JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2021-047
http://journal-arc.jp

Original Research Article

Morphological Analyses of Colorectal Adenocarcinomas in Japanese Familial Adenomatous Polyposis Patients

Yozo Suzuki[1)2)], Fumio Ishida[2)3)], Hideyuki Ishida[2)4)], Hideki Ueno[2)5)], Hirotoshi Kobayashi[2)6)], Tatsuro Yamaguchi[2)7)], Tsuyoshi Konishi[2)8)], Yukihide Kanemitsu[2)9)], Takao Hinoi[2)10)], Yasuhiro Inoue[2)11)], Naohiro Tomita[1)2)] and Kenichi Sugihara[2)12)]

1) Department of Surgery, Toyonaka Municipal Hospital, Osaka, Japan
2) Study Group for Familial Adenomatous Polyposis of the Japanese Society for Cancer of the Colon and Rectum
3) Digestive Disease Center, Showa University, Northern Yokohama Hospital, Yokohama, Japan
4) Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan
5) Department of Surgery, National Defense Medical College, Saitama, Japan
6) Department of Surgery, Teikyo University Hospital, Mizonokuchi, Kanagawa, Japan
7) Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
8) Department of Gastroenterological Surgery, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan
9) Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan
10) Department of Gastroenterological and Transplant Surgery, Hiroshima University, Hiroshima, Japan
11) Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Mie, Japan
12) Tokyo Medical and Dental University, Tokyo, Japan

Abstract

Objectives: This retrospective study was conducted to clarify the morphological characteristics of colorectal cancer (CRC) in Japanese familial adenomatous polyposis (FAP) patients.

Methods: This study was carried out by the study group for FAP of the Japanese Society for Cancer of the Colon and Rectum. FAP patients who underwent surgical resection between 2000 and 2012 were included in the study.

Results: Of the 303 patients enrolled, 119 patients without CRC were excluded. Of 523 lesions, 49 lesions with missing morphological information were excluded; hence, only 474 CRC lesions in 178 patients (328 superficial lesions in 122 patients and 146 non-superficial lesions in 92 patients) were included in the study. Depressed lesions accounted for 3.0% of superficial lesions and ulcerated lesions accounted for 84.9% of non-superficial lesions. The depressed superficial lesions were observed only in patients with sparse and attenuated FAP (P = 0.003). The age of the patients at surgery differed between the two groups, with patients with depressed superficial lesions being significantly older than those with non-depressed superficial lesions (P = 0.009). Moreover, the age of the patients at FAP diagnosis differed between the two groups, with patients with ulcerated non-superficial lesions being significantly older than those with protruded non-superficial lesions (P = 0.006).

Conclusions: In patients with FAP, depressed superficial CRC lesions rarely developed but were detected in our study group, and ulcerated non-superficial CRC lesions were also present with similar ratios. Clinicians should pay attention to depressed superficial lesions during endoscopic surveillance of FAP patients.

Corresponding author: Yozo Suzuki, yozosuzuki77@gmail.com
Received: July 5, 2021, Accepted: November 15, 2021

Keywords
familial adenomatous polyposis, colorectal cancer, colorectal neoplasm, non-polypoid colorectal neoplasm, depressed superficial lesion, morphology

J Anus Rectum Colon 2022; 6(2): 121-128

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by germline mutations in the adenomatous polyposis coli (*APC*) gene and is characterized by the development of numerous adenomatous polyps throughout the colon and rectum. FAP is classified into the following three phenotypes according to the number of colorectal adenomatous polyps: profuse (>1,000), sparse (100-1,000), and attenuated (10-99); the phenotypes are known to be correlated with mutations in the *APC* gene[1,2]. The pattern of onset and development of colorectal cancer (CRC) in FAP patients is also correlated with the FAP phenotypes; the development of colorectal polyps and CRC in the attenuated type occurs later than that in the profuse and sparse types[1,3,4].

Because almost all FAP patients develop CRC, unless FAP is identified and treated at a young age, due to the inactivation of the *APC* gene through germline mutations and additional somatic mutations or deletions of the normal alleles[5,6], the standard prophylactic treatment for FAP is total colectomy with ileorectal anastomosis or proctocolectomy with ileal pouch anal anastomosis[7,8]. However, colectomy can cause postoperative complications such as desmoid tumors[9,10] and decreased fertility[11]. Thus, endoscopic management of FAP patients has recently received attention. In a cohort of 90 patients with FAP who refused to undergo colectomy, endoscopic management was performed as it is a safe and feasible method[12].

Gross appearance is one of the most important factors for the endoscopic detection of CRC. In a retrospective review, depressed lesions accounted for only 2.3% of superficial lesions, but were responsible for 32.4% of superficial CRC lesions and 29.5% of T1 CRC lesions (Union for International Cancer Control [UICC] TNM Classification of Malignant Tumors, 8th edition[13])[14]. Thus, depressed lesions must be identified at an early stage to allow for endoscopic management.

It is reasonable to assume that FAP patients have polypoid CRC, considering the fact that they have at least one *APC* allele is inactive, and have a higher chance of developing traditional adenoma-carcinoma sequence than other patients. However, the morphological features of CRC lesions in patients with FAP have not been fully elucidated.

Thus, to clarify the morphological features of CRC lesions in Japanese FAP patients, we analyzed the data obtained by the study group for FAP of the Japanese Society for Cancer of the Colon and Rectum (JSCCR).

Methods

Original data sources and patient selection

This study used the original data of a multicenter retrospective cohort study on FAP conducted in Japan by the FAP study group of the JSCCR. Patients diagnosed with FAP who underwent colorectal surgery between January 2000 and December 2012 were included from 23 institutes. Patients whose surgical specimen showed absence of CRC and lesions with missing morphological information were excluded.

The diagnosis of FAP was established according to the following three criteria of the 2012 JSCCR guidelines for the Clinical Practice of Hereditary Colorectal Cancer[15]: (1) detection of 100 or more adenomas in the large intestine, irrespective of the presence/absence of family history; (2) detection of fewer than 100 adenomas in patients with a family history of FAP; and (3) confirmation of pathogenic germline mutations in the *APC* gene. FAP was classified into the following three types according to the number of colorectal adenomas: profuse type (>1,000), sparse type (between 100 and 1,000), and attenuated type (between 10 and 99)[8]. The details of the treatment were reported previously[16]; the most common procedure for FAP was restorative proctocolectomy with ileal pouch anal anastomosis, irrespective of the phenotype.

Data extracted from the database for the purpose of this study included the following preoperative variables: clinical characteristics, including age at the diagnosis of FAP and at surgery, sex, and FAP phenotype; details of the surgical procedures; and pathological findings, including the number and location, histological grade, and pathological stage of the CRC based on the UICC TNM Classification of Malignant Tumors, 8th edition[13].

Study endpoints

The primary study endpoint was the ratio of the depressed type superficial and non-superficial CRC lesions in patients

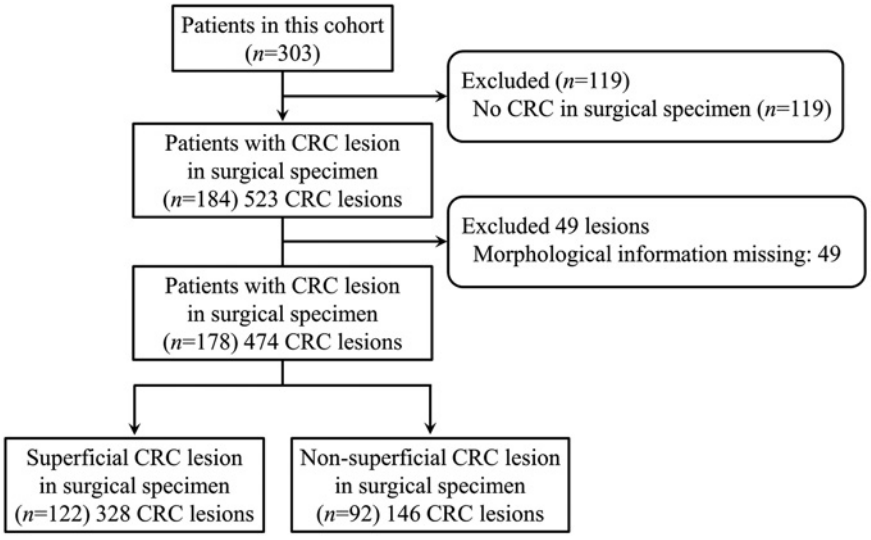

Figure 1. Flow diagram of the patient selection process. *CRC* colorectal cancer.

Table 1. Baseline Characteristics of the Patients.

	Total (*n*=178)
Age at diagnosis (years)	34.5 (27–44.3)
Age at surgery (years)	35 (29–45)
Sex (female:male)	87 (48.9):91 (51.1)
Phenotype (Profuse:Sparse:Attenuated)†	50 (28.1):97 (54.5):25 (14.0)
Pathological stage (0:I:II:III:IV)‡	50 (28.1):38 (21.3):26 (14.6):43 (24.2):20 (11.2)
Number of cancer lesion in surgical specimen	2 (1–3)
Macroscopic type	
Superficial lesions	328
0-Ip:0-Isp:0-Is:0-IIa:0-IIc:0-IIa+IIc	175 (53.4):78 (23.8):47 (14.3):18 (5.5):3 (0.9):7 (2.1)§
Non-superficial lesions	146
1:2:3:4:5	13 (8.9):111 (76.0):13 (8.9):0 (0.0):9 (6.2)¶
Surgical procedure	
Total colectomy with ileostomy	6 (3.4)
Subtotal colectomy with IAA	64 (36.0)
Subtotal colectomy with IACA	39 (21.9)
Subtotal colectomy with IRA	48 (27.0)
Hartmann's procedure	1 (0.6)
Right hemicolectomy	1 (0.6)
Partial colectomy	8 (4.5)

Data are shown as *n* (%) or median (interquartile range).

IAA ileo-anal anastomosis, *IACA* ileo-anal canal anastomosis, *IRA* ileo-rectal anastomosis

† Phenotype information in six patients is missing.

‡ Information on the pathological stage in one patient is missing.

§ Ratio among superficial lesions. None of the patients had 0-IIb lesions.

¶ Ratio among non-superficial lesions. None of the patients had type 4 lesions.

with FAP. "Depressed type" lesions were defined as macroscopic 0-IIc and 0-IIa+IIc lesions in the superficial type CRC. "Non-depressed" lesions were defined as macroscopic 0-Ip, 0-Isp, 0-Is, and 0-IIa lesions in the superficial type CRC. "Protruded type" lesions were defined as macroscopic type 1 and type 5 CRC lesions, and "Ulcerated type" lesions were defined as macroscopic type 2 and type 3 CRC lesions in the non-superficial type[17,18]. The secondary study endpoints were factors related to depressed type CRC lesions in FAP patients.

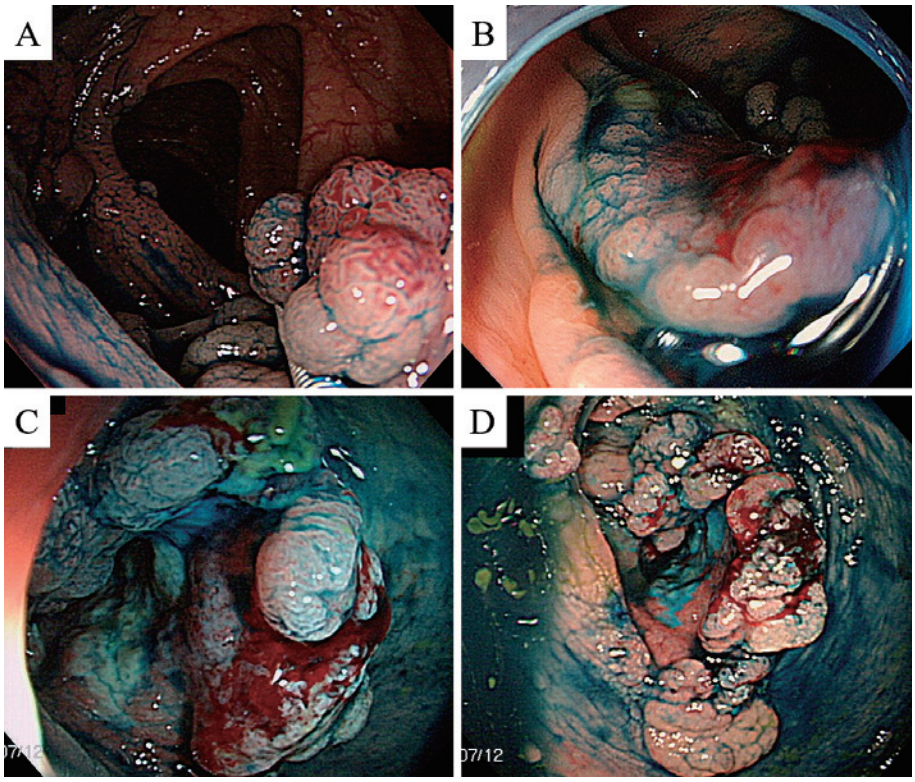

Figure 2. Endoscopic images of a non-depressed and depressed superficial CRC lesions, and protruded and ulcerated non-superficial CRC lesions with indigo carmine spray. A. Endoscopic image of a non-depressed (0-Isp) transverse colon lesion of a 29-year-old female with sparse FAP (pT1b). B. Endoscopic image of a depressed superficial lesion (0-IIa+IIc) in the transverse colon of a 64-year-old female with sparse FAP (pT1b). C. Endoscopic image of a protruded non-superficial (type 1) sigmoid colon lesion of a 59-year-old female with sparse FAP (pT2). D. Endoscopic image of an ulcerated non-superficial (type 2) sigmoid colon lesion of a 59-year-old patient with sparse FAP (pT3). Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [18].

Statistical analyses

Variables were expressed as the number (and percentage) of patients or lesions or as median (and interquartile range) values. Between-group differences for continuous variables were analyzed using the Wilcoxon rank-sum test, while categorical variables were analyzed using Fisher's exact test. All statistical analyses were performed using JMP 15.1.0 (SAS Institute Inc., Cary, NC, USA), and a P value of <0.05 was considered significant.

Ethical approval

The cohort study protocol was approved by the JSCCR Ethics Committee (Approved number 90-5) and the Institutional Review Board of each center. This study's conduct followed the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Results

A total of 303 patients from 23 institutes diagnosed with FAP who underwent colorectal surgery between January 2000 and December 2012 were included. Meanwhile, 119 patients who had no CRC in surgical specimens and 49 lesions with missing morphological information were excluded; hence, only 474 CRC lesions in 178 patients (328 superficial lesions in 122 patients and 146 non-superficial lesions in 92 patients) were included in the final analysis (Figure 1).

The clinical characteristics of the patients are presented in Table 1. Depressed lesions accounted for 3.0% of superficial lesions and 84.9% of non-superficial lesions. Representative images of non-depressed and depressed superficial CRC lesions and protruded and ulcerated non-superficial CRC le-

Table 2. Characteristics of Superficial Colorectal Adenocarcinomas in FAP Patients.

	Total (328 lesions)	Depressed (10 lesions)	Non-depressed (318 lesions)	*P* value
Age of patient at FAP diagnosis (year)	35 (30–41)	37 (35–54.5)	35 (29–40.5)	0.101
Age of patient at surgery (year)	35 (30–41)	48.5 (36.5–56.5)	35 (30–41)	0.009
Sex (Female)	124 (37.8)	5 (50.0)	119 (37.4)	0.419
Phenotype[†]				0.003
Profuse	89 (27.6)	0 (0.0)	89 (28.5)	
Sparse	206 (64.0)	6 (60.0)	200 (64.1)	
Attenuated	27 (8.4)	4 (40.0)	23 (7.4)	
Tumor Location[‡]				0.307
Right	104 (32.9)	5 (50.0)	99 (32.4)	
Left	212 (67.1)	5 (50.0)	207 (67.7)	
Pathological T stage of the lesion				0.266
pTis	248 (75.6)	6 (60.0)	242 (76.1)	
pT1	80 (24.4)	4 (40.0)	76 (23.9)	
Histological grade[§]				1.000
Well differentiated	289 (88.1)	9 (90.0)	280 (88.1)	
Moderately differentiated	34 (10.4)	1 (10.0)	33 (10.4)	
Poorly differentiated	1 (0.3)	0 (0.0)	1 (0.3)	

Data are shown as *n* (%) or median (interquartile range).

FAP familial adenomatous polyposis

[†] Phenotype information of six patients is missing.

[‡] Right, cecum to transverse colon; left, descending to rectosigmoid colon. Information on location in 12 patients is missing.

[§] Information on histological grade in four patients is missing.

sions in FAP patients are shown in Figure 2. The characteristics of the superficial lesions are shown in Table 2. The age of the patients at surgery differed significantly between the two groups, with patients with depressed lesions being significantly older than those with non-depressed lesions (P = 0.009). The phenotype of FAP was significantly different between groups, with depressed lesions being observed only in sparse and attenuated type patients (P = 0.003). The characteristics of non-superficial lesions are shown in Table 3. The age of the patients at FAP diagnosis differed significantly between the two groups, with patients with non-depressed lesions being significantly younger than those with depressed lesions (P = 0.006). Results of the comparison of morphologic types between lesions in this FAP cohort and lesions in multi-institutional (82 institutes) registry data of CRC by the JSCCR[19-21], which include no genetic information, are shown in Table 4.

Discussion

The incidence of depressed superficial lesions (3.0%) observed in this study was lower than that (18.4%-20.5%) reported in the registry data of CRC lesions provided by the JSCCR, and the incidence of ulcerated non-superficial lesions (84.9%) observed in this study was higher than that (74.6%-75.2%) reported in the multi-institutional registry data of CRC lesions in the general Japanese population[19-21]. Although the time periods and the source of the data differ between datasets, it can be assumed that depressed superficial lesions rarely occur in FAP patients, while ulcerated non-superficial lesions are common in both FAP and non-FAP patients.

After Vogelstein and Fearon proposed the multi-hit genetic model of CRC development[22], accumulated evidence has refined the understanding of various genetic and epigenetic changes that underlie the development and progression of CRC. In accordance with the "adenoma-carcinoma sequence" theory[23,24], most CRC lesions are believed to arise from premalignant, typically protruded, traditional tubular adenomas due to mutations in the *APC* gene[25]. On the contrary, approximately 15% of CRCs are thought to arise from serrated adenomas, particularly from typically non-protruded, sessile serrated lesions (SSLs), due to mutations in the *BRAF* gene[26-28]. According to a previous meta-analysis, fewer *KRAS* mutations and more *BRAF* mutations are observed in non-polypoid CRC than in protruded CRC[29]. This might explain the difference in the incidence of depressed superficial CRCs between FAP and non-FAP patients since CRC lesions in FAP patients are more likely to be initiated by mutations in the *APC* gene than in the *BRAF* gene. As CRC develops into non-superficial lesions, additional genetic and epigenetic changes accumulate and

Table 3. Characteristics of Non-superficial Colorectal Adenocarcinomas in FAP Patients.

	Total (146 lesions)	Ulcerated lesion (124 lesions)	Protruded lesion (22 lesions)	*P* value
Age of patient at FAP diagnosis (year)	35 (30–45)	36.5 (31.3–48.8)	31 (23–37.5)	0.006
Age of patient at surgery (year)	36.5 (33–46)	37.5 (32–48)	33 (33–39.3)	0.408
Sex (Female)	83 (56.9)	77 (57.9)	6 (46.2)	0.419
Phenotype[†]				0.612
Profuse	39 (28.9)	33 (27.5)	6 (40.0)	
Sparse	80 (59.3)	72 (60.0)	8 (53.3)	
Attenuated	16 (11.9)	15 (12.5)	1 (6.7)	
Tumor Location[‡]				0.382
Right	34 (24.5)	28 (20.1)	6 (33.3)	
Left	105 (75.5)	93 (66.9)	12 (66.7)	
Pathological T stage of the lesion[§]				0.632
pT2	43 (31.4)	36 (29.8)	7 (43.8)	
pT3	76 (55.5)	69 (57.0)	7 (43.8)	
pT4a	15 (11.0)	13 (10.7)	2 (12.5)	
pT4b	3 (2.2)	3 (2.5)	0 (0.0)	
Histological grade[¶]				0.403
Well differentiated	63 (45.6)	52 (43.3)	11 (61.1)	
Moderately differentiated	73 (52.9)	66 (55.0)	7 (38.9)	
Poorly differentiated	2 (1.5)	2 (1.7)	0 (0.0)	

Data are shown as *n* (%) or median (interquartile range).

FAP familial adenomatous polyposis

[†] Phenotype information of 11 patients is missing.

[‡] Right, cecum to transverse colon; left, descending to rectosigmoid colon. Information on location in seven patients is missing.

[§] Information on pathological tumor depth in nine patients is missing.

[¶] Information on histological grade in eight patients is missing.

often overlap[30], which may explain the reduced gap in the ratio of ulcerated and protruded CRC lesions among non-superficial tumors between FAP and non-FAP patients. With the acquisition of microsatellite instability, SSLs rapidly progress from precancerous lesions to carcinomas[31]; thus, clinicians need to pay special attention to depressed superficial CRC lesions when managing patients with scheduled endoscopic surveillance.

The reason why superficial depressed CRC lesions were observed only in attenuated FAP patients in this study remains unclear, although the lower density of polyps in attenuated FAP patients might have made it easier to identify depressed superficial lesions. The development of superficial depressed CRC lesions in older patients can be explained by the fact that CRC in patients with attenuated FAP develops later than in those with profuse and sparse FAP[1,3].

This study has some limitations. First, although 303 patients were diagnosed with FAP in this field, this sample size was too small to reach definitive conclusions. Second, the lesions collected from this cohort were from surgical samples, and endoscopically treated lesions were not included. Third, data on the size of the CRC lesions were missing, which is important for obtaining an accurate diagnosis or for selecting the appropriate treatment. Fourth, genetic analysis of the *APC* and *MUTYH* genes was not performed as we were unable to obtain informed consent from the patients. Fifth, genetic analysis of cancer lesions was not performed for the same reason. Nonetheless, considering that studies reporting the gross appearance of FAP CRC lesions are limited, we believe that the data presented herein will help clinicians to recognize and treat depressed CRC lesions in FAP patients, especially if the endoscopic management of FAP patients is proven to be feasible based in the J-FAPP III (UMIN000009365) and J-FAPP III-2 (UMIN 000018742) clinical trials.

Based on the findings of our study, depressed superficial CRC lesions rarely occurred, but were present in our study cohort, and depressed non-superficial CRC lesions were also present with similar ratios; clinicians should pay attention to depressed superficial lesions during the endoscopic surveillance of FAP patients.

Acknowledgements

The authors would like to acknowledge all the patients and their families. In addition to the investigators in the author list, we acknowledge the following investigators who also participated in this study: Koji Komori, Department of Gastroenterological Surgery Aichi Cancer Center Hospital,

Table 4. Comparison of Morphologic Types between Lesions in This Study's FAP Cohort and Lesions in the Registry Data.

	FAP[†] (474 lesions)	Registry data[‡] (2003–2004) (11,543 lesions)	Registry data[‡] (2005) (5846 lesions)	Registry data[‡] (2006) (7032 lesions)
Superficial lesions	328	1272	564	797
Non-depressed type	318 (97.0)[§]	1011 (79.5)[§]	460 (81.6)[§]	640 (80.3)[§]
0-Ip	175 (53.4)[§]	109 (8.6)[§]	47 (8.3)[§]	65 (8.2)[§]
0-Isp	78 (23.8)[§]	256 (20.1)[§]	143 (25.4)[§]	139 (17.4)[§]
0-Is	47 (14.3)[§]	188 (14.8)[§]	91 (16.1)[§]	106 (13.3)[§]
0-IIa	18 (5.5)[§]	275 (21.6)[§]	121 (21.5)[§]	176 (22.1)[§]
0-IIb	0 (0.0)[§]	8 (0.6)[§]	2 (0.4)[§]	9 (1.1)[§]
0-IIc+IIa	0 (0.0)[§]	13 (1.0)[§]	5 (0.9)[§]	48 (6.0)[§]
Depressed type	10 (3.0)[§]	261 (20.5)[§]	104 (18.4)[§]	157 (19.7)[§]
0-IIa+IIc	7 (2.1)[§]	170 (13.4)[§]	68 (12.1)[§]	114 (14.3)[§]
0-IIc	3 (0.9)[§]	91 (7.2)[§]	36 (6.4)[§]	43 (5.4)[§]
Non-superficial lesions	146	10271	5282	6235
Protruded type	22 (15.1)[¶]	2935 (28.6)[¶]	619 (11.7)[¶]	742 (11.9)[¶]
1	13 (8.9)[¶]	1055 (10.3)[¶]	484 (9.2)[¶]	597 (9.6)[¶]
4	0 (0.0)[¶]	63 (0.6)[¶]	40 (0.8)[¶]	39 (0.6)[¶]
5	9 (6.2)[¶]	175 (1.7)[¶]	95 (1.8)[¶]	106 (3.1)[¶]
Ulcerated type	124 (84.9)[¶]	8608 (83.8)[¶]	4386 (83.0)[¶]	5289 (84.8)[¶]
2	111 (76.0)[¶]	7575 (73.8)[¶]	3883 (73.5)[¶]	4677 (75.0)[¶]
3	13 (8.9)[¶]	1033 (10.1)[¶]	503 (9.5)[¶]	612 (9.8)[¶]

Data are shown as *n* (%) or median (interquartile range).

[†] Data from this series

[‡] These data were modified from references 19, 20, and 21, with some missing information. Therefore, the sum of the numbers or percentages in this table is not equal to the total number of lesions or 100%, respectively.

[§] Ratio among superficial lesions

[¶] Ratio among non-superficial lesions

Aichi; Kenjiro Kotake, Department of Surgery, Tochigi Cancer Center, Tochigi; Takeshi Nagasaka, Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; Hirotoshi Hasegawa, Department of Surgery, Keio University School of Medicine, Tokyo; Motoi Koyama, Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Aomori; Yoshito Akagi, Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka; Toshimasa Yatsuoka, Department of Gastroenterological Surgery, Saitama Cancer Center, Saitama; Masataka Ikeda, Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka; Kensuke Kumamoto, Department of Organ Regulatory Surgery, Fukushima Medical University School of Medicine, Fukushima; Kiyotaka Kurachi, Department of Surgery 2, Hamamatsu University School of Medicine, Shizuoka; Kohji Tanakaya, Department of Surgery, Iwakuni Clinical Center, Yamaguchi; and Kazuhiko Yoshimatsu, Department of Surgery, Tokyo Women's Medical University Medical Center East, Tokyo. We would like to thank Editage (www.editage.com) for English language editing.

Conflicts of Interest

There are no conflicts of interest.

Source of Funding

This work was supported by the Japanese Society for Cancer of the Colon and Rectum.

Author Contributions

FI, NT, and KS conceived and designed the study; FI, HI, HU, HK, TY, TK, YK, TH, YI, NT, and KS acquired data; YS and FI analyzed and interpreted the data; YS and FI drafted the manuscript; HI, HU, HK, TY, TK, YK, TH, YI, NT, and KS critically revised the manuscript; and HI, HU, HK, TY, TK, YK, TH, YI, NT, and KS approved the final version of the manuscript to be published.

Approval by Institutional Review Board (IRB)

The Japanese Society for Cancer of the Colon and Rectum Ethics Committee (Approved number 90-5)

Disclaimer

Naohiro Tomita is the Deputy Editor-in-Chief of Journal

of the Anus, Rectum and Colon and on the journal's Editorial Board. Hideki Ueno is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. They were not involved in the editorial evaluation or decision to accept this article for publication at all.

References

1. Sieber OM, Segditsas S, Knudsen AL, et al. Disease severity and genetic pathways in attenuated familial adenomatous polyposis vary greatly but depend on the site of the germline mutation. Gut. 2006 Oct; 55(10): 1440-8.
2. Nagase H, Miyoshi Y, Horii A, et al. Correlation between the location of germ-line mutations in the APC gene and the number of colorectal polyps in familial adenomatous polyposis patients. Cancer Res. 1992 Jul; 52(14): 4055-7.
3. Hernegger GS, Moore HG, Guillem JG. Attenuated familial adenomatous polyposis: an evolving and poorly understood entity. Dis Colon Rectum. 2002 Jan; 45(1): 127-34; discussion 34-6.
4. Kobayashi H, Ishida H, Ueno H, et al. Association between the age and the development of colorectal cancer in patients with familial adenomatous polyposis: a multi-institutional study. Surg Today. 2017 Apr; 47(4): 470-5.
5. Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. Cell. 1991 Aug; 66(3): 589-600.
6. Joslyn G, Carlson M, Thliveris A, et al. Identification of deletion mutations and three new genes at the familial polyposis locus. Cell 1991 Aug; 66(3): 601-13.
7. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut. 2020 Mar; 69(3): 411-44.
8. Ishida H, Yamaguchi T, Tanakaya K, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Clinical Practice of Hereditary Colorectal Cancer (Translated Version). J Anus Rectum Colon. 2018 May; 2(I): S1-51.
9. Saito Y, Hinoi T, Ueno H, et al. Risk factors for the development of desmoid tumor after colectomy in patients with familial adenomatous polyposis: multicenter retrospective cohort study in Japan. Ann Surg Oncol. 2016 Aug; 23(4): 559-65.
10. Inoue Y, Ishida H, Ueno H, et al. The treatment of desmoid tumors associated with familial adenomatous polyposis: the results of a Japanese multicenter observational study. Surg Today. 2017 Oct; 47(10): 1259-67.
11. Kobayashi H, Ishida H, Ueno H, et al. Childbirth after surgery for familial adenomatous polyposis in Japan. Surg Today. 2017 Feb; 47(2): 233-7.
12. Ishikawa H, Mutoh M, Iwama T, et al. Endoscopic management of familial adenomatous polyposis in patients refusing colectomy. Endoscopy. 2016 Jan; 48(1): 51-5.
13. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of malignant tumours. 8th ed. The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK: John Wiley & Sons, Ltd, 2016.
14. Kudo S, Kashida H, Tamura T, et al. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg. 2000 Sep; 24(9): 1081-90.
15. Ishida H, Iwama T, Tomita N, et al. [Diagnosis and management of hereditary colorectal cancer according to the JSCCR Guidelines 2012 for the Clinical Practice of Hereditary Colorectal Cancer]. Nihon Rinsho. 2014 Jan; 72(1): 143-9.
16. Inoue Y, Ishida H, Ueno H, et al. Therapeutic approaches for patients with coexisting familial adenomatous polyposis and colorectal cancer. Jpn J Clin Oncol. 2016 Sep; 46(9): 819-24.
17. Kudo SE, Sugihara Y, Kida H, et al. Depressed-type colonic lesions and "de novo" cancer in familial adenomatous polyposis: a colonoscopist's viewpoint. ISRN Gastroenterol. 2013; 2013: 838134.
18. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma: the 3d English Edition [Secondary Publication]. J Anus Rectum Colon. 2019 Oct; 3(4): 175-95.
19. Registry Committee of Japanese Society for Cancer of the Colon and Rectum. Cases treated in 2003-2004. Multi-institutional registry of Large Bowel Cancer in Japan. 2012 Nov; 30: 16-17.
20. Registry Committee of Japanese Society for Cancer of the Colon and Rectum. Cases treated in 2005. Multi-institutional registry of Large Bowel Cancer in Japan. 2013 Nov; 31: 16-17.
21. Registry Committee of Japanese Society for Cancer of the Colon and Rectum. Cases treated in 2006. Multi-institutional registry of Large Bowel Cancer in Japan. 2015 Nov; 32: 16-17.
22. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988 Sep; 319(9): 525-32.
23. Morson BC. Precancerous and early malignant lesions of the large intestine. Br J Surg. 1968 Oct; 55(10): 725-31.
24. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer. 1975 Dec; 36(6): 2251-70.
25. Sparks AB, Morin PJ, Vogelstein B, et al. Mutational analysis of the APC/beta-catenin/Tcf pathway in colorectal cancer. Cancer Res. 1998 Mar; 58(6): 1130-4.
26. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun; 417(6892): 949-54.
27. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterol. 2010 Jun; 138(6): 2088-100.
28. Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. Gastroenterology. 2019 Oct; 157(4): 949-66.
29. Voorham QJ, Rondagh EJ, Knol DL, et al. Tracking the molecular features of nonpolypoid colorectal neoplasms: a systematic review and meta-analysis. Am J Gastroenterol. 2013 Jul; 108(7): 1042-56.
30. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015 Nov; 21(11): 1350-6.
31. Nguyen LH, Goel A, Chung DC. Pathways of colorectal carcinogenesis. Gastroenterol. 2020 Jan; 158(2): 291-302.