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CLINICAL STUDIES ON FAMILIAL ADENOMATOUS POLYPOSIS

by

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ACADEMIC DISSERTATION

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by Roman numerals:

I Heiskanen I, Matikainen M, Hiltunen K-M, Laitinen S, Rintala R, Järvinen HJ. Colectomy and ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis. Colorect Dis 1999;1:9-13.

II Heiskanen I, Järvinen HJ. Fate of the rectal stump after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Int J Colorect Dis 1997;12:9-13.

III Heiskanen I, Järvinen HJ. Occurrence of desmoid tumours in familial adenomatous polyposis and results of treatment. Int J Colorect Dis 1996;11:157-162.

IV Heiskanen I, Kellokumpu I, Järvinen HJ. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. Endoscopy 1999;31:412-416.

V Heiskanen I, Luostarinen T, Järvinen HJ. Impact of screening examinations on survival in familial adenomatous polyposis. Scand J Gastroenterol, accepted for publication.

ABBREVIATIONS

AAPC	attenuated adenomatous polyposis coli
AFAP	attenuated adenomatous polyposis coli
APC	adenomatous polyposis coli
CAPP	concerted action for polyposis prevention
CHRPE	congenital hypertrophy of the retinal pigment epithelium
COX	cyclooxygenase inhibitor
CRC	colorectal cancer
DCC	deleted in colon cancer gene
DNA	deoxyribonucleic acid
DT	desmoid tumor
FAP	familial adenomatous polyposis
FGP	fundic gland polyp
GS	Gardner's syndrome
HNPCC	hereditary nonpolyposis colorectal cancer
IRA	colectomy and ileorectal anastomosis
NSAID	nonsteroidal anti-inflammatory drug
PC	proctocolectomy
PC+I	proctocolectomy and ileostomy
PTT	protein truncation test
p53	tumor suppressor gene protein p53
RPC	restorative proctocolectomy, proctocolectomy with ileal pouch anal anastomosis

INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomally dominant inherited disease with 50% risk in every offspring and equal distribution between the two sexes. Typically, FAP patients develop from hundreds to thousands of adenomatous polyps in the colon or rectum, but the disease does not usually manifest until late childhood or early adult life. One or a few of these benign polyps almost inevitably develop into colorectal carcinoma (CRC) (Bussey, 1975). However, FAP is a systemic disorder affecting tissues from all three germ layers, with various extracolonic manifestations: ectodermal (skin cysts, eye lesions, and endocrine tumors), endodermal (liver tumors, adenomas, and adenocarcinomas of the stomach, small bowel, and biliary tree) and mesodermal (dental abnormalities, desmoids, and osteomas) (Talbot, 1994).

The polyposis varies in severity in different families. Because of the inevitable risk of CRC in an untreated FAP patient, screening of individuals at risk begins at puberty with annual colonic examinations and prophylactic colectomy is indicated before symptomatic disease or with diffuse polyposis (Bussey, 1975).

Centralized registration of polyposis patients, screening of family members at risk, and early colectomy has led to improvement of the prognosis (Bülow et al, 1995b). As deaths from colorectal cancer remain constant or decrease in frequency, it is likely that proportional death rates from extracolonic manifestations of FAP will continue to rise (Belchetz et al., 1996). However, there are controversies over treatment methods. The present study was undertaken to study therapeutic strategies, results of treatment, and survival of patients with FAP.

REVIEW OF THE LITERATURE

History and nomenclature

In 1721, Menzel published the first known report of a polypoid condition, but it was probably of inflammatory origin (Menzel 1721). In 1881, Sklifasowski reported the first definite case of FAP and in 1882 Cripps recorded polyposis in a brother and sister, suggesting a familial tendency of the disease (Sklifasowski 1881; Cripps, 1882). The change from a polyp to carcinoma was described in 1890 by Hanford and in 1895 in a review by Hauser (Hanford, 1890; Hauser, 1895).

In 1925, Lochart-Mummery investigated three families with multiple adenomata, which was also the start of St Mark's Polyposis Register (Bussey, 1975). The autosomal dominant inheritance was described by Cockayne (Cockayne, 1927). The clinical, genetic, and pathological aspects of familial polyposis coli were more accurately defined in the 1950s and 1960s. Gardner described a kindred with polyposis, multiple osteomas, and epidermoid cysts, a disease entity called Gardner's syndrome (GS) (Gardner, 1951; Gardner and Richards, 1953), which he considered to be a distinct genetic disorder. Later on, desmoid tumors and dental abnormalities were also included (Gardner, 1962). Many authors considered GS to be a variant form of the same genetic disorder, thus representing a combination of different extracolonic manifestations of FAP (Smith, 1968; Utsunomiya and Nakamura, 1975; Watne et al., 1975).

In 1975, Alm described the results of treatment of familial polyposis coli based on the first national registry (Alm, 1975a; 1975b). Bussey published a detailed description of FAP in his extensive monograph in 1975 (Bussey, 1975).

In 1986, Herrera and coworkers detected an interstitial deletion in the long arm of chromosome 5 in a patient with GS (Herrera et al., 1986). In 1987, the FAP locus was localized by linkage analysis to the region of 5q21-22 (Bodmer et al., 1987; Leppert et al., 1987). In 1991, the adenomatous polyposis coli gene (APC) was subsequently localized and the gene sequence defined (Groden et al., 1991; Kinzler et al., 1991; Nishisho et al., 1991).

FAP has been synonymous with disseminated polypi (Cripps, 1882), polyposis intestinalis adenomatosa (Hauser, 1895), polyposis intestini (Dukes, 1930), familial adenomatosis of the colon and rectum (Lockhart-Mummery and Dukes, 1939), familial intestinal polyposis (Dukes, 1952), familial multiple polyposis (Smith, 1968), hereditary adenomatosis of the colon and rectum (Alm and Licznerski, 1973; Painter and Jagelman, 1985), familial polyposis of the colon (Lockhart-Mummery et al., 1956; Yao et al., 1977), adenomatous polyposis of the gastrointestinal tract (Hamilton et al., 1979), and familial adenomatous polyposis coli (Järvinen, 1987).

However, it became obvious that the most common term, familial polyposis coli, was inappropriate because of the various extracolonic manifestations. Therefore, the Leeds Castle Polyposis Group advocated the term familial adenomatous polyposis (FAP) (Thomson, 1987).

Registries

The first polyposis register was started in 1925 at St Mark's Hospital, London, at the initiation of JP Lockhardt-Mummery, C Dukes, and HJR Bussey (Bussey, 1975). During the last 30 years, national and regional registers have been established round the world (Jagelman, 1983; Berk et al., 1987; Bülow, 1987; Macrae et al., 1989; Morton et al., 1993), the Finnish Polyposis Registry was started in 1984 (Järvinen et al., 1984). Since the foundation of the registries, the incidence of colorectal cancer has decreased from 50-70% of patients detected by bowel symptoms to 3-10% of patients detected by screening (Alm and Licznerski, 1973; Bülow, 1987; Vasen et al., 1990).

Ideally, registries are run by a combination of surgeons, gastroenterologists and geneticists. Research work is part of the registrar's work, both nationally and internationally. Therefore, a collaborative group of specialists founded "The Leeds Castle Polyposis Group" for further co-operative studies on FAP (Northover, 1987).

Epidemiology

The most reliable data on incidence and prevalence are from countries with national parish registries, as in the Nordic countries. The frequency at birth has been reported to be 1:7600 to 1:22000 (Alm and Licznerski, 1973; Järvinen et al., 1984; Bülow, 1987). The prevalence has been $2.29\text{-}2.62 \times 10^{-5}$ (Burn et al., 1991; Maher et al., 1993). An incidence of 1 in 10,000 live births and a prevalence of 1 in 30,000 can be used as approximations.

Pathology

Adenomas of the large intestine are tubular adenomas arising from the mucus-secreting epithelium lining the interior of the intestine. Polyps are usually scattered throughout the colon and their size may vary, but most of them are under 5 mm in diameter. Some polyps may be pedunculated and others sessile. Adenomatous polyps rarely become manifest before 10 years of age. (Talbot, 1994)

Most colorectal carcinomas arise from a pre-existing adenoma, forming anadenoma-carcinoma sequence, as proposed by Muto and coworkers (Muto et

al. 1975). The adenoma-carcinoma sequence pertains to the duodenum as well as to the large bowel (Spigelman et al., 1994).

Knudson suggested a "two-hit" hypothesis of cancer formation: in the dominantly inherited form, one mutation is inherited in the germline cells and the normal copy of the gene is inactivated by a second mutation ("second hit") in somatic cells (Knudson, 1971). In accordance with this hypothesis, Vogelstein and colleagues have described a genetic model for tumorigenesis in colorectal cancer (Fearon and Vogelstein, 1990; Kinzler and Vogelstein, 1996). The APC gene mutation initiates the neoplastic process and tumor progression results from genetic changes, including oncogene activation (K-ras) and inactivation of tumor suppressor genes (APC, DCC, p53) (Fig. 1).

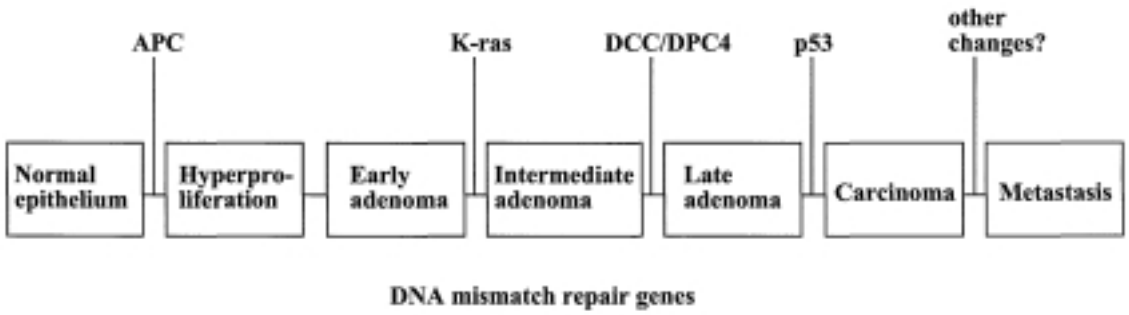

Figure 1. Genetic model of colorectal tumorigenesis (Fearon and Vogelstein, 1990; Kinzler and Vogelstein, 1996).

Genetics

In 1986, Herrera and coworkers detected an interstitial deletion of the long arm of chromosome 5 in a patient with Gardner's syndrome (GS) (Herrera et al., 1986). Thereafter the FAP locus was localized to the region of 5q21-22 in 1987 (Bodmer et al., 1987; Leppert et al., 1987). Thus, the diagnosis of FAP was possible by predictive DNA markers closely linked to the gene, but was dependent on the availability of DNA from other family members (Tops et al., 1989). However, it only gives an estimation of the risk of being a gene carrier rather than a definite risk.

The adenomatous polyposis coli (APC) gene was localized and gene sequencing performed in 1991 (Groden et al., 1991; Kinzler et al., 1991; Nishisho et al., 1991). Thereafter, the diagnosis of FAP was possible by mutation analysis. This gene on chromosome 5q21-22 consists of 15 exons and encodes a polypeptide protein of 2843 amino acids. It is considered to function as a tumor suppressor gene. The majority of mutations of the APC gene cause a stop codon via point mutations or frameshifts resulting in a truncated protein (Nishisho et al., 1991; Miyoshi et al., 1992). Over 300 mutations have been reported (van der Luijt et al., 1996).

The APC gene protein forms a complex with a protein kinase. This complex targets for degradation of b-catenin, a protein involved in both cell adhesion and intracellular signal transduction. It is also involved in cell migration up the colonic crypt and cell adhesion through association with E-cadherin. (Kinzler and Vogelstein, 1996)

Penetrance, however, has been incomplete (Reed and Neel, 1955; Alm and Licznerski, 1973). Spontaneous mutation has been reported in up to 46% of FAP cases, and is associated with a more severe form of the disease, probably due to later diagnosis (Rustin et al., 1990; Vasen et al., 1990; Maher et al., 1993). These individuals are as likely to transmit the disease to their children as individuals with a family history.

Genotype-phenotype correlations

Several studies have shown a correlation between a specific mutation of the APC gene and the phenotypic expression (Nagase and Nakamura, 1993; Fodde and Khan, 1995; van der Luijt 1996). However, individuals with identical mutations may show variability in polyp count and extracolonic manifestations (Nagase and Nakamura, 1993; Giardiello et al., 1994). Mutations nearer the 5' end of the APC gene are associated with small numbers of colorectal adenomas and late onset of CRC, described as an attenuated form of FAP (AAPC) (Spirio et al., 1993; Soravia et al., 1998). Lynch and coworkers described a syndrome of sparse and flat adenomas located in the proximal colon and upper gastrointestinal lesions, which was termed hereditary flat adenoma syndrome (HFAS) (Lynch et al., 1992). The clinical picture, pathologic features, and genetic studies of HFAS revealed it to be the attenuated form of FAP (Lynch et al., 1995a). Mutations at codon 1597 or beyond also produce an attenuated phenotype (Friedl et al., 1996). Profuse polyposis and earlier onset of CRC have been associated with a deletion in codon 1309 (Caspari et al., 1994) and with mutations between codons 1250 and 1464 (Nagase et al., 1992). Extracolonic manifestations were correlated with mutations beyond codon 1403 and severe gastroduodenal polyposis with a mutation at codon 1520 (Dobbie et al., 1996; Legget et al. 1997). Correlations are presented in Figure 2.

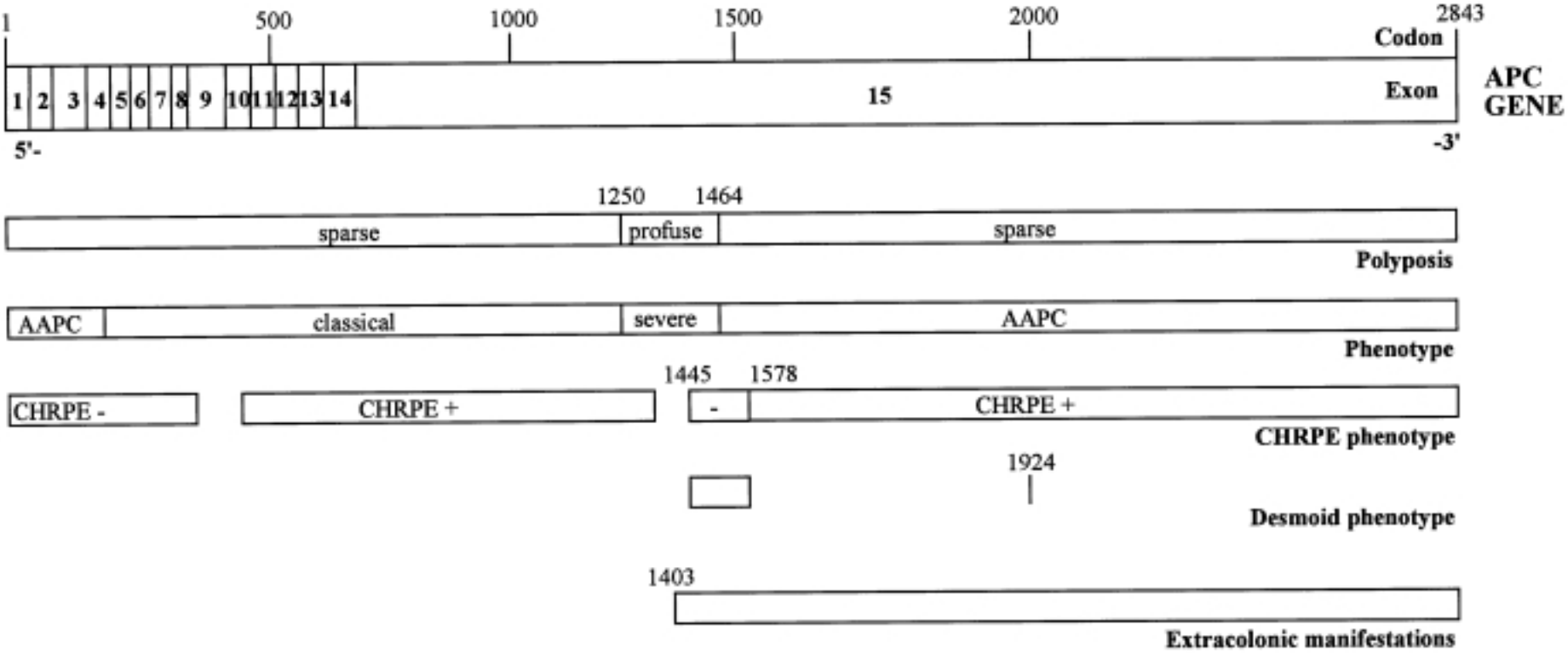

Figure 2. Correlation between the location of the APC gene mutation and the clinical phenotype in familial adenomatous polyposis.
APC = adenomatous polyposis coli, AAPC = attenuated adenomatous polyposis coli, CHRPE = congenital hypertrophy of retinal pigment epithelium, profuse > 5000 polyps, sparse = 1000-2000 polyps, - = absent, + = present.
(Nagase et al., 1992, Spirio et al., 1993, Friedl et al., 1994, Caspari et al., 1995, Dobbie et al., 1996, Friedl et al., 1996, van der Luijt 1996, Leggett et al., 1997, Soravia et al., 1998).

Modifier gene(s) and environmental factors interact with the disease-causing APC gene mutation and may be responsible for genotype-phenotype variations (Fodde and Khan, 1995; Sanabria et al., 1996). Characterization of the causative mutation will probably have significant effects on management. In the future, it may be possible to adjust counselling, surveillance, and treatment according to the genotype (Cunningham and Dunlop, 1996; Vasen et al., 1996; Soravia et al., 1998).

Genetic counselling

The diagnosis and treatment of FAP have caused great distress in an affected family in the past. Due to lack of an early diagnosis, of effective treatment and of satisfactory results, collaboration with families was difficult. In addition, the extracolonic manifestations may even lead to social problems (Gardner, 1951). The advances in surgical treatment and management of complications with a more precise knowledge of polyposis have made it much easier to keep in touch with the families. It is important to recognize that the management of the first individual still has a crucial influence on other family members (Mills et al., 1997).

The counselling of FAP patients is often complex and difficult (Macrae et al., 1989; Burn et al., 1991; Greely, 1999). The priorities of genetic testing in adults and children are different. Testing should not be offered to a child until the age of first possible onset of cancer (Kodish, 1999). Genetic counselling of the tested individual must always accompany a gene test, preferably by a clinician or a geneticist personally to the individual tested. The benefit for the person at risk, and for the parents, is reduction of uncertainty and increased compliance with screening. There have not been serious adverse psychological reactions after disclosure of the gene test results but this possibility must be taken into account (Petersen, 1994). However, the inappropriate use of genetic testing carries the risk of misinterpretation and even false-negative results (Giardiello et al., 1997).

The protein truncation test (PTT) can be used to clarify the genetic status of at-risk family members with certainty if a clinically diagnosed relative has undergone PTT and is known to have a truncated APC protein (van der Luijt, 1996). Linkage analysis can be considered in families with more than one affected family member who belong to different generations and with availability of the family members to be tested. These same criteria are met with prenatal testing. However, detection of the mutation does not predict the onset or severity of the disease.

Diagnosis and family screening

The definition proposed by Bussey states that "adenomatous polyposis coli is an inheritable condition in which the large intestine contains multiple adenomas,

multiple being defined as more than 100" (Bussey, 1975). This can no longer be a strict criterion in young patients (Bülow, 1991). Microscopic examination is mandatory to define the adenomatous nature of the polyps.

Diagnosis and screening of individuals at risk should include the medical history, a clinical examination, and bowel examination by flexible sigmoidoscopy from the age of 10-14 years with a further colonoscopy if adenomas are found (Berk et al., 1987; Dozois, 1988; Bülow, 1991). Regular examination at 2-3 year intervals should continue up to the age of 60 years, even if the endoscopies are negative, in order to exclude late onset of the disease. Upper gastrointestinal tract endoscopy should be done with patients over the age of 20 years for possible gastroduodenal polyposis with adequate biopsies when FAP has been diagnosed. Patients with adenomas should have endoscopy every 1-2 years and without adenomas every 5 years (Bülow, 1991).

Presymptomatic diagnosis of individuals at risk is of importance (Burt and Groden, 1993; Powell et al., 1993). Skin cysts, osteomas, and CHRPE may preceed the development of intestinal adenomas. These may be simple, noninvasive and inexpensive markers of gene carriers (Leppard and Bussey, 1975; Bülow et al., 1984). CHRPE is an interesting clinical marker of gene carriers with an approximate sensitivity and specificity of 85% and 98%, respectively (Traboulsi et al., 1987; Baba et al., 1990).

Various mutations of the APC gene are accurately detected by linkage analysis for carrier status (Burt and Groden, 1993; Nagase and Nakamura, 1993) but the optimal method is mutation analysis (Cunningham and Dunlop, 1996). For FAP families with an apparent new mutation or when family members are not available for linkage analysis, direct mutation analysis is the only choice (Bapat et al., 1994). Antibodies against APC products are useful for direct analysis of the truncated APC protein (van der Luijt, 1996). The commercially available test has a sensitivity of 80%, and virtually 100% when the mutation in the family is known (Powell et al., 1993; Cromwell et al., 1998). Differences in the APC mutations alone cannot solely account for the genotype-phenotype correlations. Therefore, classically described surveillance and prophylactic treatment methods do not apply to all patients with FAP (Lynch and Smyrk, 1998).

If a presymptomatic mutation of the APC gene is identified, no change in screening guidelines is recommended. Without an inherited APC mutation, screening can be reduced or omitted (Petersen, 1994; Kinzler and Vogelstein, 1996). In addition to the clinical benefits of the molecular genetic diagnosis, the reduction of screening has been cost-effective (Maher et al., 1993; Cromwell et al., 1998).

Clinical features

Large bowel

FAP is characterized by development of adenomas at the age of puberty, with the subsequent development of CRC at a young age. There may be a history of slightly increased bowel frequency with loose stools. Typical symptoms of FAP are rectal bleeding, diarrhea, abdominal pain, mucous discharge and constipation. In spite of numerous polyps, patients may be asymptomatic. Every symptomatic patient should have a total colonoscopy with multiple biopsies in order to find polyps and to exclude colon cancer.

Adenomatous polyps usually antedate the development of colorectal cancer by 10-20 years. In an untreated patient, adenomas first become apparent at the age of 20 years. Bowel symptoms occur by the age of 29 years, the diagnosis of FAP is made 3-5 years later, colorectal cancer appears 7-8 years later, and death due to colorectal cancer in the early forties. However, the ages of manifestations have wide limits. (Alm and Licznerski, 1973; Bussey, 1975; Bülow, 1987)

Extracolonic lesions

When carefully examined clinically, endoscopically and radiologically a high proportion of FAP patients have some of a variety of extracolonic manifestations, (Table 1).

Desmoid tumors

Desmoid tumors (DTs) are lesions originating from the musculoaponeurotic tissue in the abdominal wall, the mesentery or the extremities or trunk. Typically, a DT has an ill-defined margin and lacks encapsulation. Microscopically, it is acellular, with dense hyalinized areas, but a few are more aggressive. They may involve the mesentery and the retroperitoneal space, which can lead to venous infarction, intestinal obstruction, or hydronephrosis, and may even have a fatal outcome. (Farmer et al., 1994)

DTs are very rare, with an incidence of 2-4 per million (Reitamo et al., 1986). FAP patients develop DTs with a frequency of between 7 and 14% (Jones et al., 1986; Iwama et al., 1993; Penna et al., 1993d), a risk 852 times that of the general population (Gurbuz et al., 1994). When the risk of colon cancer is reduced, the importance of the desmoid disease increases, as may its frequency. DT can antedate the diagnosis of polyposis, and therefore patients with DTs should be examined for polyposis (McAdam and Goligher, 1970). Family clustering has been clearly documented (Penna et al., 1993d; Gurbuz et al., 1994).

Table 1. Extracolonic manifestations of FAP (Parks et al., 1970, Talbot, 1994).

Ectodermal origin	Mesodermal origin	Endodermal origin
Epidermoid cysts	**Connective tissue**	**Adenomas of**
Tumors of the central nervous system	Fibroma and fibrosarcoma	Stomach
	Desmoid tumors	Duodenum
Congenital hypertrophy of retinal pigment epithelium	Diffuse fibrosis	Hepatopancreaticobiliary tract
	Excessive intra-abdominal adhesions	Small intestine
		Thyroid gland
	Bone	Endocrine tissue adrenal, parathyroid, pituitary
	Osteoma	
	Exostosis	
	Sclerosis	
		Carcinomas of
	Dental	Stomach
	Dentigerous cysts	Duodenum
	Odontoma	Hepatopancreaticobiliary tract
	Supernumerary teeth	
	Unerupted teeth	Small intestine
		Thyroid gland
		Adrenal
		Fundic gland polyps
		Hepatoblastoma

The factors presumed to precipitate desmoid formation include surgical trauma, pregnancies, and other hormonal influences (Gurbuz et al., 1994). APC gene mutations are associated with DTs and other extracolonic manifestations (Caspari et al., 1995; van der Luijt 1996) in contrast to earlier registry analysis (Gurbuz et al., 1994). Other poorly understood factors also influence the risk of DT. Recently, Clark and coworkers proposed a model of DT development in which a less benign phenotype emerges as molecular genetic abnormalities accumulate. In many patients with FAP, mesenteric plaque-like desmoid precursor lesions arise before surgery as a result of abnormal fibroblast function (Clark et al., 1998). Some, perhaps stimulated by surgery, progress to mesenteric fibromatosis and these, in turn, can give rise to DTs.

Upper gastrointestinal tract

The association of gastroduodenal polyps with polyposis has been known for over a century (Hauser, 1895). In 1935, Cabot reported a patient with a carcinoma of the ampulla of Vater and MacDonald described malignant degeneration in a case of duodenal polyposis (Cabot, 1935; Macdonald et al., 1967). Gardner noticed occasional involvement of the stomach in his series (Gardner and Richards, 1953). McKusick stated that polyps could occur anywhere in the gastrointestinal tract (McKusick, 1962) and an association with gastric carcinoma was reported by Murphy (Murphy et al., 1962). In an extensive analysis of GS, the frequency of periampullary cancer was 2-3%, representing a risk 100- to 200-fold that of the general population (Pauli et al., 1980).

In 1971, Hoffman and Goligher described polyposis of the stomach and small intestine (Hoffmann and Goligher, 1971). Utsunomiya found gastric polyps in 67% of patients with FAP (Utsunomiya et al., 1974). Since then, many groups have pointed out the high incidence of both gastric and duodenal polyps in FAP (Yao et al., 1977; Järvinen et al., 1983b; Jagelman et al., 1988; Church et al., 1992; Offerhaus et al., 1992). Therefore, upper gastrointestinal endoscopy is included as part of the diagnostic workup and surveillance program (Sarre et al., 1987; Spigelman et al., 1989), although this is not without critics (Norfleet, 1992).

Stomach

Watanabe was the first to describe gastric fundic gland polyps (FGPs) (Watanabe et al., 1978). FGPs consist of hyperplasia of the fundic gland and microcysts. They are rare except in FAP, with considerably variation in number and size (Iida et al., 1984). FGP have been considered to be benign lesions with no apparent relationship to neoplasia (Talbot, 1994). Gastric adenomatous polyps are usually limited to the antrum. If adenomas are found endoscopic surveillance, every 1-2 years, has been recommended but at longer intervals if only FGP are found (Bülow, 1991). Interestingly, FGP occasionally exhibit adenomatous changes, implying a potential risk of gastric cancer (Zwick et al., 1997; Wu et al., 1998c).

Duodenum

Duodenal or periampullary cancer is an important cause of death in FAP (Arvanitis et al., 1990; Iwama et al., 1993). Endoscopies, preferably with a side-viewing endoscope, with numerous random biopsies of the ampulla and periampullary region, should be done at least every three years. If there are large or dysplastic adenomas, endoscopies should be done annually and, with severe dysplasia or numerous large polyps, surgery should be considered (Iida et al., 1989b). No genotype-phenotype correlations between the severity of periampullary polyposis and the specific germline mutation have been found, but there may be family segregation in the occurrence of periampullary malignancy (Sanabria et al., 1996).

The high prevalence of adenomas and carcinomas at or near the papilla of Vater and in the small bowel, which are exposed to high bile acid concentrations, as well as studies of bile acids, suggest that bile affects the formation of small bowel and colorectal cancer (Spigelman et al., 1989; Hill, 1991).

Small bowel

The presence of small bowel polyposis is uncommon and the exact incidence is unknown. Ross and Mara reported primary adenocarcinomas in the small bowel and suggested initial and periodical small intestinal examinations (Ross and Mara, 1974). Ileal adenomas and carcinomas have been found after colectomy (Ohsato et al., 1977; Hamilton et al., 1979; Roth and Logio, 1982; Iida et al., 1989a) and minute, asymptomatic adenomas with a push-type jejunal endoscope (Iida et al., 1990; Bertoni et al., 1993). According to these studies, the small intestine should be examined before surgery and periodically afterwards.

Congenital hypertrophy of the retinal pigment epithelium (CHRPE)

Retinal pigment abnormalities were noted in 1935 (Cabot, 1935). In 1980, Blair and Trempe found an association between these retinal pigment abnormalities and GS, later on referred as CHRPE (Blair and Trempe, 1980). The CHRPE lesions are darkly pigmented, round lesions with hypertrophied cells filled with melanosomes. There may be a hypopigmented halo around the periphery or depigmented lacunae within the lesions. Four or more lesions in one or both eyes are specific for FAP with a familial consistency in the number of lesions in the affected pedigrees and with a specificity of 98% and a sensitivity of 85% (Lynch et al., 1987; Traboulsi et al., 1987; Romania et al., 1989).

CHRPE is assocated with mutations between codons 463 and 1387 (Olschwang et al., 1993). The presence of this marker varies from two thirds to all FAP kindreds (Romania et al., 1989). CHRPE are detectable at a very early age with a direct, noninvasive and inexpensive ophthalmological examination, but a negative examination in an young, unaffected individual does not mean that rectal screening can be omitted (Berk et al., 1988).

Skin and bone

Gardner described the soft tissue tumors in FAP (Gardner, 1951; Gardner, 1962). They are mostly epidermoid cysts throughout the body but lipomas, sebaceous cysts, and neurofibromas are also encountered. In children, epidemoid cysts, especially of the face and extremities, are typical for FAP (Leppard and Bussey,

1975). Skin cysts as well as osteomas can preceed the development of intestinal adenomas (Gardner, 1962; Leppard and Bussey, 1975; Offerhaus et al., 1987).

Osteomas of the jaw are usually multiple, small, well-circumscribed, and often palpable radiodensities in the molar regions of the maxilla and mandible. Other dental abnormalities have also been found, including supernumerary teeth, unerupted teeth, odontomas, dental cysts, early onset of caries, and loss of teeth. (Utsunomiya and Nakamura, 1975)

Liver and the biliary tract

There are reports of biliary adenomas and carcinomas of the liver, gallbladder, bile duct, and pancreas (Lees and Hermann, 1981; Järvinen et al., 1983a; Willson et al., 1987). Childhood hepatoblastoma is a rare malignant embryonal tumor associated with FAP. Clinical awareness has been recommended and also screening (Giardiello et al., 1991).

Thyroid gland

Thyroid carcinomas have been associated with FAP (Camiel et al., 1968; Alm and Licznerski, 1973). They are mostly multicentric at an early age and present with extracolonic manifestations. The relative risk of thyroid carcinoma has been 20-160-fold in FAP. Therefore, regular clinical examinations of the thyroid gland with use of ultrasound were recommended (Plail et al., 1987; Giardiello et al., 1993b) but seemed unjustified in a recent registry report (Bülow and Bülow, 1997).

Other neoplasms

Various extracolonic neoplasms have been reported in FAP: carcinoid tumors, adrenal adenomas, and carcinomas (Macdonald et al., 1967; Naylor and Gardner, 1981; Painter and Jagelman, 1985; Marchesa et al., 1997), pancreatic neoplasms (Schneider et al., 1983; Giardiello et al., 1993b), parathyroid adenomas (Naylor and Gardner, 1981; Schneider et al., 1983), pituitary adenomas (Naylor and Gardner, 1981; Schneider et al., 1983), urinary bladder cancer (Watne et al., 1975), and carcinoma of the uterus and ovary (Watne et al., 1975).

Turcot et al found an association between familial polyposis and malignant tumors of the central nervous system (Turcot et al., 1959). In addition, registry evidence suggested that brain tumors were an early extracolonic manifestation of FAP (Kropilak et al., 1989). In subsequent studies, however, Turcot syndrome seemed to be genetically distinct from FAP (McKusick, 1962; Itoh et al., 1979). Tops and coworkers showed that the APC gene was not involved (Tops et al., 1992).

Nevertheless, it has been later demonstrated that brain tumors do occur in association with both FAP (predominantly medulloblastomas) and HNPCC (predominantly glioblastoma multiforme) (Hamilton et al., 1995; Aarnio et al., 1999).

Treatment

Medical treatment

Various nutritional and metabolic trials have been made. A high-fiber diet with vitamins C and E had a limited regression potential on rectal adenomas (Bussey et al., 1982; DeCosse et al., 1989). However, the strong inverse association between starch intake and CRC suggests an important role for starch in prevention of CRC (Cassidy et al., 1994). The ongoing CAPP study probably reveals the effect of aspirin and starch on FAP (Burn et al., 1995). Oral calcium has had an inconsistent effect on the risk of colon cancer (Stern et al., 1990; Thomas et al., 1993) and may, in fact, be harmful in FAP (Paraskava, 1992).

An NSAID (e.g. sulindac) reduces mucosal proliferation activity, with significant polyp regression and without side effects (Waddell et al., 1989; Labayle et al., 1991). Polyp regression was also found after IRA, with progression after omitting sulindac (Giardiello et al., 1993a). Sulindac restricts prostaglandin synthesis and reactivates the cyclic AMP- dependent control of cell growth (Waddell, 1994). In recent studies, NSAIDs have inhibited the growth of colon cancer cell lines independently of prostaglandins, probably by the apoptotic pathway (Giardiello et al., 1998).

Sulindac is a possible treatment of rectal polyposis after IRA and for patients unsuitable for the pouch procedure (Setti-Carraro and Nicholls, 1996). However, the effect has only been temporary and diminution of the adenomas did not exclude the development of cancer (Lynch et al., 1995b; Giardiello et al., 1998). Thus, whether sulindac the rectal cancer risk is obscure. Other studies suggest that NSAIDs, e.g. aspirin, reduce the risk of colon carcinoma (Thun et al., 1991; Giovannucci et al. 1994).

Surgical treatment

Surgery is the only effective treatment of FAP that prevents cancerous changes in colorectal adenomas. Initially, surgical treatment was limited to local excisions of rectal polyps. Thereafter local or segmental resections of the cancer were performed but there was considerable mortality. During the 1940s advances in anesthesia, antibiotics, electrolyte balance, and blood banks enabled major surgery.

The early reports of multiple polyposis of the colon and rectum stated that polyposis is most safely treated by complete removal of the lower intestine in order to eradicate the disease. However, an ileostomy is not without complications. Therefore a more limited operation, colectomy and ileoproctosigmoideostomy gained acceptance (Lockhart-Mummery, 1934). Colectomy became the standard operation with a choice of colectomy and ileorectal anastomosis (IRA) or proctocolectomy with an ileostomy (PC+I). IRA has been the operation of choice for FAP in many centers since its introduction by Lockhardt-Mummery in 1918 (Lockhart-Mummery et al., 1956; Bussey et al., 1985; Bülow, 1987; Jagelman, 1991). Spontaneous regression of rectal adenomas has been noticed after IRA (Hubbard, 1957), but the regression was only transient or partial (Watne et al., 1975; Feinberg et al., 1988). Restorative proctocolectomy (RPC, proctocolectomy with ileal pouch-anal anastomosis) became an alternative in ulcerative colitis and also in FAP after pouch formation (Parks and Nicholls, 1978; Utsunomiya et al., 1980).

The pros and cons of IRA and RPC have to be evaluated on the basis of the surgical results, balancing the recovery time, the morbidity rate, and the functional outcome with the preventive effect against cancer. However, the choice of the operation has been controversial (Setti-Carraro and Nicholls, 1996).

The type and time of the operation should be individualized on the basis of the patient's age and the endoscopic and histological evaluation of the disease (Phillips and Spigelman, 1996). Adult patients should be treated as soon as the diagnosis is confirmed. Early colectomy is mandatory for severe dysplasia, large adenomas, or rapidly growing adenomas. The decision is based on the desires of the patient, the preference of the surgeon, and follow-up possibilities. The effect of the surgery on the rest of the family must be remembered. Genetic testing may identify a subset of families with more benign APC gene mutations (Vasen et al., 1996; Soravia et al., 1998). IRA may be more acceptable for these patients without an adverse effect on survival.

Proctocolectomy and ileostomy (PC+I)
PC+I has little place as long as the disease is benign and is used mainly in cases with cancer in the lower third of the rectum (Jagelman, 1991). Conversion of IRA to PC+I may be necessary with rectal cancer, especially in older patients.

Colectomy and ileorectal anastomosis (IRA)
After IRA, continence is maintained, problems with an ileostomy are avoided, and sexual function is not impaired. However, before IRA, low rectal cancer must be absent, and the number of polyps in the rectum limited so that they can be managed by fulguration, follow-up should be possible, and examination of the retained rectum must be possible with a rectoscope (Dozois, 1988). In addition,

high anastomosis (between the ileum and the sigmoid colon) is associated with increased risk of malignancy (Gingold and Jagelman, 1981).

IRA is relatively easy to perform, with low complication rates and good functional results (Madden et al., 1991). The mandatory follow-up of the rectal stump after IRA must vary according to the clinical and histological findings. Follow-up is not free of complications, and, despite close follow-up, surveillance cannot always prevent rectal cancer (Bussey et al., 1985; Nugent and Phillips, 1992).

Restorative proctocolectomy (RPC)
A few cases were treated by colectomy with removal of the rectal mucosa and an ileoanal anastomosis over 50 years ago, but with little success (Dukes, 1952). A reservoir proximal to the anastomosis gives better functional results than a strait pull-through technique. Therefore, RPC became an alternative method after ileal pouch formation (Parks and Nicholls, 1978; Utsunomiya et al., 1980; Williams, 1986).

RPC is recommended as the operation of choice for prophylactic surgery in FAP (Kartheuser et al., 1996). Hand-sewn RPC eradicates all the potentially malignant large bowel mucosa, while preserving continence. However, the surgical technique in RPC is demanding, postoperative complications are more common, and the functional results may be inferior to those after IRA. RPC is the primary operation for teenagers, for patients with expected follow-up difficulties, and for patients with large carpet-like polyposis of the rectum or with synchronous colonic or high rectal cancer (Slors et al., 1989; Jagelman, 1991; DeCosse et al., 1992; Nugent and Phillips, 1992; Nance, 1993; Ziv et al., 1995).

In FAP, ileal pouches may develop adenomatous polyps and are at risk of cancer (Church et al., 1996). The natural course and the significance of pouch polyposis is not preciseley known, but the pouches should be examined annually with adequate biopsies, and stapled pouches at even closer intervals (Nugent et al., 1993b; Wu et al., 1998a).

Desmoid disease
The treatment of desmoid tumors is problematic (Penna et al., 1993d; Church, 1994). In restricted abdominal wall tumors, excisional surgery is straightforward but, when diffuse, these may be hard to remove completely, and recurrence rates are high. In mesenteric tumors, the hazards of bleeding and of short bowel syndrome are great (Church, 1994). Aggressive surgery for intra-abdominal DT has been regarded as unwise, and alternative medical therapies have been tried. In addition, DT may

preclude the conversion of IRA to RPC and further treatment of the rectal stump (Penna et al., 1993d).

There is evidence that the NSAID sulindac induces tumor regression (Tsukada et al., 1992). Anti-estrogens (tamoxifen, toremifen) have also been used with some success (Wilcken and Tattersall, 1991; Church, 1994). Cytotoxic chemotherapy and radiotherapy may be used as last resort therapies but the results have been variable and not without complications (Church, 1994).

Upper gastrointestinal tract

Conservative management has been regarded as sufficient for FGPs. Recently, gastric adenocarcinoma arising from a fundic gland polyp was reported (Zwick et al., 1997) and, therefore, large FGPs should be excised. Gastric adenomas may undergo malignant transformation, and adenomas over 10 mm need treatment. Adenomas can be removed by endoscopic polypectomy or electrocoagulation and warrant surveillance at 6-month to 3-year intervals, according to the size and histology of the adenomas (Sarre et al., 1987, Iida et al., 1988, Zwick et al., 1997) .

How and when to treat duodenal adenomas is a difficult question. Endoscopies, preferably with a side-viewing endoscope, with numerous biopsies of the ampulla and periampullary region should be done at least every three years (Sarre et al., 1987). If there are large or dysplastic adenomas, endoscopies should be done annually, and, with severe dysplasia or numerous large polyps, surgery should be considered (Spigelman et al., 1989; Spigelman et al., 1994). Several endoscopic methods can be used to treat duodenal adenomas (Saurin et al., 1999). Endoscopic removal of all polyps is impossible. Complete clearance of duodenal adenomas by duodenotomy fails because not all the microscopic adenomas can be removed and the recurrence rate is 100% (Penna et al., 1993b).

In some cases, prophylactic duodenal or pancreaticoduodenal resection has been recommended (Offerhaus et al., 1992; Penna et al., 1998). Pancreatico-duodenectomy is a major operation with potentially severe complications and cannot be justified in every case. However, recent reports have made claims of minute morbidity and no mortality from pancreaticoduodenectomies (Saurin et al., 1999). Besides this, other endoscopic and medical therapies should be evaluated as treatment methods (Penna et al., 1993b; Spigelman et al., 1994; Scates et al., 1995).

Postoperative surveillance

Most reasons for failures of surveillance are potentially correctable by a dedicated registry that is responsible for notifying clinicians and patients about the timing of surveillance procedures (Macrae et al., 1989). The location of the APC mutation predicts, at least partially, phenotype expression of the disease (Lynch and Smyrk, 1998). Therefore, the surveillance and prophylactic management strategies should be modified accordingly.

After bowel surgery

After IRA, patients are seen every 6 months, and thereafter at 3- to 12-month intervals depending on the clinical and histological findings (Bülow, 1987). Ileal adenomas may develop after colectomy and arise in pouches, even several years after the operation. Furthermore, a stapled RPC fails to remove all the mucosa at risk. Therefore, surveillance is essential. After RPC, annual follow-up of pouches should be routine (Wu et al., 1998a).

Upper gastrointestinal tract

Before a decision can be made as to whether to screen for upper gastrointestinal lesions, two important factors need consideration, i.e. the curability of the lesions found at screening and the morbidity and mortality after treatment (Vasen et al., 1990). The time-table of duodenal adenoma progression and the appropriate intervals for endoscopic surveillance and biopsies are obscure. If duodenal polyposis is of mild degree or absent, the proposed surveillance intervals of 3 to 5 years may be sufficient (Bülow, 1987; Debinski et al., 1995; Sawada and Muto, 1995). Patients who develop stage III or IV polyposis need closer surveillance with yearly endoscopies, at least, and are candidates for prophylactic surgical treatment.

AIMS OF THE PRESENT STUDY

The objective of the present clinical study was to investigate the treatment methods and results of the treatment in familial adenomatous polyposis. The specific aims were:

1) to assess the functional results and complications following restorative proctocolectomy and colectomy and ileorectal anastomosis in familial adenomatous polyposis.

2) to ascertain the risk of rectal cancer and the rectal excision rate after colectomy and ileorectal anastomosis and the results of treatment of rectal polyps in the retained rectum.

3) to determine the incidence of desmoid tumors and the outcome after treatment.

4) to evaluate the progression patterns of gastroduodenal polyposis and the results of treatment of duodenal polyposis.

5) to define the survival patterns of patients detected by screening examinations or by symptoms.

PATIENTS AND METHODS

This study includes all the patients with FAP patients who were or are recorded in the Finnish Polyposis Registry. The Registry was founded in 1984 with 160 patients belonging to 50 families (Järvinen et al., 1984). One to four further pedigrees with 1-20 new polyposis patients have been detected annually. At present, 108 pedigrees including 253 verified patients with FAP are recorded in this Registry. Thus, the number of families and patients has altered during the study period.

Type of operation (I)

The study included all the patients with FAP who had undergone RPC (33 patients) or IRA (99 patients) between January 1966 and June 1997. Before 1992, all patients with FAP had IRA as the primary prophylactic operation, but after that RPC was chosen as a rule, because a co-operative study (DeCosse et al., 1992) including the majority of the IRA patients showed a very high secondary rate of proctectomy. The RPC patients included 20 men and 13 women with a mean age of 34 years (range 6-58 years) at the operation. RPC was performed as a primary procedure in 23 cases and secondarily after IRA in 10 cases. The indication for secondary proctectomy was dysplastic changes in four, rectal carcinoma in three (two Dukes C tumors, one with two Dukes A tumors), the patient's preference in two, and suspicion of a perirectal tumor in one. There were 47 men and 52 women in the IRA group and their mean age at the time of operation was 32 years (range 18-67 years).

The surgical technique of RPC included abdominal colectomy, proximal proctectomy, mobilization of the small bowel, endoanal excision of the rectal mucosa, a stapled ileal J-pouch, and a hand-sewn anastomosis. In three patients, the rectum was everted for mucosal excision and one had stapled anastomosis without mucosal excision. Diverting loop ileostomy was used for eight patients (24%). All RPCs were done at university hospitals. IRA was preferably performed with a low (5-10cm) ileorectal anastomosis. Sixty-four patients (64%) were operated on at the Second Department of Surgery, Helsinki University Central Hospital; 35 had surgery at 15 other hospitals in Finland. The rectal stump was checked at 6- to 12-month intervals and clearly visible polyps were fulgurated to keep the rectum as clear of polyps as possible.

For every patient, the peri- and postoperative outcome was evaluated from the hospital records. In 22 patients, the functional outcome after RPC was assessed by questioning about stool frequency (day and nighttime), continence, the need of a protective pad or antidiarrhoeal medication and dietary restrictions. In addition,

anal resting and maximal squeeze pressures and the length of the high-pressure zone were determined by anal manometry. Finally, the patient's overall opinion about anal function was asked. Identical assessment was performed for an equal number of sex-matched patients with IRA by the investigator, with one exception. The mean age of the patients with RPC was 32 years at the time of operation and 28 years in those with IRA. The mean postoperative follow-up at the time of functional evaluation was 46 months in the RPC patients and 108 months in the IRA patients. Of the 11 patients not available for functional assessment, two had failure of anal preservation and five had been operated on less than 12 months previously; four were not willing to come for an additional visit.

Incontinence was graded from 1: continent, 2: incontinent to flatus, occasionally (<2/week) to a liquid stool, 3: incontinent to liquid stools, to 4: gross fecal incontinence. Anal manometry was performed by the continuous pull-through technique (2 mm/s). A polyvinyl catheter (Fr 8) with two opposite side openings 0.5 cm from the tip was perfused with saline and connected to a water-filled pressure transducer and further to a recorder. The basal resting pressure and maximal squeeze pressure were measured in centimeters of water. The length of the high-pressure zone was measured directly from the manometry chart. The functional outcome and anal manometry were assessed during the most recent outpatient visit.

Rectal remnant after surgery (II)

By the end of 1995, the Finnish Polyposis Registry had data on 94 FAP pedigrees with 333 affected patients. Nine families consisting of one solitary case with an uncertain diagnosis of FAP were excluded as well as the 73 patients with a deduced diagnosis on the basis of colorectal cancer and pedigree analysis. In addition, 23 affected members living permanently abroad were excluded because of insufficient follow-up data. The final study group consisted of 200 patients with verified FAP. By the end of 1994, 100 patients (54 women, 46 men) had undergone colectomy and ileorectal anastomosis; 63 patients had been operated on at the Second Department of Surgery, Helsinki University Central Hospital and 37 patients in 15 other hospitals in Finland.

Since 1980, the standard operation has been a low ileorectostomy (5-10 cm from anal verge) with a stapling device and removal or fulguration of all rectal polyps under the same anesthesia. Patients were seen within 2 months postoperatively and thereafter at 3- to 12- month intervall depending on the number and size of the polyps. Histological examinations and polyp fulguration or removals had been done at every follow-up, when appropriate. The cancer diagnosis was made after histological verification. The results of the surgical and medical treatment were

reviewed from the patients' records. The incidence of rectal cancer was calculated from birth and from the IRA until the end of the study, the date of death, or the first diagnosis of rectal cancer.

Desmoid tumors (III)

All clinically evident DTs with diameters of at least two centimeters were included (n=29). Unequivocal DT was established by histopathological examination in 24 cases. In four patients, only fibromatous tumor was reported. One patient had no operation or biopsy.

The incidence of DT in our FAP cohort was calculated by person-year analysis, beginning from birth until the end of the study, the date of death, or the date of first diagnosis of DT. Similar calculations were also performed for the cumulative risk of DT, using the Kaplan-Maier life-table analysis for both sexes. Considering the precipitating factors proposed, the ages at colectomy and at pregnancies were compared in patients with and without DT. In addition, the cumulative risks of DT in patients who had undergone IRA were compared with those after PC. Finally, the results of surgical and medical treatment were reviewed from the patient records.

Duodenal polyposis (IV)

Upper gastrointestinal endoscopy has been part of the diagnostic work-up of FAP since 1980. There were 98 patients who had had their first upper gastrointestinal endoscopy at the Second Department of Surgery, Helsinki University Central Hospital, and who had been or still were under surveillance at the Department by the end of December 1997. All these patients were free of upper gastrointestinal symptoms at the first endoscopy. There were 48 females and 50 males belonging to 50 families. The mean age at diagnosis of FAP was 29.5 (range 1-64) years and the age at the time of the first upper endoscopy 33.3 (range 16-68) years. Colectomy or proctocolectomy had been performed for 97 and one has thus far refused surgery. The median follow-up time after the first examination was 11 years (range 0.2 to 17.4 years). In total, 341 endoscopies were done (median 3); 27 had only one examination and 71 have had an endoscopy two to nine times.

Several biopsies were taken from all patients with polypoid lesions. In the beginning of the study, random biopsies were not routinely taken at the first endoscopy from a normal appearing mucosa. Since 1990, 65 patients have been part of the multicenter DAF study (Bülow et al., 1995), which includes random biopsies. The severity of duodenal polyposis was staged according to the Spigelman classification (Table 2). Endoscopic surveillance was arranged at two-

to three-year intervals, or more frequently if required, according to the clinical and histological results. The duodenum was not routinely hypotonized.

Table 2. The Spigelman classification (Spigelman et al., 1989).

	Grading points		
	1	**2**	**3**
Polyp number	1-4	5-20	20
Polyp size (mm)	1-4	5-10	>10
Histology	tubular/hyperplasia/ inflammation	tubulo-villous	villous
Dysplasia	mild	moderate	severe

Stage 0 = 0 points, stage I = 1-4 points, stage II = 5-6 points, stage III = 7-8 points, stage IV = 9-12.

The operative technique included a mid-line laparotomy, Kocher manoeuver and oblique duodenotomy. Adenomas over 4 mm in diameter were excised submucosally and the smaller adenomas were fulgurated. Adenomas or tumors of the ampulla of Vater were excised locally with sphincteroplasty in order to prevent scarring of biliary or pancreatic ducts.

The cumulative risk of development of any duodenal adenomas, of advanced adenomatosis, and of duodenal cancer were calculated from birth until the end date of this study or the date of death, using Kaplan-Meier analysis. The cumulative increase in duodenal adenomatosis (according to the Spigelman classification) was calculated until the last endoscopy with increased stage, death, diagnosis of duodenal cancer, or the end of this study.

Survival (V)

This study included all the patients with FAP recorded in the Finnish Polyposis Registry by the end of June 1998. The data comprised 236 patients in 98 families with verified FAP. The diagnosis had been defined by history, clinical examination, histopathological assessment, and/or genetic testing. Of the patients 116 (51 men, 65 women) had been diagnosed on the basis of symptoms (probands) at a median age of 36.8 years (range, 17-80 years), whereas 120 patients (67 men, 53 women) had been diagnosed by family screening (call-up cases) at a median age of 22.8 years (range, 6-67 years).

The postoperative cumulative relative survival rates were calculated according to Verdecchia (Verdecchia et al., 1995) for 195 patients (102 probands and 93 call-up cases). One patient, 6 years of age at operation, was excluded from postoperative survival analyses for comparability since the other proband patients were older than 15 years when operated on. Three patients with laparotomy only, six patients without laparotomy, and 25 patients under surveillance were also excluded because no operative treatment was undertaken. In addition, six patients operated on before 1952 were excluded because survival and mortality probabilities for the general population were available from 1951 onwards. The causes of death were verified from registry charts, medical records, and death certificates, and from the Central Population Register. Patients were followed up until the date of death or the end of this study.

Statistics

The cumulative risks of DT, and of rectal cancer, the rectal excision rate, and the development of any duodenal adenomas, of advanced adenomatosis, and of duodenal cancer were calculated using the Kaplan-Meier analysis. The results were analyzed using the t test for continiuous variables and the chi-square test, Fisher's exact test, the nonparametric paired sign test and the Mann Whitney U test for discontinuous variables. The equality of interval-specific relative survival rates between the patient groups was tested using a maximum-likelihood test (Hakulinen et al., 1987). A probability of less than 0.05 was accepted as significant.

RESULTS

Outcome of colectomy (I)

There was no operative mortality. The operation time and hospital stay were significantly longer and blood loss and the transfusion rate significantly higher in the RPC group, as shown in Table 3. The number of patients with postoperative complications was 10 (30%) after RPC and 18 (18%) after IRA (p=0.14, chi-square test).

One patient in the RPC group developed peritonitis following ileostomy closure. In another case, anastomotic dehiscence could not be managed without excision of the pouch, in spite of a protective ileostomy. One female patient refused closure of the protective ileostomy for fear of incontinence.

Full assessment of anal function was possible for 22 RPC patients. Each of them had a sex-matched control patient with IRA. The RPC patients were older than the IRA patients (32.0 vs 27.8 years) and the follow-up time was significantly longer in the IRA group (9.0 vs 3.9 years, p=0.0001). However, the general lifestyle did not differ between the groups. There was no difference in the proportion of patients having urgency, need for a protective pad, need for antidiarrheal medication, or dietary restrictions. Two patients in each group with full functional analysis had restrictions in sexual life. These restrictions were related to incontinence or bowel frequency.

Eighty-two percent of patients following RPC and eighty-eight percent of patients following IRA were completely satisfied with the postoperative state and functional results. All the patients were capable of working and had no restrictions in social life.

Rectal remnant after surgery (II)

Of 100 patients, nine developed cancer in the retained rectum 0.2 to 17 years after IRA. The cumulative risks of rectal cancer after IRA were 4%, 5.6%, 7.9%, and 25.2% at 5, 10, 15, and 20 years (Fig. 3). The cumulative age-dependent risks of rectal cancer were 3.9%, 12.8%, and 25.7% at the ages of 40, 50, and 60 years.

Twelve other patients had their retained rectum excised for benign conditions. RPC was attempted in 7 patients, but it failed in two cases: in one because of anastomotic breakdown and in the other because of poor sphincter function. The mean time after IRA was 9.5 years (0.2 - 29), 9.2 years (0.2-17) in the cancer patients and 9.6 years (4-29) in the non-cancer patients. The mean age at excision was 40 years (23 - 59), 44 years (34-59) in the cancer and 38 years (23-55) in the non-cancer

Table 3. Patients and operative morbidity with RPC or IRA.

	Restorative proctocolectomy (RPC) (n = 33)	Colectomy and ileorectal anastomosis (IRA) (n = 99)
Sex (men/women)	20/13	47/52
Age (years)	33.7	32.2
Follow-up (years)	3.2	11¶
Operation time (min)	216 †	182¶
Hospital stay (mean, days)	12	11¶
Blood loss (ml)	1253‡	624¶
Transfusions (units)	3 (0-22)	0.9 (0-5)¶
Temporary ileostomy	8	-
Operative morbidity		
Hemorrhage	5 [4]	3 [3]*
Anastomotic leakage	3 [3]	5 [5]
Anastomotic stricture	-	1
Wound infection	-	2
Pneumonia	2	-
Urinary tract infection	1	2
Intra-abdominal abscess	-	4 [2]
Deep venous thrombosis	-	1
Protective ileostomy for complication(s)	4	5*
No complications	23	81

*, ¶ statistical significant: * Fisher's exact test, ¶ Mann-Whitney U test.
† 199 and 250 in primary and secondary RPC, respectively.
‡ 895 and 1970 ml in primary and secondary RPC, respectively.
Values in parentheses [ ] reflect patients who required surgery.

patients. The cumulative rectal excision rate (including all rectal cancer cases) after IRA was 7.3%, 13.7%, 23.6%, and 36.6% at 5, 10, 15, and 20 years after operation, and finally 73.8% at 29 years after IRA (Fig. 3). The cumulative age-dependent rectal excision rates were 3.1%, 9.5%, 26.3%, and 44% at 30, 40, 50, and 60 years, respectively. At present 21 patients have had rectal excision or rectal cancer and seven have died from other causes; 72 remain in follow-up.

Fulguration and/or removal of rectal polyps were performed 477 times in 76 patients. The number of treated polyps was less than five in six (8%), five to ten in 41 (54%) and more than ten in 29 (38%) patients. Nineteen patients have had no detectable rectal polyps in repeated endoscopic examinations. Six patients had 12 attacks of postpolypectomy bleeding, but all were managed conservatively. One rectal perforation after snare polypectomy was managed with antibiotics and parenteral nutrition and another patient had distal ileal perforation needing operation after fulguration of an ileal adenoma. Four patients had anal/rectal strictures needing dilatation or sphincterotomy, probably due to scarring after repeated fulgurations. The total number of patients with complications related to rectoscopic check-ups was thus 12 (12%).

Twelve patients have had sulindac treatment for rectal polyps, with a complete response in four, a partial decrease in four, no effect in two patients, and not known in two. One of our patients had minor side-effects (nausea), which led to cessation of sulindac within 12 months. He had rectal excision 4 months later because of severe dysplasia in a rectal adenoma, but unexpectedly a stage C rectal cancer was found in the operative specimen.

Desmoid tumors (III)

The frequency was 29 in 202 patients (14%), 17 in women (17%) and 12 in men (12%) - a female to male ratio of 1.4. The cumulative risk estimates were slightly higher for women (23%) than for men (20%) with an average lifetime risk of 3.72/1000 person years. There were four “desmoid families” with two to five members affected. DTs were observed in 21 of the 78 separate families (27%). All the women developed their DTs when of childbearing age; however, only 10 of the 17 patients with DTs (59%) had had previous pregnancies, compared with 59 of 81 the FAP patients without DTs (78%). Of the patients with DTs, 83% had had surgical procedures before diagnosis.

Five DTs were observed after 65 proctocolectomies (7.7%), compared with 14 cases after 100 IRA (14%) - the remaining case occurred after abdominoperineal rectal excision and nine before operation. The cumulative frequency figures showed no significant difference between the two types of operation.

There was one example of complete spontaneous regression. Eleven patients with abdominal wall tumors had complete or almost complete excisions without complications. Recurrence developed in five instances (45%), and in two cases new tumors appeared at other sites, the lower back muscles and the thoracic wall. A mesenteric DT was observed in 17 patients, 16 of whom were operated on. Tumor excision with bowel resection was performed in six cases (35%); three additional patients had tumor excision later, after a primary by-pass procedure or biopsy. There were two recurrences after excisional surgery (22%). Two patients (22%) had severe complications after excisional surgery. Of the seven patients who had no tumor excision, one needed surgery for renewed bowel obstruction and ureteric stasis. In the other cases, the DTs have remained static for 3 to 9 years.

Medical therapy (sulindac, tamoxifen, toremifen) was given in 10 cases without evidence of tumor regression: the tumor remained stable in three, and progressed in seven, with further surgical treatment in four. However, there were no deaths due to DT or their treatment during the mean follow-up time of 10 years after operation (range 0.5 to 22 years). Of the 25 patients surviving, 15 have no evidence of recurrence after complete excision, six others with known residual tumor have no signs or symptoms of it, whereas four have symptomatic DT. Four patients died 3 to 13 years after diagnosis of the DT; death was due to metastatic colorectal or periampullary cancer.

Duodenal polyposis (IV)

At the first endoscopy, 53 (54%) of the 98 patients had duodenal adenomas, and gastric fundic gland polyps were observed in 55 patients. The combined number of patients with gastroduodenal polyposis at the first endoscopy was 75 (77%). During the follow-up, duodenal adenomas developed in 25 (56%) of the 45 patients who initially had no adenomas. Only seven patients had no duodenal adenomas after repeated examinations, while 13 patients have not been re-examined. In most cases, the severity of duodenal polyposis at the first endoscopy was mild.

Progression of the stage was observed in 52 (74%) of the 71 patients who came for follow-up examinations. The stage of severity also tended to increase with increasing age. The mean intervals between changes from stage 0 to I, stage I to II, stage II to III, and stage III to IV were 5.7, 4, 6, and 11 years, respectively. Two patients developed duodenal carcinoma at the ages of 38 and 42 years. Of the 98 patients, 78 had duodenal adenomas, including the two cases of duodenal carcinoma. The cumulative lifetime risk of developing duodenal adenomatosis was 97%, stage IV polyposis 30%, and duodenal cancer 4% (Fig. 4).

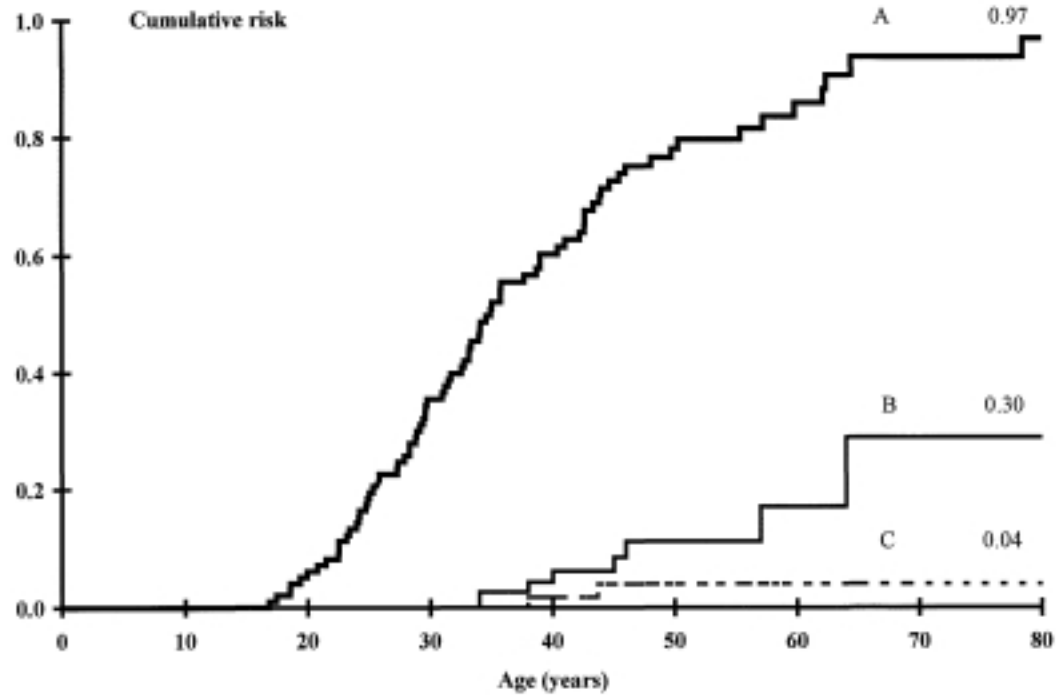

Figure 4. Cumulative risk of any duodenal adenomas (A), stage IV duodenal adenomatosis (B) and duodenal cancer (C).

Altogether 21 patients (21%) had prophylactic treatment for duodenal adenomas: open surgical excision (15 patients), endoscopic snare excision (5 patients) or YAG laser coagulation (one patient). The preoperative distribution of Spigelman stages were: stage I 1, stage II 6, stage III 7, and stage IV 6 patients (stage unknown in one patient). Ot the 17 patients eligible for postoperative endoscopic follow-up, the Spigelman stage had decreased in 10 (59%), had increased in two (12%), and was unchanged in five (29%) at the first postoperative endoscopy after a median follow-up time of 2 years (range 0.16-6.8); the difference was statistically significant (p=0.04, paired sign test). Nevertheless, after a median follow-up time of 6.8 years (range 0.4-15.1) there was no significant change in the Spigelman stage (p=0.2, paired sign test) between the preoperative and the latest endoscopy.

During the follow-up, two patients underwent a second duodenotomy for clinically and histologically severe polyposis 6 and 11 years after primary duodenotomy. In spite of these re-polypectomies, stage III and stage IV duodenal polyposis were diagnosed at the latest endoscopy. By the end of this study, four patients were under consideration for further treatment.

Survival (V)

Colorectal cancer was detected in 76 of the 236 FAP patients (32%) at the time of operation. The CRC rate was significantly less in the group of 120 call-up patients (5; 4.2%) than in the proband group (71 vs 61%); ($p<0.001$). The stage distribution of the tumors was also more favorable in the call-up group than in the probands, as shown in Table 4.

Table 4. The frequency and stage of colorectal cancer at the time of initial treatment of FAP.

Dukes stage	Call-up case (n = 120)	Probands (n = 116)
A	3	9
B	1	25
C	1	18
D	-	16
Unknown	-	3
	5 (4.2%)	71 (61%) *

* $p < 0.001$, Fisher's exact test

By the end of this study, all five call-up patients with CRC were alive after a median follow-up of 15 years (range 12 -26 years). However, one male patient had secondary RPC 11 years after IRA because of two Dukes A cancers in the rectal stump. In comparison, 54 of 71 (76%) probands with CRC at diagnosis had died after a median follow-up of 2.2 years (range 0-15 years) (49 of CRC, two of postoperative pulmonary embolism, one of suicide, one of acute myocardial infarction and one of renal failure). Only 17 (24%) probands were alive after a median follow-up of 12.5 years (range 2-35 years).

Survival advantage was observed in favor of the call-up group over the probands after colectomy or proctocolectomy. When survival figures relative to that of the general population were calculated, the difference between the two groups remained unchanged and survival of the call-up group did not differ from that of the general population up to 18 years after colectomy (Fig. 5).

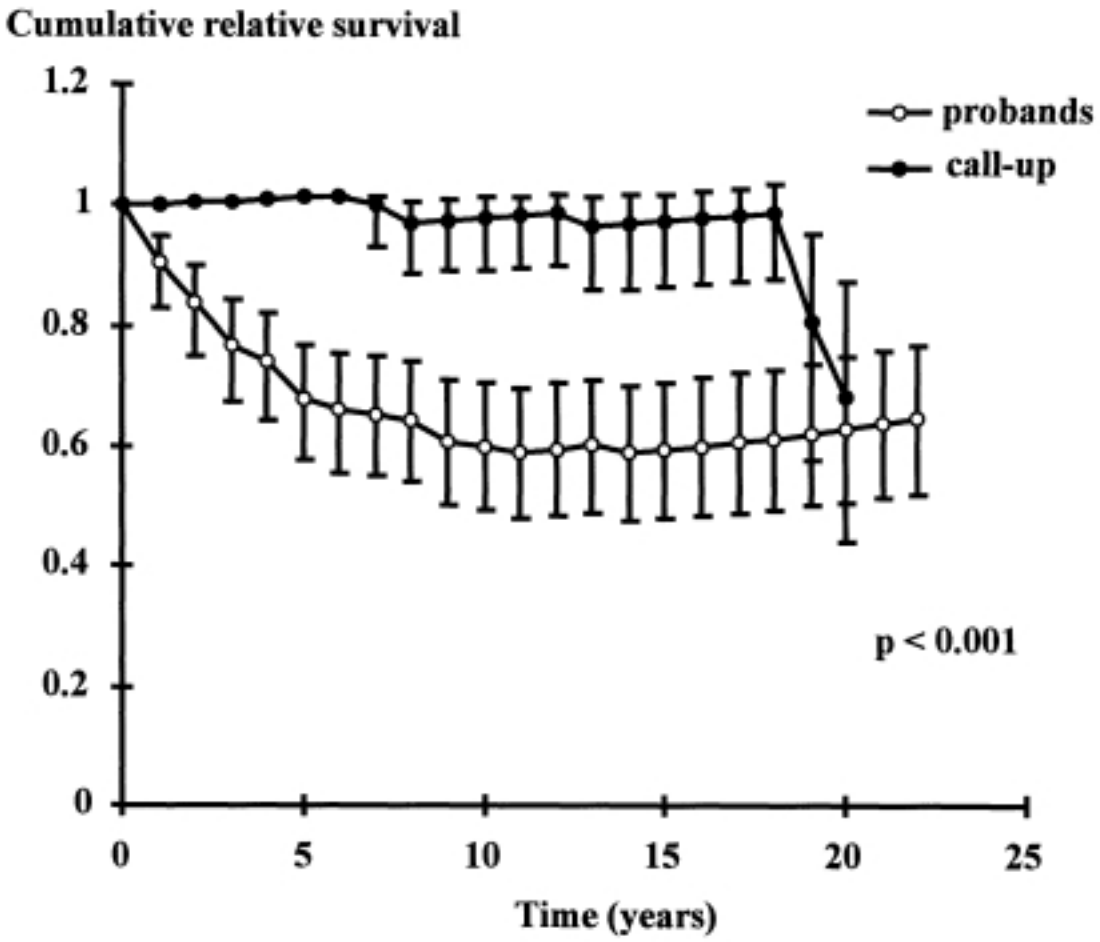

Figure 5. Cumulative relative survival after operative treatment of FAP. Bars indicate 95% confidence limits.

By the closing date of the study, 10 of the 120 call-up patients (8.3%) and 58 of the 116 probands (50%) had died. The majority of deaths were attributable to FAP, 60 of the 68 cases (88%): seven of 10 (70%) in the call-up group compared with 53 of 58 in the probands. CRC present at the time of primary colectomy caused 43 deaths in the proband group but none in the call-up patients. However, rectal stump cancer caused four deaths in the call-up patients and seven deaths in the probands. The other FAP-related causes of deaths were periampullary (duodenal) cancer, gastric cancer, and postoperative pulmonary embolism, two cases each.

DISCUSSION

Choice of operation

The choice between IRA and RPC as a prophylactic operation for FAP is not an easy issue (Setti-Carraro and Nicholls, 1996). Colectomy with ileorectal anastomosis may be associated with a lower risk of postoperative morbidity and functional problems. However, according to present results, the high long-term cancer risk of the rectal stump makes a secondary proctectomy necessary in at least half of the patients.

The early complication rate of 30% following RPC was close to that observed in other comparative studies (Ambroze et al., 1992; Kartheuser et al., 1996; Tonelli et al., 1997). Late complications occurred slightly more often after IRA, mainly on account of more frequent small bowel obstruction. RPC is technically more demanding, with a longer operation time and extensive blood loss, especially in secondary cases (Nyam et al., 1997). Long-term restoration of adequate anal function may be as good as after primary RPC and IRA, and function improves with time (Penna et al., 1993a).

The functional outcomes following RPC and IRA in regard to anal pressure, bowel movements, incontinence, and sexual life were similar, as also reported from the Mayo Clinic (Fazio et al., 1995). In the other comparitive study, the functional results were in favor of IRA at St Mark's (Madden et al., 1991) and, recently, in a large Dutch study (van Duijvendijk, 2000). The mucosal remnant remaining after stapled anastomosis carries the same risk for cancer as the original disease (Wolfstein and Neumann, 1982; Tsunoda et al., 1990). Therefore mucosectomy should always be performed (O'Connell and Williams, 1991; Kartheuser et al., 1996). Even so, the risk may not be totally eliminated, since invasive cancer has been observed developing either from the preserved transitional zone or from retained mucosal remnants (Hoehner and Metcalf, 1994; von Herbay et al., 1996).

The quality of life was not restricted by RPC, as reported earlier (Nyam et al., 1997; Tonelli et al., 1997). In a recent study, however, the quality of life was similarly and significantly worse after IRA and RPC than that of the general population (van Duijvendijk, 2000). The degree of satisfaction is correlated not only with the objective outcome but also with personality and lifestyle (Fujita et al., 1992; Daniels et al., 1999). FAP patients need to be carefully counselled before RPC so as to understand that bowel habits will be far from normal (Körsgen and Keighley, 1999).

The present results are in favor of primary RPC with mucosectomy and hand-sewn anastomosis without diversion as the operation of choice in FAP. RPC requires

surgical experience to guarantee acceptable results and therefore necessitates centralization of these operations to university hospitals or other large centers. It is important that patients know that occasionally RPC may be technically impossible because of intra-operative finding of mesenteric fibromatosis or a DT (Church, 1995).

Improved genetic testing may identify a subset of families with more benign phenotypic expressions of APC gene mutations, in which IRA may be acceptable (Bertario et al., 1994; Vasen et al., 1996; Wu et al., 1998b). The decision for prophylactic surgical treatment should be based on clinical factors and molecular diagnosis in the near future (Soravia et al., 1998; van Duijvendijk, 2000). In cases with small numbers of adenomas in AFAP, polypectomy and colonoscopic surveillance have been proposed as an option (Lynch and Smyrk, 1998).

The rectal stump

The cancer risk after IRA and its significance are debated. The rectal cancer risk of 25% at 20 years after operation comes close to the estimates from Japan (24% at 15 years) and from the Mayo Clinic (26% at 20 years) (Bess et al., 1980; Iwama and Mishima, 1994). In three other studies, there are clearly lower risk rates, from 13 to 15% at 25 years after IRA (Feinberg et al., 1988; DeCosse et al., 1992; Nugent and Phillips, 1992). This may be due to differences in patient characteristics, variable follow-up policy, or even to the wide confidence limits of estimates related to few cases with follow-up times for more than 20 years.

The justification for IRA is also influenced by the difficulties connected with regular rectal examinations. Polypectomies and fulgurations caused bleeding episodes and two patients had a bowel perforation. Increased by four cases with anorectal stricture, the total frequency of complications at follow-up was 12 (12%). More importantly, uncontrollable rectal adenomas, severe dysplastic change, or fear of cancer necessitated rectal excision in 12 patients of the present series. The total cumulative proctectomy rate reached 74% at 29 years after IRA. De Cosse et al. reported a cumulative total proctectomy rate of 44% at 25 years (DeCosse et al., 1992). In a recent registry analysis, the risks of secondary proctectomy on account of rectal cancer or for other reasons were 26% and 34%, respectively, by the age of 65 years (van Duijvendijk, 2000).

In the series at St. Mark's Hospital, the cumulative rectal cancer rate remained at 10% until the age of 50 years, but increased sharply to 29% by 60 years of age (Nugent and Phillips, 1992). They proposed IRA as the operation of choice for patients under 30 years and RPC for older patients and those who had undergone IRA. There was no steep rise in the age-dependent rectal cancer rate in this study

at any time, and seven of nine patients developed rectal cancer before the age of 50 years. The rectal cancer risk of 13 to 26% within the next 20 years is of a matter great concern, no matter how safe and simple the primary operation is. Not all patients can be kept under control and, even in those under close control, the cancer tended to be more widespread (van Duijvendijk, 2000). Furthermore, a second-stage restorative proctectomy may not result in perfect functional outcome, or may be impossible in cases of pelvic fibromatous adhesions or desmoids (Penna et al., 1993a). A planned strategy of two prophylactic operations doubles the risks of the operations and may also increase the risk of DT.

Sulindac reduces adenoma formation in FAP, and, when taken by mouth or with rectal application, often causes the disappearance of rectal polyps (Labayle et al., 1991; Nugent et al., 1993a; Winde et al., 1995; Giardiello et al., 1996). Sulindac caused at least partial regression of rectal polyposis in over half of the present patients, without side-effects. One patient had an advanced rectal stump cancer after cessation of sulindac, as has also be reported by others (Niv and Fraser, 1994; Lynch et al., 1995b). Regression is not always complete or permanent, and medical treatment does not replace prophylactic surgery (Giardiello, 1996). Endoscopic surveillance is necessary even during prophylactic medical treatment. It should be noted that the marketing licence of sulindac (Clinoril®) in Finland ceased in September 1999. Sulindac is available only with permission for each patient from the National Agency for Medicines. Whether or not the new specific cyclooxygenase inhibitors (COX-2) are effective remains to be seen (Hawk et al., 1999).

The high cumulative risk of rectal cancer, 25% at 20 years after IRA, combined with the much higher total proctectomy rate (74% in 29 years) indicates that IRA is not a satisfactory long-term treatment. The outcome may be better when sulindac is added. Otherwise, the retained rectum has to be excised prophylactically in middle age. These results underline the importance of RPC as a main option in most cases of FAP.

Management of desmoid tumors

When the colon cancer risk is reduced, the importance of the DT increases, as may its frequency. The figure of 14% is close to previous frequencies, but by the age of 60 years, the cumulative probability reaches 21%. A person-year analysis resulted in an incidence of 3.72 per 1000 person years, 1240 times the risk for the general population, which was slightly more than reported from the Johns Hopkins Hospital (Gurbuz et al., 1994).

Consistently with previous reports, the risk of DT was greater in females, with a female-to-male ratio of 1.4 (Iwama et al., 1993; Gurbuz et al., 1994). The cumulative lifetime risk was 23% for women and 19% for men. Klemmer et al. found a similar difference, but lower risk figures (Klemmer et al., 1987). Hormonal influences, e.g. pregnancies, have been thought to explain the greater DT frequency in women (Reitamo et al., 1986). However, pregnancies were not more frequent in the present DT patients than in the women without DT. The present was unable to detect any measurable estrogen or progesterone receptors in three DTs, in contrast to Reitamo et al. (Reitamo et al., 1986), who demonstrated a low estrogen receptor content in the DT of one male patient.

Surgical trauma precedes the development of most DTs, i.e. in 83% in our patients. However, in FAP surgery is unavoidable. Prophylactic colectomy at a very early age may increase the risk of DT, at least in known "desmoid families". There were no significant differences in the DT risk after different surgical procedures. Interestingly, all five mesenteric DTs after PC occurred in cases of conventional ileostomy, and none was observed after 20 RPC. This may reflect the small number of cases and short follow-up after the pouch procedure, but supports the view that RPC does not increase the risk of DT (Penna et al., 1993d).

Most authors agree that abdominal wall and other superficial DTs can often be cured by wide excision, especially when the tumor is small (Richards et al., 1981; Farmer et al., 1994; Church, 1995; Griffioen et al., 1998). Complete clearance of the abdominal wall DT was achieved in eight of the 11 cases operated on, and there was one case with complete spontaneous regression. However, local recurrence was common (45%) leading to re-excisions, and two patients developed new DTs at other sites. Some recurrent cases are probably new tumors at multiple sites near to the original one.

A large mesenteric DT is difficult to deal with, especially when it is at the mesenteric root, making complete resection hazardous (Church, 1995; Griffioen et al., 1998). Patients with relatively small DT masses or no obstructive symptoms have been operated on with small bowel or ureteric by-pass with a stable situation, as observed earlier (Church, 1995). Excisional treatment was undertaken either in suitable cases or when no other choice was seen. There were two recurrences (22%), clearly less than the high recurrence figures, from 50 to 85%, reported earlier (Berk et al., 1992; Farmer et al., 1994; Rodriguez-Bigas et al., 1994). Furthermore, in spite of two life-threatening complications, there were no postoperative deaths. This contrasts with the experience of others reporting a perioperative mortality of 50% or major morbidity of 60% (Jones et al., 1986; Farmer et al., 1994).

DTs are insensitive to radiation therapy, which is therefore of limited value in the treatment (Jones et al., 1986). Noncytotoxic medical treatment may sometimes be effective in the longterm (Tsukada et al., 1992). The present study, consistently with other reports, could not demonstrate any measurable regression in 10 cases treated with sulindac and/or antiestrogens (Itoh et al., 1988; Penna et al., 1993d). Likewise, there are a reports of favorable responses to high-dose cytotoxic chemotherapy (Patel et al., 1993; Lynch et al., 1994; Schnitzler et al., 1997). Further experience with the same or similar regimens has given disappointing results with few responses but a high frequency of severe toxicity, and even deaths (Tsukada et al., 1991).

It is impossible to give any uniformly applicable recommendations for prevention or medical treatment of DTs. Desmoids and their complications have been reported as the second most common cause of death after colectomy in FAP (Arvanitis et al., 1990; Iwama et al., 1993; Belchetz et al., 1996). There were no deaths related to DTs in this study, in accordance with the Danish experience (Søndergaard Calle et al., 1999). The St Mark's group (Clark and Phillips, 1996) has proposed a treatment protocol for DT. It consists of imaging studies, initial treatment with sulindac for 6 months, thereafter toremifene when needed, and consideration of chemotherapy. Surgery is reserved for obstructive complications and for abdominal wall DTs.

Every case of mesenteric DT seems to be different. Some authors have taken the position that excisional treatment of mesenteric DT should be totally abandoned (Farmer et al., 1994; Church, 1995). However, this study showed that there are cases with no other possibility and that a recurrence is not the rule. One aspect supporting surgery, even excisional surgery, is the absence of other treatment options.

Treatment of gastroduodenal lesions

The cumulative detection rate of duodenal adenomas was 97% even without a side-viewing endoscope and random biopsies. In previous studies, the detection rate has varied between 66 and 92% at the initial examination (Spigelman et al., 1989; Church et al., 1992). The use of side-viewing endoscope, multiple biopsies, and frequent re-examinations will probably demonstrate duodenal adenomas in every FAP patient.

The stage of the duodenal adenomas progressed in the majority (74%) of those patients who had follow-up examinations. Stage IV duodenal adenomatosis, implying the highest cancer risk, has been detected in approximately 10% of all patients with FAP (Spigelman et al., 1989; Bülow et al., 1995), as in the present series (8%). The cumulative incidence of stage IV disease, however, reached 30%

at the age of 65 years. Assuming that all FAP patients develop duodenal adenomas, which progress to stage IV in 30% of cases, the low incidence of duodenal cancer is surprising. The cumulative cancer incidence was 4%, being consistent with the reported incidence of 3 to 4% (Vasen et al., 1997). The progression of the adenoma-carcinoma sequence is probably slower in the duodenum than in the colon (Offerhaus et al., 1992; Spigelman et al. 1994). On the other hand, CRC mortality has possibly hidden other, less common, problems such as duodenal cancer. Therefore, improving control of the CRC by family screening and prophylactic colectomy will probably result in an increase in the rate of duodenal carcinoma.

The occurrence and severity of periampullary neoplasms segregates in families without any relation to a specific APC mutation (Sanabria et al., 1996). Thus, knowledge of the polyp status of a family predicts the risk and modifies the screening of family members. The extent to which surveillance and subsequent treatment of severe duodenal polyposis benefit FAP patients is not known (Sarre et al., 1987; Spigelman et al., 1989; Norfleet, 1992; Debinski et al., 1995; Marcello et al., 1996). In a decision analysis, Vasen and co-workers concluded that regular surveillance could lead to an increase in life expectancy of 7 months when pancreaticoduodenectomy is performed in cases with stage IV polyposis or early cancer (Vasen et al., 1997).

Several endoscopic methods can be used to treat advanced duodenal adenomas (Saurin et al., 1999). The effectiveness of endoscopic mucosal resections, laser therapy, argon plasma coagulation, and photodynamic therapy remains to be confirmed by prospective studies. None of our patients who had prophylactic excisions for advanced duodenal adenomas has developed duodenal cancer. In a control endoscopy, a significant decrease in the average stage was still demonstrable after two years. Unfortunately, re-growth of the adenomas occurred always, as observed earlier (Penna et al., 1993b).

In theory, stage III or IV will be reached within a mean of 10 to 20 years in all cases after open duodenotomy. In selected cases with stage IV adenomatosis, there may be a place for prophylactic pancreaticoduodenectomy with or without pylorus saving, at least in young patients with severe disease or in those who need re-operation after excisions (Chung et al., 1995; Causeret et al., 1998; Penna et al., 1998) but this is controversial (Griffioen et al., 1998).

Cell kinetic studies have shown proliferation abnormalities in the duodenal mucosa, there being two subgroups with different risks of duodenal neoplasia (Santucci et al., 1997). Duodenal adenoma formation seems strongest at the site around the papilla of Vater or at the site where the mucosa is exposed to high bile

concentrations (Spigelman et al., 1989; Debinski et al., 1995). Therefore, adenomas may appear in the upper jejunum near to the new bile duct anastomosis at a similar frequency after excision of the duodenum as after local excisions through a duodenotomy. Medical treatment in the form of some nonsteroidal anti-inflammatory drug might give a better response, but treatment with sulindac has given conflicting results in the control of duodenal adenomas (Nugent et al., 1993a; Richard et al., 1997; Wallace and Phillips, 1999). Chemopreventive agents have not demonstrated definitive efficacy against duodenal adenomas (Hawk et al., 1999).

Survival in familial adenomatous polyposis

The protective effect of screening and prophylactic colectomy is obvious. The percentage of patients with CRC was 4% in the call-up group and 61% in symptomatic group at the time of initial treatment, which is in accord with earlier reports (Alm and Licznerski, 1973; Bülow, 1986; Berk et al., 1987; Vasen et al., 1990). Almost half of the CRCs in probands were already disseminated.

The majority (79%) of deaths were caused by CRC, corresponding the previously reported figures of 58-81% (Arvanitis et al., 1990; Iwama et al., 1993; Bertario et al., 1994). The second most common cause of death in the present series was rectal stump cancer, comprising nearly one fifth of all FAP-related causes. In addition, care of the rectal stump may cause difficulties, and even deaths. Rectal stump cancer can be prevented by performing the first operation with RPC. Therefore, RPC has been recommended as the operation of choice for most FAP patients (Ambroze et al., 1992; Kartheuser et al., 1996).

Survival after prophylactic colectomy equaled that of the general population for at least 18 years, as observed earlier (Søndergaard Calle et al., 1999). On the other hand, Nugent et al. observed a more than three-fold relative risk of death in FAP patients after colectomy and ileorectal anastomosis (Nugent et al., 1993c). Corresponding to the Danish experience, there were no deaths related to desmoid disease (Søndergaard Calle et al., 1999) even though such cases are well-known in other centers (Arvanitis et al., 1990; Iwama et al., 1993; Nugent et al., 1993c; Belchetz et al., 1996). Postoperative mortality was not observed in the call-up patients, but did occur in two probands who had CRC at the time of primary colectomy.

The experience of the Finnish Polyposis Registry is limited, with a median follow up of about 10 years only in the call-up group. As the median age at the time of colectomy was 27 years, the expected follow up time may approach 50 years. Therefore, more cases of extracolonic cancer and rectal stump cancer can be

expected, especially at the ages of 50 to 60 years (Nugent and Phillips, 1992; Nugent et al., 1996). Moreover, even when deaths from colorectal cancer remain constant or decrease in frequency, it is likely that death rates from extracolonic manifestations of FAP will continue to increase (Bertario et al., 1994; Belchetz et al., 1996).

Surveillance

The screening and surveillance recommendations in an FAP family with a known mutation should be based on the site of the mutation (Brensinger et al., 1998; Wu et al., 1998b). However, differences in the APC mutation sites alone cannot completely account for the intra- and interfamilial variation of the phenotype. The presence of a modifier gene or genes and environmental factors influence the phenotypic expression of the APC. The advances in molecular genetics may lead to future identification of high-risk individuals with different schedules for screening, surveillance, and treatment.

CONCLUSIONS

1. The results favor primary restorative proctocolectomy, usually in one stage, despite the risk of less perfect functional results in some cases.

2. Colectomy and ileorectal anastomosis is not a satisfactory long-term treatment for patients with familial adenomatous polyposis because of the high risk of rectal stump cancer (25%/20 years) and the 74% risk of rectal excision.

3. The cumulative lifetime risk of a desmoid tumor is 21%. Medical treatments of desmoid tumors have limited success. Thus, surgery has an important role in the treatment of both abdominal wall and mesenteric desmoid tumors.

4. Nearly all patients with familial adenomatous polyposis will develop duodenal adenomas in the endoscopic follow-up. Surveillance and subsequent prophylactic surgical treatment are beneficial. Local endoscopic treatment is rarely possible and the choice is mostly between open duodenotomy and pancreaticoduodenotomy even though recurrence of the adenoma is probable after either procedure.

5. Screening and prophylactic surgery have improved the prognosis of patients with familial adenomatous polyposis so that, for nearly 20 years, the survival equals that of the general population. Centralization of screening, diagnosis, and treatment is recommended for all patients with familial adenomatous polyposis.

SUMMARY

Familial adenomatous polyposis is an autosomally dominant inherited cancer predisposition syndrome. The disease is characterized by multiple adenomatous polyps with an inevitable risk of colorectal cancer. Various extracolonic manifestations may also appear. The aim of the study was to investigate therapeutic strategies, results of treatment, and survival of patients with FAP, on the basis of the data from the Finnish Polyposis Registry.

The justification for colectomy and ileorectal anastomosis (IRA) as the primary treatment for FAP remains questionable because of the rectal cancer risk. The cancer risk and the need for rectal excision were estimated in 100 FAP patients. The cumulative risks of rectal cancer after IRA at 5, 10, 15, and 20 years were 4%, 5.6%, 7.9% and 25.2%. The corresponding rectal excision rates were 7.3%, 13.7%, 23.6%, and 73.8%. Age-dependent rectal cancer risks at 40, 50, and 60 years were 3.9%, 12.8% and 25.7%, and rectal excision rates were 9.5%, 26.3% and 44%, respectively. Sulindac caused at least partial regression of rectal adenomas in 71% of patients, without major adverse effects, but the long-term effects of sulindac and its impact on malignant transformation of rectal adenomas are not known. The results favor RPC as the primary operation for FAP. RPC requires sufficient surgical experience to be certain of acceptable results and therefore necessitates centralization of prophylactic operations to university hospitals or other large centers.

The operative and functional outcomes were compared in 99 IRA and 33 RPC patients. Primary RPC is the operation of choice for most patients with FAP when the long-term outcome is taken in account. In the future, improved genetic testing may identify a subset of families with more benign adenomatous polyposis gene mutations, and for these patients IRA may be more acceptable. On the other hand, for those patients in whom the rectum retained and who develop multiple rectal adenomas, treatment with sulindac may offer a possibility to reduce the rectal cancer risk, but the long-term efficacy of this treatment is not yet known.

The incidence and treatment of desmoid tumors were analyzed in 202 FAP patients. DTs were observed in 29 cases, representing a frequency of 14% and a cumulative probability of 21%. All abdominal wall and 56% of mesenteric DTs were excised, with recurrence rates of 45% and 22%, respectively. This study failed to demonstrate regression of DTs with noncytotoxic medical treatment, cytotoxic chemotherapy, or radiation therapy. According to these results surgery is the preferred treatment method when the risks are taken into account.

In the prospective follow-up study, 98 patients underwent at least one upper endoscopic examination. In these endoscopic follow-ups nearly all FAP patients are found to have developed duodenal adenomas. There was progression of the stage of duodenal adenomatosis in 74% of patients followed up, and stage Ⅳ disease developed by the age of 65 years in 30%. Even though the duodenal cancer incidence has been low, there are indications that surveillance, followed when necessary, by prophylactic surgical treatment are beneficial. Local endoscopic treatment is rarely possible and the choice is mostly between open duodenotomy and pancreaticoduodenectomy, even though adenoma recurrence is probable, whichever procedure is chosen.

The mortality rates and causes of death were studied in all 236 FAP patients included in the Finnish Polyposis Registry. Centralized registration of FAP patients, screening for at risk family members, and prophylactic colectomy have improved the prognosis of FAP patients, so that their life expectancy may reach that of the general population for almost 20 years after surgery. However, there is excess mortality in the long term, e.g. because of periampullary cancer or gastric cancer developing from gastroduodenal adenomas or because of rectal stump cancer. Further improvement of the prognosis may be possible with more frequent application of restorative proctocolectomy instead of colectomy and ileorectal anastomosis and with regular upper GI-tract endoscopies.

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