Original Article

The Evaluation of SATB2 as a Diagnostic Immunohistochemical Marker of Colorectal Adenocarcinoma in Comparison with Non-Colorectal Adenocarcinomas.

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DOI: 10.47750/pnr.2023.14.02.278

Abstract

Background Colorectal cancer (CRC) is the third most common malignancy diagnosed in both men and women and the fourth leading cause of cancer-related deaths worldwide. Special AT-rich sequence-binding protein 2 (SATB2), a nuclear matrix-associated transcription factor and epigenetic regulator, was identified as a highly tissue-type-specific protein being predominantly expressed in glandular cells of the lower gastrointestinal tract. **Objective** To determine SATB2 expression in CRC, relation of SATB2 expression in CRC with clinicopathological features and to compare its expression with non-colorectal adenocarcinoma including (gastric, hepatobiliary, intestinal and pancreatic cases). **Material and Methods** Samples from 38 known CRC cases and 41 non- colonic origin adenocarcinomas (gastric, hepatobiliary, intestinal and pancreatic cases) were studied immunohistochemically for SATB2 expression. **Results** All CRC (38 cases) showed positive SATB2 expression score. More than half of them demonstrated score +3, while (92%) of non-colonic origin adenocarcinoma cases were negative for SATB2.There was a highly statistical difference between SATB2 expression score in CRC cases and non-colonic origin adenocarcinoma group. Highly Statistically significant relation in SATB2 immunoreactivity score in different grades with the highest score in low grade tumors; (95%)**.**Also,there was statistically significant difference in SATB2 immunoreactivity score in different PDC grades with the highest score in grade 1; (82%). Inverse negative correlation between between the PDC tumor grade and SATB2 expression score. **Conclusion** Positive expression of SATB2 in all studied CRC cases with increase in its expression in low grade CRC and PDC tumor grade.

Key words: Colorectal adenocarcinoma, SATB2 expression, PDC tumor grade.

INTRODUCTION

Colorectal carcinoma (CRC) ranked among the three most common cancers in humans concerning incidence and mortality worldwide **(1).**

In Egypt, the estimated rate of CRC is 6.5 % of all malignant tumors.CRC is also widespread in Egypt, with 14.0 % of all colonoscopies revealing the presence of the disease. Meanwhile, it affects both men (4.2%) and women (3.8%) and it was the 3rd most reported cancer in males and the 2nd most common cancer in females **(2).**

Special AT-rich sequence-binding protein 2 (SATB2), a nuclear matrix-associated transcription factor and epigenetic regulator, was identified initially as a gene involved in osteoblast differentiation and craniofacial patterning in humans (**3).**

SATB2 has high levels of expression in the brain, including in the cerebral cortex and the spinal cord, and has a role in central nervous system development **(4)**

SATB2 also was found to be predominantly expressed in glandular cells of the lower gastrointestinal tract and in CRC **(5).**

It has also gained increasing attention in the recent years as a relatively specific marker of colorectal differentiation. Functional studies had revealed the tumor suppressive properties of SATB2 in experimental settings **(6)**, demonstrating that SATB2 is a complexly regulated tumor suppressor that represses CRC progression by inhibiting the transcription of SNAIL, a master regulator of epithelial-mesenchymal transition **(7).**

Some studies revealed tumor suppressive properties of SATB2 in in vitro and a potential mechanism of this suppression via inactivation of tumor-promoting factor ERK5(Extracellular signal-regulated kinase 5), demonstrating that SATB2 is a complexly regulated tumor suppressor that represses CRC progression by inhibiting epithelial-mesenchymal transition **(7).**

We had assessed expression of SATB2 as a diagnostic immunohistochemical marker in CRC cases. Analyze the expression of SATB2 in non-colonic origin adenocarcinoma cases. Compare pathological parameters of the tumor (tumor size, histological grade, pathological stage) and other clinical data with SATB2 expression in CRC cases.

Material and Methods

This was a cross sectional analytical study. A total of 79 cases (formalin fixed, paraffin embedded tumor biopsies from 38 colectomy specimens &41 non-colonic origin adenocarcinoma including (Gastric, liver, pancreatic and intestinal biopsies and specimens) were included in the present study. Cases were collected retrospectively from pathology lab at specialized medical centre, faculty of medicine Beni-Suef University during the period from September 2017 to January 2022.

Sample size (number of cases) Sample size was calculated with G*Power (3.1.9.4) software using a priori analysis with an effect size= 0.6 for Contingency tables (one group) using χ^2 tests. A total sample size of **minimally 50** cases was estimated for 96% power, α- error probability 0.05.

Inclusion criteria All colorectal and non-colorectal cases were with full available clinical data and adequate viable tumor tissue.

Exclusion criteria Cases with insufficient clinical data, cases with extensive necrosis or hemorrhage with scanty viable or burned-out tumor tissue, cases taken preoperative chemotherapy or radiotherapy and blocks inadequate for multiple sectioning.**Clinical data:** Pathology reports and slides were collected from the pathology department laboratory at which the initial diagnosis was made. Virtually, all slides were reviewed by a single pathologist without knowledge of the submit diagnosis to confirm diagnosis; maximize standardization and uniformity of diagnostic criteria across all cases.

Histopathological evaluation Paraffin blocks of the tumors were sectioned at 4 μm thickness. Then, pathological evaluation, morphologic classification according to 2019 WHO classification of colorectal tumors (**(8)** and grading system of colorectal tumors, 5th edition **(9).**

Immunohistochemical examination SATB2: SATB2 immunohistochemistry was performed for Colorectal and Non-colorectal Adenocarcinoma (79 cases). All cases were stained on positively charged slide and stained by immunohistochemical with primary antibodies against SATB2 (rabbit monoclonal antibody (Clone EP281, 7.0 mL, Cell Marque384R, Cat. No.RM0281, Ready to use, USA). Slides were stained using VENTANA GX Benchmark auto-stainer (Roche Diagnostics International AG, Rotkreuz, Switzerland). Automated technique gave brown nuclear staining on positive control cases.

Evaluation of SATB2 immunohistochemical expression and score SATB2 staining was detected as brownish staining mainly in the nucleus of tumor cells and the extent of positivity was scored considering both the percentage of neoplastic cells showing a nuclear positivity and the intensity of the staining. Cancers showing at least 5% of nuclear cells reactive for SATB2 were considered SATB2-positive, so:
Cases with positive nuclear staining considered: 1. Cases with negative nuclear staining considered: 0
In addition, H-score for SATB2, i.e., the intensity score multiplied for the percentage of cells with positive staining, was calculated to provide a SATB2 synthetic evaluation, taking into account both the intensity of expression and the density of positive cells. SATB2 expression score calculated by H score was: Score +1 weak expression. Score +2 moderate expressions. Score+3 strong expression **(10)**.

Evaluation of TILs in studied colorectal cancer cases TILs (tumor infiltrating lymphocytes) were assessed in Hematoxylin and Eosin-stained slides as a percentage of mononuclear inflammatory cells over total intratumoral stromal area and counted in 5 HPF (total magnification, ×200–400) in the invasive front or areas surrounding the deposits, except for tumor areas with crush artifacts, necrosis or regressive hyalinization.

Data Analysis The collected data were coded then entered and was analyzed using the SPSS version 22 (Statistical package for social science). Descriptive statistics for the socio-demographic characteristics of participants were first analyzed: Description of qualitative variables by frequency and percentage, Description of quantitative variables in the form of mean and standard deviation (mean ± SD).
Graphs were used to illustrate simple information. Suitable statistical tests were used (Chi-square (**χ^2**), way ANOVA test, non-parametric Spearman correlation and independent sample t test). P-values equal to or less than 0.05 were considered statistically significant.

Ethical Considerations Patients' names were removed from each case for confidentiality of data and assuring that it will never be used for purposes other than scientific research; names were replaced by numbers. This study was approved by **Beni-Suef University Ethical Committee (approval number: FMBSUREC/05012020/Mahmoud).**

Results

The current study conducted on 38 CRC and 41 non-colonic origin adenocarcinomas, which were gastrointestinal and hepatobiliary adenocarcinoma biopsies. The paraffin blocks were enrolled from pathology department, Faculty of Medicine, Beni-Suef University. In this study, we detected the expression score of SATB2 immunohistochemical marker on total 74 collected cases.

Table (1) Clinico-pathological data among studied CRC cases (n=38)

Variables		**Frequency**	**Percent**
Age group	<50y	23	60.5
	≥ 50y	15	39.5
Gender	Female	18	47.4
	Male	20	52.6
Tumor size	<5 cm	13	34.2
	≥5 cm	25	65.8
Tumor site in large bowel	Right side	26	68.4
	left side	12	31.6
Shape	Fungating	14	36.8
	Ulcerative	14	36.8
	Infiltrative	10	26.3
Histopathological types of tumors	Adenocarcinoma NOS	26	68.4
	Adenocarcinoma with mucinous differentiation	3	7.9
	Adenocarcinoma with neuro differentiation	1	2.6
	Mucinous adenocarcinoma	8	21.1
PDC grading	G1	26	68.4
	G2	7	18.4
	G3	5	13.2
Tumor grade	high grade	9	23.7
	low grade	29	76.3
Tumor infiltrating lymphocytes (TIL)	1(weak)	7	18.4
	2(moderate)	23	60.5
	3(strong)	8	21.1
pT (pathological tumor stage)	T2	4	10.5
	T3	29	76.3
	T4a	4	10.5
	T4b	1	2.6
pN (metastatic l.Ns)	pN0	18	47.4
	pN1a	7	18.4
	pN1b	3	7.9
	pN1c	4	10.5
	pN2a	3	7.9
	pN2b	3	7.9
Tumor omental Deposit	No	34	89.5
	1	2	5.3
	2	2	5.3
Lympho Vascular invasion (LV)	positive	4	10.5
	negative	34	89.5
Perineural invasion (PN)	positive	4	10,5
	negative	34	89.5
SATB2 score	1+	6	15.8
	2+	10	26.3
	3+	22	57.9

Table (2) SATB2 Expression score in colorectal adenocarcinoma cases and non-colorectal adenocarcinoma cases

		colorectal adenocarcinoma cases n=38	**Non colorectal adenocarcinoma Cases n=36**		**P value**
		Count	Count	%	
SATB2 score	Negative	0 0%	33	91.7%	**< 0.001**
	+1	6 15.8%	2	5.6%	
	+2	10 26.3%	1	2.8%	
	+3	22 57.9%	0	0%	

In our thesis, all CRC cases showed positive SATB2 expression score. More than half of them demonstrated score +3, while (92%) of non-colorectal adenocarcinoma cases were negative for SATB2. Only 3 cases were positive for SATB2.There was a highly statistical difference between SATB2 expression score in CRC cases and non-colorectal adenocarcinoma group

Table (3) Gross features of the present CRC cases and relation with SATB2 Expression score:

		SATB2 score in Studied CRC				
		+1 n=6	**+2** n=10	**+3** n=22	**Total** **Count**	**P value**
Tumor size	<5 cm	2 33.3%	3 30%	8 36.4%	13 34.2%	1.0
	≥5 cm	4 66.7%	7 70%	14 63.6%	25 65.8%	
Tumor site in large bowel	Rt side	5 83.3%	5 50%	15 68.2%	25 65.8%	0.353
	Left side	1 16.7%	5 50%	7 31.8%	13 34.2%	
Shape	Fungating	3 50 %	2 20%	9 40.9%	14 36.8%	0.676
	Ulcerative	1 16.7%	5 50%	8 36.4%	14 36.8%	
	Infiltrative	2 33.3%	3 30 %	5 22.7%	10 26.3%	

Regarding tumor location, about two third of CRC cases were found in right side, while tumor size ranged from 2.5 cm to 9 cm with mean tumor size 5.5 cm ±2 SD. More than half of cases (65.8%) had ≥ 5cm in diameter. There was no statistically significant relationship between SATB2 expression score and these gross features (including tumor size, localization and shape) of the studied CRC cases.

Table (4) Relation between histopathological types of the Studied CRC cases with SATB2 expression Score

		SATB2 score in CRC cases				
		+1 **n=6**	**+2** **n=10**	**+3** **n=22**	**Total** **Count**	**P value**
Histopathological types of tumors	Adenocarcinoma NOS	1 (16.7%)	8 8%	17 77.3%	26 68.4%	**0.002**
	Adenocarcinoma with mucinous differentiation	0 0.0%	0 0 %	3 13.6%	3 7.9%	
	Adenocarcinoma with neuroendocrine differentiation	0 0.0%	0 0%	1 4.5%	1 2.6%	
	mucoid adenocarcinoma	5 83.3%	2 20%	1 4.5%	8 21.1%	

About three quarters of CRC cases were adenocarcinoma NOS with score+3. We noted a high statistically significant difference in SATB2 expression score in different pathological types with the highest score in adenocarcinoma NOS tumors p value equal 0.002.

Table (5) Relation between SATB2 Expression score with Tumor grade**.**

		SATB2 score in studied CRC cases				
		+1 n=6	+2 n=10	+3 n=22	Total Count	P value
Tumor Grade	low grade	0 0%	8 80 %	21 95.5%	29 76.3%	**< 0.001**
	high grade	6 100%	2 20%	1 4.5%	9 23.7%	

According to tumor grade; three quarters of our CRC cases had low grade, (Table 5). There was highly statistically significant relation between SATB2 expression score and different tumor grades with most of score +3 had low grade tumors, while all score +1 cases were high grade, p value <0.001**.**

Table (6) Correlation between tumor grade of the Studied CRC Cases and SATB2 expression score

Tumor grade	**Correlation Coefficient**	-0.663-
	P value	<0.001
	N	38

A statistically significant correlation (-0.663) between the tumor grade and SATB2 expression score could be attained, i.e., more SATB2 expression was encountered with tumors showing low tumor grade. Inverse negative correlation.

Table (7) Relation between SATB2 Expression score and PDC Tumor grade in studied CRC cases

		SATB2 score in studied CRC cases				
		+1 n=6	+2 n=10	+3 n=22	Total Count	P value
PDC grading	**G1**	0 0%	8 80%	18 81.8%	26 68.4%	**< 0.001**
	G2	1 16.7%	2 20%	4 18.2%	7 18.4%	
	G3	5 83.3%	0 0%	0 0%	5 13.2%	

Among studied CRC cases, more than half of cases were grade PDC G1 (Table 7). We noted a highly statistically significant difference in SATB2 expression score in different PDC grades with the highest score in grade 1 and lowest score in grade 3, p value <0.001.

Table (8) Correlation between PDC grading of the studied CRC cases and SATB2 Expression

		SATB2 score
PDC grading	**Correlation Coefficient**	-0.543-
	P value	<0.001
	N	38

The correlation coefficient between SATB2 expression and PDC tumor grade was negative (-0.543), p value (<0.001). A high statistically significant correlation could be attained, i.e., more SATB2 expression was encountered with tumors showing low tumor grade. We found Inverse negative correlation between the PDC tumor grade and SATB2 expression score.

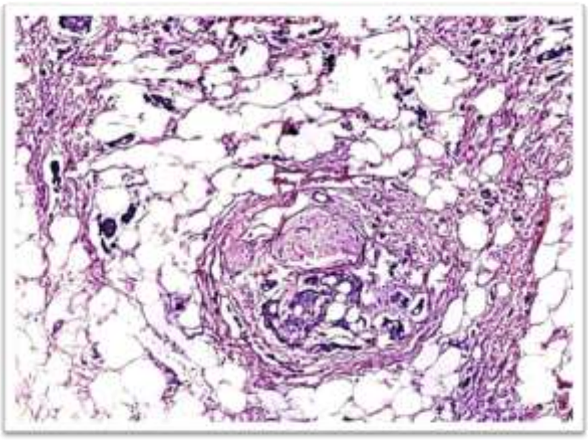

Figure (1) Invasive colorectal adenocarcinoma with perineural invasion x100.

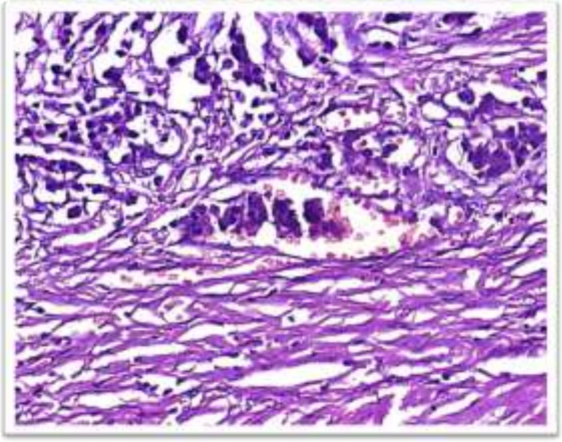

Figure (2) Invasive colorectal adenocarcinoma with Lymphovascular invasion x400. The malignat cells infiltrating the vessel wall.

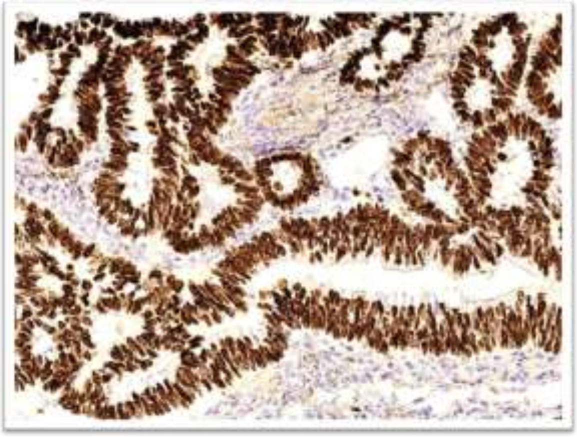

Figure (3) Positive SATB2 expression in colorectal adenocarcinoma score +3 x400.

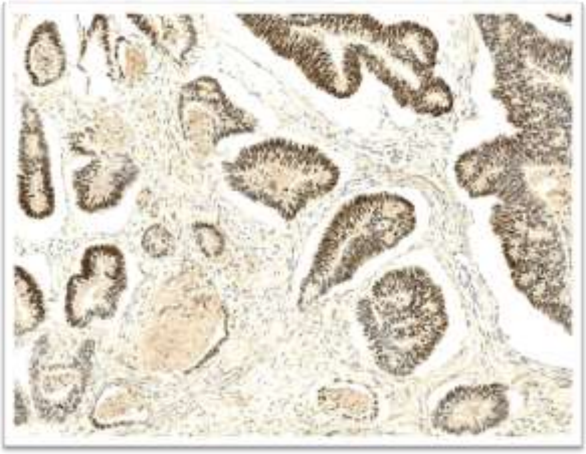

Figure (4) Positive SATB2 expression in colorectal adenocarcinoma score +2 x200**.**

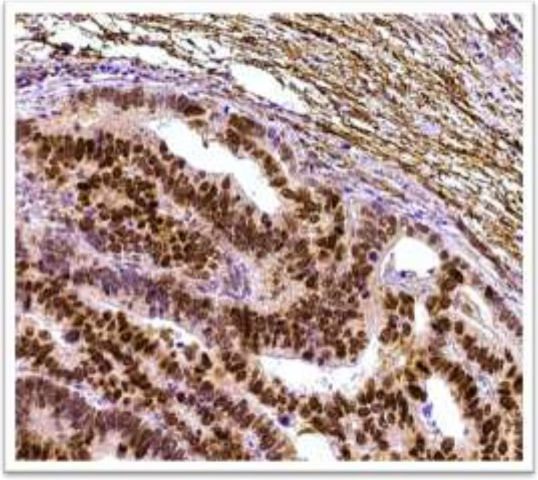

Figure (5) Positive SATB2 expression in metastatic lymph nodes of colorectal adenocarcinoma x200**.**

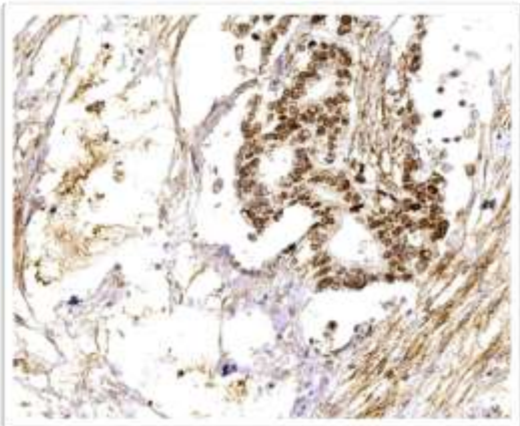

Figure (6) Positive SATB2 expression in metastatic mucinous colorectal adenocarcinoma in lymph node x200

Discussion

Colorectal carcinoma ranks among the three most common cancers in humans concerning incidence and mortality worldwide, further explorations on potentially relevant biomarkers are warranted in order to characterize these tumors precisely and improve prognostic predictions **(11).**

Special AT-rich sequence-binding protein 2 (SATB2), a transcription factor interacting with nuclear matrix attachment regions which is highly expressed in the normal colonic mucosa **(12),** attracted increasing scientific notice for the identification of the colorectal origin of cancers of unknown primary and of CRC metastases.

In the current study we found that all CRC cases (100%) showed positive SATB2 expression. These results were in compatible with **Chen et al., (13)** who demonstrated that SATB2 expression was 96 % of their primary 101 CRC cases. Also, in line with our results **Cígerová et al., (14)** recorded SATB2 expression in 103/111 (93%) and 1102/1180 (93.3%) CRC samples respectively**.**

Regarding expression score of SATB2 in our thesis, 57.9% of studied CRC cases showed + 3score, 26.3% were + 2 score and 15.8% + 1 score. Our results were matching with **Mezheyeuski et al., (15)** who demonstrated in a cohort study of 798 CRC patients that SATB2 was strongly expressed in 467 (58%) of cases.

We speculated that there are differences in expression score of SATB2 as result of different in sample size in each study, difference in selection of SATB2 cutoff and patient heterogeneity may contribute to this discrepancy.

In our thesis, all CRC cases showed positive SATB2 expression score, while (92%) of non-colorectal adenocarcinoma cases were negative for SATB2. Only 3 cases were positive for SATB2, the positive cases showed weak and scattered expression.

Our results in line with **Chen et al., (13)** who demonstrated that expression of SATB2 was (96%) in primary CRC cases and was notably lower in the other 6 types of adenocarcinomas evaluated in their study. Parallel to our findings

Magnusson et al., (5) who recorded that the gastric and pancreatic cancers were all negative for SATB2 expression. Also, in concordance to our results **Lin et al., (16)** who reported in a study of 270 GI/Pancreatic tumors that SATB2 expression was observed in only 6.7%, 0% and 4.2% of adenocarcinomas of the esophagus, stomach and pancreas, respectively, and the positive cases in these locations typically showed focal and weak SATB2 stain. In agreement of our results **Dragomir et al., (17)** who reported that only a small fraction of non-CRC tumors (3.5%) showed diffuse expression of SATB2.

Our findings were in contrast with **kim et al., (18)** in study of 50 case of small intestinal adenocarcinoma (SIA) illustrated that SATB2 is expressed in 46% of SIA cases.

These differences could be explained by different antibody clones used in each study, which may explain the differences in SATB2 expression score detected. In addition, the definition of negative expression of SATB2 was slightly different. Further, we used the whole-slide immunohistochemistry method, rather than the tissue microarray method, to analyze the expression of SATB2.

In the present study we found that there was statistical difference between SATB2 expression score in colorectal adenocarcinoma cases and non-colorectal adenocarcinoma group p value <0.001. SATB2 showed negative expression in non-colorectal adenocarcinoma group.

Similar results were reported by **De Michele et al., (19)** who showed that that there was a statistically significant difference SATB2 expression score of CRC compared with expression score of non-CRC cases (P < 0.01), including gastric, and small bowel/ampullary adenocarcinoma cases.

Concerning Pathological tumor stage (pT) in our study pT3 was the most frequent pathological tumor stage representing 76.3% of the studied CRC cases. Matching with our present study **Kirsch et al. (20)**, who reported that 77% of the cases were pT3. However, **Iwaya et al., (21)** found that pT3 was (50%) and (57%) respectively. Also, **Schmitt et al., (7)** illustrated that pT3 represented about 56% of CRC cases. In contrast with our results **Zhang et al., (22)** who recorded in study on 101 primary CRC that 29% of them were pT3.Also, in disagreement of our work **Han et al. (23)** who noted that most frequent pathological tumor stage representing (83.52%) in pT4a.

Our study demonstrated that, adenocarcinoma NOS was the most frequent histological type representing 68.4% of the studied CRC cases. On the same side, **González et al., (24)** who reported that the most frequent histological type representing 251 (73.3%) of the studied cases was adenocarcinoma NOS. while **Bhattacharya et al., (25)** who noted recorded a higher incidence that adenocarcinoma (NOS) was the most common (80%) histological type among the CRC cases. Also, (a study included 10.413 CRC patients) labeled 95% of cases as conventional adenocarcinomas. **Liu et al., (26)** recorded 90% of 130 CRC cases as conventional adenocarcinoma. As well as **Hrudka et al., (11)** who found in a study of 285 CRC specimens that adenocarcinoma NOS representing 94.4%

There was statistically significant difference in SATB2 immunoreactivity score in different pathological types with the highest score in adenocarcinoma NOS tumors; 17(77%), and lowest score in mucinous adenocarcinoma 5 (83.3%) p value =0.003, otherwise no significant difference between SATB2 immunoreactivity score and studied pathological parameters.

Our findings were supported by **Liu et al., (26)** who showed in their study on 117 CRC cases that positive expression score of SATB2 in well-differentiated and moderately differentiated adenocarcinoma are 83.33% (15/18) and 80.28% (57/71) respectively; both are significantly higher than the expression score in poorly differentiated adenocarcinoma 46.43% (13/28) (p value= 0.002).

In our present thesis there was highly statistically significant relation in SATB2 expression score and tumor grade with the highest score in low grade tumors; (95%), and lowest score in high grade (100%), p value <0.001**.**

Our findings were parallel to **Cígerová et al., (14)** who noted a significant association with the tumor grade; lower grade was associated with higher intensity and higher number of SATB2-positive cells. Matching our results, **Schmitt et al., (7)** showed that in a cohort of more than one thousand cases of CRC patients, low expression of SATB2 in CRCs were significantly and massively enriched in tumors with poorly differentiated carcinomas (high grade) according to the WHO tumor grade (p value < 0.001) which is in line with the functional studies postulating the tumor suppressive properties of SATB2.

Also, **Wang et al., (6)** illustrated that low SATB2 expression was found to be correlated with tumor progression and an independent prognostic marker in colorectal cancer.

In disagreement to our result **Zhang et al., (22)** who illustrated that there was no relation between SATB2 expression score and tumor grade. This contradiction could have occurred due to the selected limit values in assessing SATB2 expression.

In the present study, there was a statistically significant difference in SATB2 expression score in different PDC grades with the highest score in 1 (81.8%), and lowest score in grade 3 (83.3%) p value <0.001. There were no other researches discussing this point to compare with our results.

Concerning nodal metastasis in our present study more than half of our studied CRC cases had lymph node metastasis, most of them were N1. Matching with our findings **Aikawa et al., (27)** who noticed in a study of 184 CRC, pN1 (48/184) was the most commonly distributed among positive cases.

Conclusion

Positive SATB2 expression serves as a fairly novel biomarker that is chiefly utilized during diagnosis of lower gastrointestinal tract adenocarcinomas. Strong expression of SATB2 in CRC and its high expression is a marker of good prognosis. High SATB2 expression is significantly associated with low grade tumors. SATB2 expression is negative in non-colorectal adenocarcinoma (gastric, hepatic, pancreatic and intestinal) except for the only 3 positive cases where SATB2 expression was weak and scattered. SATB2 is most useful when the differential is distinguishing CRCs from non-CRCs adenocarcinoma. SATB2 might aid in improving differential diagnosis of liver, gastric, pancreatic and intestinal adenocarcinomas. Further studies are needed to clarify the possible mechanism by which SATB2 influences CRC progression. Further studies on SATB2 expression in distinguishing mucinous CRCs ovarian mucinous carcinoma.Further studies are required to establish the prognostic significance of SATB2 expression in CRCs to provide targeted therapy. Studying SATB2 expression in relation to a single variant such as incidence of recurrence, certain tumor type, subtype or grade in a larger sample size is recommended

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