

# Endoscopic management of familial adenomatous polyposis in patients refusing colectomy

## Authors

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**Background and study aims:** Colectomy protects against colorectal cancer in familial adenomatous polyposis (FAP); however, some patients with FAP refuse surgery. The aim of this study was to evaluate the feasibility and safety of endoscopic management of these patients.

**Patients and methods:** A retrospective review of medical records was performed to identify adult patients with FAP who refused colectomy and were managed by repeated colonoscopies to remove numerous polyps between 2001 and 2012. Polyps were removed by hot snare polypectomy or endoscopic mucosal resection. Polyps of <10 mm in size and without endoscopic features suggesting cancer were discarded without histological examination; the remaining polyps were examined histologically.

**Results:** Of the 95 eligible patients, five (5.3%) were excluded. The remaining 90 patients (median age at first visit 29 years [range 16–68 years];

46 males) were followed for a median of 5.1 years (interquartile range [IQR] 3.3–7.3 years). During this period, a total of 55 701 polyps were resected without adverse events such as bleeding or perforation. The median numbers of endoscopic treatment sessions and polyps removed per patient were 8 (IQR 6–11) and 475 (IQR 211–945), respectively. Five patients had noninvasive carcinoma (Category 4.2 according to the revised Vienna classification), detected within 10 months from the start of the follow-up period. All of these patients were treated endoscopically, without signs of recurrence during a median follow-up of 4.3 years (IQR 2.0–7.1 years). No invasive colorectal cancer was recorded during the study period. Two patients (2.2%) underwent colectomy because the polyposis phenotype had changed to dense polyposis.

**Conclusion:** Endoscopic management of FAP is feasible and safe in the medium term.

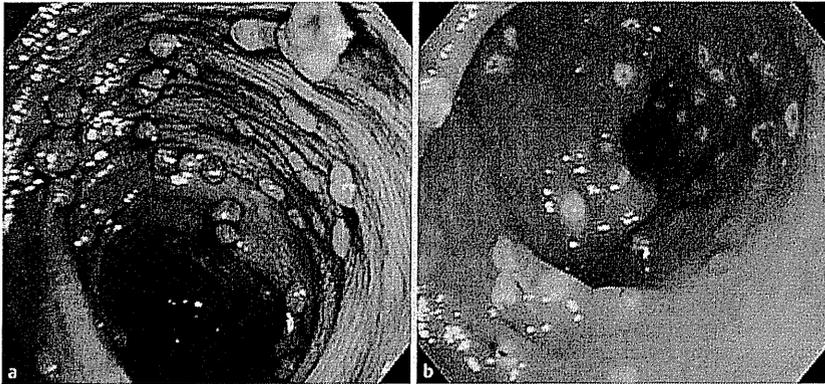
## Introduction

Familial adenomatous polyposis (FAP) is caused by a germline mutation in the tumor suppressor gene, *adenomatous polyposis coli* (APC) [1,2]. Most patients with FAP develop colorectal adenomas during their second decade of life, and a half of these patients will develop colorectal cancer (CRC) in approximately the fourth decade of life if they are not treated at a younger age [3]. To date, surgery is the only accepted method of preventing the development of CRC. Two major surgical procedures are used to treat FAP: colectomy with ileorectal anastomosis, and proctocolectomy with ileal pouch-anal anastomosis [3]. Because patients with FAP are generally asymptomatic when diagnosed, some of them refuse to undergo surgery.

Endoscopic surveillance with polyp removal has been used to prevent cancer development in the rectal stump after colectomy or in residual rectal

mucosa after proctocolectomy with ileal pouch-anal reconstruction [4,5]. It has also been suggested that endoscopic polypectomy can be considered in the management of patients with attenuated FAP [6], which is characterized by fewer adenomas, a later age of onset for colorectal adenomas and cancer, and a decreased cancer risk compared with typical FAP [7].

In the present study, the medical records of FAP patients who strongly refused colectomy and were managed endoscopically were reviewed to evaluate whether the endoscopic approach is feasible and safe, in terms of adverse events associated with removal of numerous polyps and prevention of CRC.



**Fig. 1** Endoscopic images. **a** Before polypectomy. **b** After polypectomy.

## Materials and methods

This retrospective study was conducted at three centers in Japan (Osaka Medical Center for Cancer and Cardiovascular Diseases, Kenporen Osaka Central Hospital, and the Ishikawa Gastroenterological Medical Clinic). Clinical, histological, and follow-up data were obtained from medical records. Included patients were adults with FAP who had >100 colorectal adenomas and/or a germline mutation in the *APC* gene, detected primarily by the Protein Truncation Test, and who strongly refused to undergo colectomy and were managed instead by endoscopic polyp clearance. The following patients were excluded: 1) patients with CRC, 2) those with large adenomas not amenable to endoscopic removal, 3) those with dense polyposis, or 4) patients who refused further endoscopic removal.

Patients were informed that colectomy was the only accepted method of preventing the development of CRC in FAP and that the preventive effect of endoscopic management in this setting had not been defined. They also received detailed information about the risk associated with endoscopic management, including the risks of overlooking cancer, development of de novo cancer, and possible adverse events, such as perforation and bleeding. This study was not a planned clinical study with a trial protocol, and written consent to participate was not obtained. However, all patients gave their written informed consent to undergo colonoscopy and endoscopic polyp removal.

Colonoscopy was performed following bowel preparation with 2 L of orally administered osmotically balanced polyethylene glycol solution. A mixture of normal saline and indigo carmine dye was applied to the mucosa in order to facilitate detection of colorectal polyps [8]. Polyps were removed with hot snare polypectomy or endoscopic mucosal resection; in two cases, endoscopic submucosal dissection was performed. Cold biopsy, cold snaring, hot biopsy, and argon-plasma coagulation were not used. Hot snare polypectomy was primarily performed using a bipolar snare (Xemex; Zeon Medical Inc., Tokyo, Japan) through a standard, single-channel endoscope (Olympus Optical, Tokyo, Japan). Nearly all endoscopic polypectomy procedures were performed by a single endoscopist (H.I.).

All polyps >20 mm in diameter were resected during the baseline colonoscopy, whereas polyps 10–20 mm in diameter were sometimes left in place and resected during subsequent colonoscopies; all polyps of these size ranges were submitted for histological examination. For polyps <10 mm in diameter, as many as could be removed within a 2-hour period were removed and discarded without histological examination. However, polyps of <10 mm in size were also submitted to histological evaluation

whenever high grade dysplasia or cancer was suspected, based on endoscopic appearance of the polyp. Lesions were classified according to the revised Vienna classification [9]. Representative endoscopic images of the colon before and after polyp removal are shown in **Fig. 1**. **Video 1** shows endoscopic removal of several polyps from a bowel segment.

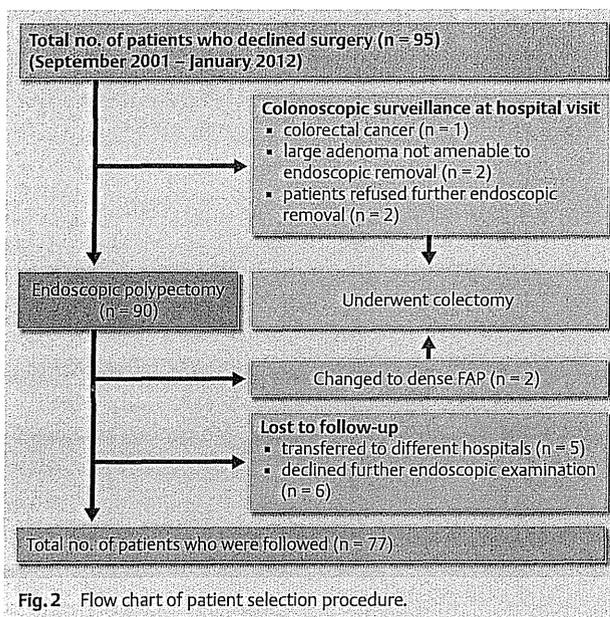
The interval between subsequent colonoscopies for polyp removal was approximately 3 months for patients in whom polyps >10 mm were left in the colon, followed by 6-month intervals until all polyps left were <4 mm. Patients in whom only diminutive polyps ≤3 mm were left underwent endoscopy at 8–12-month intervals. The interval periods could be changed at the patient's request.

## Results

A total of 95 eligible patients were identified from medical records of the participating centers between September 2001 and January 2012 (**Fig. 2**). Five patients were excluded following findings at the index colonoscopy: CRC (n=1), large adenomas not amenable to endoscopic removal (n=2), or patients refused further endoscopic removal (n=2). The remaining 90 patients

**Video 1**

Endoscopic removal of polyps from the bowel in a patient with familial adenomatous polyposis. Online content including video sequences viewable at: <http://dx.doi.org/10.1055/s-0034-1392774>



(46 males and 44 females) were included in the analysis. The median age at the start of the follow-up was 29 years (IQR 21–37 years) (● Table 1). Mutation analyses of the *APC* gene performed in 67 patients detected *APC* gene mutations in 53 (79.1%). Five patients with attenuated FAP had fewer than 100 adenomas with *APC* germline mutation. None of the included patients had symptoms suggestive of cancer, such as rectal bleeding.

The follow-up period ranged from 286 to 4145 days (0.8–11.4 years), with a median of 1871 days (5.1 years, IQR 3.3–7.3 years) (● Table 2). The total number of person–years of follow-up was 484.9. The median number of colonoscopies with polyp removal performed per patient was 8 (IQR 6–11). The median number of polyps resected per patient was 475 (IQR 211–945). The total number of resected polyps was 55701 (● Table 3). There were no adverse events related to polypectomy, such as perforation or bleeding requiring blood transfusion.

Seven polyps in five patients contained a noninvasive carcinoma (Category 4.2 according to the revised Vienna classification) (● Table 4). Carcinoma was diagnosed at the baseline colonoscopy in three patients and at colonoscopy performed 2 and 10 months from the baseline, respectively, in two patients. No recurrence was observed after endoscopic removal of these polyps during a median follow-up of 4.3 years (IQR 2.0–7.1 years). No

**Table 1** Age of the patients at the start of follow-up.

Age, years	Total (n = 90)
≤19	15
20–<30	32
30–<40	26
40–<50	12
50–<60	1
≥60	4

**Table 2** The length of follow-up.

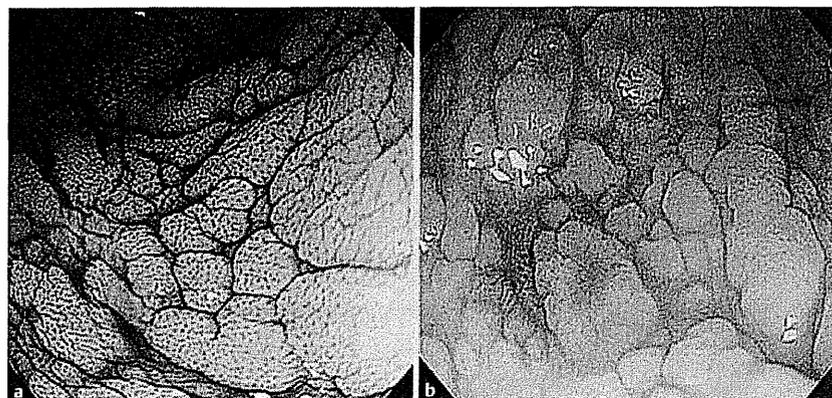
Years of follow-up	Number of patients (n = 90)
<3	12
3–<4	8
4–<5	12
5–<6	18
6–<7	16
7–<8	7
≥8	17

**Table 3** The number of polyps removed per patient.

Total number of colon polyps removed	Number of patients (n = 90)
≤99	5
100–199	17
200–499	24
500–999	28
≥1000	16

metastasis to the lymph nodes or liver was evident during the follow-up by ultrasound, which was performed annually. All of the remaining adenomas removed during the study contained only low grade dysplasia.

Two patients (2.2%) underwent subtotal colectomy with ileo-rectal anastomosis because their polyposis phenotypes changed to dense polyposis (● Fig. 3). Eleven patients (12.2%) were lost to follow-up; five were transferred to other hospitals and six declined further endoscopic examinations. The median follow-up period available for these 11 patients was 5.5 years (IQR 3.9–7.8).



**Fig. 3** Endoscopic appearance of dense polyposis. **a** With indigo carmine dye application. **b** Without indigo carmine dye application. The entire surface of the mucosa is covered with innumerable flat adenomas.

**Table 4** Patients with colorectal carcinoma.

Sex	Age at carcinoma diagnosis, years	Time of carcinoma diagnosis	Carcinoma characteristics			Length of follow-up after endoscopic removal
			Site in colon	Size, mm	Histological findings <sup>1</sup>	
Male	36	Baseline colonoscopy	Transverse	13	Non-invasive carcinoma (Category 4.2)	716 days (2.0 years)
			Descending	15	Noninvasive carcinoma (Category 4.2)	
			Sigmoid	15	Noninvasive carcinoma (Category 4.2)	
Female	26	Follow-up (2 months from baseline)	Unknown <sup>2</sup>	<10	Noninvasive carcinoma (Category 4.2)	2608 days (7.1 years)
Female	28	Follow-up (10 months from baseline)	Unknown <sup>2</sup>	<10	Noninvasive carcinoma (Category 4.2)	1579 days (4.3 years)
Female	37	Baseline colonoscopy	Unknown <sup>2</sup>	<10	Noninvasive carcinoma (Category 4.2)	4005 days (11.0 years)
Female	62	Baseline colonoscopy	Ascending	15	Noninvasive carcinoma (Category 4.2)	410 days (1.1 years)

<sup>1</sup> The revised Vienna classification was used for the pathological classification.

<sup>2</sup> Unknown because as many polyps as possible were retrieved for histological examination.

## Discussion

Colectomy, which is the standard treatment in FAP, prevents the development of CRC; however, it is also associated with morbidity and mortality. Removal of the large bowel affects quality of life [10]. Data from the Japan FAP registry showed that about 8% of patients develop desmoid tumor after colectomy [11]. Finally, colectomy does not remove the need for surveillance, because cancer can develop in the rectal stump or residual rectal mucosa after proctocolectomy with ileal pouch-anal anastomosis [12]. Endoscopic management of FAP has several potential advantages, including no risk associated with surgery, preserved normal bowel function, and no increased risk of desmoid tumor. Furthermore, endoscopic management can be performed on an outpatient basis. Endoscopic techniques are used in surveillance of patients after colectomy and to remove polyps from the rectal stump or ileal pouch [12]. Their use in FAP patients with preserved colon, as an alternative to colectomy, has been prevented by concerns about the feasibility of removing innumerable polyps and the risk of missing cancer.

In the present study, a retrospective review of medical records identified a large group of patients with FAP who strongly refused to undergo colectomy. These patients were managed endoscopically and underwent repeated colonoscopies to remove numerous polyps with the aim of colon clearance. During a median follow-up of 5.1 years, no invasive CRC was observed. Five patients had noninvasive carcinoma (Category 4.2 according to the revised Vienna classification), which was detected within 10 months from the start of the follow-up period. All of these patients were treated endoscopically with no signs of recurrence during follow-up.

Despite removing nearly 56 000 polyps, no complications related to endoscopic procedures, such as bleeding and perforation, were observed. These results suggest that endoscopic management of

FAP is feasible and safe, at least in the medium term. Because a follow-up of 5.1 years is a relatively short period in the setting of FAP, conclusions about the long-term safety of endoscopic management cannot be drawn. Other limitations of the study include the retrospective design, and possible patient selection that might have resulted in over-representation of patients with less severe polyposis and a more favorable course. Overall, 11 patients (12.2%) were lost to follow-up and it is not known whether these patients developed cancer. To overcome these limitations, a single-arm, nonrandomized, multicenter, prospective study was initiated in 2012 to evaluate the efficacy of endoscopic polypectomy in cancer prevention in patients with FAP (ID: UMIN000009365).

It should be noted that polyp clearance can only be achieved by multiple treatment sessions and removal of numerous polyps. We believe that in order to minimize the risk associated with this complex treatment it should be performed only by expert endoscopists. The optimal intervals between subsequent colonoscopies have not been determined. In the present study the intervals ranged from 3 to 12 months, depending on the number and size of polyps left in the colon after previous treatment session. In two patients in the current study, the phenotypes changed to more severe polyposis (dense FAP) and the patients underwent colectomy. Further observation is needed to select a suitable polyposis phenotype for colonoscopic polypectomy.

In conclusion, endoscopic management of FAP is feasible and safe in the medium term. It may offer an alternative to surgery in FAP patients who decline colectomy or who want to postpone colectomy by a few years. It should be strongly emphasized that the results of the present study should not be used to discourage FAP patients from prophylactic colectomy, which remains the standard treatment.

**Competing interests:** None

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# *Feasibility of Cold Snare Polypectomy for Multiple Duodenal Adenomas in Patients with Familial Adenomatous Polyposis: A Pilot Study*

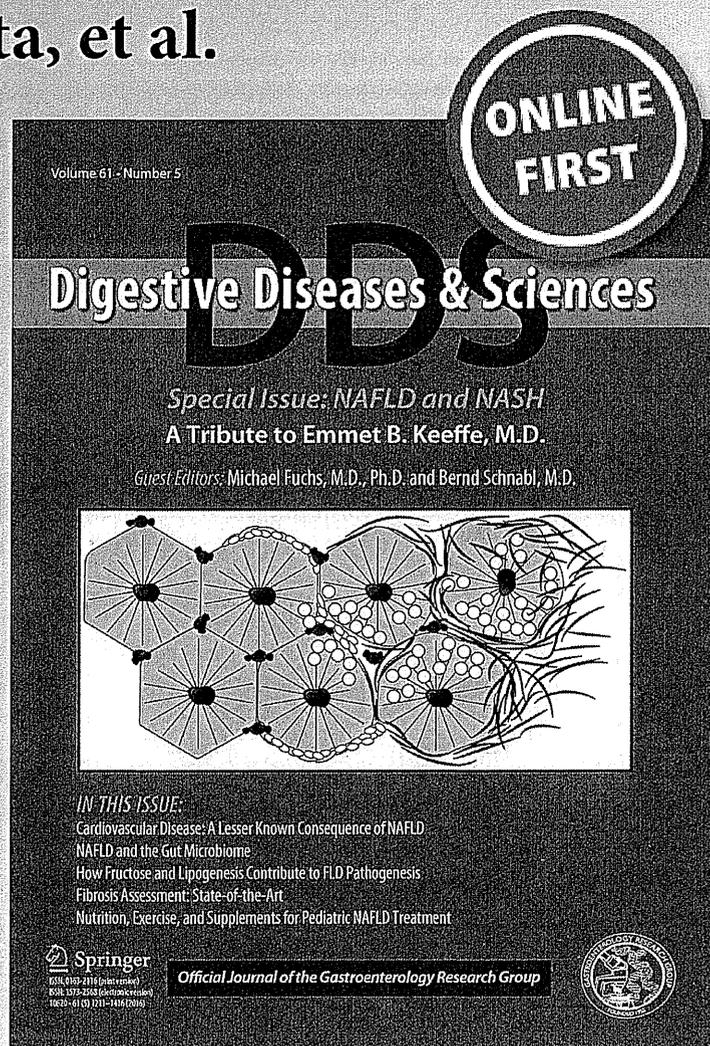
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## CASE REPORT

## Feasibility of Cold Snare Polypectomy for Multiple Duodenal Adenomas in Patients with Familial Adenomatous Polyposis: A Pilot Study

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### Introduction

Although the prognosis for patients with familial adenomatous polyposis (FAP) has improved because of preventive proctocolectomy, duodenal adenomas occur in up to 90 % of these patients [1]. The risk of developing duodenal cancer in patients with Spigelman stage IV disease (Table 1) is high at 7–36 % over follow-up periods of 7.6–10 years, compared with in patients with Spigelman stage 0–III disease, at 0.7 % over a similar period [2]. Duodenal, rather than colorectal, cancer is now the main cause of death in patients with FAP after preventive

proctocolectomy [1]. Therefore, preventive duodenectomy is recommended for patients with Spigelman stage IV disease; however, duodenectomy is invasive and carries a high mortality risk [3]. As an alternative, endoscopic treatment for duodenal adenomas is theoretically effective in preventing duodenal cancer mortality in patients with FAP; however, while endoscopic treatment for duodenal lesions is less invasive than duodenectomy, it carries a greater risk of complications such as bleeding or perforation [4, 5].

Cold snare polypectomy (CSP) for small colorectal polyps is safer than conventional hot snare polypectomy, and CSP is as effective as hot snare polypectomy [6, 7]. Cold snare piecemeal resection is also safe for large duodenal polyps [8]. Therefore, we hypothesized that CSP is also safe for small multiple duodenal adenomas in patients with FAP, and retrospectively assessed the feasibility of CSP for small multiple duodenal adenomas.

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**Table 1** Spigelman staging system of duodenal polyps in familial adenomatous polyposis

Points	1	2	3
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histological type	Tubular/hyperplasia/inflammation	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0 = 0 points; stage I = 1–4 points; stage II = 5–6 points; stage III = 7–8 points; stage IV = 9–12 points

## Case Series

This study was approved by our institutional ethics committee, and written informed consent was obtained from all patients. CSP was performed using a gastroscope (GIF-Q260J; Olympus, Tokyo, Japan) with a disposable transparent attachment (D-201-11804; Olympus, Tokyo, Japan) mounted on the tip of the endoscope. Two types of polypectomy snares (10 mm, Captivator II, Boston Scientific, Marlborough, MA, USA or 9 mm, Exacto cold snare, US Endoscopy, Mentor, OH, USA) were used for CSP, without submucosal injection. The resection wounds were inspected after CSP to confirm hemostasis (Video 1). The day before CSP, all four patients began 20 mg rabeprazole once daily, orally, which was continued for 3–4 weeks. All procedures were performed at Osaka Medical Center for Cancer and Cardiovascular Diseases.

The primary outcome was complications during the 28 days post-CSP, such as bleeding or perforation. The secondary outcome was efficacy, using the staging system developed by Spigelman et al. [1] to assess the severity of the duodenal polyposis, and to predict the risk of developing duodenal cancer. We assessed Spigelman staging before CSP and 2–4 months after CSP.

Four FAP patients with multiple small duodenal adenomas underwent CSP between July and October 2015. The patient and lesion characteristics, and treatment details are shown in Table 2. The median patient age (two men, two women) was 45 years (range 22–52 years), and all four patients had multiple duodenal adenomas (2–16 mm in size) located between the superior duodenal angle and the transverse duodenum (Fig. 1). Two patients had Spigelman stage IV disease; however, they declined duodenectomy and wished to have their duodenal polyps removed endoscopically. The remaining two patients had Spigelman stage III disease. CSP was performed for a total of 126 duodenal polyps (2–16 mm in size) in the four patients (median 30 lesions/patient). Each patient underwent CSP once during the study period. During CSP, intra-procedural oozing occurred with most polyp excisions, but stopped spontaneously without endoscopic hemostasis in all cases (Fig. 2). No prophylactic procedure, such as suturing with hemoclips or tissue shielding with

polyglycolic acid sheets and fibrin glue, was performed for any of the cases. One patient experienced mild abdominal pain between 1 and 2 days post-CSP, which resolved spontaneously without intervention. Another patient experienced tarry stool between the night of CSP and the next day, which also resolved spontaneously with no significant drop in hemoglobin level. Although a total of 126 duodenal polyps were resected in these four patients, no cases experienced severe complications requiring emergency intervention (0 %; 95 % confidence interval 0.00–0.02). Follow-up endoscopy was performed in all four patients a median of 2.75 months after CSP. All of the CSP sites were completely covered with regenerative mucosa, and the number of duodenal polyps had decreased dramatically. Because biopsy could not be performed for all of the detected polyps at follow-up endoscopy, we applied the same scores for histology and dysplasia as those before CSP. Nevertheless, the Spigelman stage was downstaged in all cases at follow-up endoscopy (Fig. 3).

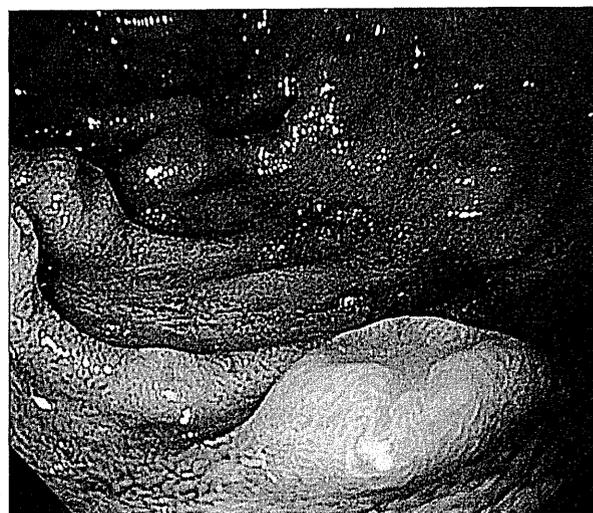
## Discussion

Currently, the interval of endoscopic surveillance for patients with FAP is determined by the Spigelman stage, with a shorter interval between examinations for more advanced stages. The aim of the surveillance is to detect stage IV disease before invasive cancer has developed [2]. One study showed that 15 % of patients progressed from stages 0–III to stage IV disease over a period of 8 years [9], and the risk of developing stage IV disease by age 70 is estimated to be between 20 and 50 % [2]. Patients with stage 0 or I disease are recommended to have repeat surveillance endoscopy every 5 years, those with stage II disease every 2–3 years, and those with stage III disease every 1–2 years. Watchful waiting has been recommended for patients with early-stage FAP (Spigelman stages 0–II), and endoscopic treatment has been proposed for patients with stage III disease because endoscopic treatment for duodenal lesions has a high risk of delayed bleeding and perforation [4, 5]. However, if secure endoscopic treatment for duodenal polyps is available, we can treat these more aggressively to downstage and avoid disease progression.

**Table 2** Patient and lesion characteristics, and treatment details

Patient #	Sex	Age (years)	History of colectomy	History of ampullectomy	Location	No. of polyps	Polyp size (mm)	Histology	Dysplasia	Spigelman stage (score) before CSP	Snare type	Number of resected polyps	Complications	Spigelman stage (score) 2-4 mo after CSP	Downstaged
1	Male	44	No	No	SDA-TD	>20	4-16	Tubular	Severe	IV (10)	Captivator II	26	No	III (7)	Yes
2	Female	22	No	Yes	SDA-TD	>20	2-10	Tubular	Moderate	III (8)	Captivator II	26	Abdominal pain	II (5)	Yes
3	Male	52	Yes	No	SDA-TD	>20	2-14	Tubular	Moderate	IV (9)	Captivator III/Exacto	34	Tarry stool	III (8)	Yes
4	Female	46	Yes	No	SDA-TD	>20	2-8	Tubular	Mild	III (7)	Exacto	40	No	II (6)	Yes

SDA superior duodenal angle, TD transverse duodenum, CSP cold snare polypectomy



**Fig. 1** Esophagogastroduodenoscopy before CSP showing multiple duodenal adenomas in the descending duodenum in case 2



**Fig. 2** Esophagogastroduodenoscopy just after CSP showed minor intra-procedural oozing that resolved spontaneously without endoscopic hemostasis in case 2

Referral to a pancreatobiliary surgeon for possible prophylactic duodenectomy has been recommended for patients with stage IV disease [5]. Standard therapy for colorectal polyps in patients with FAP is surgical total colectomy, and most patients with duodenal polyps have a history of total colectomy. Because duodenectomy for patients with FAP after total colectomy is highly invasive and carries significant morbidity and mortality risks, we must consider less invasive interventions to decrease the risk of duodenal cancer death.

CSP resulted in no major complications for multiple duodenal polyps in patients with FAP in this pilot



**Fig. 3** Esophagogastroduodenoscopy 3 months after CSP showing a dramatic decrease in the number of duodenal polyps in case 2

feasibility study. Generally, the occurrence of delayed bleeding is 0–33 % and that of perforation is 0.6–3 % in duodenal endoscopic mucosal resection, which is much higher than for colonic endoscopic mucosal resection [10, 11]. Moreover, duodenal perforation can be fatal because of intra-abdominal leakage of pancreatic and bile secretions. Complications, including perforation and delayed bleeding, after polypectomy may be related to transmural burn syndrome caused by electrocautery [7]. CSP does not require electrocautery; therefore, CSP is considered safer than conventional hot snare polypectomy [7] and has recently become popular in the treatment of small colorectal polyps [12, 13]. Endoscopic treatment for duodenal lesions, especially distal to the ampulla of Vater, has a high risk of delayed bleeding and perforation because the duodenum has a thin wall and a high concentration of digestive secretions such as pancreatic enzymes and bile [4]. Therefore, CSP may be an optimal endoscopic treatment for duodenal neoplasms.

To our knowledge, there are no reports of endoscopic resection of large numbers of duodenal polyps. This pilot feasibility study included the removal of 126 duodenal polyps without complications, and we believe that the results can be applied to the endoscopic treatment of single or small numbers of duodenal polyps in patients without FAP.

In this pilot feasibility study, all patients were downstaged following CSP. Therefore, CSP for patients with early-stage FAP may prevent upstaging of the Spigelman stage and the development of duodenal cancer. CSP may create a paradigm shift toward aggressive endoscopic treatment for multiple duodenal adenomas in patients with FAP.

Endoscopic management has been attempted in FAP patients who decline proctocolectomy [14], and endoscopic management can also be performed for FAP patients with Spigelman stage IV disease who decline duodenectomy. The present study included two patients with Spigelman stage IV disease who declined duodenectomy, and both had their disease downstaged. The use of CSP may avoid invasive surgery and prevent duodenal cancer mortality in patients with FAP.

The present study has certain limitations. First, this was a retrospective study involving a small number of patients conducted at a single center. However, although the number of cases was small, the number of lesions resected by CSP was over 100. Therefore, to our knowledge, this is one of the largest-scale reports of endoscopic resection because duodenal adenoma is uncommon in the general population. Prospective safety studies using this therapy in large numbers of patients are needed, preferably as multicenter trials. Second, the pre-CSP and post-CSP Spigelman scores for histology and dysplasia could not be compared. Despite this limitation, all patients' Spigelman stages were downstaged. Finally, it is difficult to justify CSP for removing small duodenal polyps, because this study lacked long-term follow-up, and was designed as a pilot feasibility study of CSP for duodenal adenomas in patients with FAP. Therefore, long-term follow-up studies to assess the efficacy of endoscopic removal for multiple duodenal lesions by CSP are needed.

In conclusion, CSP was feasible for multiple small duodenal adenomas in patients with FAP, and CSP may be an effective method to downstage Spigelman stage, based on our short-term endoscopic follow-up.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics** This study was approved by our institutional ethics committee.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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## Prevalence of laparoscopic surgical treatment and its clinical outcomes in patients with familial adenomatous polyposis in Japan

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### Abstract

**Background** Laparoscopic surgery is becoming the preferred technique for most colorectal interventions. This study aimed to clarify the time trend of surgical treatment for familial adenomatous polyposis (FAP) and its relevance to clinical outcomes in Japan over a 13-year period.

**Methods** This was a multicenter retrospective cohort study comprising 23 specialist institutions for colorectal disease and a cohort of 282 FAP patients who underwent total colectomy or proctocolectomy during 2000–2012. Patient clinical backgrounds and surgical outcomes were compared between the first and second halves of the study period.

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**Results** The proportion of surgical types adopted over the entire study period was 46, 21, 30, and 3 % for ileoanal anastomosis (IAA), ileoanal canal anastomosis, ileorectal anastomosis, and permanent ileostomy, respectively. FAP patients undergoing laparoscopic surgery have increased since 2008 and reached 74 % in the past 3 years. In particular, the number of patients undergoing laparoscopic proctocolectomy with IAA increased approximately four-fold from the first to the second half of the study period. A laparoscopic approach was increasingly used in patients with coexisting colorectal malignancies. Despite this trend, surgical results of the laparoscopic approach between the two study periods showed similar morbidity, pouch operation and stoma closure completion rates. No postoperative mortality was observed in this series, and laparoscopic surgery was comparable to open surgery in terms of stoma closure rate, incidence of intra-abdominal/abdominal desmoid tumors, and postoperative survival rate in both study periods.

**Conclusion** Laparoscopic approach is increasingly being adopted for prophylactic FAP surgery in Japan and may provide clinically acceptable practical outcomes.

**Keywords** Familial adenomatous polyposis (FAP) · Laparoscopic surgery · Total colectomy · Total proctocolectomy · Desmoid tumor

## Introduction

Familial adenomatous polyposis (FAP) is characterized by the development of hundreds to thousands of adenomas in the colorectum and almost all patients with FAP develop colorectal cancer by 50 years of age [1]. FAP is inherited as an autosomal dominant trait and is caused by mutations in the *APC*, and possibly *MUTYH*, gene. Prevention of colorectal cancer in FAP patients has long been managed by prophylactic surgery, i.e., total colectomy with ileorectal anastomosis (IRA) or total proctocolectomy with ileal pouch anal anastomosis (IPAA).

Laparoscopic surgery is becoming the preferred technique for most colorectal interventions, including prophylactic surgery for FAP. Early reports of the laparoscopic approach failed to demonstrate significant benefits over the conventional open approach because of the prolonged operative time, high open conversion rates, and perioperative

complications [2]. The laparoscopic approach is also costlier than the open approach [3]. Conversely, some studies demonstrating that the laparoscopic approach is technically feasible have been reported from countries such as Germany [4, 5], USA [6], France [7], UK [8], Italy [9], Brazil [10], and Korea [11]. As expected, the approach improved cosmetic results [5, 12–14] and is reported to offer several other advantages such as an earlier resumption of intestinal function [15], a shorter duration of hospital stay [15], a better preservation of fertility, and a higher postoperative pregnancy rate [16, 17]. However, many studies that have previously compared open versus laparoscopic IPAA were based on relatively small cohorts, predominantly including <100 cases, at a single institution. These studies included patients with not only FAP but also other diseases, including ulcerative colitis (UC) [14], and the disease-related factors were potentially associated with postoperative outcomes [4, 18]. Clear and reproducible advantages of laparoscopic surgery for FAP are yet to be demonstrated [10].

The aim of this multicenter retrospective cohort study was to evaluate the recent trends in surgical selection and clinical outcomes of FAP patients in Japan in order to facilitate the rational selection of surgical intervention methods and best practices for this rare disease. In Japan, IPAA has conventionally been classified into two categories allowing close distinction of the level of anastomosis as ileoanal anastomosis (IAA) for the dentate line and ileoanal canal anastomosis (IACA) for above the sphincter muscle (Japanese IPAA classification) [19]. Here we report our experience of surgical treatment for FAP patients over the past 13 years based on a multicenter clinical database that included Japanese IPAA classification data regarding anastomotic level, with emphasis on patients recently undergoing laparoscopic surgery and associated clinical implications.

## Methods

### Patients

A database was established by the multi-institutional retrospective cohort study for FAP conducted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). A total of 303 patients from 23 institutions diagnosed with FAP based on positive genetic testing or a typical clinical presentation with pathological confirmation were included in the database. These institutions included university hospitals, cancer centers and major regional hospitals all of which are core colorectal cancer treatment hospitals in Japan, and all institutions have one or more leading colorectal cancer specialists sitting on the JSCCR Familial Colorectal Cancer Committee. All patients received

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surgical resection of the large bowel between January 2000 and December 2012.

Of the 303 patients, 282 patients who underwent total colectomy or proctocolectomy were included in the study. All patients receiving only segmental resection of the bowel for malignant tumors and those for whom no detailed information regarding surgical procedure could be obtained were excluded from this study. Surgical intervention was performed as treatment for colorectal cancer identified preoperatively ( $N = 134$ ), cancerous prevention ( $N = 131$ ), or treatment for any symptoms in patients without colorectal cancer ( $N = 12$ ); no detailed information regarding surgical indications could be obtained for 5 patients. The median number of patients from an institution was 8 (1–72). In terms of the phenotype of polyp burden, the database included 78 patients with profuse type ( $\geq 2,000$  polyps), 176 patients with classical type (100–1,999 polyps), and 28 patients with attenuated type ( $< 100$  polyps). Medical records were retrospectively reviewed at each institution for patient characteristics, coexisting colorectal malignancies, operative methods, surgical complications, desmoid occurrences, and survival outcomes. All patient data were anonymously collected from each institution. The review board of JSCCR and the institutional ethics committees approved the study protocol.

Postoperative complications were recorded with particular attention to anastomotic complications (leak, stricture, and fistula), small bowel obstruction, abdominal abscess, wound infection, and cardiovascular, respiratory, and urinary complications. Complications were classified based on the Clavien–Dindo classification and those of grade  $\geq 3$  were evaluated.

### Surgical procedure

Surgical procedures were classified into IRA ( $N = 85$ ), IPAA ( $N = 188$ ), and proctocolectomy with permanent ileostomy ( $N = 9$ ). In particular, of patients with IPAA, 130 received IAA and 58 received IACA according to the Japanese JPAA classification [19]. In the majority of patients receiving IAA ( $N = 118$ ), mucosectomy was performed circumferentially to the top of the anal canal superior to the levator ani with a hand-sewn anastomosis created at the dentate line level using a perineal approach. In exceptional cases ( $N = 3$ ), a double-stapling technique was used for IAA. For IACA, anastomosis at the very distal rectum was performed using either the double-stapling ( $N = 37$ ) or hand-sewn ( $N = 18$ ) technique. Detailed information regarding the technique used for anastomosis could not be obtained for 9 patients who received IAA and 3 patients who received IACA. The choice of surgical approach (laparoscopic/open) was determined according to the preference of surgeons and patients.

### Statistical analyses

Patients were divided into two groups according to the year of surgery as follows—the first (2000–2006) and second (2007–2012) half groups. Patient backgrounds, surgical characteristics, and clinical outcomes were compared between groups.

Comparisons were analyzed using Student's *t*-test for quantitative data and the chi-squared test or Fisher's exact probability test, where appropriate, for categorical variables. Statistical analyses were performed using the SPSS Statistics 17.0 (SPSS, Inc., Chicago, IL, USA) and StatView ver.5.0 software (SAS Institute, Cary, NC, USA). Time to death, occurrence of desmoid tumor, and stoma closure were plotted on Kaplan–Meier survival curves for each group, with comparisons made using the log-rank test. A *p* value of  $< 0.05$  was considered statistically significant.

### Results

#### Time trend in using laparoscopic surgery

Figure 1 shows the time-trend incidences of laparoscopic surgery within a 2-year range. The proportion of patients receiving laparoscopic surgery began to increase from 2008–2009 and became higher than the proportion of patients receiving open surgery. In the last 3 years of this study, a laparoscopic approach was adopted in up to 74 % of FAP patients.

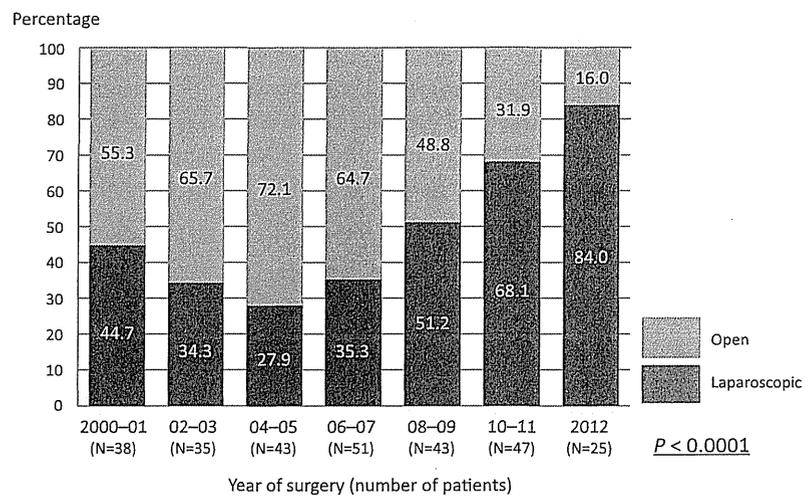
#### Background of patients treated with laparoscopic surgery

In the open surgery group, patient age at the time of large bowel resection was higher in the second half of the study (mean 38.0 years) than in the first half (mean 31.6;  $p = 0.0007$ ). In addition, the duration of illness was longer in the second half (mean 3.5 years) than in the first half (mean 1.5 years;  $p = 0.0443$ ). Conversely, no differences in age at the time of surgery and the duration of illness were observed between the first and second halves of the study period in the laparoscopic surgery group (Table 1). A laparoscopic approach was performed more often in patients diagnosed with coexisting colorectal malignancies in the second half of the study than in the first half ( $p = 0.0243$ ), although the prevalence of cancer did not significantly differ between the first and second halves in the open surgery group.

#### Time trend for the types of surgical procedure

The proportion of surgical types adopted over the entire study period was 46 % ( $N = 130$ ), 21 % ( $N = 58$ ), 30 %

**Fig. 1** Time trends in the number of patients receiving open and laparoscopic surgical interventions for familial adenomatous polyposis



**Table 1** Clinical background of surgically treated patients with familial adenomatous polyposis over the past 13 years in Japan

	Open (N = 148)			Laparoscopic (N = 134)		
	2000-2006	2007-2012	p value	2000-2006	2007-2012	p value
Gender						
Male	43 (48.3)	32 (54.2)	0.4804	27 (51.9)	42 (51.2)	0.9367
Female	46 (51.7)	27 (45.8)		25 (48.1)	40 (48.8)	
Age at operation (average)	31.6	38.0	0.0007	32.2	33.4	0.5738
Duration of illness (years, average) <sup>a</sup>	1.5	3.5	0.0443	1.3	2.1	0.2778
Phenotype						
Profuse	24 (27.0)	12 (22.3)	0.6060	17 (32.7)	25 (30.5)	0.0025
Classical	55 (61.8)	41 (69.5)		25 (48.1)	55 (67.1)	
Attenuated	10 (11.2)	6 (10.2)		10 (19.2)	2 (2.4)	
Number of remnant polyps in the rectum <sup>b</sup>						
<20	9 (60.0)	12 (85.7)	0.2161	17 (65.4)	12 (54.5)	0.1492
20-99	4 (26.7)	2 (14.3)		9 (34.6)	7 (31.8)	
≥100	2 (13.3)	0		0	3 (13.6)	
Coexisting colorectal malignancies						
Negative	43 (48.3)	22 (37.3)	0.1857	30 (57.7)	31 (37.8)	0.0243
Positive	46 (51.7)	37 (62.7)		22 (42.3)	51 (62.2)	
TIS	14 (15.7)	11 (18.6)		9 (17.3)	22 (26.8)	
Stage I	6 (6.7)	3 (5.1)		8 (15.4)	13 (15.9)	
Stage II	8 (9.0)	7 (11.9)		1 (1.9)	4 (4.9)	
Stage III	10 (11.2)	9 (15.3)		4 (7.7)	12 (14.6)	
Stage IV	8 (9.0)	7 (11.9)		0	0	

<sup>a</sup> In 242 cases for whom the data of age at diagnosis are provided

<sup>b</sup> In cases treated with ileorectal anastomosis procedure

( $N = 85$ ), and 3 % ( $N = 9$ ) for IAA, IACA, IRA, and permanent ileostomy, respectively. No significant difference in the proportion of surgical types or incidence of diverting ileostomy was observed between the first and second halves in the open surgery group (Table 2).

Conversely, a significant change in surgical types adopted was observed in the laparoscopic treatment group (Fig. 2). In particular, IRA was predominantly performed in the first half of the study period, whereas the laparoscopic approach was used most often for IAA (50.0 %),

**Table 2** Surgical procedures adopted for familial adenomatous polyposis over the past 13 years in Japan

	Open (N = 148)			Laparoscopic (N = 134)		
	2000–2006	2007–2013	p value	2000–2006	2007–2013	p value
Operation time (min, mean)	297.0	301.5	0.8580	412.4	437.5	0.3330
Blood loss (ml, mean)	375.7	506.9	0.1878	260.1	267.4	0.9063
Type of operation						
IRA	19 (21.3)	14 (23.7)	0.2050	28 (53.8)	24 (29.3)	0.0006
IACA	14 (15.7)	17 (28.8)		14 (26.9)	13 (15.9)	
IAA	53 (59.6)	26 (44.1)		10 (13.2)	41 (50.0)	
Permanent ileostomy	3 (3.4)	2 (3.4)		0	4 (4.9)	
Pouch operation <sup>a</sup>						
Performed	61 (98.4)	34 (81.0)	0.0060	23 (95.8)	52 (96.3)	0.9999
Not performed	1 (1.6)	8 (19.0)		1 (4.2)	2 (3.7)	
Diverting stoma <sup>b</sup>						
Performed	24 (28.6)	20 (35.7)	0.3725	16 (33.3)	46 (61.3)	0.0024
Not performed	60 (71.4)	36 (64.3)		32 (66.7)	29 (38.7)	
Stoma closure						
Performed	21 (91.3)	18 (90.0)	0.9999	14 (93.3)	39 (95.1)	0.9999
Not performed	2 (8.7)	2 (10.0)		1 (6.7)	2 (4.9)	
Morbidity (grade $\geq 3$ )						
Absence	58 (90.6)	49 (86.0)	0.4237	36 (76.6)	69 (86.3)	0.1651
Presence	6 (9.4)	8 (14.0)		11 (23.4)	11 (13.8)	

IRA ileorectal anastomosis, IACA ileoanal canal anastomosis, IAA ileoanal anastomosis

<sup>a</sup> In cases with proctocolectomy with anastomosis

<sup>b</sup> In cases with anastomosis

followed by IRA (29.3), and IACA (15.9 %) in the second half (Table 2). In the laparoscopic group, no significant difference in pouch operation rates was observed between the first and second halves; however, the number of patients receiving a diverting stoma in the laparoscopic group significantly increased in the second half of the study compared with the first half ( $p = 0.0024$ ; Table 2).

### Clinical outcomes of open and laparoscopic surgery

No significant difference in morbidity rate was observed between the first and the second halves of the study in both the open and laparoscopic groups (Table 2). The incidence of small bowel obstruction with grade  $\geq 3$  was lower in the second half (8.1 %) than in the first half (23.7 %;  $p = 0.0289$ ). On the other hand, when focusing on other types of postoperative complications including anastomotic complications and intra-abdominal abscesses, we observed no significant difference between the two periods in the laparoscopic group. In the second half when the laparoscopic approach was actively adopted, the morbidity rate in the laparoscopic group (13.8 %) was comparable to that in the open surgery group (14.0 %).

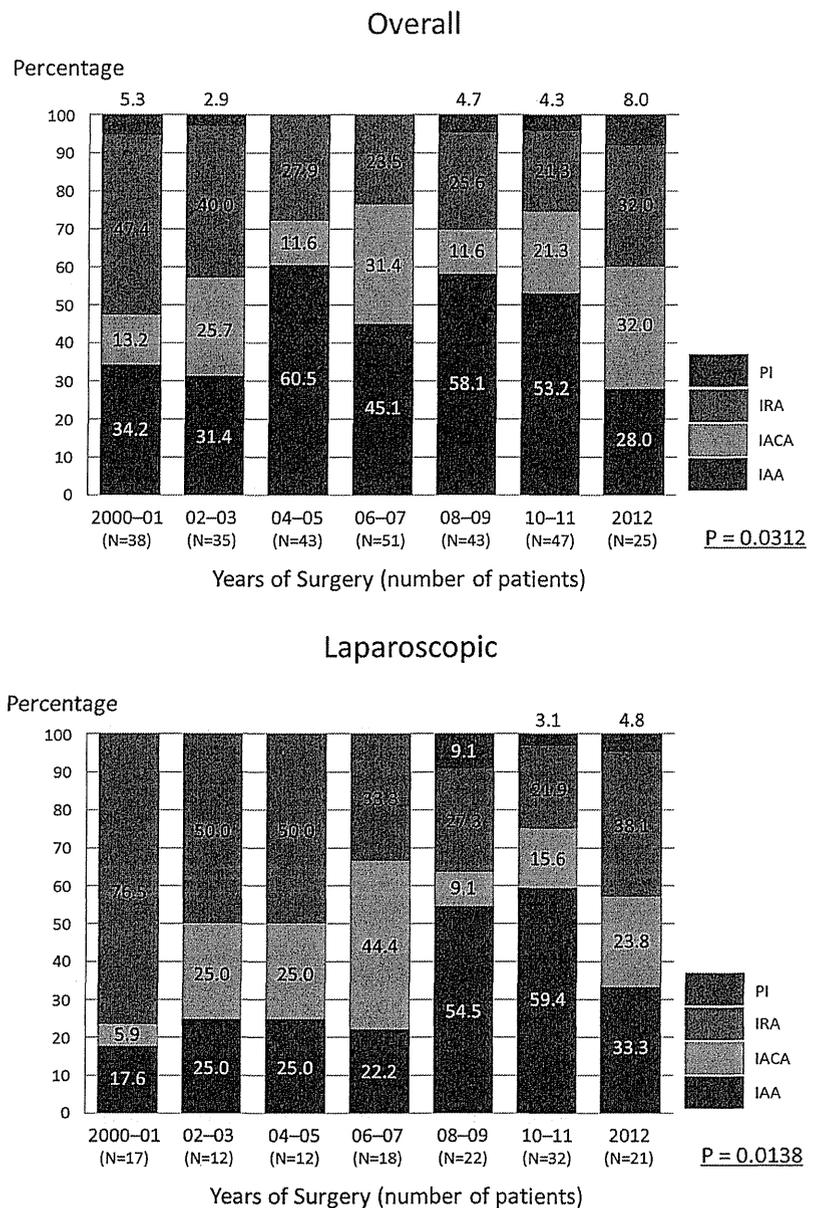
No statistical difference in the stoma closure rate, incidence of intra-abdominal/abdominal desmoid tumor, or

postoperative survival rate was observed between the open and laparoscopic surgery groups irrespective of the operative period (Fig. 3). No patient died in the laparoscopic group during the second half.

### Discussion

Here, we describe our multicenter experience of surgical treatment for FAP patients over a 13-year period in Japan. Although this cohort study is limited by its retrospective nature, we believe its results reflect the actual status of surgical treatment of FAP because this nationwide study included 23 representative institutions specializing in the treatment of colorectal diseases in Japan. An advantage of this study was that our database included prospectively accumulated information regarding the level of anastomosis of IPAA, which significantly impacted postoperative clinical outcomes. Surgical procedures involving sphincter preservation for FAP patients have conventionally been classified into IRA and IPAA [1, 20]. The level of anastomosis in IPAA has not always been described in previous studies, although anastomotic techniques are occasionally distinguished between hand-sewn and stapled techniques [20].

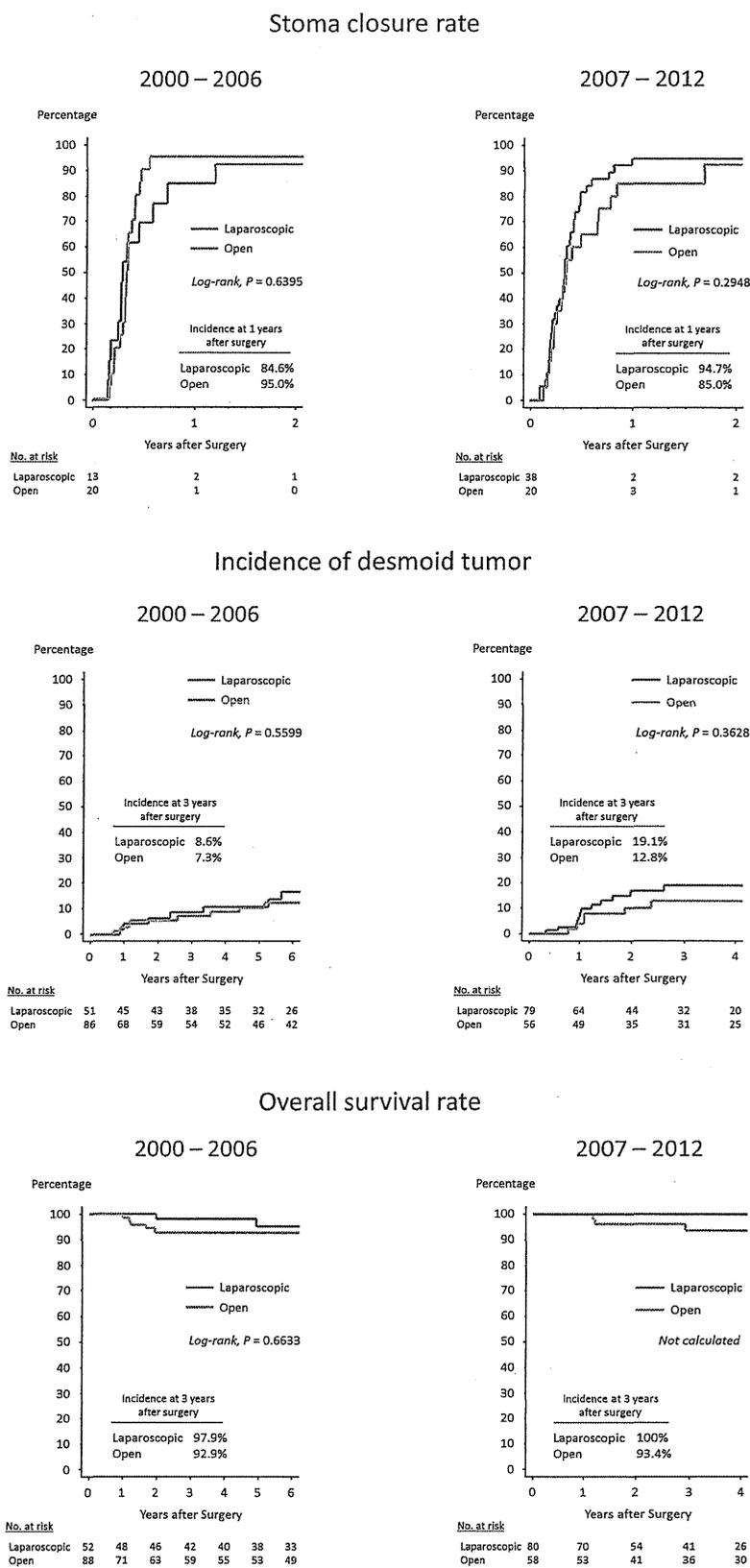
**Fig. 2** Time trend of the types of surgery adopted for the treatment of familial adenomatous polyposis in Japan



We observed several original findings regarding recent surgical treatments in Japan. First, we found that the number of patients undergoing laparoscopic surgery for FAP began to increase after 2008 and reached 74 % in the past 3 years. It is adequately conceivable that this trend is influenced by the increased incidence of laparoscopic rectal resection in Japan. Our analyses indicated that extended application of the laparoscopic approach in FAP patients with coexisting malignancy contributed to this increase. Another reason was that the laparoscopic approach is increasingly applied in IPAA, particularly in IAA, which is technically complex but preferentially selected over IACA in Japan. Our data demonstrate that,

in comparison with patients undergoing other types of surgery, the number of patients undergoing IAA in the laparoscopic group was comparable to that in the open group during the second half. The proportion of procedures performed laparoscopically in FAP patients treated during 2000–2007 at the Cleveland Clinic, a representative leading high-volume center in the Western world, was 23 % for IPAA and 58 % for IRA [21]. However, there is a lack of data regarding the proportion of patients receiving laparoscopic surgery for FAP treatment worldwide. Japan may currently be one of the few countries where laparoscopic techniques are actively adopted in routine practice.

**Fig. 3** Comparison of the stoma closure rate, incidence of intra-abdominal and abdominal desmoid tumor, and overall survival rate between open and laparoscopic surgery during the first and second halves of the study period



A current concern regarding the state of FAP surgical treatment in Japan is the influence of the rapidly increasing popularity of laparoscopic surgery on the quality of surgery. However, we observed no evidence in the present study indicating that laparoscopic surgery was inferior to open surgery in terms of clinical outcomes such as morbidity, overall survival rate, stoma closure rate, and postoperative desmoid tumor incidence. There have been no reported randomized studies comparing open and laparoscopic treatments for FAP. Ahmed et al. reported a meta-analysis of 11 studies comparing open versus laparoscopic IPAA for FAP and UC, of which only one was a randomized clinical trial. A total of 607 patients with FAP and UC were analyzed, and no significant differences in mortality or complications were observed between the two groups [14]. In future, nationwide prospective randomized studies are required to determine the long-term effects of laparoscopic surgery on a range of outcomes including functional and oncological consequences.

The present study evaluated the actual time trend of the surgical type selected as prophylactic surgery in Japan. IPAA and IRA have individual merits; however, there is no clear consensus regarding which approach has greater utility or efficacy [1, 20, 22]. We observed no remarkable change in the proportion of surgical types during the 13-year period of the present study, with IPAA representing approximately 67 % of prophylactic surgical procedures for FAP in Japan. Conversely, according to a previous report analyzing the database of the Polyposis Registry of Japan, which includes patients treated during a 14-year period (1990–2003), the proportion of patients who received total resection of the colorectum and rectum-preserving surgery was 55 % ( $N = 527$ ) and 45 % ( $N = 439$ ), respectively [23]. The figures reported from the Polyposis Registry 1990–2003 are comparable to those in the study reported by Aziz et al. who analyzed 12 observational studies (1991–2003) that compared the results of IRA and IPAA for FAP ( $n = 1002$ ), with IPAA and IRA selected as the primary treatment for FAP in 53 and 47 % of cases, respectively [22]. Accordingly, the choice of surgical procedure in Japan apparently changed around 2000, with total proctocolectomy, rather than total colectomy, preferentially selected compared to the 1990s. The most likely explanation for this observation may be that surgeons increased their appreciation of the risk of cancer development in the rectum following IRA surgery and IPAA is now regarded as the standard surgical procedure for the treatment of the majority of FAP patients in routine practice in Japan.

With regard to patients receiving laparoscopic surgery, we observed a smaller proportion of patients undergoing total colectomy with IRA and a higher proportion of patients undergoing total proctocolectomy in the second half of the study period. The proportion of patients

undergoing IAA in the second half was found to be approximately four-fold higher than the corresponding figure in the first half. The reason for this observation is unclear; however, the increased use of laparoscopic surgery enables surgeons to increase their understanding of intra-pelvic anatomy, particularly regarding the autonomic nerve and pelvic floor, and surgeons were able to preferentially choose laparoscopic techniques for IAA surgery in the second half of the study. In the recent literature, the reported proportion of IRA adopted in patients treated with laparoscopic operation varies widely from 2 [11] to 80 % [9]. These results indicate that there is large international variation in the surgical type adopted for laparoscopic surgical interventions in FAP patient, and presumably, the indication criteria at individual institutions may subsequently change according to the increased use of laparoscopic surgery.

The third major finding of the present study was that diverting stoma is increasingly performed in laparoscopic IPAA surgery in Japan. The most important role of diverting loop ileostomy following IPAA is to facilitate healing of the ileal pouch and the anastomosis and minimize the risk of anastomotic deficiency and pelvic sepsis, both of which are closely correlated with a subsequent poorer sphincter function. A number of authors have argued that laparoscopic restorative proctocolectomy can be safely performed without a diverting stoma in cases where tension-free anastomosis can be created following appropriate mesentery lengthening [24, 25]. However, as demonstrated by a recent report [26], one-stage IPAA patients are at an increased risk of short-term complications such as anastomotic leak and reoperation compared with two-stage IPAA. This study indicates that surgeons in Japan consider this point at great length and have a careful attitude toward one-stage colectomy following the recent expansion of indications for laparoscopic surgery.

Finally, this study indicates that a preference of surgeons and patients for particular surgical approaches may have an effect on the age of patients undergoing prophylactic surgical interventions. Although it is widely accepted that colectomy is indicated in all patients with FAP for cancer prevention, the timing or age at which surgery should be performed remains undefined [1]. Timing for surgical intervention is generally determined on the basis of subjective criteria, i.e., when polyposis becomes severe or when social situations are appropriate for individual patients. The present study demonstrated a difference in the age of patients undergoing surgery between the first and the second halves of the study in the open surgery group. We observed a delay of surgical intervention in the second half compared with the first half; however, no such difference was observed in the laparoscopic group. This observation may be because of better cosmesis associated with the long-term