Original Article

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Pathology Section

Study of CDX2 and E-cadherin Expression in Colorectal Cancer and their Association with Clinicopathological Parameters: A Cohort Study

SURENDRAN DHANASREE VELLIKAL[1], RANJITA PANIGRAHI[2], PRAJNA DAS[3], SAROJ RANJAN SAHU[4]

ABSTRACT

Introduction: Colorectal Cancer (CRC) is the third most common cancer worldwide. Inspite of new treatment modalities and early diagnostic tools, 935,000 cancer related deaths are recorded worldwide every year. Among various biological markers caudal-type homeobox 2 (CDX2) and adhesion molecules (E-cadherin, Beta-catenin), are said to be implicated in the invasion and advancement of colon cancer.

Aim: To study the Immunohistochemical (IHC) expression of CDX2 and E-cadherin in CRC and their association with various clinicopathological parameters.

Materials and Methods: This ambispective cohort study included 51 histologically proven CRC cases in a Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India, for four years nine months. IHC for CDX2 and E-cadherin was done. Staining intensity and proportion were noted, multiplied and scored. Immunoreactive Score (IRS) of >3 was considered as positive for CDX2, while E-cadherin expression was categorised as low expression (score 0, 1) and high expression (score 2, 3). Statistical analysis of CDX2 and E-cadherin expression in CRC and association with clinicopathological parameters (age, sex, tumour site, histopathological type, histopathological grade, Lymphovascular Invasion (LVI), Perineural Invasion (PNI) and lymph node status) was done by using Microsoft Excel and IBM SPSS V 26. Chi-square test was done for association and p-value of <0.05 was considered as significant.

Results: A significant association was found between CDX2 expression with gender and lymph node status (p-value=0.004 and 0.038, respectively). A linear trend was observed between CDX2 and E-cadherin expression with histological grade. The higher grades of tumours showed negative CDX2 and low E-cadherin expression with p-value of 0.001 for both the markers. Cumulative survival rates for both the markers did not show any significant association statistically (p-value of 0.324 and 0.630, respectively).

Conclusion: Higher grades of tumour was associated with negative CDX2 and low E-cadherin expression. Nodal metastasis was linked to negative CDX2 expression. Significant association was observed between CDX2 and E-cadherin. This may help in better understanding and prognostication of CRC when both the markers are studied.

Keywords: Caudal-type homeobox 2, Epithelial-mesenchymal transition, Immunohistochemistry

INTRODUCTION

The CRC is a major health issue globally. It is the third most common cancer in the world and second in terms of mortality [1]. According to the Global Cancer Observatory (GLOBOCAN) estimates, new cases of CRC were 1.9 million with 935,000 cancer related deaths for the year 2020 [1]. Out of all cancer cases in 2020, the World Health Organisation (WHO) estimated CRC to be the third most common newly diagnosed cancer in men and second most common in women [1].

In India, CRC is the sixth most common cancer and ranks seventh in terms of mortality [1]. According to GLOBOCAN estimates, in India, there were 70,038 new cases and 40,993 deaths for the year 2022 [1]. Out of all cancer cases, CRC is the fourth most common newly diagnosed cancer in men and fifth most common in women [1].

The CRC arises through a gradual aggregation of mutations in Adenomatous Polyposis Coli (APC) gene at early stages; Tumour protein 53 (TP53) and Rat Sarcoma virus oncogene homolog (RAS) at later stages [2]. It was observed that only 7% of CRCs had mutations in all three genes, indicating that additional genes might be responsible for tumour genesis [3]. Therefore, a better understanding of the molecular mechanism and study of further biological markers are crucial. Among various biological markers CDX2 and adhesion molecules (E-cadherin, beta-catenin), are said to be implicated in the invasion and advancement of colon cancer.

In the normal intestinal epithelium, columnar morphogenesis and cell differentiation depend on the nuclear transcription factor CDX2 [4]. It has a role in tight adherens and desmosomal junctions of colonic epithelial cells [5]. It helps in tumour-inhibition [4,6,7]. However, a thorough analysis of its anti-tumour effects has not been conducted yet.

E-cadherin, a transmembrane cell adhesion molecule, is essential for growth and maturation of epithelial cells. It maintains the cohesiveness of epithelial cells and is essential for the integrity of epithelial tissues [8]. Epithelial-Mesenchymal Transition (EMT) is characteristically associated with E-cadherin loss [9]. Since CDX2 was found to inhibit metastasis and EMTs in CRC [6], interest in role of CDX2 for regulation of E-cadherin activity has increased. E-cadherin is therefore a helpful biomarker to assess differentiation, malignant phenotype and invasiveness in CRC [10].

The present study will help us to understand the relationship of CDX2 and E-cadherin for a better comprehension of the molecular mechanisms behind colon carcinogenesis in order to provide the best treatment plan for each. Aim of this study was to analyse CDX2 and E-cadherin expression by immunohistochemistry in histologically proven cases of CRC in radical surgical specimens and their association with histological types, grades, LVI, PNI, and lymph node status along with various clinical parameters like age, sex and location of the tumour. Correlation of CDX2 and E-cadherin

expression with above clinicopathological parameters along with short term follow-up was done whenever possible.

MATERIALS AND METHODS

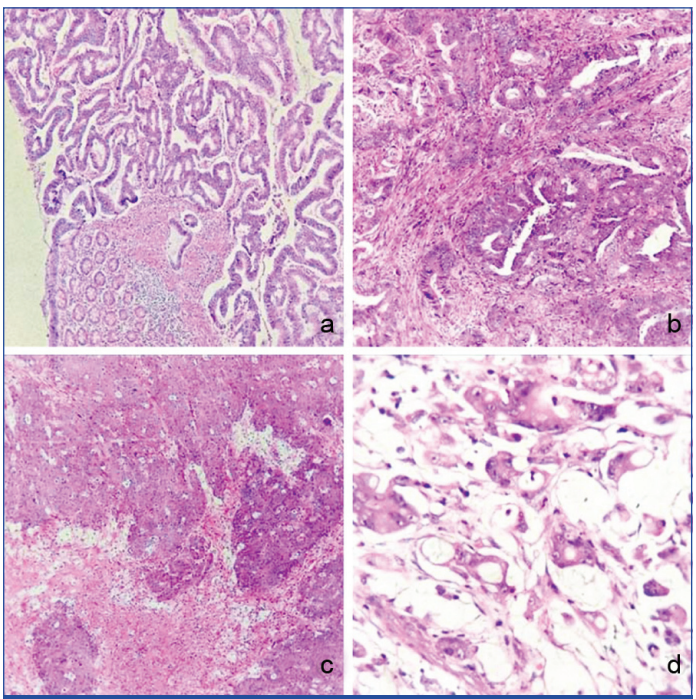
This ambispective cohort study was conducted in the Department of Pathology, of a tertiary care hospital of Eastern India. It was approved by the Institutional Ethics Committee (KIIT/KIMS/IEC/939/2022). Total 51 cases of histologically proven cases of CRC from radical surgical specimen received to the Pathology Department were included in this study, of which 33 cases from March 2022 to December 2024 were prospective study. Eighteen archival blocks from the Pathology department of KIMS retrieved from the year December 2019 to December 2021 were also included. Poorly fixed or autolysed samples and patients with post neoadjuvant chemotherapy/radiotherapy were excluded from our study. Clinicopathological parameters like age, sex, tumour site, histopathological type, histopathological grade, LVI, PNI and lymph node status were noted for each case.

Study Procedure

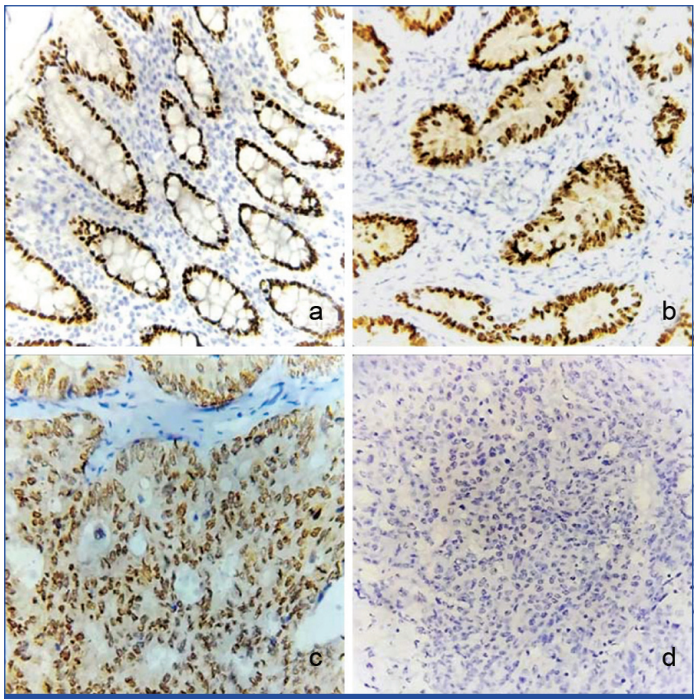
Histology [Table/Fig-1]: All radical surgical specimen of CRC received from Department of Surgical Oncology to the department of pathology were processed for 16 hours in Leica automated tissue processor (Leica TP 1020 Histokinette) as per standard protocol followed in the laboratory. The specimen were grossed in accordance with the 8th edition of American Joint Committee on Cancer (AJCC) [11]. The routine Haematoxylin and Eosin stain (H&E) stained sections were examined for the histopathological type, histopathological grade, LVI, PNI, nodal status and pathological staging as per pTNM classification, AJCC 8th edition [11]. The current version (June 2024) Cap protocol for CRC reporting was followed for the histopathology reporting. Tumour subtyping and grading were done according to the WHO classification of Digestive system tumour (5th Edition, 2019) [12].

Immunohistochemistry (IHC) staining: Rabbit monoclonal antibodies for CDX2 (Rabbit Monoclonal Antibody, clone EP25, Master Diagnostica) and E-cadherin (Rabbit monoclonal Antibody, clone QR035, Quartett) were used for IHC examination by secondary labelling method on 4-5 µm thick formalin-fixed, paraffin-embedded tissue slices. IHC was done according to standard protocols. Normal colonic mucosa was taken as positive control for both the markers. Omission of primary antibody and Phosphate Buffer Saline (PBS) incubation in a test case for each batch of staining was taken as negative control.

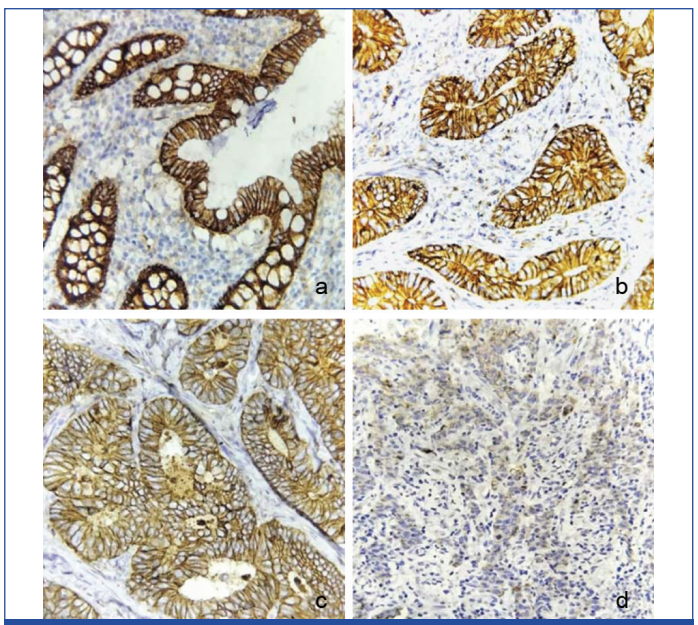
IHC interpretation [Table/Fig-2,3]: For CDX2 analysis, nuclear staining was considered as positive. Scoring was done according to percentage of tumour cells and intensity of nuclear staining. Percentage of tumour cells that had taken up the stain were scored as 0-0 to 5%; 1-6 to 25%; 2-26 to 50%; 3-51 to 75%; 4-76 to 100% and intensity of staining was scored as 0-negative; 1-light brown;



[Table/Fig-1]: Adenocarcinoma: (a) Well differentiated (Grade 1): Tumour cells arranged mostly in glandular pattern (H&E, 100X); (b) Moderately differentiated (Grade 2): 50-95% of tumour cells in glandular pattern with focal solid areas (H&E, 100X); (c) Poorly differentiated (Grade 3): Tumour cells arranged mostly in solid pattern with areas of necrosis (H&E, 100X); (d) Mucinous adenocarcinoma: Tumour cell clusters floating in the mucin pools with extracellular mucin comprising of >50% of tumour area (H&E, 400X).



[Table/Fig-2]: IHC for CDX2 (400X): (a) External control for CDX2 showing strong nuclear positivity in normal colonic mucosa; (b) Positive CDX2 expression showing dark brown nuclear staining in >75% of tumour cells with IRS 12 in well differentiated adenocarcinoma; (c) Positive CDX2 expression showing brown nuclear staining in >75% of tumour cells with IRS 8 in moderately differentiated adenocarcinoma; (d) Poorly differentiated adenocarcinoma showing negative CDX2 expression: IRS 0.



[Table/Fig-3]: IHC for E-cadherin (400X): (a) External control for E-cadherin showing strong cytoplasmic membranous positivity in normal colonic mucosal glands; (b) High E-cadherin expression showing strong cytoplasmic membrane staining in >67% of tumour cells in well differentiated adenocarcinoma; (c) High E-cadherin expression showing moderate cytoplasmic membrane staining in >67% of tumour cells in moderately differentiated adenocarcinoma; (d) Low E-cadherin expression in poorly differentiated adenocarcinoma: Weak cytoplasmic membrane staining in 11-33% of tumour cells.

2-brown; 3-dark brown. Total scoring was done by multiplication of score of proportion and intensity for obtaining the IRS. IRS of >3 was considered as CDX2 positive [13].

For E-cadherin analysis, cytoplasmic membranous staining was considered as positive. Intensity of staining was estimated as follows: 0: none, 1: weak, 2: moderate and 3: strong, while the proportion of the stained cells was scored as follows: 0: <10%, score 1-11: 33%, score 2-33:66%, and score 3:>67% positive cancer cells. Product of intensity and proportion was noted and graded as follows: 0=0, 1=1-3, 2=4-6, and 3=7-9. Score of 0,1 was considered as low expression and 2,3 as high expression [14,15].

STATISTICAL ANALYSIS

Statistical analysis was done by using Microsoft Excel and IBM Statistical Package for Social Sciences (SPSS) V 26. All the descriptive statistics was calculated. For association, Chi-square statistics was used. Kaplan-Meier plotting was done for survival analysis. The p-value of less than 0.05 was considered as significant.

RESULTS

Clinicopathological parameters [Table/Fig-4]: The age of patients in this study ranged from 23 years to 72 years with mean age of 53.27 years and median age of 54 years. Males were more affected with 34 (66.67%) cases as compared to females 17 (33.33%) cases. Right colon was common site comprising of 26 (50.98%) cases followed by left colon 20 (39.22%) cases and rectum 5 (9.80%) cases. Majority of the cases {47 (92.16%) cases} were adenocarcinoma, while the rest were mucinous adenocarcinoma {4 (7.8%) cases}. Grade 1 adenocarcinoma was the most common comprising of 21 (41.18%) cases followed by 17 (33.33%) cases of Grade 2 and 13 (25.49%) cases of grade 3. LVI and PNI was found in 22 (43.13%) cases and 11 (21.57%) cases respectfully. A total of 28 (54.90%) cases showed nodal metastasis. 43 (84.31%) cases belonged to stage T3 followed by 4 (3.92%) cases of T2 stage and 2 (3.92%) cases each were in T1 and T4 stage.

Parameters		No. of cases	%
Age (years)	<53	24	47.059
	≥53	27	52.941
Sex	Male	34	66.667
	Female	17	33.333
Site	Right colon	26	50.98
	Left colon	20	39.216
	Rectum	5	9.8039
Histological type	Adenocarcinoma	47	92.157
	Mucinous adenocarcinoma	4	7.8431
Histological grade	Grade 1	21	41.176
	Grade 2	17	33.333
	Grade 3	13	25.49
T stage	T1	2	3.9216
	T2	4	7.8431
	T3	43	84.314
	T4	2	3.9216
LVI	Positive	22	43.137
	Negative	29	56.863
PNI	Positive	11	21.569
	Negative	40	78.431
Lymph node status	Involved	28	54.902
	Uninvolved	23	45.098

[Table/Fig-4]: Distribution of cases according to various clinicopathological parameters.

IHC expression of CDX2 and E-cadherin [Table/Fig-5,6]: Out of 51 cases, 19 (37.35%) cases and 32 (62.75%) cases were CDX2 negative and positive respectively. 7 (13.72%) cases and 44 (86.27%) cases showed low and high E-cadherin expression, respectively.

Association between CDX2 expression and clinicopathological parameters [Table/Fig-5]: Among 32 CDX2 positive cases, 26 (81.3%) were males, out of 19 CDX2 negative 11 (57.9%) cases were females. Most of the cases 14 (73.7%) cases showing negative CDX2 expression showed metastasis to the lymph node. With increasing grade, number of cases showing negative CDX2 expression were seen to increase with 2 (10.5%) cases belonging to grade 1, 8 (42.1%) cases and 9 (47.4%) cases belonging to grade 2 and 3, respectively. Reverse trend was seen in cases showing positive CDX2 expression. A significant association was found between CDX2 expression and gender, histological grade and lymph node status (p-value=0.004, 0.001 and 0.038, respectively). Out of 32 cases with positive CDX2 expression, 25 (78.1%) cases belonged to T3 stage. 2 (6.3%) cases each were of T1 and T4 stage and 3 (9.4%) cases belonged to T2 stage. No significant association was found with stage of tumour (p-value=0.388). Out of 19 CDX2 negative cases, 12 (63.2%) cases were <53 years, 6 (31.6%) cases presented with left colon mass and 13 (68.4%) cases with right colonic mass, 3 (15.8%) cases was mucinous adenocarcinoma, 11 (57.9%) cases and 4 (21.1%) cases showed LVI and PNI, respectively while 18 (94.7%) cases belonged to T3 stage. No significant association was found with site of tumour (p-value=0.073), histological types (p-value=0.104), histological grades (p-value=0.388, LVI (p-value=0.101), PNI (p-value=0.945).

Association between E-cadherin expression and clinicopathological parameters [Table/Fig-5]: With increasing grade, number of cases showing high E-cadherin expression were seen to decrease with highest number seen in grade 1 tumour comprising of 21 (47.7%) cases, followed by 16 (36.4%) cases and 7 (15.9%) cases of grade 2 and 3, respectively. This was found to be statistically significant with a p-value of 0.001. Out of seven cases showing low E-cadherin expression, 4 (57.1%) cases were <53 years, 4 (57.1%) cases were males and all cases (100%) were adenocarcinoma. Among seven cases showing low E-cadherin expression, only 2 (28.6%) cases, 1 (14.3%) case showed LVI and PNI, respectively and 6 (85.7%) cases belonged to T3 stage. No significant association was found with age (p-value=0.867), sex (p-value=0.565), site of tumour (p-value=0.643), histological type (p-value=0.406), LVI (p-value=0.402), PNI (p-value=0.614), pathological stage of tumour (p-value=0.785).

Association between CDX2 and E-cadherin expression [Table/Fig-6]: Association of CDX2 with E-cadherin was studied. Out of 19 cases showing negative expression of CDX2, 7 (36.8%) cases showed low E-cadherin expression while 12 (63.2%) cases showed high E-cadherin expression. All 32 (100%) cases showing positive expression for CDX2 showed high E-cadherin expression. Therefore, there was a positive association between CDX2 and E-cadherin expression which is statistically significant (p-value=0.001).

Parameters		CDX2		p-value	E-cadherin		p-value
		Negative n (%)	Positive n (%)		Low expression n (%)	High expression n (%)	
Age (years)	<53	12 (63.2%)	12 (37.5%)	0.076	4 (57.1%)	20 (45.5%)	0.867
	≥53	7 (36.8%)	20 (62.5%)		3 (42.9%)	24 (54.5%)	
Sex	F	11 (57.9%)	6 (18.8%)	0.004	3 (42.9%)	14 (31.8%)	0.565
	M	8 (42.1%)	26 (81.3%)		4 (57.1%)	30 (68.2%)	

Site	LC	6 (31.6%)	14 (43.8%)	0.073	3 (42.9%)	17 (38.6%)	0.643
	R	0 (0.0%)	5 (15.6%)		0 (0.0%)	5 (11.4%)	
	RC	13 (68.4%)	13 (40.6%)		4 (57.1%)	22 (50.0%)	
H. Type	Adenocarcinoma	16 (84.2%)	31 (96.9%)	0.104	7 (100.0%)	40 (90.9%)	0.406
	Mucinous adenocarcinoma	3 (15.8%)	1 (3.1%)		0 (0.0%)	4 (9.1%)	
H.grade	1	2 (10.5%)	19 (59.4%)	0.001	0 (0.0%)	21 (47.7%)	<0.001
	2	8 (42.1%)	9 (28.1%)		1 14.3%	16 36.4%	
	3	9 (47.4%)	4 (12.5%)		6 (85.7%)	7 (15.9%)	
T stage	1	0 (0.0%)	2 (6.3%)	0.388	0 (0.0%)	2 (4.5%)	0.785
	2	1 (5.3%)	3 (9.4%)		1 (14.3%)	3 (6.8%)	
	3	18 (94.7%)	25 (78.1%)		6 (85.7%)	37 (84.1%)	
	4	0 (0.0%)	2 (6.3%)		0 (0.0%)	2 (4.5%)	
LVI	Absent	8 (42.1%)	21 (65.6%)	0.101	5 (71.4%)	24 (54.5%)	0.402
	Present	11 (57.9%)	11 (34.4%)		2 (28.6%)	20 (45.5%)	
PNI	Absent	15 (78.9%)	25 (78.1%)	0.945	6 (85.7%)	34 (77.3%)	0.614
	Present	4 (21.1%)	7 (21.9%)		1 (14.3%)	10 (22.7%)	
LN status	Uninvolved	5 (26.3%)	18 (56.3%)	0.038	3 (42.9%)	20 (45.5%)	0.898
	Involved	14 (73.7%)	14 (43.8%)		4 (57.1%)	24 (54.5%)	

[Table/Fig-5]: Association of CDX2 and E-cadherin with clinicopathological parameters.

Markers		CDX2 Negative (n=19)	CDX2 Positive (n=32)	p-value
E-cadherin	Low (n=7)	07 (36.8%)	00 (0.0%)	0.001
	High (n=44)	12 (63.2%)	32 (100.0%)	

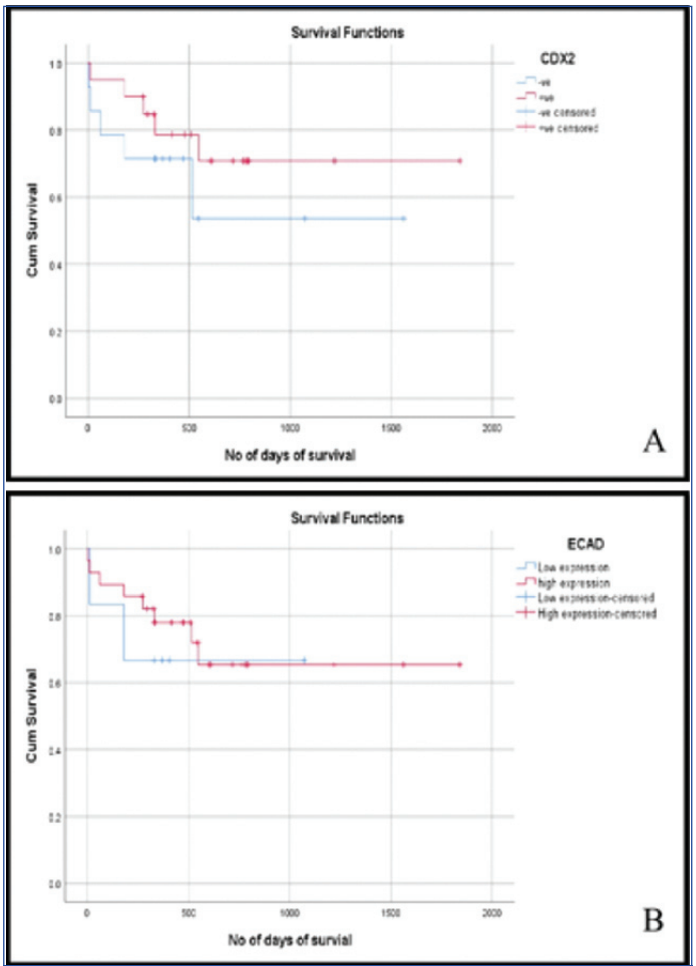
[Table/Fig-6]: Association of CDX2 with E-cadherin.

Follow-up was done for 34 cases, out of which 24 patients were alive. Ten patients had died, but the cause of death could not be ascertained. The mean overall survival time calculated for the patients that were followed-up was 1280.133 days. Kaplan-Meier graph [Table/Fig-7] was plotted to analyse cumulative survival rates which did not show any significant association statistically with the expression of CDX2 and E-cadherin (p-value of 0.324 and 0.630, respectively).

DISCUSSION

Colorectal carcinoma is one of the leading causes of cancer mortality. It is common in elderly, however due to changing dietary habits and lifestyle modification associated with urbanisation, incidence in younger age group has increased at present [16,17]. Hereditary as well as sporadic genetic mutation also increases the probability of developing CRC at a younger age [18]. The accumulation of these mutations, for example APC gene at an early stage and RAS mutation at a later stage, results in tumourigenesis [2]. Various biomarkers are being introduced for diagnosis, early detection along with prognostication of CRC. One amongst them is caudal-type homeobox transcription factor 2 (CDX2), a key nuclear transcription factor playing a role in the columnar morphogenesis and cell differentiation along with tumour inhibition properties [4,6,7]. E-cadherin, a cell adhesion molecule, maintains epithelial cell cohesion necessary for epithelial tissue integrity [8]. E-cadherin mutation leads to invasion, metastasis, progression of tumour grade and loss of differentiation [19], making it a useful marker in case of poorly differentiated carcinomas and also as a marker for invasiveness [10]. Loss of E-cadherin is known to be a hallmark of EMT [10].

The present study showed age range from 23 years to 72 years, with mean age of 53.27 years. Male predominance was seen with male to female ratio of 2:1. There was a decreasing incidence from proximal to distal colon with 50.98% cases presenting with right sided mass. Majority of the cases were of adenocarcinoma type with maximum cases presenting as grade 1 comprising of 41.2%



[Table/Fig-7]: Kaplan- Meier analysis of CDX2: (a) and E-cadherin; (b) expression and patient survival.

cases. Presence of LVI and PNI was noted in 43.13% and 21.57% of cases, respectively. 84.3% of cases was in stage 3 and 55% cases showed metastasis to lymph node.

Out of 51 cases, 32 cases (62.75%) were CDX2 positive. CDX2 positivity was higher in males as compared to females. There was significant association of CDX2 expression with gender (p-value-0.004). Similar finding was found by Bakaris S et al., (p-value-0.05) [20]. Most of the grade 1 tumours (19 cases, 59.4%) were CDX2 positive, while most of the grade 3 tumours {9 (47.4%) cases} were CDX2 negative which was found to be statistically significant

(p-value=0.001). Bakaris S et al., and Singh J et al., also found similar results with (p-value=0.001 and 0.045, respectively) [20,21].

This study revealed T3 was the most common stage {25 (78.1%) cases} majority of which were CDX2 positive. There was no significant association between CDX2 expression and T stage (p-value=0.388). This finding was incongruent with study by Den Uil SH et al., in which most of the T3 cases showed low CDX2 without any statistical significance (p-value=0.98) [22].

Present study shows out of 19 cases of CDX2 negative, most {14 (73.7%) cases} showed lymph node metastasis, which was found to be statistically significant (p-value=0.038). Bakaris S et al., found only 25% of CDX2 negative cases showed lymph node metastasis which was statistically significant (p-value=0.001) [20].

A total of 44 (86.27%) cases showed high E-cadherin expression in this study, out of which all were grade 1 tumours. Most of the cases showing low E-cadherin expression were grade 3 {6 (85.7%) cases} which was statistically significant (p-value=0.001). Choi JE et al., stated that most of the grade 3 tumours showed loss of E-cadherin expression (p-value=0.001) [23]. Study by Iseki Y et al., showed that most of the lower grade tumours (grade 1 and 2) had high expression (p-value=0.815) [24]. They also found higher stage (T3) tumours showed high E-cadherin expression with no statistical significance (p-value=0.785). Tunguntla A et al., showed higher stage cases showed low expression which was statistically significant (p-value=0.03) [25].

Present study revealed that there is a positive association between positive CDX2 expression and high E-cadherin expression. This result was found to be statistically significant with p value of 0.001. Keller MS et al., and Funakoshi S et al., studied the expression of CDX2 and E-cadherin in colon cancer cell culture [26,27]. Keller MS et al., found in their study that CDX2 restored the binding activity of E-cadherin [26]. They stated that CDX2 expression induced E-cadherin activity but had no effect on the levels of E-cadherin. Funakoshi S et al., [27] noted similar findings and further explained that CDX2 modulated E-cadherin by regulating Receptor Tyrosine Kinase (RTK) activity [27].

Study done by Slik K et al., and Wang YS et al., found significant relation between loss of CDX2 and low E-cadherin expression which was statistically significant (p-value=0.04 and 0.01, respectively) [28,29].

Kaplan - Meier plot showed that positive expression of CDX2 was associated with better survival of the patient in our study. However, these results were not significant statistically (p-value=0.324). These findings were consistent with the study by Singh J et al., [21]. Dawson H et al., which was statistically significant (p-value-0.014) [30].

Additionally, by using Kaplan – Meier plot, high E-cadherin expression was seen to be associated with better patient survival. These results were statistically insignificant (p-value=0.630). Study by Choi JE et al., revealed that low E-cadherin expression was associated with poor survival which was found to be statistically significant (p-value=0.028) [23]. However, study by Iseki Y et al., showed no relation between E-cadherin expression and patient survival [24].

Limitation(s)

The sample size of our study was small. There was uneven distribution of cases, for example, majority of the cases belonged to T3 stage, resulting in inadequate representation. The period of follow-up was short with many cases lost to follow-up. More retrospective cases may be included so that the follow-up period is longer which will ensure an accurate survival analysis. We also used limited IHC markers. Hence, further study with a larger sample size, more retrospective case inclusion along with study of other molecular markers is necessary to validate our approach.

CONCLUSION(S)

In conclusion, higher grade of tumour was associated with negative CDX2 and low E-cadherin expression. Nodal metastasis was linked to negative CDX2 expression. In addition, a significant association between CDX2 and E-cadherin expression was studied indicating that combination of both markers may have a role in prognostication of CRC. However, elaborate studies regarding the mechanism by which CDX2 drives the activity of E-cadherin is necessary for better understanding of the evolution and progression of carcinomas. This will help is identifying high risk patients and provide optimum care for patients.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
2. Professor, Department of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
3. Professor, Department of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
4. Senior Consultant, Department of Surgical Oncology, Bagchi Sri Shankara Cancer Centre and Research Institute, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Prajna Das,
Plot No. 196 (784/786), Lane-3, Jaydev Vihar, Bhubaneswar-751013, Odisha, India.
E-mail: prajna.das@kims.ac.in

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