Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1149–1153, 1995

0959–8049/95 $9.50+0.00

0959-8049(95)00171-9

Upper Intestinal Surveillance in Familial Adenomatous Polyposis

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Our understanding of the natural history of upper gastrointestinal (GI) involvement in familial adenomatous polyposis (FAP) is still evolving, although we know that the main cause of death after colectomy in FAP is upper GI malignancy, affecting 5% of patients. The aim of duodenal surveillance is to target high risk individuals and identify cancers early. We have screened 200 patients prospectively and have observed that duodenal polyposis progresses slowly, but there are some young people who have severe disease who merit close observation. We pay particular attention to endoscopic technique and histological detail, and use a duodenal staging system. Patients are offered randomisation to studies of chemopreventive agents, and those with advanced disease are considered for surgery. Successful management is inhibited by our deficient knowledge of the natural history of upper gastrointestinal polyposis, and by our inability to identify high risk individuals with histological markers rather than because of any technological deficiencies in endoscopic equipment.

Key words: familial adenomatous polyposis, surveillance, endoscopy, duodenal cancer
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1149–1153, 1995

INTRODUCTION

PATIENTS WITH familial adenomatous polyposis (FAP) will develop colorectal cancer unless they have prophylactic surgery. Thereafter, cancer risk remains for the rectum (if retained), the remainder of the gastrointestinal (GI) tract (the duodenum most frequently; the stomach, small intestine, biliary tree and liver uncommonly) and for extra-intestinal sites (thyroid, adrenal glands).

Although extracolonic phenotypic features are recognised with varying frequency in patients with FAP, it is almost universal for patients to have involvement of the upper GI tract [1, 2]. It is common to find large numbers of polyps in the stomach, but these are usually benign gastric fundic polyps and are rarely adenomas. Fundic gland polyposis is non-neoplastic and is found in approximately 50% of patients [3–5]; 1–5 mm hemispherical polyps stud the fundus of the stomach (Figure 1). Histological examination shows cystic dilated fundic glands without epithelial dysplasia. Their natural history is as follows: they may appear in the first decade of life before the development of adenomas in the GI tract; in some patients, growth is attenuated, although in others there is a gradual increase in number and size of polyps [6]; but there is no cancer.

Gastric adenomas, which only occur infrequently (in the order of 5% of patients) [1], usually appear in the antrum. The risk of adenocarcinoma of the gastric antrum is probably not increased in Western families, but is reported to be high in Korean and Japanese families with FAP [7, 8]. Even allowing for the high background incidence of gastric cancer in these countries, the incidence of FAP-associated gastric cancer in a large Korean series (4.2%) and that reported from a Japanese series (2.1%) [9] was much higher than the 0.6% incidence reported from Western countries [7]. Iwama and associates [8] compared organ-specific morbidity and mortality rates of malignant tumours in FAP, and found that, for gastric carcinoma in FAP, the observed/expected

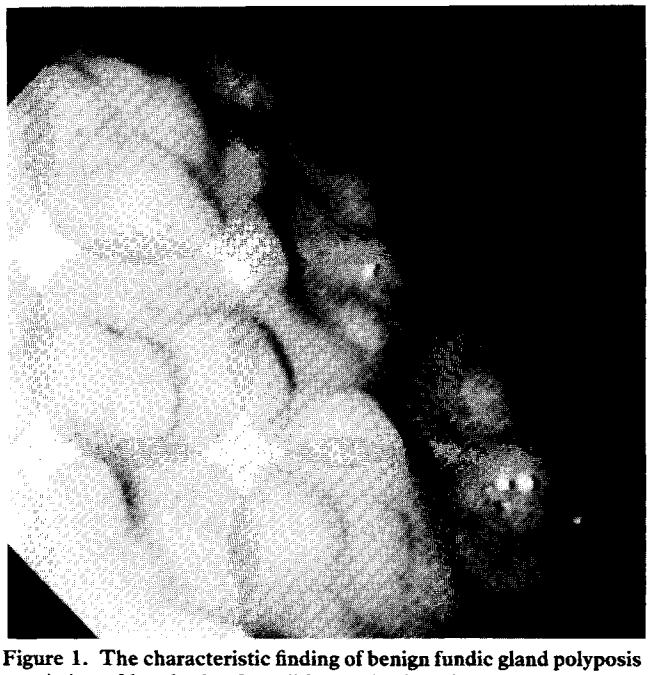

Figure 1. The characteristic finding of benign fundic gland polyposis consisting of hundreds of small hyperplastic polyps scattered in the fundus of the stomach.

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morbidity ratio was 3.08 and the mortality ratio 3.43 compared with the general population of Japan.

The reported incidence of duodenal adenomas has increased in recent large series, and this clearly relates to careful endoscopic and histological examination of the duodenum. Spigelman highlights the fact that in combined retrospective series, only 60% of patients were reported as having adenomas, whereas the figure in recent prospective series is greater [10]. Both the St. Mark's Hospital, U.K. and the Cleveland Clinic, U.S.A. series put the figure closer to 90% [1, 2] and the incidence increases with age. Patients typically have more than 20 polyps scattered throughout the second and third parts of the duodenum, with maximal involvement in the ampullary area. Spigelman and associates, [1] found that 100 of the 102 patients with FAP had duodenal abnormalities (dysplasia in 94 (91%), and hyperplasia in 6), usually in the second and third parts of the duodenum. The peri-ampullary area was abnormal in 87 of 97 patients (dysplasia 72, hyperplasia 13, and inflammation 2). The adenomas histologically resemble those found in the colon, usually being tubular with mild or moderate epithelial dysplasia [11]. Even biopsies from macroscopically normal mucosa may show early adenomatous changes in histology [12] so that the incidence probably approximates 100%.

Although described in 1935 [13], the clinical importance of duodenal cancer in FAP has only recently been appreciated. As premalignant adenomatous polyps occur so frequently in the duodenum, it is not surprising that there is a strong associated risk of duodenal cancer postcolectomy. A life table analysis performed on 222 patients with FAP, who had undergone total colectomy and ileorectal anastomosis, confirmed that the relative risk of dying compared to the normal population was 3.4 [14]. The major cause of this increase in mortality was upper gastrointestinal malignancy. Overall, death due to duodenal cancer occurred in 5% of the study population [14]. Jagelman and associates [15] reported invasive upper GI adenocarcinoma in 4.5% of 1255 patients from 10 FAP registries, although in a Danish series an incidence of only 1% was reported [16].

It has been estimated that the risk of duodenal cancer around the ampulla of Vater is 100–200-fold greater than the normal population [15, 17]. The Johns Hopkins Registry, U.S.A. demonstrated a relative risk for duodenal adenocarcinoma of 331, and for ampullary adenocarcinoma of 124, with no significant increased risk for gastric or non-duodenal small intestinal cancer [18].

There is no easy way of determining which patients are at greatest risk of developing duodenal cancer. In contrast to the findings with congenital hypertrophy of the retinal pigment epithelium (CHRPE) in FAP, where the extent of CHRPE is dependent on the position of the mutation along the coding sequence [19], mutation analysis has not yielded a strong genetic correlation between the site of *APC* germline mutations and the severity of duodenal disease [20–22]. We have found that there is poor correlation between the staging of duodenal disease and colonic polyp count, although there may be a correlation between the stage of duodenal polyposis and colorectal cancer risk (data not shown). The lack of correlation between duodenal disease and the number of colonic polyps is paralleled by the findings in the hereditary flat adenoma syndrome, an autosomal dominant disorder linked to the same locus on chromosome 5q21-q22 as FAP. Patients have multiple fundic gland polyps, duodenal and gastric adenomas and develop peri-ampullary carcinoma, even though they atypically develop less than 100 flat colonic adenomas [23]. To date, there is no clinically useful index to predict duodenal cancer risk.

In the absence of such information, the high incidence of potentially malignant polyps in patients with FAP and the definite risk of duodenal or peri-ampullary cancer with advancing age have dictated the need for an appropriate screening programme of the upper GI tract.

METHOD OF SURVEILLANCE

The following account is based on our experience at St. Mark's Hospital, U.K. with an endoscopic surveillance programme commenced in 1988. The ideal time to perform the initial screening endoscopy is around the time when patients enter hospital for a colectomy, usually around 20 years of age.

There are both advantages and disadvantages in selectively using a conventional forward viewing gastroscope or a side viewing duodenoscope in examination of the upper GI tract in FAP. The area of greatest cancer risk is the ampulla of Vater and the adjacent peri-ampullary region, which are often poorly seen with end viewing instruments. An alternative is to use a side viewing duodenoscope which allows excellent views of this region and the added advantage of a biopsy forceps elevator for accurate targeting of lesions. However, with the side viewer, adequate views of the remainder of the duodenum depend on the technical skill of instrument rotation whilst maintaining anatomical orientation, and in some cases this may not be possible. In addition, the patient may be uncomfortable as a result of stretching of the duodenum.

One option is to use both instruments for every patient, but as an alternative we have been using an oblique viewing video duodenoscope (Olympus GIF XK Evis 200). Using this endoscope, we have now performed 90 surveillance endoscopies and obtained excellent views of the second and third part of the duodenum and the peri-ampullary region. Some skill is required to biopsy the ampulla which may be difficult to target with this instrument, although the forceps elevator simplifies the task.

Recording information is critical to any surveillance programme. At the time of endoscopy, the site, size and number of polyps are recorded on a data sheet. Video prints for the case record are taken from the stomach, the second and third part of the duodenum, and in particular the ampullary and peri-ampullary region. Open and closed biopsy forceps (2 mm, 6 mm) are used as a size reference. The endoscopist comments on landmarks, and each patient has their own tape to compare serial examinations.

Biopsies are taken from the largest polyps seen in the gastric antrum and duodenum, the ampulla and peri-ampullary region, and from normal appearing duodenum in those few cases where no polyps are seen. These samples are examined using routine histological stains (haematoxylin and eosin, modified Giemsa stain); for research purposes, we also measure markers of cell proliferation and gene mutation.

The stage of duodenal polyposis can be calculated utilising the classification derived by Spigelman (Table 1). This staging system is based on risk factors for cancer and assigns arbitrary scores to size and number of polyps, the degree of dysplasia and villous change.

RESULTS

We have now examined 200 patients prospectively from 1988 to 1994. They have entered duodenal surveillance at a median age of 39 years (14–77), and been examined by endoscopy at 1–3 yearly intervals, depending on the stage of polyposis found on first examination.

Table 1. The Spigelman classification based on risk factors for cancer can be used to clinically stage patients with duodenal FAP

	Duodenal disease grading: points		
	1	2	3
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular*	Tubulo-villous	Villous
Dysplasia	Mild	Moderate	Severe

*or hyperplasia, inflammation; stage 0 = 0 points, I = 1–4 points, II = 5–6 points, III = 7–8 points, IV = 9–12 points.

Gastric fundic polyps have been noted endoscopically in 60% of patients. Characteristically, these small (less than 5 mm), soft shiny lesions cluster in the fundus and body of the stomach with antral sparing, and present an alarming appearance to the uninitiated. Gastric adenomas are uncommon and when found, occur in the gastric antrum. We have had no case of gastric cancer.

Duodenal adenomas are recognised at endoscopy as discrete white plaques, larger areas where polyps of varying size coalesce to produce a diffuse field of change crossing multiple duodenal folds, or diffuse adenomatous enlargement of the ampulla (Figure 2). Polyps occur most commonly in the peri-ampullary region, but are also seen in the third and fourth part of the duodenum and range in size from 1 mm to large polyps greater than 2 cm in diameter. Histological examination reveals that they are usually tubular adenomas with mild dysplasia, but in 30% of cases more advanced histological changes will be seen. The absence of microadenomas at biopsy (less than 10% of patients) might raise the question of attenuated forms of FAP or a variant polyposis syndrome. In our first 200 patients, 65% have mild disease (stages 0, I and II) according to our classification, while 35% have advanced disease (stages III and IV).

To date, we have observed endoscopy-related complications in 2 patients. One patient had an episode of iatrogenic pancreatitis [24], and a second with occult cerebral metastases had an episode of respiratory suppression with routine sedation, which was reversed with the antidotes anexate and naloxone. There have been no duodenal perforations, no bleeding and no deaths.

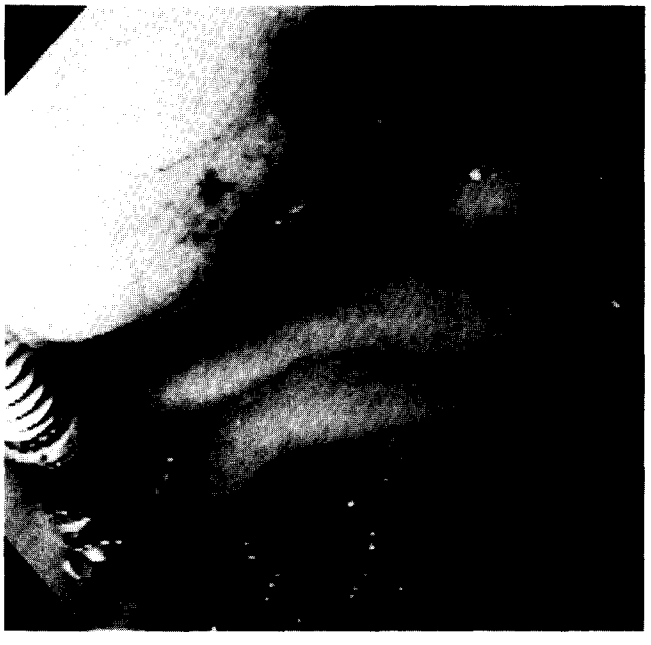

Figure 2. Diffuse adenomatous enlargement of the ampulla of Vater.

Of these 200 patients entered into our FAP upper intestinal surveillance programme, follow-up endoscopic data are available in 106 patients. These patients have been re-examined by endoscopy at a mean of 46 months (range 6–79 months) following their index endoscopy. During surveillance, two definite cases of duodenal cancer have developed; and in 4 patients malignant transformation was suspected, although not confirmed because of metastatic disease or contraindication to surgery. Over the mean period of 46 months between endoscopies, the clinical staging of duodenal polyposis worsened in 9% of patients. More detailed follow-up results will be published in the near future after the blinded review of video tapes from 50 patients currently completing a controlled clinical study.

DISCUSSION

The natural history of duodenal FAP is still unclear. To date, published series dealing with this have not resolved the question of the rate of progression of duodenal disease. The numbers are small, the periods of follow-up too short, and it is unclear whether polyp number, size or clinical staging of the duodenum in the individual patient reflect cancer risk [25, 26].

Nonetheless, the potential risk of carcinoma is substantial enough to justify regular upper gastrointestinal surveillance [27]. We do not yet know enough about the natural history to delineate age limits or to define screening intervals. Our policy is to perform an initial surveillance endoscopy at about 20 years of age when patients enter hospital for elective colectomy. This will provide a baseline assessment, and define the patients with stage III or IV disease at age less than 30 years (17 out of 200 or 8.5%) who require close attention. Currently, we do not know whether patients having attenuated forms of FAP (with mutations at the 5′ end of the *APC* gene [28]) have a lesser propensity to develop duodenal cancer; at present they need to be managed in an identical way.

It is inadequate to use an end viewing endoscope alone, and either a side viewer or oblique viewing instrument should be used. Multiple biopsies should be taken of the ampulla, peri-ampullary region and the largest polyps visualised. Further screening intervals will be determined by the findings at endoscopy and the stage of the duodenal disease. If disease is mild (stage 0–II), then surveillance can be performed every 2–3 years. For more advanced (stage III–IV) disease, endoscopy every 6–12 months (and if in doubt a baseline endoscopic ultrasound plus ERCP) should be performed.

Most patients who develop advanced duodenal adenomas do so beyond the age of 40 years, when most cancers are also detected. Prospective studies may perhaps demonstrate benefit from screening all patients over the age of 40 on an annual basis. Patients with large polyps can be asymptomatic, but clearly if at any time symptoms suggestive of malignant transformation intervene (bleeding, pain, jaundice, outlet obstruction, loss of weight, overt pancreatitis) then urgent endoscopy with endoscopic ultrasound, CT scanning and ERCP should all be considered. Once patients have symptoms, the risk of invasive cancer is high (6/8 patients or 76%) and the outcome dismal. In contrast, long term survival is excellent in patients where the lesion is detected in the context of surveillance endoscopy [29].

So where do we go from here? The options are listed below.

Endoscopic ultrasound (EUS)

Endoscopic ultrasound may add to the accuracy of duodenal staging and further facilitate clinical management in advanced cases of upper GI polyposis. In a prospective study, endoscopic ultrasound was compared with transabdominal ultrasound, computed tomography, and angiography in 60 patients with non-FAP pancreatic and ampullary cancers, and was significantly superior to abdominal ultrasound and conventional computed tomography in determining tumour size and extent, lymph node metastases and vascular invasion [30]. Endosonography is useful in allowing assessment of extramucosal gastric, duodenal or pancreaticobiliary involvement, and may allow better selection of appropriate candidates for surgery. We now prospectively perform EUS in patients with advanced stage III or IV duodenal polyposis. Where there is diffuse adenomatous change of the ampulla, EUS helps to reveal whether lesions have broached the muscularis propria and are potentially operable. We are also assessing new high frequency ultrasound miniprobes that can be selectively introduced through a biopsy channel into the biliary or pancreatic ducts. This technology may be a simple way to image ampullary and bile duct lesions.

With EUS, we documented a large ampullary lesion that proved to have broached the muscularis propria. Further assessment with the high frequency ultrasound miniprobe (12 MHz Olympus/Keymed) confirmed a 'T3' lesion extending from ampulla to pancreas (Figure 3). Another patient had a T2 lesion diagnosed by EUS confirmed at surgery to be an ampullary adenocarcinoma, and a third patient was found to have gastric changes suggestive of Menetrier's disease, with disruption of the duodenal muscularis propria resulting from photodynamic laser therapy to a large peri-ampullary polyp.

Jejunal enteroscopy

The prevalence and the degenerative risk of gastric and duodenal adenomas has been relatively well documented, but little is known about the occurrence of jejunal polyps in these patients. In a pilot study, push-type jejunal endoscopy using a long forward viewing duodenofibrescope detected jejunal tubular adenomas in 9 of 10 patients (90%). These lesions were sessile, whitish, but only measured 3 mm or less [31]. Utilising a standard gastroduodenoscope or a longer fibrescope 15–80 cm beyond the ligament of Treitz with a push-type technique, Bertoni and associates [32] found that 50% of FAP patients had adenomatous polyps (including a 4-cm tubulovillous adenoma with severe dysplasia) almost exclusively located in the proximal 20 cm of jejunum. The upper jejunum has a high prevalence of adenomas, and undetected small bowel malignant degeneration may explain some of the cases of postcolectomy metastatic adenocarcinoma where no clear primary has been identified. Proximal jejunoscopy, utilising push enteroscopy and possibly ultrasound miniprobe technology, should be assessed prospectively in screening protocols. This is because, in practice, jejunal cancer is rare in FAP and ileal cancer extremely rare, so routine surveillance of these areas seems clinically unnecessary.

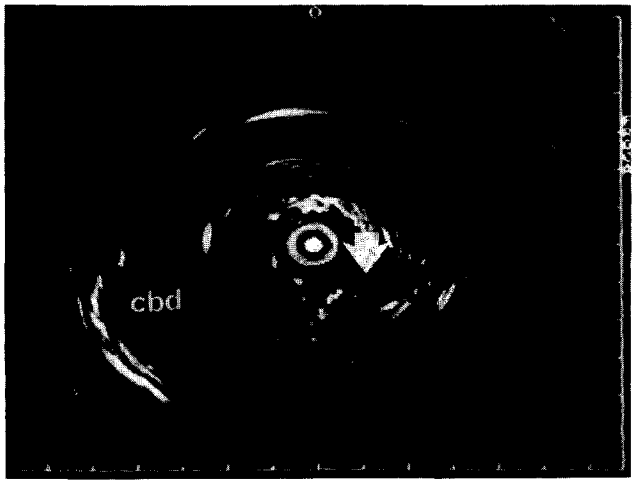

Figure 3. This asymptomatic patient had diffuse adenomatous change of the ampulla. Assessment with a high frequency ultrasound miniprobe (12 MHz Olympus/Keymed) inserted into the pancreatic duct confirmed a T3 lesion (arrow) extending from the ampulla to the pancreas and a dilated common bile duct (cbd).

Biological markers

If multiple specimens are to be taken from areas of concern in the upper GI tract, then biomarkers predictive of malignant transformation need to be refined to yield a better risk assessment than that supplied by the degree of villous architecture and severity of dysplasia. Application of molecular techniques to a surveillance programme may yield new ways of assessing risk.

One approach might be to identify the relationship between specific early genetic changes and tumour morphology and progression. In small (non-FAP) benign colorectal lesions, *APC* mutations are closely associated with dysplasia. In contrast, *KRAS* mutations are common in small nondysplastic lesions with limited potential to progress to larger tumours [33]. Recent work examining colorectal adenomas from FAP patients identified somatic inactivating mutations of the second *APC* allele in the majority of tumours (19 of 24) [34]. New and known potential markers, such as *APC*, need to be explored as additional tools in surveillance.

In conclusion, the optimal management of upper GI polyps in FAP patients is still unresolved. It is apparent that there is no reason to act with haste in order to clear the duodenum of polyps. Attempts to remove all small polyps by snare, electrocautery or laser should be avoided as this may be dangerous owing to the risks of perforation. Management of the difficult case needs to be planned between skilled interventional endoscopists and hepatobiliary surgeons, using EUS and ERCP for fullest assessment. Non-surgical management using chemopreventive strategies [35] and photodynamic laser therapy [36] are currently under investigation.

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Acknowledgements—We thank Dr D. Desai, Chief Nurse Margaret Boland and her endoscopy staff at St. Mark's Hospital for their invaluable assistance.