Twenty years of familial adenomatosis polyposis syndromes in the Singapore Polyposis Registry: an analysis of outcomes

Chew M H, Quah H M, Teh K L, Loi T T C, Eu K W, Tang C L

ABSTRACT

Introduction: The Singapore Polyposis Registry (SPR) was established in 1989 at the Singapore General Hospital. This initiative was aimed at providing a central registry service to facilitate identification, surveillance and management of families and individuals at high risk of colorectal cancer. The aim of the present study was to provide a comprehensive review of all patients with familial adenomatous polyposis (FAP) syndrome in the SPR.

Methods: All patients diagnosed with FAP in 1989–2009 were analysed. Data was extracted from a prospectively collected database.

Results: 122 patients from 88 families were analysed. The median age of this cohort was 29 (range 10–68) years. 97 percent of the cases were FAP and 3 percent were attenuated FAP. 92 patients tested positive for adenomatous polyposis coli gene. 42 percent of patients were diagnosed with colorectal cancer, of which 78 percent were diagnosed at an advanced stage. 73 percent of patients underwent restorative proctocolectomy and 21 percent had total colectomy. The median age at operation was 30 years. At median follow-up of 98 months, ten-year overall survival was 75.6 percent (95 percent confidence interval 67.0–84.2) and the median age at death was 40 years. For cancer cases, the overall recurrence was 13.5 percent. Recurrence and disease-free survival were not significant for the type of surgery performed (p-value is 0.486).

Conclusion: The SPR plays an important and integral part in counselling patients and families with FAP. Improved surveillance programmes may be required to detect the development of cancers in these patients at an earlier stage.

Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608

Chew MH, MBBS, MRCSE, FRCSE
Associate Consultant

Quah HM, MBBS, FRCSE, FAMS
Consultant

Loi TTC, MSc HCM, GDipGenetCouns
Genetic Counsellor

Eu KW, MBBS, FRCSE, FAMS
Senior Consultant

Tang CL, MBBS, FRCSE, FAMS
Senior Consultant and Head

Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Singapore 119228

Teh KL
Medical Student

Correspondence to:
Dr Hak-Mien Quah
Tel: (65) 6321 4677
Fax: (65) 6226 2009
Email: quah.hak.mien@sgh.com.sg

Keywords: colorectal cancer, familial adenomatous polyposis, outcomes

Singapore Med J 2011;52(4):246-251

INTRODUCTION

The first polyposis registry, the St Mark's Hospital Polyposis Register, was conceived by JP Lockhart-Mummery and C Dukes in 1924.[1] It was only around 1950 that a policy for cancer prevention and early detection of polyposis evolved with the improved knowledge of the epidemiology and incidence of polyposis cancers.[1] Since then, many national and regional registries have been set up, with considerable impact on the reduction of colorectal cancer (CRC) in familial adenomatous polyposis (FAP). These include registries in Europe,[2-5] Canada[5] as well as Asia,[6, 7] and number more than 50 worldwide.

The Singapore Polyposis Registry (SPR) was established in 1989 at the Singapore General Hospital (SGH).[8] The aim of this initiative was to provide a central registry service to all doctors in Singapore in order to facilitate identification, surveillance and management of families and individuals at high risk of CRC. From an initial emphasis on FAP and hereditary non-polyposis CRC, patients with other polyposis types, such as Peutz Jeghers, juvenile polyposis and hereditary mixed polyposis syndromes, have also been included.

The SPR has also evolved and is currently backed by molecular biology, cell-kinetic and anorectal physiology laboratories. Patients are thus assured of accurate pre- or post-clinical diagnosis, genetic testing and detailed post-surgical functional assessments for those who undergo pouch operations. Various research projects performed using data from the SPR have also resulted in important genetic testing and identification of at-risk individuals. This has led to important data that improve diagnosis as well as survival and genetic counselling for patients.[9,10]

The aim of the present study was to provide a comprehensive review of all high-risk individuals with FAP in the SPR, and to evaluate phenotypic

characteristics, surgical outcomes as well as survival data.

METHODS

This study was approved by the Institutional Review Board of SGH. The records of all patients in the SPR have been prospectively collected in a computerised database. The clinical data from case records were obtained for analysis. FAP was diagnosed based on the clinical criteria of > 100 adenomas in the colon and rectum without family history, or in patients < 30 years of age with any number of adenomas and a positive family history of FAP.[11] Attenuated FAP (AFAP) is a distinctive phenotype that is recognised as a subset of FAP patients, and is defined in an individual who is characterised by a lower number of colorectal adenomas (< 100).[12] Patients with features that are suggestive of Gardner's syndrome were classified as FAP. The cases in the registry were voluntarily registered by doctors who treated these patients across the country. Information was sought regarding the patients, and their family pedigrees were constructed based on detailed interviews conducted by the SPR coordinator. Histological data and reports were obtained whenever possible.

As of December 2009, 88 families were registered with the SPR, comprising 524 patients and their first-degree relatives. Complete histological reports were available for 122 patients, and these were investigated retrospectively. The rest of the patients' histological reports were unavailable and thus not included in the analysis. Cases with unknown or incomplete data were excluded from the evaluation. Patients were divided into two time periods, 1989–1999 and 2000–2009, for analysis.

The location of the index CRC was considered to be right-sided when it arose proximal to the splenic flexure, while lesions at or distal to the splenic flexure were deemed be left-sided. Synchronous CRC was defined as one found during the index operation for the CRC or diagnosed within 12 months after the resection of the index CRC. In the case of synchronous lesions, the most advanced lesion was used for comparison of tumour stage classification. The stage of disease was evaluated using plain chest radiograph, ultrasonography and/or computed tomography of the abdomen and pelvis. After surgical resection, pathologic staging of disease was based on the American Joint Committee on Cancer Staging Manual, 6th edition,[13] with review of the resected specimen and investigations of distant metastases. Local recurrence was defined as the first clinically, radiologically and/or pathologically evident tumour of the same histological type within or contiguous to the previously treated tumour bed. Distant recurrence was defined as similar evidence of spread outside the primary tumour site, at sites including but not limited to the liver, lungs, bone, brain and para-aortic region. Mortality data and the cause of death were obtained from the Singapore Cancer Registry.

All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, IL, USA). For statistical significance analysis, Pearson's chi-square test and Fisher's exact test were used for comparison between groups. Continuous nonparametric data was analysed using the Mann Whitney U test. In the analysis of disease-free survival (DFS), a patient was considered to have an event if there was local or systemic recurrence after completion of the primary treatment. DFS was calculated from the date of surgery till the date of first recurrence. Patients with

Table I. Demographics and clinicopathologic characteristics of the FAP cohort.

Factor	No. (%)
Gender	
Male	73 (60)
Female	49 (40)
Ethnic group	
Chinese	84 (69)
Malay	29 (23)
Indian	7 (6)
Others	2 (2)
Median age; range (yrs)	
At diagnosis	29; 12–68
At surgery	30;13–68
≤ 40	97 (80)
> 40	25 (20)
Disease type	
FAP	118 (97)
Attenuated FAP	4 (3)
Mutation results	
Positive APC	92 (76)
Negative APC	2 (2)
Not done	28 (23)
Cancer at diagnosis	
Yes	52 (43)
No	70 (57)
Site of tumour (n = 47)*	
Rectum	25 (53)
Rectosigmoid	6 (13)
Sigmoid	6 (13)
Descending colon	3 (6)
Transverse colon	3 (6)
Ascending colon	3 (6)
Caecum	1 (2)
AJCC Stage (n = 52)	
I	6 (12)
II	5 (10)
III	31 (60)
IV	10 (18)

* Data is missing for 5 patients.
FAP: familial adenomatous polyposis; APC: adenomatous polyposis coli; AJCC: American Joint Committee on Cancer

Table II. Types of extra-colonic manifestations.

Type	No. (%)
Desmoids	16 (14)
Abdominal wall	9
Mesenteric	7
Gastroduodenal polyps	36 (29)
Cutaneous skin lumps	21 (17)
Extra-colonic carcinomas	10 (8)
Stomach	2
Periampullary	1
Thyroid	6
Trachea SCC	1

SCC: squamous cell carcinoma

Table III. Types of surgical resection performed.

Surgical resection	No. (%)	
	Cancer (n = 52)	Prophylaxis (n = 70)
Proctocolectomy and IPAA	37 (71)	52 (75)
Total colectomy and IRA	8 (15)	18 (25)
Others*	5 (10)	-
No operation	2 (4)	-

* Data includes 3 palliative resections, 1 loop colostomy and 1 left hemicolectomy in a newly diagnosed case.
IPAA: ileal pouch anal anastomosis; IRA: ileorectal anastomosis

no evidence of disease after treatment were censored at the date of the last follow-up. Similarly, overall survival (OS) was computed from the date of surgery to the date when the patient was last known to be alive. The DFS and OS curves were constructed using the Kaplan-Meier method, and comparisons between groups of clinical interest were made using the log-rank test. Finally, multivariate Cox regression analysis was done to evaluate independent prognostic factors, adjusting for possible confounding factors. All statistical tests were assessed at the conventional 0.05 level of significance.

RESULTS

Out of the 122 patients evaluated, 118 (97%) cases were FAP and four (3%) were AFAP. 60% of the study cohort (n = 73) were male and 40% (n = 49) were female. The main ethnic group of the patients was Chinese (n = 84, 69%) followed by Malay (n = 29, 23%), reflecting the predominantly Chinese population in our country. The median age at diagnosis was 29 (range 13–68) years, while the median age at surgery was 30 (range 13–68) years. 97 (80%) patients had surgery before the age of 40 years. Of the 94 patients who underwent adenomatous polyposis coli (APC) gene testing, 92 tested positive. 52 (43%) patients presented with cancer at diagnosis, and the majority (n = 41, 78%) were advanced stage III and IV cancers (Table I). The most common site of cancers was the rectum (n = 25, 48%), and 11 (21%) patients had synchronous cancers. Interestingly, six out of the 11 cases had synchronous lesions in the rectum as well.

Extra-colonic manifestations are presented in Table II. The most common manifestations were stomach fundic gland polyps and duodenal adenomatous polyps (n = 36, 29%). Various cutaneous lumps, such as sebaceous cysts and osteomas, were found in 21 (17%) cases. Desmoids, located either in the abdominal wall (n = 9) or mesentery (n = 7), were found in 16 (14%) patients. Ten (8%) patients had extra-colonic cancers, of which thyroid cancers were the most common (n = 6). Of these ten patients, five had synchronous CRC. Dental abnormalities and congenital hypertrophy of the retinal pigment epithelium were not routinely evaluated in our patients.

A comparison between surgery performed for CRC cases and that for prophylaxis was made (Table III). Overall, 89 (73%) patients underwent restorative proctocolectomy and 26 (21%) had total colectomy with ileorectal anastomosis (IRA). All ileal pouch anal anastomosis (IPAA) procedures were performed with the double stapling technique except for one case, for which mucosectomy and handsewn anastomosis were performed. For CRCs, 37 (71%) patients underwent restorative proctocolectomy, eight (15%) underwent total colectomies, three had palliative resection, one had loop colostomy and two did not undergo any operation in view of the advanced nature of the disease on presentation. One patient initially underwent a left hemicolectomy but subsequently had a total colectomy and anastomosis performed five years later for metachronous cancer. This was because the patient initially declined a radical colectomy, opting instead for a segmental colectomy despite adequate counselling.

Comparative analysis was performed between the two periods, 1989–1999 (n = 76) and 2000–2009 (n = 46). In 1989–1999, there were fewer cases of cancers at presentation (n = 30, 40%) but more total colectomies performed (n = 18, 24%) (IPAAs n = 54, 71%). In the period 2000–2009, more cases of cancers were identified on presentation (n = 22, 48%) and more IPAAs were performed (n = 35, 76%) compared with total colectomies (n = 8, 17%). There was, however, no statistical significance in the surgical procedures performed between the two periods (p = 0.203).

At the median follow-up of 98 months, the ten-year

OS was 75.6% (95% confidence interval [CI] 67.0–84.2). 82 (67%) patients were alive and had no disease. 33 (27%) patients had died on review, 24 (20%) of whom died from CRC, seven (6%) from extra-colonic disease and two (1%) from other causes. The median age of death was 40 years. The overall five-year survival of patients with either CRC or extra-colonic cancer was 57.1% (95% CI 43.0–71.2) compared to 98.0% (95% CI 94.1–100.0) for those who had not developed cancer (Fig. 1). For cancer cases, the overall recurrence rate was 13.5% (n = 7), of which four (7.7%) cases were distant metastasis and three (5.8%) were locoregional metastasis. Recurrence and DFS were not significantly different between IPAA and IRA (p = 0.486).

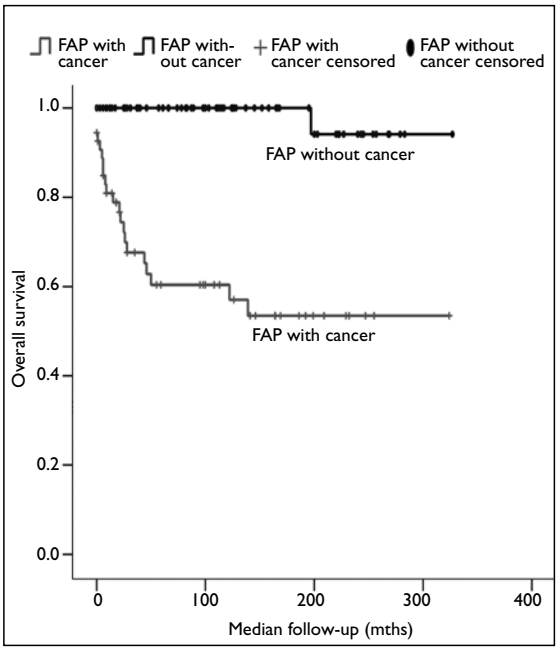

Fig. 1 Comparison of survival between FAP patients with and without cancer (p < 0.0001).

DISCUSSION

FAP is an autosomal dominant multiorgan disease with variable expressivity. Inactivating mutations in the APC gene located on chromosome 5q21[11] results in the characteristic development of multiple colorectal adenomatous polyps, which, without timely surgical intervention, would invariably develop into colorectal carcinoma in an individual by 35–40 years of age. FAP patients are also at risk of developing neoplasms in various tissues, such as osteomata of the jaw and skull bones, epidermoid cysts, congenital hypertrophy of the retinal pigment epithelium, dental anomalies, as well as gastric, duodenal, brain and desmoids tumours. These patients are noted to have a higher risk of developing brain tumours, papillary cancers of the thyroid and hepatoblastoma.[11,14,15]

As a result of the autosomal dominant nature of this disease and the various phenotypes with which patients present, early diagnosis, treatment and careful follow-up of high-risk patients are essential. The development of FAP registries, in which pedigrees are constructed around an affected proband, is considered to be effective in structuring care for these patients and their families. Since its inauguration in 1989, the SPR has evolved into a service that is available to all doctors in Singapore in order to facilitate identification, surveillance and management of all FAP patients and their families. Its main objectives include the registration of all FAP families in Singapore so that at-risk individuals may be offered current screening procedures and treatments, as well as identification of family members for genetic testing and counselling services. The overall aim is to prevent the development of cancer in these high-risk patients. The workflow of the SPR is illustrated in Fig 2.

The main benefits obtained from a detailed registry enable appropriate decisions to be made on the suitable treatment for these young patients. It is paramount to provide the most appropriate treatment so as to reduce the risk of patients developing advanced CRC, and at the same time, ensuring that patients have the best possible quality of life. This is especially so for FAP patients who undergo radical surgery when they have no disabling clinical symptoms or only mild ones. The age of 30 years is a critical age for surgical prophylaxis, and colectomy should be offered from the age of 20 years.[6] This enables young patients to develop physically, grow in maturity in dealing with the disease as well as achieve educational and career milestones. These patients are thus able to complete crucial examinations or their tertiary/diploma education before undergoing surgery, which may take several months for complete recovery.

The choice of surgery remains debatable. While IPAA was the most common procedure performed in our department, a relatively large number of IRAs were performed in both cancer cases and for prophylaxis. Restorative proctocolectomy was first described by Parks et al,[16] and was reported to eradicate all at-risk colorectal mucosa and maintain the anal canal with good functional results. IPAA thus appears to be the most appropriate procedure for FAP patients. IPAA is the procedure of choice in the presence of dysplasia in the rectum or rectal cancer. In our study cohort, the high incidence of rectal primary cancers (53%) and synchronous cancers in the rectum may suggest that IPAA should be advocated routinely in FAP patients. However, developing knowledge of the disease has suggested that IRA may be

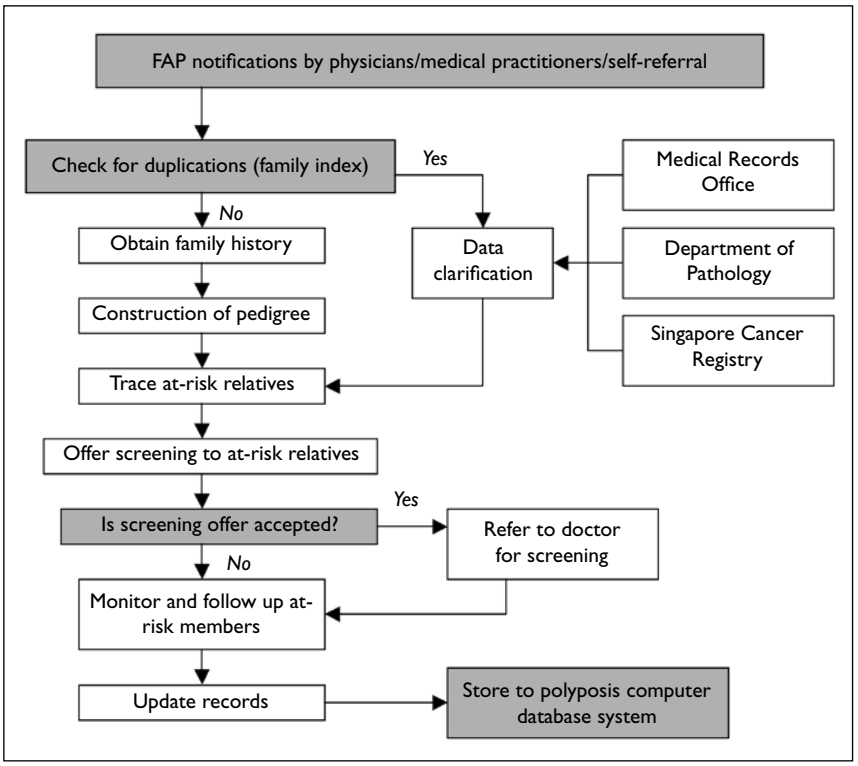

Fig. 2 Chart shows the workflow of the Singapore Polyposis Registry for FAP patients.

a more suitable option in a select group of patients; the proposed criteria include clinical manifestations, social circumstances and the severity of genetic mutations.[17] Patients undergoing IRA may have an AFAP form of disease or fewer rectal polyps (usually recommended < 20 polyps), and may thus be willing to undergo lifelong annual endoscopic surveillance. For genetic mutations, several reviews have identified the correlation between the clinical and genetic aspects, with preference for one surgical technique over another. Bulow et al identified patients with genetic errors in codon 0–200 or > 1,500, and proposed IRA over IPAA for these patients with mild genetic mutations.[18] The patients must, however, be compliant to surveillance.

Patients' wishes play an important part in the choice of procedure. The decision by a young patient is usually dependent on a family member's experience[19] or information obtained from the internet.[20] They may thus be inclined to opt for or reject the same procedure that one of their family relatives had undergone, depending on the outcome experience. The lack of patient-oriented information content on the internet also does not facilitate surgical decisions and may add to further decision dilemmas.[19] Furthermore, complications in IPAAs include a higher risk of night-time soilage, sexual and urinary dysfunction as well as a need for temporary defunctioning ileostomy.[21] These potentially embarrassing and distressing issues that may arise from an IPAA may dissuade the patient from opting for the procedure. This may require specially trained counselling methods.

The surgical therapy for FAP is complex and patient-centric; hence, despite the suggested oncologic benefits of an IPAA, in carefully selected FAP patients, there may still be a role for IRA. As evident from our results, locoregional recurrence rates are low (5.7%) and there is no statistical significance in survival and recurrence between the type of surgery performed in both cancer and surgical prophylaxis cases. Likewise, this is observed in other registries and in a recent meta-analysis of 1,002 patients from 12 studies, in which the risk of rectal cancer after IRA was reported to be 5.5%.[22] Meticulous follow-up is cited as one of the most important criteria if IRA is performed.[22,23] Iwama et al, who reviewed the data from the Japan Polyposis Registry where rectal-preserving operations are popular, cautioned that the cumulative risk of recurrence in the preserved rectum was 12% at ten years and 23% at 15 years.[6] This cumulative risk was also noted by other registries.[21,24] We still await long-term follow-up data in our own study cohort.

Certain limitations are evident from this review. Difficulty in obtaining complete histological data from our registered FAP patients and the inability to perform surveillance and genetic testing in all patients are some of the limitations. This is due to the large number of migrant population in Singapore, with various family

members residing in other countries. In addition, as the registration of patients by public and private sector physicians is voluntary, it is unlikely that all FAP patients in the country were captured. It is thus necessary to create greater awareness of the presence of the SPR in Singapore. Furthermore, it may not be possible for a physician or hospital to follow up on a patient for more than 20 years, as the patients are likely to move to other local hospitals for follow-up or migrate due to studies, work or marriage.

In conclusion, clinical management of affected families in our registry has led to a good life expectancy for patients with FAP in our registry. In these high-risk individuals, early diagnosis and early appropriate prophylactic surgery are effective in preventing CRC. The choice of IPAA or IRA remains largely debatable, but as knowledge of the disease develops, better selection can be made to ensure good clinical outcome and low cancer recurrence. As our population continues to grow, there is an important need for the registry to train up more coordinators to educate FAP patients regarding the need for compliance to dedicated surveillance and follow-ups. In the long run, this would be crucial to further improving outcomes in FAP patients.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Ming-Hian Kam, Dr Jit-Fong Lim, Dr Kheng-Hong Ng and Dr Kok-Sun Ho for their invaluable contributions to the study, and former Heads of Department of Colorectal Surgery, SGH, Dr Hak-Su Goh and Dr Seow-Choen Francis, for their vision and tireless commitment to the development of the Singapore Polyposis Registry.

REFERENCES

1. Bussey HJR. The St Mark's Hospital Polyposis Registry. In: Contributions from St Mark's Hospital. Sesquicentenary Volume 1935-1985. Munich: Mann CV, 1988: 313-8.
2. Bülow S. Results of national registration of familial adenomatous polyposis. Gut 2003; 52:742-6.
3. Bertario L, Presciuttini S, Sala P, Rossetti C, Pietroiusti M. Causes of death and postsurgical survival in familial adenomatous polyposis: results from the Italian Registry. Italian Registry of Familial Polyposis Writing Committee. Semin Surg Oncol 1994; 10:225-34.
4. Heiskanen I, Luostarinen T, Järvinen HJ. Impact of screening examinations on survival in familial adenomatous polyposis. Scand J Gastroenterol 2000; 35:1284-7.
5. Belchetz LA, Berk T, Bapat BV, Cohen Z, Gallinger S. Changing causes of mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1996; 39:384-7.
6. Iwama T, Tamura K, Morita T, et al. Japanese Society for Cancer of the Colon and Rectum. A clinical overview of familial adenomatous polyposis derived from the database of the Polyposis Registry of Japan. Int J Clin Oncol 2004; 9:308-16.
7. Ho JW, Chu KM, Tse CW, Yuen ST. Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry. Hong Kong Med J 2002; 8:342-7.
8. Goh HS, Wong J. The Singapore Polyposis Registry. Ann Acad Med Singapore 1992; 21:290-3.
9. Cao X, Eu KW, Seow-Choen F, Zao Y, Cheah PY. APC mutations and phenotypic spectrum of Singapore familial adenomatous polyposis patients. Eur J Hum Genet 2000; 8:42-8.
10. Koh PK, Loi C, Cheah PY, et al. Mesenteric desmoids tumours in Singapore familial adenomatous polyposis patients: clinical course and genetic profile in a predominantly Chinese population. Dis Colon Rectum 2007; 50:75-82.
11. Bussey HJR. Familial Polyposis Coli. John Hopkins University Press, Baltimore 1975:1-104.
12. Knudsen AL, Bisgaard ML, Bülow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2003; 2:43-55.
13. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th Ed. New York: Springer-Verlag, 2002.
14. Vasen HF, Möslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008; 57:704-13.
15. Vasen HF, BÜlow, The Leeds Castle Polyposis Group. Guidelines for the surveillance and management of familial adenomatous polyposis (FAP): a worldwide survey among 41 registries. Colorectal Dis 1999; 1:214-21.
16. Parks AG, Nicholls RJ, Belliveau P. Proctocolectomy with ileal reservoir and anal anastomosis. Br J Surg 1980; 67:533-8.
17. E. Contessini-Avesani E, Botti F, Negri C, et al. Familial Adenomatous polyposis. Surgical treatment: when and how. Tech Coloproctol 2004; 8:S309-14.
18. Bulow C, Vasen H, Jarvinen H, Bjork J, Bisgaard ML, Bulow S. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. Gastroenterology 2000; 119:1454-60.
19. Neuman HB, Robbins L, Duarte J, et al. Risk-reducing surgery in FAP: role for surgeons beyond the incision. J Surg Oncol 2010; 101:570-6.
20. Neuman HB, Cabral C, Charlson ME, Temple LK. Is internet information adequate to facilitate surgical decision-making in familial adenomatous polyposis? Dis Colon Rectum 2007; 50:2135-41.
21. Bjork J, Akerbrant H, Iselius L, et al. Outcome of primary and secondary ileal pouch-anal anastomosis and ileorectal anastomosis in patients with FAP. Dis Colon Rectum 2001; 44:984-92.
22. Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial abdenomatous polyposis. Br J Surg 2006; 93:407-17.
23. 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; 46:1175-81.
24. Campos FG, Imperiale AR, Seid VE, et al. Rectal and pouch recurrences after surgical treatment for familial adenomatous polyposis. J Gastrointest Surg 2009; 13:129-36.