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ORIGINAL ARTICLE

Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry

香港的遺傳腺瘤狀息肉病患者的表型與處理：遺傳性腸胃癌資料庫的前瞻

Objectives. To report on the phenotypic spectrum and clinical management of Chinese patients suffering from the rare autosomal dominant colorectal cancer syndrome of familial adenomatous polyposis.

Design. Analysis of prospectively collected data from the database of a regional registry.

Setting. The Hereditary Gastrointestinal Cancer Registry, Hong Kong.

Participants. One hundred and eight patients with proven familial adenomatous polyposis from 36 local Chinese families with the condition recruited to the Registry from 1995 to 2001.

Interventions. Screening programme for at-risk family members, prophylactic surgery at presymptomatic diagnosis, and surveillance programme for extracolonic lesions in affected individuals.

Main outcome measures. Rate of colorectal cancer, type of surgical treatment, spectrum of extracolonic lesions, and management of the syndrome.

Results. Fifty patients suffered from colorectal cancer with a mortality rate of 78.0%. The strategy of presymptomatic diagnosis by screening and appropriate prophylactic surgery reduced the incidence of colorectal cancer. Affected individuals were prone to develop potentially serious extracolonic lesions including thyroid cancer (5.7%), desmoid tumour (15.7%), gastroduodenal adenomas (7.1%), duodenal microadenoma (17.1%), and pouch polyposis (17.4%).

Conclusions. Screening and prophylactic surgery are effective ways to prevent colorectal cancer for patients with familial adenomatous polyposis. Lifelong regular surveillance is necessary to detect and manage extracolonic lesions. A dedicated registry is essential to coordinate clinical management and to compile data for furthering knowledge of this rare but complex syndrome.

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目的：報告患有罕見的常染色體顯性遺傳腺瘤狀息肉病的華人患者，其表型範圍和臨床處理。

設計：於地區資料庫預期搜集的資料分析。

安排：香港遺傳性腸胃癌資料庫。

參與者：由1995年到2001年，資料庫內36個本地華人家庭中的108名被證實患有遺傳腺瘤狀息肉病的患者。

療法：對有可能患病的家庭成員進行篩查、預兆診斷的預防性手術、及對個別患者進行結腸外損害的監察。

主要結果測量：結直腸癌率，手術治療類型，結腸外損害的範圍，以及徵狀的治理。

結果：50名病人患上結直腸癌，死亡率為78.0%。通過篩查進行預兆診斷和適當的預防性手術，減少了結直腸癌的發生。受影響的患者有較大機會患上具潛在嚴重性的結腸外損害，包括甲狀腺癌(5.7%)、硬纖維瘤(15.7%)、胃十二指腸腺瘤(7.1%)、十二指腸微腺瘤(17.1%)、及袋狀息肉病(17.4%)。

結論：對於遺傳腺瘤狀息肉病患者，篩查和預防性手術可有效預防結直腸癌的發生。此外，終生定期監察可以發現和醫治結腸外的損害。專門的資料庫對於協調臨床治療和綜合資料的工作，並進一步了解這種罕見而複雜的綜合病症是必需的。

Introduction

Familial adenomatous polyposis (FAP) is one of two hereditary colorectal cancer syndromes. It is an autosomal dominant condition with an estimated frequency in the population of 1 in 10 000 and a penetrance rate of almost 100%.[1] This condition accounts for 1% of all colorectal cancers.[2-4]

Affected individuals are healthy at birth. During the second or third decade of life, however, adenomatous polyps begin to develop until the colon and rectum are covered by hundreds or thousands of growths.[5] If left untreated, one or more of these polyps will inevitably develop into colorectal adenocarcinoma at a mean age of 40 years.[6,7] Offspring of an affected individual will have a 50% chance of inheriting and developing the disease. Presymptomatic diagnosis by screening of at-risk first-degree relatives and prophylactic proctocolectomy are effective ways to prevent malignant transformation, and thus reduce mortality and morbidity from colorectal cancer. Apart from colorectal involvement, patients with FAP are at risk for a broad spectrum of extracolonic manifestations (ECMs) involving all three embryonic cell lineages. Some ECMs, including epidermoid cyst, osteoma, dental odontoma, and gastric fundic gland polyps, have benign courses. Certain ECMs have, however, potentially life-threatening consequences. Upper gastrointestinal malignancies (especially ampullary adenocarcinoma) and desmoid tumours represent the two major causes of morbidity and mortality after prophylactic colectomy for patients with FAP. Therefore, regular surveillance for ECMs is recommended. Familial adenomatous polyposis is also associated with a variety of other malignancies including pancreatic, biliary tree, small intestine, thyroid, adrenal, and brain tumours.

Clinical management of families with FAP requires a multidisciplinary approach and is best achieved by a dedicated registry. The first FAP registry was established in 1925 by Lockhart-Mummery.[8] In Hong Kong, the Hereditary Gastrointestinal Cancer Registry was established in 1995 with the aim of achieving secondary colorectal cancer prevention for high-risk families through early detection, timely treatment, education, and ongoing research. One of the service targets is families affected by FAP in Hong Kong.

The aims of this paper are to report on the phenotypic manifestations of the local population with FAP and to discuss the clinical management of individuals with this rare syndrome.

Methods

The Hereditary Gastrointestinal Cancer Registry, based at Queen Mary Hospital, accepts voluntary referrals of families with FAP throughout Hong Kong, both by medical practitioners in the private and public sectors and by

Box 1. Endoscopic surveillance programme for patients with familial adenomatous polyposis after prophylactic colectomy

(1) Flexible sigmoidoscopy every 6 months after total abdominal colectomy and ileorectal anastomosis
(2) Pouchoscopy every 2 years after proctocolectomy and ileal pouch anal anastomosis
(3) Upper endoscopy and duodenoscopy every 2 years for all patients

Box 2. Genetic-guided screening programme for a family with familial adenomatous polyposis

(1) Detection of pathogenic mutation from the blood of a surviving index patient
(2) If the mutation is known, genetic testing will be offered to at-risk family members older than 12 years
   (a) Flexible sigmoidoscopy will be offered biennially to members found to carry the mutated gene. When polyps develop, prophylactic surgery will be arranged
   (b) Further screening will be discontinued for members who do not carry the mutated gene
(3) If the mutation cannot be identified, all at-risk family members will be offered flexible sigmoidoscopy biennially until they reach the age of 50 years or until polyps develop, whichever comes first

self-referral of affected families. Upon referral, pedigrees (family trees) are established by obtaining family histories from patients and their relatives during face-to-face and telephone interviews. These interviews are conducted by a trained Registry coordinator. From the pedigrees, family members at risk of inheriting the condition are identified.

Medical records of patients with FAP are traced from the referral hospitals or from the hospitals where patients underwent investigation and treatment. Relevant clinical data are entered into the Registry database. Regular endoscopic surveillance is arranged after colectomy (Box 1). A genetic-guided screening programme is offered to at-risk family members (Box 2). New patients with FAP identified by the screening programme are referred to a specialist surgical unit for operative treatment and regular surveillance. Data presented in this paper were obtained from the Registry database. Statistical analysis was performed by Statistical Package for Social Science (Windows version 10.1; SPSS Inc., Chicago, United States).

Results

From November 1995 to July 2001, the Hereditary Gastrointestinal Cancer Registry recruited 36 Chinese families with FAP. Eighteen (50.0%) of these families were referred from Queen Mary Hospital where the Registry was based; 11 (30.6%) were referred from other public hospitals; two (5.6%) were referred from private practitioners; and five (13.9%) were self-referred.

From pedigree analysis, 108 patients with FAP were identified from these 36 families—59 were male and 49 were female. The median number of patients with FAP from each family was 2 (range, 1-19; standard deviation [SD], 3.3). At recruitment, 15 patients from separate families reported no history of FAP in other family members, suggesting
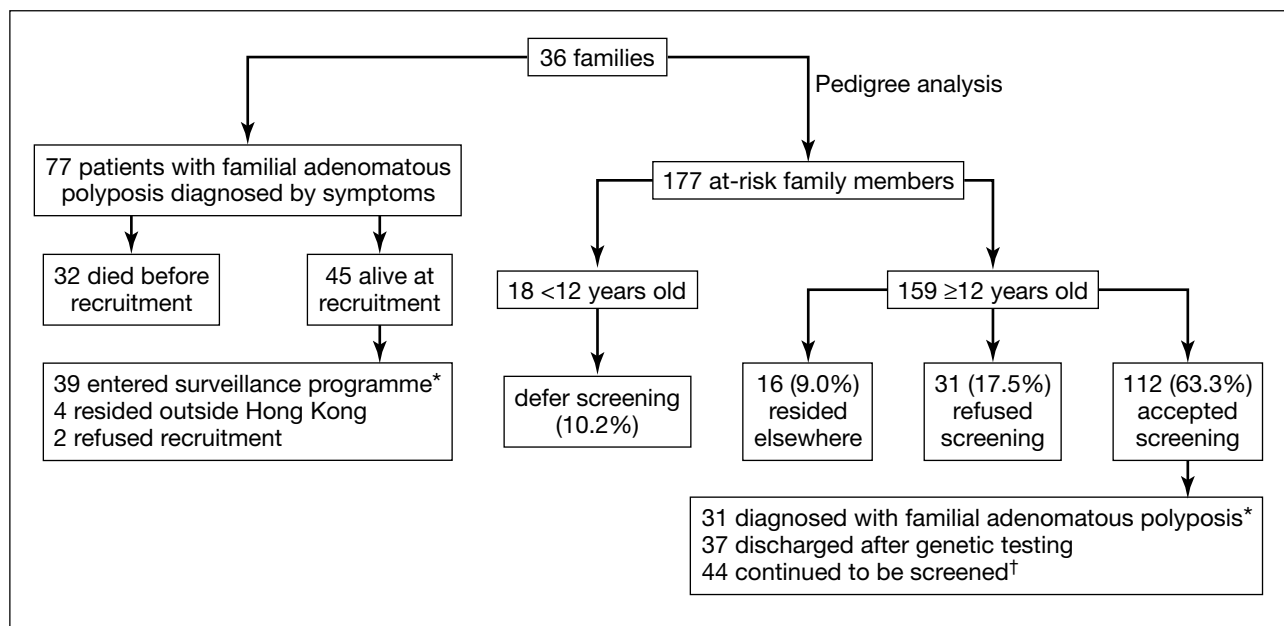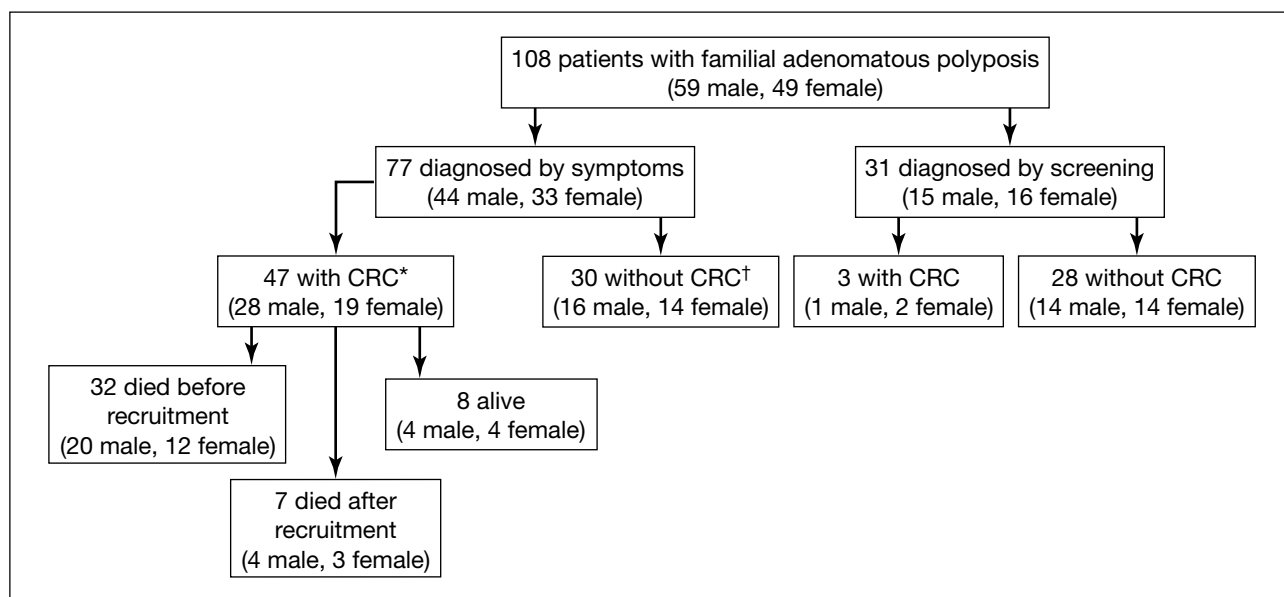
* 70 patients with familial adenomatous polyposis had treatment and surveillance data available for detailed study
† Reasons: genetic testing was not possible (no surviving index patient); mutation could not be found; or waiting for results of genetic testing

Fig 1. Flowchart showing the involvement of patients and at-risk family members in the surveillance and screening programmes

spontaneous mutation at a rate of 41.7%. One hundred and seventy-seven family members with a 50% risk of inheriting the condition were identified. Involvement of patients and their family members in the surveillance and screening programmes is shown in Fig 1. The colorectal phenotypes of the 108 patients with FAP are shown in Fig 2. Thirty-one patients were diagnosed with FAP by the Registry screening programme. The median age at diagnosis was 34.0 years (range, 12.0-69.0 years; SD, 14.1 years). Patients diagnosed by screening were, however, significantly younger than those diagnosed due to colorectal symptoms (median age, 29.0 years; SD, 15.2 years against median age, 36.0 years; SD, 13.3 years; P=0.002). Fifty (46.3%) patients developed

colorectal cancer: 47 were diagnosed when the patients presented with symptoms, and three were diagnosed during the screening process. In other words, 61.0% of patients with FAP had already developed colorectal cancer by the time they presented with symptoms. However, only 9.7% of them had already developed colorectal malignancy when FAP was diagnosed by screening. Among these 50 patients, four (8.0%) also had multicentric cancers. The median age at colorectal cancer diagnosis was 40.0 years (range, 24.0-65.0 years; SD, 12.7 years). There was no difference between male and female patients regarding the age at FAP diagnosis, the rate of colorectal cancer, and the age at colorectal cancer diagnosis.

* CRC colorectal cancer
† Six not recruited (2 male, 4 female)

Fig 2. Flowchart outlining the colorectal phenotype of the 108 patients with familial adenomatous polyposis

Table 1. Types of surgical resection performed

Surgical resection	For cancer	For prophylaxis	Total
Proctocolectomy and ileal pouch anal anastomosis	6	17	23
Total abdominal colectomy and ileorectal anastomosis	5	9	14
Koch pouch	0	1	1
End ileostomy	4	5	9
Others*	3	2	5

* These included two Hartmann's procedures and one right hemicolectomy for cancer palliation, one proctocolectomy and straight ileal-anal anastomosis, and one unknown procedure for prophylaxis

Two patients were initially diagnosed to have FAP when they were screened 8 and 22 years previously. However, they refused prophylactic colectomy only to present later with colorectal cancer symptoms. At the time of this survey, one of these patients had already died from metastatic disease. In another patient, a stage IV rectal cancer developed 1 year after total abdominal colectomy (IRA) at another hospital. The patient later died from metastatic disease. Up to July 2001, 39 patients had died from colorectal cancer, giving an overall colorectal cancer mortality rate of 78.0%. For those colorectal cancer patients diagnosed based on symptoms, the colorectal cancer mortality rate was 83.0%.

Among the 108 patients with FAP, 70 (37 male and 33 female) were recruited to the Registry. Therefore, more detailed clinical and surveillance data were available from these individuals for further analysis. To date, 52 of these patients have already received surgery for large bowel polyposis. This includes 34 prophylactic operations and 18 operations for colorectal malignancy. The types of operation performed are shown in Table 1. Among these 52 patients, 40 (76.9%) received sphincter-saving procedures, including 12 (66.7%) procedures for colorectal cancer and 28 (82.4%) procedures for cancer prophylaxis. At the time of writing, 15 newly diagnosed patients with FAP were awaiting further examination before preventive surgery. Three patients refused to have an operation. Apart from colorectal cancer, four female patients with FAP from different families developed papillary thyroid cancer at the ages of 18, 20, 22, and 23 years. All these cancers were diagnosed before the clinical diagnosis of FAP was made. The median interval between thyroid cancer and FAP diagnosis was 5.0 years (range, 1.0-19.0 years; SD, 8.1 years). Eleven (5 male, 6 female) patients had desmoid tumours. One patient developed an extra-abdominal desmoid tumour (over the pubic region) before colorectal resection, the remaining 10 developed desmoid tumours after surgery. The median interval between colorectal resection and desmoid tumour diagnosis was 2.0 years (range, 1.0-18.0 years; SD, 5.1 years). The sites of the desmoid tumours are shown in Table 2. The median age at desmoid tumour diagnosis was 33.0 years (range, 21.0-43.0 years; SD, 7.5 years). Three patients with abdominal wall desmoid tumours underwent surgical excision without recurrence. The two extra-abdominal desmoid tumours (one over the pubic region and the other on the back) were also excised without recurrence. One patient with tumours on both the abdominal wall and inside the peritoneal cavity underwent excision

Table 2. Sites of desmoid tumour

Desmoid tumour	No. of patients
Intra-abdominal	3
Abdominal wall	4
Extra-abdominal	2
Combined*	2

* Intra-abdominal and abdominal wall

of the abdominal wall component. Another patient underwent a debulking procedure of the abdominal wall component. All three patients with intra-abdominal desmoid tumours were medically treated.

At surveillance upper endoscopy, four patients (1 male and 3 female) were found to have duodenal adenomas. The median age at diagnosis was 43.0 years (range, 30.0-67.0 years; SD, 16.0 years). The median interval from colectomy was 11.5 years (range, 1.0-34.0 years; SD, 14.6 years). One patient who had a single pedunculated adenoma underwent endoscopic polypectomy. The remaining three had multiple polyps and were expectantly treated. No ampullary adenocarcinoma has been diagnosed in the patients so far. One patient was found to have adenomas at the antral region of the stomach. Fundic gland polyposis was found in 18 (25.7%) patients at a median age of 32.0 years (range, 14.0-52.0 years; SD, 11.4 years). During surveillance duodenoscopy, the periampullary region was routinely biopsied to look for dysplastic changes, although no gross polyps were identified. In 12 (17.1%) patients (6 male, 6 female), microscopic adenomatous changes were identified in the periampullary region at a median age of 35.0 years (range, 21.0-47.0 years; SD, 8.7 years). Such changes were found at a median interval of 5.0 years (range, 0-18.0 years; SD, 5.9 years) after colectomy. Among the 23 patients with pelvic pouches, pouch polyposes were found in four (17.4%) individuals (2 male, 2 female) at surveillance pouchoscopy. The median age at diagnosis of pouch polyposis was 33.0 years (range, 29.0-38.0 years; SD, 4.0 years). Pouch polyposis occurred at a median interval of 11.5 years (range, 7.0-15.0 years; SD, 3.9 years) after restorative proctocolectomy.

Discussion

This is the first paper on the phenotypic spectrum and clinical management of FAP in Chinese patients in Hong Kong. Familial adenomatous polyposis is a rare yet complex condition that poses challenging management issues to clinicians. By compiling clinical data through a dedicated registry, we hope that enough information can be obtained

to provide insights into the treatment of this rare colorectal cancer syndrome.

Based on the estimated worldwide population frequency of 1 in 10 000,[1] there should be at least 700 patients with FAP in Hong Kong. However, the number of patients enrolled by the Registry, which is the largest in Hong Kong, is much lower than this estimate. Even if the second largest collection by another university hospital in Hong Kong is added, the total number of local patients still falls short of the estimation. Whether the current number represents gross underdiagnosis of the condition or true lower incidence than in other parts of the world can only be answered by a population study. The reported spontaneous mutation rate for FAP varies from 10% to 30%.[9] The local rate of 41.7% is high, which may be due to ascertainment bias or a truly higher mutation rate than in other population groups. Although FAP is a deleterious dominant condition with dire consequences for the affected patients, the selective disadvantage associated with the presence of the mutation is equal to the frequency of new mutation.[10] As a result, this condition is maintained in the population by such a mutation-selection balance. As expected, patients with FAP diagnosed by screening are significantly younger than those diagnosed as a result of bowel symptoms. This may explain why the incidence of colorectal cancer in those diagnosed by symptoms was much higher than that in those diagnosed by screening. The median age at colorectal cancer diagnosis for the patients in this study was similar to previous reports.[11,12] The colorectal cancer mortality in the patients was high, which supports the view that presymptomatic diagnosis by screening followed by appropriate prophylactic surgery are effective ways to prevent colorectal cancer and its associated mortality in families with FAP.

All patients with FAP require surgical therapy for colorectal polyposis. Prophylactic surgery should be performed shortly after the clinical diagnosis is established by endoscopy. The objectives of prophylactic surgery are to remove all at-risk colorectal mucosa as well as to maintain a continent and low frequency anal evacuation.[11] The colorectal phenotype, particularly the number of rectal adenomas and the coexistence of cancer, is the main determinant for the most appropriate surgical procedure to be performed. Other factors for consideration are anal sphincter function, site of adenomatous polyposis coli (APC) gene mutation,[13] personal or family history of desmoid tumour, and the feasibility of close endoscopic surveillance. Colorectal resections of the patients in this study were performed by a number of local surgeons over a span of 38 years. The first proctocolectomy and ileal pouch anal anastomosis (IPAA) in Hong Kong was performed in 1984. Since that time, IPAA has become the most commonly used surgical procedure. Over the years, there has been an increasing use of the sphincter-saving procedure as the surgical treatment of choice for cancer therapy as well as prophylaxis. The only exception is bulky and/or low rectal cancer for which proctocolectomy and end-ileostomy is the only feasible treatment. The appropriate choice of surgical procedure is important for achieving colorectal cancer prevention. For the patient who died of metastatic rectal cancer shortly after IRA, it is apparent that IPAA instead of IRA should have been the surgical procedure because of the extent of rectal polyposis. However, for patients with limited rectal polyposis who are willing to undergo lifelong endoscopic surveillance every 6 months and ablation of rectal polyps, IRA can be a suitable surgical option.[11]

Extracolonic manifestations can be a cause of morbidity and later mortality for FAP patients.[10] Papillary thyroid cancer is reported to affect 1% to 2% of patients with FAP,[14] but the rate for the Registry was high at 5.7%. Similar to the experience of the Registry, papillary thyroid cancer showed female predominance.[15] The reported mean age at thyroid cancer diagnosis was 34 years[15] whereas the patients in this study were much younger. Similar to the sporadic form, the prognosis of FAP-associated papillary thyroid cancer is good. Desmoid tumour affects 10% to 17% of patients with FAP.[11,16,17] Despite being slow growing with no metastatic potential, desmoid tumours can cause significant morbidity and mortality due to their ability to surround, compress, and erode adjacent structures.[11] Among the patients in this study, enterocutaneous fistula and ureteric obstruction with hydronephrosis were the observed complications. Predisposed by surgical trauma, up to 85% of abdominal desmoid tumours were reported to develop within 5 years of abdominal procedures.[11] Extra-abdominal and abdominal wall desmoid tumours can usually be resected with good outcomes. However, attempts at resection of an intra-abdominal desmoid tumour are often fraught with difficulty, in that there is significant risk of bowel injury as well as a high recurrence rate. Therefore, medical treatment is often adopted unless complications occur.

The remaining gastrointestinal tract is also at risk of adenomatous change and malignant transformation. After prophylactic colectomy, patients with FAP should continue to have lifelong regular surveillance for the remaining at-risk gastrointestinal mucosa.[18] Gastric and duodenal adenomas have been reported to occur in 44% to 91% of patients[19] with duodenal adenomas usually occurring 10 to 20 years after development of colorectal polyposis.[11] The incidence of duodenal carcinoma in FAP is between 1% and 5%,[11] and it accounts for the largest number of cancer-related deaths in patients with FAP after colectomy.[20,21] Due to the short follow-up period and the relatively young age of the five patients with gastroduodenal adenoma, no malignant transformation has been detected so far. The patients in this study with duodenal microadenoma were younger than those with gross gastroduodenal adenomas. Whether these duodenal microadenomas will develop into gross adenoma and whether they have malignant potential remain unknown. Only long-term follow-up can determine the outcome of these microadenomas. It is increasingly recognised that polyposis can develop in the pelvic pouches after IPAA[22,23] with a theoretical risk of malignant transformation.

The growth defect conferred by APC gene mutation, the altered surgical anatomy, and faecal stasis in the pouch are contributory factors for pouch adenomatous change.[21] Upon identification, pouch adenoma can be controlled using a combination of endoscopic ablation and sulindac treatment.[21,24] The efficacy of endoscopic surveillance for the remaining gastrointestinal tract is unknown. However, a decision analysis by Vasen et al[25] for the management of duodenal polyposis suggested that regular surveillance resulted in an increased life expectancy of patients with FAP.

Clinical management of families with a complex hereditary colorectal cancer syndrome of FAP requires a multidisciplinary approach. Vigilant and lifelong surveillance of these individuals can be demanding from an administrative perspective. Therefore, coordination by a dedicated regional registry with its concentrated expertise and resources is important.[18] Clinical management of affected families by regional registry has led to improvement in life expectancy of patients with FAP.[2,26-28] From analysis of the data obtained from 36 Chinese families with FAP in Hong Kong, presymptomatic diagnosis by screening followed by appropriate prophylactic surgery are effective ways to prevent colorectal cancer in these high-risk individuals. Apart from colorectal polyposis and cancer, patients with FAP are also prone to develop a number of ECMs with potentially serious consequences. Therefore, lifelong regular surveillance is necessary to detect and to manage these ECMs. Clinical management of families with FAP can best be coordinated by a dedicated registry.

Acknowledgement

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