Original Article

Optimizing Diagnosis, Timing, and Surgical Approach in Patients with Familial Polyposis Coli: A Single-institution Experience of 151 Patients

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Key Words
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Purpose. Familial polyposis coli (FPC) is diagnosed in patients with more than 100 colorectal polyps. Molecular genetic testing aids diagnosis, especially when histopathological findings are unclear. However, optimal timing and surgical approaches for FPC remain debated. This study explores two questions: why are germline mutations sometimes undetected in FPC patients, and what are the optimal timing and surgical strategies?

Methods. We analyzed 151 patients with clinically diagnosed FPC who underwent surgery at our institution between 1995 and 2020. The analysis included molecular genetic testing and long-term follow-up.

Results. Among 151 patients, 7 (4.6%) had less than 100 polyps and no detectable mutations. Of the remaining 144 patients with more than 100 polyps from 89 unrelated families, 72 families had APC germline mutations, 8 had non-APC mutations, and 9 had no detectable mutations. Younger age at surgery (< 30 years) and cancer staging were significantly associated with overall survival (OS). The type of surgery — ileorectal anastomosis (IRA) vs. ileal pouch-anal anastomosis (IPAA) — and the presence of desmoid tumors did not significantly impact OS. Rectal stump cancer developed in 6.2% of IRA patients.

Conclusions. Colonoscopy to detect more than 100 polyps is essential for identifying germline mutations, and multi-gene panels should be used due to the varied polyposis syndromes. For APC mutation carriers, surgery before age 30 is recommended. IRA and IPAA do not differ in terms of OS or desmoid risk, but thorough follow-up after IRA is crucial to minimize rectal stump cancer risk.

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According to Bussey in 1975,[1] patients with familial polyposis coli (FPC) have more than 100 colorectal polyps in the colon and rectum. Importantly, the pathogenesis of familial adenomatous polyposis (FAP) was linked to mutations in the *adenomatous polyposis coli* (*APC*) gene in 1991.[2] However, the use of these terms is not consistent and they are sometimes misapplied. This confusion may stem from challenges

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in differentiating rare polyposis syndromes, such as hamartomatous polyposis syndrome caused by non-*APC* genes, from adenomatous polyposis based solely on macroscopic colonoscopy findings.[3,4] Moreover, it is challenging to differentiate among various types of hamartomatous polyps.[5]

Molecular diagnostics can address these challenges and have thus become essential.[2-5] However, approximately 30% of families with FAP have *APC* mutation-negative polyposis patients based on conventional molecular diagnosis.[2,6,7] Although most clinically defined cases of polyposis coli are due to germline mutations in *APC*, various other types of polyposis coli caused by different molecular alterations, are now recognized.[3-5,8] Consequently, genetic testing for polyposis colorectal syndrome is shifting from phenotype-directed, single-gene testing to multigene testing using next-generation sequencing (NGS). However, the optimal number of genes that should be included in the panel for effective patient counseling remains unclear.

Most patients with classic FAP are recommended to undergo surgery between the ages of 20 and 25 years. However, there is no consensus among clinicians regarding the optimal age and type of surgery for patients with FAP.[9-12] In general, the older the patient at the time of colectomy, the higher the risk of malignant polyp transformation and advanced neoplasia.[9-11] Additionally, desmoid tumors have been reported in 15-20% of patients' post-surgery.[13,14] Surgery-related complications include reduced postoperative quality of life (bowel frequency and incontinence) and infertility, that can vary depending on the type of procedure, such as ileorectal anastomosis (IRA) or ileal pouch-anal anastomosis (IPAA).[12] Some surgeons opt for earlier surgery when the polyps are still manageable. Balancing survival outcomes and quality of life presents a considerable clinical challenge.

Therefore, in this retrospective study, we combined molecular genetic testing and long-term clinical follow-up to address two clinical questions: why are *APC* germline mutations not detectable in patients with clinically diagnosed FPC, and what is the best timing and type of prophylactic surgery for these patients?

Materials and Methods

The colorectal cancer registry at the Chang Gung Memorial Hospital was established in 1985 as a clinical database for research on sporadic and hereditary colorectal cancer and was updated in 1995 to a computerized version. This prospective database comprised records of postoperative patients who were consecutively and actively followed up. Data collection included five significant components: detailed family history, demographic information, preoperative evaluations, surgical records, and postoperative follow-ups. All data were gathered through patient interviews and clinical and pathological records, then converted into numeric codes for entry into a computerized system for subsequent analysis. Follow-up data were updated annually by reviewing patient records medical charts. If patients' medical records were unavailable, telephone interviews or mail questionnaires were conducted. All patients underwent formal cancer risk counseling, and detailed medical and family histories were obtained. Pedigree charts were constructed for each family.[15]

This database, included 191 patients from 101 unrelated families who were clinically diagnosed with FPC and underwent surgery between January 1995 and January 2020. Blood samples were collected after patients were provided detailed explanations and obtained their informed consent. Genomic DNA was extracted using a Wizard Genomic DNA Extraction Kit (Promega, Madison, WI, USA) and stored in a tumor bank for future use. This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Lin-Kou Medical Center (IRB2018 01201B0).

Surgical procedures were categorized as IPAA, performed with hand-sewn sutures following rectal mucosal stripping, or stapled sutures preserving the rectum as in IRA, or other procedures such as total proctocolectomy with permanent ileostomy.

Blood samples were obtained from patients with FAP registered in the Hereditary Colorectal Cancer Database. Germline mutations in *APC* were analyzed prior to 2020.[15] All *APC* codons were first analyzed for mutations using single-strand conformational po-

lymorphisms or protein truncation test assays. Polymorphisms and truncated protein variations were confirmed using DNA sequencing. Multiplex ligation-dependent probe amplification was used to analyze large deletions in *APC* in families that did not show any apparent changes in *APC*.

In 2020, we designed an NGS colorectal cancer susceptibility gene panel for all patients with FAP and those who were not diagnosed using traditional methods. This panel included 30 genes, as described previously.[16] Of these, 13 genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *TP53*, *MLH3*, *CHEK2*, *CDH1*, *ATM*, *BRCA1*, *BRCA2*, and *RPS20*) were associated with nonpolyposis syndrome, ten genes (*STK11*, *PTEN*, *BMPR1A*, *SMAD4*, *GREM1*, *RNF43*, *BLM*, *GALNT12*, *AKT1*, and *PIK3CA*) were associated with nonadenomatous polyposis diseases, and seven genes (*APC*, *MUTYH*, *POLE*, *POLD1*, *NTHL1*, *AXIN2*, and *CTNNA1*) were associated with the adenomatous polyposis syndrome.

Variant calling was done through the platform-specific pipeline of "Variant Callerv 5.10" (Life Technologies). Variant annotation was performed by uploading VCF files from the Variant Caller to the Ion Reporter (Thermo Fisher Scientific) and wANNOVAR (Wang Genomics Lab, http://wannovar.wglab.org/). Pathogenic and likely pathogenic variants were identified using the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and VarSome (https://varsome.com/) databases. All filtered variants were confirmed by Sanger sequencing.

Statistical analysis

Clinical characteristics and follow-up status were analyzed to assess changes related to treatment outcomes. The analysis included the effect of clinical features such as age at the time of surgery, follow-up duration, type of surgical procedure, follow-up status, and presence of extracolonic tumors. All parameters were analyzed using SPSS software (version 26.0; IBM Corp., Armonk, NewYork). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, whereas continuous variables were compared using the independent samplet-test. Survival analysis was performed using Kaplan-Meier curves and the log-rank test. The Cox proportional hazards model was used to investigate the effect of clinical variables on survival, adjusting for other explanatory factors. $p < 0.05$ was considered statistically significant.

Results

From our cancer registry database, we identified 177 patients diagnosed with FPC who underwent surgery in our department between 1995 and 2020. DNA samples from these patients were used for genetic testing for germline mutations. Among them, 151 patients had complete clinicopathological and follow-up data. Of these 151 patients, 75 were female, and 76 were male. The median age at surgery was 36 years (18-69 years). After a detailed review of colonoscopy and double-contrast barium enema records, the number of polyps did not exceed 100 in 7 patients, accounting for 4.6% (7/151 patients).

Germline mutation of 151 patients with FPC

Germline mutations were analyzed in 151 patients with FPC. Among these, 7 patients had a polyp count less than 100 and were from different families, and no known gene mutations were detected in this group.

The remaining 144 patients with FPC with a definite number of more than 100 polyps were from 89 unrelated families. Of these, *APC* germline mutations were detected in 72 (80.9%) families, whereas non-*APC* germline mutations were detected in 8 (9.0%; 8/89). The 8 non-*APC* germline mutations were in *ATM*, *GALNT12*, *BMPR1A*, *BRCA2*, *PTEN*, *NTHL1*, *POLE*, and *RNF43* (Supplementary Table 1). Additionally, double germline mutations were found in one family with *APC* and *TP53* mutations. Details of the genetic mutations are listed in Supplementary Table 1. The remaining 9 families had no known mutations (9/89, 10.1%). Among patients with FPC and a confirmed polyp count more than 100, 89.9% (80/89) of the families exhibited germline mutations. Of these, 90.0% (72/80) of the families had *APC* gene muta-

tions, whereas 10.0% (8/80) had non-*APC* gene mutations.

Comparisons of clinical features among 144 patients with FPC with different germline mutations

Table 1 depicts that, after excluding patients with < 100 polyps, the clinical and histological characteristics of these 144 patients with FPC were compared among subgroups with *APC* gene mutation, non-*APC* mutation, and no known mutation. Age at diagnosis, type of surgery, incidence of malignancy, and distribution of stages were not significantly different among the three subgroups. However, Table 2 shows that extracolonic tumors significantly differed among the various germline mutation subgroups. Desmoid tumors, which were exclusively present in the subgroup of *APC* germline mutations (24 of 113 patients, 21.2%, $p < 0.05$). In this study, thyroid cancer ranked as the second most common tumor. 7 out of 113 patients (6.1%) exhibited *APC* gene mutations, compared to 1 of 17 patients (5.8%) without such mutations. No extracolonic tumors were detected during follow-up in patients with polyposis without known germline mutations. The family with an *NTHL1* germline mutation included one early-onset breast cancer, one ampullary carcinoma, and one colorectal tumor (Table 2).

Table 1. Clinical characteristics of 144 familial polyposis coli patients

Clinical characteristics	Patient number (N = 144)	APC gene mutation (N = 113)	Non-APC(+) mutation (N = 17)	No mutation (N = 14)
Age				
< 20	14	7	4	3
20-39	94	80*	10	4
40-59	33	23	3	7
> 60	3	3	0	0
Sex				
M	73	53	10	10
F	71	60	7	4
Patients in same family				
N ≥ 2	75	65	10	0
N = 1	69	48	7	14
Final pathologic staging				
0-I	19	11	6	2
II	22	17	2	3
III	27	22*	4	1
IV	7	6	1	0
Benign	69	57	4	8
Location of malignancy				
Colon	37	24	10	3
Rectum	42	34	5	3
Type of operation				
IPAA	63	50	6	7
IRA	64	51	5	8
Other	17	12	3	2
Rectal stump cancer	5	4	1	0
Follow-up				
Alive	112	85	13	14
Dead	30	26	1	3
Loss follow-up	2	2	0	0

* Statistically significant differences (p value < 0.05) were identified between mutation groups (APC gene mutation group, Non-APC mutation group, and No mutation group) within the same clinical characteristics through logistic regression analyses.

Table 2. Associated extra-colonic tumors among 144 FPC patients

	Total patient (N = 144)	APC gene mutation (N = 113)	Non-APC mutation (N = 17)	No mutation (N = 14)
Patients No. with extra-colonic tumor	N = 46	N = 41	N = 4	N = 1
Desmoid tumor	24	24	0	0
Epidermal inclusion cyst	6	4	1	1
Thyroid cancer	8	7	1	0
Ampullar vater cancer	1	0	1	0
Breast Ca	2	1	1	0
Adrenal carcinoma	1	1	0	0
Endometrial Ca	1	1	0	0
Lung	1	1	0	0
Oral Ca	1	1	0	0
Pilometrixoma	1	1	0	0

Comparison of age at surgery with the incidence of malignancy and tumor stage

We analyzed the relationship between age at surgery, incidence of malignant tumors, and tumor stage. The median age at surgery was 33 years (12-69 years). As presented in Fig. 1, the mean age at surgery for patients across different tumor stages was 36.76, 41.24, 38.38, and 39.86 years for stages I, II, III, and IV respectively. There were significant difference in mean age among these subgroups. However, patients with benign lesions had a significantly younger mean age at surgery (28.05 years) compared to those with malignant tumor, regardless of stage, with the difference being statistically significant.

The incidence of malignancy in patients with FPC increased with age at the time of surgery. Fig. 2 demonstrates that 20.9% of the patients who underwent surgery before the age of 30 years had malignancies.

Additionally, 68.8% (11/16) of these 16 patients under 30 years with malignancies at the time of surgery had early-stage malignancies (Table 3). Of the 75 patients with malignant tumors, 78.6% (59/75) were over the age of 30 years at the time of surgery. Table 3 also reveals that all patients with FPC older than 60 years who underwent surgery presented with malignant tumors.

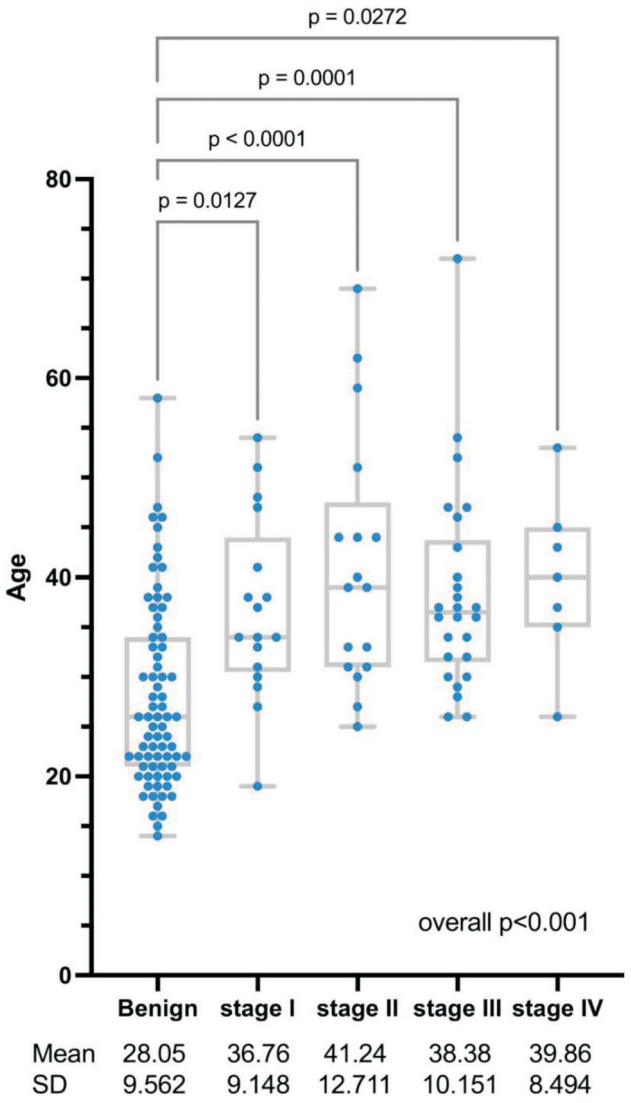

Fig. 1. Mean age of operation related to benign lesion and varied stages of malignancies.

Overall survival related to age and type of surgical treatments

Figs. 3a and 3b illustrate that the relationships be-

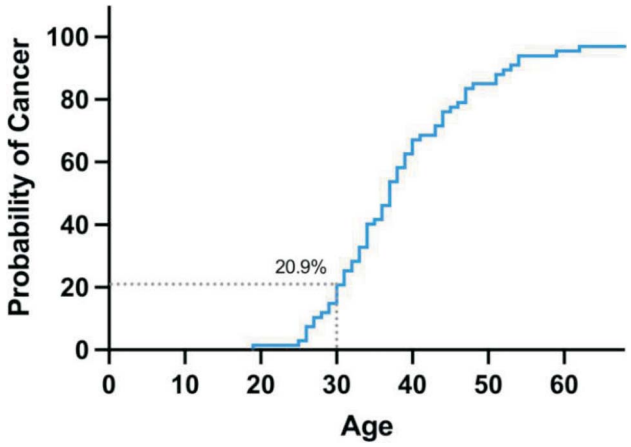

Fig. 2. Cumulative probabilities of occurrence of malignancy related to operation age.

Table 3. Stage distribution of malignancies related to age at operation

Age range	Average age	0-I	II	III	IV	Benign
< 20	17	1	1	0	0	12*
20-29	24.1	6	3	4	1	30*
30-39	34.3	6	9	15	2	18
40-49	43.8	4	5	5	3	7
50-59	53.8	2	2	2	1	2
≥ 60	67.7	0	2	1	0	0

* Statistically significant differences (p value < 0.05) in tumor stages (0-I, II, III, IV, Benign) were identified between groups within the same age range through logistic regression analyses.

tween age at surgery, pathological stage, and overall survival were statistically significant. (The younger, ≤ 30 years vs. the older ≥ 30 years; $p < 0.001$) and (early stage, I/II vs. late stage, III/IV; $p < 0.001$) subgroups who underwent colectomy exhibited significantly better overall survival (OS). Comparing 64 patients who underwent total colectomy with IRA to 63 patients who underwent IPAA, however, the type of surgery (IPAA or IRA) did not significantly influence the surgical outcome in terms of OS ($p = 0.407$) (Fig. 4). Additionally, the presence of postoperative desmoid tumors did not significantly impact overall survival, as the postoperative development of desmoid tumors was not significantly associated with OS ($p = 0.443$) (Fig. 5). At a mean of 9.3 years (2-17.3 years) postoperative follow-up, patients who underwent IRA faced a 7.8% (five out of 64 patients) risk of developing rectal stump cancer.

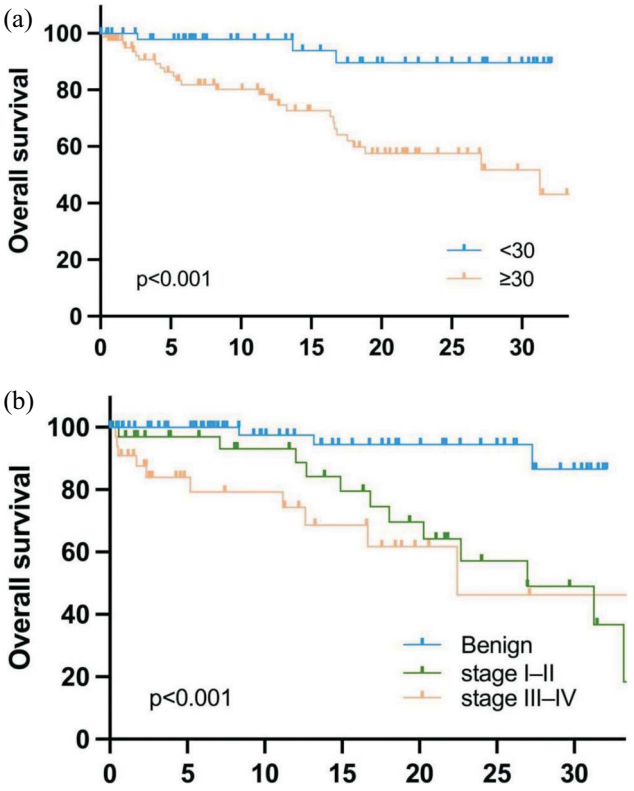

Fig. 3. (a) Overall survival related to age of operation among 144 FAP patients. (b) Overall survival related to tumor stages among 144 FPC patients.

Discussion

In this study, the detection rate of germline mutations in patients with FPC was 89.9% (80/89 families), which is consistent with previous studies.[6] Our results underscore several key factors influencing germline mutation rates. It is specifically employed in clinical practice when the number of polyps in a patient with FPC exceeds 100. The number of polyps did not exceed 100 in seven of 151 patients (4.6%), and none of the 30 gene panels used in this study, including the *MUTY* gene, were mutated in these seven patients. Clinically, if the number of polyps does not exceed 100, it may not be adequate to classify them as FPC, because they may not result from germline mutations. Thus, our study demonstrates that accurate polyp counting is clinically critical as it may affect the detection rate of germline mutations.

A polyp counts more than 100 was first proposed for FPC by Bussey in 1975.[1] Since that time, various

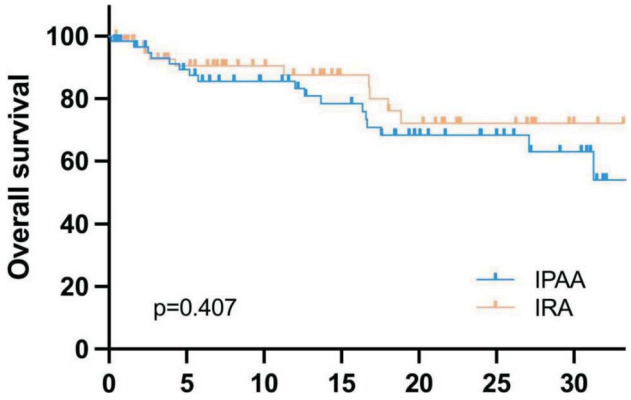

Fig. 4. Overall survival related to types of operation.

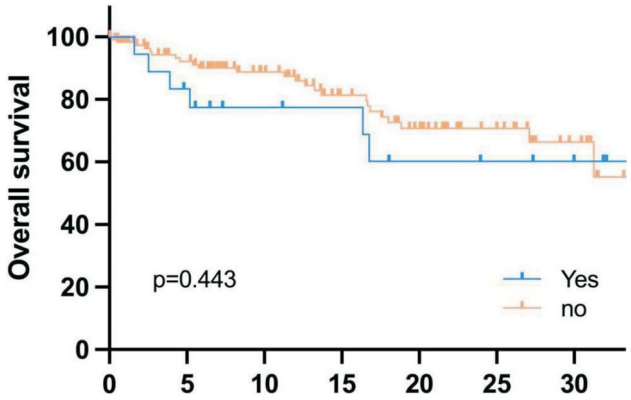

Fig. 5. Overall survival related to occurrence of desmoid tumor.

histological types of colonic polyposes have been identified. Definitions of polyp numbers may vary among different types of polyposis coli syndrome. However, when diagnosing a patient with FAP, it should be associated with the type of adenomatous polyposis based on the histological findings. Therefore, pending the precise histology of the polyps,[17] were commend using FPC clinically to characterize these patients. Upon histological confirmation, FPC is defined as FAP or any other less common polyposis syndrome. For instance, in this study, two out of 144 patients were diagnosed with hamartomatous polyposis syndrome and one out of 144 with serrated polyposis syndrome. Additionally, these results underscore that the rate of germline mutation detection varies with the number of genes included in the testing panel.[3-5,17] Here, using a 30-gene panel commonly mutated in colorectal cancer, as opposed to a single *APC* gene, the detection rate increased from 80.9% (72/89 families) to 89.8% (80/89 families). Moreover, delaying colectomy may be considered over annual colonoscopic surveillance when genetic testing in patients without germline mutations or when non-*APC* genes are detected. Genetic testing for these patients can yield further information for optimal clinical management.

When treating patients with FPC, surgeons face two clinical challenges: the optimal age of the patient for surgery and the optimal type of operation. The adequate timing of prophylactic surgery has not been strictly defined.[9-13] Conventionally, surgery is recommended to be performed after the age of 18 years. Many surgeons recommend early intervention following diagnosis because of the potential development of cancer, and an increase in advanced colon cancer is significantly associated with older age at surgery.[9-13] The increasing number and size of adenomas complicate follow-up examinations.[18] Furthermore, our study and existing literature indicate that older the patient undergoing colectomy have a higher chance of polyp malignancy and tumor stage.[9,11] Therefore, the timing of prophylactic surgery is influenced by the age at diagnosis and the colonoscopy findings. However, some postoperative complications may include reduced quality of life (bowel frequency and incontinence), infertility,[12,19] and the development of desmoid tumors.[13,20] To balance survival and quality of life, some surgeons opt to delay surgery if they believe that the patient's polyps are still under control. Our study demonstrated a statistically significant difference in survival of patients who underwent surgery before and after 30 years of age (Fig. 2). The incidence of malignant tumors was 20.1% in patients who underwent surgery before the age of 30; however, this rapidly increased thereafter (Fig. 2). These findings align with those of previous studies, which documented notably low cancer rates — specifically, 0.5% in patients who underwent surgery before the age of 20 years and 6.9% in those operated on before the age of 25.[1] Although the timing of colectomy primarily relies on the clinician's personal experience and patient preference, we recommend not delaying colectomy in patients with FAP after the age of 30 years.

The choice of surgical approach for patients with FPC remains controversial. Traditionally, total proctocolectomy with IPAA has been the standard treatment for FAP.[19,22,23] Two key concerns regarding the type of surgery are the incidence of desmoid tumors and rectal stump cancer. Surgical trauma, a major factor affecting survival, is considered the primary trigger for desmoid tumor development. Previous studies[13,14] have reported that 15-25% of patients with FAP develop desmoid tumors, and in our study, 20% (24 of 120) of patients with *APC* germline mutations developed desmoid tumors post-surgery (Table 2). However, the true risk might be higher, as suggested by a cumulative risk of up to 30% over 50 years for desmoid tumors.[20] Our finding showed no statistically significant difference in OS between the IRA and IPAA groups (Fig. 4). Additionally, no significant difference in OS between patients with and without desmoid tumors post-surgery was observed (Fig. 5). These results are consistent with those of other studies.[22] In this study, the incidence of desmoid tumors was similar following both IRA surgery (17.2% [11 of 64]) and IPAA surgery (20.6% [13 of 63]), with no clear evidence that one procedure was more likely to lead to desmoid tumors. However, conflicting reports exist in the literature regarding this issue.[23]

Despite opting for IRA over IPAA to enhance quality of life, rectal stump cancer remains a potential complication following IRA. Three primary factors were evaluated: the length of the preserved rectum,[24,25] the status of rectal polyps,[25] and the follow-up interval. Data regarding the incidence of rectal stump cancer post-IRA show variability.[11,24,25] We reviewed two long-term follow-up studies from Mayo Clinic[24] and St. Mark Hospital. According to the Mayo Clinic data, the incidence of rectal stump cancer was significant: 46 of 143 patients (32%) developed rectal stump cancer. Conversely, the long-term follow-up report from San Marco's Hospital indicated a lower incidence rate of 6.6% (166 rectal cancers in 11 of 2 patients).[26] Cumulative rates increased over time. Mayo Clinic reported cumulative rates of 13%, 26%, and 55% at 10, 20, and 30 years, respectively, while St. Mark Hospital reported rates of 6%, 10%, and 18%. In line with St. Mark's findings and other large recent cohort studies,[24,25,29] we detected rectal cancer in five out of 144 patients (3.5%). The relatively low incidence in this study could be attributed to factors such as the ease of access to follow-up care in Taiwan for patients with polyposis and the typically short rectal length of < 15 cm.[25,27] Additionally, recent research suggests that regular long-term follow-up with colonoscopy can reduce the incidence of rectal stump cancer without impacting patient survival.[11,25]

This retrospective, observational, single-center study presented limitations due to its small sample size and selection bias.

Conclusions

In conclusion, our findings highlight that colonoscopy is crucial for detecting > 100 polyps and plays a critical role in identifying patients with germline mutations. A multigene panel is recommended due to the genetic heterogeneity of polyposis syndromes. For patients with *APC* germline mutations, the age at surgery should not exceed 30 years. Furthermore, the choice between IRA or IPAA, does not affect the risk of desmoid tumor development or OS. The risk of rectal stump cancer remains low with adequate post-IRA follow-up.

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Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Concept and Design: Jy-Ming Chiang, Chun-Kai Liao. Study Patient Provision: Yueh-Chen Lin, Yu-Jen Hsu, Jy-Ming Chiang, Chun-Kai Liao. Data Collection and Assembly: Jy-Ming Chiang, Chun-Kai Liao, Yueh-Chen Lin, Yen-Lin Huang, Yu-Jen Hsu. Data Analysis and Interpretation: Jy-Ming Chiang, Chun-Kai Liao, Yen-Lin Huang. Manuscript Writing: Jy-Ming Chiang, Ai-Lun Lo, Chun-Kai Liao. Final Approval of the Manuscript: All authors have read and approved the final manuscript.

References

1. Bussey H. Familial polyposis coli. Baltimore: The Johns Hopkins University Press; 1975.
2. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, Stevens J, Spirio L, Robertson M, et al. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 1991;66(3):589-600. doi: 10.1016/0092-8674(81)90021-0. PMID: 1651174.
3. Orloff MS, He X, Peterson C, Chen F, Chen JL, Mester JL, Eng C. Germline PIK3CA and AKT1 mutations in Cowden and Cowden-like syndromes. *Am J Hum Genet* 2013;92(1): 76-80. doi: 10.1016/j.ajhg.2012.10.021. Epub 2012 Dec 13. PMID: 23246288. PMCID: PMC3542473.
4. Mafficini A, Brosens LAA, Piredda ML, Conti C, Mattiolo P, Turri G, Mastrosimini MG, Cingarlini S, Crinò SF, Fassan M, Piccoli P, Simbolo M, Nottegar A, Lawlor RT, Guglielmi A, Scarpa A, Pedrazzani C, Luchini C. Juvenile polyposis diagnosed with an integrated histological, immunohistochemical and molecular approach identifying new SMAD4 pathogenic variants. *Fam Cancer* 2022;21(4):441-51. doi: 10.1007/s10689-022-00289-x. Epub 2022 Jan 25. PMID: 35075588. PMCID: PMC9636285.
5. Miyahara Y, Ishida H, Kawabe K, Eto H, Kasai T, Ito T, Kaneko K, Arai M, Kamae N, Momose S, Eguchi H, Okazaki Y. A novel germline BMPR1A variant (c.72_73delGA) in a Japanese family with hereditary mixed polyposis syndrome. *Jpn J Clin Oncol* 2020;50(7):826-9. doi: 10.1093/jjco/hyaa059. PMID: 32378721. PMCID: PMC7345204.
6. Kerr SE, Thomas CB, Thibodeau SN, Ferber MJ, Halling KC. APC germline mutations in individuals being evaluated for familial adenomatous polyposis: a review of the Mayo Clinic experience with 1591 consecutive tests. *J Mol Diagn* 2013;15(1):31-43. doi: 10.1016/j.jmoldx.2012.07.005. Epub 2012 Nov 14. PMID: 23159591.
7. Van der Luijt RB, Khan PM, Vasen HF, Tops CM, van Leeuwen-Cornelisse IS, Wijnen JT, van der Klift HM, Plug RJ, Griffioen G, Fodde R. Molecular analysis of the APC gene in 105 Dutch kindreds with familial adenomatous polyposis: 67 germline mutations identified by DGGE, PTT, and Southern analysis. *Hum Mutat* 1997;9(1):7-16. doi: 10.1002/(SICI)1098-1004(1997)9:1<7::AID-HUMU2>3.0.CO;2-8. PMID: 8990002.
8. Lee JK, Kwon WK, Hong SN, Chang DK, Kim HC, Jang JH, Kim JW. Necessity of multiplex ligation probe amplification in genetic tests: germline variant analysis of the APC gene in familial adenomatous polyposis patients. *Cancer Genet* 2022;262-263:95-101. doi: 10.1016/j.cancergen.2022.02.002. Epub 2022 Feb 11. PMID: 35189564.
9. Kobayashi H, Ishida H, Ueno H, Hinoi T, Inoue Y, Ishida F, Kanemitsu Y, Konishi T, Yamaguchi T, Tomita N, Matsubara N, Watanabe T, Sugihara K. Association between the age and the development of colorectal cancer in patients with familial adenomatous polyposis: a multi-institutional study. *Surg Today* 2017;47(4):470-5. doi: 10.1007/s00595-016-1398-1. Epub 2016 Aug 9. PMID: 27506752.
10. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008;57:704-13.
11. Vasen HFA, Ghorbanoghli Z, de Ruijter B, Trinidad RA, Langers AMJ, Peeters KCMJ, Bonsing BA, Hardwick JCH. Optimizing the timing of colorectal surgery in patients with familial adenomatous polyposis in clinical practice. *Scand J Gastroenterol* 2019;54(6):733-9. doi: 10.1080/00365521.2019.1621930. Epub 2019 Aug 11. PMID: 31401889.
12. Church JM. Controversies in the surgery of patients with familial adenomatous polyposis and Lynch syndrome. *Fam Cancer* 2016;15(3):447-51. doi: 10.1007/s10689-016-9886-4. PMID: 26869170.
13. Inoue Y, Ishida H, Ueno H, Kobayashi H, Yamaguchi T, Konishi T, Tomita N, Matsubara N, Ishida F, Hinoi T, Kanemitsu Y, Watanabe T, Sugihara K. The treatment of desmoid tumors associated with familial adenomatous polyposis: the results of a Japanese multicenter observational study. *Surg Today* 2017;47(10):1259-67. doi: 10.1007/s00595-017-1500-3. Epub 2017 Mar 1. PMID: 28251376.
14. Campos FG, Martinez CAR, Bustamante-Lopez LA, Mendonça RLDS, Kanno DT. Intra-abdominal desmoid tumors in famil-

ial adenomatous polyposis: how much do clinical and surgical variables interfere with their development? *Clinics (Sao Paulo)* 2023;78:100144. doi: 10.1016/j.clinsp.2022.100144. PMID: 36476966. PMCID: PMC9723922.

15. Chiang JM, Chen HW, Tang RP, Chen JS, Changchien CR, Hsieh PS, Wang JY. Mutation analysis of the APC gene in Taiwanese FAP families: low incidence of APC germline mutation in a distinct subgroup of FAP families. *Fam Cancer* 2010;9(2):117-24. doi: 10.1007/s10689-009-9292-2. Epub 2009 Sep 19. PMID: 19768578.
16. Chang PY, Chang SC, Wang MC, Chen JS, Tsai WS, You JF, Chen CC, Liu HL, Chiang JM. Pathogenic germline mutations of DNA repair pathway components in early-onset sporadic colorectal polyp and cancer patients. *Cancers (Basel)* 2020;12(12):3560. doi: 10.3390/cancers12123560. PMID: 33260537. PMCID: PMC7761471.
17. Gilad O, Rosner G, Fliss-Isakov N, Aharon-Kaspi S, Strul H, Gluck N, Kariv R. Clinical and histologic overlap and distinction among various hamartomatous polyposis syndromes. *Clin Transl Gastroenterol* 2019;10(5):1-9. doi: 10.14309/ctg.0000000000000035. PMID: 31107726. PMCID: PMC6602765.
18. Murano T, Ikematsu H, Shinmura K, Okumura K, Kuwata T, Ushiama M, Yoshida T, Takashima K, Nakajo K, Kadota T, Yoda Y, Oono Y, Yano T. Endoscopic management of familial adenomatous polyposis targeting colorectal lesions greater than 5 mm in size: a single-center retrospective study. *Fam Cancer* 2023;22(1):83-9. doi: 10.1007/s10689-022-00308-x. Epub 2022 Aug 5. PMID: 35930210.
19. Aziz O, Athanasiou T, Fazio VW, Nicholls RJ, Darzi AW, Church J, Phillips RK, Tekkis PP. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. *Br J Surg* 2006; 93(4):407-17. doi: 10.1002/bjs.5276. PMID: 16511903.
20. Ashar S, Lipsa A, Khan N, Sarin R. High cumulative risk of colorectal cancers and desmoid tumours and fibromatosis in South Asian APC mutation carriers. *J Med Genet* 2022;59(5): 492-5. doi: 10.1136/jmedgenet-2021-107731. Epub 2021 Mar 25. PMID: 33766935.
21. Konishi T, Ishida H, Ueno H, Kobayashi H, Hinoi T, Inoue Y, Ishida F, Kanemitsu Y, Yamaguchi T, Tomita N, Matsubara N, Watanabe T, Sugihara K. Feasibility of laparoscopic total proctocolectomy with ileal pouch-anal anastomosis and total colectomy with ileorectal anastomosis for familial adenomatous polyposis: results of a nationwide multicenter study. *Int J Clin Oncol* 2016;21(5):953-61. doi: 10.1007/s10147-016-0977-x. Epub 2016 Apr 19. PMID: 27095110.
22. Sinha A, Burns EM, Latchford A, Clark SK. Risk of desmoid formation after laparoscopic versus open colectomy and ileorectal anastomosis for familial adenomatous polyposis. *BJS Open* 2018;2(6):452-5. doi: 10.1002/bjs5.90. PMID: 30511045. PMCID: PMC6253786.
23. Xie M, Chen Y, Wei W, He X, Li X, Lian L, Lan P. Does ileoanal pouch surgery increase the risk of desmoid in patients with familial adenomatous polyposis? *Int J Colorectal Dis* 2020;35(8):1599-605. doi: 10.1007/s00384-020-03578-y. Epub 2020 May 20. PMID: 32435838.
24. Church J, Burke C, McGannon E, Pastean O, Clark B. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. *Dis Colon Rectum* 2003;26(9): 1175-81. doi: 10.1007/s10350-004-6710-2. PMID: 12972960.
25. Colletti G, Ciniselli CM, Signoroni S, Cocco IMF, Magarotto A, Ricci MT, Brignola C, Bagatin C, Cattaneo L, Mancini A, Cavalcoli F, Milione M, Verderio P, Vitellaro M. Prevalence and management of cancer of the rectal stump after total colectomy and rectal sparing in patients with familial polyposis: results from a registry-based study. *Cancers (Basel)* 2022; 14(2):298. doi: 10.3390/cancers14020298. PMID: 35053462. PMCID: PMC8774025.
26. Bülow S. The risk of developing rectal cancer after colectomy and ileorectal anastomosis in Danish patients with polyposis coli. *Dis Colon Rectum* 1984;27(11):726-9. doi:10.1007/BF02554599. PMID: 6499606.
27. Anele CC, Xiang J, Martin I, Hawkins M, Man R, Clark SK, Faiz OD, Latchford A. Regular endoscopic surveillance and polypectomy is effective in managing rectal adenoma progression following colectomy and ileorectal anastomosis in patients with familial adenomatous polyposis. *Colorectal Dis* 2022;24(3):277-83. doi: 10.1111/codi.15981.

Supplementary Material

Supplementary Table 1.

FAP No.	Family	Names of mutation fragments	Codon	Nucleotide change	Mutation type
1	FAP-1-1	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
1	FAP-1-2	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
2	FAP-2-1	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
2	FAP-2-2	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
2	FAP-2-3	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
2	FAP-2-4	APCE 15-11	1309-1311	3927-3931 del AAAGA	5bp deletiion (aaaga)
3	FAP-3-1	APCE 15-11	1309-1311	gaaaagatt→gatt	5bp deletiion (aaaga)
3	FAP-3-2	APCE 15-11	1309-1311	3927-3931 del AAAGA	5bp deletiion (aaaga)
3	FAP-3-3	APCE 15-11	1309-1311	3927-3931 del AAAGA	5bp deletiion (aaaga)
4	FAP-4-1	APCE 13	554	cga→tga (Arg→Stop)	1bp substition
4	FAP-4-2	APCE 13	554	cga→tga (Arg→Stop)	1bp substition
5	FAP-5	APCE 15-13	1451	cga→tga (Arg→Stop)	1bp substition
6	FAP-6	APCE 15-7	1061-1063	aaacaaag→aag	5bp deletiion (acaaa)
7	FAP-7-1	APCF 8	302	cga→tga (Arg→Stop)	1bp substition
7	FAP-7-2	APCF 8	302	cga→tga (Arg→Stop)	1bp substition
7	FAP-7-4	APCF 8	302	cga→tga (Arg→Stop)	1bp substition
7	FAP-7-5	APCF 8	302	cga→tga (Arg→Stop)	1bp substition
8	FAP-8-1	APCE 15-11	L1342X	T4025A	stopgain
8	FAP-8-2	APCE 15-11	L1342X	T4025A	stopgain
9	FAP-9	No mutation			unknown
10	FAP-10	APC 9-2	436	aat→at	1bp deletiion
11	FAP-12	No mutation			unknown
12	FAP-13	APCE 15-12	1372	4118 del T	
13	FAP-14-1	APCE 6	R232X	C694T	stopgain
13	FAP-14-2	APCE 6	R232X	C694T	stopgain
14	FAP-15	APCE 15-11	1307-1309	ataaaagga→atga	5bp deletiion (aaaag)
15	FAP-16-1	APCE-8	283	cga→tga (Arg→Stop)	1bp substition
15	FAP-16-2	APCE-8	283	cga→tga (Arg→Stop)	1bp substition
16	FAP-18	APCE 15-6	935-936	tacaat→tt	4bp deletiion (acaa)
17	FAP-19	APCE-12	535	1603insA	
18	FAP-20-1	APCE 15-7	1061-1063	aaacaaag→aag	5bp deletiion (acaaa)
18	FAP-20-3	APCE 15-7	1061-1063	aaacaaag→aag	5bp deletiion (acaaa)
19	FAP-21-1	APCE 15-12	1377	tatgtt→tgtt	2bp deletion(at)
19	FAP-21-2	APCE 15-12	1377	tatgtt→tgtt	2bp deletion(at)
19	FAP-21-3	APCE 15-12	1377	tatgtt→tgtt	2bp deletion(at)
19	FAP-22-1	APCE 15-10	1221	tcatct→catcatct	2bp insertion(ca)
19	FAP-22-2	APCE 15-10	1221	tcatct→catcatct	2bp insertion(ca)
19	FAP-22-3	APCE 15-10		tcatct→catcatct	2bp insertion(ca)
20	FAP-23	EXON 1-15	MLPA		
21	FAP-24-1	RNF43-exon9	A365T	G1093A	nonsynonymous SNV
21	FAP-24-2	RNF43-exon9	A365T	G1093A	nonsynonymous SNV
21	FAP-24-3	RNF43-exon9	A365T	G1093A	nonsynonymous SNV
21	FAP-24-6	RNF43-exon9	A365T	G1093A	nonsynonymous SNV
21	FAP-24-7	RNF43-exon9	A365T	G1093A	nonsynonymous SNV
22	FAP-25-1	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-2	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-3	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition

Supplementary Table 1. Continued

FAP No.	Family	Names of mutation fragments	Codon	Nucleotide change	Mutation type
22	FAP-25-4	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-6	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-7	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-8	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-16	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-18	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-19	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-20	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-21	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
22	FAP-25-22	APCE 5	213	637 Cga→Tga (Arg→Stop)	1bp substition
23	FAP-26	No mutation			No mutation detected
24	FAP-27	No mutation			No mutation detected
25	FAP-28	APCE 15-6	947-948	2840delTGTTC	5bp del(tgttc)
26	FAP-32	PTEN-exon6	V166fs	498dupA	frameshift insertion
27	FAP-33	No mutation			No mutation detected
28	FAP-34		Deletion of promoter region		
29	FAP-35	APCF 8	302	904 CGA-TGA (Arg-Stop)	
30	FAP-36				no mutation detected
31	FAP-37-1	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-2	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-3	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-4	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-5	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-6	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
31	FAP-37-7	APCE 5	R213X	C637T	stopgain
		APCE 15-13	T1493fs	4479delG	frameshift deletion
32	FAP-38	APC Exon 10	460	1378delG	
33	FAP-39	APCE 15-21	2032	6094delAG insT	
34	FAP-40	APCE 12	541	1621insA	
35	FAP-42	APCE 12	527	1579insA	
36	FAP-43	Chromo 16&2			
37	FAP-44	APCE 15-12	1413	4238insT	
38	FAP-45	APCE 10	464	1393delC	
39	FAP-46-1	APCE 15-11	1309	3927delAAAGA	
39	FAP-46-2	APCE 15-11	1309	3927delAAAGA	
40	FAP-47	Deletion of exon 1-15			
41	FAP-48	APCE 15-7	1061-1063	3181delACAAA	
42	FAP-49	No mutation			no mutation detected
43	FAP-50	No mutation			no mutation detected
44	FAP-51	APCE 15-11	1309	3927delAAAGA	
45	FAP-53	No mutation			no mutation detected
46	FAP-54	APCE 15-11	1309	3927 del AAAGA	
47	FAP-55	APCE 15-7	1061-1063	3181 del ACAAA	
48	FAP-56	APCE 10	460	1378 del G	
49	FAP-64-1	APC 15-12	1413	4238 ins T	
50	FAP-67	APC 15-11	1309	3927 del AAAGA	5bp deletiion (aaaga)
51	FAP-71-1	APCE 15-11	1342	ttatct→tttatct	1bp insertion (t)

Supplementary Table 1. Continued

FAP No.	Family	Names of mutation fragments	Codon	Nucleotide change	Mutation type
51	FAP-71-2	APCE 15-11	1342	ttatct→tttatct	1bp insertion (t)
51	FAP-71-3	APCE 15-11	1342	ttatct→tttatct	1bp insertion (t)
52	FAP-72-1	APC 15-7	1061-1063	3183 del ACAAA	5bp deletiion (acaaa)
52	FAP-72-2	APC 15-7	1061-1063	3183 del ACAAA	5bp deletiion (acaaa)
53	FAP-73-1	APCE 8	302	904 CGA-TGA (Arg-Stop)	
53	FAP-73-2	APCE 8	302	904 CGA-TGA (Arg-Stop)	
53	FAP-73-3	APCE 8	302	904 CGA-TGA (Arg-Stop)	
53	FAP-73-4	APCE 8	302	904 CGA-TGA (Arg-Stop)	
53	FAP-73-5	APCE 8	302	904 CGA-TGA (Arg-Stop)	
54	FAP-75	No mutation			no mutation detected
55	FAP-77	No mutation			no mutation detected
56	FAP-78	No mutation			no mutation detected
57	FAP-81	APC 15-7	1061-1063	3181 del ACAAA	5bp deletiion (acaaa)
58	FAP-82-1				No mutation detected
58	FAP-83-1	APCE 15-11	1309	3927~3931 del AAAGA	5bp deletiion (aaaga)
59	FAP-84	APCE 15-11	1343	4,029 ins T	
60	FAP-85	APCE 12	542	1,624 CAG Gln >TAG Stop	
61	FAP-86	No mutation			no mutation detected
62	FAP-87	APCE 8	302	904 Cga→Tga (Arg→Stop)	
63	FAP-88	APCE 10	463	1389 del A	
64	FAP-89	BMPR1A-exon-10	R361X	C1081T	
65	FAP-90	APCE 9-2	421	1262 tGg→tAg (Trp→Stop)	
66	FAP-91	APC 15-12	1381	4143delA	
67	FAP-92	APCE 15-4	849	2547-2550 del TAGA	
68	FAP-93-1	APCE 15-11	1309	3927-3931 del AAAGA	5bp deletiion (aaaga)
69	FAP-94	APCE 10	463	1389 del A	
70	FAP-95	ATM-exon-50	E2446G	A7337G	
71	FAP-96	APC 15-7	1067	3200dupA	NGS
72	FAP-97	APCE 15-13	1450	4348 Cga→Tga (Arg→Stop)	NGS
73	FAP-100-1	APCE 15-12	1406	4216 Cag à Tag (Gln à stop)	
73	FAP-100-2	APCE 15-12	1406	4216 Cag à Tag (Gln à stop)	
74	FAP-102	APCE 9-2	423	1268 tGg→tAg (Trp→Stop)	
75	FAP-104	GALNT12			GALNT12
76	FAP-105	APCF 8	302	904 Cga→Tga (Arg→Stop)	
77	FAP-106	APCE 5	213	637 Cga→Tga (Arg→Stop)	NGS
78	FAP-107-1	POLE	61	exon-2, p.G61A	
78	FAP-107-2	POLE	61	exon-2, p.G61A	unknown
78	FAP-107-3	POLE	61	exon-2, p.G61A	unknown
79	FAP-108	MUTYH-exon-2	G25D	G74A	
			P18L	C53T	
80	FAP-109	APC 6	R216X	C646T	NGS
81	FAP-110	APCE 15-11	1305	3913 del G	
82	FAP-112-1	NTHL1-exon-3	I176T	T527C	
82	FAP-112-2	NTHL1-exon-3	I176T	T527C	
83	FAP-113	APCE 15-9	1127	Cag→Tag (Gln→Stop)	
84	FAP-114	APCE 15-12 del G	1394	4180 del G	
85	FAP-116	APCF 8	302	904 Cga→Tga (Arg→Stop)	
86	FAP-117	APCE 15-7	1061-1063	3183 del ACAAA	5bp deletiion (acaaa)
87	FAP-118-1	APC 10	460	1378 del G	
87	FAP-118-2	APC 10	460	1378 del G	
88	FAP-119	AXIN2-exon-8	T689Dfs*17	2063dupT	frameshift insertion
89	FAP-120	BRCA2-I1929V	exon11	A5785G	p.I1929V

原　著

家族性結腸息肉病患者的診斷、手術時機及手術方式的優化：單一機構 151 例患者的經驗研究

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引言　家族性結腸息肉病 (Familial polyposis coli, FPC) 通常臨床診斷於患者腸道內出現超過 100 顆結直腸息肉。結腸息肉綜合徵的分子遺傳檢測有助於解決診斷上的挑戰，特別是在組織病理學結果 不確定的情況下。然而，針對 FPC 患者的最佳手術時機及手術方式尚存爭議。本研究探討兩個臨床 問題：為何在 FPC 患者中無法識別生殖細胞突變，以及這些患者的最佳手術時機與手術方式為何。

病人與方法　本研究分析 1995 年至 2020 年間在本科接受手術的 151 位臨床診斷為 FPC 的患者，結 合分子遺傳檢測與長期臨床追蹤進行探討。

結果　在 151 位患者中，有 7 位患者 (4.6%) 息肉數量少於 100 顆，且未檢測到突變。在來自 89 個無血緣關係家族的 144 名息肉數量超過 100 的患者中，72 個家族檢測到腺瘤性結腸息肉病基因 (APC) 的生殖細胞突變，8 個家族檢測到非 APC 基因的生殖細胞突變，9 個家族未檢測到任何突變。手術年齡 (< 30 歲) 及惡性腫瘤分期與總生存率 (OS) 顯著相關。然而，手術類型 (回腸直腸吻合術 [IRA] vs. 回腸囊肛吻合術 [IPAA]) 及是否存在硬纖維瘤對 OS 無顯著影響。在接受 IRA 的患者中，有 6.2% 發生了直腸殘端癌。

結論　結腸鏡檢查以確定超過 100 顆息肉對識別生殖細胞突變至關重要。由於息肉綜合徵種類繁多，應使用多基因檢測面板。對於檢測到 APC 基因生殖細胞突變的患者，理想的手術時間應在 30 歲之前。此外，IRA 與 IPAA 的選擇對總生存率或硬纖維瘤的發展風險無顯著影響。只要術後追蹤充分， IRA 後發生直腸殘端癌的風險較低。

關鍵詞　結直腸癌、息肉病、家族性息肉病、家族性腺瘤性息肉病。