Development of ileal adenomas after ileal pouch-anal anastomosis versus end ileostomy in patients with familial adenomatous polyposis

Arthur S. Aelvoet, MD,[1,2,3,*] Victorine H. Roos, MD, PhD,[1,2,3,*] Barbara A. J. Bastiaansen, MD,[1,2,3] Roel Hompes, MD, PhD,[2,4] Willem A. Bemelman, MD, PhD,[2,4] Cora M. Aalfs, MD, PhD,[5] Patrick M. M. Bossuyt, PhD,[6] Evelien Dekker, MD, PhD[1,2,3]

Amsterdam, Utrecht, the Netherlands

Background and Aims: Patients with familial adenomatous polyposis (FAP) undergo (procto)colectomy to prevent colorectal cancer from developing. Interestingly, after proctocolectomy with ileal pouch-anal anastomosis (IPAA), most patients develop adenomas in the pouch. This is not well described for patients with end ileostomy. We aimed to compare ileal adenoma development in patients with IPAA with those with end ileostomy.

Methods: This historical cohort study included FAP patients with IPAA or end ileostomy who underwent surveillance endoscopies between 2001 and 2021. Primary outcomes were the proportion of patients with ileal adenomas, location of adenomas, and proportion of patients undergoing surgical excision of pouch/end ileostomy.

Results: Overall, 144 patients with IPAA (n = 111) and end ileostomy (n = 33) were included. Five years after surgery, 15% of patients with IPAA had ileal adenomas versus 4% after ileostomy. At 10 years, these estimates were 48% versus 9% and at 20 years were 85% versus 43% (log-rank $P < .001$). Adenomas developed more often in the pouch body (95%) in the IPAA group and more often at the everted site of the ileostomy (77%) in the ileostomy group. Numbers for surgical excision of the pouch (n = 9) or ileostomy (n = 3) for polyposis or cancer were comparable. Taking into account potential confounders in a multivariable Cox regression analysis, having an IPAA was significantly associated with ileal adenoma development.

Conclusions: After proctocolectomy, FAP patients with IPAA more often developed ileal adenomas than patients with end ileostomy. This could potentially affect long-term management, and patients with end ileostomy might benefit from less-frequent endoscopic surveillance. (Gastrointest Endosc 2023;97:69-77.)

Abbreviations: APC, *adenomatous polyposis coli [gene]; FAP, familial adenomatous polyposis; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range; IRA, ileorectal anastomosis.*

DISCLOSURE: *The following authors disclosed financial relationships: B. A. J. Bastiaansen: Speaker for Olympus, Tillotts Pharma AG, and Ovesco Endoscopy. R. Hompes: Research funding from Stryker; consultant and speaker for Applied Medical. W. A. Bemelman: Research funding from VIFOR; consultant and speaker for Takedo, Braun, and Johnson. E. Dekker: Consultant for Fujifilm, Olympus, GI Supply, PAION, and Ambu; speaker for Fujifilm, Olympus, GI Supply, PAION, Roche, Norgine, and Ipsen; equipment on loan from Fujifilm and Olympus; research funding from Fujifilm. All other authors disclosed no financial relationships.*

*Drs Aelvoet and Roos contributed equally to this article.

0016-5107
https://doi.org/10.1016/j.gie.2022.08.031

Received April 28, 2022. Accepted August 19, 2022.

Current affiliations: Department of Gastroenterology and Hepatology (1), Department of Surgery (4), Department of Epidemiology and Data Science (6), Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; Cancer Center Amsterdam, Amsterdam, the Netherlands (2), Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, the Netherlands (3), Department of Clinical Genetics, UMC Utrecht, Utrecht University, Utrecht, the Netherlands (5).

Reprint requests: Evelien Dekker, MD, PhD, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, location University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Familial adenomatous polyposis (FAP) is a rare autosomal dominant disease caused by a mutation in the adenomatous polyposis coli (*APC*) gene, characterized by the distribution of hundreds of adenomas throughout the colon and rectum.[1] Because the risk of colorectal cancer approaches 100% at a median age of 35 to 45 years, most patients require a prophylactic (procto)colectomy as young adults.[2]

Cuurently, patients with FAP generally undergo either a (sub)total colectomy with ileosigmoidal or ileorectal anastomosis (IRA) or proctocolectomy with ileal pouch-anal anastomosis (IPAA). End ileostomy can be avoided in most patients and is usually reserved for those in whom IPAA construction is unfeasible or undesirable, such as patients with locally advanced rectal cancer, a significant mesenteric desmoid, or dysfunctional anal sphincter.[3,4]

A (procto)colectomy is not a definitive solution in FAP however, and patients remain at risk of developing new adenomas and cancer in the remaining rectum after IRA and in the ileal pouch or rectal cuff after IPAA.[5,6] Current guidelines therefore recommend lifelong endoscopic surveillance for patients with both IRA and IPAA. Recommended surveillance intervals are based on expert opinion and vary from 1 to 2 years.[7] Patients with end ileostomy may also develop ileal adenomas as well as cancers as described in small case series, but a general surveillance recommendation has not been provided in the literature or in guidelines.[8-10]

Because predicting the location, severity, and timing of ileal adenomas after proctocolectomy is currently not possible, a better understanding of the development of adenomas in the ileal mucosa is needed. This information would be helpful in establishing personalized endoscopic surveillance for patients with IPAA or end ileostomy. Moreover, long-term outcomes of surveillance and endoscopic and surgical interventions after these operations would support preoperative counseling and appropriate timing of surgery.

Risk factors for the development of adenomas after IPAA are reported in literature, including male sex, younger age as well as older age, increased duration of follow-up, advanced duodenal adenomas, gastric adenomas, and a high adenoma count at the time of colectomy.[5,11-15] Apart from these factors, luminal factors, such as fecal stasis or changes in the microbiome, might also contribute to the development of adenomas in the ileum.[5] The fact that generally no adenomas are seen in the terminal ileum when the colon is in situ and during first surveillance endoscopies after proctocolectomy advocates for this hypothesis. We aimed to compare long-term follow-up on ileal adenoma development in patients with IPAA with those with end ileostomy, hypothesizing that patients with IPAA are more prone to develop ileal adenomas.

METHODS

Study design, setting, and participants

In this historical cohort study, all patients with FAP and IPAA or end ileostomy undergoing surveillance endoscopies in Amsterdam UMC were identified. Patients with FAP were included if the disease was either genetically confirmed by a germline *APC* gene mutation or a clinical diagnosis was made by the presence of more than 100 colorectal adenomas and other genetic causes had been ruled out.

Patients with surveillance endoscopies between January 2001 and November 2021 were included for analysis. All endoscopies were performed at dedicated endoscopy programs, performed or directly supervised by endoscopists with expertise in FAP. Since 2010, patients were prepared with a protocolized bowel preparation scheme using 1 L polyethylene glycol before lower GI endoscopy. High-definition 180 colonoscopes (Olympus, Tokyo, Japan) were used from November 2011, and from October 2012 onward these were replaced by high-definition 190 colonoscopes (Olympus). Dye-based chromoendoscopy was not routinely used; digital chromoendoscopy (narrow-band imaging) was used at the discretion of the endoscopist.

Because data were collected as part of standard care, the Institutional Review Board decided that this study did not fall under the Dutch legislation on Medical Research Involving Human Subjects Act, and ethical review was not required. The study was carried out in accordance with the Declaration of Helsinki.[16]

Variables and data sources

Data regarding gender, age, *APC* mutation, smoking status, medical history of colorectal cancer and desmoid disease, surgical history, severity of duodenal disease assessed using the Spigelman stage,[17] presence of an advanced duodenal adenoma (defined as an adenoma $\geq$10 mm and/or containing high-grade dysplasia), use of chemopreventive agents, compliance with follow-up (follow-up interval of 2 years after IPAA and 5 years after end ileostomy), and duration of follow-up were extracted from patients' medical charts and endoscopy and pathology reports.

The primary outcome parameter of the study was the proportion of patients with ileal adenomas during endoscopic follow-up. The cumulative number of adenomas was defined as the number of adenomas detected during the last surveillance endoscopy plus the cumulative number of resected adenomas during surveillance. The cumulative number of ileal adenomas was grouped in categories of 0, 1 to 10, 11 to 25, 26 to 50, 51 to 100, and over 100 adenomas.

Duration of follow-up was subdivided into time intervals of 1 to 5 years, 5 to 10 years, 10 to 15 years, 15 to 20 years, and >20 years after the index surgery. The size of the most advanced adenoma according to the endoscopy report was documented as well as the most advanced histology according to the histopathology report. Histopathology data were classified according to the Vienna classification.[18] Location of the adenomas after IPAA was categorized as located in the prepouch ileum and pouch body and after end ileostomy in the terminal ileum and everted

side of the ileostomy. If the exact number of adenomas or the size of the most advanced adenoma was not described, these were estimated based on the endoscopy reports and photographs by 1 of 2 expert endoscopists (B.A.J.B. or E.D.). Missing data were not included. The proportion of patients undergoing excision of the pouch or end ileostomy because of polyposis or cancer during follow-up was also assessed.

Statistical analysis

The proportion of patients developing ileal adenomas during endoscopy surveillance and the proportion of patients undergoing surgical excision of the pouch or end ileostomy were estimated using Kaplan-Meier analysis, using the log-rank test statistic for evaluating differences between the IPAA group and the end ileostomy group. The distribution of the number of cumulative adenomas and the size of the most advanced adenomas were compared using χ^2 test statistics. We additionally performed multivariable Cox proportional hazards regression analysis to reduce bias because of confounding. Potential causal effects between variables are shown in the directed acyclic graph in Supplementary Figure 1 (available online at www.giejournal.org).

Differences in characteristics and outcomes between the IPAA and end ileostomy groups were evaluated for statistical significance using the Mann-Whitney U test for normally distributed continuous variables and the χ^2 test for categorical variables. Differences were considered significant if $P <$ .05. All analyses were performed using SPSS 26 (version 26.0; IBM SPSS Statistics for Windows, Armonk, NY, USA).

RESULTS

Cohort

Of 144 patients with FAP undergoing follow-up endoscopies, 111 had IPAA and 33 had end ileostomy. Two patients are represented in both groups because they first underwent IPAA and then later end ileostomy. Table 1 summarizes the baseline characteristics. Although the median age at primary (procto)colectomy did not significantly differ between the IPAA group (24 years; interquartile range [IQR], 18-32) and end ileostomy group (25 years; IQR, 20-38), median age at end ileostomy construction (44 years; IQR, 34-54) was higher than the median age at IPAA construction (27 years; IQR, 20-36; $P < .01$).

Eighty-nine IPAA patients (80%) had primarily undergone proctocolectomy with IPAA, whereas 22 (20%) had primarily undergone total colectomy and IRA followed by secondary proctectomy and IPAA creation later. In 9 end ileostomy patients (27%), the end ileostomy was created at the time of proctocolectomy, whereas in 24 patients (73%), the end ileostomy was created after previous IRA and/or IPAA. A history of colorectal cancer or pouch carcinoma was present in 13 IPAA patients (12%; in 9 patients at the time of IPAA surgery) and in 11 end ileostomy patients (33%; in 9 patients at time of end ileostomy creation).

Follow-up outcomes

The median time from surgery (creation of IPAA/end ileostomy) to last surveillance endoscopy was 152 months (IQR, 77-240) in the IPAA group and 174 months (IQR, 72-272) in the end ileostomy group (Table 2). The median number of surveillance endoscopies of the pouch and end ileostomy was 6 (IQR, 3-10) and 2 (IQR, 1-3), respectively.

During follow-up, more patients with end ileostomy had an advanced duodenal adenoma (76% vs 46%) and were Spigelman stage IV (67% vs 31%). Chemopreventive agents were used by 23% of patients with IPAA and 5% of patients with end ileostomy at the time of 1 or more endoscopies at follow-up.

Ileal adenoma development after IPAA versus end ileostomy

Eighty patients (72%) with IPAA developed ileal adenomas compared with 10 patients (30%) with end ileostomy ($P < .01$). Kaplan-Meier curves (Fig. 1) show that at 5 years after surgery, 15 patients (15%) with IPAA had developed ileal adenomas versus 1 patient (4%) with end ileostomy. After 10 years, these numbers were 41 (48%) versus 2 (9%) and after 20 years 64 (85%) versus 6 (43%) (log-rank test: $P < .01$) (Fig. 1). The estimated median time to ileal adenoma development was 140 months in the IPAA group (95% confidence interval, 111-169) and 434 months in the end ileostomy group (95% confidence interval, 180-688).

Table 3 shows a more detailed description of the cumulative number of ileal adenomas in each time period. The cumulative number of ileal adenomas gradually increased in the IPAA group, whereas this was less so in the end ileostomy group. Although no patient with end ileostomy cumulatively developed over 25 ileal adenomas, 54% of patients with IPAA and $\geq$20 years of follow-up developed over 25 ileal adenomas, including 18% with over 100 adenomas. Of note, not all patients are represented in each time period. From all 2983 ileal adenomas detected in the IPAA group, 2830 (95%) were located in the pouch body and 153 (5%) in the prepouch ileum. Of the 77 ileal adenomas detected in the end ileostomy group, 18 (23%) were located at the luminal site and 59 (77%) at the everted site of the ileostomy. Size of the most advanced lesion, histology, and dysplasia grade were comparable for both groups. Figure 2 shows endoscopic images of patients with IPAA and end ileostomy with extensive ileal polyposis.

Excision of pouch or end ileostomy because of polyposis or cancer

During follow-up, 9 patients (8%) in the IPAA group underwent pouch excision because of extensive polyposis (n = 6) or pouch carcinoma (n = 3) compared with 3 patients (9%) with end ileostomy who underwent excision of

TABLE 1. Patient characteristics

			IPAA (n = 111)	End ileostomy (n = 33)	*P* value
Male			60 (54)	21 (64)	.33*
Age at (procto)colectomy, y			24 (18-32)	25 (20-38)	.19†
Age at construction IPAA or end ileostomy, y			27 (20-36)	44 (34-54)	<.01†
Proven adenomatous polyposis coli gene mutation	Yes		96 (86)	24 (73)	.09*
	No		5 (5)	4 (12)	
	Unknown		10 (9)	5 (15)	
Mutation location	Premutation cluster (5′ of 1250)		71 (64)	19 (58)	.18*
	Mutation cluster region (1250-1464)		14 (13)	0	
	Postmutation cluster region (3′ of 1464)		2 (2)	0	
	Large deletion		3 (3)	0	
Presence of mutation in codon 1309			10 (9)	0	.13*
Polyposis drug treatment before surgery			14 (13)	7 (21)	.22*
Smoking	Yes		23 (21)	6 (19)	.01*
	Former		18 (16)	14 (44)	
	Never		70 (63)	13 (39)	
Surgical history	Total colectomy with ileorectal anastomosis and secondary proctectomy		22 (20)	18 (55)	<.01*
	Proctocolectomy with IPAA		89 (80)	6 (18)	<.01*
	Proctocolectomy with end ileostomy		0	9 (27)	<.01*
	Pouch excision with end ileostomy		0	12 (36)	<.01*
	Pouch excision with redo IPAA		2 (2)	0	.437*
	Duodenal surgery		16 (14)	17 (52)	<.01*
Medical history	Desmoid disease		13 (12)	6 (18)	.34*
	Malignancy	Colon	10 (9)	0	<.01*
		Sigmoid	2 (2)	3 (9)	
		Rectum	1 (1)	6 (18)	
		Ileal pouch	0	2 (6)	
Indication for IPAA or end ileostomy	Severe polyposis		75 (68)	10 (30)	<.01*
	Malignancy		9 (8)	9 (27)	
	Desmoid disease preventing IPAA		0	2 (6)	
	Adverse events/ dysfunction		1 (1)	6 (18)	
	Unknown		26 (23)	6 (18)	
Type of ileoanal anastomosis	Handsewn		22 (20)	NA	NA
	Stapled		78 (70)		
	Unknown		11 (10)		

Values are n (%) or median (interquartile range).
IPAA, Ileal pouch-anal anastomosis; *NA,* not applicable.
**P* value was calculated using the χ^2 test statistic.
†*P* value was calculated using the Mann-Whitney U test statistic.

TABLE 2. Follow-up characteristics

Follow-up characteristics		Ileal pouch-anal anastomosis (n = 111)	End ileostomy (n = 33)	*P* value
Time from surgery to last endoscopy, mo		152 (77-240)	174 (72-272)	.69†
No. of surveillance endoscopies		6 (3-10)	2 (1-3)	<.01†
No. of patients on chemopreventive agents		25 (23)	5 (15)	.47*
No. of endoscopies under chemopreventive agents		128/791 (16)	5/74 (7)	.03*
Development of ileal adenomas after surgery		80 (72)	10 (30)	<.01*
Development of rectal cuff adenomas after surgery		65 (59)	NA	
No. of adenomas per location	Prepouch ileum	4 (2-13)	NA	
	Pouch body	20 (5-50)	NA	
	Rectal cuff	6 (3-10)	NA	
	Luminal site ileostomy	NA	2 (2-7)	
	Everted site ileostomy	NA	6 (5-10)	
Size of the most advanced lesion, mm		5 (3-15)	7 (3-11)	.99†
Histology of the most advanced lesion	Tubular	31 (28)	4 (12)	.69*
	Tubulovillous	26 (23)	4 (12)	
	Villous	5 (5)	0	
Grade of dysplasia of the most advanced lesion	Low-grade dysplasia	59 (53)	8 (24)	.72*
	High-grade dysplasia	2 (2)	0	
	Cancer	2 (2)	0	
Presence of advanced duodenal adenoma during follow-up		48 (46)	25 (76)	<.01*
Presence of Spigelman stage IV during follow-up		33 (31)	22 (67)	<.01*

Values are n (%) or median (interquartile range).
NA, not applicable.
**P* value was calculated using the χ^2 test statistic.
†*P* value was calculated using Mann-Whitney U test statistic.

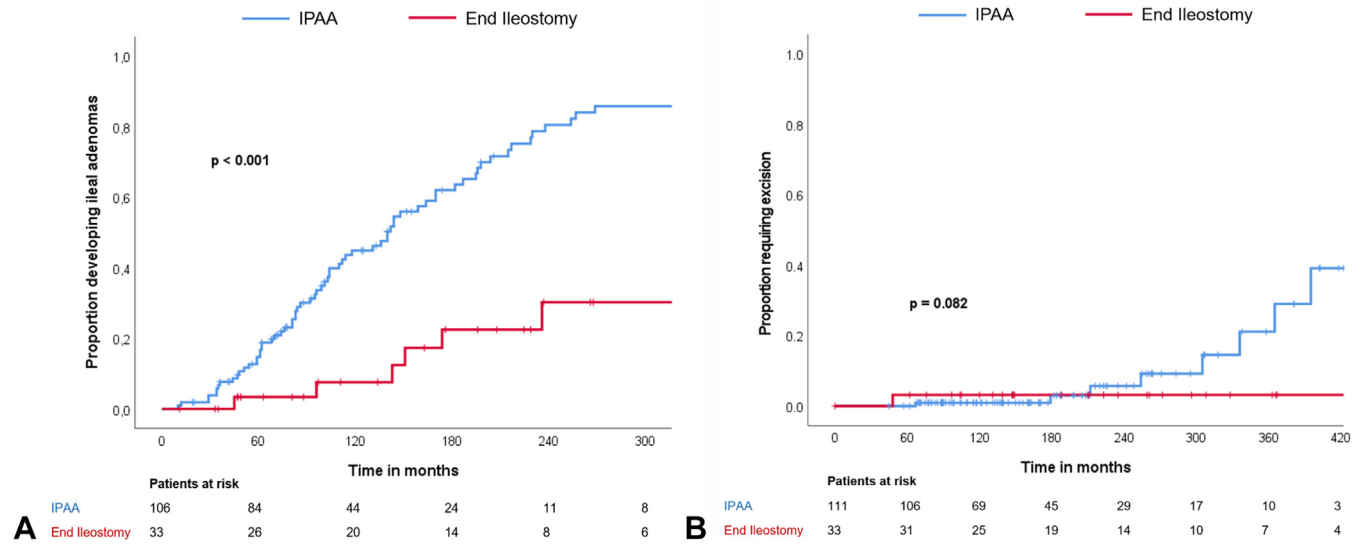


Figure 1. A, Proportion of patients developing ileal adenomas. **B,** Proportion of patients developing ileal adenomas and requiring excision of pouch or end ileostomy because of polyposis or cancer. *IPAA*, Ileal pouch-anal anastomosis.

TABLE 3. Cumulative number of ileal adenomas per time period after Ileal pouch-anal anastomosis or end ileostomy

Cumulative no. of adenomas		Time from surgery				
		5 y	10 y	15 y	20 y	>20 y
Ileal pouch-anal anastomosis (n = 111)	Available	103	82	54	34	22
	0	81 (79)	47 (57)	24 (44)	9 (26)	0
	1-10	14 (14)	18 (22)	7 (13)	7 (21)	3 (14)
	11-25	5 (5)	5 (6)	9 (17)	6 (18)	7 (32)
	26-50	2 (2)	7 (9)	12 (22)	8 (24)	6 (27)
	51-100	1 (1)	3 (4)	2 (4)	2 (6)	2 (9)
	>100	0	2 (2)	1 (2)	2 (6)	4 (18)
End ileostomy (n = 33)	Available	31	25	18	13	9
	0	29 (94)	22 (88)	16 (89)	11 (85)	4 (44)
	1-10	1 (3)	2 (8)	2 (11)	2 (15)	3 (33)
	11-25	1 (3)	1 (4)	0	0	2 (22)
	26-50	0	0	0	0	0
	51-100	0	0	0	0	0
	>100	0	0	0	0	0
P value		.41	.126	.02	.01	.01

Values are n (%). The cumulative number of ileal adenomas was determined based on the endoscopy performed the closest to 5, 10, 15, and 20 years after surgery. Not all patients were represented in each time period.
P value was calculated using the χ^2 test statistic.

the ileostomy because of extensive polyposis of the everted site of the ileostomy and 1 patient of the luminal site. After 10 years of follow-up, excision of the pouch was performed in 1 patient (1%) with IPAA versus 1 patient (4%) with end ileostomy. At 20 years these numbers were 3 (9%) versus 1 (7%) and at 30 years 6 (37%) versus 1 (12%) (Fig. 1) (log-rank test: $P = .08$).

The median time from surgery to pouch excision was 305 months (IQR, 212-365) and to end ileostomy excision 449 months (IQR, 249-462). In all patients with end ileostomy undergoing excision, a new end ileostomy was created. Of 9 patients who underwent a pouch excision, in 3 a new IPAA was created, 1 had a continent ileostomy (Kock pouch), and 5 patients had an end ileostomy.

Adjustment for potential confounders

The results of the multivariable Cox proportional hazards regression analysis are shown in Table 4. After adjusting for potential confounders in multivariable analysis, having an IPAA (hazard ratio, 5.22; 95% confidence interval, 2.10-12.99) was still significantly associated with ileal adenoma development. Age at IPAA/end ileostomy construction and use of chemopreventive agents before surgery were also associated with ileal adenoma development.

DISCUSSION

In this historical cohort study including 144 FAP patients with long-term follow-up, we observed that patients with IPAA more often developed adenomas in the ileum than patients with end ileostomy. In the IPAA group, the cumulative number of adenomas increased over time, whereas this trend was less evident in the end ileostomy group. However, this difference did not translate into a significant difference in the number of patients undergoing excision of the pouch or end ileostomy. Preferred locations of adenomas were the pouch body in the IPAA group and the everted part of the ileostomy in the end ileostomy group. When adjusting for potential confounders in multivariable analysis, having an IPAA was still associated with ileal adenoma development. In addition, older age at surgery and the use of chemopreventive agents before surgery were associated with ileal adenoma development.

The reported incidence of ileal adenomas after IPAA varies greatly in the literature, from 6.7% to 73.9%.[5] Our study showed a rather high overall incidence rate of ileal adenomas of 72% and higher incidence rates at 5 and 10 years after IPAA, which could be the result of improved quality of endoscopy over time (use of high-definition endoscopes, standardized bowel preparation scheme) and the dedicated endoscopy setting with endoscopists with specific expertise in FAP.[5,19] These high incidence rates at 5 and 10 years could also be because this study was conducted in a tertiary referral center with a cohort of patients with a relatively more severe phenotype, as some of them may have been referred to this center because of the severity of the polyposis. Adenoma incidence of 69% at 15 years was also comparable with those in previous reports.[5] In line with these findings, the overall 30% incidence of adenomas after end

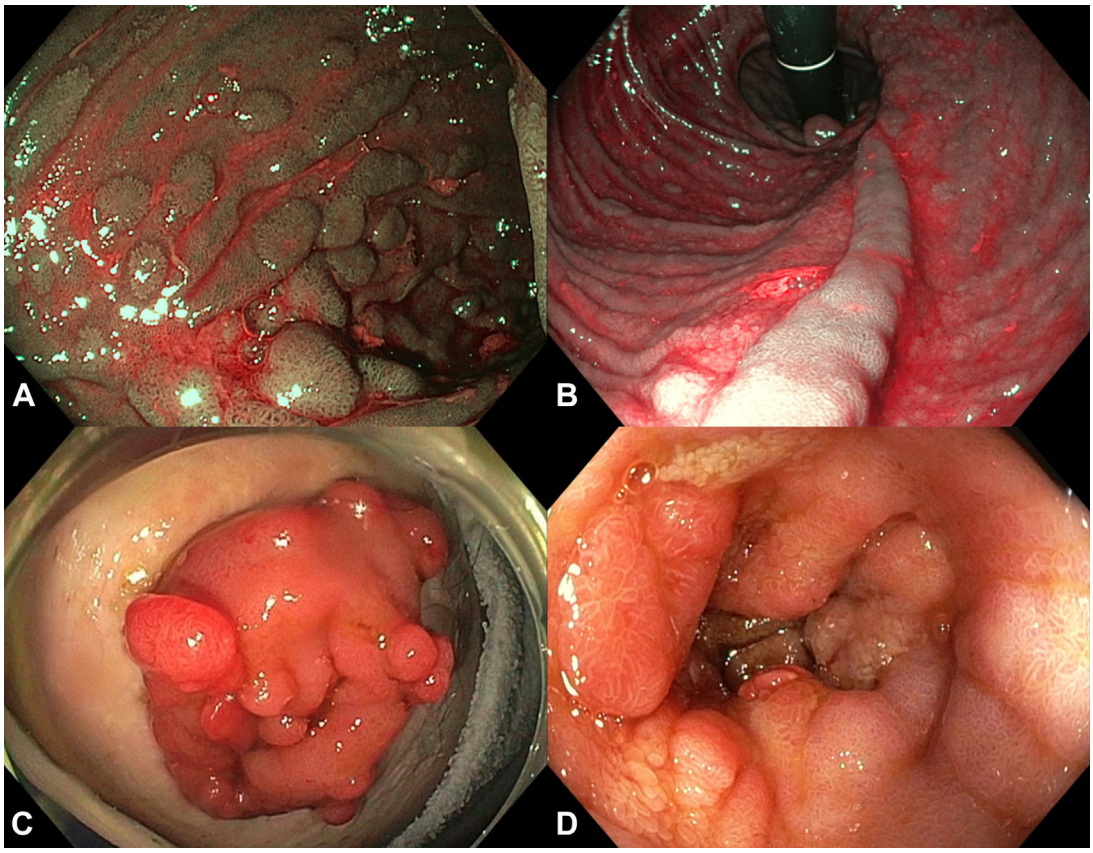


Figure 2. Endoscopic images of (**A**) adenomas in the ileal pouch body, (**B**) an elongated adenoma on top of the longitudinal surgical staple line, (**C**) adenomas at the everted site of the end ileostomy, and (**D**) adenomas at the luminal site of the end ileostomy.

TABLE 4. Multivariable Cox proportional hazards regression analysis adjusting for potential confounders

	No. of patients	Hazard ratio	95% Confidence interval	*P* value
Age at (procto)colectomy increasing by 1 y	144	.99	.95-1.02	.47
Age at ileal pouch-anal anastomosis/end ileostomy construction increasing by 1 y	144	1.04	1.01-1.07	.02
APC mutation between codon 1250 and 1464	109	.96	.32-2.89	.96
APC mutation site codon 1309	109	1.01	.25-4.10	.99
Chemopreventive treatment before surgery	116	2.97	1.47-6.01	<.01
Male gender	144	1.13	.67-1.90	.65
Smoking	144	1.33	.72-2.47	.36
Having an advanced duodenal adenoma	138	.77	.44-1.38	.39
Ileal pouch-anal anastomosis	144	5.22	2.10-12.99	<.01

APC, Adenomatous polyposis coli [gene].

ileostomy was also higher than the 20% rate reported in the literature more than 20 years ago.[8,9] Because the incidence of ileal adenoma was rather high in both groups, this will presumably not greatly influence the comparison between groups. An interesting finding is the higher proportion of patients with advanced duodenal adenomas and Spigelman stage IV in the end ileostomy group during follow-up. Unfortunately, we were not be able to evaluate whether this difference was caused by the intervention itself or by confounders such as a higher age in the end ileostomy group.

The location of preference (ie, the pouch body and the everted site of the ileostomy) suggests that luminal factors might contribute to the risk of ileal adenoma development.[8,13,20] Studies in mice have shown that the ileum partly displays a colon-like transformation after total

colectomy including villous atrophy and crypt hyperplasia, which might be the result of changes in luminal contents, fecal stasis, and/or chronic inflammation. This colon-like transformation might stimulate the development of adenomas in the ileal mucosa.[21-25] Moreover, the flora of the ileal pouch changes to a more colon-like flora after proctocolectomy, which might also influence adenoma development.[26,27] For example, glutathione S-transferases, which have a protective role in carcinogenesis, are significantly lower in activity in the ileal pouch compared with the afferent prepouch ileum.[28] The gut microbiome in general changes with aging, which might also influence adenoma development.[29] Despite the lack of reliable data on the functional outcomes of the ileal-anal pouch patients in our study, which could have informed us on the degree of fecal stasis, we believe that luminal factors, such as fecal stasis or a different microbiome, might play a role in ileal adenoma development.

We should bear in mind that this was a retrospective study, with limited options to reduce confounding, and, as such, we only could adjust for measured confounders. Therefore, we cannot make a definitive statement whether the observed differences can be attributed to the difference in intervention. Although the age at primary (procto)colectomy and *APC* mutation sites were comparable, we were not able to further demonstrate a comparable colorectal phenotype between the groups. Moreover, the mechanism behind the potential difference is not yet unraveled. As mentioned earlier, this study was performed in a tertiary referral setting, and therefore findings might not generalize well to the general FAP population. We aimed to compare patients who had undergone resection of both the entire colon and rectum in which an IPAA or end ileostomy was created. We did not include patients with an IRA. However, these patients might also develop adenomas in the terminal ileum proximal to the IRA, and this would be interesting to study. Nevertheless, to our knowledge, this is the first study comparing IPAA with end ileostomy in terms of ileal adenoma development. Moreover, the study cohort is relatively large with a long period of follow-up.

We believe this study contributes to optimal care for patients with FAP. One of the goals in the management of these patients is to limit the number of surgical interventions and thereby improve the quality of life of the patients. Most patients in this study cohort had an extensive history of abdominal surgery (Table 1). Subsequent surgical interventions are technically demanding and might negatively impact quality of life and/or functional outcomes.[30] Although the proportion of patients requiring pouch/end ileostomy excision was not significantly different between groups, creating a new ileo-anal pouch is a more complex operation than creation of a new ileostomy. In all patients undergoing excision of the end ileostomy, a new end ileostomy was created. However, 5 of 9 patients undergoing pouch excision ended up with an end ileostomy. In general, whether it is technically possible to create a new IPAA primarily depends on remaining small-bowel length and anal sphincter function. Moreover, a redo IPAA after pouch excision often results in impaired function.[30]

The median time to pouch excision in the current cohort was 25.4 years. IPAA was introduced in the 1980s and is still in some centers the procedure of choice for most FAP patients.[31,32] Therefore, we believe the number of pouch excisions might increase over the forthcoming years. This should encourage discussion on the choice of operation and reconstruction (IRA vs IPAA) and its timing in patients with FAP.

Whereas redo-IPAA after pouch excision is technically demanding and not always possible, secondary proctectomy with IPAA creation after initial IRA is nearly always possible. If patients have severe rectal polyposis for which IPAA is indicated, it might be preferable to postpone IPAA creation, if safe, to lower the risk of pouch excision at a later age because of severe pouch polyposis. However, with improving endoscopic techniques for multiple polypectomies, performing polypectomies on the most relevant lesions in the pouch (eg, polyps >5 mm as proposed in guidelines[7]) might lower the risk of pouch excision in the long term. More data on safety and long-term follow-up of such strategies are needed. Although current evidence for chemoprevention in FAP is limited, medication might contribute to slowing down polyp progression in patients with ileal polyposis. In our study, use of chemopreventive drugs before IPAA/end ileostomy creation was associated with ileal adenoma development after surgery. Chemopreventive drugs were mostly used for severe polyposis, which might also be associated with the risk of ileal adenomas after surgery. Although our data did not allow us to study this association, having a mutation associated with a more severe colorectal phenotype was not associated with ileal adenoma development in our study. This is in line with several other studies.[12,14,33]

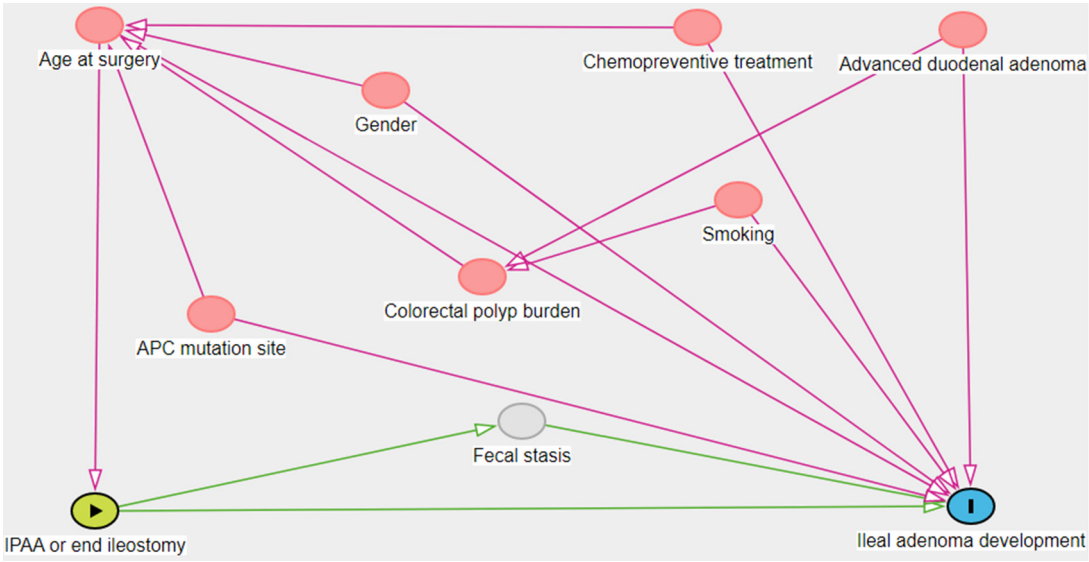
We believe the high incidence of ileal adenomas after IPAA with a considerable risk of pouch excision in the long term, together with an at-risk rectal cuff, demands close endoscopic surveillance with intervals between .5 and 2 years. We propose polypectomies to be performed for all ileal adenomas of $\geq$5 mm or adenomas with a suspicious aspect. For patients with end ileostomy, surveillance intervals may be extended to once every 3 to 5 years, because these patients seem to have a milder polyposis course. Because in those patients most adenomas develop on the everted site of the ileostomy, patients should be encouraged and trained to examine their ileostomy themselves regularly.

In conclusion, this study showed that patients with FAP who underwent proctocolectomy were more prone to develop ileal adenomas in the pouch than in the end ileostomy, and the cumulative number of adenomas in pouches were higher as well. IPAA is still the preferred option for most patients. However, all patients should be accurately informed about the risks of developing polyps and cancer in

the pouch or end ileostomy, and advantages and disadvantages should be balanced for decision-making on the type of surgery. We believe the results of this study call for a further evaluation of the pathogenesis of ileal adenoma development after colectomy. Improved understanding of the underlying processes may then improve risk classification, facilitate counseling on surgery, and, in due time, inform the development of stratified endoscopic surveillance strategies.

REFERENCES

1. Powell SM, Petersen GM, Krush AJ, et al. Molecular diagnosis of familial adenomatous polyposis. N Engl J Med 1993;329:1982-7.
2. Bussey HJR. Familial polyposis coli. Family studies, histopathology, differential diagnosis, and results of treatment. Baltimore: Johns Hopkins University Press; 1975.
3. Jagelman DG. Choice of operation in familial adenomatous polyposis. World J Surg 1991;15:47-9.
4. Campos FG. Surgical treatment of familial adenomatous polyposis: dilemmas and current recommendations. World J Gastroenterol 2014;20:16620-9.
5. Tajika M, Niwa Y, Bhatia V, et al. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. World J Gastroenterol 2013;19:6774-83.
6. Tajika M, Tanaka T, Ishihara M, et al. Long-term outcomes of metachronous neoplasms in the ileal pouch and rectum after surgical treatment in patients with familial adenomatous polyposis. Endosc Int Open 2019;7:E691-8.
7. van Leerdam ME, Roos VH, van Hooft JE, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2019;51:877-95.
8. Thompson-Fawcett MW, Marcus VA, Redston M, et al. Adenomatous polyps develop commonly in the ileal pouch of patients with familial adenomatous polyposis. Dis Colon Rectum 2001;44:347-53.
9. Iida M, Yao T, Ohsato K, et al. Diagnostic value of intraoperative fiberscopy for small-intestinal polyps in familial adenomatosis coli. Endoscopy 1980;12:161-5.
10. Hammad A, Tayyem R, Milewski PJ, et al. Primary adenocarcinoma in the ileostomy of a woman with familial adenomatous polyposis: a case report and literature review. J Med Case Rep 2011;5:556.
11. Parc Y, Piquard A, Dozois RR, et al. Long-term outcome of familial adenomatous polyposis patients after restorative coloproctectomy. Ann Surg 2004;239:378-82.
12. Groves CJ, Beveridge IG, Swain DJ, et al. Prevalence and morphology of pouch and ileal adenomas in familial adenomatous polyposis. Dis Colon Rectum 2005;48:816-23.
13. Pommaret E, Vienne A, Lefevre JH, et al. Prevalence and risk factors for adenomas in the ileal pouch and the afferent loop after restorative proctocolectomy for patients with familial adenomatous polyposis. Surg Endosc 2013;27:3816-22.
14. Tonelli F, Ficari F, Bargellini T, et al. Ileal pouch adenomas and carcinomas after restorative proctocolectomy for familial adenomatous polyposis. Dis Colon Rectum 2012;55:322-9.
15. Ganschow P, Trauth S, Hinz U, et al. Risk factors associated with pouch adenomas in patients with familial adenomatous polyposis. Dis Colon Rectum 2018;61:1096-101.
16. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
17. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2:783-5.
18. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-5.
19. Kaminski MF, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. United Eur Gastroenterol J 2017;5:309-34.
20. Wu JS, McGannon EA, Church JM. Incidence of neoplastic polyps in the ileal pouch of patients with familial adenomatous polyposis after restorative proctocolectomy. Dis Colon Rectum 1998;41:552-6; discussion 6-7.
21. Fukushima K, Haneda S, Takahashi K, et al. Molecular analysis of colonic transformation in the ileum after total colectomy in rats. Surgery 2006;140:93-9.
22. Church J. Ileoanal pouch neoplasia in familial adenomatous polyposis: an underestimated threat. Dis Colon Rectum 2005;48:1708-13.
23. de Silva HJ, Millard PR, Kettlewell M, et al. Mucosal characteristics of pelvic ileal pouches. Gut 1991;32:61-5.
24. Corfield AP, Warren BF, Bartolo DC, et al. Mucin changes in ileoanal pouches monitored by metabolic labelling and histochemistry. Br J Surg 1992;79:1209-12.
25. Shepherd NA, Jass JR, Duval I, et al. Restorative proctocolectomy with ileal reservoir: pathological and histochemical study of mucosal biopsy specimens. J Clin Pathol 1987;40:601-7.
26. Nasmyth DG, Godwin PG, Dixon MF, et al. Ileal ecology after pouch-anal anastomosis or ileostomy. A study of mucosal morphology, fecal bacteriology, fecal volatile fatty acids, and their interrelationship. Gastroenterology 1989;96:817-24.
27. Natori H, Utsunomiya J, Yamamura T, et al. Fecal and stomal bile acid composition after ileostomy or ileoanal anastomosis in patients with chronic ulcerative colitis and adenomatosis coli. Gastroenterology 1992;102(4 Pt 1):1278-88.
28. Friederich P, Berkhout M, Roelofs HM, et al. Decreased levels of mucosal detoxification enzymes in the pouch of patients with familial adenomatous polyposis. Br J Surg 2006;93:1108-14.
29. Bana B, Cabreiro F. The microbiome and aging. Annu Rev Genet 2019;53:239-61.
30. Mascarenhas C, Steele SR, Hull T. The ABC's of re-do ileoanal pouches: What every gastroenterologist should know. Curr Opin Gastroenterol 2019;35:321-9.
31. Kartheuser A, Stangherlin P, Brandt D, et al. Restorative proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis revisited. Fam Cancer 2006;5:241-60; discussion 61-2.
32. Vasen HF, van Duijvendijk P, Buskens E, et al. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: a Dutch-Scandinavian collaborative study including 659 patients. Gut 2001;49:231-5.
33. Moussata D, Nancey S, Lapalus MG, et al. Frequency and severity of ileal adenomas in familial adenomatous polyposis after colectomy. Endoscopy 2008;40:120-5.



Supplementary Figure 1. This directed acyclic graph describes the associations between type of surgery, ileal adenoma development, and other factors considered in the analysis. In *pink* are confounders, which are common causes of type of surgery and adenoma development. In *gray* are unobserved variables. *IPAA*, Ileal pouch-anal anastomosis.