Morphological Analyses of Colorectal Adenocarcinomas in Japanese Familial Adenomatous Polyposis Patients

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

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]. 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].

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
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.

Table 1. Baseline Characteristics of the Patients.

| Characteristic                                      | 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: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-Ia: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.
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.

...other text...

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 (UMIN000018742) 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.

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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) (3846 lesions) | Registry data‡ (2006) (7032 lesions) |
|-----------------------|--------------------|---------------------------------------------|--------------------------------------|--------------------------------------|
| Superficial lesions   |                    |                                             |                                      |                                      |
| Non-depressed type    | 328 (97.0)%§       | 1272 (79.5)%§                              | 564 (81.6)%§                        | 797 (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-Ia                  | 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-Ilb                 | 0 (0.0)%§          | 8 (0.6)%§                                 | 2 (0.4)%§                          | 9 (1.1)%§                          |
| 0-Ilc+IIa             | 0 (0.0)%§          | 13 (1.0)%§                                | 5 (0.9)%§                          | 48 (6.0)%§                         |
| Depressed type        |                    |                                             |                                      |                                      |
| 0-IIa+IIc             | 10 (3.0)%§         | 261 (20.5)%§                              | 104 (18.4)%§                       | 157 (19.7)%§                       |
| 0-Ilc                 | 7 (2.1)%§          | 170 (13.4)%§                              | 68 (12.1)%§                        | 114 (14.3)%§                       |
| Non-superficial lesions |                   |                                             |                                      |                                      |
| 0-IIc                 | 3 (0.9)%§          | 91 (7.2)%§                                | 36 (6.4)%§                         | 43 (5.4)%§                         |
| Protruded type        |                    |                                             |                                      |                                      |
| 0                      | 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        |                    |                                             |                                      |                                      |
| 0                      | 124 (84.9)%§       | 8608 (83.0)%§                             | 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

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Conflicts of Interest
There are no conflicts of interest.

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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.

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Disclaimer
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