohort was selected based on the availability of tissue and immunohistochemical status data. Ten cases of lobular carcinoma were collected, one case of mucinous carcinoma, one case of papillary carcinoma and the rest were invasive ductal carcinoma (58 cases).

In the present study, E-cadherin expression was positive in 72.5% of infiltrating ductal carcinomas, noting that it was negative in the nearby areas of DCIS; All the lobular carcinomas were negative for E-cadherin expression, even for the lobular in situ components. These data indicate that loss of E-cadherin expression is an early event in the formation of the lobular type of breast carcinoma. The mucinous carcinoma and the papillary carcinoma cases showed strong positivity to E-cadherin staining.

Our results were close to those of Moll et al (79% of E-cadherin positivity in IDC cases)[22], but less than those of Howard et al (84% positivity)[23] and Gamello et al (94% positivity).[24]

All the lobular carcinoma were negative for E-cadherin expression, which is consistent with most of the published data.[23-25] The absence of E-cadherin indicates a partial loss of epithelial differentiation and may account for the extended spread of lobular carcinoma in situ and the peculiar diffuse invasion mode of the ILC.

In the current study, the staining was strong linear at the cell borders of the well and moderately differentiated tumors but was heterogeneous and dotted over cell borders in the most of the high grade tumors. That was concordant with Moll et al and Gamello [22,24] that proved that high grade tumor are associated with less E-cadherin expression. This was in contrast with the finding of Howard et al [23].

The persistence of E-cadherin expression in high grade tumors and large size tumors is opposite to most of the reports of E-cadherin in breast cancer which have showed down regulation of this molecule in tumor progression. The significance of its expression is unclear at this point. Staining of E-cadherin may persist into late stages of breast carcinoma though it may be functionally inactivated. [25] Another scenario is a change in the function of E-cadherin molecule that enables the tumor cells to adhere to the vascular epithelium, thus improving the capacity to metastasize. Another possible explanation is that only the complete E-cadherin/catenin complex is associated with no evidence of metastasis. It is possible that a defect in the E-cadherin/catenin complex without a change in its expression may be responsible for the malignant progression. [26-29]

In our study the node negative tumors showed association with the strong E-cadherin expression which is consistent with the results of Banklavi et al. [28] and in contrast with the findings of Howard et. al.[23] who found persistence of strong expression in cases with more lymph node positivity and proposed that increased expression of E-cadherin is necessary for tumor progression in patients with aggressive breast cancer.

Regarding the role of E-cadherin development of lymphatic tumor emboli, of the 44 E-cadherin positive cases, 27 cases did not show lymph vascular invasion and 17 cases showed lymph vascular invasion. In the lymph, vascular invasion positive cases the majority of tumor cells (including intralymphatic emboli) expressed E-cadherin with high intensity. Emboli also exhibit high intensity expression. These finding suggest that E-cadherin plays an important role in tumor development and growth within the lymphatics, and challenges the hypothesis that loss of expression is necessary for metastases.

In the current study there was a statistically significant correlation between E-cadherin expression and Her2 similar to the work of Howard but in contrast with the work of D, Souza et al.[30]

One of many observations in this study is the strong correlation between the E cadherin expression and conservative surgery rates, which suggest that this biomarker can be used as a clinical guide to predict the most suitable treatment options for patients. The loss of expression may guide surgeons to shift to mastectomy in equivocal cases where other parameters are not consistent with each other's. These data require further research. No similar results were obtained from other studies.

The disparity between the results of different studies may be due to differences in the population under investigation, which might be indicative of the disparity in the biology of breast cancer in divergent populations and may be due to late discovery of the disease in our country due to lake of screening programs.

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