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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic and pathological characteristics of *de novo* colorectal cancer: Retrospective cohort study

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Abstract

BACKGROUND

Endoscopy has rapidly developed in recent years and has enabled further investigation into the origin and features of intestinal tumors. The small size and concealed position of these tumors make it difficult to distinguish them from nonneoplastic polyps and carcinoma in adenoma (CIA). The invasive depth and metastatic potential determine the operation regimen, which in turn affects the overall survival and distant prognosis. The previous studies have confirmed the malignant features and clinicopathological features of *de novo* colorectal cancer (CRC).

AIM

To provide assistance for diagnosis and treatment, but the lack of a summary of endoscopic features and assessment of risk factors that differ from the CIA prompted us to conduct this retrospective study.

METHODS

In total, 167 patients with small-sized CRCs diagnosed by endoscopy were reviewed. The patients diagnosed as advanced CRCs and other malignant cancers or chronic diseases that could affect distant outcomes were excluded. After screening, 63 cases were excluded, including 33 *de novo* and 30 CIA cases. Patient information, including their follow-up information, was obtained from an electronic His-system. The characteristics between two group and risk factors for invasion depth were analyzed with SPSS 25.0 software.

RESULTS

Nearly half of the *de novo* CRCs were smaller than 1 cm (n = 16, 48.5%) and the majority were located in the distal colon (n = 26, 78.8%). The IIc type was the most common macroscopic type of *de novo* CRC. In a Pearson analysis, the differential degree, Sano, JNET, and Kudo types, surrounding mucosa, and chicken skin

mucosa (CSM) were correlated with the invasion depth ($P < 0.001$). CSM was a significant risk factor for deep invasion and disturbed judgment of endoscopic ultrasound. A high degree of tumor budding and tumor-infiltrating lymphocytes are accompanied by malignancy. Finally, *de novo* CRCs have worse outcomes than CIA CRCs.

CONCLUSION

This is the first comprehensive study to analyze the features of *de novo* CRCs to distinguish them from nonneoplastic polyps. It is also the first study paying attention to CSM invasive depth measurement. This study emphasizes the high metastatic potential of *de novo* CRCs and highlights the need for more research on this tumor type.

Key Words: *De novo* colorectal cancer; Carcinoma in adenoma; Endoscopic features; Clinical characteristics; Pathological features

Core Tip: *De novo* colorectal cancer (CRC) is a specific tumor with a small lesion. Many different features of *de novo* CRCs exist to distinguish them from non-neoplastic polyps. Moreover, the study highlights that *de novo* CRCs have special endoscopic and pathological features that distinguish them from traditional adenocarcinomas. Different pit pattern types indicate various tumor types; for example, the III-type pit pattern often occurs in tubular adenomas. For CRCs, invasion depth evaluation is a vital issue. Computed tomography imaging and endoscopic ultrasound are used for judging invasive depth. Besides, chicken skin mucosa may also be a risk factor.

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INTRODUCTION

A *de novo* colorectal cancer (CRC) is a unique CRC that represents a significant public health challenge with high morbidity and mortality globally[1,2]. At present, CRCs have four recognized pathways of development: The carcinoma in adenoma (CIA) pathway (aka chromosomal instability pathway), the *de novo* carcinoma pathway, the serrated lesion-carcinoma pathway, and the inflammatory-carcinoma pathway. In the 1950s, *de novo*-originated CRCs emerged increasingly after the definition "de novo" was proposed. In recent decades, the Japanese proposed a *de novo* carcinoma pathway[3]. Unlike other pathways, a *de novo* CRC is a tumor derived from cancer cells without progression of adenomatous changes, as shown in Figure 1, and its true pathway remains unknown. Normal I type around tumor and lack of III or IV type pits is a hallmark of *de novo* CRC under endoscopy[4-6].

For endoscopists, the endoscopic featrures occupied a key position in diagnosis and treatment. Magnified chromoendoscopy and narrow-band imaging (NBI) technology can be used to observe pit pattern and extimate depth of invasion[7-11]. Apart of pit pattern, there existed several indicators could forecast depth of invasion, such as chicken skin mucosa (CSM), mucosa pulling and converging. The CSM is an area of 0.5 mm of pale-yellow speckles adjacent to colonic neoplasms resulting from fat accumulation in the lamina propria[12]. CSM was more common in neoplastic and advanced polyps [13]. In this study, we concentrate on relationship between CSM and depth of invasion. For the whole CRCs, we should get to know three things: Get to know who they are firstly, estimate depth of invasion secondly, and predict the risk of metastasis at last.

Epithelial-mesenchymal transition (EMT) refers to a cellular reprogramming process in which epithelial cells acquire a mesenchymal phenotype[14]. EMT has an important role in development, wound healing, and malignant progression[15]. Mueller *et al*[16] have found that E-cadherin express lower in *de novo* than ex adenoma carcinomas through immunohistochemistry (IHC)[16]. We further want to know the relationship between E-cadherin proportion and distant metastsis.

Until now, there was no a complete study about *de novo* CRC, so we make this study to construct a comprehensive system for diagnosis and treatment of *de novo* CRC.

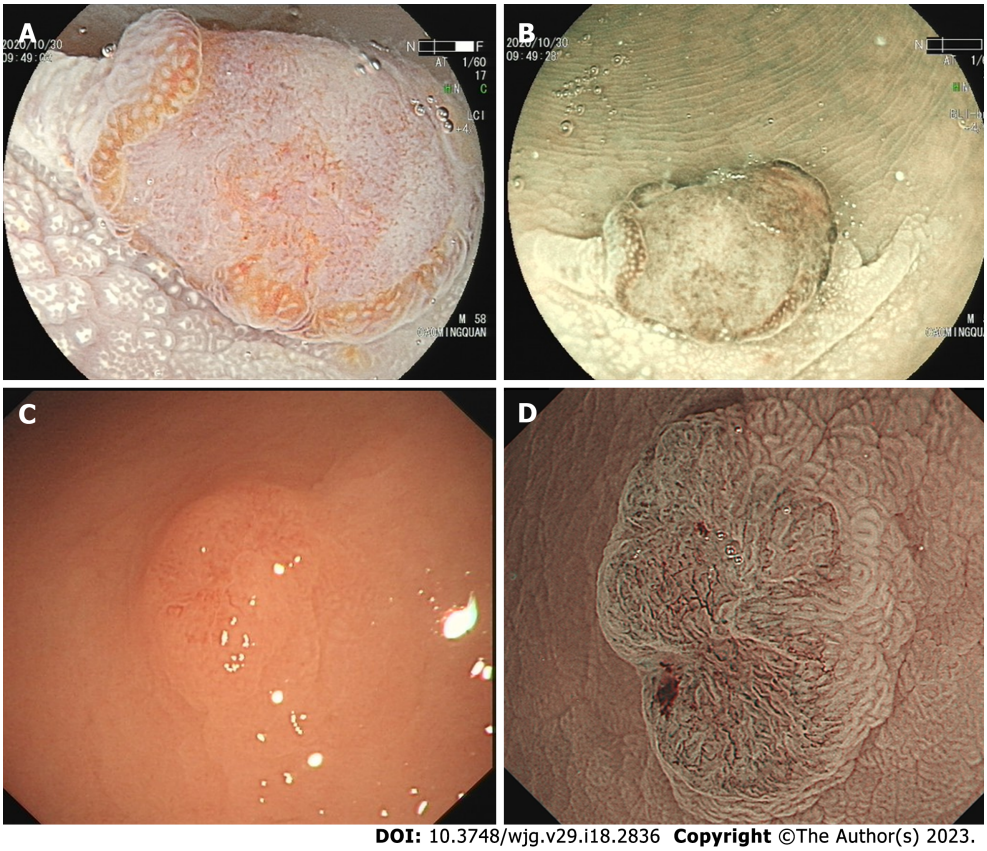

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Figure 1 The *de novo* colorectal cancer under endoscopy. A: A *de novo* colorectal cancer (CRC) under linked color imaging; B and D: The surface structure under the narrow bind imaging pattern; C: A *de novo* CRC under white light.

MATERIALS AND METHODS

We retrospectively reviewed patients diagnosed with CRCs between 2010 to 2020 year. We selected all *de novo* CRC and CIA-type patients on the His Electric System. All lesions were diagnosed by a senior pathologist and confirmed by two pathologists. The results from two pathologists had more than 90% similarity, and discrepant results were determined by a cheif pathologist. These patients did not have other comorbidities that could significantly impact the distant outcomes. Essential clinical information was collected, including endoscopic features and pathological results (size, endoscopic features, macroscopic type, pit pattern, clinical diagnosis, pathologic diagnosis, infiltration (IFN), immunohistology, invasive depth, tumor budding (TB), grading, lymphocyte IFN, perineural IFN, growth pattern, and lymph node metastasis). Pearson and χ^2 tests were performed using SPSS (25.0) software. The difference between each group was statistically significant ($P < 0.05$). Oral informed consent was obtained from all participants *via* telephone calls.

The degree of staining was scored according to the staining intensity (0, no staining; 1, weak; 2, moderate; 3, strong) and the proportion of positive cells (0: 0%; 1: < 25%; 2: < 50%; 3: < 75%; 4: ≥ 75%). The score of each slice was determined by the staining index (staining intensity × proportion of positive cells). A staining index > 4 was classified as high-grade expression, while an index ≤ 4 was defined as low-grade expression.

The pathological film used in the study was IHC, with the patient's consent, and the patient's information was kept confidential; therefore, ethical approval was not required.

RESULTS

Clinical features of de novo CRCs

Nearly half (n = 16, 48.5%) of the *de novo* CRCs were less than 1 cm in size and located in the distal colon (n = 26, 78.8%). In contrast, CIA CRCs were mostly 2 cm (n = 21, 70.0%) and located at the proximal colon (n = 21, 70.0%). There were no significant differences in the other risk factors between the *de novo* and CIA groups ($P > 0.05$). In addition, we focused on the choice of treatment. All submucosa *de novo* CRCs were treated surgically, and seven CIA submucosa CRCs were treated endoscopically. The results are presented in Table 1.

Table 1 The clinical information of *de novo* and carcinoma in adenoma colorectal cancers

		De novo (*n* = 33)	CIA (*n* = 30)	χ^2	*P* value
Clinical information					
Age (%)	> 55	30 (90.9)	25 (83.3)	0.814	> 0.05
	< 55	3 (9.1)	5 (16.7)		
Gender (%)	Male	16 (48.5)	16 (53.3)	0.148	> 0.05
	Female	17 (51.5)	14 (46.7)		
Smoking history (%)	Yes	27 (81.8)	19 (63.3)	2.725	> 0.05
	No	6 (18.2)	11 (36.7)		
Location (%)	Proximal	7 (21.2)	21 (70.0)	15.149	< 0.05
	Distal	26 (78.8)	9 (30.0)		
Depth of invasion	M	8 (24.2)	9 (30.0)	1.504	> 0.05
	SMp	9 (27.3)	11 (36.7)		
	SMd	16 (48.5)	10 (33.3)		
Treatment (%)	Surgery	21 (63.6)	16 (53.3)	0.688	> 0.05
	Endoscopy	12 (36.4)	14 (46.7)		
Supplement chemotherapy (%)	Yes	21 (63.6)	12 (40.0)	3.520	> 0.05
	No	12 (36.4)	18 (60.0)		
Distal metastasis (%)	Yes	5 (15.2)	2 (6.7)	1.145	> 0.05
	No	28 (84.8)	28 (93.3)		
Overall survival (%)	1 yr	33 (100.0)	30 (100.0)		
	3 yr	30 (90.9)	28 (93.3)		
	5 yr	23 (69.7)	28 (93.3)		
DSS	Yes	26 (78.8)	28 (93.3)	2.715	> 0.05
	No	7 (21.2)	2 (6.7)		
Endoscopic gross characteristics					
Size%	1 cm < S ≤ 2 cm	14 (42.4)	9 (30.0)	30.514	< 0.05
	≤ 1 cm	16 (48.5)	0 (0.0)		
	> 2 cm	3 (9.1)	21 (70.0)		
Macroscopic type%	Is	5 (15.2)	6 (20.0)	35.187	< 0.05
	IIa + IIc	11 (33.3)	1 (3.3)		
	IIc	17 (51.5)	4 (13.3)		
	Is + IIc	0 (0.0)	19 (63.3)		
Surface change	Erosion	24 (72.7)	13 (43.3)	9.457	< 0.05
	Ulceration	2 (6.1)	11 (36.7)		
	None	7 (21.2)	6 (20.0)		
Color change	Reddened mucosa	26 (78.8)	2 (6.7)	33.104	< 0.05
	None	7 (21.2)	28 (93.3)		
NICE	Type 1	0 (0.0)	0 (0.0)		> 0.05
	Type 2	0 (0.0)	0 (0.0)		
	Type 3	33 (100.0)	30 (100.0)		
Sano	I	0 (0.0)	0 (0.0)	5.292	< 0.05
	II	0 (0.0)	0 (0.0)		

	IIIA	17 (51.5)	7 (23.3)		
	IIIB	16 (48.5)	23 (76.7)		
JNET	1	0 (0.0)	0 (0.0)	3.094	> 0.05
	2A	0 (0.0)	0 (0.0)		
	2B	12 (36.4)	5 (16.7)		
	3	21 (63.6)	25 (83.3)		
Chemical staining (crystal violet)					
Pit pattern	Vi	1 (3.0)	6 (20.0)	15.774	< 0.05
	Vn	13 (39.4)	15 (50.0)		
	Vi + Vn	19 (57.6)	5 (16.7)		
	IV + Vi	0 (0.0)	4 (13.3)		
Pit pattern at the edge of the tumors	I	33 (100.0)	0 (0.0)	63.000	< 0.05
	III + VI	0 (0.0)	30 (100.0)		
Surrounding mucosa					
Pulling	Yes	9 (27.3)	21 (70.0)	11.501	< 0.05
	No	24 (72.7)	9 (30.0)		
Converging folds	Yes	27 (81.8)	15 (50.0)	7.159	< 0.05
	No	6 (18.2)	15 (50.0)		
CSM	CSM1	11 (33.3)	4 (13.3)	3.553	> 0.05
	CSM2	17 (51.5)	21 (70.0)		
	CSM3	5 (15.2)	5 (16.7)		

CRC: Colorectal cancer; DSS: Disease specific survival; CSM: Chicken skin mucosa; CIA: Carcinoma in adenoma; NICE: Narrow-band imaging International Colorectal Endoscopic.

Endoscopic characteristics of de novo CRCs

Based on endoscopic appearance, small CRCs were classified as type I (polypoid), type IIa (slightly raised), type IIb (flat), or type IIc (depressed)[12]. Type IIa + IIc is the most common type of *de novo* CRC. Notably, 15 (45.5%) *de novo* CRCs were Is type. We showed different macroscopic types of *de novo* CRCs, as shown in Figure 2. For CIA CRCs, the Is + IIc type (polypoid with depression) was the most common presentation (n = 19, 63.3%). Another significant finding was surface changes: We found that erosion and reddened mucosa are hallmark features of *de novo* CRCs. In the CIA group, erosion was the same as ulceration. Furthermore, reddened mucosa was seldom observed in the CIA group (n = 28, 93.3%). The endoscopic results are shown in Table 2.

There was a significant difference in the Sano and pit pattern types (P < 0.05) but no significant difference in the NBI International Colorectal Endoscopic (NICE) classification and JNET types between the two groups (P > 0.05). About half of the *de novo* CRCs were IIIA type (n = 17, 51.5%) with a Vi + Vn type pit pattern (n = 19, 57.6%). The most striking difference was in the pit pattern around the edges of the lesions: I type pit patterns (small and round pits) were observed in all *de novo* CRCs (n = 33, 100%), and III + VI type pit patterns were observed in all CIA CRCs (n = 30, 100%).

We also analyzed the risk factors associated with the invasive depth (Table 3). A third (33.3%) of the *de novo* group had a CSM1 × *vs* 13.3% of the CIA group. CSM was associated with the depth of invasion [r (correlation coefficient) = -0.796, P < 0.001]. CSM1 has a high invasive potential for CRC. In addition to CSM, pulling and converging folds also appear in the mucosa surrounding CRCs. Mucosal pulling appeared more frequently in the CIA group (n = 21, 70.0%) than in the *de novo* group (n = 9, 27.3%). In contrast, the converging fold was more frequent in the *de novo* group (n = 27, 81.8%) than that in the CIA group (n = 15, 50%). After analyzing the relationship between these parameters and invasive depth, we found that mucosal pulling (r = 0.567, P < 0.001) and converging folds (r = 0.620, P < 0.001) were also significantly associated with invasive depth.

Pathological characteristics of de novo CRCs

Pathological results revealed that TB was significantly associated with invasive depth (r = 0.669, P < 0.001) (Table 4). Although there was no significant difference between the two groups, budding grade 3 (BD3) accounted for 33.3% of the *de novo* group, which is far more than that of the CIA group (n = 6,

Table 2 The endoscopic characteristics in *de novo* and carcinoma in adenoma groups

		De novo (*n* = 22)	CIA (*n* = 20)	χ^2	*P* value
Budding	BD1	8 (24.2)	4 (13.3)	6.161	> 0.05
	BD2	8 (24.2)	6 (20.0)		
	BD3	11 (33.3)	6 (20.0)		
	None	5 (18.2)	14 (46.7)		
Grading	G1	6 (18.2)	13 (43.3)	8.878	> 0.05
	G2	11 (33.3)	9 (30.0)		
	G1-2	10 (30.3)	8 (26.7)		
	G3-2	6 (18.2)	0 (0.0)		
TIL	Yes	27 (81.8)	19 (63.3)	2.725	> 0.05
	No	6 (18.2)	11 (36.7)		
Perineural infiltration	Yes	16 (48.5)	3 (10.0)	11.050	< 0.05
	No	17 (51.5)	27 (90.0)		
Lymphovascular invasion	Yes	16 (48.5)	7 (23.3)	4.289	< 0.05
	No	17 (51.5)	23 (76.7)		
Growth pattern	INFa	0 (0.0)	27 (90.0)	63.000	< 0.05
	INFb	0 (0.0)	3 (10.0)		
	INFc	33 (100.0)	0 (0.0)		
Lymph node metastasis	Yes	10 (30.3)	1 (3.3)	7.931	> 0.05
	No	23 (69.7)	29 (96.7)		
Adjacent lesions	Inflammation	33 (100.0)	0 (0.0)	63.000	< 0.05
	Adenoma	0 (0.0)	17 (56.7)		
	Hyperplasia	0 (0.0)	13 (43.3)		
IHC-E-cadherin	No staining	0 (0.0)	0 (0.0)	22.609	< 0.05
	Weak	17 (51.5)	2 (6.7)		
	Moderate	15 (48.5)	19 (63.3)		
	Strong	0 (0.0)	9 (30.0)		
IHC-Vimentin	No staining	0 (0.0)	0 (0.0)	23.182	< 0.05
	Weak	13 (39.4)	18 (60.0)		
	Moderate	1 (3.0)	10 (33.3)		
	Strong	19 (57.6)	2 (6.7)		

CIA: Carcinoma in adenoma; TIL: Tumor Infiltrating Lymphocyte; IHC: Immunohistochemistry; BD: Budding grade.

Table 3 The risk factors are related to the depth of invasion

Depth of invasion	M	SM-S	SM-d and deeper	*r*	*P* value
Size, %				-0.002	> 0.05
1 cm < S ≤ 2 cm	1 (12.5)	0 (0.0)	13 (81.3)		
≤ 1 cm	7 (87.5)	9 (100.0)	0 (0.0)		
> 2 cm	0 (0.0)	0 (0.0)	3 (18.8)		
Growth pattern					> 0.05

IFNa	0 (0.0)	0 (0.0)	0 (0.0)		
IFNb	0 (0.0)	0 (0.0)	0 (0.0)		
IFNc	8 (100.0)	9 (100.0)	16 (100.0)		
Differential degree				0.904	< 0.001
G1	5 (62.5)	1 (11.1)	0 (0.0)		
G2	3 (37.5)	8 (88.9)	0 (0.0)		
G1-2	0 (0.0)	0 (0.0)	10 (62.5)		
G3-2	0 (0.0)	0 (0.0)	6 (37.5)		
Macroscopic type				-0.093	> 0.05
Is	2 (25.0)	0 (0.0)	13 (81.3)		
IIa + IIc	6 (75.0)	9 (100.0)	0 (0.0)		
IIc	0 (0.0)	0 (0.0)	3 (18.8)		
Is + IIc	0 (0.0)	0 (0.0)	0 (0.0)		
NICE					> 0.05
Type 1	0 (0.0)	0 (0.0)	0 (0.0)		
Type 2	0 (0.0)	0 (0.0)	0 (0.0)		
Type 3	8 (100.0)	9 (100.0)	16 (100.0)		
Sano				0.938	< 0.001
I	0 (0.0)	0 (0.0)	0 (0.0)		
II	0 (0.0)	0 (0.0)	0 (0.0)		
IIIA	8 (100.0)	9 (100.0)	0 (0.0)		
IIIB	0 (0.0)	0 (0.0)	16 (100.0)		
JNET				0.649	< 0.001
1	0 (0.0)	0 (0.0)	0 (0.0)		
2A	0 (0.0)	0 (0.0)	0 (0.0)		
2B	5 (62.5)	7 (77.8)	0 (0.0)		
3	3 (37.5)	2 (22.2)	16 (100.0)		
Pit pattern				-0.491	< 0.001
Vi	1 (12.5)	0 (0.0)	0 (0.0)		
Vn	0 (0.0)	0 (0.0)	13 (81.3)		
Vi + Vn	7 (87.5)	9 (100.0)	3 (18.8)		
IV + Vi	0 (0.0)	0 (0.0)	0 (0.0)		
Pit pattern at the edge of the tumors					> 0.05
I	8 (100.0)	9 (100.0)	16 (100.0)		
III + VI	0 (0.0)	0 (0.0)	0 (0.0)		
Surrounding mucosa					
Pulling				-0.567	< 0.001
Yes	0 (0.0)	0 (0.0)	9 (56.3)		
No	8 (100.0)	9 (100.0)	7 (43.8)		
Converging folds				-0.62	< 0.001
Yes	3 (37.5)	8 (88.9)	16 (100.0)		
No	5 (62.5)	1 (11.1)	0 (0.0)		
CSM				-0.796	< 0.001

CSM1	0 (0.0)	0 (0.0)	11 (68.8)
CSM2	3 (37.5)	9 (100.0)	5 (31.3)
CSM3	5 (62.5)	0 (0.0)	0 (0.0)

IFN: Infiltration; CSM: Chicken skin mucosa; NICE: Narrow-band imaging International Colorectal Endoscopic.

Table 4 The risk factors are related to tumor budding

	BD1	BD2	BD3	No budding	*r*	*P* value
Infiltrative depth, %					0.669	< 0.001
M	0 (0.0)	3 (21.4)	0 (0.0)	14 (70.0)		
SMp	10 (83.3)	1 (7.1)	3 (17.6)			
SMd	2 (16.7)	10 (71.4)	14 (82.4)			
Lymphovascular invasion					0.663	< 0.001
Yes	2 (28.6)	4 (21.1)	16 (94.1)	1 (5.0)		
No	5 (71.4)	15 (78.9)	1 (5.9)	19 (95.0)		
Lymph node metastasis					0.489	< -0.001
Yes	1 (14.3)	1 (5.3)	9 (52.9)	0 (0.0)		
No	6 (85.7)	18 (94.7)	8 (41.7)	20 (100.0)		
Perineural infiltration					0.601	< 0.001
Yes	2 (28.6)	4 (21.1)	13 (76.5)	0 (0.0)		
No	5 (71.4)	15 (78.9)	4 (23.5)	20 (100.0)		
Tumor infiltrating lymphocytes					0.476	< 0.001
Yes	7 (100.0)	19 (100.0)	14 (82.4)	6 (30.0)		
No	0 (0.0)	0 (0.0)	3 (17.6)	14 (70.0)		
Differential degree					0.706	< 0.001
G1	0 (0.0)	0 (0.0)	0 (0.0)	19 (95.0)		
G1-2	2 (28.6)	9 (47.4)	7 (41.2)	0 (0.0)		
G2	5 (71.4)	10 (52.6)	4 (23.5)	1 (5.0)		
G3-2	0 (0.0)	0 (0.0)	6 (35.3)	0 (0.0)		

BD: Budding grade.

20%). Regarding other pathological characteristics, perineural IFN, lymph node metastasis, and tumor-infiltrating lymphocytes (TIL) have also emerged in CRC tissues. There was a significant difference in perineural IFN and lymph node metastasis between the two groups ($P < 0.05$).

Another critical issue that deserves attention is IHC. In both groups, approximately 70% of the cases were MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), CDX2 (+), Ki67 (+), and P53 (+). We extracted several sections that were stained for E-cadherin and vimentin (VIM). In the *de novo* group, the E-cadherin expression was low in the epithelial regions and VIM was high in the mesenchyma. The CIA group showed opposite results to the *de novo* group, as shown in Figure 3. We analyzed risk factors for distant metastasis in *de novo* group, the results are shown in Supplementary Table 1. Differential degree, Sano classification, expression of E-cad and VIM were correlated with distant metastasis. High expression of E-cad was negatively related with distant metastasis and VIM had an opposite result.

In addition, we explored whether the *de novo* type was correlated with relapse and survival. In the *de novo* group, 11 subjects developed neoplastic polyps again within 5 years, and 10 relapsed within 5 years. The 5-year survival rate was 93.3% for CIA and 69.7% for *de novo* CRCs. Log-rank analysis revealed no significant difference in relapse between the two groups ($\chi^2 = 0.49$, $P = 0.515$); however, there was a significant difference in the survival probability between the two groups ($\chi^2 = 7.08$, $P = 0.020$). Survival curves are shown in Figure 4.

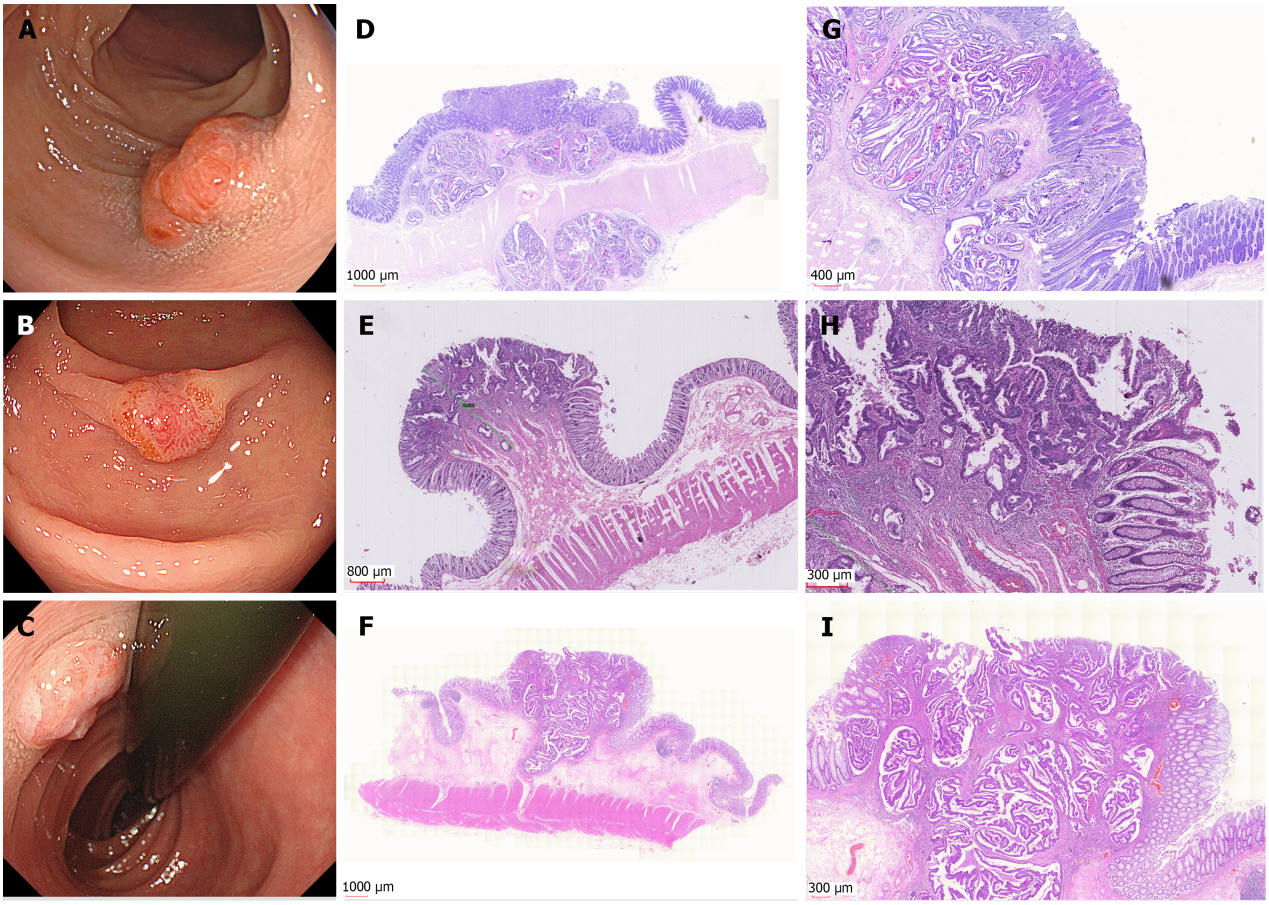

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Figure 2 The examples of I-type *de novo* colorectal cancer. A-C: Endoscopic images of different types *de novo* colorectal cancers (CRCs); D-I: Pathological images of *de novo* CRCs.

DISCUSSION

In this study, we present our novel findings pertaining to the characteristics of *de novo* CRC. The key findings included the following: (1) The incidence rate of *de novo* CRCs is considered lower than CIA CRCs, but our study showed that it is related to the classification of CRC. Although some *de novo* CRCs are limited to intramucosal cancer, they are not the same as high-grade dysplasia or cancer with high-grade intraepithelial neoplasia, which could be called advancing adenoma. An advancing adenoma is a precancerous lesion, whereas a *de novo* CRC is a type of early CRC. Some endoscopic physicians misdiagnose advanced adenomas as early CRCs; this will improve the diagnostic rate of CRC but reduce the incidence rate of *de novo* cancer. Therefore, we believe that the diagnostic bias of endoscopic physicians affects the incidence rate. One of the aims of this study was to bolster the standardized diagnostic requirements of endoscopic physicians and to understand *de novo* cancer from the molecular, pathological, and endoscopic perspectives. According to the Vienna classification, category 4 includes advanced adenoma/dysplasia and noninvasive carcinoma. The reason for the lower incidence of *de novo* CRCs in the previous study may be eliminated by comprehensively evaluating the characteristics comprehensively[17-20]; (2) In our study, 48.5% of *de novo* CRCs were < 1 cm in size. Some investigators excluded tumors > 1 cm because they thought that the adenomatous component might be obliterated by the expanding tumor mass[12]. In our study, 42.4% of the *de novo* CRC-derived tumors diagnosed by endoscopists and pathologists were ≥ 1 cm and ≤ 2 cm. In addition, there were three lesions larger than 2 cm. Therefore, warning regarding small lesions without adenomatous components should be escalated; and (3) In addition to platform lift, converging mucosa, pulling, and CSM are significant indicators of invasive depth. Fibroplasia causes surface changes during cancer cell invasion. Converging mucosa was more likely to occur in *de novo* CRCs than that in CIA group, and nearly half of the lesions (n = 16, 48.5%) had deeper invasion. Mucosal pulling may be caused by shrinkage of the mucosa or muscularis mucosa, indicating superficial layer invasion.

The cause of CSM may be fat accumulation in macrophages, which may result from the breakdown of lipids within colonocytes or adjacent tumors. These findings suggest that CSM is a valuable marker for differentiating between neoplastic and advanced polyps using conventional white colonoscopy[21]. Lee *et al*[13] divided CSM into three types based on their characteristics. Type 1 CSM was confirmed before

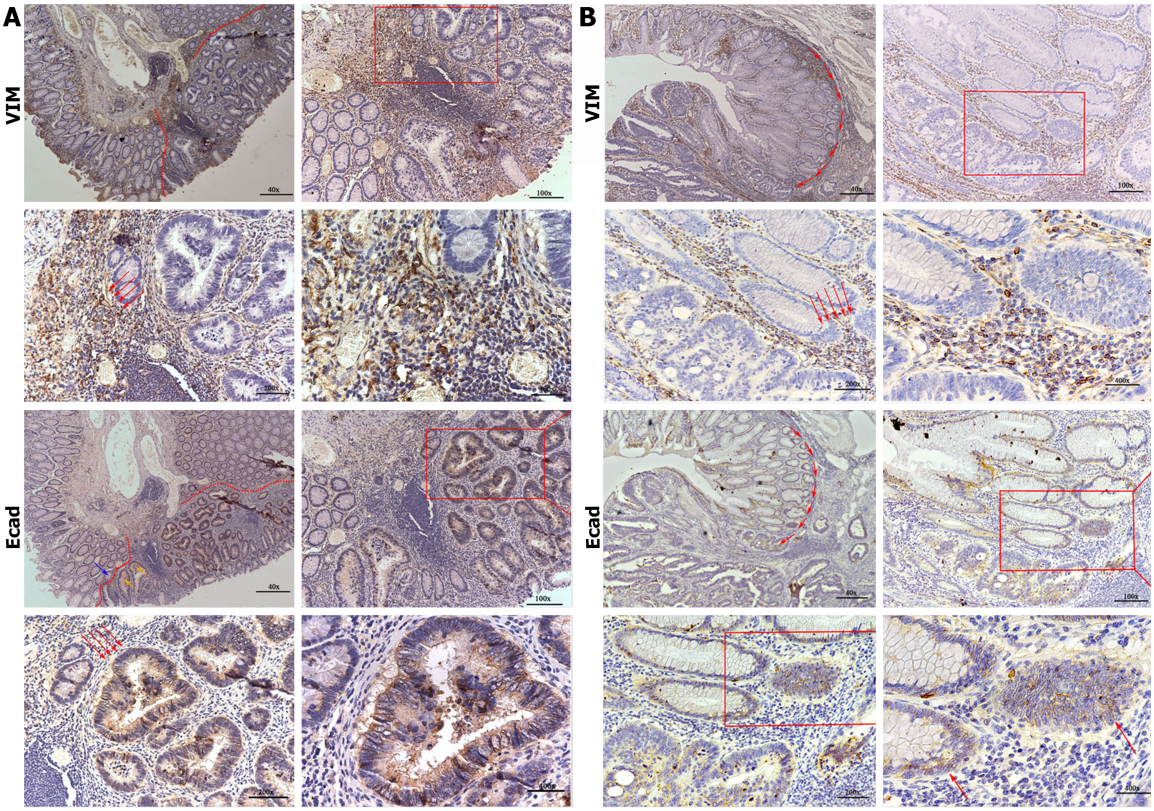

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Figure 3 The immunohistory results. A: A *de novo* colorectal cancer (CRC) pathological section stained with E-cad and vimentin (VIM); B: A carcinoma in adenoma CRC pathological section stained with E-cad and VIM. VIM: Vimentin.

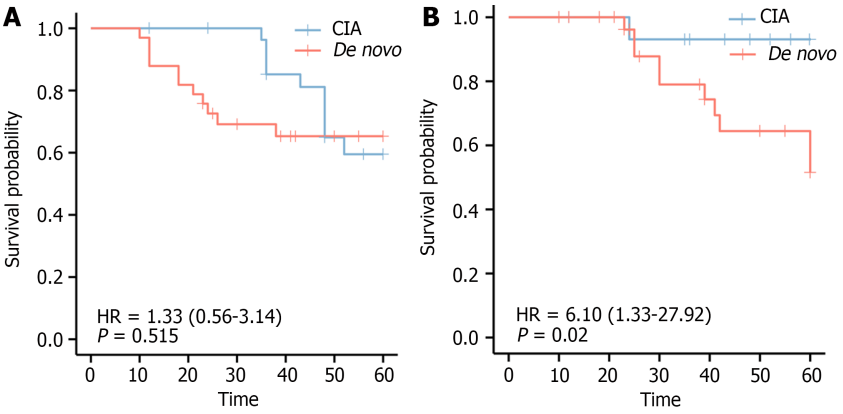

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Figure 4 The association of *de novo* colorectal cancer and over survival. A: Relationship between relapse rate and colorectal cancer (CRC) types; B: Relationship between rate of death and CRC types. CIA: Carcinoma in adenoma.

injection; type 2 CSM was observed after injection; and type 3 CSM was not observed. Types 1 and 2 were considered positive CSM findings. CSM is accompanied by an increased IFN of foam macrophages in the lamina propria, representing a large-scale inflammatory reaction. The appearance of CSM is also related to the increased expression of Ki-67 and COX2, which suggests that the early appearance of CSM symbolizes a high malignancy. However, whether the appearance of CSM and the IFN of macrophages in the lamina propria affect the determination of the depth of IFN by endoscopic ultrasound (EUS) is unknown. After diagnosing white light endoscopy, magnifying endoscopy, and endoscopic ultrasonography, we concluded that the lesion was a *de novo* cancer with deep invasion, which was no longer suitable for endoscopic treatment. However, after surgical resection, pathology showed that the depth of invasion only reached the M2 layer. After further analysis of the pathology, we found that many inflammatory cells infiltrated the lesion, leading to errors in determining the IFN depth.

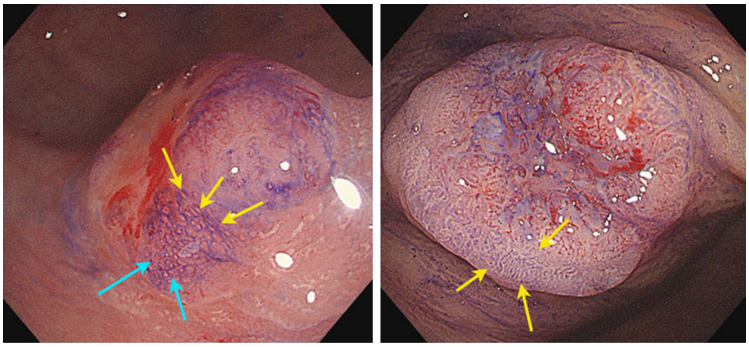

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Figure 5 The surrounding pit of *de novo* colorectal cancer and carcinoma in adenoma group. The surrounding pit around *de novo* colorectal cancer (CRC) is elongated I-type and IIIL-type around carcinoma in adenoma CRC.

Under NBI and magnifying endoscopy patterns, the surface and vascular microstructures can be clearly evaluated. The NICE classification is a method for assessing the characteristics of lesions under the NBI model, which is based on the color, vessel, and general surface pattern[22]. The NICE classification can help reduce the risk of failing to detect diminutive and small lesions, which are easily regarded as polys[23]. Nevertheless, the NICE classification had no differential ability for *de novo* CRCs and CIA CRCs. The pit pattern of CRC characteristics was categorized according to the Kudo and Tsuruta classification system. Type IIIL and IV patterns are often observed in adenomas and CIA CRCs. Type V is subclassified into Vi and Vn, and occurs in cancers. The surrounding I type pit is a landmark in the diagnosis of *de novo* CRCs. However, the normal I type often deforms and confounds with an abnormal pit due to the extrusion or invasion of cancer. The IIIs type pit was round and smaller than the I type pit, and IIIL was more irregular than the elongated I type pit. An example is shown in Figure 5.

De novo CRCs have greater metastatic potential, and all pathological indicators indicate that *de novo* carcinoma has a higher metastatic potential and worse prognosis. All *de novo* cancers were classified as microsatellite stability (MSS). In the *de novo* group, the degree of TB and lymphocyte IFN was higher than that in the CIA group and was positively correlated with the depth of invasion and poor prognosis. The IHC results also showed that the expression of E-cadherin in the *de novo* group was lower than that in the CIA group. At the same time, the interstitial-related index VIM was higher than that in the CIA group, which means that the metastatic potential of the tumor in the *de novo* group was higher than that in the CIA group. TB is defined as "a single cancer cell or a cell cluster of 5 cancer cells or less". Larger tumors are called poorly differentiated tumor cell nests. TB is closely correlated with disease recurrence and poor prognosis in SM-invasive CRCs[24-27].

In addition, the TB degree had a relationship with other pathological features. In general, tumor tissues with BD2/3 are considered for further surgery[28]. The lymphocytic reaction is another crucial part of pathological changes in CRCs, which includes Crohn's-like reaction, peritumoral reaction, intratumoral periglandular reaction, and TIL[29]. TIL are defined as lymphocytes on the top of cancer cells, which can be used to predict immunotherapy response and survival outcomes. One study reported that tumors with microsatellite instability-high and sufficient CD8+ TIL had better outcomes than those with MSS/microsatellite instability-low and lower CD8+ TIL[30]. Compared to typical pathological indicators, TIL are a better factor for overall survival[29,31,32]. TIL are related to the expression of exhaustion and senescence markers in the tumor microenvironment[33,34].

This study have several promising implications during clinical practice. Due to the highly invasive and metastatic ability of *de novo* CRC, endoscopic mucosal resection or endoscopic submucosal dissection could not be performed without exact observation when we find small protruded or depressed lesions. Observing the lesions with magnified endoscopy and chromoendoscopy is necessary to confirm the diagnosis. If we suspect the lesions may be *de novo* CRCs, it is crucial evaluating invasion depth by magnified endoscopy and chromoendoscopy, or by computed tomography imaging and EUS when necessary. Then, the treatment regimens should be chosen cautiously. In the future, we will further study the molecular biological difference between *de novo* CRC and CIA CRC to find out the molecular mechanism of invasion and metastasis of *de novo* CRCs.

However, there exists some limitations in the study. The sample size appear to be small for deficience of acknowledge of *de novo* CRCs. Moreover, this appears as a single center study, and the pathogenesis/incidence of *de novo* CRC might be different in other countries.

CONCLUSION

This review summarizes the characteristics of *de novo* CRCs and confirms the conclusions of our study.

A *de novo* CRC is a small, but malignant tumor that requires more attention during colonoscopy examination. *De novo* CRCs have special endoscopic and pathological features that distinguish them from the traditional adenocarcinomas. However, more studies are needed to determine the molecular characteristics to explain the genesis mechanism.

ARTICLE HIGHLIGHTS

Research background

The small colorectal small tumors usually be ignored during colonoscopy. However, many depressed or flat lesions have substantial invasion and metastasis. *De novo* colorectal cancer (CRC) is one type of small tumor related to poor prognosis. And some endoscopists could not distinguish *de novo* CRC during the examination.

Research motivation

Some small lesions were cut off directly in the examination without computed tomography imaging and endoscopic ultrasound. This may lead to mistreatment because endoscopists often ignore the judgment of invasion depth. The *de novo* CRC may have a deep invasion layer.

Research objectives

This study aimed to comprehensively review *de novo* CRCs and provide a reference atlas for future studies and analyze the features of *de novo* CRCs to distinguish them from non-neoplastic polyps.

Research methods

This study collected clinical and pathological information on *de novo* patients and stained E-cadherin and vimentin by immunohistochemistry. Based on this information, we analyzed the characteristic of *de novo* CRC and the relative correlation between different indicators.

Research results

This study highlights that *de novo* CRCs have special endoscopic and pathological features that distinguish them from traditional adenocarcinomas. It is also the first study paying attention to chicken skin mucosa invasive depth measurement. More importantly, this study summarized several factors relevant to invasion depth and provide tremendous help in clinical practice to increase diagnostic ability.

Research conclusions

This first study pointed out the relationship between *de novo* CRC and epithelial-mesenchymal transition related genes. And it is the first study put forward that chicken skin mucosa indicates the depth of invasion.

Research perspectives

We will further study the molecular biological difference between *de novo* CRC and carcinoma in adenoma CRC to discover the mechanism of invasion and metastasis of *de novo* CRCs.

FOOTNOTES

Author contributions: Zhang HJ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Zhang HJ, Li SY, and Yang MQ were responsible for protocol/project development; Li SY, Yang MQ, and Zhang HJ performed data analysis; Li SY, Yang MQ, Liu YM, and Sun MJ performed data collection or management; Yang MQ and Zhang HJ were responsible for manuscript writing/editing; Li SY and Yang MQ, these two authors, contributed equally to this work.

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REFERENCES

1 **Lieberman DA**, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; **343**: 162-168 [PMID: 10900274 DOI: 10.1056/NEJM200007203430301]
2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
3 **Papagiorgis PC**, Zizi AE, Tseleni S, Oikonomakis IN, Nikiteas NI. Clinicopathological differences of colorectal cancers according to tumor origin: Identification of possibly de novo lesions. *Biomed Rep* 2013; **1**: 97-104 [PMID: 24648902 DOI: 10.3892/br.2012.17]
4 **Koga Y**, Hirahashi M, Ohishi Y, Oda Y. Clinicopathological features and phenotypic classification of de novo-type colorectal carcinomas differ from those of colorectal carcinomas derived from flat adenomas. *Pathol Int* 2019; **69**: 331-340 [PMID: 31282116 DOI: 10.1111/pin.12803]
5 **Trinh A**, Lädrach C, Dawson HE, Ten Hoorn S, Kuppen PJK, Reimers MS, Koopman M, Punt CJA, Lugli A, Vermeulen L, Zlobec I. Tumour budding is associated with the mesenchymal colon cancer subtype and RAS/RAF mutations: a study of 1320 colorectal cancers with Consensus Molecular Subgroup (CMS) data. *Br J Cancer* 2018; **119**: 1244-1251 [PMID: 30385823 DOI: 10.1038/s41416-018-0230-7]
6 **Goto H**, Oda Y, Murakami Y, Tanaka T, Hasuda K, Goto S, Sasaki Y, Sakisaka S, Hattori M. Proportion of de novo cancers among colorectal cancers in Japan. *Gastroenterology* 2006; **131**: 40-46 [PMID: 16831588 DOI: 10.1053/j.gastro.2006.04.010]
7 **Matsuda T**, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am J Gastroenterol* 2008; **103**: 2700-2706 [PMID: 18853968 DOI: 10.1111/j.1572-0241.2008.02190.x]
8 **Glover B**, Patel N, Ashrafian H, Teare J. Diagnostic accuracy of i-scan image enhancement for real-time endoscopic diagnosis of small colorectal polyps: a meta-analysis. *Therap Adv Gastroenterol* 2018; **11**: 1756284818814948 [PMID: 30574190 DOI: 10.1177/1756284818814948]
9 **Kuramoto S**, Oohara T. How do colorectal cancers develop? *Cancer* 1995; **75**: 1534-1538 [PMID: 7889487 DOI: 10.1002/1097-0142(19950315)75:6+<1534::aid-cncr2820751525>3.0.co;2-2]
10 **Mueller J**, Mueller E, Hoepner I, Jütting J, Bethke B, Stolte M, Höfler H. Expression of bcl-2 and p53 in de novo and ex-adenoma colon carcinoma: a comparative immunohistochemical study. *J Pathol* 1996; **180**: 259-265 [PMID: 8958802 DOI: 10.1002/(SICI)1096-9896(199611)180:3<259::AID-PATH654>3.0.CO;2-1]
11 **Kinzler KW**, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996; **87**: 159-170 [PMID: 8861899 DOI: 10.1016/s0092-8674(00)81333-1]
12 **Shatz BA**, Weinstock LB, Thyssen EP, Mujeeb I, DeSchryver K. Colonic chicken skin mucosa: an endoscopic and histological abnormality adjacent to colonic neoplasms. *Am J Gastroenterol* 1998; **93**: 623-627 [PMID: 9576459 DOI: 10.1111/j.1572-0241.1998.177_b.x]
13 **Lee YM**, Song KH, Koo HS, Lee CS, Ko I, Lee SH, Huh KC. Colonic Chicken Skin Mucosa Surrounding Colon Polyps Is an Endoscopic Predictive Marker for Colonic Neoplastic Polyps. *Gut Liver* 2022; **16**: 754-763 [PMID: 35000932 DOI: 10.5009/gnl210271]
14 **Thiery JP**, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell* 2009; **139**: 871-890 [PMID: 19945376 DOI: 10.1016/j.cell.2009.11.007]
15 **Shibue T**, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. *Nat Rev Clin Oncol* 2017; **14**: 611-629 [PMID: 28397828 DOI: 10.1038/nrclinonc.2017.44]
16 **Mueller JD**, Bethke B, Stolte M. Colorectal de novo carcinoma: a review of its diagnosis, histopathology, molecular biology, and clinical relevance. *Virchows Arch* 2002; **440**: 453-460 [PMID: 12021919 DOI: 10.1007/s00428-002-0623-z]
17 **Tsuda S**, Veress B, Tóth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. *Gut* 2002; **51**: 550-555 [PMID: 12235079 DOI:

10.1136/gut.51.4.550]

18 **Rembacken BJ**, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 2000; **355**: 1211-1214 [PMID: 10770302 DOI: 10.1016/s0140-6736(00)02086-9]

19 **Gao Z**, Jiang J, Hou L, Zhang B. Dysregulation of MiR-144-5p/RNF187 Axis Contributes To the Progression of Colorectal Cancer. *J Transl Int Med* 2022; **10**: 65-75 [PMID: 35702180 DOI: 10.2478/jtim-2021-0043]

20 **Hornick JL**, Farraye FA, Odze RD. Clinicopathologic and immunohistochemical study of small apparently "de novo" colorectal adenocarcinomas. *Am J Surg Pathol* 2007; **31**: 207-215 [PMID: 17255765 DOI: 10.1097/01.pas.0000213383.17418.a9]

21 **Hayashi N**, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013; **78**: 625-632 [PMID: 23910062 DOI: 10.1016/j.gie.2013.04.185]

22 **Hattori S**, Iwatate M, Sano W, Hasuike N, Kosaka H, Ikumoto T, Kotaka M, Ichiyanagi A, Ebisutani C, Hisano Y, Fujimori T, Sano Y. Narrow-band imaging observation of colorectal lesions using NICE classification to avoid discarding significant lesions. *World J Gastrointest Endosc* 2014; **6**: 600-605 [PMID: 25512769 DOI: 10.4253/wjge.v6.i12.600]

23 **Tanaka S**, Hayashi N, Oka S, Chayama K. Endoscopic assessment of colorectal cancer with superficial or deep submucosal invasion using magnifying colonoscopy. *Clin Endosc* 2013; **46**: 138-146 [PMID: 23614123 DOI: 10.5946/ce.2013.46.2.138]

24 **Landau MA**, Zhu B, Akwuole FN, Pai RK. Histopathological Predictors of Recurrence in Stage III Colon Cancer: Reappraisal of Tumor Deposits and Tumor Budding Using AJCC8 Criteria. *Int J Surg Pathol* 2019; **27**: 147-158 [PMID: 29992847 DOI: 10.1177/1066896918787275]

25 **Liu P**, Zhu H, Zhang X, Feng A, Zhu X, Sun Y. Predicting Survival for Hepatic Arterial Infusion Chemotherapy of Unresectable Colorectal Liver Metastases: Radiomics Analysis of Pretreatment Computed Tomography. *J Transl Int Med* 2022; **10**: 56-64 [PMID: 35702189 DOI: 10.2478/jtim-2022-0004]

26 **Nagata K**, Shinto E, Yamadera M, Shiraishi T, Kajiwara Y, Okamoto K, Mochizuki S, Hase K, Kishi Y, Ueno H. Prognostic and predictive values of tumour budding in stage IV colorectal cancer. *BJS Open* 2020; **4**: 693-703 [PMID: 32472647 DOI: 10.1002/bjs5.50300]

27 **Zhang Y**, Liu Y, Qiu X, Yan B. Concurrent Comparison of the Prognostic Values of Tumor Budding, Tumor Stroma Ratio, Tumor Infiltrating Pattern and Lymphocyte-to-Monocyte Ratio in Colorectal Cancer Patients. *Technol Cancer Res Treat* 2021; **20**: 15330338211045826 [PMID: 34658263 DOI: 10.1177/15330338211045826]

28 **Pan S**, Sun S, Liu B, Hou Y. Pan-cancer Landscape of the RUNX Protein Family Reveals their Potential as Carcinogenic Biomarkers and the Mechanisms Underlying their Action. *J Transl Int Med* 2022; **10**: 156-174 [PMID: 35959452 DOI: 10.2478/jtim-2022-0013]

29 **Ogino S**, Nosho K, Irahara N, Meyerhardt JA, Baba Y, Shima K, Glickman JN, Ferrone CR, Mino-Kenudson M, Tanaka N, Dranoff G, Giovannucci EL, Fuchs CS. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. *Clin Cancer Res* 2009; **15**: 6412-6420 [PMID: 19825961 DOI: 10.1158/1078-0432.CCR-09-1438]

30 **Zou Q**, Wang X, Ren D, Hu B, Tang G, Zhang Y, Huang M, Pai RK, Buchanan DD, Win AK, Newcomb PA, Grady WM, Yu H, Luo Y. DNA methylation-based signature of CD8+ tumor-infiltrating lymphocytes enables evaluation of immune response and prognosis in colorectal cancer. *J Immunother Cancer* 2021; **9** [PMID: 34548385 DOI: 10.1136/jitc-2021-002671]

31 **Phillips SM**, Banerjea A, Feakins R, Li SR, Bustin SA, Dorudi S. Tumour-infiltrating lymphocytes in colorectal cancer with microsatellite instability are activated and cytotoxic. *Br J Surg* 2004; **91**: 469-475 [PMID: 15048750 DOI: 10.1002/bjs.4472]

32 **Jenkins MA**, Hayashi S, O'Shea AM, Burgart LJ, Smyrk TC, Shimizu D, Waring PM, Ruszkiewicz AR, Pollett AF, Redston M, Barker MA, Baron JA, Casey GR, Dowty JG, Giles GG, Limburg P, Newcomb P, Young JP, Walsh MD, Thibodeau SN, Lindor NM, Lemarchand L, Gallinger S, Haile RW, Potter JD, Hopper JL, Jass JR; Colon Cancer Family Registry. Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: a population-based study. *Gastroenterology* 2007; **133**: 48-56 [PMID: 17631130 DOI: 10.1053/j.gastro.2007.04.044]

33 **Newman AM**, Steen CB, Liu CL, Gentles AJ, Chaudhuri AA, Scherer F, Khodadoust MS, Esfahani MS, Luca BA, Steiner D, Diehn M, Alizadeh AA. Determining cell type abundance and expression from bulk tissues with digital cytometry. *Nat Biotechnol* 2019; **37**: 773-782 [PMID: 31061481 DOI: 10.1038/s41587-019-0114-2]

34 **Yang R**, Cheng S, Luo N, Gao R, Yu K, Kang B, Wang L, Zhang Q, Fang Q, Zhang L, Li C, He A, Hu X, Peng J, Ren X, Zhang Z. Distinct epigenetic features of tumor-reactive CD8+ T cells in colorectal cancer patients revealed by genome-wide DNA methylation analysis. *Genome Biol* 2019; **21**: 2 [PMID: 31892342 DOI: 10.1186/s13059-019-1921-y]

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