Surveillance of duodenal polyps in familial adenomatous polyposis: progress report

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Summary

Familial adenomatous polyposis (FAP) is characterized by the presence of premalignant adenomas of the large and small bowel. Prophylactic colectomy deals with the risk for colon cancer, leaving duodenal cancer as the leading cause of death. Although most FAP patients have duodenal adenomas, only approximately 5% develop duodenal cancer. This study looks at progression of duodenal polyps with time.

The outcome of endoscopic surveillance in the duodenum of 70 patients with familial adenomatous polyposis was determined. A mean of 40 months elapsed between endoscopies. Outcome was measured using video comparison and a staging system that includes histological assessment.

Duodenal cancer developed in one patient, and was suspected in two others. The stage of duodenal polyposis worsened in another seven patients. When histology was ignored, comparison of video recordings in 52 patients showed a worsening in 21 (40%).

In conclusion, further surveillance appears warranted so that patients at high risk for duodenal cancer might receive early treatment. Should slow progression of duodenal polyposis be shown to be associated with low risk, then most patients can be safely offered less frequent endoscopies than hitherto.

Introduction

FAP was, until recently, known as familial polyposis coli. One of the reasons behind the change in nomenclature was the recognition that the premalignant adenomatous polyps which occur in the large bowel also occur in the duodenum of virtually all affected patients[1]. Moreover, duodenal cancer has become one of the leading causes of death in FAP patients after a prophylactic colectomy has been performed[2,3]. We report interim results from a prospective endoscopic surveillance study of the duodenum in 109 patients with FAP; the results of endoscopy of 102 of these patients have been previously reported[1].

Patients and methods

Of the 109 FAP patients, 39 have been excluded from the follow-up series. Six have died (two from desmoid disease, one from lymphoma, one rectal cancer, one gastric cancer and one from metastases from an unknown primary); two were too young to be included on our surveillance programme; eight were on active sulindac treatment[4]; four were followed up elsewhere; six have failed to turn up for endoscopy; and 13 are due this year.

There were 70 evaluable FAP patients (39 men and 31 women). Each patient was endoscoped twice with a mean time between endoscopies of 40 months (range 26-57 months). The mean age at first endoscopy was 42 years (range 20-67 years). No patients were on active treatment for their duodenal disease.

All but four endoscopies were performed by the same endoscopist (CBW), using the same side viewing endoscope (Olympus 'JFV10', Keymed), which allows good visualization of the peri-ampullary region. The size of the polyps was measured using biopsy forceps. Each endoscopy was recorded on video, the video tapes clearly marked and stored separately from the rest of the library; in the case of a technical failure of the video system a photograph was taken. The site, number, size, distribution and histological features of the polyps were recorded at each endoscopy on a standard form. Biopsies were taken from the papilla, from polyps and, if no polyps were seen, random biopsies were taken for histological assessment.

Four assessments of the severity of duodenal polyposis were made:

1 The development of malignant change
2 Raw score: Points were awarded for the number, size, histology (tubular, tubulovillous and villous in ascending order of cancer risk) and degree of dysplasia of polyps[1] (Table 1)
3 Stage of duodenal polyposis. Our classification utilizes these raw scores and allocates a patient to one of six stages[1,5]
4 Video assessment: Two independent viewers were shown the first and second videos, randomized for chronological order, and asked to score whether the duodenal polyposis was 'worse', 'same' or 'better'. No account of histology or degree of dysplasia is included in this assessment.

In addition, because the number of duodenal biopsies taken at each endoscopy varied, analysis was performed to test for correlation between the histology obtained and the number of biopsies taken at each endoscopy.

Statistical tests used were Wilcoxon signed rank test (two-tailed) for comparison and simple regression analysis for correlation.

Results

Malignant change

Malignant change was suspected in three patients. However, confirmation was obtained in only one of these patients, a 71-year-old woman who developed an adenocarcinoma of the duodenum during the surveillance programme.

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Table 1. Spigelman classification. Points are awarded for number and size of polyps, degree of dysplasia and histological architecture. A stage is calculated by adding the total number of points at each endoscopy

	Points awarded		
	1	*2*	*3*
Polyp number	1-4	5-20	>20
Polyp size (mm)	1-4	5-20	>10
Degree of dysplasia	Mild	Moderate	Severe
Histological architecture	Tubular	Tubulo-villous	Villous

0 Points=stage 0, 1-4=I, 5-6=II, 7-8=III, 9-12=IV. Stage V=duodenal cancer[5]

She had stage IV duodenal disease at the time of her first endoscopy, when her duodenum was carpeted with sessile and pedunculated polyps greater than 4 cm in size and biopsies showed a tubular adenoma with moderate dysplasia. Biopsies at second endoscopy showed a severely dysplastic villous adenoma, but no evidence of malignancy. She was referred for open surgery in view of concern that the tumours were hard and immobile at endoscopy. She had a local resection of an 11 cm×4 cm tumour. This was a moderately differentiated adenocarcinoma arising in a severely dysplastic villous adenoma. The carcinoma extended through the duodenal wall into the subserosa. Two lymph nodes included in the specimen showed no evidence of metastatic disease and the resection margins were clear. She remains cancer-free on computerized tomography scanning but has recurrent adenomas at endoscopy at 14 months.

Malignant change is thought to have occurred in two other patients.

The first of these patients, a 60-year-old man, had a tubulovillous adenoma on duodenal biopsy and carpeting of the second and third parts of the duodenum in association with multiple sessile polyps (stage IV polyposis). He was referred for definitive surgery but died preoperatively from a myocardial infarction. Permission for a post mortem was denied. The other patient has severe duodenal polyposis (stage IV) with progression of a tubulovillous adenoma at first endoscopy to a villous adenoma at the second endoscopy. This 54-year-old man had a Dukes stage C rectal cancer resected recently and has a raised CEA of 450 post operatively. He has metastatic cancer in his right femur on bone scan and is undergoing radiotherapy.

Raw scores

The raw scores for dysplasia alone were significantly different between the first and second endoscopy (19 better, seven worse, $P=0.02$, Wilcoxon). When the raw scores for histological architecture were added to those for dysplasia there was no significant difference; with a median score of 3 at the first endoscopy, and of 3 at the second endoscopy ($P=0.06$). No significant differences were detected for the size, number, or histology of polyps between the first and second endoscopies (Table 2).

Staging system

Of the 70 patients studied, 42 remained in the same stage, 18 improved and 10 worsened between endoscopies. Table 3 shows the patient distribution and age at first endoscopy. Table 4 shows the details of changes between 1st and 2nd endoscopy.

Table 2. Comparing the raw scores for duodenal polyposis at 1st and 2nd endoscopy. There was a significant improvement in the degree of dysplasia

2nd endoscopy	*Size*	*No.*	*Histology*	*Dysplasia*
Worse	5	4	6	7
Same	59	55	50	44
Better	6	11	14	19
P value (Wilcoxon)	0.76	0.16	0.25	0.02

Video assessment

Videos were available for comparison in 52 patients (29 men, 23 women, average age at first endoscopy 43 years, range 20-67 years). Duodenal polyposis was judged to be the same in 26, worse in 21 patients and better in five. The video assessment correlated well with the raw scores for the size and the number of polyps ($P=0.0007$, $r=0.5$). There was good correlation between the staging system and video assessment with those whose duodenal polyposis was judged the same or who were judged better on videos ($P=0.002$, $r=0.6$). However, of the 21 judged to be worse on video scores, only three were worse using staging, 16 were the same and two were better. Of these 21 patients, the raw scores for histology and dysplasia improved in eight, remained the same in 11 and worsened in only two. This effect tended to offset the increase in points for larger and more numerous polyps in calculating the stage of duodenal polyposis.

Effect of the number of biopsies per patient on histology reports

Significantly more biopsies were taken at the first endoscopy, (average 5.2, range 2-10) than at the second (average of 2.9, range 1-7; $P=0.0001$). An increase in the number of biopsies correlated with an increase in tubulovillous and villous

Table 3. Patient distribution and age at first endoscopy

Stage	*No. of patients*	*Male:female*	*Average age at 1st OGD*
0	3	2:1	42
I	12	7:5	42.3
II	18	11:7	43.1
III	27	14:13	40.7
IV	10	5:5	50.4

OGD=Endoscopy

Table 4. Details of change in Spigelman stage between 1st and 2nd endoscopy

	Change in stage at 2nd OGD		
Stage at 1st OGD	*Same*	*Better*	*Worse*
0	1	0	2
I	10	0	2
II	11	6	1
III	18	7	2
IV	2	5	3
Total	42	18	10

OGD=Endoscopy

adenomas (r^s=0.2, P=0.014), and an increase in the degree of dysplasia (r^s=0.2, P=0.04). Significantly fewer biopsies were taken from the group of patients whose stage of duodenal polyposis remained the same (median 2.5) or improved (median 2) than were taken from those whose duodenal polyposis worsened (median 4; Mann-Whitney U comparing worse with same and better, P=0.026).

Morbidity

One complication, a case of pancreatitis in a 71-year-old woman following an ampullary biopsy, occurred in this series[6].

Discussion

Having established a very high prevalence of duodenal polyposis in our FAP patients[1], we have kept these patients under endoscopic surveillance. Our aims are to determine the natural history of duodenal polyps, and to achieve earlier detection of malignant change. A concomitant improvement in survival is hoped for[7], but by no means certain[8].

Use of the staging system as an endpoint suggests that most patients undergo little change when re-examined after a mean period of 40 months. This is in agreement with the Japanese studies where 20 FAP patients with duodenal polyposis were followed-up with endoscopies over a mean of 7 years and where both gross appearance and histological assessment were used to measure the change in severity of duodenal polyposis[9,10].

The results of video assessment are less reassuring than those obtained using the staging system, as they imply that over 40% of the evaluable patients worsened over the period of the study. Ranzi *et al.*[11] also observed an increase in the number and size of duodenal adenomas in a long-term study of 15 patients with FAP. Use of the video appearance of polyps alone eliminates the contribution that histology makes to the assessment of malignant change. Histology is the most important risk factor for malignant change in the recto-sigmoid colon[12]. It seems logical, therefore, to include it when determining the risk for duodenal cancer. It is noteworthy that in this study technical reasons resulted in videos being unavailable for assessment in 26% of the patients. Nevertheless, video recordings are useful in allowing longer-term changes to be objectively recorded, as well as helping monitor the effect of intervention either by limited surgery[13] and/or medication[4].

Thus, video assessment revealed that duodenal polyposis worsened in 40% of patients. On the other hand, use of the staging system implied that duodenal polyposis worsened in only 14% of patients. However, the staging system depends on the degree of dysplasia and on the histology of biopsies, features which in this study correlated well with the number of biopsies taken. As the number of biopsies fell significantly between examinations, the rate of progression of duodenal polyposis observed in this study (as judged by the staging system) is probably a conservative estimate.

More biopsies were taken at the time of the first endoscopy than at the time of the second. This was because the initial endoscopy was part of a screening study to determine the prevalence of adenomas in FAP patients[1]. Although the ideal number of biopsies that should be taken is unknown, more, rather than fewer, biopsies should be taken in order to give an accurate view of the pathology present. For example, the multicentre Scandinavian study of duodenal polyposis in FAP involves the taking of 10 biopsies from patients with visible polyps and at least six from those without visible polyps (Bulow, personal communication).

On the basis of these interim results we confirm that upper gastrointestinal endoscopy every 3 years is safe in the majority of FAP patients. In time, it may be possible to recommend surveillance every 5 years, with more frequent examinations reserved for the small group of patients who have the most severe duodenal polyposis. In this context it is interesting to note that of the original 10 patients with stage IV duodenal polyposis, three are thought to have developed duodenal cancer. Whether the stage of polyposis correlates with the risk for malignant change and whether early treatment leads to improved survival will, however, be determined by the long-term outcome of this and of other studies[7].

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