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Gross and histological abnormalities of the foregut in familial adenomatous polyposis: A study from a South East Asian Registry

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Abstract. Polyps in the stomach and duodenum are frequently found in familial adenomatous polyposis. Cancer arising from some of these polyps may be an important cause of death in patients who have had large bowel resections. This study aims to determine the nature and distribution of foregut polyps in Chinese patients. Twenty-five patients with familial adenomatous polyposis were gastroscoped by a single operator using the end viewing video-endoscopy system. Representative biopsies of normal mucosa or polyps where appropriate were taken from the gastric fundus, antrum and the duodenum. Twenty-five patients were studied. Male = 17, female = 8. Median age was 32 years (range = 17–63 yrs). Nineteen patients were found to have macroscopically visible polyps in the foregut. Ten patients had gastric polyps alone, three patients had duodenal polyps alone whilst six patients had both gastric and duodenal polyps. Twelve, one and three patients had more than 20 polyps in the gastric fundus, antrum and duodenum respectively. Only one patient had polyps which were larger than 10 mm. The commonest polyp in the gastric fundus was the fundic gland polyp whilst hyperplastic and adenomatous polyps were the commonest polyps in the gastric antrum and duodenum respectively. Five patients had adenomatous polyps of which four had duodenal adenomas alone whilst one patient had adenomas in the duodenum, gastric antrum and fundus. Seventy-six per cent of our patients with familial adenomatous polyposis had foregut polyposis. Adenomatous polyps were found in 56% of patients with duodenal polyps or 20% of patients with foregut polyps but hyperplastic and hamartomatous polyps occur commonly in patients with familial adenomatous polyposis as well.

Résumé. Des polypes gastriques et duodénaux sont fréquemment rencontrés au cours de la polypose adénomateuse familiale. La transformation cancéreuse de ces polypes peut être une importante cause de décès chez les malades qui ont eu des résections coliques. Le but de cette étude est de déterminer la nature et la distribution des polypes de cette région chez les patients chinois. 25 patients atteints de polypose adénomateuse familiale ont été gastroscopés par un même opérateur utilisant un système de vidéoendoscopie à vue terminale. Des biopsies représentatives de la muqueuse normale ou de polypes existants ont été réalisées au niveau du fundus de l'antre et du duodénum. 25 malades ont été étudiés, 17 hommes, 8 femmes d'un âge moyen de 32 ans (17–63 ans). 19 patients avaient des polypes macroscopiquement visibles dans le tube digestif supérieur. 10 malades avaient des polypes gastriques seuls, 3 avaient des polypes duodénaux seuls tandis que 6 avaient à la fois des polypes gastriques et duodénaux. 12, 1 et 3 patients avaient plus de 20 polypes dans le fundus, l'antre ou le duodénum respectivement. 1 seul malade avait des polypes d'un diamètre supérieur à 10 mm. Le type le plus common de polype du fundus était un polype des glandes fundiques tandis que des polypes hyperplasiques et adénomateux étaient les polypes les plus communs dans l'antre et dans le duodénum respectivement. 5 malades avaient des polypes adénomateux dont 4 avaient uniquement des adénomes duodénaux tandis que 1 patient avait des adénomes duodénaux, gastriques au niveau de l'antre et du fundus. 76% de nos patients avec une polypose adénomateuse familiale avaient une polypose au niveau du tube digestif supérieur. Les polypes adénomateux ont été trouvés chez 56% des malades avec des polypes duodénaux ou 20% des malades ayant des polypes du tube digestif supérieur mais les polypes hyperplasique et hamartomateux surviennent fréquemment chez les patients qui ont une polypose adénomateuse familiale.

Introduction

Case reports of gastric and duodenal polyps in patients with familial adenomatous polyposis appeared as early as 1895 and 1935 respectively [1, 2]. Nonetheless, the important macroscopic pathology in familial adenomatous polyposis was thought to be limited to the colorectum and the disease thus known as familiar polyposis coli [3].

In 1974, the first series showing the frequent occurrence of gastric polyps in familial polyposis coli was published with 10 of 15 Japanese patients with familial polyposis coli manifesting gastric polyps [4]. Following this, duodenal polyps were reported in patients with familial polyposis coli [5–8]. Subsequently, polyps were also found in the small intestine in familial polyposis coli and thus it was suggested that this syndrome be more appropriately termed familial gastrointestinal polyposis [9]. We now know that patients with familial adenomatous polyposis can manifest a wide range of non-colorectal pathology [10] and the name familial adenomatous polyposis does not adequately describe the clinical entity.

Gastroduodenal polyps in familial adenomatous polyposis occur in up to 100% of patients [4, 15] and as adenomas are precursors of cancer [26] it is not surprising that patients with familial adenomatous polyposis treated with various forms of colectomy have been reported to be at greater risk of dying from upper gastrointestinal cancer then from colorectal cancer [27–30]. Patients with familial adenomatous polyposis under our care were therefore screened to establish the incidence and type of gastroduodenal polyps as well as to identify possible risk factors for developing gastroduodenal cancer.

Patients and methods

All affected members with familial adenomatous polyposis registered with the Singapore Polyposis Registry and who were under the care of the Department of Colorectal Surgery at the Singapore General Hospital were prospectively reviewed. Each patient was gastroduodenoscoped by one surgeon endoscopist (Olympus GIFXQ10, Olympus, Tokyo). Twenty five Chinese patients (male = 17, female = 8) from 14 families were examined. Their median age was 32 years with a range of 17 to 63 years. Thirteen patients had had restorative proctocolectomy with a pelvic ileal pouch, 3 had had panproctocolectomy and ileostomy, 3 patients had had total colectomy with ileo-rectal anastomosis, 1 patients had a palliative anterior resection whilst 5 patients had not yet had surgery. One patient had had Dukes A colorectal carcinoma, whilst 2 had had Dukes B, four Dukes C and 2 distantly disseminated colorectal carcinoma.

A standard examination protocol was used in all patients. The duodenum was intubated and visual inspection made of the first, second and third parts of the duodenum with special attention to the duodenal papilla. The gastroscope was then withdrawn into the stomach and the gastric antrum inspected. Retroflexion of the gastroscope then allowed examination of the rest of the gastric body and fundus. The oesophagus was examined on withdrawal of the scope. Multiple biopsies were taken from representative polyps in the duodenum, gastric antrum and fundus respectively. Where no macroscopic polyp was seen, random biopsies were taken from the duodenum, gastric antrum and fundus respectively. The site, size and number of polyps seen were recorded. All biopsies were examined by one consultant histopathologist.

Results

Of 25 patients, 19 (76%) had macroscopic upper gastrointestinal polyps. Their ages ranged from 27–60 years (median age = 25 years). No oesophageal lesion was seen. Ten patients had gastric polyps alone, 3 patients had duodenal polyps only, 6 patients had both gastric and duodenal polyps. Six patients (median age = 33.5 years, range 30–63) did not have upper gastrointestinal polyps and random biopsies did not reveal any microadenomas in these patients.

Table 1. Table showing the number and size of polyps present in the upper gastrointestinal tract in 25 patients with familial adenomatous polyposis

	Number of polyps			Size of polyps (mm)		
	<5	5–20	>20	<5	5–10	>10
Gastric fundus	1	2	12	11	3	1
Gastric antrum	3	1	1	5	0	0
Duodenum	5	1	3	8	1	0

Gastric fundus

Fifteen patients had polyps in the gastric fundus; 12 had fundic gland polyps, 2 had hyperplastic polyps and 1 had adenomatous polyps. Of the 11 patients with fundic gland polyps 9 had more than 20 polyps carpeting the gastric fundus. Two patients had between 5 and 20 polyps and 1 patient had less than 5 polyps in the gastric fundus. The 2 patients with hyperplastic polyps and the 1 patient with adenomatous polyps also had carpeting of the gastric fundus. Of our patients with fundic glands polyps 90%, 81% and 72% showed these polyps by 40, 35 and 30 years respectively. The likelihood for the occurrence of fundic gland polyps is not dependent on a family history of fundic gland polyps as these polyps are as common in patients with or without a family history of such polyps.

Gastric antrum

Five patients had gastric antral polyps, 4 of whom had hyperplastic polyps and 1 had adenomatous polyps. Of the four patients with hyperplastic polyps 1 patient had gross carpeting of the antrum without concomitant polyps in the gastric fundus. The other 3 patients with hyperplastic polyps had less than 5 polyps in the gastric antrum. The 1 patient with adenomatous polyps had less than 20 antral polyps.

Duodenum

Nine patients had duodenal polyps of which 4 patients had hyperplastic polyps whilst 5 patients had adenomatous polyps. All hyperplastic polyps were found in the first part of the duodenum and 1 patient had hyperplastic polyps extending into the second part of the duodenum as well. Duodenal adenomas occurred mainly in the second part of the duodenum and only 1 patient had adenomas in the first part of the duodenum. Of 4 patients with adenomatous polyps 2 patients had more than 20 polyps in the duodenum. Two patients had less than 5 adenomatous polyps and 1 had between 5 to 20 ade-

Table 2. Table showing the type of polyps in the upper gastrointestinal tract in 25 patients with familial adenomatous polyposis

Patient number	Sex	Kindred number	Age (years)	Duodenum	Antrum	Fundus
1.	M	16	23	nil	nil	FGP
2.	F	8	40	nil	hyperplastic	hyperplastic
3.	M	16	60	adenoma	nil	nil
4.	M	14	33	adenoma	nil	nil
5.	M	5	22	nil	nil	FGP
6.	M	8	17	nil	nil	FGP
7.	F	13	30	nil	nil	nil
8.	M	5	51	hyperplastic	hyperplastic	FGP
9.	M	9	32	hyperplastic	nil	FGP
10.	F	12	63	nil	nil	nil
11.	F	9	30	nil	nil	hyperplastic
12.	M	18	21	adenoma	adenoma	adenoma
13	M	1	22	hyperplastic	nil	FGP
14.	F	14	27	nil	hyperplastic	FGP
15.	M	14	32	nil	nil	nil
16.	M	4	36	hyperplastic	nil	nil
17.	M	19	25	adenoma	nil	FGP
18.	M	1	20	nil	nil	FGP
19.	M	1	18	nil	nil	FGP
20.	F	6	35	nil	nil	nil
21.	M	12	35	nil	nil	FGP
22.	F	2	37	nil	hyperplastic	nil
23.	F	10	32	nil	nil	nil
24.	M	12	41	nil	nil	nil
25.	M	4	19	adenoma	nil	FGP

FGP = Fundic gland polyp

nomatous polyps. Of 3 patients with hyperplastic polyps 2 had less than 5 of these polyps whilst 1 had more than 20 hyperplastic polyps. There were no observed statistical difference between the number or size of duodenal polyposis and age of patients.

Histological features

The commonest polyp in the gastric fundus was the fundic gland polyps whilst hyperplastic polyp and adenomatous polyps were the commonest polyp in the gastric antrum and duodenum respectively. Of the 12 patients with fundic gland polyps 11 were males. Of 25 patients 5 (20%) had adenomatous polyps; all 5 occured in males. One of these had adenomas in the gastric fundus and antrum as well. The latter patient who was 21 years old had a palliative anterior resection for disseminated rectal carcinoma at the time of gastroscopy. Overall, hyperplastic polyps were equally common in males and females but varied in their site of distribution between the sexes, being commoner in the duodenum in males (4 of 4) and in the stomach in females (3 of 4).

Five patients had histological features of gastritis and 6 patients had duodenitis. Seven of these showed the presence of *Helicobacter pylori.*

Gastric biopsies in 3 of our patients showed foveolar hyperplasia with congestion, oedema and minimal inflammatory reaction. Of these patients 1 had hyperplastic gastric polyps while the other 2 patients had fundic gland polyps. These histological features are often seen in bile-associated gastritis of the stomach.

Discussion

With the exception of the oesophagus, the upper gastrointestinal tract appears to be at high risk of polyp formation. Gastroduodenal polyps occurring in patients with familial adenomatous polyposis include gastric fundic gland polyps, gastric and duodenal hyperplastic polyps, adenomas and carcinomas [4–25]. The newer term familial adenomatous polyposis [32] is therefore not adequate and perhaps the eponym Gardner's syndrome should be applied to all cases of this syndrome as it is now generally accepted that the division of patients into those with polyposis coli alone and those with extracolonic manifestations (Gardner's) is unnecessary [10, 22].

Fundic gland polyps were first described as a distinct entity in patients with familial adenomatous polyposis [4, 6, 22, 33]. However, they do occur in patients without familial adenomatous polyposis [15, 34–37]. Iida et al. found it to be rare in the latter patients, occurring in 0.085% of 27000 Japanese without familial adenomatous polyposis [36]. It is common in familial adenomatous polyposis, occurring in 48% of patients in the present series. There are some interesting differences between fundic gland polyps in patients with and without familial adenomatous polyposis. The latter patients tend to be middle aged women while patients with adenomatous polyposis manifesting fundic gland polyps tend to be younger males [15, 34–37]. The number of polyps tend to be greater in patients with familial adenomatous polyposis [34–37]. Interestingly, although most of our patients showed numerous fundic gland polyps, 1 patient had a single fundic gland polyp only. The superficial and foveolar epithelium

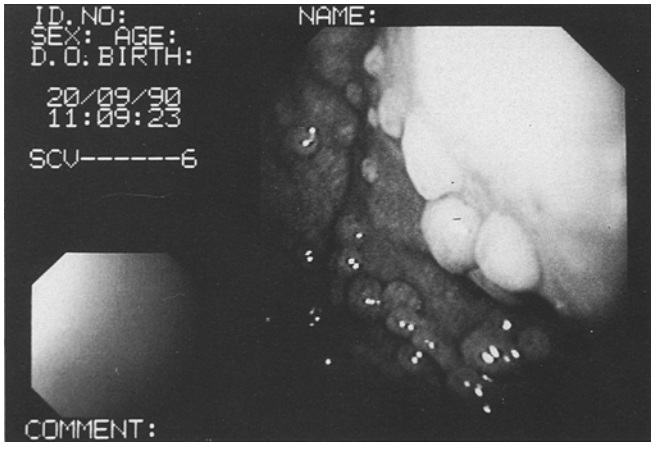

Fig. 1. Video-gastroscopy picture showing multiple fundic glandular polyps. Fundic glandular polyps are seen characteristically as hemispherical sessile polyps in the gastric fundus

of fundic gland polyps in FAP is said to stain positively for *O*-acylated sialic acid whilst polyps from patients without familial adenomatous polyposis do not [15]. This difference is said to be related to intestinal metaplasia within fundic gland polyps in familial adenomatous polyposis as *O*-acylated sialic acid is not present in normal fundic gland epithelium but present in normal large intestinal epithelium [15]. At endoscopy, fundic gland polyps tend to appear as multiple sessile hemispherical polyps located over the gastric fundus and occasionally extended into the body and antrum. Each polyp is usually less than 5 mm in diameter with a smooth surface similar in colour to the surrounding mucosa [13, 14, 20, 22]. Microscopically, fundic gland polyps show proliferation of distorted fundic glands lined by parietal, chief and mucous secreting cells. The deeper parts of the mucosa show cystic dilatation which is the single best criterion in recognizing the lesion in small biopsy specimens [19]. The origin of these polyps have been subject of some controversy with some authors referring to them as hyperplastic [14, 17, 18, 29] whilst other prefer to call them hamartomatous [21, 22, 34, 37] and yet others are undecided [15, 38]. Fundic gland polyps are generally not thought to be premalignant [20]. Regression and disappearance of these polyps is not uncommon [12, 36, 39, 40] and these polyps have been reported to change quickly and extensively with respect to size and number [35]. Although fundic gland polyps and gastric of duodenal hyperplastic polyps have little malignant potential, there are already reports of gastric carcinoma occurring amongst fundic gland polyps in patients with familial adenomatous polyposis [38].

Simple hyperplastic polyps occur frequently in familial adenomatous polyposis in contrast to one report [21]. We found that the commonest polyp in the gastric antrum is the hyperplastic polyp and that three out of four were females whilst all four patients with hyperplastic duodenal polyps were males. This difference may be a function of the small numbers involved as other series have not showed any significant difference between the sexes in any category of polyp in familial adenomatous polyposis [19].

The endoscopic appearance of duodenal polyps may be subtle and these polyps may be difficult to detect [13, 18, 27] and indeed microadenomas have been reported on biopsy in the absence of visible polyps [7, 27]. The number of polyps seen may vary from a single lesion to gross carpeting. Polyps occurring in the first part of the duodenum tend to be hyperplastic whilst polyps in the second part of the duodenum tend to be adenomatous. Duodenal polyps tend to have a sessile irregular shape with a nodular or granular surface. A consistent feature appears to be the whitish colouration of these polyps in contrast to the normal darker hue of the duodenal mucosa. Abnormalities of the papilla of Vater are perhaps the most difficult to recognise and several authors have commented on the normal looking appearance of the papilla in spite of adenomatous change [7, 18, 19]. The involved papilla may look slightly larger than normal, irregular or abnormally white [20].

Although we did not find a deterioration of the histological characteristics of fundic gland polyps nor indeed of hyperplastic foregut polyps with increasing age, fundic gland polyps tend to grow in large numbers and some of our patients had gross carpeting with hyperplastic polyps as well. These polyps are therefore evidence of the general propensity to gastrointestinal mucosal overgrowth that occurs with familial adenomatous polyposis. The presence of fundic gland polyps did not depend on a family history of fundic gland polyps as these polyps are as common in patients with or without a family history of such polyps [15, 19]. Furthermore, adenomas and carcinomas can occur in the absence of non-adenomatous polyps. All patients with familial adenomatous polyposis must therefore undergo regular foregut surveillance so that foregut malignancies are not missed.

It is interesting that the only patient in our series with fundic adenomas also had gastric and duodenal adenomas. However, there was no histological evidence of bile reflux into the stomach in this patient. Gastric adenomas and carcinomas in familial adenomatous polyposis have been reported in association with bile reflux [41] as abnormalities of bile acid metabolism in these patients is thought to be important in the genesis of these tumours [42]. The three patients in our series who had histological evidence of bile reflux did not have any adenomatous foregut polyps. Histologically, foveolar hyperplasia, mucosal congestion and oedema with minimal inflammatory reaction is characteristic of biliary reflux [31], although biliary reflux may not be accompanied invariably by this distinctive histological picture.

The majority of our patients, that is 15 out of 25 had stage 0 duodenal polyposis. Furthermore only five patients had duodenal adenomas although duodenal biospies were performed in every case. All 5 patients were males but Spigelman et al. had shown that gender is not related to the severity of duodenal polyposis [27]. The only patient in our series with stage IV duodenal polyposis was 60 years old. However, age probably is not the sole factor responsible for adenoma formation [13, 19, 39]. Our youngest patient with adenomatous polyps was 19 years of age. Environmental carcinogens responsible for adenoma formation probably appear early and re-

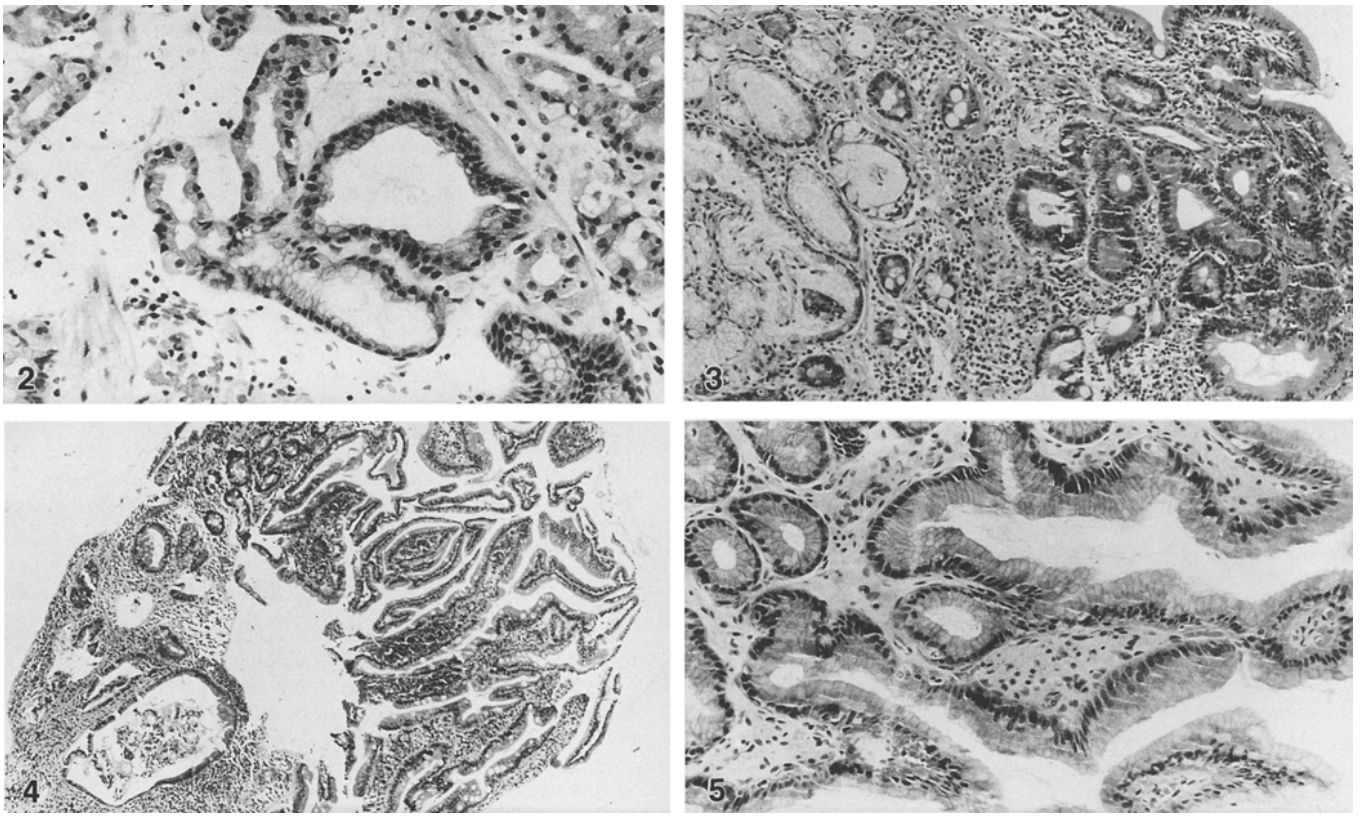

Fig. 2. Fundic gland polyp. Photomicrograph showing cystically dilated glands in the deeper part of the mucosa lined by oxyntic and mucus secreting columnar epithelium. Such glands are a characteristic feature of fundic glandular polyps. Haematoxylin and eosin (200 ×)

Fig. 3. Duodenal adenomatous polyp. A group of dysplastic cells is seen in the superficial part of the duodenal mucosa indicating adenomatous change in this biopsy of a duodenal polyp. Haematoxylin and eosin (200 ×)

Fig. 4. Duodenal hyperplastic polyp. Polypoidal duodenal mucosa showing foveolar hyperplasia with cystic dilatation and inflamed lamina propria. Haematoxylin and eosin (200 ×)

Fig. 5. Bile reflux. Gastric antral mucosa showing oedema of the lamina propria with a paucity of inflammatory infiltrate. Haematoxylin and eosin (200 ×)

Table 3. Table showing the severity of duodenal polyposis in 25 patients with familial adenomatous polyposis

Stage	Number	Age (Median and range) years
0	15	30 (17–63)
I	4	36 (20–51)
II	5	22 (22–33)
III	0	–
IV	1	60

Polyp number (1–4 polyps = 1 point, 5–20 polyps = 2, >20 polyps = 3); polyp size (1–4 mm = 1 point, 5–10 mm = 2, >10 mm = 3); histological type (tubular/hyperplastic/inflammation = 1 point, tubulovillous = 2, villous = 3); dysplasia (mild = 1, moderate = 2, severe = 3). An overall score of 0 points = stage 0, 1–4 = I, 5–6 = II, 7–8 = III and 9–12 = IV (according to Spigelman et al. [27])

peated or prolonged contact over time then leads to carcinomatous change in these polyps. Rarely, gastroduodenal adenomas have been reported to regress and even disappear [12, 43]. The mechanism for this regression is unknown but regression and disappearance of adenomas have been noted in colonic adenomas in familial adenomatous polyposis following colectomy and ileorectal anastomosis as well as after a diet high in fibre [44, 45].

Currently we follow our patients according to the following regimen. The initial gastroduodenoscopy is performed at the time of colectomy for colorectal polyposis. An empirical regimen is then followed; three yearly gastroduodenoscopy for patients diagnosed with a stage 0 or I duodenal polyposis, 2 yearly screening for stage II or III duodenal polyposis, and a yearly endoscopy for patients with stage IV disease.

The difficulty with the treatment of gastroduodenal polyps in familial adenomatous polyposis has to do with treatment options. Current therapy options either do not treat the disease adequately or else are too radical as a prophylactic procedure for a benign albeit pre-malignant condition. Endoscopic polypectomy or electrocoagulation is often impractical owing to the large numbers of polyps present and to the danger of perforation or periampullar stricturing. Medical treatment with vitamin C [46], calcium [47] and non-steroidal anti-inflammatory drugs [48] are still experimental but have shown some

promise. Minimal surgery such as duodenotomy and submucous excision of gross polyps probably does more harm than good and is a temporary measure at best. Major excisional surgery with removal of part of the stomach and duodenum may be the only option at the present time for very high risk patients with severe gastroduodenal polyposis or potentially curative carcinoma. Indeed, effective screening is carried out, regular surveillance may enable early intervention so that prevention and cure of foregut malignancies will be possible in patients with familial adenomatous polyposis.

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