Risk of cancer and reoperation after ileorectal anastomosis and ileal pouch-anal anastomosis in familial adenomatous polyposis

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Risk of Cancer and Reoperation After Ileorectal Anastomosis and Ileal Pouch-Anal Anastomosis in Familial Adenomatous Polyposis

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INTRODUCTION: **To prevent colorectal cancer, most patients with familial adenomatous polyposis (FAP) undergo (procto) colectomy with ileorectal anastomosis (IRA) or ileal pouch-anal anastomosis (IPAA). After surgery, these patients remain at risk of developing cancer in the remnant rectum or rectal cuff/pouch. We aimed to compare the long-term risk of cancer after IRA or IPAA in FAP.**

METHODS: **We performed an international multicenter historical cohort study of FAP patients undergoing IRA or IPAA from 1990 to 2023. The proportion of patients developing cancer after surgery was estimated using the Kaplan-Meier method.**

RESULTS: **(Procto)colectomy was performed in 685 patients (53.6% female); 366 (53.4%) had IRA, and 319 (46.6%) had IPAA. Median age at IRA and IPAA was 23 and 27 years, and the median follow-up was 12 and 15 years, respectively. Overall, 8 patients (2.2%) developed rectal and/or rectal cuff/pouch cancer after IRA and 0.9% after IPAA. The estimated 10- and 20-year cancer incidence after IRA vs IPAA was 1.6% vs 0.4% and 2.5% vs 0.9%, respectively (log-rank $P = 0.15$). Reoperations, mainly for extensive polyposis, were performed in 39 (10.7%) patients with an IRA and 24 (7.5%) patients after IPAA. The number of postoperative endoscopic surveillance endoscopies was higher in patients with an IRA compared with those with an IPAA ($P < 0.001$).**

DISCUSSION: **Over the past 3 decades, few patients were diagnosed with cancer in the rectum or rectal cuff/pouch after (procto)colectomy in FAP. This might be due to an improved selection of the type of (procto) colectomy and close endoscopic surveillance including prophylactic polypectomies.**

KEYWORDS: familial adenomatous polyposis; cancer; colectomy; reoperation

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D508; http://links.lww.com/AJG/D509

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INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited condition that is characterized by the formation of numerous colorectal polyps that would ultimately lead to colorectal cancer (CRC) if left untreated (1). Patients require regular endoscopic surveillance and timely prophylactic surgery. The timing of surgery is influenced by patient preferences and considerations such as the desire to defer surgery in those at higher risk of desmoid disease (2,3). In most patients, prophylactic surgery is performed before the age of 35 years (4,5).

The 2 main surgical options for colorectal polyposis in FAP are total colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal pouch-anal anastomosis (IPAA). The choice between these 2 types of operation is primarily based on the burden and location of the polyposis (6). Studies demonstrated the effectiveness of both IRA and IPAA in preventing CRC in patients with FAP (7,8). Nevertheless, patients undergoing these operations remain at risk of developing polyps and cancer in the rectum or pouch (9–12). The reported cumulative risk of rectal cancer after IRA varies from 0.5% to 13% (10–14), whereas cancer risks after IPAA range from 1.0% to 1.8% (10,15,16). After pouch surgery, cancers occur predominantly in the rectal cuff rather than the pouch body (17). Lifelong endoscopic surveillance is, therefore, required, with guidelines recommending endoscopic surveillance of the rectum or pouch with intervals ranging from 1 to 3 years (6,18,19).

It is important to note that some of the mentioned studies on IRA include data from the prepouch period. At this time, patients with severe rectal polyposis underwent IRA, resulting in a higher risk of postoperative cancer. The establishment of pouch surgery and improvements in endoscopic surveillance may have contributed to a decrease in cancer risk over recent decades.

Another potential disadvantage for patients undergoing IRA is the risk of needing a proctectomy at a later stage. This proportion has been estimated at 29.3%, with half of all patients undergoing proctectomy at the age of 60 years (20). A more recent cohort from 1990 onward reported reoperations in only 4% of IRA patients (14). For IPAA, the risk of reoperation was 8.1% (15). Despite these well-documented risks, the exact role of postoperative surveillance in mitigating both the cancer risk and risk of secondary surgery remains unclear in the literature.

Optimizing our future management strategies requires an evaluation of the outcomes of IRA and IPAA over the past 30 years (pouch era). We aimed to evaluate the long-term risk of cancer development in the rectum after IRA or in the pouch/rectal cuff after IPAA. We also assessed differences in endoscopic surveillance, interventions, and reoperations. Our hypothesis was that the risk of cancer after both IRA and IPAA would be low because of the establishment of IPAA surgery and improved endoscopic surveillance over the past decades.

METHODS

Study design and population

This multicenter historical cohort study was conducted at centers that are affiliated with the European FAP Consortium. Patients were enrolled from centers in Denmark, the Netherlands, the United Kingdom, Spain, and Italy. The study population consisted of patients diagnosed with FAP who underwent IRA or IPAA at participating institutions between 1990 and 2023. In addition, patients who underwent surgery at other centers and had subsequent endoscopic surveillance at 1 of the participating centers were also included. FAP diagnosis was confirmed genetically by the presence of a constitutional pathogenic variant in the *APC* gene or clinically based on the presence of more than 100 colorectal adenomas without another genetic etiology. To evaluate the current management and the differences in cancer occurrence, we excluded data from FAP patients within this consortium who underwent surgery before 1990. We chose this year as the cutoff year from when pouch surgery became widely established.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (21) and was approved by the Institutional Review Board at each participating institution. Informed consent was obtained from the patients at the participating centers when needed according to each Institutional Review Board before data collection.

Data collection

Data for this study were collected through the review of medical records at each participating institution. Data included patient's sex, age, presence and location of pathogenic germline *APC* variant, surgical history, presence of CRC at time of colectomy, endoscopic follow-up data, pathology reports, and diagnosis of postoperative cancer in the rectum or pouch. Patients with *APC* pathogenic variants within 1250–1450, the mutation cluster region, may present with a severe phenotype (22). In our study, *APC* pathogenic variants were categorized into 3 groups according to their position relative to the gene: 3′ to codon 1250, 1250–1450, and 5′ to codon 1450. For the postoperative endoscopic surveillance data, we included the total number of polypectomies irrespective of endoscopic resection technique. Patient records were reviewed up to the most recent endoscopy report, unless significant events occurred, such as the development of cancer, secondary proctectomy, pouch excision, or death.

The primary outcome of this study was the incidence of rectal and pouch cancers after either IRA or IPAA. Secondary outcomes were the incidence of reoperations (proctectomy or pouch excision) and frequency of endoscopic surveillance and interventions in the 2 groups.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and surgical outcomes. For categorical variables, the χ^2 statistic was used to determine differences in both surgical groups. For continuous variables, the Mann–Whitney *U* test was performed. The proportions of patients developing cancer after IRA and IPAA were estimated using the Kaplan-Meier method and the log-rank statistic to detect any differences between these groups. A P value < 0.05 is considered a significant difference. The statistical analyses were performed by IBM SPSS statistical software version 28 (SPSS, Armonk, NY) (23).

RESULTS

Cohort

A total of 685 patients with FAP were included in this study. Among these patients, 366 underwent IRA, and 319 underwent IPAA between 1990 and 2023. Patient characteristics and the geographical distribution of patients are summarized in Table 1.

At surgery, patients who underwent IRA were significantly younger compared with those who underwent IPAA (23 vs 27 years; $P < 0.001$). Nineteen percent of the patients in the IRA

Table 1. Demographics

	Ileorectal anastomosis (n = 366)	Ileal pouch-anal anastomosis (n = 319)	*P* value
Median age at time of (procto)colectomy in years (IQR)	23 (17–34)	27 (19–35)	0.021
Sex, female n (%)	207 (56.6%)	160 (50.2%)	0.107
Geographical distribution of patients n (%)			
Denmark	47 (12.8%)	28 (8.8%)	0.089
Italy	0	6 (1.9%)	0.010
Netherlands	47 (12.8%)	102 (32.0%)	<0.001
Spain	46 (12.6%)	40 (12.5%)	1
United Kingdom	226 (61.7%)	143 (44.8%)	<0.001
APC pathogenic variant present/reported	345 (95.3%)	290 (90.9%)	0.092
3′ to codon 1250	242 (83.4%)	165 (66.5%)	<0.001
Between codon 1250–1450	23 (7.9%)	52 (21%)	<0.001
5′ to codon 1450	25 (8.6%)	31 (12.5%)	0.158
CRC present at time of (procto)colectomy, N (%)	20 (5.5%)	42 (13.2%)	<0.001
Median follow-up time (IQR)	12 (6–19)	15 (8–21)	0.003

group and 39% of the patients in the IPAA group were diagnosed with FAP after they presented with symptoms/CRC (probands) ($P < 0.001$). Median follow-up time was 12 years for the IRA group and 15 years for the IPAA group. Genetic information was available for 78.5% of the patients. Pathogenic variants between codon 1250 and 1450 were significantly more common in the IPAA group ($P < 0.001$). Furthermore, 5.5% had CRC at the time of colectomy in the IRA group compared with 13.2% in the IPAA group ($P < 0.001$). In patients receiving a pouch, 38.1% of cancers (16 patients) were located in the rectum.

Cancer incidence after (procto)colectomy

Cancer occurred in 8 patients (2.2%) in the IRA group and 3 patients (0.9%) in the IPAA group.

The median time from surgery to diagnosis of rectal cancer in patients after IRA was 5 years (range 1–25 years). The median number of endoscopic surveillance procedures per year was 1.3 (interquartile range [IQR]: 0.3–2.6) with 1 patient being non-compliant and undergoing only 1 single surveillance endoscopy over a 21-year period. The majority of cancers were stage I (n = 6), 1 stage II, and 1 stage IV. Genetic information was available for 7 patients with rectal cancer after IRA. Among these, 4 patients had a constitutional pathogenic variant on the 5′ of codon 1250, 1 had a pathogenic variant between codon 1250–1450, and 2 had a pathogenic variant on the 3′ of codon 1450. One patient with stage IV cancer after IRA died, whereas the other patients were diagnosed with cancer after IRA underwent curative surgery and survived.

Two patients in the IPAA group were diagnosed with cancer in the rectal cuff and 1 patient with cancer in the pouch body. The time between surgery and cancer diagnosis in the pouch body was 29 years, whereas in the rectal cuff, this was 5 and 12 years, respectively. The median number of endoscopic surveillance procedures per year was 0.6 (IQR: 0.5–1). CRC stages were stage I in 1 patient and stage II in 2 patients. Genetic status was only available for 1 patient with rectal cuff cancer, having a pathogenic variant between codon 1250–1450. All patients with cancer after IPAA underwent surgery and survived.

Figure 1 displays the Kaplan-Meier curves comparing the cancer-free survival in the IRA and IPAA groups. The proportion of patients in the IRA group developing cancer in 10 years was 1.6% vs 2.5% at 20 years. Correspondingly, in the IPAA group, the proportion of patients developing cancer was 0.4% at 10 years and 0.9% at 20 years, respectively. There was no statistically significant difference between the 2 groups ($P = 0.15$). In Supplementary Figure 1 (http://links.lww.com/AJG/D508), the overall cancer-free survival after surgery is presented per country ($P = 0.93$).

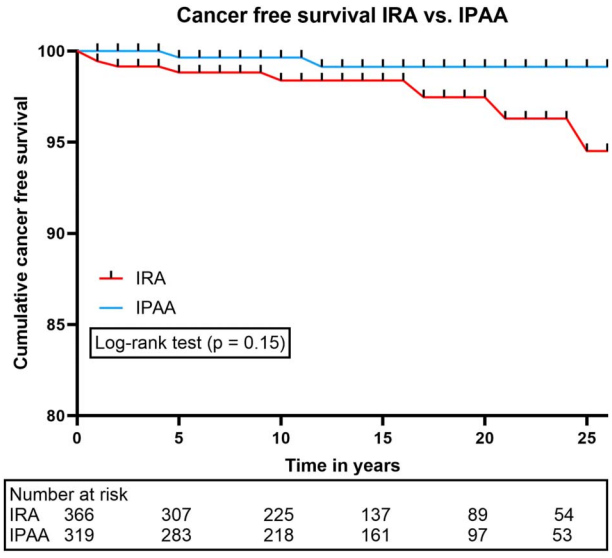

Figure 1. Kaplan-Meier curve for the cancer-free survival. IRA, ileorectal anastomosis; IPAA, ileal pouch-anal anastomosis.

Secondary surgery and end-ileostomy incidence

Figure 2 illustrates the cumulative proportions of reoperation after IRA and IPAA, with significantly more reoperations performed in the IRA group compared with the IPAA group (39 vs 24) ($P = 0.047$). Secondary proctectomy was performed in 39 (11%) patients with IRA. The most common indications were extensive polyposis not amenable to endoscopic management (n = 24) and rectal cancer (n = 8) (Table 2). Twenty-five patients with a median age of 29 years underwent proctectomy with IPAA procedure, whereas 14 patients with a median age of 42 years underwent proctectomy with permanent end-ileostomy.

Pouch excision was performed in 24 (8%) IPAA patients. The most common indication was extensive polyposis not amenable to endoscopic management (n = 11) and pouch dysfunction (n = 6), whereas 3 patients underwent pouch excision for cancer (Table 2). Nineteen patients with a median age of 41 years underwent pouch excision followed by end-ileostomy creation, whereas 5 patients with a median age of 36 years underwent pouch excision with a redo IPAA procedure. The cumulative incidence of end-ileostomy at 20 years of follow-up was 5.5% for IRA and 8.8% for IPAA ($P = 0.44$) (Figure 3). Supplementary Figure 2 (http://links.lww.com/AJG/D509) shows the overall proportion of reoperations per country ($P = 0.87$).

Postoperative endoscopic surveillance

Endoscopic follow-up data were available for 600 patients (88%), as shown in Table 3. Among these patients, the median number of postoperative lower surveillance endoscopies was 10 (IQR: 5–18) for those with IRA and 8 (IQR: 4–13) for those with IPAA ($P < 0.001$). The median number of postoperative lower surveillance endoscopies per year was 1 (IQR: 0.7–1.4) in the IRA group and 0.7 (IQR: 0.4–0.8) in the IPAA group ($P < 0.001$). The median number of polypectomies per year performed was 2.6 (IQR: 0.5–7.7) in patients with IRA and 0.1 (IQR: 0–0.7) in patients with IPAA ($P < 0.001$). The median number of polypectomies per postoperative lower surveillance endoscopy was 2.9 (IQR: 0.5–7.4) in the IRA group compared with 0.3 (IQR: 0–1.1) in the IPAA group ($P < 0.001$).

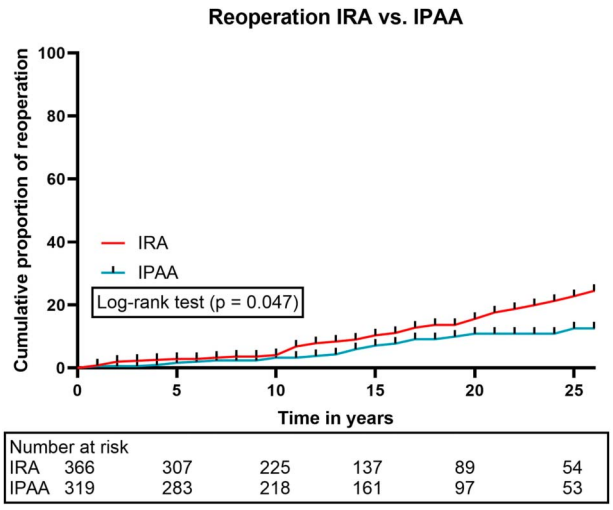

Figure 2. Kaplan-Meier curve for the reoperations. IRA, ileorectal anastomosis; IPAA, ileal pouch-anal anastomosis.

DISCUSSION

In an era where IRA or IPAA are both established surgical procedures for FAP patients, we aimed to study the cancer incidence in both the rectal remnant and pouch after initial surgery as well as the risk of secondary surgery in a large international multicenter cohort. The cumulative cancer incidence was low after both procedures. Reoperations and postoperative endoscopic surveillance were more frequently performed in patients with an IRA compared with those with an IPAA.

The low incidence of cancer after IPAA aligns with previous studies reporting proportions ranging from 1.0% to 1.8% (15,16). The rectal cancer incidence in the IRA group was relatively low compared with most studies that described incidences from 0.5% to 13% (10,11,13,14,20). Most studies with higher cancer incidences included patients who were operated in the prepouch era (10,11,13,20). In line with this, a low incidence of rectal cancer (0.5%) was also reported in the study of Anele et al, which included patients who underwent surgery from 1990 onward (14).

Among patients who underwent IPAA, 3 developed cancer: 2 at the rectal cuff and 1 in the pouch body. In a systematic review analyzing 92 pouch cancers, 75% were located in the rectal cuff and 25% in the pouch body (17). The time from surgery to cancer development in the pouch body was longer compared with cancer in the rectal cuff (29 vs 5 and 12 years). For patients with IRA, the median time until the development of rectal cancer in our study was 5 years. In comparison, another study reported a median time of 13 years (24). These findings suggest that the development of cancer in the pouch body mucosa may occur later than the development of cancer in the rectum or rectal cuff, although this is based on a single case of pouch body cancer. Because of these time differences in cancer development, there might be an impact on postsurgical endoscopic surveillance, suggesting that IRA patients should undergo more extensive surveillance in the initial decade after surgery compared with patients after IPAA particularly those without a remnant rectal cuff. During pouch surveillance in patients with a rectal cuff, the cuff should be assessed with high precision as (pre)cancerous lesions located here seem to progress to cancer sooner than those located in the pouch mucosa.

In this study, IRA patients underwent significantly more surveillance endoscopies and polypectomies compared with IPAA patients. During median follow-up times of 12 years for the IRA and 15 years for the IPAA group, we observed a median of 32 polypectomies per patient after IRA, whereas patients with an IPAA had a median of 2 polypectomies per patient. These findings are consistent with a recent study reporting a median number of 35 polypectomies per patient with an IRA and a median follow-up time of 8.6 years (14). Other studies have described the presence of adenomas in the pouch in 15%–19% of the patients 5 years after the operation, 48%–57% after 10 years, and 74%–85% after 20 years of follow-up (15,25,26). For rectal cuff adenomas, Patel et al reported cumulative incidences of 26%, 40%, and 63% at 5, 10, and 20 years, respectively (26).

The choice between either IRA or IPAA as a first prophylactic operation in FAP patients is mainly based on the severity of rectal polyposis. Although our analysis did not show significant differences in the proportions of IRA and IPAA surgeries among female patients of different age groups, fertility concerns may still influence surgical decisions in some younger women. Current guidelines recommend IPAA in patients with more than 20 rectal

Table 2. Reoperation after (procto)colectomy

	IRA (n = 39, 10.7%)	IPAA (n = 24, 7.5%)	*P* value
Indication for reoperation[a] n (%)			
Cancer	8 (20.5%)	3 (12.5%)	0.381
Severe polyposis not amenable to endoscopic management	24 (61.5%)	11 (45.8%)	0.180
High-grade dysplasia	4 (10.3%)	—	—
Functional issues	0	6 (25%)	—
Fistula	—	3 (12.5%)	—
Combination of Lynch and FAP	—	1 (4.2%)	—
Type of reoperation n (%)			
Resection pouch or rectum with IPAA	25 (64.1%)	5 (20.8%)	0.001
Resection pouch or rectum with end-ileostomy	14 (35.9%)	19 (79.2%)	0.001

FAP, familial adenomatous polyposis; IRA, ileorectal anastomosis; IPAA, ileal pouch-anal anastomosis.
[a]Three patients with unknown indications.

adenomas. Advances in endoscopic techniques, such as cold snare polypectomy, may have led to more rectal-sparing surgery. In the study by Anele et al, patients with more than 20 (range 0–50) rectal adenomas underwent IRA and resulted in an overall cancer incidence of 0.5% (14). Future studies should evaluate whether it is a safe strategy to perform IRA in patients with more than 20 rectal adenomas. A novel strategic approach could be to attempt rectal clearance by extensive cold snare polypectomies in patients typically indicated for IPAA and avoid initial proctectomy. If a secondary proctectomy becomes necessary at a later stage, patients can still undergo IPAA in most cases, and an end-ileostomy thus be avoided. Rectum-preserving surgery is advantageous over pouch creation because of its favorable functional outcomes in terms of stool frequency and nocturnal defecation (27). In addition, studies indicate a significantly reduced risk of desmoid tumor development in FAP patients undergoing IRA compared with IPAA (2,3). The observed low and comparable proportions of cancer diagnoses in patients with both

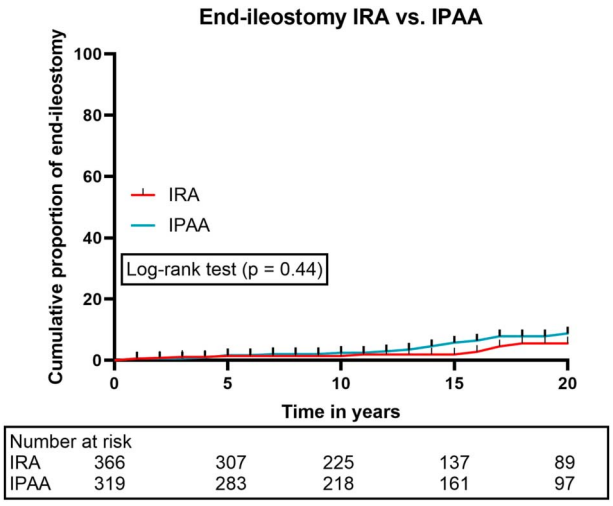

Figure 3. Kaplan-Meier curve for the end ileostomies. IRA, ileorectal anastomosis; IPAA, ileal pouch-anal anastomosis.

IRA and IPAA suggest that initial rectal preserving treatment in FAP is an attractive option. It is crucial for patients who undergo IRA and IPAA to commit to endoscopic surveillance at an expert center. The initial surgical decision-making process should also be guided by such experienced centers. In the present series, 7.5% pouch excisions were observed, with the majority resulting in an end-ileostomy.

The establishment of pouch surgery and the improvement in endoscopic surveillance may have contributed to lower cancer incidences in this particular cohort. Current guidelines recommend endoscopic surveillance for patients with an IRA and IPAA without specifying the interval, typically suggesting surveillance everyone to 3 years. Optimal surveillance strategies for patients with both IRA and IPAA should be developed. Our series shows different numbers of interventions and surveillance endoscopies between the 2 groups, and it is important to perform high-quality endoscopies on dedicated endoscopy programs in expert centers. The European FAP consortium recently published a new personalized endoscopic surveillance and intervention protocol to determine the most effective strategy for FAP patients (28). Adhering to endoscopic surveillance is essential in both surgical procedures, especially considering the higher risk of cancer with noncompliance in IRA patients. Polypectomy should be performed for clinically relevant adenomas measuring greater than 5 mm. This approach avoids unnecessary endoscopic surveillance, thereby reducing the burden on patients.

This international multicenter study provides valuable insights into the current management (i.e. pouch era) and cumulative cancer risk rates in a large cohort of FAP patients. We would also like to acknowledge the limitations inherent to its retrospective design, which may have introduced a bias. The data collection across different European centers may have resulted in variability in reporting. The indication for polyp removal may have varied among endoscopists in the respective participating centers in the past. Decisions about initial surgery and even surveillance were not always made in expert centers. For example, some patients were referred to our centers after IRA or IPAA. Despite these limitations, the large and diverse data set from several European centers contributes to the reliability of our findings.

Table 3. Endoscopic follow-up data

	Ileorectal anastomosis (n = 366)	Ileal pouch-anal anastomosis (n = 319)	*P* value
Endoscopic follow-up, n (%)	335 (91.5%)	265 (83.1%)	0.008
Median no. lower surveillance endoscopies (IQR)	10 (5–18)	8 (4–13)	<0.001
Median no. lower surveillance endoscopies per year (IQR)	1 (0.7–1.4)	0.7 (0.4–0.8)	<0.001
Median no. polypectomies (IQR)	24 (4–98.3)	2 (0–8)	<0.001
Median no. polypectomies per surveillance endoscopy (IQR)	2.9 (0.5–7.4)	0.3 (0–1.1)	<0.001
Median no. polypectomies per year (IQR)	2.6(0.5–7.7)	0.1 (0–0.7)	<0.001

In conclusion, the risk of patients with FAP developing cancer after IRA and IPAA is low and comparable between operations. We hypothesize that the use of high-definition endoscopy equipment enhanced surveillance practices including polypectomies, and improved patient selection for surgical procedures played key roles in treatment optimization, thereby contributing to the observed low rates of cancer in patients observed in patients with both IRA and IPAA. The focus should be on minimizing cancer and reoperation risk in FAP patients with IRA or IPAA through personalized and effective endoscopic surveillance, while avoiding both overtreatment and undertreatment.

CONFLICTS OF INTEREST

Guarantor of the article: Evelien Dekker, MD, PhD.

Specific author contributions: H.B., A.A., M.P., B.B., M.v.L., A.L., F.B., P.B., L.R., R.J., R.L., J.K., A.L., and E.D. were involved in the concept and design of the study. H.B., A.A., T.M. C.C., M.D., and J.K. were involved in data collection. H.B., A.A., and P.B. were involved in data analyses. All authors interpreted the data. All authors revised the manuscript and gave final approval.

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Study Highlights

WHAT IS KNOWN

- ✓ After ileorectal anastomosis (IRA) and ileal pouch-anal anastomosis (IPAA), familial adenomatous polyposis patients remain at risk of adenomas and cancer.
- ✓ Reported postoperative cancer incidences vary and range from 0.5% to 13% after IRA and 1.0%–1.8% after IPAA.

WHAT IS NEW HERE

- ✓ Since 1990, when pouch surgery became well established, low cancer incidences of 2.5% for IRA and 0.9% for IPAA have been observed over a 20-year follow-up period.
- ✓ IRA patients more often underwent surveillance endoscopies, polypectomies, and reoperations than patients with IPAA.

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