Long-term outcomes of metachronous neoplasms in the ileal pouch and rectum after surgical treatment in patients with familial adenomatous polyposis

Authors
Masahiro Tajika¹, Tsutomu Tanaka¹, Makoto Ishihara¹, Yutaka Hirayama¹, Sachiyo Oonishi¹, Nobumasa Mizuno², Takamichi Kuwahara², Nozomi Okuno², Shinpei Matsumoto², Taihei Ooshiro³, Takashi Kinoshita³, Koji Komori³, Vikram Bhatia⁴, Kazuo Haraj, Yasushi Yatabe⁵, Yasumasa Niwa¹

Introduction
Familial adenomatous polyposis (FAP) is an inherited, autosomal-dominant disease caused by a germline mutation of the adenomatous polyposis coli gene (APC) [1]. The phenotype is characterized by development of hundreds of colorectal adenomas, leading to a 100% life-time risk of colorectal cancer [2]. For this reason, a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) [3–6] is recommended for patients with FAP to prevent development of colorectal cancer.
However, because patients with FAP are generally young and often asymptomatic at the time of surgery, proctocolectomy is not easy to accept from functional and social perspectives.

Another widely accepted surgical procedure is colectomy with ileorectal anastomosis (IRA), performed in patients with a low risk of rectal cancer, especially in female patients who wish to have children. The major advantage of IRA is preservation of rectal innervation and subsequent better quality of life. However, continuing endoscopic surveillance for adenomas in the rectum is necessary, and a 13% to 25% cumulative risk of rectal cancer is reported after 15 to 25 years despite surveillance [7–9]. On the other hand, IPAA was theorized to eliminate risk of colorectal cancer and adenomas and, perhaps, need for further lower gastrointestinal surveillance. However, in 1982, Beart et al. [10] first described a FAP patient with a Kock pouch continent ileostomy, in whom a large sessile tubulovillous adenoma and multiple smaller adenomatous polyps developed. Since then, there have been around 30 reports of ileal pouch adenomas developing in these patients [4, 9–22], and the necessity for endoscopic surveillance for patients with IPAA is becoming recognized. Furthermore, there are several reports of cancers arising from the ileal pouch mucosa, as opposed to the anastomotic site, in patients with FAP [15–17, 19, 20]. It is clear that adenomas or carcinomas develop not only in the residual rectal mucosa after IRA, but also in the ileal pouch mucosa after IPAA. However, long-term outcomes of metachronous adenomas and carcinomas in the ileal pouch after surgical treatment in patients with FAP are still unclear. In addition, there is little information about when endoscopic surveillance for the ileal pouch should start, and how much of the ileal mucosa should be examined, only the ileal pouch or also the distal ileum?

The aim of this study was to determine the prevalence and nature of adenomas and carcinomas developing in ileal pouch mucosa, rectum, and distal ileal mucosa of the afferent limb in patients with FAP after surgery.

Patients and methods

Endoscopic and medical records of all patients with FAP treated in Aichi Cancer Center Hospital (ACCH), Nagoya, Japan, between January 1965 and December 2017 were reviewed. FAP was defined by presence of more than 100 colorectal adenomas (all patients) and/or a family history of FAP. Patients who had at least one endoscopic examination during follow-up were eligible for this study. In general, it was recommended that IRA patients have endoscopic examinations every 6 months, and that Kock’s pouch and IPAA patients have annual examinations after surgery. The IPAA patients underwent anal mucosectomy leaving a short rectal muscular cuff above the dentate line and a trans-anal hand-sewn ileoanal anastomosis. Pouch construction with two ileal limbs, 15 cm in length (J-pouch), was used. In this study, patients who had undergone pouch construction, either Kock or IPAA, were defined as pouch patients. Patient demographic data, surgical data, details of pathological specimens, and details of upper gastrointestinal endoscopy were obtained from the medical records. The study was approved by the ethics committee of ACCH, and all patients provided their informed consent for collection and subsequent use of data for research purposes. The study was carried out in accordance with the Helsinki Declaration.

The interval between surgery and adenoma appearance was defined as the time from surgery to the first report showing histologically confirmed adenomas in the ileal mucosa. Number, size, and histology of adenomas occurring in the ileal mucosa were determined based on the first report in which an adenoma had been histologically confirmed or the last report before treatment. For each patient, the most advanced histologic diagnosis was taken as valid. The endoscopic examination protocol was as follows. All patients were administered 1 L of polyethylene glycol-electrolyte solution on the morning of the examination. Scopolamine butylbromide (10 mg) or glucagon (0.5 mg) was administered intravenously in patients without contraindications to reduce bowel movements. A flexible endoscope (GF H260, GF H260Z, GF H290Z; Olympus Optical Co. Ltd., Tokyo, Japan) was used for the examination. In addition to a thorough examination of the pouch in Kock or IPAA patients and rectum in IRA patients, the distal 25 to 30 cm of the anastomotic site, in patients with FAP [15–17, 19, 20]. It is clear that adenomas or carcinomas develop not only in the residual rectal mucosa after IRA, but also in the ileal pouch mucosa after IPAA. However, long-term outcomes of metachronous adenomas and carcinomas in the ileal pouch after surgical treatment in patients with FAP are still unclear. In addition, there is little information about when endoscopic surveillance for the ileal pouch should start, and how much of the ileal mucosa should be examined, only the ileal pouch or also the distal ileum?

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Results

Eighty-four patients with FAP were treated in our hospital between January 1965 and December 2016; of them, 47 patients from 36 families (27 females; median age: 52.0 years; age range: 24–80 years) were eligible for this study. Fourteen patients had undergone Kock and IRA up to May 1987. After March 1988, 32 patients had undergone IPAA, and one patient with advanced cancer in the lower rectum had undergone Kock. ▶ Table 1 lists characteristics of the pouch patients (Kock and IPAA) and IRA patients, as well as details of endoscopic surveil-
There were no significant differences in age at the time of surgery, sex, median polyp count at surgery, and coexistence of gastric polyps, papillary adenomas, or extra-papillary adenomas between pouch patients and IRA patients.

Median follow-up of all patients was 21.0 years (range: 1–38.8 years). Although median duration to first endoscopy after surgery and median duration of endoscopic surveillance after first endoscopy were significantly longer in the pouch patients than in the IRA patients ($P < 0.001$ and $P = 0.0385$, respectively), there was no significant difference in median time of endoscopic surveillance after first endoscopy.

Maximum size, number, shape, and histology of polyps found in each patient and the age of the pouch are shown in Table 2. In pouch patients, adenomas developed in 24 of 34 patients (70.6 %), ranging in number from one to more than 300. Adenoma size ranged from 2 to 40 mm. Two cases of adenocarcinoma and six cases of advanced adenoma developed in the pouch patients. These tumors developed in the ileal pouch mucosa itself, as opposed to the ileoanal anastomosis site. In IRA patients, from one to 20 adenomas were observed in all cases in the rectum, and their sizes varied from 2 to 10 mm.

Risk of rectal adenoma development after colectomy with IRA was 85 % and 100 % at 5- and 10-year follow-up, respectively. This was significantly higher than risk of adenomas in ileal pouch patients ($P < 0.001$). However, risk of adenoma development in the ileal pouch was also substantial, with 12 %, 33 %, 52 %, and 68 % of pouch patients (Kock’s pouch and IPAA) developing adenomas at 5, 10, 15, and 20 years of follow-up, respectively (Fig. 1).

Tiny adenomas of 1 to 3 mm were observed in the pre-pouch ileal mucosa in four of 24 patients (16.7 %). However, no patient had adenomas in the ileal mucosa above the IRA site. Prevalence of ileal adenoma was significantly higher in the ileal pouch mucosa than in the pre-pouch ileal mucosa ($P < 0.001$). Risk of adenoma development in the pre-pouch after surgery was 4.4 % and 36 % at 20- and 30-year follow-up, respectively, and it was significantly lower than risk of ileal pouch adenomas ($P < 0.001$) (Fig. 2).

There was a positive correlation between maximum size of ileal pouch adenomas and time since surgery in pouch patients ($r = 0.4671$, $P = 0.0214$). Linear regression analysis (Fig. 3) showed the positive relationship between maximum size of ileal pouch adenomas and time since surgery as: Adenoma size (mm) = 0.29 + 0.69 × time (y).

### Discussion

IPAs have been used for patients with FAP after proctocolectomy because they theoretically eliminate risk of colorectal cancer and adenomas and need for further lower gastrointestinal surveillance. However, despite a reduction in colorectal cancer and adenomas after the surgery, occurrence of adenomas in the constructed pouch brings new concerns about surveillance and management [23, 24]. In the current study, overall inci-

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**Table 1** Characteristics of pouch patients and IRA patients and details of endoscopic surveillance.

| Factor                                      | Pouch patients | IRA patients | $P$ value |
|---------------------------------------------|----------------|--------------|-----------|
| Median age at surgery, y (range)            | 34.6 (17 – 52) | 36.7 (19 – 67) | 0.2630    |
| Sex female, n (%)                           | 18 (52.9)      | 10 (71.4)    | 0.2480    |
| Median polyp count at surgery               |                |              |           |
| Total                                       | 648 (105 – 20000) | 570 (100 – 9436) | 0.1803    |
| Colon                                       | 1970 (77 – 17200) | 420 (80 – 9340) | 0.2523    |
| Rectum¹                                     | 200 (5 – 5282)  | 70 (1 – 1071) | 0.1686    |
| Gastric polyp, n (%)                         | 26 (76.5 %)    | 11 (84.6 %)  | 0.5417    |
| Papillary adenoma, n (%)                    | 16 (47.0 %)    | 5 (38.5 %)   | 0.5959    |
| Extrapapillary adenoma, n (%)               | 15 (44.1 %)    | 6 (46.2 %)   | 0.9000    |
| Median follow-up period, y (range)          | 21.6 (3.7 – 38.8) | 17.3 (1 – 37.8) | 0.7662    |
| Median duration to 1st endoscopy            |                |              |           |
| after surgery, months (range)               | 108.6 (12 – 305) | 8.4 (5 – 17) | $< 0.001$ |
| Median duration of endoscopic surveillance   |                |              |           |
| after 1st endoscopy, months (range)         | 12 (6 – 60)    | 6 (6 – 12)   | 0.0385    |
| Median time of endoscopic surveillance       |                |              |           |
| after 1st endoscopy, n (range)              | 9 (3 – 38)     | 11 (1 – 56)  | 0.2456    |

IRA, ileorectal anastomosis

¹ except for lower rectum in patients with IRA.
Incidence of ileal pouch adenomas was as high as 70.6% in pouch patients at median follow-up of 21.0 years (range: 1–38.8 years) after surgery. Cumulative risk of adenoma in the pouch was 12%, 33%, and 68% at 5-, 10-, and 20-year follow-up, respectively (Fig.1). Incidence of pouch adenomas increases steadily with pouch age. These findings are similar to previous studies. There are approximately 30 reports of development of pouch adenomas [4,9–22], including three studies with more than 100 FAP patients [15, 16, 18]. Overall incidence of ileal pouch adenomas was 15.8% to 48.3% at median follow-up of 6.8 to 15 years after surgery. Furthermore, risk of adenoma development in the ileal pouch increased with time: 7%, 35%, and 75% at 5-, 10-, and 15-year follow-up, respectively [4]. To the best of our knowledge, this is the first report of long-term follow-up of more than 20 years after surgery in patients with FAP. Several predictors that may favor development of pouch adenomas have been investigated, such as severity of duodenal polyposis [11,13,17], presence of advanced duodenal adenoma prior to surgery [18], high polyp counts (>1000) at colectomy [17], and types and locations of APC mutations [13,14,25]. However, because incidence of pouch adenomas increased steadily according to time after surgery, most, if not all, of these patients are destined to develop adenomas. Hence, investigating predictors for pouch adenoma development may be meaningless. The problem is not whether patients with IPAA develop pouch adenomas, but whether these adenomas harbor clinically relevant malignant potential.

In the current study, there were two cases of adenocarcinomas and six cases of advanced adenomas in pouch patients. To date, 22 cases of ileal pouch adenocarcinomas have been reported in the literature (Table3) [15–17,19,20]. Although several other cases of adenocarcinoma after restorative proctocolectomy seem to have arisen from residual rectal mucosa at the ileoanal anastomosis [26], these pouch cancers have clearly appeared in the ileal pouch, and not in the anal transit zone. Until now, malignant potential of pouch adenomas and lifetime risk of pouch cancer for patients with FAP have not been clear. Friederich et al. [15] reported a cumulative risk of pouch adenocarcinoma of 1% after 10 years in their cohort of 212 FAP patients. If ileal pouch adenomas progress to carcinoma following a similar pattern seen in the colon, factors that may determine risk of malignant transformation are number of polyps, large size, severity of dysplasia, and villous architecture. Among our series of 34 pouch patients, 6 (17.6%) had advanced adenomas or adenocarcinomas. In the current study, two cases of adenocarcinomas were large, more than 30 mm in size, and six cases of advanced adenomas were observed among the multiple adenomatous polyps. Groves et al. reported that of 60 patients with adenomas in ileal pouch, 11 (18%) had advanced histological features [13], and a substantial minority of patients with pouch adenomas developed multiple polyps, large sessile

| Table 2 Characteristics of polyps in pouch patients and IRA patients. |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                | Pouch patients (n=34) | IRA patients (n=14) |
|                                | ileal pouch mucosa (n=24) | Pre-pouch mucosa (n=4) | Rectal mucosa (n=14) | ileal mucosa (n=0) |
| Maximum size of polyp, n       |                          |                    |                  |                  |
| • 1–4 mm                        | 12                       | 4                 | 11              | 0               |
| • 5–9 mm                        | 6                        | 0                 | 2               | 0               |
| • ≥10 mm                       | 6                        | 0                 | 1               | 0               |
| Number of polyps                |                          |                    |                  |                  |
| • <50                           | 10                       | 4                 | 14              | 0               |
| • ≥50                          | 5                         | 4                   | 14              | 0               |
| Shape of polyps                 |                          |                    |                  |                  |
| • Sessile                       | 23                       | 4                  | 14              | 0               |
| • Semi-pedunculated             | 1                         | 4                   | 14              | 0               |
| Histology                       |                          |                    |                  |                  |
| • Low-grade dysplasia           | 21                       | 1                 | 14              | 0               |
| • High-grade dysplasia          | 1                         | 0                  | 0               | 0               |
| • Carcinoma                     | 2                         | 0                  | 0               | 0               |
| Advanced adenoma                | 6                         | 0                  | 0               | 0               |
| Time since operation, y         | 11.8 ± 6.1                | 23.1 ± 5.8         | 2.1 ± 2.3       |

Values are mean±SD
IRA, ileorectal anastomosis.
polyps, or adenomas with more advanced histological features. In the current study, there was a significant relationship between maximum size of ileal pouch adenomas and time since surgery (P = 0.0214). If pouch adenomas follow the classic adenoma-carcinoma sequence, pouch age becomes one of the risk factors for malignant transformation. Using linear regression analysis in the current study, growth time for the ileal pouch adenoma to reach 10 mm was 14.1 years. However, in the current series, one case of advanced adenoma developed 8 years after surgery. Tonelli et al. [17] reported that in some patients, development of neoplasia in the ileal pouch may not always follow the classic adenoma-carcinoma sequence, because ileal polyps were not present during endoscopic follow-up until development of pouch carcinoma. Furthermore, the mean interval between pouch construction and diagnosis of carcinoma can be very short compared to the colorectum. Table 3 summarizes the 22 cases of ileal pouch cancer. In some cases, cancer had developed as early as 3 years after pouch construction surgery. It is also remarkable that in several cases, endoscopic surveillance had been done within 1 year before the discovery of cancer. Thus, we must start annual endoscopic surveillance of the ileal pouch at least 3 years after surgery.

In contrast to adenomas in the ileal pouch, development of adenomas in the afferent ileal loop above the pouch (pre-pouch) may be rare. In this study, there were four ileal adenomas in the pre-pouch in 34 pouch patients (12%) at median follow-up of 21.6 years after surgery. Cumulative risk of adenoma development in the pre-pouch after surgery was 4.4% and 36% at 20- and 30-year follow-up, respectively, which was significantly lower compared to risk for ileal pouch adenomas (P < 0.001). In previous publications, development of pre-pouch adenomas was reported in 10 of 26 (4%) patients by Wu et al. [11], in two of 20 patients (10%) by Groves et al. [13], in one of 24 patients (4%) by Thompson-Fawcett et al. [12], and in eight of 118 patients (6.9%) by Pommaret et al. [18]. The difference in incidence of adenoma development between the ileal pouch and the pre-pouch may be due to differences in transit time of bowel contents. The mucosa of the ileal pouch may not only be subjected to the tumorigenic consequences of APC gene mutations [27], but luminal factors due to fecal stasis may also have an important effect. Fecal stasis, such as occurs in a reconstructed pouch, may promote neoplastic changes in the ileal mucosa. Several authors have implicated colonic metaplasia of the ileal mucosa as a precursor for development of ileal adenomas [28-30], and even carcinomas in surgically constructed pouches of patients with FAP [31-33]. Colonic metaplasia was frequently recognized even in earlier descriptions of changes ob-

![Fig. 1](image) Cumulative incidence of adenoma in IRA patients and Pouch patients

![Fig. 2](image) Cumulative incidence of adenoma in the pre-pouch.

![Fig. 3](image) Relationship between maximum size of ileal pouch adenomas and time since pouch surgery.
| Authors                  | Sex | Type of pouch | Staging of initial surgery | Age of pouch construction (y) | Shape of pouch cancer | Size of cancer (mm) | Staging of cancer | No. of pouch polyps | Time to cancer (y) | Outcome of patient | Interval since last endoscopy (y) |
|--------------------------|-----|---------------|-----------------------------|-------------------------------|-----------------------|---------------------|-------------------|-------------------|-------------------|------------------|-------------------------------|
| 1 Bassiuni and Billings | M   | IPAA          | No cancer                   | 28                            | Large polypoid        | N                   | T3, N+            | N                 | 3                 | N                | No follow-up                  |
| 2 Palkar et al.          | F   | IPAA          | No cancer                   | 39                            | Large polypoid        | 40 × 35             | T4N0              | Exist            | 4.7               | Alive            | 0.3                            |
| 3 Kim et al.             | N   | N             | N                            | N                             | N                     | N                   | N                 | N                 | N                 | N                | N                             |
| 4 Cherki et al.          | F   | IPAA          | TisN0M0                      | 35                            | N                     | N                   | T3N1M1            | N                 | 3.5               | Died             | 0.5                            |
| 5 Linehan et al.         | M   | IPAA          | Dukes A                      | 30                            | N                     | N                   | T3N0              | N                 | 9                 | Alive            | No follow-up                  |
| 6 Friederich et al.      | M   | IPAA          | No cancer                    | 21.3                          | N                     | N                   | Dukes C           | 0                 | 14                | N                | 4.4                            |
| 7 M                      | M   | IPAA          | No cancer                    | 26.7                          | N                     | N                   | Dukes B           | 0                 | 10                | N                | 2.1                            |
| 8 M                      | M   | IPAA          | No cancer                    | 16                            | N                     | N                   | Dukes B           | N                 | 16                | N                | No follow-up                  |
| 9 F                      | F   | IPAA          | No cancer                    | 29.6                          | N                     | N                   | Dukes B           | Exist            | 6                 | N                | 0.6                            |
| 10 Tajika et al.         | F   | IPAA          | TisN0M0                      | 46                            | Type 2                | 30 × 25             | T4N2M0            | <10               | 8.6               | Dead 3Y           | 0.75                           |
| 11 M                     | M   | Kock          | No cancer                    | 48                            | Type 1                | 40 × 35             | T3N0M0            | >10               | 20                | Dead by U        | No follow-up                  |
| 12 Ault et al.           | M   | IPAA          | Four cancer                  | 61                            | N                     | 20–30               | T2N1              | N                 | 11                | Dead by U        | 6                              |
| 13 F                     | F   | IPAA          | No cancer                    | 40                            | Type 1                | N                   | N                 | N                 | 13                | Meta             | no follow-up                  |
| 14 Lee et al.            | F   | IPAA          | T2N0                         | 56                            | Type 2                | 30 × 25             | T3N2              | 0                 | 7                 | Meta 2Y          | 4                              |
| 15 Banasiewicz et al.    | N   | IPAA          | N                            | N                             | N                     | N                   | N                 | N                 | N                 | N                | N                             |
| 16 N                     | N   | IPAA          | N                            | N                             | N                     | N                   | N                 | N                 | N                 | N                | N                             |
| 17 N                     | N   | IPAA          | N                            | N                             | N                     | N                   | N                 | N                 | N                 | N                | N                             |
| 18 N                     | N   | IPAA          | N                            | N                             | N                     | N                   | N                 | N                 | N                 | N                | N                             |
| 19 Tonelli et al.        | M   | IPAA          | No cancer                    | 26                            | Type 2                | >20                 | T3N0M0            | N                 | 3                 | Dead 6 mo        | 1                              |
| 20 F                     | F   | IPAA          | TisN0M0                      | 47                            | Il + Ic               | N                   | T2N0M0            | 0                 | 11                | Alive at 56 mo   | 0.5                            |
| 21 Makni et al.          | F   | IPAA          | No cancer                    | 26                            | N                     | 20                  | many              | 10                | 0.66              | Dead 1Y+         | 0.66                           |
| 22 Alwahbi               | M   | IPAA          | N                            | 34                            | Type 2                | N                   | T4N2M0            | N                 | 2                 | Lost to follow-up | 0.58                           |

FAP, familial adenomatous polyposis; IPAA, ileal pouch-anal anastomosis; Kock, Kock’s continent ileostomy; N, not reported; AV, anal verge; U, unrelated disease. Time to cancer, interval between cancer diagnosis and pouch construction.
served in ileal pouch mucosa. Some authors have considered colonic metaplasia as an adaptive response of the ileal pouch to its role as a neorectum [34,35]. At present, it does not seem possible to predict who is at risk for developing polyps in the pre-pouch. Pommaret et al. [18] reported that the only significant risk factor for pre-pouch adenoma was presence of pouch adenomas. The pre-pouch ileum has the same gene as the pouch ileum, and its destiny may be to develop adenomas. However, the cumulative incidence rate was delayed for one or two decades compared to that of the ileal pouch. Furthermore, no case of pre-pouch adenocarcinoma has been reported in the literature. Surveillance of the pre-pouch ileum may not be as important as that of the ileal pouch.

A drawback of this study is that older patients in the pouch group had not undergone endoscopic surveillance, because the necessity for endoscopic surveillance for patients with IPAA had not been recognized. Another one is that an APC gene mutation study was not performed because it was not permitted by the Japanese health insurance system. Thus, the cumulative incidence rate of adenomas may increase in pouch patients. On the other hand, the strength of this study is that high-definition endoscopes with magnification were used, allowing detection of tiny adenomas in the rectum, ileal pouch, and pre-pouch.

**Conclusion**

In conclusion, this study demonstrated a very high cumulative risk of developing adenomas in the ileal pouch, with a lower risk of pre-pouch adenomas. Although pouch adenocarcinomas may be rare, their development may be rapid compared to the colorectum, and thus intensive annual endoscopic surveillance may be appropriate.

**Competing interests**

None

**References**

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