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Immunohistochemical evaluation of colorectal carcinoma: experience of a four-year study

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Colorectal carcinomas (CRC) is the third most common cause of death in developed countries. Invoking of primary site of carcinoma of unknown origin using immunohistochemistry is essential for accurate diagnosis, and also for targeted therapies.

Aim. This study aimed to assess immunohistochemical expression of CK7, CK20, and CDX2 in colorectal carcinomas, and to evaluate their diagnostic role.

Materials and methods. A retrospective study was performed on 36 paraffin blocks of documented colorectal carcinomas were stained by immunohistochemical technique using a tissue microarray with CK7, CK20 and CDX2 markers. The resulted data were statistically analyzed.

Results. There was a negative association between CDX2 expression and histologic grade (p = 0.03), as well as T-pathologic stage (p = 0.01). CK7-ve / CK20+ve immune profile showed a specificity of 95 % in predicting the colorectal adenocarcinomas, which was superior to that of CDX2. CDX2 loss is related to tumour grade and depth (T-stage).

Conclusions. Both CDX2 expression, and CK7-ve / CK20+ve are the most sensitive, and specific markers to diagnose the colorectal carcinoma. CK7-ve / CK20+ve expression is used as specific marker for colorectal carcinoma for targeted therapy.

Keywords: colorectal carcinoma, immunohisto-chemistry, CDX2, CK7, CK20.

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Імуногістохімічне оцінювання колоректальної карциноми: досвід чотирирічного дослідження

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Ключові слова: колоректальний рак, імуногістохімія, CDX2, CK7, CK20.

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Колоректальні карциноми (КРР) є третьою за поширеністю причиною смерті в розвинених країнах. Виявлення первинного осередку карциноми невідомого походження за допомогою імуногістохімії має важливе значення для точної діагностики, а також для цільової терапії.

Мета роботи – вивчити імуногістохімічну експресію CK7, CK20 і CDX2 у колоректальних карциномах й визначити їхню діагностичну роль.

Матеріали і методи. Здійснили ретроспективне дослідження 36 парафінових блоків документально підтверджених колоректальних карцином, забарвлених імуногістохімічним методом, використали мікроматрицю тканини з маркерами CK7, CK20 і CDX2. Отримані дані опрацювали, застосувавши статистичні методи.

Результати. Виявлено негативний зв'язок між експресією CDX2 і гістологічним ступенем (p = 0,03), а також патологічною стадією T (p = 0,01). Імунний профіль CK7-ve / CK20+ve характеризувався специфічністю на рівні 95 % під час прогнозування перебігу колоректальних аденокарцином; цей показник вищий, ніж визначений для CDX2. Втрата CDX2 пов'язана зі ступенем і глибиною пухлини (стадія T).

Висновки. Експресія CDX2, як і CK7-ve / CK20+ve – найбільш чутливий і специфічний маркер для діагностики колоректальної карциноми. Експресію CK7-ve / CK20+ve застосовують як специфічний маркер колоректальної карциноми для цільової терапії.

Colorectal carcinomas (CRC) are the third most prevalent and second deadliest cancer. The age incidence rises beyond the age of 40. Men were more affected than women [1,2]. Genetic and environmental / lifestyle risk factors for CRC include sedentary habits, red meat consumption, a low-fat diet, alcohol, and tobacco use. The majority of CRCs are spontaneous, and carcinogenesis begins along a typical stepwise pattern known as the adenoma carcinoma sequence, with adenoma as the early lesion. This mechanism is related with mutations in genes such as APC, p53, KRAS, SMAD2, SMAD4, or MMR; specifically, KRAS was observed in up to 50 % of villous adenoma and up to 18 % of tubular adenoma [3].

The most common immunohistochemical markers for CRC are CK7, CK20, and CDX2. Colorectal carcinomas are identified by their immunoprofile of CK20+ / CK7– / CDX2+.

Several studies have shown that a lack of CDX2 expression in CRC is related with aggressive behaviour, a poor prognosis, a high tumour grade, a high tumour stage, a BRAF mutation, and a high MSI phenotype due to tumor-suppressor activity [4,5].

Table 1. Distribution of colorectal cancer cases

Parameter	Frequency (n)	Percentage (%)
Age distribution		
<30	4	11.11
31–40	6	16.67
41–50	11	30.56
51–60	8	22.22
61–70	3	8.33
>70	4	11.11
Sex		
Male	23	63.89
Female	13	36.11
Histologic type		
Adenocarcinoma	25	69.4 %
Mucinous adenocarcinoma	6	16.6 %
Signet ring cell Carcinoma	3	8.3 %
Medullary adenocarcinoma	1	2.7 %
Tumor size		
<5 cm	11	28
>5 cm	25	72
Tumor grading		
Well differentiated	05	13.9
Moderately differentiated	24	66.7
Poorly differentiated	07	19.4
Tumor localization		
Right	12	33.33
Left	22	61.11
Missing	2	5.56
Primary tumor		
T1	0	0.0
T2	05	13.9
T3	19	52.8
T4	07	19.4
Missing	05	13.9
Nodal metastasis		
Positive	07	19.4
Negative	29	80.6
Differential CK20/CK7 staining		
CK20+ / CK7-	24	66.8
CK20- / CK7-	09	25
CK20- / CK7+	2	5.5
CK20+ / CK7+	1	2.7

The CK20+ / CK7 immunoprofile is expressed in around 75–95 % of CRC patients, with the remainder having various profiles [6].

CDX2 is a specific marker of intestinal epithelial cells and is positive in almost all well-differentiated CRC; however, approximately 10–20 % of poorly differentiated carcinomas can be weakly positive or negative.

Typically, the immunophenotype of CRC is CDX2+ve, CK20+ve, and CK7-ve. Aberrant expression has been observed in a variety of colorectal carcinomas, although its relationship to morphological characteristics and survival data remains unclear.

Aim

This study aimed to assess immunohistochemical expression of CK7, CK20, and CDX2 in colorectal carcinomas, and to evaluate their diagnostic role.

Materials and methods

Study design – a retrospective study. Study duration – four years of study in the Department of Pathology at SVS Medical College in Mahabubnagar, Telangana (India), from January 2019 to December 2022.

Sample size – formalin fixed gross pathological specimens of 36 colorectal carcinomas were studied.

Inclusion criteria – primary malignant tumors of colon. Exclusion criteria – benign tumors of colon; inflammatory lesion of colon; metastatic malignancy of colon.

Data collected retrospectively from medical records and also from department of pathology. All cases of colonic biopsies & surgically resected colon specimens. 4 microns sections were taken from these paraffin embedded tissue blocks. Histological sections stained with Haematoxylin & Eosin were used. These slides were studied under Camera mounted Compound light microscope and quantified. Immunohistochemistry was done using a tissue microarray with CK7, CK20 and CDX2, and expression of these proteins were evaluated.

SPSS version 25 (SPSS, Inc, Chicago, IL, USA) was used for all statistical analysis. For continuous data, descriptive statistics such as the mean and standard deviation were calculated, for discrete / categorical data, percentages were generated and chi square test was carried out to test the significance. An overall p value of less than 0.05 was considered statistically significant.

Results

Age distribution shows majority cases were between 41–50 years accounts 30.56 %, followed by 51–60 years accounts 22.22 %. Majority were female accounts 63.89 %. Majority of histological type was adenocarcinoma accounts 69.4 % whereas medullary adenocarcinoma accounts 2.7 %. Tumor size was >5 cm in 72 % of cases. 66.7 % of tumors were moderately differentiated tumor grading. 61.11 % of tumors are of left origin. Majority tumors are in 52.8 % of T3 stage. CK20+ / CK7- phenotype expression observed in 66.8 % of samples *(Table 1)*.

Discussion

Colorectal carcinomas accounts for 53 % of gastrointestinal tract malignancies [7,8]. Metastatic tumour of unknown primary location is a prevalent clinical concern, accounting for 3–5 % of malignancies and ranking among the top ten cancers in terms of incidence and death in both men and women, with 90 % of cases proving to be carcinoma [9]. The identification of the main location is critical for further therapy.

Age distribution shows majority cases were between 41–50 years accounts 30.56 %. female accounts 63.89 %. Adenocarcinoma accounts 69.4 %. Majority tumors are in 52.8 % of T3 stage.

Metastasis is the cause of death for CRC patients who come with metastases before the main tumour is identified. In these circumstances, immunostaining is one of the most useful approaches for determining the main site [10].

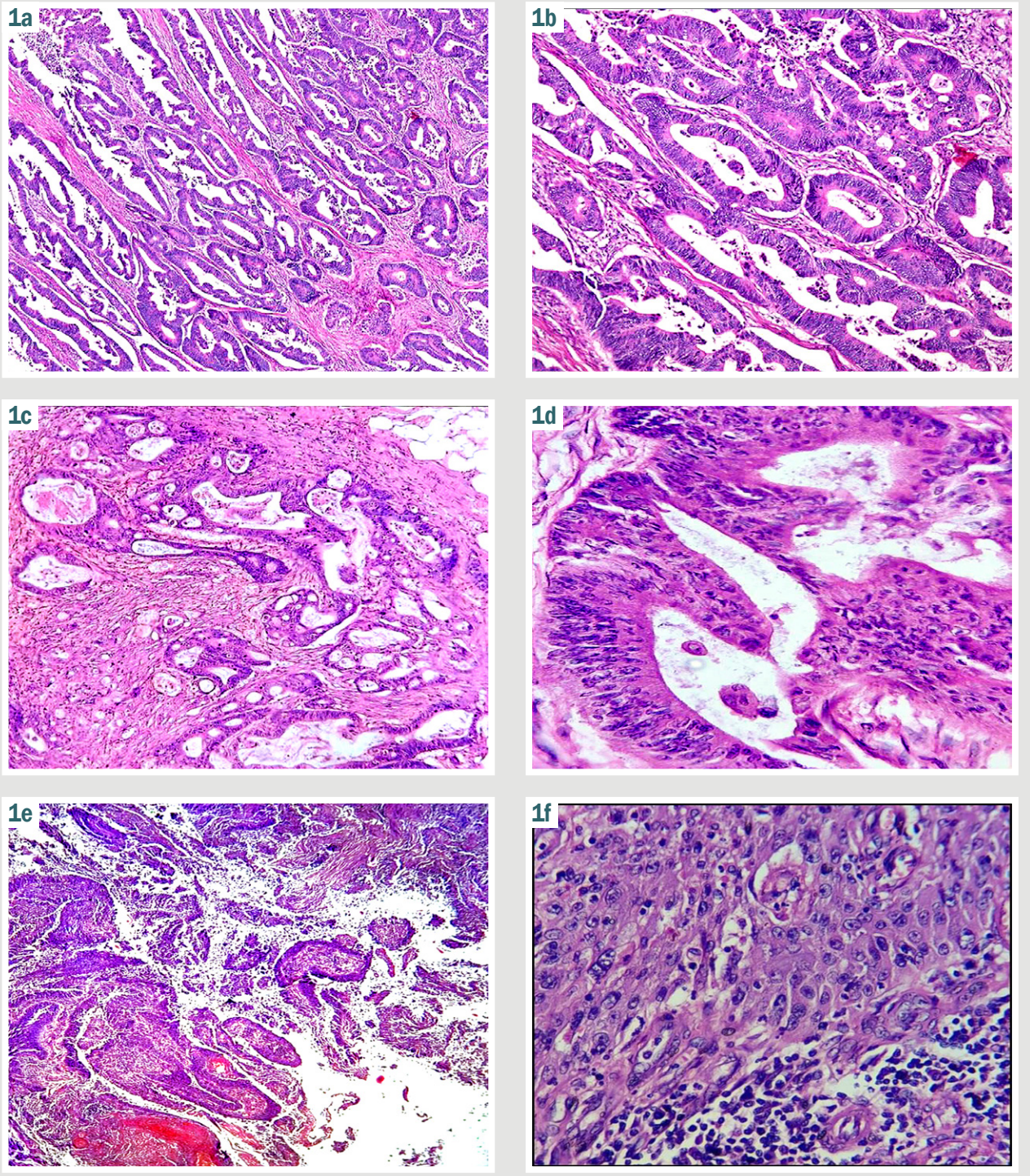

Fig. 1. a, b: well differentiated adenocarcinoma with >95 % gland formation (a – ×100, b – ×400); **c, d:** moderately differentiated with 50–95 % gland formation (c – ×100, d – ×400); **e, f:** poorly differentiated with <50 % gland formation (e – ×100, f – ×400).

A combination of clinical symptoms, diagnostic imaging modalities, haematoxylin and eosin, and immunohistochemical marker examination can lead to an appropriate diagnosis [11]. The relative expression of CK7 / CK20 remains the cornerstone in narrowing the differential diagnosis of metastatic cancer with unclear primary [12].

CK20 is unique to the gastrointestinal system, particularly colorectal, urothelial, and Merckel cell carcinoma. On the other hand, CK7 is found in glandular cancers of the breast, lung, biliary system, thyroid, and Mullerian epithelium. Despite this obvious tissue-specific distribution, ectopic CK20 expression in occasional cases of carcinomas, generated from typically CK20 negative tissues, has also been identified, but this aberrant expression is localised to a relatively limited subpopulation of tumour cells [13,14].

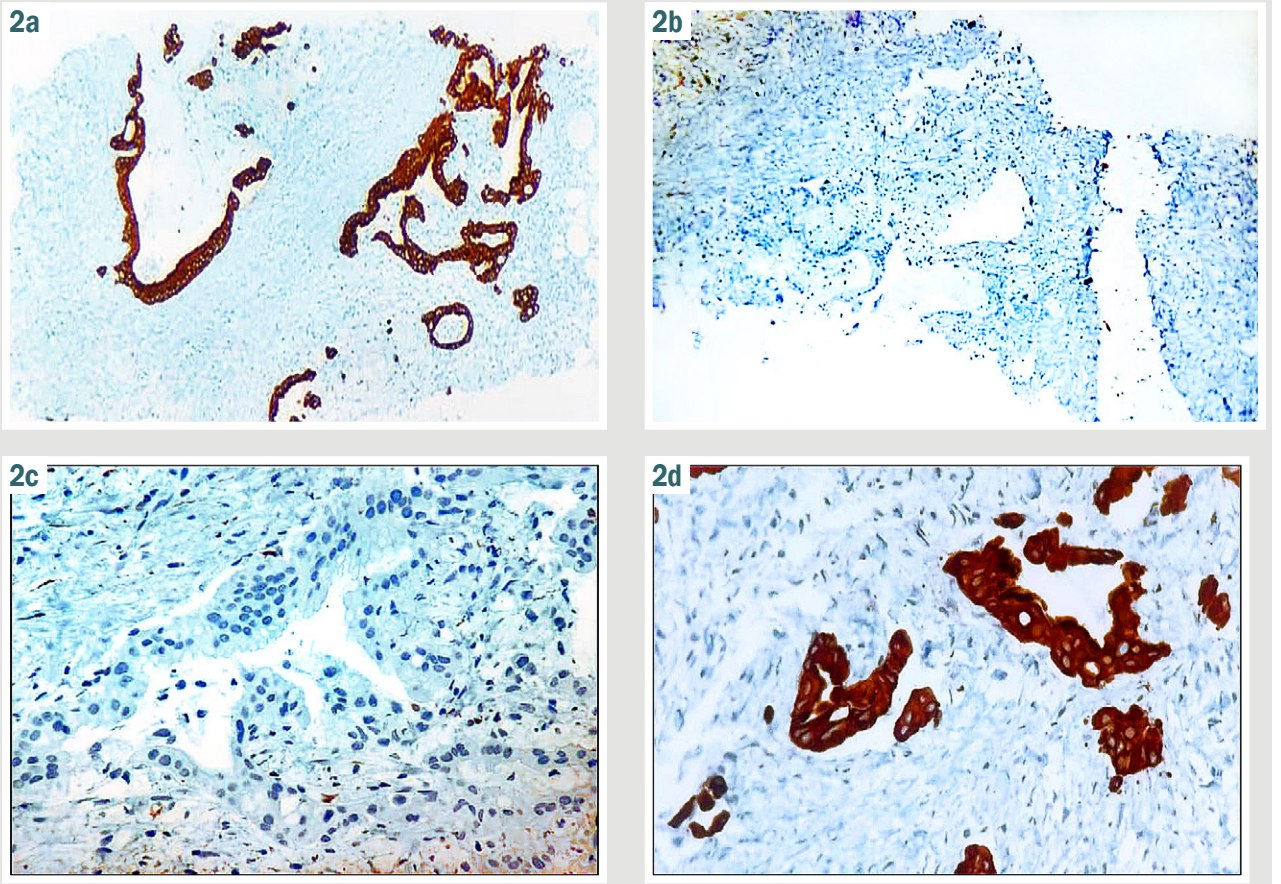

Fig. 2. Differential CK20 / CK7 immunostaining in CRC. **a:** CK20 positive; **b:** CK7 negative; **c:** CK20 negative; **d:** CK7 positive.

Table 2. Correlation between CK20 and histopathological characteristics of CRC

Parameter		Number of cases, n = 36 (100.0 %)	CK20 retained, n = 24 (66.8 %)	Loss of CK20 expression, n = 12 (33.2 %)	p value (Fisher's exact test)
Localization (n = 31)	Right colon	20	13 (65.0 %)	7 (35.0%)	1.00
	Left colon	11	7 (63.6 %)	4 (36.4%)	
Grade (n = 36)	Well-differentiated	5	4 (80.0 %)	1 (20.0 %)	0.012
	Moderately-differentiated	24	17 (70.8 %)	7 (29.1 %)	
	Poorly-differentiated	7	3 (42.8 %)	4 (57.2 %)	
Staging (n = 31)	T2	5	2 (40.0 %)	3 (60.0 %)	0.502
	T3	19	13 (68.4 %)	6 (31.5 %)	
	T4	7	4 (57.1 %)	3 (42.9 %)	
Nodal metastases(n = 36)	Present	7	6 (85.7 %)	1 (14.3 %)	0.757
	Absent	29	18 (62.1 %)	11 (37.9 %)	

Table 3. Correlation between CDX2 and histopathological characteristics of CRC

Parameter		Number of cases, n = 36 (100.0 %)	CDX2 retained, n = 32 (88.9 %)	Loss of CDX2 expression, n = 4 (11.1 %)	p-value (Fisher's exact test)
Localization (n = 31)	Right colon	20	13 (65.0 %)	7 (35.0 %)	1.00
	Left colon	11	7 (63.6 %)	4 (36.4%)	
Grade (n = 36)	Well-differentiated	5	4 (80.0 %)	1 (20.0 %)	0.028
	Moderately-differentiated	24	17 (70.8 %)	7 (29.1 %)	
	Poorly-differentiated	7	3 (42.8 %)	4 (57.2 %)	
Staging (n = 31)	T2	5	2 (40.0 %)	3 (60.0 %)	0.013
	T3	19	13 (68.4 %)	6 (31.5 %)	
	T4	7	4 (57.1 %)	3 (42.9 %)	
Nodal metastases (n = 36)	Present	7	6 (85.7 %)	1 (14.3 %)	0.672
	Absent	29	18 (62.1 %)	11 (37.9 %)	

CDX2 is a nuclear transcription factor that plays an important role in intestinal cell proliferation and differentiation and can be employed as an immunohistochemical marker for neoplasms of intestinal origin. Although CDX2 is utilised to diagnose adenocarcinoma of the colon and small intestine, it is also expressed in gastric, pancreatic ductal, and cholangiocarcinoma [15].

The relative expression of CK20 / CK7 is a diagnostic tool for determining the site of origin in metastatic carcinomas. CK20 is specific for colonic and urothelial cancers. CK7 expression identified in glandular cancers of the breast, respiratory tract, biliary tract, and mullerian epithelium [16]. CK7 expression is uncommon, and positive results are used to rule out CRC tumours. In our study, CK7 positive was 7 % with no significant histopathological correlations. A study demonstrated that CK7 positive tumours were more likely to have strong metastatic and invasive characteristics [17].

Park J. H. et al. found an association between CK20 loss, higher tumor grade, and tumors located on the right side of the colon [12].

Our study found that 12 % of CRCs lost CDX2 staining; however the exact reasons for this drop in expression are unknown *(Table 3)*.

There was a negative association between CDX2 expression and histologic grade (p = 0.03), as well as T pathologic stage (p = 0.01). However, no statistically significant relationships were seen with tumour location, N or M stage. CK7-ve / CK20+ve immune profile shows a specificity of 95 % in predicting the colorectal adenocarcinomas, which was superior to that of CDX2 *(Fig. 1)*. In our study, CK20+ / CK7 – phenotype expression observed in 66.8 % of samples *(Fig. 2)*.

Our findings are similarly consistent with those of R. Bayrak et al., who discovered that the CK7-ve / CK20+ve phenotype has a specificity of 96.7 % in detecting CRC [18].

A study conducted by Bae et al. indicated that lower CDX2 expression was related with proximal tumour site, infiltrative growth, advanced T, N, M stages, and poor differentiation. They reported that patients with CDX2 deletion had poorer overall survival [19].

Previous research has found that the CK7-ve/ CK20+ve pattern detects CRC between 65 % and 95 %, compared to one-third of gastric carcinomas and fewer than 10 % of pancreatic carcinomas [6,19,20].

In the lack of morphologic or immunohistochemical support, CK7 and CK20 are ineffective for predicting the place of origin of adenocarcinoma. CDX2 is a nuclear transcriptional regulator that controls intestinal cell differentiation and survival. It is thought to be selective for enterocytes [21,22].

This study's findings are similarly compatible with those of Zhang et al, who discovered that CDX2 expression is much higher in gastric carcinoma compared to normal gastric mucosa, showing that CDX2 is up-regulated in gastric carcinogenesis, with a reported positivity in 53.3 % of 60 cases. In relation to CDX2 expression in pancreatic ductal adenocarcinoma. Ahmed et al. reported CDX2 expression in 38.75 % of gastric carcinoma cases. Although this has been questioned by others who found no CDX2 expression [23].

Conclusions

1. Our findings confirm CRC heterogeneity.

2. 33.2 % of cases showed an atypical CK7 / CK20 immunological profile, which influenced metastatic CRC diagnosis.

3. CK7 had no histopathologic connection, however CK20 was associated to histological grade. CDX2 loss is related to tumour grade and depth (T-stage). Both the CK7-ve / CK20+ve phenotype and CDX2 expression are extremely specific and sensitive indicators of CRC.

Prospects for further researches. More thorough research is needed to investigate association between immunohistochemistry patterns and colorectal carcinoma features.

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