Characteristics and Risk Factors of Interval Colorectal Advanced Adenomas after Negative Index Colonoscopy

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Abstract

Objectives

Interval colorectal advanced adenoma (I-CRAA) carries insidious risk of interval colorectal cancer (I-CRC). The study aims to determine the frequency of I-CRAA after negative colonoscopy and discover the characteristics and the risk factors.

Methods

We retrospectively analyzed the information of the patients undergoing colonoscopy in the endoscopic center (2015-2019). Frequency of I-CRAA was calculated. The clinical features of I-CRAA were compared with sporadic colorectal advanced adenoma (Sp-CRAA).

Results

The frequency of I-CRAA was 0.71% (112/15759) per colonoscopy. I-CRAA was more likely to be located in the proximal colon (65.2% vs 34.8%, $p<0.05$) and has high pathological grade (5.4% vs 1.6%, $p<0.05$). Diabetes, family history of CRC, smoking, alcohol intake and diverticulosis are risk factors for I-CRAA ($p<0.05$). Excellent bowel preparation (OR 3.727; 95% CI 2.425–5.73, $p<0.001$) and higher adenoma detection rate (OR 1.924; 95% CI 1.153–3.21, $p = 0.012$) are helpful for the detection of I-CRAA. I-CRAA found within 1 year other than 2 or 3 years after the initial colonoscopy were usually found by an endoscopist with higher ADR.

Conclusions

I-CRAA is usually located in the proximal colon and has high pathological grade. Diabetes, diverticulosis, smoking history, alcohol intake, and family history of CRC are the risk factors. Its occurrence is more related to low-quality colonoscopy, especially within one year.

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in humans, and the incidence in the Asia-Pacific region has increased rapidly in recent years[1]. Nearly half of patients have a survival time of less than 5 years due to late diagnosis and potentially advanced disease. Existing studies have shown that the identification of early lesions (adenomas) of CRC through colonoscopy and subsequent endoscopic resection can prevent disease progression, thereby reducing the incidence and mortality of CRC[2]. However, we often encounter some patients who has a negative initial colonoscopy and are diagnosed with CRC before the next recommended screening, which is defined as interval colorectal cancer (I-CRC)[3]. I-CRC usually occurs within 6–36 months of the index colonoscopy, which reduces the effectiveness of CRC screening and gradually attracts everyone's attention.

The majority of CRC arise from adenoma, that is the classical adenoma-carcinoma sequence (ACS)[4]. ACS is a series of events whereby colorectal adenomas develop, initially showing low grade dysplasia, from which some will progress to high grade dysplasia and eventually invasive carcinoma. The current studies are mostly limited to the interval cancer stage, and there is no relevant research on the interval advanced colorectal adenoma (I-CRAA), which is the precancerous stage of I-CRC. Therefore we will analyze the clinical features and risk factors of patients with I-CRAA in this study, so as to provide a new theoretical basis for the early prevention of colorectal tumors.

Patients And Methods

Research design

We retrospectively analyzed the detailed information of all patients undergoing colonoscopy at the Digestive Endoscopy Center of Beijing Tsinghua Changgung Hospital from January 2015 to December 2019. All colonoscopy examinations were completed by 10 endoscopists of the center. Patients who met the following criteria were included: (1) between the ages of 40 and 80; (2) patients who underwent colonoscopy again within 3 years after a negative index colonoscopy; (3) both colonoscopies reached the cecum. All negative colonoscopy including normal colonoscopy or non-cancerous lesions were completely excluded. The exclusion criteria were: (1) a history of colectomy for CRC or inflammatory bowel disease or familial adenomatous polyposis; (2) a history of CRC at index colonoscopy or incomplete histologic information. In order to compare the clinical and pathological characteristics of patients, patients with sporadic colorectal advanced adenoma (Sp-CRAA) who were examined at the same period in this center were also included in the study. This part of patients received colonoscopy for the first time due to CRC screening.

Definition

The advanced adenoma includes tubular adenoma with diameter > 10 mm, villous or tubulovillous adenoma, any adenoma with high-grade dysplasia. I-CRAA is defined as advanced adenoma diagnosed within 1–36 months after index negative colonoscopy. As a comparison, Sp-CRAA is defined as advanced adenoma detected at the first colonoscopy due to CRC screening, in which the patient had never undergone a colonoscopy before. Index colonoscopy is defined as a negative colonoscopy performed prior to the diagnosis of advanced adenoma which including normal colonoscopy or non-cancerous lesions were completely excluded. We defined the annual adenoma detection rate (ADR) for a physician as the proportion of annual (calendar year) screening colonoscopies where at least one adenoma (adenomatous polyp) was found. The quality of bowel preparation was evaluated using the Boston Bowel Preparation Scale (BBPS), and it was divided into excellent and good categories[5].

Data Collection

We collected the basic information of the patients (age, gender, history of hypertension, diabetes, coronary artery disease and hyperlipidemia, family history of CRC, smoking and alcohol intake),

colonoscopy report characteristics (follow-up time, operating endoscopist, bowel preparation quality, diverticulosis, lesion location, pathological classification). We divided the colon into the proximal (cecum, ascending colon, hepatic flexure, transverse colon) and the distal (splenic flexure, descending colon, sigmoid colon, rectum). The landmarks of the cecum were the appendiceal orifice and ileocecal valve; hepatic flexure was defined as a gray-blue colored impression of the liver, splenic flexure as a gray-blue colored impression of the spleen. During the study, all patients used polyethylene glycol electrolyte for bowel preparation.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation and categorical data as number (percentages). For comparison of risk factors, χ^2 analysis and logistic regression analysis were performed. $p < 0.05$ was considered statistically significant. SPSS 23.0 (IBM, US) software was used for statistical analysis.

Results

A total of 12622 patients underwent 15759 colonoscopies at the Digestive Endoscopy Center of Beijing Tsinghua Changgung Hospital from January 2015 to December 2019. A total of 4773 adenomas and 615 advanced adenomas were identified, of which 112 were I-CRAA and 503 were Sp-CRAA. The frequency of I-CRAA was 0.71% (112/15759) among all colonoscopies, 2.35% (112/4773) among all diagnosed adenomas and 18.21% (112/615) among all diagnosed advanced adenoma. In patients with I-CRAA, 68.6% were men, and 42.9% were 60–69 years old at index colonoscopy. When I-CRAA patients were screened at index colonoscopy, only 33.9% of the patients had excellent bowel preparation quality, and half of the patients were performed by doctors with an ADR of less than 30%. 38.4% of patients had more than 3 polyps, and more than half of the patients had polyps in different intestinal segments. In addition, 64.3% of patients had a maximum adenoma diameter of more than 10 mm. (Table 1)

Table 1
Clinical Features of Index Colonoscopy in Patients with I-CRAA

	N (%)
Sex	
Male	77(68.8)
Female	35(31.2)
Age (yr)	
50	9(8)
50–59	31(27.7)
60–69	48(42.9)
70	24(21.4)
Bowel preparation	
7	74(66.1)
≥ 7	38(33.9)
ADR of endoscopists	
30	58(51.8)
30-34.9	29(25.9)
≥ 35	25(22.3)
Number of lesions	
≤ 3	69(61.6)
3	43(38.4)
Distribution (colon segment)	
1	52(46.4)
≥ 2	60(53.6)
Diameter(mm)	
0	11(9.8)
10	29(25.9)
10–19	60(53.6)

Data are presented as number (%)

	N (%)
≥ 20	12(10.7)
Data are presented as number (%)	

We compared 112 patients with I-CRAA and 503 patients with Sp-CRAA (Table 2 and Table 3). There were no significant differences in gender and age between the two groups, but patients with I-CRAA have a higher probability of diabetes, smoking history, alcohol history, and family history of CRC (27.7% vs 15.3%, 40.2% vs 26.6%, 25.9% vs 16.1%, 14.3% vs 7.8%, respectively; all $p < 0.05$). Further analysis of colonoscopy characteristics found that the bowel preparation of diagnostic colonoscopy in I-CRAA is better (52.7% vs 23.7%, $p < 0.05$), the probability of finding a diverticulum is greater (5.4% vs 1.8%, $p < 0.05$), and the ADR of the diagnostic colonoscopy is higher (29.5% vs 20.9%, $p < 0.05$) compared with Sp-CRAA. A larger proportion of I-CRAA were located in the proximal colon, compared with Sp-CRAA (65.2% vs 34.8%, $p < 0.05$). Frequency of tubular adenoma with low-grade dysplasia was identical in both I-CRAA and Sp-CRAA. However, I-CRAA had more high-grade dysplasia, villous structures or sessile serrated adenoma (5.4% vs 1.6%, 9.8% vs 8.5%, 7.1% vs 2.6%, respectively, $p < 0.05$).

Table 2
Comparison of Baseline Characteristics of Patients Between I-CRAA or Sp-CRAA

	Total (n = 615)	I-CRAA (n = 112)	Sp-CRAA (n = 503)	χ^2	*p*
Sex					
Male	392	77(68.8)	315(62.6)	1.487	0.234
Female	223	35(31.2)	188(37.4)		
Age(yr)					
≤50	68	9(8)	59(11.7)	5.984	0.110
50–59	177	26(23.2)	148(29.4)		
60–69	272	51(45.6)	221(44)		
≥70	101	26(23.2)	75(14.9)		
Hypertension					
Yes	255	52(46.4)	203(40.4)	2.147	0.173
No	360	60(53.6)	300(59.6)		
Diabetes					
Yes	108	31(27.7)	77(15.3)	9.638	0.003
No	507	81(72.3)	426(84.7)		
CAD					
Yes	49	13(11.6)	36(7.2)	2.454	0.124
No	566	99(88.4)	467(92.8)		
Hyperlipidaemia					
Yes	116	25(22.3)	91(18.1)	1.071	0.349
No	499	87(77.7)	412(81.9)		
Family history					
Yes	55	16(14.3)	39(7.8)	4.8	0.042
No	560	96(85.7)	464(92.2)		
Smoking history					
Yes	179	45(40.2)	134(26.6)	8.137	0.006

	Total (n = 615)	I-CRAA (n = 112)	Sp-CRAA (n = 503)	χ^2	*p*
No	436	67(59.8)	369(73.4)		
Alcohol history					
Yes	110	29(25.9)	81(16.1)	6.167	0.015
No	505	83(74.1)	422(83.9)		

CAD: coronary artery disease

Family history: family history of colorectal cancer

Table 3
Comparison of Diagnostic Colonoscopy Features between I-CRAA and Sp-CRAA

	Total (n=615)	I-CRAA (n=112)	Sp-CRAA (n=503)	χ^2	*p*
ADR					
<30	299	43 (38.4)	256 (50.9)	6.502	0.039
30-34.9	178	36 (32.1)	142 (28.2)		
≥35	138	33 (29.5)	105 (20.9)		
Bowel preparation					
<7	437	53 (47.3)	384 (76.3)	37.512	<0.001
≥7	178	59 (52.7)	119 (23.7)		
Diverticulum					
Yes	15	6 (5.4)	9 (1.8)	4.9	0.039
No	600	106 (94.6)	494 (98.2)		
Location					
Proximal	263	73 (65.2)	190 (37.8)	28.108	<0.001
Distal	354	39 (34.8)	313 (62.2)		
Cecum	35	12 (10.7)	23 (4.6)	32.283	<0.001
Ascending	87	28 (25)	59 (11.7)		
Hepatic flexure	47	10 (8.9)	37 (7.4)		
Transverse	94	23 (20.5)	71 (14.1)		
Splenic flexure	10	1 (0.9)	9 (1.8)		
Descending	51	7 (6.3)	44 (8.7)		
Sigmoid	231	22 (19.7)	209 (41.6)		
Rectum	60	9 (8)	51 (10.1)		
Pathology					
Tubular, L	526	87 (77.7)	439 (87.3)	11.603	0.014
Tubular, H	14	6 (5.4)	8 (1.6)		
Tubulovillous, L	41	9 (8)	32 (6.3)		

Tubulovillous, H	13	2（1.8）	11（2.2）
Sessile serrated	21	8（7.1）	13（2.6）

Tubular, L: Tubular adenoma, low grade;

Tubular, H: Tubular adenoma, high grade;

Tubulovillous, L: Tubulovillous adenoma, low grade;

Tubulovillous, H: Tubulovillous adenoma, high grade;

Sessile serrated: Sessile serrated adenoma.

Through multivariate logistic regression analysis after adjusting for age and gender, we found that diabetes (OR 1.937; 95% CI 1.19–3.151, $p = 0.008$), family history of CRC (OR 2.156; 95% CI 1.145–2.059, $p = 0.017$), smoking history (OR 1.953; 95% CI 1.206–3.164, $p = 0.007$), alcohol history (OR 1.9; 95% CI 1.122–3.217, $p = 0.017$) and diverticulosis (OR 3.083; 95% CI 1.068–8.898, $p = 0.037$) are risk factors for I-CRAA. Excellent bowel preparation (OR 3.727; 95% CI 2.425–5.73, $p < 0.001$) and higher ADR (OR 1.924; 95% CI 1.153–3.21, $p = 0.012$) at diagnostic colonoscopy are conducive to the detection of I-CRAA. In addition, compared with the rectum, the cecum (OR 2.749; 95% CI 1.03–7.338, $p = 0.044$) and ascending colons (OR 2.351; 95% CI 1.037–5.328, $p = 0.041$) have a higher probability of developing I-CRAA. They are more likely to be high-grade (OR 3.926; 95% CI 1.312–11.747, $p = 0.014$) or sessile serrated adenoma (OR 3.227; 95% CI 1.276–8.163, $p = 0.013$). (Table 4)

Table 4
Multivariate logistic regression analysis of clinical characteristics of I-CRAA compared with Sp-CRAA

	OR(95% CI)	Wald value	*p*
Diabetes			
No	1(ref)		
Yes	1.937(1.19–3.151)	7.077	0.008
Family history			
No	1(ref)		
Yes	2.156(1.145–2.059)	5.66	0.017
Smoking history			
No	1(ref)		
Yes	1.953(1.206–3.164)	7.404	0.007
Alcohol history			
No	1(ref)		
Yes	1.9(1.122–3.217)	5.703	0.017
ADR			
30	1(ref)		
30-34.9	1.554(0.95–2.541)	3.083	0.079
≥ 35	1.924(1.153–3.21)	6.28	0.012
Bowel preparation			
7	1(ref)		
≥ 7	3.727(2.425–5.73)	35.981	< 0.001
Diverticulum			
No	1(ref)		
Yes	3.083(1.068–8.898)	4.333	0.037
Location			
Rectum	1(ref)		
Sigmoid	0.556(0.247–1.251)	2.012	0.156
Descending	0.803(0.281–2.296)	0.167	0.683

	OR(95% CI)	Wald value	*p*
Splenic flexure	0.66(0.074–5.883)	0.139	0.71
Transverse	1.591(0.694–3.648)	1.204	0.273
Hepatic flexure	1.256(0.463–3.411)	0.2	0.655
Ascending	2.351(1.037–5.328)	4.191	0.041
Cecum	2.749(1.03–7.338)	4.075	0.044
Pathology			
Tubular, L	1(ref)		
Tubular, H	3.926(1.312–11.747)	5.981	0.014
Tubulovillous, L	1.61(0.733–3.535)	1.41	0.235
Tubulovillous, H	0.962(0.207–4.474)	0.02	0.961
Sessile serrated	3.227(1.276–8.163)	6.122	0.013

According to the follow-up time of I-CRAA diagnostic colonoscopy, we divide the I-CRAA into 1-year, 2-year and 3-year periods. Within 2 years, the proportion of advanced adenoma in the proximal colon is higher at the I-CRAA diagnostic colonoscopy (1-year: 64.5 vs 33.9, $p < 0.05$; 2 year: 66.7 vs 27.3, $p < 0.05$). However, there was no difference in adenoma distribution between index colonoscopy and 3-year diagnostic colonoscopy. Furthermore, for I-CRAA diagnosed at 1-year periods, the index colonoscopy was usually performed by endoscopists with lower ADR (62.9% vs 43.5%, $p = 0.041$). However, this difference was not significant for I-CRAA diagnosed at 2-year and 3-year periods. However, the quality of bowel preparation did not differ between index and diagnostic colonoscopies. (Table 5)

Table 5
Trend of I-CRAA location, bowel preparation and ADR between index and diagnostic colonoscopy according to the follow-up time (1, 2 and 3-year periods)

Period	1-year(n = 62)		2-year(n = 33)		3-year(n = 17)	
	Index	Diagnosis	Index	Diagnosis	Index	Diagnosis
Location						
normal	4(6.5)	0(0)	3(9.1)	0(0)	4(23.5)	0(0)
Proximal	21(33.9)	40(64.5)	9(27.3)	22(66.7)	4(23.5)	10(58.8)
Distal	37(59.6)	22(35.5)	21(63.6)	11(33.3)	9(53)	7(41.2)
χ^2	9.609		8.453		2.33	
p	0.003		0.005		0.159	
ADR						
30	39(62.9)	27(43.5)	14(42.4)	11(33.3)	7(41.2)	5(29.4)
30-34.9	9(14.5)	20(32.3)	11(33.3)	11(33.3)	9(52.9)	5(29.4)
≥ 35	14(22.6)	15(24.2)	8(24.3)	11(33.3)	1(5.9)	7(41.2)
χ^2	6.36		0.86		5.849	
p	0.041		0.676		0.056	
Bowel Preparation						
7	40(64.5)	30(48.4)	21(63.6)	13(39.4)	13(76.5)	10(58.8)
≥ 7	22(35.5)	32(51.6)	12(36.4)	20(60.6)	4(23.5)	7(41.2)
χ^2	3.28		3.882		1.209	
p	0.103		0.084		0.465	

Discussion

This study is the first systematic study of the clinical features and risk factors of I-CRAA. It found that the frequency of I-CRAA was 0.71% per colonoscopy. Firstly, this finding suggests that the occurrence of interval lesions is more related to missed diagnosis, especially found within one year. Secondly, I-CRAA is more located in the proximal colon and related to diabetes, family history of CRC, smoking, drinking, and diverticulosis.

Colorectal cancer (CRC) is one of the leading causes of death in the world, and it usually develops through ACS sequences. Understanding the clinical characteristics and risk factors of this disease is an

indispensable part of formulating an effective strategy to prevent CRC. Experts from all over the world have been committed to preventing I-CRC through population-based screening programs, but there are few studies on I-CRAA that are focused on interval precancerous lesions.

In recent years, a large number of studies in different countries show that I-CRC accounts for 2.6–10.3% of newly diagnosed CRC[6, 7]. Kim et al. evaluated how often I-CRC could be detected by follow-up colonoscopy in clinical practice and they found that the rate of I-CRC detection during the surveillance period was at 0.09%[8]. In our study, 112 of 615 patients with CRAA were classified as I-CRAA, which accounted for 0.71% of the total number of examinations, and the detection rate of I-CRAA was much higher than I-CRC. In-time detecting and resecting the intermittent advanced adenoma is a major step for prevention of I-CRC and improve the patients' quality of life.

In terms of the clinical characteristics of patients, previous studies have shown that I-CRC is more common in women and elderly, which are considered to be risk factors[9, 10]. However, in our study, I-CRAA were found in more male and elder patients, but the distribution difference was not statistically significant. Among them, the trend of gender distribution is similar to the results of several studies on I-CRC patients in Asian populations. They found that Asian male patients have a higher proportion of I-CRC, which shows that there is a possibility of racial difference in the occurrence of interval tumors and the differences may have emerged early in the tumor generation[8, 11]. Our study also demonstrated that I-CRAA were more frequently detected in proximal colon, and more often manifests as a high-grade or sessile serrated adenoma, compared with Sp-CRAA. Our finding is in accordance with Samadder's study that most I-CRC appears in the proximal colon, and sporadic colorectal cancer is often found in the distal colon[12]. It suggests that interval tumors are more likely to occur in the proximal colon, more likely to have small and flat nature and may result in limited effectiveness of colonoscopy in the proximal colon. Thus, CRC risk reduction after a negative index colonoscopy was less pronounced for proximal lesions, especially in the caecum and ascending colon. In addition, in view of the fact that interval I-CRAA usually show high-grade dysplasia, we should pay more attention to improve the efficiency of lesion detection in proximal colon.

There are sufficient evidences to prove that diabetes is an independent risk factor for I-CRC. The study of Laish et al. also found that cases with I-CRC had higher prevalence of diabetes[13, 14]. Our study reveals the relationship between diabetes, diverticulosis and I-CRAA for the first time. One explanation for the relationship between diabetes and CRC is that the hyperinsulinemia-induced increase in IGF-I bioactivity may promote the survival of transformed and mutated cells that would normally undergo apoptosis and increase the risk of CRC eventually[15]. This mechanism may have played a role in the early stage of ACS sequence. The research of Hou et al. also indicates that metformin therapy is correlated with a significant decrease in the risk of CRC and advanced adenoma in type 2 diabetic patients[16]. Using a population-based cohort from Canada, Bressler and colleagues found that diverticulosis was documented in 38% of I-CRC, compared to only 7% in detected CRC[17]. On one hand, the presence of diverticulum may interfere with the ability to recognize precancerous and malignant lesions at colonoscopy[18]. On the other hand,

the high pressure in the colon that causes diverticulosis can prolong the time that the mucosa is in contact with potential carcinogens [19]However, a meta-analysis demonstrated that diverticulosis was not associated with an increased risk of advanced colorectal neoplasia[20]Thus, it is necessary to conduct a prospective cohort study to elucidate not only the association of diverticulosis with colorectal neoplasia but also the causality. In addition, we found that smoking and alcohol history are risk factors for I-CRAA, and if the patient's family has CRC, the risk of I-CRAA is also higher.

I-CRC can be divided into three subcategories: 1) missing sporadic colorectal cancer (Sp-CRC) and precancerous lesions; 2) incomplete resection of precancerous lesions; 3) de novo I-CRC that arise rapidly due to abnormal molecular biology[21]. However, the role of its biological characteristics has not yet reached consensus during the formation of I-CRC, and most of them are believed to be caused by missing or incompletely removed precancerous lesions[22]. Therefore, the incidence of I-CRC is also considered to be a key indicator of the quality of colonoscopy in medical institutions and endoscopists. Previous studies have shown that an endoscopist's ADR is a powerful indicator of their skill in performing colonoscopy, with a proven inverse association with I-CRC[23]. The study showed that patients with endoscopists whose ADR > 33% had a 57% lower risk of developing I-CRC than those with ADR < 19%[24]. Consequently, ADR has become the key quality indicator for colonoscopy. Our research on I-CRAA found that patients with the index colonoscopy are usually completed by a doctor with a lower ADR, their bowel preparation is relatively poor, the diameter of the lesion is relatively large, and the lesions are usually found in more than one colon segments. Interestingly, according to the detecting time, the I-CRAA is divided into 1-year, 2-year and 3-year periods after index colonoscopy. It can be found that the index colonoscopy was usually performed by endoscopists with lower ADR and the diagnostic colonoscopy was usually performed by endoscopists with higher ADR for the I-CRAA found within 1-year period. This association was not statistically significant for I-CRAA detected in 2-year and 3-year periods. In addition, we also found that there was no significant difference in the quality of bowel preparation between the index and diagnostic colonoscopy within the same patient. This finding suggests that early I-CRAA is more likely to be caused by missing than late I-CRAA, which may be more relevant to the skill of endoscopists.

The limitation of this study is that it was a single center retrospective study that only represents the characteristics of the population in a limited region. Although we have collected all the information in the patients' medical record system, there are still some patient-related factors potentially related to the risk of interval tumor, such as obesity, diet or physical activity, were not available. In the future, we will analyze the clinical features and risk factors of interval tumors through further prospective research.

In conclusion, I-CRAA has its unique clinical characteristics, and its occurrence is more related to low-quality colonoscopy. It is worthy of special attention for the prevention of CRC.

Declarations

Ethics approval and consent to participate

This study was conducted accordingly to the Declaration of Helsinki, approved by Institutional Review Board. (Medical Ethics Committee of Beijing Tsinghua Changgung Hospital□1100000158761)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Haibin Dong: design of the work, analysis and interpretation of the data, drafting of the article

Yutang Ren: substantively revised it

Bo Jiang: final approval of the article

All authors read and approved the final manuscript.

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