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# Loss of E-Cadherin Expression in Colorectal Carcinoma and its Prognostic Significance

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# Abstract

Aim: The current work is assumed to assess E-cadherin expression in a series of Libyan patients with colorectal carcinoma cases to acquire an perception in its likely prognostic value in colorectal cancer.

Materials and Methods: A series of 81 Libyan patients with colorectal carcinoma were retrospectively considered. All carcinomas were chosen from the records of the Department of pathology, Benghazi University, derived from the period from January 2007 to December 2011. All cancers were classified using the histopathological measures of the World Health Organization (WHO) classification, and staging was made fitting to the criteria of tumor-node-metastasis (TNM) classification of the International Union against Cancer.

**Results and Discussion:** Immunohistochemical (IHC) analysis was done operating the automatic system (BenchMark XT, Ventana Medical System, Inc. Tucson, Arizona, USA). This entirely automated processing of code-labeled slides involved baking of the slides, solvent free deparaffinization, antigen retrieval in a cell conditioning buffer CCI (Mild: 36 minutes conditioning, and standard: Two staining indexes were calculated: the membrane index (MI) and cytoplasmic index (CI). These indices were estimated with both the intensity of staining and the fraction of positively-stained cells taken into account using the following formula:  $I = 0 \times f0 + 1 \times f1 + 2 \times f2 + 3 \times f3$  Our records showed that loss of E-cadherin expression is more often detected in older age group and in colorectal cancer patients with lymph node involvement; 75% of tumors with lymph node involvement exhibited negative expression of E-cadherin. One of the most significant finding of the existing study is the association of E-cadherin expression with the disease sequel.

**Conclusion:** These data propose that the loss of the E-cadherin function could be connected with invasiveness, lymph node metastasis and distant metastasis resulting in poor prognosis.

Keywords: Colorectal Carcinoma; Cadherin; Immunohistochemistry

# Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer expiries, with 1 million new cases identified annually and more than half a million cases die from this illness, accounting for 8% of all cancer-related deaths globally [1,2] Unluckily, the conventional prognostic issues for patient survival and the traditional staging system are unsuitable for identifying those CRC patients who convey high risk of poor prognosis. Thus, there is a necessity for identification of more effectual prognostic factors, including molecular markers to guess cancer outcome and improve therapeutic choices [3-6], it has been stated that CRC is a potentially remediable disease if spotted at an earlier stage [7]. Consequently, it is important to distinguish clinically beneficial biomarkers that can identify CRC at an initial stage. Ecadherin is a transmembrane Type I glycoprotein containing a cytoplasmic domain of 150 aminaocids and an extracellular domain of 550aa. E. caderin is involved in the generation and upholding of adherens junctions (AJ) via hemophilic (E-cadheri-E-candherin) interaction and most often homotypic (epithelial-epithelial cell interaction) adhesion. Therefore, the adhesion molecule E-cadherin, a cell surface glycoprotein plays a vital role in the maintenance of the normal structure and function of adult epithelial tissues [8,9]. These complexes are classically dispersed in the adherens junctions [10-12]. Studies conducted throughout the past decades have informed that the loss of these normal intercellular junctions precedes the tumor invasion and metastasis [13,14]. Thus, loss of E-cadherin-mediated adhesion seems to be of chief value in the neoplastic process, allowing cells to escape normal growth control signals, resulting in loss of differentiation and augmented cell proliferation with invasive behavior [15]. As it was not too extensively studied, we assessed E-cadherin expression in a chain of Libyan colorectal cancer cases and its connection with a variety of clinicopathological variables, disease relapse and long term outcome to get perception in its potential predictive value in colorectal cancer in Libyan patients.

### **Patients and Methods**

A sequence of 81 Libyan patients with colorectal carcinoma was retrospectively studied. All carcinomas were designated from the archives of the Department of pathology, Benghazi University, derived from the period from January 2007 to December 2011, based on accessibility of representative paraffin blocks. Informed agreement was obtained from all the patients and endorsement for the study was attained from Institute Ethics Review Board. All the patients were followed up until death or when last met alive at their clinical appointment (June 2012) with the median FU-time of months (range: 3-142 month, mean: 45 month). The extent of follow-up and the outcomes at the end of follow-up were determined for each patient from hospital and clinic records. One skilled pathologist confirmed all histological diagnoses. All tumors were classified using the histopathological criteria of the World Health Organization (WHO) classification, and staging was made according to the criteria of tumor-node-metastasis (TNM) classification of the International Union against Cancer [16]. Clinical data of the patients are obtainable in Figure a.

#### **E-cadherin Immunostaining**

Formalin-fixed, paraffin-embedded primary colorectal tumor tissue was acquired from 81patients. Sections were cut consecutively at 5µm for immunohistochemical (IHC) analysis. IHC analysis was done using the automatic system (BenchMark XT, Ventana Medical System, Inc. Tucson, Arizona, USA). This fully automated handling of code-labeled slides included baking of the slides, solvent free deparaffinization, antigen retrieval in a cell conditioning buffer CCI (Mild: 36 minutes conditioning, and standard: 60 minutes conditioning), incubation with Rabbit monoclonal anti-E-cadherin antibody, 7.0ml ready-to-use from Spring Bioscience (clone: SP64, Catalog no. M3641, 6920 Koll Center Parkway, CA 94566, USA), for 32 min, at 37°C. Application of I-ViewTM DAB Detection Kit (Lot no. B05860AZ), which, involves: I-View DAB HRP, I-View DAB Inhibitor, I-View DAB Biotin, I-View DAB H<sub>2</sub>O<sub>2</sub>, and I-View DAB Copper. Counterstaining with haematoxylin II (C00758) was done for 4 minutes, and post-counterstaining with bluing reagent (B11129) was done for 4 minutes as well. After staining, the sections were dehydrated in ethanol, cleared in xylene, and covered with Mountex and cover slips.

#### **Evaluation of E-cadherin staining**

The evaluation of the E-cadherin staining was accomplished with a light microscope at X40 magnifications and with the evaluator blinded to the information on tumor grade, stage, or clinical outcome. Membranous and cytoplasmic staining was gauged. For cell membrane staining, four categories were used, (3+++, 2++, 1+, -) (0) no expression, no detectable staining in < 10% of the membrane. (1) Weak but detectable discontinuous staining present in 10-39% of the membranes. (2) Moderate, clearly positive discontinuous staining present in 40-90% of the membranes and (3) Intense, continuous staining of the membrane creates a honeycomb pattern. The cytoplasmic staining was also graded into four categories: (0) Negative, no detectable staining, (1) Weak, but detectable still staining, (2) Moderate, clearly positive but still weak, (3) Heavy staining, intense .Two staining indexes were calculated: the membrane index (MI) and cytoplasmic index (CI). These indices were estimated with both the intensity of staining and the fraction of positively-stained cells taken into account using the following formula:

 $I=0 \ge f0 + 1 \ge f1 + 2 \ge f2 + 3 \ge f3$ 

Where I; is the staining index, f0-f3 are the fractions of the cells showing a defined level of staining intensity (from 0 to 3). Hypothetically, the index scores could vary between 0 and 3 [17,18]. The reproducibility of the evaluation of E-cadherin staining indices was tested by employing intra-observer reproducibility.

#### **Statistical analysis**

The extracellular domain interacts homotypically with the Ecadherin molecules of adjacent cells and maintains intercellular adhesion Its cytoplasmic tail comprises a complex group of proteins including intracytoplasmic proteins, such as catenins.

Statistical analyses were made using the IBM SPSS Statistics (IBM Company, NY, USA) and STATA (StataCorp., Texas, USA) software packages (IBM PASW Statistics for Windows, version 19). Frequency tables were analyzed using the Chi-square test, with likelihood ratio (LR) or Fischer's exact test being used to assess the significance of the correlation between the categorical variables. Analysis of variance (ANOVA) was only used deriving the mean values (and their 95%CI) of each individual stratum. Univariate

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survival analysis for the outcome measure (DSS, DFS) was built on Kaplan-Meier technique, with log-rank (Mantel-Cox) assessment test. In all tests, the values p<0.05 were regarded statistically note-worthy.

#### Results

## Patterns of E-cadherin expression in CRC samples

The expression pattern of E-cadherin was membranous and cytoplasmic in normal colonic epithelium and in the tumor area as well. Examples of the staining patterns of E-cadherin are demonstrated in Figures 1a, b, c and d. Of the 81 tumors, 41 (51%) were considered negative (staining intensity 0; figure 1d), while 40 (49%) were considered positive (staining intensity >1; figure 1b, c). Strong expression of E-cadherin was observed in normal colonic mucosa (figure 1a).



Figure 1: Immunohistochemical staining for E-cadherin expression in colorectal adenocarcinoma; (A) Normal colonic epithelium showed membranous expression of E-cadherin;
(B) Adenocarcinoma of colon showed cytoplamic expression of E-cadherin; (C) Adenocarcinoma of colon showed cytoplamic and membranous expression of E-cadherin; (D) Adenocarcinoma of colon showed no expression of E-cadherin. Magnification of all samples is at (X40).

# Correlation of E-Cadherin expression with clinicopathological features

The distribution of E-cadherin expression in tumor samples in relation to clinicopathological features is presented in (Figure a and b). Using different cut-off points (mean, median, and 2-teir score (0 Vs 1, 2, 3) and (0,1, Vs 2,3). The existent study revealed that a meaningful correlation between E-cadherin expression and tumor localization in that tumors appearing in the right and left colon express E-Cadherin farther than tumors arising in the Rectum (p< 0.043), loss of E-Cadherin expression was more recurrently detected in the Rectal adenocarcinomas. Moreover, E-Cadherin expression displayed a significant connection with the age (p< 0.002), in that tumors of the younger patients (< 55years), expressed E-Cadherin more than tumors of the old patients, loss of E-Cadherin was more frequently detected in older patients (>55 years). Remarkably, Loss of E-Cadherin expression associated Considerably (p< 0.039) with lymph node metastasis.

Features	Number of cases (%)	E-cadherin expression		
		Negative (0)	Positive (1,2,3)	p-varue
Gender				0.996
Male	39 (49%)	20 (51%)	19 (49%)	
Female	41 (51%)	21 (51%)	20 (49%)	
Age group (years)				0.996
≤ 55	41 (51%)	20 (51%)	20 (49%)	
> 55	40 (49%)	21 (51%)	20 (50%)	
Lymph node involvement				0.751
Yes	33 (52%)	20 (61%)	13 (39%)	
No	30 (48%)	17 (57%)	13 (43%)	
Tumor grade				0.490
We11	23 (29%)	10 (50%)	13 (57%)	
Moderate	48 (60%)	25 (52%)	23 (48%)	
Poor	9 (11%0	6 (67%)	3 (33%)	
Tumor location				0.043
Right colon	20 (25%)	10 (50%)	10 (50%)	
Left colon	42 (53%)	17 (40%)	25 (60%)	
Rectum	17 (22%)	13 (77%)	4 (23%)	
Tumor stage				0.863
I	9 (12%)	5 (56%)	4 (44%)	
п	24 (32%)	11 (46%)	13 (54%)	
ш	17 (22%)	9 (53%)	8 (47%)	
IV	26 (34%)	15 (58%)	11 (42%)	
Recurrence				0.433
No	73 (91%)	36 (49%)	37 (51%)	
Yes	7 (9%)	5 (71%)	2 (29%)	
Distance metastasis				0.524
No	50 (66%)	25 (50%)	25 (50%)	
Yes	26 (34)	15 (58%)	11 (42%)	

Figure a

Table 2. Correlation of E-Cadherin Expression (below mean vs. above mean) and Clinico-pathological Features of CRC samples.

Feetener	Number of cases (%)	E-cadherin expression		
r earures		< Mean	> Mean	p-value
Gender				0.537
Male	39 (49%)	24 (62%)	15 (38%)	
Female	41 (51%)	23 (55%)	19 (45%)	
Age group (years)				0.002
≤55	41 (51%)	17 (41%)	24 (59%)	
> 55	40 (49%)	30 (75%)	10 (25%)	
Lymph node involvement				0.039
Yes	30 (48%)	15 (50%)	15 (50%)	
No	33 (52%)	24 (73%)	9 (27%)	
Tumor grade				0.259
Well	23 (29%)	16 (70%)	7 (30%)	
Moderate	48 (60%)	26 (54%)	22 (46%)	
Poor	9(11%0	5 (56%)	4 (44%)	
Tumor location				0.220
Colon	62 (73%)	37 (63%)	22 (37%)	
Rectum	17 (26%)	13 (77%)	4 (24%)	
Tumor stage				0.470
I	9 (12%)	6(67%)	3 (33%)	
Π	24 (32%)	13 (54%)	11 (46%)	
ш	17 (22%)	11 (65%)	6 (35%)	
IV	26 (34%)	17 (65%)	9 (35%)	
Recurrence				0.715
No	73 (91%)	43 (60%)	30 (41%)	
Yes	7 (9%)	4(57%)	3 (43%)	
Distance metastasis				0.185
No	50 (66%)	27 (54%)	23 (46%)	
Yes	26 (34)	17 (65%)	9 (35%)	

Figure b

of E-Cadherin Expression (negative vs. positive) and CI

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On the other hand, tumor recurrence, tumor invasion, gender, distance metastasis and status at end point had no weighty link with the expression of E-cadherin.

#### Survival outcome of CRC patients

In Kaplan-Meier survival analysis (at mean as cut-off point) there was a significant (p< 0.03) difference in DFS between patients who have E-cadherin expression above mean and those with E-cadherin expression below mean (Figure 2). Interestingly, 98% of the patients with tumors expressing E-cadherin above mean showed longer disease free survival in contrast with only 50% of patients with tumors expressing E-cadherin below mean. In Kaplan-Meier survival analysis (0 vs 1, 2, 3 as a cut-off point), there was a difference (p< 0.08) in DFS between patients with E-cadherin positive tumors (longer DFS) and those with negative tumors. At 4-year follow-up, 98% of the patients with E-cadherin positive tumors showed longer DFS as compared with 53% of patients with no E-cadherin expression (Figure 3).



Figure 2: E-cadherin expression (below mean vs. above mean) as determinant of disease- free survival (DFS) of CRC in univariant Kaplan Meier analysis (p<0.03, log rank).



**Figure 3:** E-cadherin expression (negative vs. positive) as determinant of disease-free survival (DFS) of CRC in Univariant Kaplan Meier analysis (p<0.08).

#### Discussion

In present study, we have inspected the expression of E-cadherin in colorectal cancer of Libyan patients. In unity with previous reports, we showed that the pattern of expression of E-cadherin was both membranous and cytoplasmic in primary colorectal tumors [19,20]. Moreover, our data showed that loss of E-cadherin expression is more often detected in older age group and in colorectal cancer patients with lymph node involvement; 75% of tumors with lymph node involvement exhibited negative expression of E-cadherin. The same remark was demonstrated by Fang., *et al.* [21], who testified that loss of E-cadherin expression was allied with lymph node involvement. A parallel finding has been conveyed by Miladi-Abdennader., *et al.* [22], who witnessed that expression of E-cadherin was associated with age of patients at diagnosis and (tumor size) in colorectal cancer.

Results from the existing work suggest that the expressions of E-cadherin were different in relation to the primary site of tumor. Rectal tumors tend to have negative E-cadherin expression whereas left site tumors revealed increased E-cadherin expression. This finding is unswerving with Aamodt., *et al.* [23], who spotted that there is difference between rectal and colon cancer in expression of E-cadherin. The reason for this difference regarding the prognostic value of E-cadherin between rectal and colon adenocarcinomas is hard to clarify, but could be accredited to diverse tumor biology within these two entities.

In the present research, we did not find any major associations between E-cadherin expression and both tumor differentiation and depth of primary tumor dissimilar to the reports stated concerning the expression of E-cadherin and tumor differentiation in colorectal carcinoma [24-26]. All these findings involve E-cadherin as biologic factor that might affect the performance of the tumor cell population. Numerous studies have testified that down-regulation of E-cadherin in colorectal cancer is seldom attributed to E-cadherin gene mutation [27,28], a phenomenon frequently perceived in diffuse-type gastric [29] and lobular breast carcinomas [30]. Efstathiou., et al. detected E-cadherin inactivating mutation discovered in only 7% of colorectal carcinoma cell lines. Also, basic mutations or loss of heterozygosity do not perform a central part for E-cadherin inactivation in colon cancer. He decided that other epigenetic events such as promoter methylation have been implicated [31,32].

One of the most vital finding of the present study is the connotation of E-cadherin expression with the disease sequel. The mean DFS was meaningfully (p< 0.03) longer among patients with Ecadherin positive tumors than in those with negative E-cadherin expression. This is steady with the report described by Ngan., *et al.* who told that loss of E-cadherin (and CD44) expression was point-

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edly associated with shorter survival than did the high expression tumors and loss of both marker has been interconnected to poor prognosis in colorectal cancer [33].

Reduced levels of E-cadherin expression were described in many immunohistochemical studies on epithelial malignancies [34-36]. In some tumor types, including CRC, the loss of E-cadherin expression is linked with the loss of tumor differentiation and is exposed to be correlated with an increased probability of distant metastasis [37]. The down-regulation of E-cadherin is seen most obviously in carcinomas showing infiltrative growths related with tiny intercellular cohesion, such as invasive lobular carcinoma of the breast and diffuse gastric adenocarcinoma including gastric signet-ring cell carcinoma [38-40]. These records advocate that the loss of the E-cadherin function could be accompanying with invasiveness, lymph node metastasis and distant metastasis ending in poor prognosis. Therefore, the current study disclosed that loss of E-cadherin expression in advanced stage of the disease stages lead toward metastatic phenotype and poor prognosis in colorectal cancer.

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