



# Long-Term Outcomes After Colectomy in Patients With Familial Adenomatous Polyposis

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The aim of this study was to evaluate the long-term prognosis of patients who underwent colectomy for familial adenomatous polyposis. The clinical data of 29 familial adenomatous polyposis patients who underwent colectomy were retrospectively reviewed. Five patients died of causes that included colorectal cancer (CRC), desmoid tumor, cancer of the small intestine, and pancreatitis. The 30-year survival rate was 72%. Among the 15 patients who had CRC at primary surgery, the 5-year survival rate was 100% in stages 0, I, and II, and 75% in stage IIIA. Stage I desmoid tumor showed slow or no growth, whereas a stage IV tumor showed rapid growth and was fatal. Extracolonic malignancies were seen in the small intestine, stomach, duodenum, thyroid, kidney, breast, and ovary. Among 8 patients with ileorectal anastomosis, 4 had a second primary rectal cancer and 6 had a

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**salvage reoperation. None of the patients who underwent either stapled or handsewn ileal pouch–anal anastomosis had second primary rectal cancers. The stage of primary CRC at colectomy is the most important prognostic factor. But in addition to second primary CRC, the management of desmoid tumors and extracolonic malignancies is important for long-term survival regardless of the anastomotic technique used.**

*Key words:* Familial adenomatous polyposis – Long-term outcome – Desmoid tumor – Extracolonic malignancies – Surgical techniques

**F**amilial adenomatous polyposis (FAP) is an inherited autosomal dominant syndrome caused by germ line mutations of the adenomatous polyposis coli (APC) gene on chromosome 5.<sup>1</sup> The disease is characterized by the presence of more than 100 colorectal adenomatous polyps. Left untreated, these polyps progress to colorectal cancer (CRC), typically by age 40 years. Although several studies have shown some beneficial effects of chemoprevention on colorectal adenomas, prophylactic surgical treatment is still required.<sup>2–10</sup>

The 2 main surgical options for FAP are colectomy with an ileorectal anastomosis (IRA) and restorative proctocolectomy with an ileal pouch–anal anastomosis (IPAA).<sup>2–4</sup> IPAA eradicates virtually the entire colonic mucosa, thereby eliminating the risk of CRC. Furthermore, IPAA can be performed using 2 different techniques: a stapled IPAA with double-stapling technique (stapled), or a handsewn IPAA with mucosectomy (handsewn).<sup>5–10</sup> There is no consensus regarding the superiority of either technique.

Concerning long-term outcome after colectomy, it was reported that the appearance of a second primary CRC from remnant colonic mucosa affected long-term outcomes after colectomy.<sup>5</sup> However, desmoid tumors and other extracolonic diseases also cause death in many FAP patients.<sup>11</sup> The impact of specific lesions on long-term prognosis is unclear. The aim of this study was to evaluate long-term outcomes after colectomy in patients with FAP in our affiliated institutions.

## Patients and Methods

### *Patients*

We identified 29 patients (25 family lines) who underwent primary surgery of the colon for FAP between 1978 and 2010. They were operated on or followed up at the Department of Gastroenterological Surgery, Yokohama City University (Yokohama, Japan), or its affiliated institutions (YCOG study

group). Operative data and clinical course were retrospectively reviewed from patient charts. Clinical outcomes of CRC, desmoid tumors, and extracolonic malignancies were analyzed. The type of polyposis was defined according to the number of polyps in the colon at the time of resection, with >1000 defined as a dense polyposis type and <1000 defined as a sparse polyposis type. A standard oncologic analysis was performed on all patients, and the TNM classification of CRC was used for prognostic analysis. Desmoid tumors were analyzed using the Church staging system<sup>12</sup> (stage I: asymptomatic, maximum diameter <10 cm, and not growing; stage II: mildly symptomatic, maximum diameter <10 cm, and not growing; stage III: moderately symptomatic or bowel/ureteric obstruction, maximum diameter of 10–20 cm, and slowly growing; stage IV: severely symptomatic, maximum diameter >20 cm, and rapidly growing). After colectomy, all of the patients were regularly examined by colonoscopy and abdominal and pelvic CT scanning at least every 2 to 3 years.

### *Statistical analysis*

For statistical analysis, comparisons between different groups were made using nonparametric methods. Categorical variables were compared using the  $\chi^2$  or Fisher exact test. Continuous variables were expressed as median and range, and were compared using the Mann-Whitney *U* test. The survival rate was estimated with the Kaplan-Meier method. Factors with a  $P < 0.05$  were considered to be statistically significant. The IBM SPSS statistics version 20 software package (IBM, Tokyo, Japan) was used to perform all of the analyses.

## Results

### *Patient characteristics*

The patients' characteristics are shown in Table 1. The surgical indication was CRC treatment in 11

Table 1 Patients' characteristics (n = 29)

Characteristic	Value
Family lines	25
Sex, M:F	14:15
Age at diagnosis of FAP, y, median (range)	32 (11–56)
Age at primary surgery, y, median (range)	33 (11–63)
Type of polyposis	
Dense polyposis	2
Sparse polyposis	20
Unknown	7
Surgical indication	
CRC	11
Prophylactic	18
Surgical procedure	
IRA	8
IPAA (stapled)	13
IPAA (handsewn)	7
APR	1

APR, abdominoperineal resection.

cases and CRC prevention in 18 cases. Total colectomy with IRA was performed in 8 patients; total proctocolectomy with stapled IPAA in 13; total proctocolectomy with handsewn IPAA in 7; and total proctocolectomy with abdominoperineal resection in 1. The surgical specimens from 4 of the 18 patients who underwent prophylactic surgery tested positive for CRC. Finally, 15 patients [52%; median age at surgery, 40 years (range, 16–63 years)] had CRC at the time of primary surgery.

#### Cause of death

Five patients (17%) died during a median follow-up period of 11 years (range, 1–32 years). Two patients with CRC died of CRC recurrence 4 and 9 years after colectomy, respectively. One patient died of desmoid tumor causing small bowel obstruction 11 years after colectomy. One patient died of cancer of the small intestine 30 years after colectomy, and one died of other disease (multiple organ failure due to pancreatitis) 13 years after colectomy. The 5-, 10-, 20-, and 30-year overall survival rates were 94.7%, 88.4%, 72.0%, and 72.0%, respectively (Fig. 1).

#### Colorectal cancer

Fifteen patients had CRC. The median number of cancerous tumors was 2.6 (range, 1–7). A total of 8, 1, 1, 4, and 1 of the CRC patients had TNM stages 0, I, II, IIIA, and IIIB disease, respectively.

Seven patients (47% of the CRC patients) underwent adjuvant chemotherapy. Six patients received leucovorin calcium + fluorouracil, and 1 received

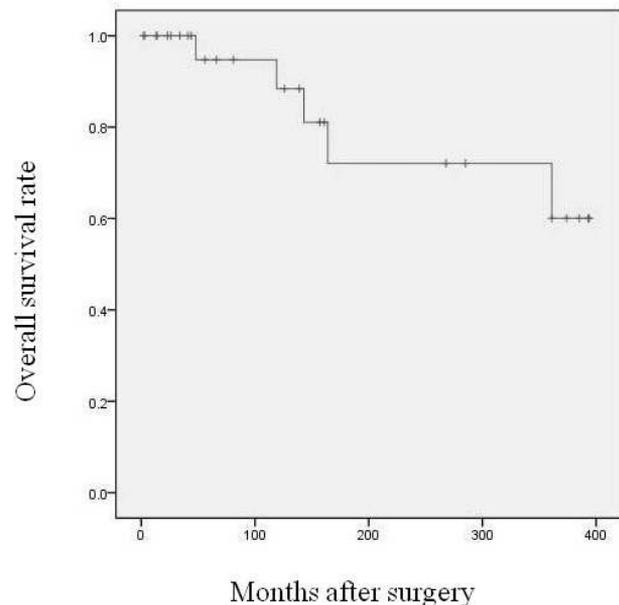


Fig. 1 The overall survival rate after colectomy. The 5-, 10-, 20-, and 30-year overall survival rates were 94.7%, 88.4%, 72.0%, and 72.0%, respectively.

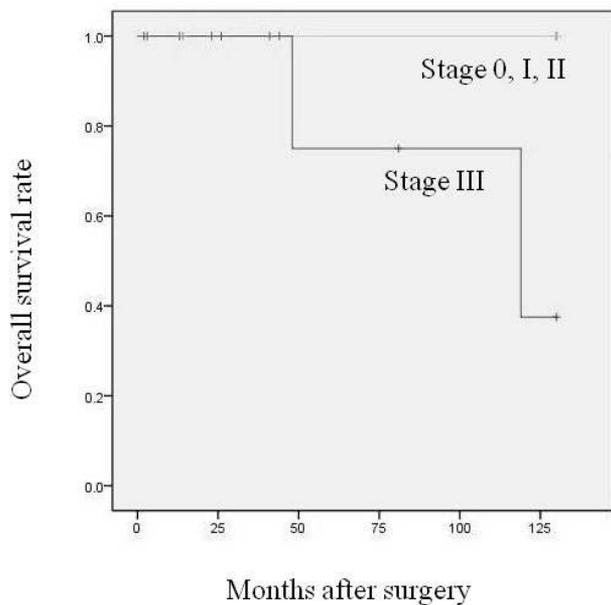
fluorouracil only. Three patients (2 had stage IIIA disease and 1 had stage IIIB disease) experienced CRC recurrence at the site of the para-aortic lymph nodes, liver, and lung. FOLFIRI and FOLFOX were administered, and hepatic arterial infusion, excision of the metastatic lymph nodes, or excision of the lung was performed. A total of 2 of the 3 patients ultimately died of multiple metastases. The overall 5-year survival rate was 100% in stage 0, I, and II patients, and 75% in stage III patients (Fig. 2).

#### Desmoid tumor

A total of 4, 0, 1, and 1 of the patients had desmoid tumors classified as stages I, II, III, and IV, respectively, according to the Church classification system. The 4 cases of stage I desmoid tumors were characterized by slow or no growth. On the contrary, the case of stage IV tumor showed rapid growth and no response to drug treatment, and ultimately became fatal (Table 2).

#### Extracolonic malignancies

Extracolonic malignancies were seen in 6 patients (7 lesions) at a median age of 52 years (range, 25–72 years), in locations such as the small intestine, stomach, duodenum, thyroid, kidney, breast, and ovary. Extracolonic malignancies were diagnosed



**Fig. 2** The survival rate according to the stage of colorectal cancer. The overall 5-year survival rate was 100% in stage 0, I, and II patients and 75% in stage III patients.

more than 20 years after colectomy in 4 of the 6 patients. There was no relation between the occurrence of CRC and the occurrence of extracolonic malignancies. A period of the treatment, prognosis, and survival time for each malignancy is shown in Table 3.

#### Surgical procedure

Table 4 shows the clinical course of each surgical procedure. A second primary rectal cancer occurred in 4 of the 8 patients (50%) at a median of 26 years (range, 3–32) after undergoing IRA. A total of 6 of the 8 IRA patients (75%) had a salvage reoperation because of the occurrence of rectal cancer (4 patients) or uncontrollable rectal polyps (2 patients) at a median of 20 years (range, 3–32 years) after IRA. An additional IRA patient who did not undergo reoperation required an endoscopic mucosal resection for early rectal cancer. No second primary rectal cancers occurred in the patients who underwent either stapled or handsewn IPAA. None of the patients died of second primary cancers (Table 4).

#### Discussion

The risk of CRC exists in every FAP patient. The aim of prophylactic surgery is to reduce or eliminate the potential for developing CRC. Such a procedure

**Table 2** Desmoid tumor ( $n = 6$ )

Stage	Cases, n	Clinical course	Prognosis	Survival time, y (range)
I	4	No enlargement (no medication: 3; NSAIDs: 1)	Alive	9 (1–30)
II	0			
III	1	Surgery, chemotherapy	Alive	6
IV	1	Chemotherapy	Died	11

NSAID, nonsteroidal anti-inflammatory drug.

must be acceptable to young asymptomatic patients with FAP, delivering a good functional outcome and quality of life with low morbidity and favorable long-term outcomes.<sup>2–10</sup> IRA and IPAA are the main surgical options for the treatment of FAP. IRA is selected for patients with a mild phenotypic expression of the disease in the rectum.<sup>2</sup> This has been considered to be a relatively easy and safe procedure that provides good functional outcome with low morbidity.<sup>2,3</sup> However, the major disadvantage of IRA has been the cumulative risk of cancer evolving in the remnant rectum.<sup>3</sup> In our study, 6 of the 8 IRA patients subsequently had a salvage operation, such as re-IPAA, for rectal cancer or uncontrollable multiple polyps. The prognosis of IRA is satisfactory under regular endoscopic surveillance, but many IRA patients ultimately require reoperation. Recent technical enhancements in IPAA will probably decrease the functional risks.<sup>4</sup> We therefore think that because of the need for reoperation after IRA, IPAA should be recommended for most FAP patients.

Furthermore, IPAA can be performed using either a stapled or handsewn surgical technique.<sup>5–10</sup> A stapled anastomosis is usually done at the top of the anal columns to preserve the anal transitional zone and proximal part of the internal anal sphincter.<sup>8</sup> A stapled IPAA gives better functional results compared with handsewn IPAA at the dentate line. As another advantage, stapled IPAA can avoid temporary diversion ileostomy.<sup>7</sup> Handsewn IPAA was recommended because of the risk of anal transitional zone cancer. In fact, Kartheuser *et al*<sup>5</sup> indicated that histologically examined anorectal mucosal strips taken at the time of proctocolectomy for FAP already contained dysplasia in 75% to 100% of cases, so they concluded that stapled IPAA is unacceptable and a handsewn IPAA should be obligatory in FAP. However, Ozdemir *et al*<sup>9</sup> showed that control of anal transitional zone neoplasia results in a similar risk of cancer development, and Slors *et al*<sup>10</sup> also concluded

Table 3 Extracolonic malignancies (n = 6)

	Age at diagnosis, y	Diagnosis after colectomy, y	Treatment	Prognosis	Survival time, y
Small intestine	72	29	Excision	Died	1
Stomach (same case as above)	71	28	Gastrectomy	Died of cancer of the small intestine	2
Duodenum (periampullary)	41	22	PpPD	Alive	8
Thyroid	25	(Before colectomy)	Excision	Alive	15
Kidney	52	31	Excision	Alive	1
Breast	69	26	Excision	Alive	6
Ovary	37	11	Excision	Alive	22

PpPD, pylorus-preserving pancreaticoduodenectomy.

that residual rectal mucosa of the stapled IPAA did not seem to influence clinical results at follow-up. Regardless of the anastomotic technique used, careful regular endoscopic surveillance of all patients surgically treated for FAP is critical.<sup>6</sup> We did not investigate quality of life after surgery because our study had a retrospective nature and relied on medical records, but there was no difference in long-term prognostic outcomes between stapled and handsewn anastomoses. Our data suggested that the stage of primary CRC is the most important prognostic factor after colectomy, and no second primary cancer occurred after either stapled or handsewn procedures. We concluded that the residual mucosa of stapled IPAA does not matter for long-term outcomes, but further research is needed.

Despite the introduction of prophylactic surgery of the colon, patients with FAP are at risk of dying from other complications, such as desmoid tumors and extracolonic malignancies.<sup>11</sup> Desmoid tumors

occur in approximately 10% of FAP patients.<sup>1</sup> Surgical trauma and pregnancy may hasten the onset and progression of intra-abdominal desmoid disease. Desmoid tumors show a range of behaviors, from spontaneous resolution to relentless rapid growth. Most deaths from desmoid disease are in patients with rapidly growing tumors.<sup>12</sup> In this study, 6 patients had desmoid tumors and the 1 patient with stage IV disease died of the rapid growth of the tumor. Meanwhile, the 4 stage I cases in our study had long-standing tumors without enlargement. The severity of desmoid tumors seems to be subject to hormonal influences (pregnancy and sex) and mutation location (family history and polyp count).<sup>12</sup> Although nonsteroidal anti-inflammatory drugs, tamoxifen, and chemotherapy regimens, such as dacarbazine + doxorubicin or vinblastine + methotrexate, were administered and tumor excision was performed, treatment of desmoid tumors remained unsatisfactory.<sup>1</sup>

Table 4 Comparison of clinical course between IRA and IPAA groups

	IRA (n = 8)	IPAA		P value (IRA vs IPAA)
		Stapled (n = 13)	Handsewn (n = 7)	
Sex, n, M:F	3:5	7:6	3:4	0.686
Age at primary surgery, y, median (range)	21 (14–38)	42 (11–63)	29 (19–40)	0.15
Diverting ileostomy, n (%)	0	4 (31)	3 (43)	0.053
Mortality	0	0	0	—
Morbidity (Clavien-Dindo grade 3 or higher)	0	0	0	—
Second primary rectal cancer, n (%)	4 (50)	0	0	<0.001
Period after primary surgery, y, median (range)	26 (3–32)			
Need for reoperation, n (%)	6 (75)	0	0	<0.001
Procedure of reoperation	IPAA 5, APR 1			
Indication of reoperation	Rectal cancer 4, multiple polyp 2			
Died of primary CRC, n	0	1	1	0.353
Died of second primary CRC, n	0	0	0	—
Cancer of the ileum or ileal pouch	0	0	0	—

APR, abdominoperineal resection.

Duodenal (periampullary) carcinoma is a common malignancy, occurring in approximately 5% to 6% of patients with FAP.<sup>13</sup> It is the major cause of death in patients with FAP who have had a prophylactic colectomy. Deaths from these cancers might be reduced by early diagnosis with appropriate follow-up examination. A surveillance gastroduodenoscopy interval of 6 months is recommended.<sup>14</sup> Cancer also appears in the lung, stomach, thyroid, pancreas, small intestine, uterus, and esophagus.<sup>13</sup> In our study, 6 of the 29 cases (21%; 7 lesions) had malignancies other than CRC. It is therefore necessary to pay attention to multiple organs besides the duodenum. To improve the survival of FAP patients, further research should be aimed at the prevention and treatment of desmoid tumors and extracolonic malignancies.

## Conclusions

The prognosis of IRA is satisfactory under regular endoscopic surveillance, but IPAA should be recommended because of the need for reoperation after IRA.

The residual rectal mucosa of stapled IPAA does not matter for long-term outcomes.

The stage of primary CRC at colectomy is the most important prognostic factor. But in addition to second primary CRC, the management of desmoid tumors and extracolonic malignancies is important for long-term survival regardless of the anastomotic technique used.

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