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 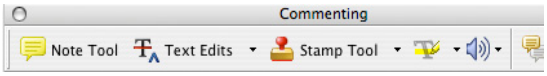

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 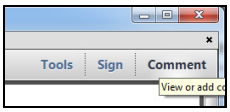

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 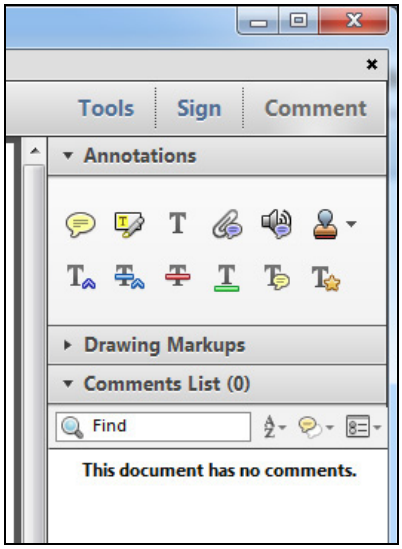
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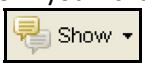
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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ORIGINAL ARTICLE

The impact of chromoendoscopy for surveillance of the duodenum in patients with MUTYH-associated polyposis and familial adenomatous polyposis

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Background and Aims: Duodenal polyposis and cancer have become a key issue for patients with familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP). Almost all patients with FAP will develop duodenal adenomas, and 5% will develop cancer. The incidence of duodenal adenomas in MAP appears to be lower than in FAP, but the limited available data suggest a comparable increase in the relative risk and lifetime risk of duodenal cancer. Current surveillance recommendations, however, are the same for FAP and MAP, using the Spigelman score (incorporating polyp number, size, dysplasia, and histology) for risk stratification and determination of surveillance intervals. Previous studies have demonstrated a benefit of enhanced detection rates of adenomas by use of chromoendoscopy both in sporadic colorectal disease and in groups at high risk of colorectal cancer. We aimed to assess the effect of chromoendoscopy on duodenal adenoma detection, to determine the impact on Spigelman stage and to compare this in individuals with known pathogenic mutations in order to determine the difference in duodenal involvement between MAP and FAP.

Methods: A prospective study examined the impact of chromoendoscopy on the assessment of the duodenum in 51 consecutive patients with MAP and FAP in 2 academic centers in the United Kingdom (University Hospital Llandough, Cardiff, and St Mark's Hospital, London) from 2011 to 2014.

Results: Enhanced adenoma detection of 3 times the number of adenomas after chromoendoscopy was demonstrated in both MAP ($P = .013$) and FAP ($P = .0.002$), but did not affect adenoma size. In both conditions, there was a significant increase in Spigelman stage after chromoendoscopy compared with endoscopy without dye spray. Spigelman scores and overall adenoma detection was significantly lower in MAP compared with FAP.

Conclusions: Chromoendoscopy improved the diagnostic yield of adenomas in MAP and FAP 3-fold, and in both MAP and FAP this resulted in a clinically significant upstaging in Spigelman score. Further studies are required to determine the impact of improved adenoma detection on the management and outcome of duodenal polyposis. (Gastrointest Endosc 2018;■:1-8.)

INTRODUCTION

The autosomal dominant disorder familial adenomatous polyposis (FAP) and the autosomal recessive disorder *MUTYH*-associated polyposis (MAP) are characterized by the development of colorectal adenomas that over time have the potential to progress to colorectal cancer. They are also defined by the development of extra-colonic

Abbreviations: APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; HGD, high-grade dysplasia; MAP, MUTYH-associated polyposis; NBI, narrow band imaging.

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manifestations, including duodenal adenomas and cancer, which in FAP have now become a leading cause of death as patients undergo prophylactic colectomy at an early stage in their disease. Duodenal polyposis is seen less frequently in MAP than FAP, occurring in up to 17% to 34%[1,2] compared with 70% or more of patients with FAP,[3] but the very limited available data suggest a comparable increase in relative risk and lifetime risk of duodenal cancer.

The Spigelman scoring system (Table 1) for risk stratification of duodenal polyps in FAP was developed to allow an estimation of the risk of developing duodenal carcinoma and guide surveillance intervals.[4] The Mallorca group advocated the same upper GI surveillance program for MAP.[3] In FAP, the risk of developing cancer in Spigelman stages III to IV is reported to be between 7% and 36% despite an overall cancer risk in all patients of 5%. Recent data suggest this risk may be even higher with 1 study reporting a lifetime risk of duodenal carcinoma of 18%.[5] Accurately identifying patients at increased risk of harboring or developing duodenal cancer is the principal goal of surveillance but, because many patients with FAP develop duodenal polyps, yet most patients do not develop invasive cancer, the clinical management remains problematic. There are few published data on the natural history of duodenal adenomatosis in MAP, and only 1 retrospective study describing 92 patients undergoing upper GI surveillance.[2]

In the colon, there is an overall polyp miss rate of 22% using white-light endoscopy for sporadic polyps[6] and many studies that have examined the impact of pan-chromoendoscopy on polyp detection rates. A Cochrane review of chromoendoscopy excluding patients with polyposis syndromes and inflammatory bowel disease concluded that chromoendoscopy identifies more patients with at least 1 adenoma and significantly more patients with 3 or more adenomas.[7] The detection or miss rate of lesions within the upper GI tract has not been as widely studied, and rarely in the duodenum. Moreover, many of the factors associated with miss rates in the colon are not applicable to upper GI endoscopic examination.

The effect of chromoendoscopy on duodenal adenoma detection in MAP has not been investigated. This study aims to evaluate the use of dye spray with indigo carmine in the duodenum to improve the identification of polyps that may be overlooked during standard white-light endoscopic examination. It also aims to determine the impact of dye spray on Spigelman stage and to compare this in individuals with MAP and FAP.

METHODS

The research was approved by the South-East Wales research ethics committee in January 2010 (reference number 10-MRE09-43) and the North West London Hospitals NHS Trust (reference number RD12/078). Cases for the study were recruited prospectively. Patients with confirmed FAP or MAP on genetic testing were recruited from University Hospital Llandough, Cardiff, UK, the Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK, and St Marks Hospital, Harrow, UK. All patients gave informed consent. There were no healthy volunteer controls recruited for the study. Between August 2011 and January 2014, 51 consecutive patients scheduled for surveillance endoscopy of the upper GI tract were invited to participate in the study. The endoscopies were performed in 2 academic centers in the UK (University Hospital Llandough, Cardiff, and St Mark's Hospital, London).

TABLE 1. Modified Spigelman classification of duodenal polyposis in FAP

	1 point	2 points	3 points
No. of polyps	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Low grade		High grade

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

At each center, experienced endoscopists performed all endoscopies for this study (S.D., J.H., A.H., and N.S.) using high-resolution forward-viewing video endoscopes (GIF-Q260, GIF-H260, GIF XQ260; Olympus Medical Systems) and a side-viewing duodenoscope for optimal visualization of the ampulla. Procedures were performed with the patients under general anesthetic (propofol) or conscious sedation using standard doses of fentanyl and midazolam in line with British Society of Gastroenterology guidance,[8] depending on patient preference and the presence of comorbid conditions. Antispasmodic medication (hyoscine butylbromide) was given during endoscopy at the discretion of the endoscopist.

At introduction, the forward-viewing endoscope was advanced until the duodeno-jejunal junction was reached. During withdrawal, the different parts of the duodenum (D2, D3, and duodenal bulb) were evaluated, and the number and sizes of polyps recorded on a standardized proforma before staining with indigo carmine dye (Fig. 1). Polyp size was estimated using Radial Jaw 3 biopsy forceps (Boston Scientific, Natick, Mass), with a closed diameter of 2.2 mm and an open diameter of 8 mm. The endoscopist then sprayed a 0.3% solution of indigo carmine (3 mL of indigo carmine 1% and 7 mL of water for injection) from D3 proximally to the duodenal bulb onto the duodenal mucosa, distributed in a homogeneous fashion by a spraying catheter passed through the endoscope channel. The residual dye was then suctioned away. After adequate coating of the duodenum with the dye solution, a second endoscopist unaware of the findings and polyp count from the first part of the examination, recorded the size and number of polyps seen (Fig. 2). Biopsy samples were not taken

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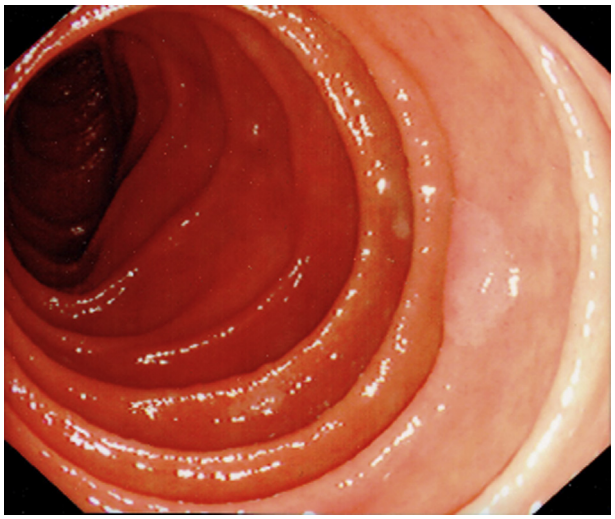

Figure 1. Duodenum of a patient with 1999 before chromoendoscopy.

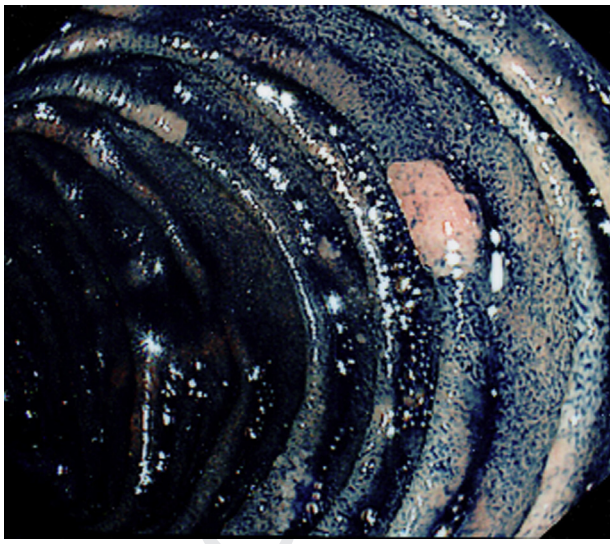

Figure 2. Duodenum of the same patient with FAP after chromoendoscopy.

until after staining and counting had taken place. Samples were taken from all lesions with high-grade morphology (disrupted surface pattern, ulceration, or depressed areas within the polyp) and lesions greater than 1 cm. If the number of polyps was small, all lesions were sampled, but if there were numerous polyps, at least 3 of the largest adenomas were sampled in addition to the criteria above. To further aid accurate staging of duodenal disease, our protocol asked for examination using a side-viewing endoscope in patients where the ampulla was inadequately visualized using the forward-viewing endoscope. If it appeared adenomatous, biopsy specimens were taken. All procedures were conducted using the same structural and color enhancement settings in both centers.

For all patients, Spigelman point totals and stage before and after the application of chromoendoscopy were assessed. The following criteria were used: number of adenomas, largest size, the most advanced histology, and most advanced grade of dysplasia. All lesions sampled for histology were confirmed as adenomas. The biopsy specimens were evaluated by 2 expert gastrointestinal pathologists (M.M. and G.T.W.) who graded dysplasia according to the Vienna (low-grade/high-grade) classification[9] and the 3-tier grading system used by Spigelman et al.[4]

Statistical analysis

Statistical analysis for the study was performed using R (version 3.0.2) software. Statistical significance for the frequency of duodenal adenomas was calculated using the Wilcoxon signed-rank test and Mann-Whitney U test, and a one-sided sign test was used to compare the Spigelman stages. A P value of less than .05 was considered statistically significant. The study was powered for 92% at a 5% significance level to detect a difference in the number of polyps in MAP versus FAP (1 degree of freedom using a chi-squared test to compare the 2 conditions). Statistical data are expressed as medians.

RESULTS

Between August 2011 and January 2014, 51 patients (19 FAP and 32 MAP) underwent gastroduodenoscopies. Of the FAP patients, 8 were female and 11 were male; median age was 41 years (range, 32-69 years). There were 17 female and 15 male patients with MAP; median age 54 years (range, 25-81 years). No patient was on any pharmacological treatments for their duodenal disease or for their colonic disease. There were no adverse events relating to endoscopic examination (bleeding or perforation), and no adverse events relating to general anesthesia or sedation were observed.

Patients in the MAP group were significantly older than those with FAP ($P = .0.001$). There was no difference in the calculated overall Spigelman stage before or after dye spraying for any patient when comparing the traditional 3-tiered grading system with the modified (Vienna classification) Spigelman score.

Number of adenomas

In MAP patients before staining, 10 lesions were found in 32 patients (range, 0-6), and this increased significantly to 34 lesions after dye spraying (range, 0-15) (Table 2). Additional duodenal adenomas were detected in 9 patients (28%). The median number of additional adenomas detected was 2 per patient (total, 24; range, 1-9).

The median number of adenomas in the FAP cohort with white light, per patient, was 4 (total, 150; range, 0-46). After staining, the median number of adenomas detected was 14 per patient (total, 442; range, 0-100)

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TABLE 2. Duodenal adenoma characteristic in patients with MAP (n = 32)

Gastroduodenoscopy findings	Pre-staining	Post-staining	*P* value
Median number of duodenal adenomas (total)	0 (10)	0 (34)	.01368*
Largest size (mm), median (range)	5 (2-50)	6 (2-50)	.3711
Spigelman stage, median (range)	0 (0-III)	0 (0-III)	.03125*

Despite no change in the median Spigelman scores, the Mann-Whiney and Wilcoxon tests are rank sum tests and not median tests. It is possible for groups to have different rank sums and yet have equal or nearly equal medians.
*Statistically significant difference ($P < .05$).

TABLE 3. Duodenal adenoma characteristics in patients with FAP (n = 19)

Gastroduodenoscopy findings	Pre-staining	Post-staining	*P* value
Number of duodenal adenomas, median (total)	4 (150)	14 (442)	.002516*
Largest size (mm), median (range)	6 (2-23)	6 (2-30)	.1814
Spigelman stage, median (range)	II (0-IV)	II (0-IV)	.03125*

*Statistically significant difference ($P < .05$).

($P = .0.002$) (Table 3). Additional adenomas after chromoendoscopy were detected in 13 patients (68% of FAP cases).

The number of duodenal adenomas observed after staining was significantly higher in FAP than MAP ($P = .0002452$; Mann-Whitney U test).

Size of adenomas

The median largest adenoma size was 5 mm compared with 6 mm after dye spray in MAP, and the size of the largest adenomas (15 mm, 15 mm, 25 mm, and 50 mm) did not change after dye spraying with indigo carmine.

In FAP, there was also no statistically significant change in the median adenoma size after staining. No statistically significant difference was observed between the post-staining size of the largest duodenal adenomas observed in MAP versus FAP ($P \approx 1$; Mann-Whitney U test). There was no significant statistical difference in the overall numbers of adenomas greater than 1 cm in patients with MAP versus FAP before or after staining ($P \approx 1$; Mann-Whitney U test).

The numbers of polyps of different sizes detected after chromoendoscopy in MAP and FAP are given in Tables 4 and 5.

Histology of adenomas

All polyps in patients with MAP were tubular adenomas with low-grade dysplasia. Three patients had moderate-grade dysplasia when assessed according to the 3-grade system used by Spigelman et al.[4] Among the cases of FAP, there were tubular adenomas in 8 patients (42%), tubulovillous adenomas in 4 patients (21%), and villous adenoma in 1 patient (5%), all with low-grade dysplasia. Four of the patients with FAP had moderate dysplasia according to the Spigelman criteria,[4] with no high-grade dysplasia (HGD) detected.

Endoscopic technique

Use of the side-viewing endoscope did not detect any additional ampullary adenomas compared with the forward-viewing endoscope, and only 1 patient had an ampullary adenoma detected in this study. One patient was observed to have 4 further polyps detected by side-viewing endoscopy after dye spraying and counting. Twenty-three patients (45%) of the total cohort of 51 required side-viewing endoscopy to ensure clear ampullary visualization.

Spigelman staging

Before dye spraying, the Spigelman classification was stage 0 in 27 patients (84%), stage I in 2 patients (6.25%), stage II in 2 patients (6.25%), and stage III in 1 patient (3.5%) with MAP (Table 6). Staining resulted in an increased Spigelman point total in 9/32 individuals (28%), with a corresponding upgrade in Spigelman stage in 6 patients (18%) (from 0 to I, n = 1; from 0 to II, n = 3; from I to II, n = 2; $P < .05$). Among the patients with FAP, staining resulted in an increased Spigelman point total in 13 of 19 individuals (68%), with a corresponding upgrade in Spigelman stage in 5 patients (26%) (from 0 to I, n = 1; from I to II, n = 1; from I to IIII, n = 2; from III to IV, n = 1; $P < .05$).

The post-staining Spigelman stage is significantly higher in FAP versus MAP ($P = .0009646$; Mann-Whitney U test). The change in Spigelman grade reflected the increased number of adenomas detected.

Mutation data

The mutation analysis of the 32 patients with MAP and the total number of duodenal adenomas detected are presented in Table 7.

DISCUSSION

This study is the first to assess the impact of chromoendoscopy in the evaluation of duodenal adenomas in patients with MAP, a group in which upper GI disease has not been extensively studied, and compares this to the findings in patients with FAP. Potential applications of chromoendoscopy within the upper GI tract in FAP appear promising; the diagnostic yield of standard surveillance

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TABLE 4. Adenoma numbers by size pre-and post-staining in MAP

	No. of polyps					
	1-4 mm		5-10 mm		>10 mm	
Case	Pre-staining	Post-staining	Pre-staining	Post-staining	Pre-staining	Post-staining
1-3, 5-11, 14, 16, 17, 22, 24-27, 29-32	0	0	0	0	0	0
4	0	1	0	0	0	0
12	0	6	2	6	2	2
13	0	0	0	1	0	0
15	1	2	1	1	0	0
18	0	0	1	1	0	0
19	0	0	1	2	0	0
20	0	1	0	1	1	1
21	0	0	0	1	1	1
23	0	2	0	1	0	0
28	0	3	0	1	0	0

TABLE 5. Number of adenoma by size pre-and post-staining in FAP

	No. of polyps					
	1-4 mm		5-10 mm		>10 mm	
Case	Pre-staining	Post-staining	Pre-staining	Post-staining	Pre-staining	Post-staining
33-34, 41-42, 48-49	0	0	0	0	0	0
35	3	10	4	7	0	0
36	14	34	5	22	5	5
37	0	1	0	0	0	0
38	8	19	10	18	0	0
39	1	13	5	8	0	0
40	1	3	2	3	0	0
43	29	81	14	23	3	3
44	8	53	4	21	2	2
45	0	6	0	2	0	0
46	5	6	1	25	4	4
47	4	12	0	4	0	0
50	2	4	8	10	0	0
51	4	11	3	15	0	0

upper GI endoscopy was demonstrated to be improved by dye spraying alone in a small study of 10 patients with FAP undergoing upper GI endoscopic surveillance.[10] A more recent study of 43 patients also demonstrated that chromoendoscopy increased the detection of duodenal adenomas in FAP but did not lead to a considerable change in the Spigelman stage.[11]

This study demonstrates that there is a significant increase in the numbers of duodenal adenomas identified after indigo carmine dye spraying in cases of both MAP and FAP, and that this resulted in a significant increase in the Spigelman stage in both conditions. This study identified duodenal adenomas in 28% of patients with MAP, similar to the series recently reported by Walton et al[2] who identified duodenal adenomas in 34% of patients with MAP, and higher than the 17% observed in a previous multicenter European study.[1]

Two previous studies have assessed adenoma number while investigating the role of chromoendoscopy in the duodenum in FAP. Picasso et al[10] studied 10 patients undergoing upper GI surveillance and found a statistically significant increase in the number of duodenal polyps

TABLE 6. Distribution of Spigelman stages in patients with FAP and MAP before and after staining, compared with results reported in previous case series of patients with FAP

	Present series MAP (n = 32), n (%)		Present series FAP (n = 19), n (%)		Previous case series[11] (n = 43 FAP), n (%)	
Spigelman stage	Before staining	After staining	Before staining	After staining	Before staining	After staining
0	27 (84)	23 (72)	7 (37)	6 (32)	3 (7)	2 (4)
I	2 (6.25)	1 (3)	2 (10)	1 (5)	2 (4)	2 (4)
II	2 (6.25)	7 (22)	4 (21)	4 (21)	11 (26)	10 (23)
III	1 (3.5)	1 (3)	3 (16)	4 (21)	14 (33)	15 (36)
IV	0	0	3 (16)	4 (21)	13 (30)	14 (33)

after chromoendoscopy ($P = .0.03$), revealing additional polyps in 8 of the 10 patients. Unlike our study, the overall change in Spigelman stage was not assessed. Dekker et al[11] studied 43 patients with FAP and showed that significantly more duodenal adenomas were detected after the application of indigo carmine, but this did not result in a considerable change in Spigelman stage or result in any major additional clinical consequences. Of the 43 patients, only 26 had an APC mutation that had previously been identified; the other 17 patients all had undergone colectomy because of >100 histologically confirmed colorectal adenomas but without confirmation of pathogenic mutations. In contrast, our cohort of patients comprises a specific subgroup with known mutations. In addition, the endoscopist in Dekker et al.'s study was not blinded to the number of adenomas before staining, which may have biased the results. Although our current study was designed to blind the second counting endoscopist, there remains the possibility of a systematic bias due to counting differences between the 2 endoscopists. Both previous studies of dye spray duodenoscopy are in agreement with our findings in FAP, but the impact on adenoma detection in MAP has never been studied and is a novel finding.

The small number of patients with MAP reported to have developed duodenal cancer appear to have done so on a background of minimal duodenal polyps,[1] in contrast to those with FAP, and it is not necessarily that the total polyp number is as important as other factors in the assessment of duodenal cancer risk in patients with MAP. Recent molecular genetic analysis revealed a greater burden of somatic mutations in MAP than in FAP adenomas, suggesting the MAP-associated DNA repair defect may drive a more rapid progression of adenoma to cancer.[12] Although none of the studies to date have established the clinical interpretation of multiplicity of duodenal adenomas in MAP, the improved adenoma detection rate seen in MAP after chromoendoscopy in this study has the potential to be clinically meaningful, because it is likely to lead to more appropriate surveillance intervals for some patients.

Generally, in studies of the outcomes of surgical intervention in FAP, it is the patient's Spigelman stage that has been reported rather than the sizes of lesions harboring cancer.[5,13,14,15] Lopez-Ceron et al[16] found that when using narrow band imaging (NBI) for detection of duodenal adenomas, the only trait that was significantly associated with advanced histology was an estimated polyp size of greater than 1 cm, with a 3-fold increased risk. Although high Spigelman stages do not necessarily imply advanced histologic lesions, Saurin et al[13] reported that an original Spigelman score equal to or greater than 7 or 8 was predictive of HGD development. The use of chromoendoscopy in the colon to highlight high-risk features for biopsy, such as an advanced Kudo pit pattern, which may be overlooked by white-light endoscopy, has been described in the literature, and use of image enhancement techniques (digital or chromoendoscopic) can improve diagnostic accuracy in lesion assessment.[17] In the duodenum, this may also be of direct benefit to identify advanced surface characteristics and enable targeted biopsy.

This study has shown no significant effect of chromoendoscopy on the sizing of adenomas in either MAP or FAP. Dekker et al[11] reported that the largest adenomas detected at chromoendoscopy appeared significantly larger than before staining, possibly due to better visualization of the adenoma borders. In contrast, Picasso et al[10] reported that polyps appeared smaller after dye spraying ($P = .0.03$), which was also explained by more precise demarcation than normal. Although some lesions may look larger or smaller after dye spray, the detection of additional smaller lesions would of course result in a smaller median size of polyps detected. Our study suggests that, like NBI,[16] chromoendoscopy does not significantly affect the apparent size of adenomas in the FAP duodenum.

Dekker et al[11] attributed the minor change in Spigelman score in their study to the use of high-resolution endoscopy. They concluded that considerably improved endoscopic visualization of duodenal adenomatosis with high-resolution endoscopy leaves little room for further improvement of clinical consequence. However, the

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TABLE 7. MAP mutation analysis data and number of duodenal adenomas detected

Case	Mutation 1	Mutation 2	Total number of duodenal polyps detected
1	Y104X	Y104X	0
2	G396D	G396D	0
3	Y179C	V130EfsX98	0
3	Y179C	Y179C	1
5	E480X	E480X	0
6	Y179C	G396D	0
7	Y179C	G396D	0
8	Y179C	Y179C	0
9	Y179C	G396D	0
10	Y104X	Y104X	0
11	Y104X	Y104X	0
12	Y179C	Y179C	15
13	Y104X	Y104X	1
14	Y104X	Y104X	0
15	Y179C	G396D	1
16	E466X	E466X	0
17	E466X	E466X	3
18	Gln 414 + Gln 414 + Tyr 104	1240 C>T + 312 C>A	0
19	E466X	E466X	0
20	E466X	E466X	1
21	E480X	E466X	3
22	E480X	E466X	2
23	E480X	E466X	0
24	E466X	E466X	3
25	E480X	E466X	0
26	E480X	E466X	0
27	E466X	E466X	0
28	Y179C	Y179C	4
29	Y179C	Y179C	0
30	E480X	E466X	0
31	E480X	E466X	0
32	Y179C	R244X	0

endoscopist was not blinded to the number of adenomas before staining. A previous study has suggested that in patients who have duodenal disease progression, both time lapse and technical improvements were determinant factors.[18] In a mixed-model analysis, time lapse, change to high-resolution technology, and dysplasia ranking contributed consistently to an increased Spigelman score and stage. This suggests visibility and histology may result in an overestimation of the clinical significance of duodenal polyposis by using the Spigelman system. However, other studies appear to demonstrate a lack of correlation between the findings at endoscopy and pathology results from biopsy specimens, and between progressive structural changes within the polyps and pathology findings.[19] This led the authors to argue that the overall aim of identifying patients who are at high risk of developing duodenal and ampullary cancer remains problematic. Currently, there is no comprehensive picture of the risk of duodenal adenomas and cancer in patients with MAP, and the risks of duodenal disease remains uncertain. Further research is required to prospectively validate the Spigelman classification in the risk stratification of duodenal polyposis, because its suitability for MAP has not been established.

Lopez-Ceron et al[16] are the only group to have evaluated the effect of NBI (after examination with high-resolution endoscopy) on the detection rates of duodenal adenomas in patients with FAP. In contrast to this current study, they found that in their study group of 37 patients, there was no clinically relevant upgrade in the Spigelman classification using NBI. They also concluded that there was no improvement in the detection of gastric polyps using NBI. More duodenal adenomas were detected in 16 examinations (35.6%), but Spigelman stage increased in only 2 patients (2.2%), which was not statistically significant. The current study therefore supports the use of chromoendoscopy over NBI in the improvement of adenoma detection in duodenal polyposis, but larger prospective studies are needed to confirm this.

The patients with MAP in this study were significantly older than the patients with FAP. In patients with FAP, time since diagnosis, age, and Spigelman stage at initial endoscopy have been found to be determining features of the severity of duodenal polyposis.[3,13,20,21] These variables may not apply for MAP. Our study suggests that the effect of increasing age on the number of polyps is not the same for MAP as it is for FAP. The natural history of duodenal polyposis in MAP is a topic that requires further study.

A limitation of this study is the inability to determine the additional value of chromoendoscopy in the assessment of ampullary adenomas; because examination of this area with the side-viewing endoscope was done after dye spaying had taken place (current recommendations suggest use of a side-viewing duodenoscopy as standard). We found that almost half of the patients required further side-viewing endoscopy to satisfactorily visualize the ampulla, suggesting this should continue to be included in protocols for duodenal surveillance. In addition, our study was not designed to systematically assess the utility of side-viewing endoscopy itself on the number of polyps in the peri-ampullary region. A previously reported case series found ampullary adenomas in 66% of patients with FAP when using a side-viewing endoscope,[22] however our study did not detect many ampullary adenomas (only 2 patients had ampullary adenomas), which may have caused bias because most malignancies occur in the periampullary region. No lesions with HGD were

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detected, and our series may not be representative of the FAP and MAP population although it involves 2 large UK centers with relatively high-volume surveillance caseloads for polyposis. In their prospective five-nation study of the long-term natural history duodenal adenomas in FAP, Bulow et al[21] reported that 12% of adenomas were diagnosed only histologically, where no visible polyps were seen. The current study did not incorporate taking routine biopsy specimens of the background duodenal mucosa to exclude dysplasia and relied on visualization of precisely demarcated adenomatous tissue as morphologic polyps. Picasso et al[10] did take random biopsy specimens of mucosal folds in the second and upper third part of the duodenum, including the papilla, but found no additional adenomatous tissue. Dekker et al[11] did not include taking random background biopsy specimens in their protocol.

CONCLUSIONS

This study demonstrates that chromoendoscopy of the duodenum enhances adenoma detection in both MAP and FAP, and that use of a side-viewing endoscope is essential to ensure that the ampulla is adequately visualized. In both conditions, there was a significant increase in Spigelman stage after chromoendoscopy and therefore of clinical consequence to the patient in terms of follow-up according to current management guidelines. The increase in Spigelman stage was due to increased detection of numbers of polyps rather than by enlarged polyps or high-grade adenomas. Because screen-detected duodenal cancers have been shown to have a much better prognosis than symptomatic cancers in FAP (overall survival of 8 years after a screen-detected cancer versus 0.8 years[5]), there is a strong argument for regular endoscopic surveillance. However, there are shortcomings in applying the same surveillance program to MAP as for FAP because of a paucity of knowledge of the risk of malignant progression in MAP duodenal adenomas. Further studies are needed to focus on this question.

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