Article published online: 2022-10-10

Intensive endoscopic resection for downstaging of polyp burden in patients with familial adenomatous polyposis (J-FAPP Study III): a multicenter prospective interventional study ▶

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ABSTRACT

Background Total colectomy is the standard treatment for familial adenomatous polyposis (FAP). Recently, an increasing number of young patients with FAP have requested the postponement of surgery or have refused to undergo surgery. We aimed to evaluate the effectiveness of intensive endoscopic removal for downstaging of polyp burden (IDP) in FAP.

Method A single-arm intervention study was conducted at 22 facilities. Participants were patients with FAP, aged ≥16 years, who had not undergone colectomy or who had undergone colectomy but had ≥10 cm of large intestine remaining. For IDP, colorectal polyps of ≥10 mm were removed, followed by polyps of ≥5 mm. The primary end point was the presence/absence of colectomy during a 5-year intervention period.

Results 222 patients were eligible, of whom 166 had not undergone colectomy, 46 had undergone subtotal colectomy with ileorectal anastomosis, and 10 had undergone partial resection of the large intestine. During the intervention period, five patients (2.3%, 95% confidence interval [CI] 0.74%–5.18%) underwent colectomy, and three patients died. Completion of the 5-year intervention period without colectomy was confirmed in 150/166 patients who had not undergone colectomy (90.4%, 95%CI 84.8%–94.4%) and in 47/56 patients who had previously undergone colectomy (83.9%, 95%CI 71.7%–92.4%).

Conclusion IDP in patients with mild-to-moderate FAP could have the potential to be a useful means of preventing colorectal cancer without implementing colectomy. However, if the IDP protocol was proposed during a much longer term, it may not preclude the possibility that a large proportion of colectomies may still need to be performed.

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary disease caused by an *APC* gene germline variant and characterized by multiple colon adenomas; it is an ultra-high risk disease that, without treatment, leads to colorectal cancer (CRC) in almost all patients [1]. In the nondense-type FAP, CRC occurs in 0.2% of patients between the ages of 11 and 15 years [2]. However, CRC may occur in severe phenotypes/dense-type FAP in patients younger than 10 years [3]. Half of patients with FAP develop CRC by the age of 40 years. In attenuated FAP (AFAP), the incidence of CRC occurs 10–15 years later than in typical FAP, [4]. Therefore, surveillance is generally recommended at 1– to 2-year intervals for typical FAP, and at 2–3-year intervals for AFAP.

The leading cause of death in patients with FAP is CRC [1], and a reliable preventive method for CRC according to guidelines is total resection of the large intestine prior to the occurrence of CRC [5]. However, patients who have undergone colectomy suffer from various life-long complications, including frequent diarrhea, dehydration, ileus due to postoperative adhesion, occurrence of desmoid tumor, anal dysfunction, and decreased fertility. Of course, these complications vary greatly from person to person and our statement should not be misleading. In addition, total resection is the appropriate treatment for patients with severe phenotypes of FAP. However, in long-term follow-up after ileorectal anastomosis (IRA), which is one of the standard treatments in the USA and Europe, it has been reported that 24%–43% of patients develop CRC in the residual rectum [6, 7]. Notably, desmoid tumors are the second cause of death following CRC in patients with FAP [1], and their development is related to the colectomy procedure. Prevention of desmoid development could be a major reason for wanting to avoid surgery. Thus, an effective alternative method to prevent CRC without performing total colectomy is desired.

Actually, altering a polyp burden does not change the underlying disease biology; however, endoscopic removal of colorectal polyps has been reported to inhibit the development of CRC [8], and the theoretical explanation for this is the adenoma–carcinoma sequence [9, 10]. Advances in colonoscopy techniques have allowed the safe implementation of intensive endoscopic resection of multiple polyps. Recently, therapeutic endoscopic treatment with extended rectal preservation has been demonstrated to be a safe alternative to ileoanal J-pouch anastomosis [11]. We previously conducted a study on intensive endoscopic resection of multiple polyps in patients with FAP who refused to undergo surgery [12]. We found no perforation or serious bleeding during endoscopic treatment, and no advanced CRC occurred during the follow-up period [12]. Because this study was performed at a single medical facility, we initiated the present study to clarify the effects of this novel method – intensive endoscopic removal for downstaging of polyp burden/intensive downstaging polypectomy (IDP) – using a nationwide, multicenter, prospective, interventional study design.

Methods

Study design

This nationwide, multicenter (22 centers) clinical trial used a single-arm design. The study protocol was prepared and approved by the institutional review boards of all participating facilities.

Participants

Written consent was obtained from each patient. Consent acquisition and registration of patients were performed at each facility, and the registration information, progress status, medical records of patients, and information on adverse events were managed in a data center selected for the study. The trial was performed in accordance with the principles of the Helsinki Declaration.

Patients who met the following criteria were eligible for the study: (i) male or female patients with FAP, defined as those with at least 100 polyps in the large intestine; (ii) those aged 16 years or older; (iii) those who needed colectomy but did not undergo surgery because they were unwilling, or those who had undergone colectomy and had ≥10 cm of large intestine remaining; and (iv) patients who had fewer than 100 polyps at the time of registration, but had 100 or more polyps when they underwent colonoscopic resection before registration. Presence or absence of the pathologic variant of the germ cell line *APC* was not a criterion. Of note, polyposis conditions other than FAP, such as Peutz–Jeghers syndrome, Cowden syndrome, juvenile polyposis syndrome, Cronkhite–Canada syndrome, or hyperplastic polyposis syndrome, were not included. In addition, the trial did not include any patients with AFAP.

The exclusion criteria were as follows: (i) patients who had serious diseases in other organs; (ii) those on antiplatelet treatment, which could not be discontinued during endoscopic treatment; (iii) those on anticancer drug therapy; (iv) patients for whom the attending doctor judged scheduled follow-up to be difficult because patients resided far from the hospital, etc.; and (v) patients who had dense polyps in at least one-third of the area of the large intestine. Dense polyps were determined to be present if the mucosal area of the polyps was greater than the normal mucosal area when sufficiently extended.

Procedures

Colorectal polyps were removed according to the following procedure. First, polyps measuring ≥10 mm were removed. If the first colonoscopy session failed to remove all polyps measuring ≥10 mm, colonoscopy was repeated within 4 months until all such large polyps were removed. In principle, all lesions measuring ≥10 mm were collected and subjected to histopathological analysis. After all polyps measuring ≥10 mm were removed, polyps measuring ≥5 mm were then removed by colonoscopy to the greatest extent possible (a typical case is presented in ▶ Video 1), and only lesions that were suggestive of cancer were sent for histopathological examination. Next,

polyps measuring <5 mm were removed, if possible. The diameter of the snare sheath was 2.5 mm and polyps equal to or more than double the diameter of the snare sheath of the endoscope were considered to be ≥5 mm. After all polyps measuring ≥5 mm were deemed to be completely removed, the interval of colonoscopic examinations was extended to ≥4 months, but not to >1 year.

Efforts were made to remove all polyps measuring ≥5 mm, with due attention paid to removing smaller polyps, if possible, during colonoscopic examinations in the follow-up period. If polyps measuring ≥5 mm remained, the next colonoscopic examination was performed within 4 months.

For removal of polyps, each facility was allowed to use its preferred procedure from among bipolar snare, monopolar snare, hot biopsy, and argon plasma coagulation (APC). However, the use of bipolar snares was recommended because there is almost no bleeding caused by the burning effect.

Indigo carmine dye was sprayed more than once for close observation of polyps during colonoscopic examination. Image-enhanced endoscopy and magnifying endoscopy were not essential.

The presence/absence of cancer, presence/absence of dense polyps, maximum polyp diameter, number of polyps removed, number of polyps collected, and highest grade of dysplasia were recorded for each of the six regions of the large intestine (i.e. cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum).

There were no restrictions on the use of sedatives and antispasmodics. One session of colonoscopic treatment was limited to approximately 1 hour and performed by specialists who were accredited by the Japan Gastroenterological Endoscopy Society and were skilled in endoscopic treatment.

At the time of participation in the study, each patient answered a self-administered questionnaire [13] about alcohol drinking, smoking, use of oral nonsteroidal anti-inflammatory
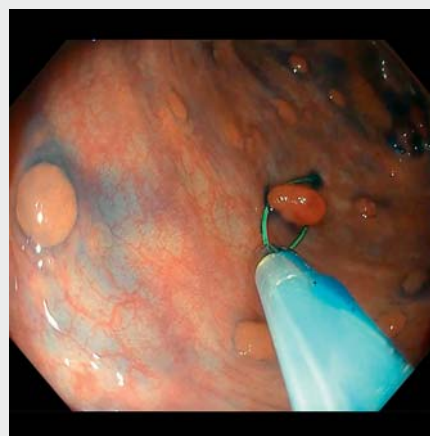
▶ **Video 1** The intensive downstaging polypectomy approach for patients with familial adenomatous polyposis.
Online content viewable at:
https://doi.org/10.1055/a-1945-9120

drugs (NSAIDs), drug history, height, and weight. Participants were not restricted from using NSAIDs, such as aspirin, sulindac, and nimesulide, or *Lactobacillus* preparations, vitamins, or health foods and dietary supplements, but their use was documented.

Participants were registered between 24 November 2012 and 25 September 2014. The registration period was 2 years, and the intervention was implemented for 5 years after registration. The intervention period commenced from the day of consent acquisition and continued until 5 years after registration. The first set of colonoscopic examinations after registration were performed between 24 November 2012 and 19 December 2015. At 5 years after registration, death/survival of the patient and the presence/absence of colectomy were confirmed. Treatment information until 5 years after the registration of the last patient was collected, and the data were fixed.

Patients who stopped receiving colonoscopic examination 1, 2, 3, or 4 years after registration were regarded as dropouts within 1, 2, 3, or 4 years, respectively. Patients who underwent colonoscopic examination between 4 and 5 years after registration were considered to have completed follow-up.

Central monitoring was conducted by the data center every month. Monitoring involved checking the progress of patients and the occurrence of adverse events, and reporting these data to the investigators and to the Data and Safety Monitoring board members by e-mail every month.

Outcomes

The primary end point was the presence/absence of colectomy during the intervention period. The following conditions were considered to be decisions for performing surgery: endoscopic treatment-related difficult-to-control bleeding, emergency surgery for perforation or other conditions, and treatment of CRC not amenable to endoscopic resection (invasion into the submucosal layer). When the state of polyps changed to the dense type or when intestinal adhesion made endoscopic follow-up observation difficult, colectomy was strongly recommended. Colectomies performed at the request of the patient were also included. This definition ensured uniformity of decision making across the centers.

Secondary end points were perforation or bleeding due to endoscopic treatment, occurrence of CRC, occurrence of tumors not amenable to endoscopic treatment, and death due to CRC and other causes.

Statistical analyses

The target number of patients was 200. As colectomy was the standard treatment at the time of diagnosis, no histological follow-up data are available. Hence, this was an exploratory study rather than a verification study, and the number of patients was calculated based on the number of outpatients with FAP who had not undergone surgery at each participating facility. Registration of more than 200 patients was allowed as long as it was within the registration period.

All patients who registered after providing consent to participate in the study were analyzed. Patient information was sent to the data center on the case report form and digitized before the data were fixed at the University hospital Medical Information Network (UMIN) data repository.

The implementation rate of colectomy – the primary end point – was calculated as the percentage of registered patients who were confirmed to have no colectomy at 5 years. The 95% CI for an accurate binomial distribution was calculated. The percentage of patients with no colectomy and the 95%CI were calculated.

The occurrence of CRC and high grade dysplasia during the 5-year intervention period, incidence of adverse events, and follow-up completion status were analyzed.

Results

A total of 223 patients were recruited and 222 provided consent to participate in the study. **Table 1 s** in the online-only Supplementary material shows the number of entries at each facility.

Among the 222 patients, 166 (74.8%) had not undergone colectomy at the time of registration (non-colectomy group), 46 (20.7%) had undergone subtotal colectomy and IRA, and 10 (4.5%) had undergone partial colectomy (post-colectomy group). Among those who had undergone partial colectomy, cecectomy was performed in one patient, resection of the ascending colon in one, right hemicolectomy in one, subtotal colectomy and cecorectal anastomosis in two, left hemicolectomy and rectectomy in two, sigmoid colectomy in one, and rectectomy in two. Demographic characteristics of these 222 patients are shown in ▶ Table 1. The mean age was approximately 10 years older and smoking was more common in those who had undergone colectomy than in those in the non-colectomy group.

During the intervention period, five of the 222 patients (2.3%; 95%CI 0.74%–5.18%) underwent colectomy, four of whom were from the non-colectomy group and one from the post-colectomy group (post-IRA). Surgery in four patients from the non-colectomy group was performed owing to the occurrence of submucosal invasive CRC in two (0.9%) (▶ Fig. 1), difficulty in performing colonoscopy due to adhesion after surgery for uterine body cancer in one (0.5%), and on patient request in one (0.5%). Surgery was performed for one case in the post-colectomy group when the risk was judged to be higher owing to the finding of multiple intramucosal tumors in the remaining rectum (▶ Table 2, ▶ Fig. 2).

Three patients (two in the non-colectomy group and one in the post-colectomy group) died (1.4%) during the intervention period. The causes of death of the three patients were suicide due to academic failure (17-year-old male without history of colorectal surgery; duration of intervention 717 days), senility (82-year-old female without history of colorectal surgery; duration of intervention 956 days), and acute aortic occlusion (73-year-old female with rectectomy; duration of intervention 922 days). All of these deaths were inferred to have no causal relationship with FAP.

As shown in ▶ Fig. 2, dropouts comprised 10 patients (6.0%) in the non-colectomy group and 7 (12.5%) in the post-colectomy group. Seven of these patients in the non-colectomy group

▶ **Table 1** Demographic characteristics of 222 participants.

	Non-colectomy group (n = 166)	Colectomy group (n = 56)
Male sex, n (%)	87 (52.4)	29 (51.8)
Age, years		
• Mean (range)	35.1 (16–82)	45.5 (22–82)
Age group, n (%)		
• ≤19	16 (9.6)	0 (0)
• 20–29	44 (26.5)	3 (5.4)
• 30–39	49 (29.5)	15 (26.8)
• 40–49	36 (21.7)	22 (39.3)
• 50–59	15 (9.0)	7 (12.5)
• ≥60	6 (3.6)	9 (16.1)
Height, mean (SD), cm	164.1 (9.1)	163.9 (8.9)
Weight, mean (SD), kg	59.5 (11.2)	60.8 (12.8)
Alcohol, n (%)		
• Every day	20 (12.0)	8 (14.3)
• 1–3/month	16 (9.6)	4 (7.1)
• ≥4/month	51 (30.7)	18 (32.1)
• None	79 (47.6)	26 (46.4)
Smoking, n (%)		
• Non-smoker	120 (72.3)	31 (55.4)
• Ex-smoker	25 (15.1)	13 (23.2)
• Smoker	21 (12.7)	12 (21.4)
History of CRC, n (%)		
• No history	145 (87.3)	26 (46.4)
• 1	18 (10.8)	21 (37.5)
• 2	3 (1.8)	6 (10.7)
• 3	0 (0)	2 (3.6)
• 4	0 (0)	1 (1.8)
History of other cancer, n (%)		
• Gastric cancer	5 (3.0)	5 (8.9)
• Duodenal cancer	4 (2.4)	4 (7.1)
• Thyroid cancer	13 (7.8)	2 (3.6)
• Small-bowel cancer	0 (0)	1 (1.8)

CRC, colorectal cancer.
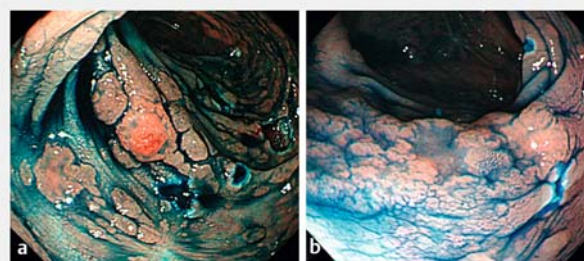
▶ **Fig. 1** Submucosal invasive cancer found in the transverse colon. **a** Case 1 – Colonoscopic examination performed 160 days after the preceding examination detected a IIa lesion, 5 mm in diameter, in the transverse colon. **b** Case 2 – Colonoscopic examination performed 181 days after the preceding examination detected IIa + IIc lesions, 5 mm in diameter, in the transverse colon.
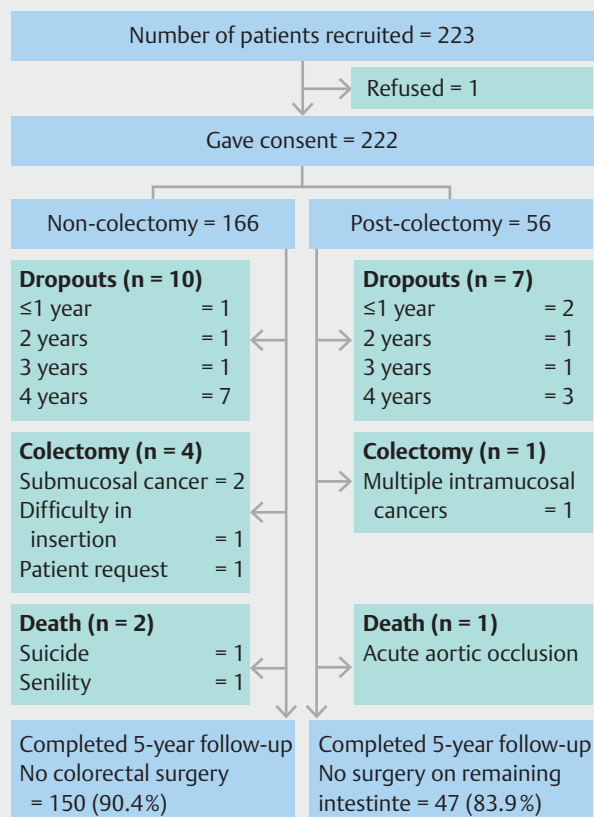
▶ **Fig. 2** Flow chart of study participants.

and three in the post-colectomy group underwent colonoscopic examination for 3 years after registration, but stopped visiting the facility in the 4th year or thereafter.

Excluding dropouts, patients who had undergone colectomy, and deaths during the intervention period, completion of the 5-year intervention period without colectomy was confirmed in 150/166 patients (90.4%; 95%CI 84.8%–94.4%) in

▶ **Table 2** Reasons for performing colectomy during the intervention period.

Sex	Age at colectomy, years	History of prior colorectal surgery	Time of colectomy during intervention period, Day	Reason for colectomy
M	30	IRA	234	The doctor in charge recommended surgery because there were multiple colorectal intramucosal cancers (four lesions).
M	45	None	579	Submucosal cancer was found in the transverse colon by colonoscopic examination performed at 160 days after the preceding examination; colectomy was performed[1]
F	34	None	589	Colonoscopic examination was difficult to perform because of adhesion after surgery for uterine body cancer
F	54	None	790	Colectomy was performed at the patient's request
F	37	None	1001	Submucosal cancer was found in the transverse colon by colonoscopic examination performed at 181 days after the preceding examination; colectomy was performed[1]

IRA, ileorectal anastomosis.
[1] See ▶ **Fig. 1**.

the non-colectomy group and 47/56 patients (83.9%; 95%CI 71.7%–92.4%) in the post-colectomy group.

▶ **Table 3** shows the characteristics of colorectal polyps removed by colonoscopy during the intervention period. The mean number of colonoscopic examinations and the mean total number of polyps removed during the 5 years were 6.62 and 524.5, respectively, in the non-colectomy group, and 6.23 and 132.1, respectively, in the post-colectomy group. The maximum diameter of the resected polyp was most frequently observed to be 6–10 mm. High grade dysplasia or intramucosal cancer was found in 35 patients (21.1%) in the non-colectomy group and in 17 patients (30.4%) in the post-colectomy group. ▶ **Fig. 3** shows the Kaplan–Meier curve for the cumulative incidence rates of these lesions.

A summary of adverse events that occurred in the 5-year intervention period, excluding the aforementioned colectomy cases and dropouts, is given in **Table 2 s**. Endoscopic colorectal polypectomy-related adverse events included bleeding after polyp removal in three patients (1.4%). Bleeding in all these cases could be controlled endoscopically. Perforation occurred during APC treatment on two occasions in one patient. Adverse events presumably not related to colorectal polypectomy were bleeding after ileal polyp resection, bleeding after duodenal papillary resection, occurrence of uterine body cancer, and hepatic dysfunction, which occurred in one patient each. There were no deaths from CRC and no occurrence of intra-abdominal desmoid tumors.

Some of the study patients had participated in a CRC prevention study that administered aspirin and mesalazine (J-FAPP Study IV) [14]. The patients from the J-FAPP Study IV were in the non-colectomy group and were enrolled between September 2015 and March 2017. As the administration period of the study drugs was 8 months, the duration of the J-FAPP Study IV overlapped with the intervention period of the present study. In total, 88 patients (39.6%) participated in both studies. The J-FAPP Study IV used a 2×2 factorial design and included 42 patients on aspirin, 46 on aspirin placebo, 43 on mesalazine, and 45 on mesalazine placebo. There were no differences in background characteristics among these patient groups.

Discussion

In this study, implementation of IDP in patients with FAP who refused to undergo total colectomy (IRA) resulted in 5-year preservation of the large intestine in most patients, without serious complications. Currently, the only effective way to prevent CRC from occurring in patients with FAP is the implementation of total colectomy (IRA) at around 20 years of age. However, the results of this study indicate the possibility that IDP can prevent CRC without surgery.

Total resection of the large intestine performed in patients with FAP may cause various problems, such as frequent diarrhea or dehydration and postoperative intestinal obstruction. Recently, however, the percentage of laparoscopic surgical IRA treatments has increased, suggesting a lower incidence of postoperative events, such as bowel obstruction, fertility issues [15], and development of desmoid tumors [16, 17]. Our treatment – IDP – performed once or twice a year allowed patients with FAP to perform normal activities of daily living; the treatment was also associated with a reduced occurrence of intra-abdominal desmoid tumors.
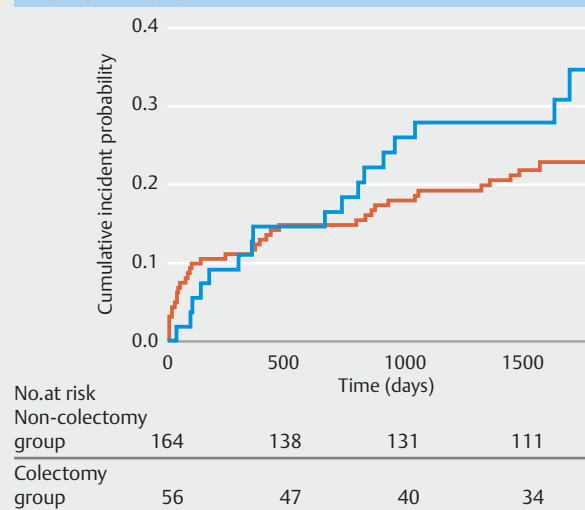
In this trial, we observed multiple perforations due to APC. Only one participating center used APC because it was a familiar and regular treatment method at the center. However, it seems that the use of APC for IDP may not be recommended.

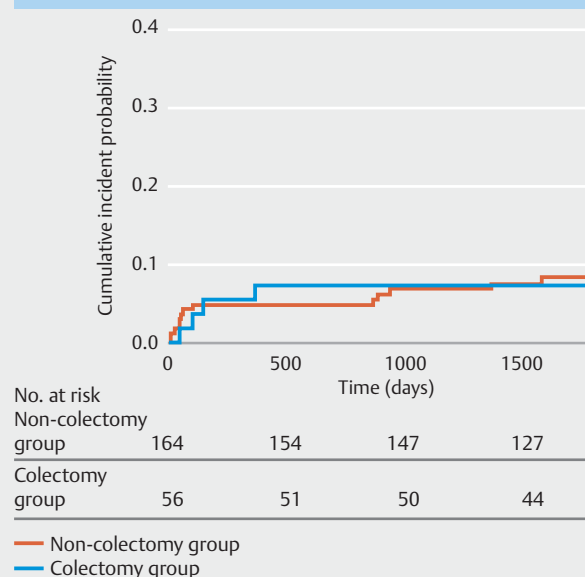▶Table 3 Characteristics of polyps resected during the 5-year intervention period.

	Non-colectomy group (n = 166)	Colectomy group (n = 56)
Colonoscopic examinations during 5 years		
▪ Mean (SD)	6.6 (2.3)	6.2 (2.4)
n (%)		
▪ ≤4	23 (13.9)	13 (23.2)
▪ 5–6	66 (40.0)	19 (33.9)
▪ 7–8	44 (26.5)	12 (21.4)
▪ 9–10	23 (13.9)	12 (21.4)
▪ ≥11	10 (6.0)	0 (0)
Polyps resected during 5 years, n	87061	7398
▪ Mean (SD)	524.5 (503.4)	132.1 (161.6)
n (%)		
▪ ≤100	36 (21.7)	34 (60.7)
▪ 101–300	37 (22.3)	14 (25.0)
▪ 301–600	35 (21.1)	6 (10.7)
▪ 601–900	25 (15.1)	2 (3.6)
▪ ≥901	33 (19.9)	0 (0)
Maximum polyp diameter, n (%), mm		
▪ ≤5	40 (24.1)	16 (28.6)
▪ 6–10	97 (58.4)	30 (53.6)
▪ 11–15	13 (7.8)	4 (7.1)
▪ 16–20	11 (6.6)	3 (5.4)
▪ ≥21	5 (3.0)	3 (5.4)
Endoscopic examinations that detected high grade atypical adenoma/intramucosal cancer, n (%)		
▪ None	131 (78.9)	39 (69.6)
▪ 1	20 (12.0)	9 (16.1)
▪ 2	3 (1.8)	3 (5.4)
▪ 3	6 (3.6)	3 (5.4)
▪ 4	5 (3.0)	1 (1.8)
▪ 5	0 (0.0)	1 (1.8)
▪ 6	0 (0.0)	0 (0.0)
▪ 7	1 (0.6)	0 (0.0)

▶Fig. 3 Cumulative incidence of high grade dysplasia and intramucosal cancer during the intervention period.

This study has several limitations. First, the study lacked a control group. However, it would not be ethical to include a control group that underwent endoscopy without receiving treatment. Second, the study provided the results of a 5-year intervention; owing to the resultant small effective sample size and low number of colectomies performed during the study, longer follow-up will be necessary to confirm the current findings. Moreover, it is unclear whether IDP is effective in preventing cancer-related death, including in patients with high grade dysplasia, after the observation period. Therefore, it is necessary to conduct future long-term studies. Third, it is very difficult to distinguish patients with "dense FAP" from those with "nondense FAP", and to measure the complete number of adenomas before surgery. Fourth, the study population appeared to be highly heterogeneous, which could be linked to a population selection bias. Fifth, the outcomes of patients lost to follow-up remain unknown.

The IDP treatment has the following limitations: (i) an extremely advanced technique is required, and thus, training of skilled endoscopists is essential; (ii) the burden on the operating endoscopist is heavy; (iii) operating time is longer than the time taken for routine colonoscopic examination, causing greater medico-economic burden for medical institutions; (iv) the patient must undergo colonoscopic examination several times per year. Furthermore, it is still unclear for how long this treatment can be continued. There are several other issues that require consideration. For instance, aggressive tumors that develop into invasive adenocarcinomas from adenomas in a short period of time cannot be addressed (two cases of intramucosal invasive cancer occurred in this study; ▶ Fig. 1), and cancer in the appendix cannot be addressed. Thus, IDP is not a treatment that negates the need for colectomy, and it is necessary to accumulate data on such cases in the future in order to identify those patients in whom IDP is difficult to perform.

Our proposed IDP approach will be effective in the management of patients with AFAP or FAP after IRA. Surgery is the first choice in Japan, but it may be important to include a treatment plan for postoperative IDP from the beginning of decision making at the time of primary surgery. In order to move toward individualized treatment, our results, which included 20.7 % of patients undergoing IRA, may lead to future studies to determine the prognostic value of combinations such as IRA + IDP.

We have previously reported a study to prevent colorectal polyps using low-dose aspirin (J-FAPP Study IV) [14], which demonstrated that administration of low-dose aspirin for 8 months suppressed the occurrence of adenomas measuring ≥ 5 mm. In the future, it is expected that the combined use of aspirin with our novel IDP method will facilitate safer and easier use of IDP.

The International Society for Gastrointestinal Hereditary Tumours aims to establish the interval between consecutive colonoscopic examinations and an indication for surgery according to the staging system via endoscopic assessment [18]. Additionally, it has been proposed that worsening of the characteristics of colorectal polyps over time, as well as the disease stage, should be taken into consideration when evaluating indications for surgery [19]. We believe that the results of the present study will have a strong influence on the evaluation of this staging system.

In conclusion, the results of this study imply that IDP in patients with mild-to-moderate FAP may be an effective alternative method of preventing CRC without performing total colectomy (IRA). At the current time, IDP may at least postpone the time to colectomy to coincide with life events, such as employment or childbirth, and give the patient a non-surgical treatment option. In addition, registries have provided clear data to support the benefit of IDP in this rare patient group. Internationally, the concept of personalized care in FAP is broadly accepted. We believe that patients' wishes be given top priority when determining the course of treatment. Therefore, the clear data on surgery, endoscopic treatment, and treatment timing are important for decision making in patients with FAP.

In a very selected population of patients with FAP, without genetic data, a 5-year-aggressive therapeutic follow-up showed limited data of evolution into invasive CRC to justify colectomy. This does not preclude the possibility that over a much longer period a large proportion of colectomies may still need to be performed if this protocol was adopted.

Conflict of Interests

Funding

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