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Long-term Prognostic Impact of Metachronous Rectal Cancer in Patients With Familial Adenomatous Polyposis: A Single-center Retrospective Study

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Abstract. *Aim: To evaluate the risk factors and long-term prognosis of metachronous rectal cancer in the remnant rectum of patients with familial adenomatous polyposis (FAP). Patients and Methods: Sixty-five patients (49 families) who underwent prophylactic surgery, including bowel resection, for FAP between January 1976 and August 2022 at Hamamatsu University Hospital were included and divided into two groups based on the presence of metachronous rectal cancer. Risk factors for metachronous rectal cancer development were analysed in cases treated with total colectomy with ileorectal anastomosis (IRA) and stapled total proctocolectomy with ileal pouch anal anastomosis (IPAA) (IRA, n=22; stapled IPAA n=20; total, n=42). Results: The median surveillance period was 169 months. Twelve patients developed metachronous rectal cancer (IRA, n=5; stapled IPAA, n=7), of which six with advanced cancer died. Patients who temporarily dropped out of surveillance were significantly more likely to have metachronous rectal cancer (metachronous vs. non-metachronous rectal cancer: 33.3% vs. 1.9%, p<0.01). The mean duration of surveillance suspension was 87.8 months. Cox regression analysis revealed that temporary surveillance drop-out independently affected the risk (p=0.04). The overall survival associated with metachronous rectal cancer was 83.3% at 1 year and 41.7% at 5 years. Overall survival was significantly worse in advanced cancer than in early cancer cases (p<0.01). Conclusion: Temporary drop-out from surveillance was a risk factor for metachronous rectal cancer development, and advanced cancer had a poor prognosis. Continuous surveillance of patients with FAP, without temporary drop-out, is strongly recommended.*

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Key Words: Familial adenomatous polyposis, metachronous rectal cancer, ileal pouch anal anastomosis, ileorectal anastomosis.

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Familial adenomatous polyposis (FAP) is a genetic disease typically characterized by the development of multiple colon polyps until the patient reaches their 20s, which eventually harbour colorectal cancer (CRC) at 100% penetrance by their 60s (1-3). Prophylactic surgery of the colon and rectum remains the only curative method of CRC prevention for patients with FAP.

Total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) and total colectomy with ileorectal anastomosis (IRA) are often indicated as prophylactic procedures for FAP. Although the choice of procedure is based on considerations such as expression type, number of polyps, quality of life, and fertility (4-6), this choice in prophylactic surgery determines the risk of subsequent carcinogenesis. IRA is known to cause metachronous rectal cancer in the remnant rectum (7, 8). In a recent national cohort study in Finland, long-term surveillance over approximately 30 years after IRA revealed that 24% of patients developed metachronous rectal cancer (9). Moreover, the rate of metachronous rectal cancer development after stapled IPAA was similar to that after IRA, after a median surveillance period of approximately 19 years

(10). Although studies have evaluated the incidence of metachronous rectal cancer (7, 8), few have attempted to explore the long-term survival of patients with metachronous rectal cancer.

We hypothesized that metachronous rectal cancer would closely influence the long-term survival of patients with FAP. The main objective of this study was to evaluate the risk factors for and the long-term prognoses of metachronous rectal cancer in the remnant rectum of patients with FAP.

Patients and Methods

Study design. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study design was approved by the institutional review board of Hamamatsu University School of Medicine (IRB number: 17-132). The requirement for patient consent was waived owing to the retrospective nature of the study. The records of patients who underwent prophylactic surgery for FAP, including bowel resection, between January 1976 and August 2022 at Hamamatsu University Hospital were retrospectively collected from a prospectively maintained database. FAP was defined by either an identified adenomatous polyposis coli (APC) gene mutation or the presence of >100 colorectal adenomas.

Patient population. Among the collected cases, we investigated patients with FAP who were followed-up, including those who mainly underwent treatment during surveillance at other hospitals or temporarily dropped out of surveillance. During the surveillance period, 143 patients (80 families) received a diagnosis of FAP at Hamamatsu University Hospital. Among these, after excluding cases with inadequate data (n=54) and those who permanently dropped out of surveillance (n=24), 65 patients (49 families) were included and divided into two groups based on the presence of metachronous rectal cancer.

Surgical procedures. All surgeries were performed by or under the supervision of surgeons with sufficient experience in FAP. All patients underwent one of the following four surgical procedures following a diagnosis of FAP: i) IRA; ii) hand-sewn IPAA; iii) stapled IPAA; and iv) TPC with ileostomy. Hand-sewn IPAA was the standard procedure. Stapled IPAA was performed for patients for whom hand-sewn IPAA was preferable but who were unable to accept living with a defecation disorder. In cases wherein it was determined preoperatively that a complete hand-sewn IPAA was not feasible due to obesity or other reasons, stapled IPAA was performed. IRA was selected when relevant conditions were applicable, such as attenuated FAP, presence of <20 rectal adenomas, 1,000 colonic adenomas, ≤1 cm rectal adenoma, no high-grade dysplasia or cancer, or the patient was a young woman without definitive offspring. In some cases, IRA was also selected despite preoperative CRC when it was difficult for the patient to accept living with a defecation disorder due to mental illness or other reasons. TPC with ileostomy was generally not performed, except for cases with advanced lower rectal cancer close to the anus or with multiple distant metastases. These surgical indications are similar to those reported previously (5, 11, 12).

Postoperative surveillance after TPC or total colectomy. Most patients underwent imaging examinations, with esophagogastroduodenoscopy and colonoscopy (CS) performed once a year and computed tomography (CT) performed every few years. The presence of the remnant rectal mucosa was assessed using CS.

Metachronous rectal cancer. In all cases, lesions were identified by CS or CT and subsequently confirmed pathologically. The progression of metachronous rectal cancer was defined as early cancer (T0-2N0M0) and advanced cancer (T1-4N+M0 or T1-4N+M+) based on the eighth edition of the Union for International Cancer Control TNM Classification of Malignant Tumours (13). For the progression of metachronous rectal cancer, patients who had undergone surgery were pathologically diagnosed, while those who had not undergone surgery were diagnosed by CT. The treatment plan involved surgical resection as the first choice, but the final decision was made based on the judgment of several surgeons, including those with sufficient experience of FAP. When radical surgical resection was performed, patients underwent continued surveillance. When treatment was continued, CT and CS were performed periodically to determine treatment efficacy.

Statistical analyses. Statistical analyses were performed using JMP® 16 (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as the median and range and were tested using the Mann–Whitney *U*-test. Categorical data are expressed as the frequency and proportion and were analysed using Fisher's exact test. Statistical significance was set at $p<0.05$. Multivariate comparisons of risk factors for metachronous rectal cancer were performed using Cox regression models. Survival outcomes were analysed using the Kaplan–Meier method and log-rank tests.

Results

Clinical characteristics and postoperative surveillance after TPC or total colectomy. The characteristics of all study participants are summarised in Table I. Thirty-seven lesions of preoperative CRC, including multiple synchronous CRC, were observed: 19 lesions of early cancer and 18 of advanced cancer. Among patients with preoperative FAP-associated malignant lesions, thyroid cancer was noted in one patient. The median surveillance period was 169 months. Five patients temporarily dropped out of surveillance (Table I).

Metachronous rectal cancer. Table II shows the clinical details and survival outcomes in all cases of metachronous rectal cancer. Metachronous rectal cancer was found in 12 cases: five cases of early CRC and seven cases of advanced CRC. Both stapled IPAA and IRA had similar incidence rates of metachronous rectal cancer (35% and 22.7%, respectively). Although in three out of 20 hand-sewn IPAA cases, polyps developed at the anastomotic site, hand-sewn IPAA and TPC without remnant rectal mucosa showed no evidence of metachronous rectal cancer. The median period from surgery to a definitive diagnosis of metachronous rectal cancer was 256 months.

Of the 12 metachronous rectal cancer cases, genetic testing was performed in seven at the time of FAP diagnosis.

Table I. *Clinical characteristics and postoperative surveillance for patients treated with total proctocolectomy or total colectomy (n=65).*

Characteristic		Value
At diagnosis of FAP		
Age, years	Median (range)	32 (16-66)
Sex, n (%)	Male	27 (41.5)
	Female	38 (58.5)
Family history, n (%)	Yes	41 (63.1)
Expression type, n (%)	Classical or severe	59 (90.8)
	Attenuated	6 (9.2)
Operation date, n (%)	Until 1999	44 (67.7)
	From 2000	21 (32.3)
FAP-related malignancies, n (%)		
CRC		29 (44.6)
Early CRC*	T0-2N0	19 (29.2)
Advanced CRC*	T1-4N+M0	15 (23.1)
	T1-4N+M+	3 (4.6)
Other		1 (1.5)
Surgical approach, n (%)	Open	48 (73.8)
	Laparoscopic	17 (26.2)
Surgical procedure, n (%)	IRA	22 (33.8)
	Stapled IPAA	20 (30.8)
	Hand-sewn IPAA	20 (30.8)
	TPC	3 (4.6)
Postoperative surveillance for TPC/total colectomy		
Surveillance duration, months	Median (range)	154 (1-651)
Temporary drop-out of surveillance, n (%)	Yes	5 (7.7)
FAP-related malignancies, n (%)	Metachronous rectal cancer	12 (18.5)
	Stapled IPAA	7 (10.8)
	IRA	5 (7.7)
	Gastric cancer	8 (12.3)
	Duodenal cancer	3 (4.6)
	Thyroid cancer	3 (4.6)
	Brain tumor	2 (3.1)
	Pouch cancer	1 (1.5)
	Desmoid tumor	19 (29.2)
Other		2 (3.1)
Death during surveillance	Yes	18 (27.7)
Cause of death		
FAP-related malignancy	Total	12 (18.5)
	Metachronous rectal cancer	6 (9.2)
	CRC	5 (7.7)
	Malignant extra-colonic manifestations of FAP	1 (1.5)
Other		6 (9.2)

CRC: Colorectal cancer; FAP: familial adenomatous polyposis; IPAA: ileal pouch-anal anastomosis; IRA: ileorectal anastomosis; TPC: total proctocolectomy. *Including multiple synchronous CRC.

Two cases showed APC gene germline mutation between codons 1250 and 1464 (Table II).

All patients with metachronous rectal cancer underwent treatment, including nine cases of surgical resection (secondary bowel resection, n=8; endoscopic submucosal dissection, n=1), two cases of chemoradiation therapy, and one case of chemotherapy. Three of the secondary bowel resection cases resulted in incomplete resection due to advanced cancer invasion to the pelvic sidewall. All cases of early CRC involved radical resection. Curative resection was considered challenging in three patients who received chemoradiation therapy or chemotherapy because of advanced bladder invasion (one case) or pelvic desmoid tumour (two cases).

During surveillance, six out of 12 patients died due to metachronous rectal cancer; all had advanced cancer (T3-4N+M0, n=5; T3-4N+M+, n=1). The long-term survivor of advanced cancer was the only patient with radical secondary bowel resection.

Table II. *Characteristics of patients with metachronous rectal cancer.*

Case	Age, years	Sex	Genotype of APC	Surgical procedure for initial CRC resection	TTD, months	Preoperative surveillance	pTNM stage	Subsequent therapy	Follow-up	Outcome
1	60	F	Unexamined	IRA	420	Continuous	TisN0M0	TPC (radical resection)	No recurrence	Survival
2	71	F	Unexamined	Stapled IPAA	306	Continuous	T1N0M0	ESD (radical resection)	No recurrence	Survival
3	40	F	c.4791delT (p.Ala1598 Leufs*52)	IRA	254	Voluntary temporary drop-out	T2N0M0	TPC (radical resection)	No recurrence	Survival
4	74	F	Not examined	Stapled IPAA	232	Continuous	T2N0M0	TPC (radical resection)	No recurrence	Survival
5	80	F	c.1866C>G (p.Tyr622Ter)	IRA	258	Voluntary temporary drop-out	T2N0M0	TPC (radical resection)	No recurrence	Survival
6	32	F	Not examined	Stapled IPAA	55	Voluntary temporary drop-out	T2NXM0	TPC (incomplete resection)	Pelvic and lymph node recurrence	Death from MRC
7	32	M	c.832C>T (p.Gln278Ter)	Stapled IPAA	164	Voluntary temporary drop-out	T3N0M0	TPC (incomplete resection)	Liver and lung metastasis	Death from MRC
8	51	M	c.3926_3929 delAAAA (p.Glu1309 Glyfs*11)	Stapled IPAA	438	Continuous	T3N0M0	TPC (radical resection)	No recurrence	Survival
9	43	F	c.3747C>A (p.Cys1249Ter)	Stapled IPAA	251	Continuous*	T4N1M0	CRT	Pelvic recurrence and lung metastasis	Death from MRC
10	54	F	c.1730T>A (p.Leu577Ter)	IRA	266	Continuous*	T4N1M0	Chemotherapy	Pelvic recurrence, lymph node and lung metastasis	Death from MRC
11	77	M	Not examined	Stapled IPAA	236	Continuous	T4N1M0	CRT	Pelvic recurrence and lung metastasis	Death from MRC
12	54	F	c.2417_2418 delAT (p.His806 Argfs*2)	IRA	270	Continuous	T2NXM+	TPC (incomplete resection) + chemotherapy	Liver and lung metastasis	Death from MRC

APC: Adenomatous polyposis coli; CRT: chemoradiation therapy; ESD: endoscopic submucosal dissection; F: female; FAP: familial adenomatous polyposis; IPAA: ileal pouch-anal anastomosis; IRA: ileorectal anastomosis; M: male; TPC: total proctocolectomy; TTD: time to definitive diagnosis. *Interruption of bowel surveillance for more than 5 years during surveillance duration.

Comparison of clinical characteristics in patients with and without metachronous rectal cancer. A remarkable difference in incidence according to the surgical procedure was noted, with metachronous rectal cancer only being found in cases involving IRA or stapled IPAA. No differences were observed in other clinical characteristics at diagnosis of FAP. Patients who temporarily dropped out of surveillance were significantly more likely to have metachronous rectal cancer. No between-group differences in the other surveillance aspects were observed (Table III).

The drop-outs were self-determined for four patients and owing to monetary reasons for one patient; all of them returned to surveillance with chief complaints of haemorrhage, abdominal pain, and anal pain. The mean duration of

Table III. *Comparison of clinical characteristics of patients with and without metachronous rectal cancer.*

	Metachronous rectal cancer (n=12)	No-metachronous rectal cancer (n=53)	*p*-Value
Clinical characteristics at diagnosis of FAP			
Age, years, median (range)	29 (16-59)	34 (18-66)	0.77
Male	3 (25)	24 (45.3)	0.33
Female	9 (75)	29 (54.7)	
Family history, cases (%)	8 (66.7)	33 (62.3)	>0.99
Expression type			
Classical or severe	12 (100)	47 (88.7)	0.58
Attenuated	0	6 (11.3)	0.31
Operation date			
Until 1999	10 (83.3)		
From 2000	2 (16.7)		
FAP-related malignancies, n (%)			
CRC	6 (50.0)	23 (43.4)	>0.99
Early CRC*			
T0-2N0	6 (50.0)	13 (24.5)	0.16
Advanced CRC*			
T3-4N+M0	5 (41.7)	10 (18.9)	0.13
T3-4N+M+	1 (8.3)	2 (3.8)	0.46
Other	0 (0)	1 (1.9)	>0.99
Surgical procedure after diagnosis of FAP			
IRA	5 (41.7)	17 (32.1)	0.03
Stapled IPAA	7 (58.3)	13 (24.5)	
Hand-sewn IPAA	0 (0)	20 (37.7)	
TPC	0 (0)	3 (5.7)	
Postoperative surveillance for TPC/total colectomy			
Temporary drop-out of surveillance, n (%)	4 (33.3)	1 (1.9)	<0.01
Malignant extra-colonic manifestations of FAP, n (%)	4 (33.3)	12 (22.6)	0.47
Other malignant lesions, n (%)	0 (0)	4 (7.5)	>0.99

CRC: Colorectal cancer; FAP: familial adenomatous polyposis; IPAA: ileal pouch-anal anastomosis; IRA: ileorectal anastomosis; TPC: total proctocolectomy. *Including multiple synchronous CRC.

postoperative surveillance before dropping out was 97.2 months, and the mean duration of the surveillance suspension was 87.8 months (Table IV).

Risk factors for metachronous rectal cancer. Since metachronous rectal cancer was found only in cases involving IRA or stapled IPAA, risk factors were analysed only in these cases. Cox regression analysis, including variables such as age at diagnosis of FAP, sex, expression type, family history, early CRC at diagnosis of FAP, advanced CRC at diagnosis of FAP, and temporary drop-out of surveillance revealed that temporary drop-out of surveillance was an independent risk factor for metachronous rectal cancer (p=0.04) (Table V).

Long-term survival of patients with metachronous rectal cancer. The overall survival was considered as the time from the start of treatment for metachronous rectal cancer to all-cause death or last follow-up. The Kaplan–Meier curves for overall survival are shown in Figure 1. Overall survival was 83.3% at 1 year and 41.7% at 5 years.

Discussion

This study retrospectively analysed the long-term prognosis of metachronous rectal cancer in the remnant rectum of patients with FAP. Herein, metachronous rectal cancer was significantly more likely to occur in patients who underwent IRA or stapled IPAA and temporarily dropped out from surveillance. Among cases with metachronous rectal cancer, those with advanced cancer have an especially poor prognosis and it is one of the leading causes of death in patients with FAP. To our knowledge, this is the first study to evaluate the long-term prognosis of metachronous rectal cancer in patients with FAP who underwent IRA or stapled IPAA. The findings of this study can be expected to

Table IV. *Details of patients who temporarily dropped out of surveillance.*

Sex (case number)	Surgical procedure for initial CRC resection	Postoperative surveillance before drop-out, months	Adenoma in the remnant rectal mucosa before drop-out	Reason for drop-out	Duration of surveillance suspension, months	Reason for return to surveillance	Diagnosis at initial examination after return to surveillance
Female (case 3*)	IRA	181	–	Self-determined decision	73	Hemorrhage	Metachronous rectal cancer
Female (case 5*)	IRA	164	+**	Self-determined decision	94	Hemorrhage	Metachronous rectal cancer
Female (case 6*)	Stapled IPAA	24	–	Self-determined decision	31	Anal pain	Metachronous rectal cancer
Male (case 7*)	Stapled IPAA	43	–	Monetary reason	121	Abdominal pain	Metachronous rectal cancer
Female (NA)	Stapled IPAA	74	–	Self-determined decision	120	Abdominal pain	No malignancy

CRC: Colorectal cancer; IPAA: Ileal pouch-anal anastomosis; IRA: ileorectal anastomosis; NA: not applicable. *From Table II. **All adenomas were removed by endoscopic mucosal resection.

Table V. *Cox regression analyses of risk factors for metachronous rectal cancer during surveillance (multivariate analysis).*

Factor	HR	95% CI	*p*-Value
Age at diagnosis of FAP, ≥50 years	1.75	0.69-3.87	0.22
Male sex	1.02	0.57-1.81	0.93
Expression type, classical or severe	0.88	0.34-3.00	0.81
Family history	1.39	0.75-2.57	0.29
Early colorectal cancer at diagnosis of FAP	1.14	0.55-2.23	0.71
Advanced CRC at diagnosis of FAP	2.02	0.79-4.76	0.14
Temporary drop-out from surveillance	5.44	1.06-100.36	0.04

CI: Confidence interval; CRC: colorectal cancer; FAP: familial adenomatous polyposis; HR: hazard ratio.

substantially impact the recommendations of surveillance for FAP.

In the past, CRC was the most common reason for death in patients with FAP (14, 15). Metachronous rectal cancer after IRA was reported to account for nearly one-fifth of FAP-related causes of death (16). In our study, metachronous rectal cancer was the most common cause of death. In previous studies, the surveillance period was approximately 5-10 years, and long-term prognosis of metachronous rectal cancer remains unknown (11, 14-17). In our study, the median surveillance period was 169 months. Long-term surveillance of more than 10 years showed that metachronous rectal cancer was one of the leading causes of death of patients with FAP. We believe this is a new finding because of the longer duration of surveillance compared to that in previous reports of FAP.

In our study, the 5-year survival rate for patients with metachronous rectal cancer was very poor (41.7%). Previous observational studies have reported a 5-year survival rate of 66% for metachronous rectal cancer after IRA (18). Thus, the results of our study indicated a worse prognosis than that reported previously. We believe this was influenced by the fact that more advanced cancer cases were included in our study (58.3%) than in previous reports (34.0%). In rectal cancer surgery, it is generally difficult to achieve a negative resection margin in surgery for repeated pelvic surgery for rectal cancer (19-21). Thus, the evidence indicates that surgical margin status remains the most significant factor for long-term survival in patients undergoing operations for recurrent rectal cancer (19-21). In our study, three out of four patients underwent incomplete bowel resection for advanced rectal cancer, and all died of metachronous rectal cancer. Since most patients with FAP undergo prophylactic surgery, surgery for advanced metachronous rectal cancer may be associated with an increased rate of incomplete resection and a poor prognosis.

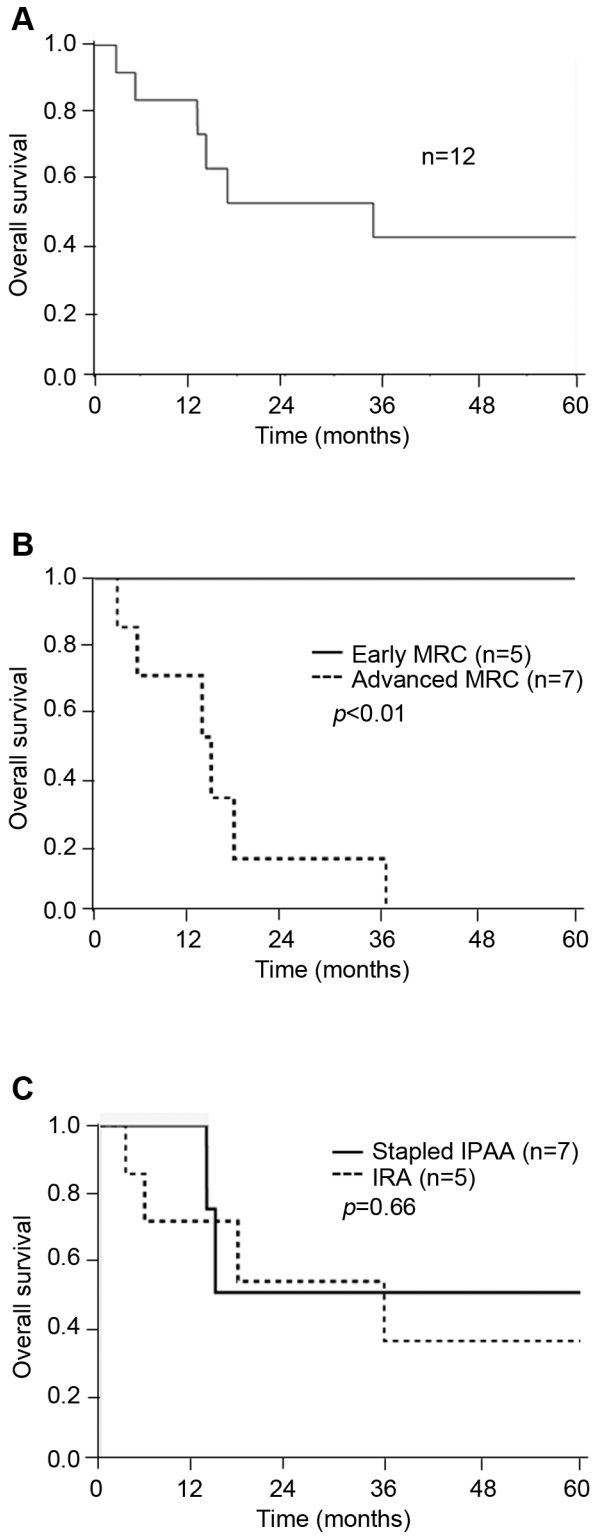

Figure 1. *Kaplan–Meier analysis of the overall survival of patients with metachronous rectal cancer (MRC). A: All cases of MRC. B: Survival according to tumour progression. C: Survival according to surgical procedure. IRA: Total colectomy with ileorectal anastomosis; IPAA: total proctocolectomy with ileal pouch anal anastomosis.*

The risk factor for metachronous rectal cancer in our study was temporary drop-out from surveillance. Some studies have reported a correlation between the risk of cancer incidence and age at pouch surgery and the type of anastomosis (stapled vs. hand-sewn) (5, 22). However, previous studies examined the cumulative risk of development of adenomas or dysplasia (5, 22), and the risk of metachronous rectal cancer development, including advanced cancer, as in our study, has received limited attention. In our study, 7.7% of patients temporarily dropped out of regular surveillance, and the mean duration of the surveillance suspension was long, about 7 years (87.8 months). Intensive endoscopic removal of adenoma is reportedly effective in both postponing colectomy and in preventing carcinogenesis in the remnant rectum after colectomy. We believe that temporary drop-out from surveillance delays the resection of adenomas arising in the remnant rectum, resulting in carcinogenesis (23). Establishment of a long-term surveillance system to improve the prognosis of FAP patients will be a future challenge. On the other hand, the results of genetic analysis showed APC gene germline mutations between codons 1250 and 1464, which are risk factors for rectal cancer (6, 24, 25), in only two out of seven of our cases. Therefore, we believe that selection of the surgical procedure based on the results of genetic analysis does not reduce the risk of metachronous rectal cancer.

Our study had several limitations. Firstly, and most importantly, it was a retrospective, single-centre investigation with a small sample size. The reason for the small sample size was that life events, such as marriage or moving, made it difficult to follow-up patients continuously despite the need for long-term surveillance at the same hospital. Secondly, the 5-year survival rate of patients with metachronous rectal cancer is limited due to the lack of standardized treatment strategies. Similarly, in a previous study, the survival rate of patients with metachronous rectal cancer was analysed for various treatment strategies (20). In cases of advanced cancer, survival outcomes differ greatly depending on whether curative treatment is chosen. Thus, accurate survival evaluation of patients with metachronous rectal cancer requires analysis on a national basis. Thirdly, the results of the genetic analysis were limited because we did not conduct a comprehensive gene analysis in our study. In recent years, besides germline mutations in the APC gene or rarely in the mutY DNA glycosylase (MUTYH) gene, the genes nth-like DNA glycosylase 1 (NTHL1), DNA polymerase delta 1, catalytic subunit (POLD1) and DNA polymerase epsilon, catalytic subunit (POLE) have been reported in previously unexplained FAP cases (26). Further genetic analysis will be an issue in the future.

Conclusion

Advanced metachronous rectal cancer is one of the leading causes of death in patients with FAP. Continuous surveillance

is strongly recommended because temporary drop-out of surveillance is a risk factor for the development of metachronous rectal cancer.

Conflicts of Interest

The Authors declare no competing financial interests.

Authors' Contributions

Kyota Tatsuta wrote the article. Mayu Sakata, Katsunori Suzuki and Kiyotaka Kurachi conceived of and designed the analysis. Moriya Iwaizumi conducted and analysed genetic testing. Kosuke Sugiyama, Tadahiro Kojima and Toshiya Akai were involved in data collection and performing the analysis. Yoshifumi Morita, Hirotoshi Kikuchi and Yoshihiro Hiramatsu critically revised the report and commented on drafts of the article. Hiroya Takeuchi approved the final version to be published. All listed Authors approved the article before submission.

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