Role of endoscopy in patients with familial adenomatous polyposis

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ABSTRACT
Familial adenomatous polyposis (FAP) is a hereditary disease that, without intervention, will cause nearly all patients to develop colorectal cancer by the age of 45. However, even after prophylactic colorectal surgery the eventual development of duodenal adenomas leads to an additional risk of duodenal and ampullary cancers. Endoscopy is an essential part of the multidisciplinary management of FAP to aid the early identification or prevention of advanced gastrointestinal malignancy. This review article details the current evidence and consensus guidance available regarding the role of endoscopic surveillance and treatment strategies for FAP.

INTRODUCTION
Familial adenomatous polyposis (FAP) is a hereditary colorectal cancer (CRC) disease that without intervention, virtually all patients will develop CRC by the age of 35–45. FAP-related cancer currently accounts for 2%–5% of CRC, however, with timely colorectal surgery, life expectancy has improved which has led to polyposis and cancer of the ampulla and duodenum now becoming a more significant cause of mortality. Appropriate recognition of FAP and introduction of endoscopic surveillance and treatment strategies are an essential part of the multidisciplinary management to reduce advanced gastrointestinal malignancy. This review article will review the evidence and current consensus opinion for the role of endoscopy in caring for patients with FAP.

Epidemiology and Presentation of FAP
The prevalence of FAP is estimated to be 1 in 10 000 and accounts for 2%–5% of CRC. FAP is caused by an inherited, autosomal dominant mutation in the adenomatous polyposis coli (APC) gene located on the long arm of chromosome 5. APC is a tumour suppressor gene, which usually prevents the growth of premalignant cells, but in FAP this is non-functioning, leading to the development of the classical phenotype where an excess of 100 polyps distributed throughout the colon can be initially identified but then polyps also develop in the duodenum and stomach. Without prophylactic colorectal surgery, CRC will develop in all patients with FAP at a mean age between 35 and 45. Duodenal polyps also eventually develop in nearly all patients (88%–98%) with two-thirds of patients harbouring ampullary adenomas also. Previous estimates of developing duodenal cancer by the age of 70 were initially 4%, however, this is now considered to be nearer 18% by the age of 75 with ampullary cancer risk of 10% by the age of 60.

In 10% of patients with FAP a less aggressive, attenuated, variant of FAP (AFAP) is seen with a phenotype developing polyps 10 years later on average and...
CRC 15 years later than non-attenuated variants at an average age between 50 and 60 years.\textsuperscript{9–11} Patients with AFAP demonstrate a right sided colon polyp distribution and duodenal polyposis development is lower, however, the duodenal cancer risk remains similar.\textsuperscript{9–11}

It is also important to note a similar genetic polyposis syndrome not caused by the APC gene, which is MUTYH-associated polyposis (MAP). Although MAP is a recessively inherited disease caused by variants in the MUTYH base-excision repair gene, there is a substantial phenotypic overlap with FAP. Given the later development of polyps and lower risk of CRC (63\% at age 60)\textsuperscript{12} MAP is sometimes classed with AFAP especially with a right sided CRC predominance but there is significant phenotypic variation and duodenal polyposis can occur in MAP and duodenal cancer risk again remains similar to FAP.\textsuperscript{13,14}

### The role of endoscopy

Endoscopy forms part of the multidisciplinary management of patients with FAP and their families; alongside access to genetic counselling, testing, specialist nurse support and specialist surgical support. Given the onset of polyposis around puberty all recommendations suggest testing and colonoscopy screening starting by the age of 12 in patients with an affected family member (table 1), therefore, paediatric to adult transition services and communications are required.

### Lower gastrointestinal endoscopy

The combination of endoscopic surveillance and surgery for FAP have caused a significant decrease in CRC incidence and mortality.\textsuperscript{15,16} A systemic review of 30 non-randomised studies including 8016 patients compared CRC incidence and mortality in screened and symptomatic patients with FAP: all studies showed an improvement in both long-term survival and CRC incidence. The studies in the systemic review from the United Kingdom (UK) demonstrated an incidence of CRC in 33.6\%–66.2\% in FAP patients presenting symptomatically compared with 3.8\%–9.4\% in those FAP under surveillance with a delay in CRC development of up to 16 years and mean survival improved by up to 12 years.\textsuperscript{17} The Danish polyposis registry is a near complete national FAP registry which initially showed only 2/116 (2\%) patients enrolled in a surveillance programme had CRC vs 142/205 (69\%) probands (a person serving as the starting point for the genetic study of a family). The 10-year cumulative survival was 94\% in patients on surveillance compared with only 41\% in probands.\textsuperscript{18}

### Starting surveillance

European databases have demonstrated he development of colorectal adenomas between the ages of 12 and 17 years\textsuperscript{19–21} leading to European and UK guidance recommending the age to start lower gastrointestinal endoscopy surveillance between the ages of 12–14 (table 1).\textsuperscript{22,23} The same European databases have also shown the risk of developing CRC before the age of 20 to be 1.3\% and absent before the age of 10.\textsuperscript{2} Yearly colonoscopy rather than flexible sigmoidoscopy is recommended by UK and ESGE guidance as the phenotype and polyp distribution can vary significantly, notably AFAP showing a right sided predominance of adenomas as previously noted which would be missed with a flexible sigmoidoscopy.\textsuperscript{13,14} UK guidelines support extending colonoscopy surveillance in some cases to 2 yearly if there is an absence or low polyp yield, however, this interval should be individualised alongside genetic specialist input.

Recommendation for surgery that are identified during colonoscopy currently include relative indications which include a significant change in polyp burden; polyps >10 mm; or the identification of high-grade dysplasia (HGD) and absolute indications which are the identification of confirmed or suspected cancer or symptoms due to the polyps.\textsuperscript{23}

### Postoperative surveillance

Options for colorectal surgery include total colectomy with either an ileorectal anastomosis (IRA), ileal pouch and anal anastomosis (IPAA) or end ileostomy. All three colectomy options require initial annual surveillance as adenomas can develop in the retained rectum with IRA, then anal transition zone (ATZ) or pouch after IPAA or in the stoma in an end ileostomy.

If there is rectal sparing or any polyps >5 mm can be removed an IRA can be performed. It has been shown that the risk of cancer incidence and future rectal excision is significantly higher if >20 polyps are present in the rectum (CRC incidence 1.6\%<20 vs 10.8\% if >20).\textsuperscript{24} Indications to consider rectal excision that are identified on future surveillance are rectal cancer, polyps>10 mm, polyps with HGD and a significant increase in polyp load.\textsuperscript{25}

The risk of polyps developing in an IPAA has been shown to be 45\%–51\% at 10 years, however, there is a very low risk of developing CRC (0\%–1.9\%) in the same time period.\textsuperscript{25,26} A systematic review showed 75\% of the cancers (69/92) identified in an IPAA performed
for FAP have been shown to be predominant in the ATZ so is particularly important for surveillance (figure 1). Therefore, despite the low risk of cancer, given the progressive incidence of polyps continued annual surveillance is recommended (table 1).

Polyectomy in the rectum or pouch following colectomy has been shown to be possible and reduce polyp burden by argon photocoagulation for small polyps, cold snare polypectomy for polyps <10 mm and submucosal dissection for more complex polyps at the anastomosis. No strong evidence exists that shows polypectomy in the rectum or pouch following surgery reduces CRC risk to date, however, European guidelines via consensus opinion strongly recommends removal of polyps >5 mm especially in the ATZ in patients with an IPAA (figure 1).

Upper gastrointestinal endoscopy

With the risk of duodenal polyposis and duodenal cancer being recognised in FAP, AFAP and MAP upper gastrointestinal endoscopic surveillance is recommended. Gastric cancer and adenomatous change should also be considered in FAP. Fundic gland polyps are a common feature in FAP but have a very low malignant potential and can serve as a distraction for what seem to be increasing reports of distal gastric cancer when fundic glands are present (figure 1). Although historical data demonstrated gastric cancer to be just common in FAP as the rest of the population a more recent report from the USA demonstrated gastric adenocarcinoma in 10/767 (1.3%) of patients with FAP at upper gastrointestinal surveillance with standardised incidence ratio of 140 compared with the USA’s Surveillance, Epidemiology and End Results Programme. It has been shown that upper gastrointestinal FAP surveillance improves life expectancy with survival after a screen-detected cancer of 8 years vs 0.8 years if an upper gastrointestinal cancer is diagnosed when symptomatic.

Starting surveillance

Nearly all patients with FAP will eventually develop duodenal adenomas with studies estimating levels of 88%–98% and with duodenal cancer risk estimated to be 18% at by the age of 75. The severity of duodenal polyposis increases with age, with high risk duodenal adenoma features found in 50% by 70 years old. Consensus guidance in the UK, Europe and USA agree that upper gastrointestinal surveillance should start at age 25. In MAP the risk of developing duodenal adenomas is lower at 17%–34% with only 6% developing ampullary adenomas. Duodenal adenomas develop later in MAP also at a median age of 50 years therefore duodenal surveillance is suggested to start at age 35 in patients with MAP (table 1).

Continued upper gastrointestinal surveillance

Ongoing duodenal surveillance in patients with FAP and MAP is then guided by the duodenal findings using the Spigelman classification for non-ampullary duodenal polyposis. The Spigelman classification scores the number, size, histology and the dysplasia severity to stage duodenal adenoma disease (table 2) (figure 2). The Spigelman classification is graded 0–IV and can be used to estimate the risk of developing duodenal cancer which was validated with a 10-year follow-up study showing duodenal cancer developing in 36% (4/11) of patients with stage IV disease but only 2% in both stage III (1/41) and stage II disease (1/44). The weakness of the Spigelman classification is that it does not incorporate ampullary lesions or predict ampullary cancer which has been shown to be an
Endoscopy

Endoscopy in independent risk factor. Visualisation of the ampulla should also be sought and the appearance included into risk assessment. Ampullary adenoma presence and size has now also been stratified and validated into both UK and European surveillance guidance (table 2). A duodenoscope may be needed to complete the exam and visualise the ampulla, however, a clear cap on the end of the gastroscope has been shown to visualise the ampulla in 94% of patients with FAP and advisable to be used as first line option. The reported increase of gastric cancer or dysplasia in FAP means using a forward viewing gastroscope has the advantage of being able to survey the stomach in more detail for significant gastric lesions.

More recently consensus guidance has encouraged use of a modified Spigelman classification which advises a biopsy only if a polyp is suspicious for invasion or not endoscopically resectable and avoids routine biopsies. Biopsy avoidance prevents interference for future optical diagnosis and possible endoscopic resection. The initial base line biopsy to determine histological polyp type can be used to calculate the Spigelman score, this guidance includes routine biopsy of ampullary adenomas which can cause pancreatitis (figure 2). Endoscopic therapy for duodenal adenomas

Although duodenal adenoma removal is possible with an accepted complication rate there is currently no long-term or strong evidence that resecting adenomas reduces cancer risk or the need for surgery. Multiple cohort studies have shown successful duodenal adenoma removal and ampullectomy down staging of patients with Spigelman IV score with prolonged follow-up without the development of duodenal cancer. A retrospective dual centre French study performed duodenal adenoma removal and ampullectomy in 35 patients with stage IV disease reducing the Spigelman score by an average of 6 points and mean

### Table 2 Calculation of the modified Spigelman score incorporating the presence of an ampullary adenoma and subsequent screening recommendations

<table>
<thead>
<tr>
<th>No of points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of polyps</td>
<td>1–4</td>
<td>5–20</td>
<td>&gt;20</td>
</tr>
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<td>Polyp size (mm)</td>
<td>1–4</td>
<td>5–10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubulous</td>
<td>Tubulovillous</td>
<td>Villous</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Stage</th>
<th>Surveillance endoscopy</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5 years</td>
</tr>
<tr>
<td>1–4</td>
<td>I</td>
<td>5 years</td>
</tr>
<tr>
<td>5–6</td>
<td>II</td>
<td>3 years</td>
</tr>
<tr>
<td>7–8</td>
<td>III</td>
<td>1 year (+endoscopic therapy BSG only)</td>
</tr>
<tr>
<td>9–12</td>
<td>IV</td>
<td>6 months (ESGE)—6–12 months (BSG)±endoscopy or surgery</td>
</tr>
</tbody>
</table>

**Ampulla Assessment**

Minimum interval adjustment if longer with Spigelman score for earlier surveillance interval if minor or major ampullary adenoma detected (see also figure 2). BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; HGD, high-grade dysplasia; LGD, low grade dysplasia.

**Initial biopsy histology can be used for histology score, with adjustment for earlier surveillance interval if minor or major ampullary adenoma detected (see also figure 2).**

**Figure 2** Examples of modified endoscopic Spigelman white light assessment of the duodenum in FAP (A). Stage I <5 small duodenal adenoma. (B) stage II 5–20 small adenomas with low grade tubulo-villous histology. (C) Stage III 5–20 adenomas with some >10 mm and low grade tubulo-villous histology. (D) Stage IV >20 adenomas with many >10 mm and but low grade histology. (E) 15 mm ampullary adenoma visualised with a forward viewing gastroscope and cap previous biopsy showing low grade tubulovillous appearance—further biopsy not required but despite no other duodenal polyps annual surveillance recommended. (F) Abnormal appearance of ampullary adenoma (loss of central mucosa pattern and depression) on surveillance therefore biopsied which showed HGD as consideration for surgical assessment. FAP, familial adenomatous polyposis; HGD, high-grade dysplasia.

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*Hopper AD. Frontline Gastroenterology 2022;13:e72–e79. doi:10.1136/flgastro-2022-102125*
follow-up of 9.5 years with no cancers detected in this period. Another retrospective single centre study from the Netherlands showed 49 patients undergoing endoscopic treatment reduced Spigelman score and observed surgery-free survival for duodenal polyp resection at 74% after 7 years and 71% after 6 years for ampullary resection. Both studies also highlight the complication rate of endoscopic duodenal adenoma resection with bleeding up to 13% and pancreatitis in up to 14% of patients with ampullary adenoma resection subsequently advising careful consideration before ampullectomy is performed. One further retrospective study demonstrated that patients previously down-staged with endoscopic therapy from Spigelman stage IV showed an increased rate of polyp growth compared so patients at similar lower stages without previous therapy. Despite the small number of patients in these cohort studies with stage IV disease no duodenal cancers were reported prompting European and UK guidance to advise removal of non ampullary duodenal adenomas larger than 1 cm and in Spigelman stage III–IV disease and to only consider ampullectomy in expert centres if ampullary adenomas show progressive growth or invasive growth is suspected. Prior to considering endoscopic ampullectomy, full staging and assessment with endoscopic ultrasound and magnetic resonance cholangiopancreatography is required. It is important to note that there is a recognised rate of false negative biopsy results of 20%–30% when ampullary cancer is present. A recent study found an initial endoscopic biopsy showing HGD and ductal dilatation are very high predictors of malignancy in ampullary adenomas (specificity: 96% and positive predictive value: 84%), therefore, should be considered for surgery rather than endoscopy.

There have been a number of guidelines and descriptions of the techniques regarding the endoscopic removal of duodenal and ampullary adenomas stressing the complexity and complications even in high volume centres. The consensus agreements agree that technique for large duodenal adenomas remains an endoscopic mucosal resection with a significant rate and an attempt to place a pancreatic stent when an adenoma is removed from the ampulla or periamplullary region (figure 3).

Referral for surgery during duodenal surveillance

Given the risk of cancer development in patients with the findings of Spigleman III that includes HGD or stage IV disease are recommended to undergo pancreas preserving duodenectomy (PPD) with pancreatic duct anastomosis or pancreatoduodenectomy. If cancer is identified a pancreatoduodenectomy is advised given the risk of lymph node metastases. The operations are complex with a 30-day mortality of 3%–29% and significant morbidity of 49%–76%. Although pancreatoduodenectomy would appear the more invasive, short-term complications are comparable and in fact PPD has shown to cause more later complications of pancreatitis and exocrine insufficiency. The

Figure 3  Endoscopic resection of ampullary and non-ampullary duodenal adenomas. A prestaged sessile ampullary adenoma (A) is removed using a side viewing endoscope using a snare closed with its neck positioned at the distal polyp base without a submucosal injection (B). The resulting defect is examined for bleeding (C) and a pancreatic duct stent attempted to reduce pancreatitis risk (D). A cap can confirm non ampullary involvement of large duodenal adenomas >10 mm (E) which can be resected with endoscopic mucosal resection including a large fluid cushion (F), and sequential snare resection from one side of the lesion. The resulting mucosal defect (G) can be closed if possible to reduce post resection bleeding (H).
recurrence of adenomas in the neoduodenum after PPD has been demonstrated in 14/18 (78%) patients after a mean follow-up of 4 years, therefore, post-operative surveillance access requirements should also be considered before surgery undertaken. Continued surveillance and treatment strategies should incorporate a patient's comorbidity given the invasive nature of duodenal surgery.

Surgery for FAP can be complicated by the presence of desmoid tumours which would be detected on CT performed prior to any surgery being performed. Desmoid tumour risk increases with abdominal surgery, CT performed prior to any surgery being performed. The presence of desmoid tumours would be detected on surveillance and treatment strategies should incorporate a patient's comorbidity given the invasive nature of duodenal surgery.

Capsule endoscopy
Capsule endoscopy is not been able to confidently detect duodenal or ampullary polyps. In a series of 23 FAP patients undergoing capsule endoscopy only 4 out of the 11 patients with duodenal adenomas had the polyps identified by the capsule and the ampulla was not identified in any of the 23 patients. In the same study, jejunal polyps were identified only in patients with duodenal polyps therefore the role of capsule endoscopy could be used to identify significant more distal polyps in patients with duodenal adenomas prior to considering surgery (recommended by USA guideline) or for investigation of anaemia. Although jejunal adenomas occur in FAP the occurrence of a jejunal cancer is rare (figure 1).

CONCLUSION
The endoscopist plays a key role in the care of patients with FAP. The combination of endoscopic surveillance and recognition of factors that require referral for therapy or surgery are an essential part of the multi-disciplinary management of patients with FAP. The recommended endoscopic management of patients with FAP can reduce morbidity and mortality from advanced gastrointestinal malignancy.

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