Long-term prognosis of familial adenomatous polyposis with or without mucosectomy

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Kyota Tatsuta and Mayu Sakata. The first draft of the manuscript was written by Kyota Tatsuta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Abstract

Purpose: This study primarily aimed to compare the long-term prognosis of patients who underwent total colectomy/proctocolectomy with or without mucosectomy to the dentate line for the diagnosis of familial adenomatous polyposis (FAP).

Methods: Patients who underwent total colectomy/proctocolectomy for FAP between January 1979 and December 2020 and were followed up at Hamamatsu University Hospital were included in this study. Those who underwent total proctocolectomy with hand-sewn ileal pouch–anal anastomosis were defined as the mucosectomy group. Those who underwent total colectomy or total proctocolectomy using the stapled ileal pouch–anal anastomosis approach were defined as the no mucosectomy group.

Results: A total of 61 individuals (37 families) were diagnosed during the surveillance period (median, 191 months). Between the mucosectomy (n = 24) and no mucosectomy groups (n = 34), metachronous rectal cancer was significantly more common in the no mucosectomy group (21% in no mucosectomy vs. 0% in mucosectomy, $P = 0.02$). Overall survival in the no mucosectomy group was worse than that in the mucosectomy group (84.5% in no mucosectomy vs. 100% in mucosectomy at 120 months, 81.1% vs. 90.0% at 240 months, 50.6% vs. 75.0% at 360 months, $P = 0.09$). Cox regression analysis revealed an independent effect of not performing mucosectomy on overall survival ($P = 0.03$).

Conclusion: Long-term surveillance revealed that colectomy or total proctocolectomy without mucosectomy had a negative impact on the overall survival of patients with FAP. Therefore, we recommend total proctocolectomy with mucosectomy, i.e., hand-sewn ileal pouch–anal anastomosis, for FAP.

Keywords: familial adenomatous polyposis, total colectomy, total proctocolectomy, hand-sewn ileal pouch–anal anastomosis, stapled ileal pouch–anal anastomosis, mucosectomy

Introduction

Familial adenomatous polyposis (FAP) is a genetic disorder that typically develops in individuals in the form of multiple colon polyps until such individuals reach their 20s and eventually harbor colorectal cancer at 100% penetrance until their 60s [1-3]. Although chemoprevention may have an antineoplastic effect on the recurrence of colonic adenomas [4], prophylactic surgery of the colon and rectum remains the only curative option for the treatment of FAP. Three major surgical procedures are available for patients with FAP: total colectomy with ileorectal anastomosis (IRA), total proctocolectomy with ileal pouch–anal anastomosis (IPAA), and total proctocolectomy (TPC) with ileostomy. Two forms of IPAA are available: hand-sewn anastomosis with mucosectomy or stapled anastomosis without mucosectomy [5-7].

Appropriate surgical procedure can be chosen based on various considerations such as expression type, number of polyps, quality of life, and fertility [5-7]. From the perspective of long-term prognosis, IRA is associated with a higher risk of metachronous rectal cancer and poorer prognosis than IPAA owing to the presence of residual rectum [6, 8]. At present, IPAA is believed to be the standard surgical procedure for minimizing the risk of rectal cancer death and is commonly performed in patients with FAP [9, 10].

In IPAA, the long-term prognosis may depend on whether stapled or hand-sewn anastomosis is utilized. Rectal mucosa is mostly retained in stapled anastomosis because mucosectomy is not performed. Rectal adenomas are found considerably more often after a stapled anastomosis than a hand-sewn anastomosis [11]. However, because of the short surveillance duration in previous studies, the long-term prognosis of patients with IPAA using a different anastomosis method remained unknown [12-14].

We hypothesized that TPC with mucosectomy, i.e., hand-sewn IPAA, would contribute to satisfactory long-term outcomes. The primary aim of this study was to compare the long-term prognosis of patients who underwent total colectomy/proctocolectomy for FAP with or without mucosectomy.

Materials and Methods

Study design and patient population

The study design was approved by the institutional review board of Hamamatsu University School of Medicine (IRB number: 21-220). The requirement for patient consent was waived owing to the retrospective nature of the study. The records of patients who underwent bowel resection, including prophylactic surgery, for FAP between January 1979 and December 2020 at Hamamatsu University Hospital were retrospectively collected from a prospectively maintained database. FAP was defined on the basis of either an identified adenomatous polyposis

coli mutation or the presence of >100 colorectal adenomas. We investigated patients from the collected cases that could be followed up, including those who temporarily underwent surveillance at other hospitals or temporarily dropped out of surveillance.

Surgical procedures

All surgeries were performed by or under the supervision of surgeons with sufficient experience in FAP. We performed four surgical procedures: IRA, hand-sewn IPAA, stapled IPAA, and TPC with ileostomy.

Hand-sewn IPAA was the standard procedure. Stapled IPAA was performed in patients for whom hand-sewn IPAA was preferable but who were unable to accept defecation disorder. IRA was selected when patients presented with the following conditions: attenuated FAP, <20 rectal adenoma or 1,000 colonic adenoma, ≤1 cm rectal adenoma, no high-grade dysplasia or cancer, and young women without definitive offspring. However, IRA was selected even if colorectal cancer was identified preoperatively in some cases when it was difficult to accept defecation disorder due to mental illness or other reasons. TPC with ileostomy was generally not performed, with the exception of cases with advanced lower rectal cancer and multiple distant metastases. These indications for surgical procedures are similar to those previously reported [6, 14-16].

In this study, patients were divided into two groups: the no mucosectomy group, which underwent stapled IPAA or IRA, and the mucosectomy group, which underwent hand-sewn IPAA. Because TPC with ileostomy was selected for patients with advanced lower rectal cancer and multiple distant metastases, we excluded TPC with ileostomy cases from these groups to account for the selection bias of surgical procedure.

Postoperative surveillance

Most patients underwent imaging examinations with esophagogastroduodenoscopy and colonoscopy once a year and computed tomography every few years, although it varied by era and surgical procedure. Colonoscopy was used to determine whether the residual rectum mucosa remained.

Statistical analyses

Statistical analyses were conducted using JMP® 16 (SAS Institute Inc., Cary, NC, USA). Continuous variables were represented by median and range and tested using the Mann–Whitney *U* test. Categorical data were expressed as number and frequency and analyzed using Fisher's exact test. The cumulative risk of overall survival (OS) during the surveillance period was calculated using the Kaplan–Meier method and generalized Wilcoxon test. The

Cox proportional hazards model was used to identify the independent predictors of survival parameters. *P*-values <0.05 were regarded as statistically significant.

Results

Clinical characteristics

During the surveillance period, 137 individuals (74 families) received a diagnosis of FAP at Hamamatsu University Hospital. Among these, 61 individuals (37 families) were eligible and underwent hand-sewn IPAA (n = 24), stapled IPAA (n = 14), IRA (n = 20), and TPC with ileostomy (n = 3). The median age of patients at surgery was 32 years. Exclusion criteria were patients who received treatment mainly at other hospitals (n = 36), dropped out of surveillance (n = 24), and inadequate data (n = 16). Approximately 70% of the patients underwent surgery before 1999. Thirty cases of preoperative colorectal cancer, 12 cases of early cancer, and 18 cases of advanced cancer were observed. One case of thyroid cancer was found in the preoperative FAP-related malignancies. The median length of the residual rectum was 1.5 cm for stapled IPAA and 10 cm for IRA (Table 1).

Three patients who were selected for TPC with ileostomy had advanced lower rectal cancer and multiple distant metastases. These patients died within a few years due to early recurrence.

Postoperative surveillance

The median surveillance period was 191 months. Four patients temporarily dropped out of surveillance, but all resumed surveillance after symptoms, such as hematochezia and intestinal obstruction, were relieved.

During this period, 7 cases of metachronous rectal cancer, 3 cases of gastric cancer, 3 cases of duodenal cancer, 2 cases of thyroid cancer, 1 case of pouch cancer, and 19 cases of desmoid tumor were observed. These results include duplications. Four cases of rectal cancer were observed in IRA and three were observed in stapled IPAA. Pouch cancer was only observed in hand-sewn IPAA. There were 15 deaths, among which 10 were attributable to FAP-related cancer (Table 1).

The OS was 93.1% at 5 years, 87.2% at 10 years, 82.5% at 15 years, 79% at 20 years, and 53.5% at 30 years (Fig. 1).

Metachronous rectal cancer

All seven cases of metachronous rectal cancer were those of advanced cancer, including three cases of stapled IPAA and four cases of IRA. Both stapled IPAA and IRA had similar incidence rates for rectal cancer (21% and 20%, respectively). The median age at the definitive diagnosis of metachronous rectal cancer was 40 years. The median period from surgery to the definitive diagnosis of metachronous rectal cancer was 232 months.

Two of the seven cases temporally dropped out of our planned regular examination voluntarily. They had

hematochezia and returned our surveillance. A detailed examination revealed the presence of metachronous rectal cancer. The other five patients had no symptoms and were diagnosed with metachronous rectal cancer by regular examination.

Five of the seven cases were of preoperative colorectal cancer, three cases were of early cancer, and two cases were of advanced cancer. Even among patients with preoperative colorectal cancer, no metachronous rectal cancer was found in patients who underwent mucosectomy.

All patients underwent secondary bowel resection, with the exception of two patients who did not undergo radical resection caused by distant metastasis. These two patients died of metachronous rectal cancer-related metastasis (Table 2).

Comparison with or without mucosectomy

A comparison was made between the no mucosectomy group (stapled IPAA/IRA) and the mucosectomy group (hand-sewn IPAA). Although a remarkable difference in the surgical approach was noted, no differences in other clinical characteristics were observed. During surveillance after surgery, the incidence of metachronous rectal cancer and rate of secondary bowel resection were considerably higher in the no mucosectomy group. Moreover, the number of deaths during the surveillance period was remarkably higher in the no mucosectomy group. The common reason for death in the no mucosectomy group was metachronous rectal cancer (Table 3).

The OS in the metachronous colorectal cancer group was worse than that in the preoperative colorectal cancer group.

Risk factors for OS

Cox regression analysis, including the variables of age at surgery, sex, expression type, operation date, not performing mucosectomy (mucosectomy group vs. no mucosectomy group), preoperative early colorectal cancer, preoperative advanced colorectal cancer, and preoperative FAP-related malignancies, revealed that not performing mucosectomy showed an independent factor on OS ($P = 0.03$) (Table 4).

Discussion

This study analyzed the long-term surveillance of patients with FAP at a single-center, with a median surveillance period of 191 months. We compared the results of not performing mucosectomy (mucosectomy group vs. no mucosectomy group), which is an independent factor affecting the long-term prognosis of patients with FAP derived from the surveillance results. Based on the long-term surveillance results, surgical procedures without mucosectomy, such as stapled IPAA and IRA, resulted in poor prognosis. To our knowledge, this is the first study to compare the long-term prognosis of patients who underwent total colectomy/proctocolectomy for FAP with or without mucosectomy. This study would influence the choice of surgical procedure for FAP to a considerable extent.

Previous retrospective cohort studies showed the incidence of adenomas at the residual rectum after stapled or hand-sewn anastomosis [8, 13, 17]. The development of adenomas in the residual rectum mucosa after IPAA is common; however, the development of carcinoma is rare [8]. However, the surveillance period was approximately 10 years and the cumulative risk of developing metachronous rectal cancer remains unknown [12-14, 17]. In this study, the median period from surgery to the definitive diagnosis of metachronous rectal cancer was found to be approximately 19 years (232 months), i.e., the incidence of metachronous rectal carcinoma after IPAA was not rare but was rather unknown owing to the short surveillance duration.

In a recent national cohort study, long-term surveillance after IRA revealed that 24% of patients develop metachronous rectal cancer [18]. Some retrospective cohort studies previously showed a similar incidence of metachronous rectal cancer in patients who underwent IRA [19, 20]. Similarly, in our study, the incidence of metachronous rectal cancer in patients with FAP after IRA was 21%. Moreover, the incidence of metachronous rectal cancer in patients with FAP after stapled IPAA was 20%. This result showed that the presence of residual rectum, but not its length, was associated with the development of metachronous rectal cancer. Postoperative surveillance of patients who underwent stapled IPAA and IRA should be treated equally.

Multivariate analysis showed that not performing mucosectomy (mucosectomy group vs. no mucosectomy group) had an only independent factor on OS. Moreover, the presence of residual rectum affected the OS rate during the surveillance period. The incidence of metachronous rectal cancer was remarkably higher in the no mucosectomy group; therefore, this finding was associated with the incidence of metachronous rectal cancer. Previous studies have also reported that IRA was associated with poor survival mainly due to residual rectal cancer [21, 22]. According to a recent retrospective study, colorectal cancer is still a major cause of death in patients with FAP [23]. We believe that the choice of surgical procedure is crucial to minimize the risk of rectal cancer-related

death.

The hand-sewn IPAA approach has some restrictions in terms of postoperative functional outcomes such as defecation function, experienced surgeons, and the presence of rectal adenomas. Furthermore, a study in the early years of pouch surgery showed that mucosal islets of rectal mucosa might persist even after mucosectomy and hand-sewn anastomosis, while also estimating a 10 % risk of adenoma development following hand-sewn IPAA [24]. Although this study did not investigate mucosal islets in detail, no metachronous rectal carcinoma was observed in patients who underwent hand-sewn IPAA. Therefore, we believe that the relationship between mucosal islets and metachronous rectal carcinoma is a subject for future studies.

In many countries, registration systems for patients with FAP have elucidated the prognosis of such patients [25, 26]. In Japan, nationwide studies based on registry systems are limited [27]. Therefore, previous reports described only short-term clinical outcomes within several years of radical surgery, although guidelines for hereditary colorectal cancer were published by the Japanese Society for Cancer of the Colon and Rectum in 2016 and 2020 [10, 28]. The results of long-term surveillance of patients with FAP for more than 10 years, mainly from specialized facilities in Japan, were recently reported [29, 30]. However, little information is available and investigations are ongoing. Our study has the longest surveillance period (191 months) compared with previous reports and will substantially contribute to the treatment of FAP in Japan.

This study had several limitations. First and most importantly, it was a retrospective single-center investigation with a small sample size. A small sample size was chosen because events, such as marriage or moving, made the continuous follow-up of patients in the same hospital challenging despite the need for long-term surveillance. As a result, approximately half of all cases were excluded. Second, it was impossible to evaluate the disease-specific survival because of the small sample size. In the future, it would be desirable to analyze the results of long-term surveillance on a national basis.

Conclusion

Long-term surveillance revealed that colectomy or total proctocolectomy without mucosectomy, such as IRA and stapled IPAA, had a negative impact on the OS of patients with FAP. We recommend total proctocolectomy with mucosectomy, i.e., hand-sewn IPAA, for a better prognosis in patients with FAP.

Statements and Declarations

Competing interests

The authors declare no competing financial interests.

Funding

This study received no funding.

Ethics approval

This study design was approved by the institutional review board of Hamamatsu University School of Medicine (IRB number: 21-220).

Informed consent

The requirement for patient consent was waived because of the retrospective nature of the study.

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Figure Captions

Fig. 1 Overall survival during the surveillance period

The overall survival rate of eligible cases was 93.1% at 5 years, 87.2% at 10 years, 82.5% at 15 years, 79% at 20 years, and 53.5% at 30 years.

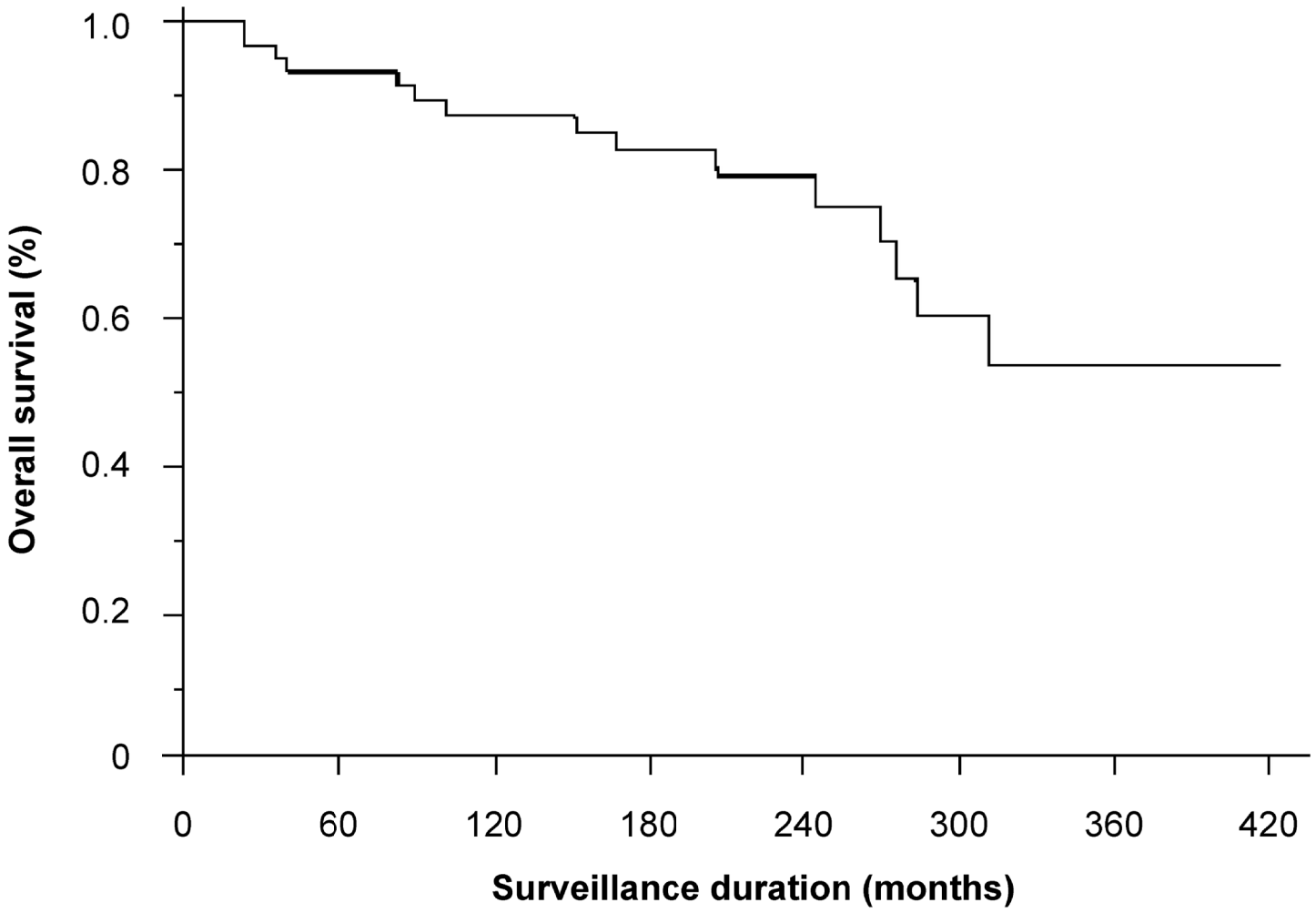
CI, confidence interval

Fig. 2 Comparison of overall survival between the mucosectomy and no mucosectomy groups

Overall survival in the no mucosectomy group was worse than that in the mucosectomy group ($P = 0.09$).

HR, hazard ratio; CI, confidence interval; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis

Fig. 1



Month	0	60	120	180	240	300	360	420
Case	61	52	42	33	19	10	6	1

	Survival rate	95% CI
10 year (%)	87.2	75.3 – 93.8
20 year (%)	79.0	64.6 – 88.7
30 year (%)	53.5	33.4 – 72.5

Fig. 2

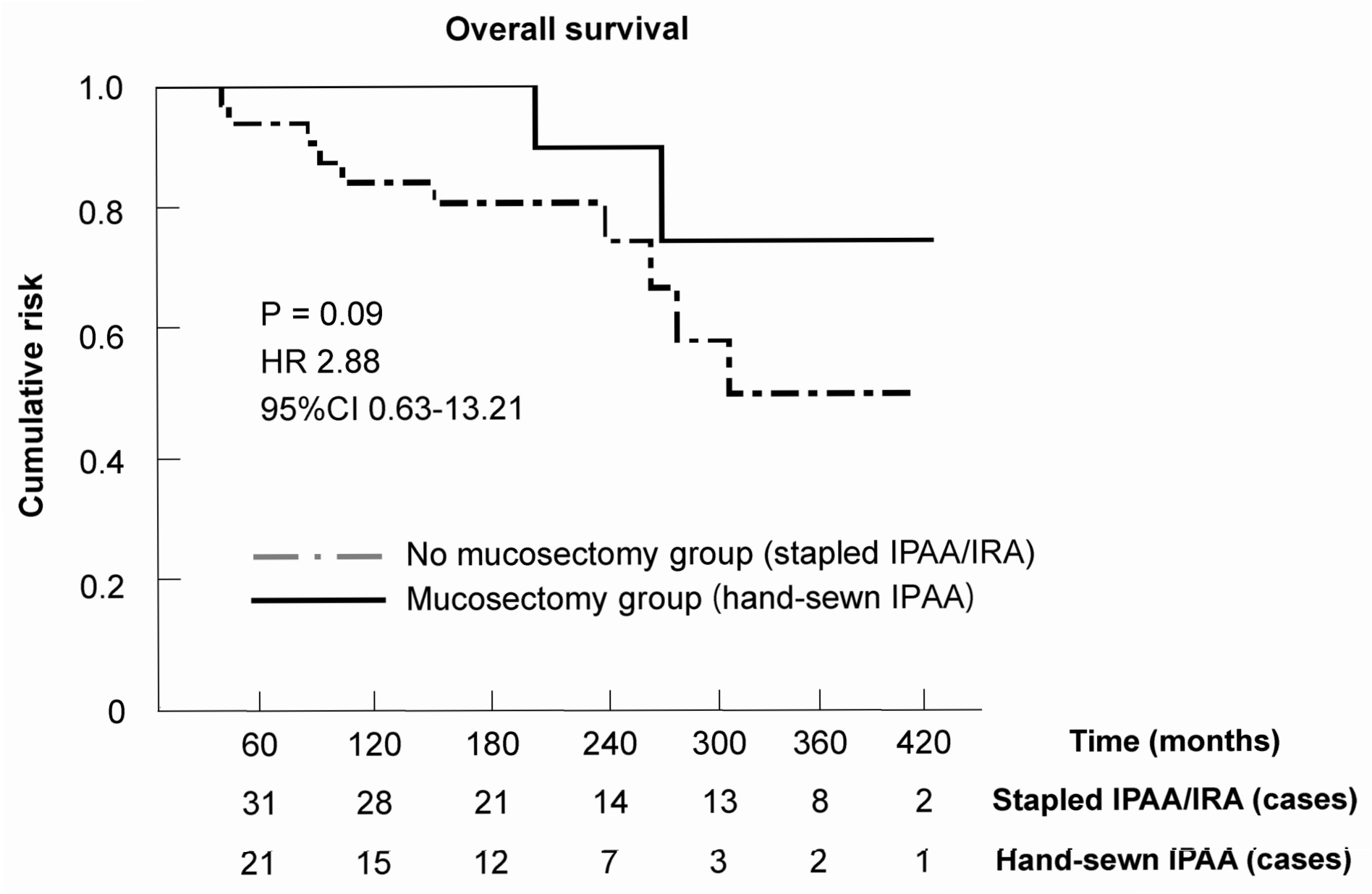

Overall survival
Cumulative risk
1.0
0.8
0.6
0.4
0.2
0
P = 0.09
HR 2.88
95%CI 0.63-13.21
No mucosectomy group (stapled IPAA/IRA)
Mucosectomy group (hand-sewn IPAA)
60 120 180 240 300 360 420
Time (months)
31 28 21 14 13 8 2
Stapled IPAA/IRA (cases)
21 15 12 7 3 2 1
Hand-sewn IPAA (cases)

Table 1. Clinical characteristics and surveillance after initial bowel resection.

	n = 61
Clinical characteristics	
Age at surgery, years, median (range)	32 (16–66)
Sex, male/female	24/37
Family history, cases (%)	40 (66)
Expression type, classical or severe/attenuated	55/6
Operation date, until 1999/from 2000	42/19
Preoperative FAP-related malignancies	
Early colorectal cancer, cases (%)	12 (20)
Advanced colorectal cancer, cases (%)	18 (30)
Other, cases (%)	1 (2)
Surgical approach, open/laparoscopy	46/15
Surgical procedure, IRA/stapled IPAA/hand-sewn IPAA/TPC	20/14/24/3
Residual rectum	
IRA, cm, median (range)	10 (8–13)
stapled IPAA, cm, median (range)	1.5 (1.0–2.0)

Postoperative surveillance	
Surveillance duration, months, median (range)	191 (10–424)
Temporary drop-out of surveillance, cases (%)	4 (7)
FAP-related malignancies	
Metachronous rectal cancer, cases (%)	7 (11)
Stapled IPAA, cases	3
IRA, cases	4
Gastric cancer, cases (%)	3 (5)
Duodenal cancer, cases (%)	3 (5)
Thyroid cancer, cases (%)	2 (3)
Pouch cancer, cases (%)	1 (2)
Desmoid tumor, cases (%)	19 (31)
Other, cases (%)	2 (3)
Additional surgery for FAP-related lesions	
All surgery, cases (%)	22 (36)
Secondary bowel resection, cases (%)	10 (16)
Death during surveillance	15 (25)
Cause of death	

FAP-related malignancies, cases (%)	10 (16)
Other, cases (%)	5 (8)

FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis; TPC, total proctocolectomy

Table 2. Metachronous cancer.

	Sex	Expression type	Age, years	Preoperative early CRC	Preoperative advanced CRC	Surgical procedure	Duration until definitive diagnosis, months	Follow-up	Bowel resection	Prognosis
Case 1	F	Typical	19	(+)	(−)	IRA	254	Continuance	TPC, radical resection	Survival, no recurrence
Case 2	F	Typical	25	(−)	(−)	IRA	96	Continuance	Stapled IPAA, radical resection	Survival, no recurrence
Case 3	F	Typical	32	(+)	(−)	IRA	270	Continuance	TPC	Cancer death due to multiple organ metastasis
Case 4	F	Typical	59	(+)	(+)	IRA+ DG	258	Continuance	TPC, radical resection	Survival, no recurrence
Case 5	M	Typical	19	(+)	(−)	stapled IPAA	196	Temporary drop-out voluntarily	TPC, radical resection	Survival, no recurrence

Case 6	F	Typical	27	(−)	(+)	Stapled IPAA	55	Temporary drop-out voluntarily	TPC	Cancer death due to liver metastasis
Case 7	F	Typical	31	(−)	(−)	Stapled IPAA	232	Continuance	TPC, radical resection	Survival, no recurrence

CRC, colorectal cancer; DG, distal gastrectomy; FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis; TPC, total proctocolectomy

Table 3. Clinical characteristics and postoperative surveillance.

	Mucosectomy group hand-sewn IPAA n = 24	**No mucosectomy group stapled IPAA/IRA n = 34**	***P*-value**
Clinical characteristics			
Age at surgery, years, median (range)	32.0 (16–58)	32.5 (18–66)	0.29
Sex, male/female	13/11	10/24	0.05
Family history, cases (%)	17 (71)	23 (68)	0.51
Expression type, classical or severe/ attenuated	22/2	30/4	0.51
Operation date, until 1999/from 2000-	13/11	26/8	0.07
Surgical approach, open/laparoscopy	13/11	30/4	<0.01
Preoperative FAP-related malignancies			
Early colorectal cancer, cases (%)	6 (25)	10 (29)	0.47
Advanced colorectal cancer, cases (%)	7 (29)	11 (32)	0.51
Other*, cases (%)	0 (0)	1 (3)	0.59
Surveillance situation after initial bowel resection			
Surveillance duration, months, median (range)	168 (10–424)	197 (36–414)	0.23

FAP-related malignancies			
Metachronous rectal cancer, cases (%)	0 (0)	7 (21)	0.02
Other*, cases (%)	4 (17)	4 (12)	0.44
Additional surgery for FAP-related lesions			
All surgery, cases (%)	6 (25)	12 (35)	0.29
Secondary bowel resection, cases (%)	1 (4)	9 (26)	0.03
Death during surveillance	2 (8)	10 (29)	0.05
Cause of death			
Metachronous rectal cancer-related, cases (%)	0 (0)	2 (6)	0.50
The other FAP-related malignancies, cases (%)	1 (4)	3 (9)	0.64
Other, cases (%)	1 (4)	5 (17)	0.20

* Cases with gastric cancer, duodenal cancer, thyroid cancer, and pouch cancer

FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis

Table 4. Cox regression analyses of overall survival during the surveillance period.

	Hazard ratio	95% CI	*P*-value
Clinical characteristics			
Age at surgery	0.42	0.03–4.35	0.49
Sex	1.69	0.30–9.49	0.55
Family history, yes	2.78	0.69–11.26	0.15
Expression type, classical or severe	0.21	0.09–1.27	0.09
Operation date, until 1999	0.26	0.03–2.02	0.20
Not performing mucosectomy	11.5	1.34–98.96	0.03
(mucosectomy group vs. no mucosectomy group)			
Preoperative early colorectal cancer	0.32	0.04–1.59	0.20
Preoperative advanced colorectal cancer	2.53	0.55–12.55	0.22
Preoperative FAP-related malignancies	26.29	0.66–1181.85	0.06

CI, confidence interval; FAP, familial adenomatous polyposis

Online Resource 1 Clinical characteristics and postoperative surveillance.

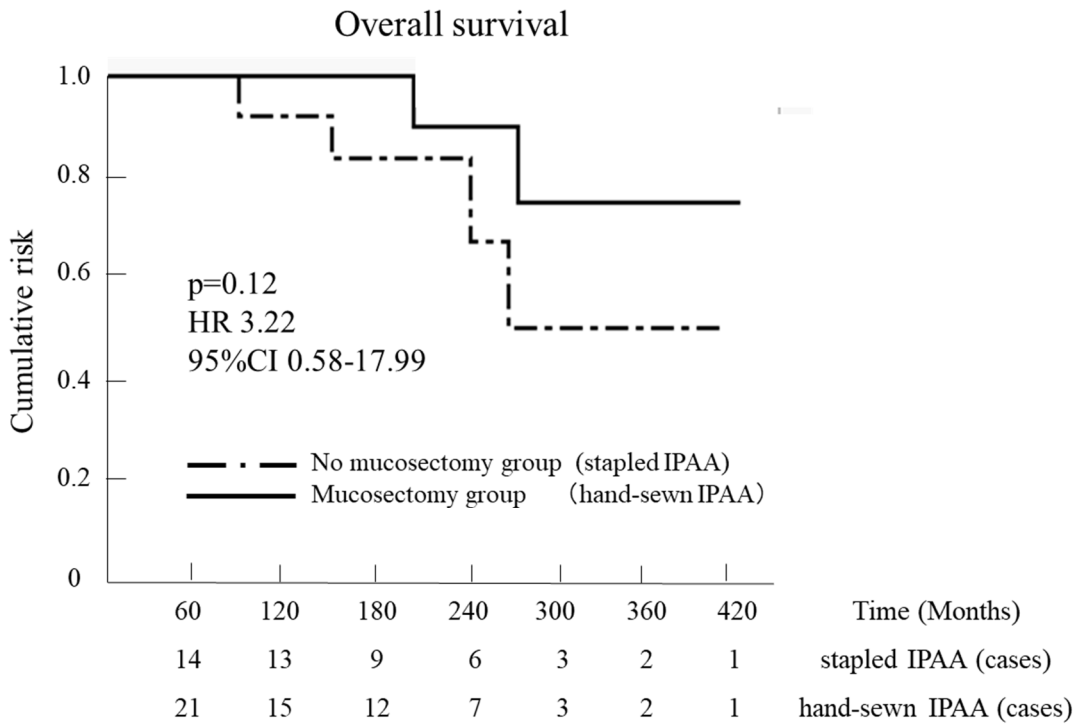
	hand-sewn IPAA **n = 24**	**stapled IPAA** **n = 14**	***P*-value**
Clinical characteristics			
Age at surgery, years, median (range)	32.0 (16–58)	32 (19–52)	0.58
Sex, male/female	13/11	5/9	0.33
Family history, cases (%)	17 (71)	10 (71)	1.00
Expression type, classical or severe/attenuated	22/2	12/2	0.62
Operation date, until 1999/from 2000-	13/11	9/5	0.74
Surgical approach, open/laparoscopy	13/11	12/2	0.08
Preoperative FAP-related malignancies			
Early colorectal cancer, cases (%)	6 (25)	5 (36)	0.71
Advanced colorectal cancer, cases (%)	7 (29)	3 (21)	0.72
Other*, cases (%)	0 (0)	0 (0)	1.00
Surveillance situation after initial bowel resection			
Surveillance duration, months, median (range)	168 (10–424)	194.5 (51–318)	0.30

FAP-related malignancies			
Metachronous rectal cancer, cases (%)	0 (0)	3 (21)	0.04
Other*, cases (%)	4 (17)	4 (29)	0.43
Additional surgery for FAP-related lesions			
All surgery, cases (%)	6 (25)	6 (43)	0.30
Secondary bowel resection, cases (%)	1 (4)	4 (29)	0.05
Death during surveillance	2 (8)	4 (29)	0.17
Cause of death			
Metachronous rectal cancer-related, cases (%)	0 (0)	1 (7)	0.37
Other FAP-related malignancies, cases (%)	1 (4)	2 (14)	0.54
Other, cases (%)	1 (4)	2 (14)	0.54

* Cases with gastric cancer, duodenal cancer, thyroid cancer, and pouch cancer

FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis

Online Resource 2 Comparison of the overall survival between stapled IPAA and hand-sewn IPAA



Overall survival for stapled IPAA was worse than that for hand-sewn IPAA (92.3% vs. 100% at 120 months, 83.9% vs. 90.0% at 240 months, 50.3% vs. 75.0% at 360 months; $P = 0.12$).

HR, hazard ratio; CI, confidence interval; IPAA, ileal pouch–anal anastomosis; IRA, ileorectal anastomosis