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Management of familial adenomatous polyposis and MUTYH-associated polyposis; new insights

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ABSTRACT

Familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) are rare inherited polyposis syndromes with a high colorectal cancer (CRC) risk. Therefore, frequent endoscopic surveillance including polypectomy of relevant premalignant lesions from a young age is warranted in patients. In FAP and less often in MAP, prophylactic colectomy is indicated followed by lifelong endoscopic surveillance of the retained rectum after (sub)total colectomy and ileal pouch after proctocolectomy to prevent CRC. No consensus is reached on the right type and timing of colectomy. As patients with FAP and MAP nowadays have an almost normal life-expectancy due to adequate treatment of colorectal polyposis, challenges in the management of FAP and MAP have shifted towards the treatment of duodenal and gastric adenomas as well as desmoid treatment in FAP. Whereas up until recently upper gastrointestinal surveillance was mostly diagnostic and patients were referred for surgery once duodenal or gastric polyposis was advanced, nowadays endoscopic treatment of premalignant lesions is widely performed. Aiming to reduce polyp burden in the colorectum as well as in the upper gastrointestinal tract, several chemopreventive agents are currently being studied.

1. Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder caused by a germline mutation in the adenomatous polyposis coli *(APC)* gene. FAP has an incidence rate of 1 per 8.300 births and equally affects both sexes [1]. The disease is characterised by the formation of hundreds to thousands colorectal adenomas, typically arising at teenage years. Although most patients are identified at a young age due to a positive family history of FAP, a quarter of patients has a de novo *APC* mutation, presenting with symptoms and often advanced disease [2]. FAP is characterised by an anticipated, multifocal adenoma-carcinoma sequence and it takes 15–20 years before polyps progress into cancer, comparable to sporadic adenomas. Without treatment, the risk of developing colorectal cancer (CRC) approaches 100% at a young age with a median of 35–45 years. Therefore, prophylactic colorectal surgery is indicated at a young age [3]. After colectomy, lifelong endoscopic surveillance remains important since adenomas will arise and grow in the retained rectum or ileal pouch [4]. Patients with FAP also may develop several extra colonic manifestations. Nearly all patients with FAP develop duodenal polyps that require endoscopic surveillance to in an effort to prevent duodenal surgery as well as duodenal cancer. The diagnosis and treatment of gastric adenomas and gastric cancer recently has become a growing concern [5,6]. The most challenging non-gastrointestinal manifestation of FAP are desmoid tumours, benign myofibroblastic proliferations that may result in major morbidity and mortality especially when developing in the mesentery [7,8].

MUTYH-Associated Polyposis (MAP) was first described in 2002 in a Welsh family in which three siblings presented with multiple colorectal adenomas and carcinomas. No germline mutation of *APC* was found but a defective gene, *MUTYH*, was identified on both alleles [9]. *MUTYH* is a base excision repair gene located on chromosome 1p34.3-p32.1 and its

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mutation leads to somatic G > T transversions in multiple genes, including *APC* and K-ras [10]. It has been reported that MAP is responsible for less than 1% of all CRCs [11]. In a cohort of 405 patients with oligopolyposis 7% was diagnosed with MAP at molecular genetic testing [12]. MAP is associated with a 28-fold increase in the risk of CRC [13]: the risk is 48% in patients younger than 60 and the lifetime risk in non-surveilled patients is 80–90% [14]. Unlike FAP and other hereditary CRC syndromes, MAP follows an autosomal recessive inheritance pattern [15,16]. MAP is not to be considered an attenuated form of FAP, but a distinct clinical entity with an overall higher cancer susceptibility and peculiar features [17]. First of all, colorectal adenomas are not the only finding in MAP: sessile serrated lesions and hyperplastic polyps are a common finding and considered part of the phenotype [18]. Secondly, the clinical spectrum of MAP is wide and very variable: overall, the disease is mild and is more similar to an attenuated FAP (aFAP, between 10 and 100 polyps), but sometimes the disease is more severe and patients present with a higher number of polyps. Moreover, polyps in MAP seem to have an accelerated carcinogenesis driven by a high mutational burden and KRAS gene involvement [19]. Therefore endoscopic surveillance in MAP can be insidious and challenging: CRC can occur isolated with no other polyps or with a very low polyp burden; metachronous CRC after surgery has been reported regularly [20]. Furthermore, whereas polyps and CRC in FAP patients are mainly located in the left side of the colorectum, in MAP the preferred location is the right colon (adding challenges for the endoscopist) and rectal involvement is uncommon [20,21]. Notably, MAP patients seem to be more predisposed to Lynch-like extraintestinal malignancies such as ovarian, endometrial, urinary, skin, thyroid and breast cancers as well as sebaceous adenomas [14]. From the above, it is clear that much attention and focus should be paid to endoscopic surveillance in MAP patients. Unfortunately, still little is known and most of the current knowledge is translated from observational and FAP studies.

This review aims at summarizing the available evidence on management in FAP and MAP and giving practical advice to the clinician.

1.1. Surveillance of the colon and rectum

The adenoma development in the colorectum in patients with FAP begins at a median age of 13.5–17 years [22–24]. However, colorectal phenotype in terms of onset of disease and the number of polyps greatly varies, and is partially explained by a difference in mutation site on the *APC* gene. Patients with a mutation spanning between codon 1250 and 1464 of the *APC* gene, seem to have a more severe phenotype compared to patients with a mutation at the 5′ and 3’ end of the gene [25].

Several guidelines recommend 1–3 yearly sigmoidoscopy/colonoscopy surveillance starting from 10 to 14 years in FAP and 18–20 years in MAP to monitor the progression of colorectal polyposis (Table 1) [26–28]. The later age in MAP is based on the slightly later onset of CRC encountered in MAP patients with a mean age at diagnosis of 48.5 years according to Nieuwenhuis et al. [29]. On the contrary, CRC risk in patients carrying only a monoallelic mutation of *MUTYH* is debated: some authors report a 2.5-5-fold increased risk, depending on familiar history [30], while others report a cancer risk comparable to the general population, and thus no need for intensive surveillance [31,32].

During surveillance endoscopies in FAP and MAP, polypectomy is performed for larger lesions to prevent progression to advanced lesions and CRC and to postpone colorectal surgery. The European Society of Gastrointestinal Endoscopy (ESGE) recommends resection of polyps larger than 5 mm [26]. The recommended resection technique for polyps 10 mm and less is cold snare polypectomy, when larger endoscopic mucosal resection (EMR) either hot or cold can be used as long as the lesion is not invasive [33,34]. Matsumoto et al. [35] showed that the use of dye chromoendoscopy during colonoscopy in patients with FAP results in higher polyp numbers. The detection of every single small polyp with chromoendoscopy might not be relevant in terms of cancer risk at that moment, but it might help in predicting the future course of the disease and might therefore contribute to the selection of the type of colectomy. Fig. 1 shows 3 endoscopic images of the same colonic segment with white light endoscopy, narrow band imaging (NBI) and chromoendoscopy. In FAP and sometimes also in MAP, the severity of colorectal polyposis reaches a point from where endoscopic surveillance is not accurate and safe to prevent CRC anymore (“unmanageable” polyposis). Although one study showed that intensive endoscopic surveillance was safe on the short-term in 95 patients with FAP who refused surgery as no CRCs occurred [36], prophylactic colorectal surgery remains the standard care to prevent colorectal cancer in these circumstances.

Table 1
Risk of cancer and recommendations for endoscopic surveillance.

	FAP	MAP
Germline mutation	*APC*	*MUTYH*
Risk of cancer		
Colorectum	100%	80–90%
Duodenum	5–10%	1%
Stomach	1%	2%*
Endoscopic surveillance frequency		
Colonoscopy (pre-colectomy)	1 to 3-yearly from age 10-14	1 to 3-yearly from age 18-20
Pouchoscopy/sigmoidoscopy (post-colectomy)	½ to 3-yearly	½ to 3-yearly
Gastroduodenoscopy	½ to 5-yearly from age 20-25	½ to 5-yearly from age 30-35
Endoscopic polypectomy indications		
Colorectum/ileal pouch	Adenomas > 5 mm	Adenomas > 5 mm
Duodenum	Duodenal or ampullary adenomas ≥10 mm	Duodenal or ampullary adenomas ≥10 mm
Stomach	Adenomas > 5 mm	Adenomas > 5 mm

Data presented in this table are extracted from three guidelines: Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) guideline [26], Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) [27] and the American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes [28] *Data on gastric cancer in MAP are limited, and, at the moment, not significant.

1.2. Timing and type of colorectal surgery

Surgical management between FAP and MAP is globally equal. Patients with FAP and MAP may undergo colorectal surgery for two reasons: CRC or unmanageable polyposis. In the case of CRC, it is not unusual for patients with very little or no polyp burden (mostly MAP) to undergo surgery prior to a genetic diagnosis, with the result of having a right or left hemicolectomy [20].

In the ideal situation, patients with FAP and MAP would undergo a prophylactic colectomy shortly before CRC would otherwise have developed. However, it is difficult to predict when exactly the adenomas will develop into cancer. The number, size, endoscopic and histopathological aspect of colorectal adenomas determine whether further endoscopic surveillance is safe. Indications for colectomy generally include the presence of multiple polyps >10 mm, polyps that are high-grade dysplastic and a rapid increase in the number of polyps [27]. Yet, timing of colectomy in FAP should always be a shared decision with the patient taking into account social and educational/career factors. Colectomy should be performed on a moment in time that suits both the severity of polyposis and the preference of the patient.

When the indication for colectomy is set, the next decision to be made is on the type of operation, i.e. whether only the entire colon will be removed or also the rectum. The preferred and most often performed procedures are a (sub)total colectomy with an ileorectal or ileosigmoidal anastomosis (IRA/ISA) or a more extensive proctocolectomy with ileal pouch-anal anastomosis (IPAA). An end ileostomy is rarely constructed

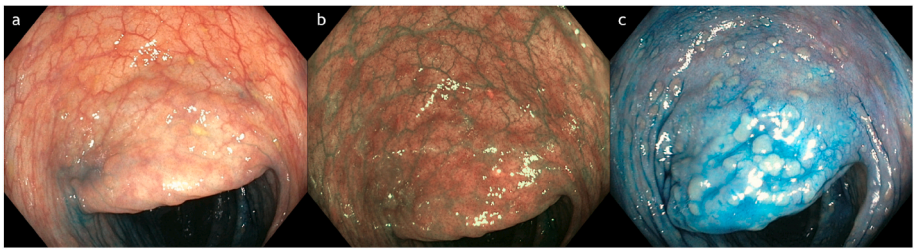

Fig. 1. Three times the same colonic segment in a patient with FAP using white light endoscopy (a), narrow band imaging (NBI) (b) and dye chromoendoscopy (c).

at time of colectomy but might be necessary in case of locally advanced rectal cancer, extensive mesenterial desmoid or a dysfunctional anal sphincter making construction of an IPAA unfeasible. Whether the rectum can be safely preserved largely depends on the rectal polyp burden at time of colectomy. The overall incidence of rectal cancer after IRA in FAP is 6.1–11.2% [37,38]. Church et al. showed that the risk of rectal cancer after IRA was 10.8% for patients with more than 20 rectal polyps at time of IRA construction compared to 1.6% for patients with less than 20 rectal polyps [39]. The incidence of rectal cancer drastically decreased since the introduction of IPAA in 1978, probably since before patients with severe rectal polyposis underwent IRA and were at higher risk of developing rectal cancer [40]. The incidence of developing cancer after IPAA in FAP is 1.1–1.9% [38,41]. Most of these cancers are located in the rectal cuff rather than in the pouch body itself. In MAP, polyp burden is often low and the rectum is rarely involved and therefore IRA is often a reasonable choice in these patients in order to preserve rectal function [42], provided that the patient will undergo a strict endoscopic surveillance program. The main concern in post-colectomy MAP patients is metachronous CRC, which is reported to be as high as 17% [19,43], possibly driven by the accelerated carcinogenesis, as previously discussed [43,44].

A widely used indication for IPAA is the presence of more than 20 adenomas in the rectum. Moreover, severe colonic polyposis with more than 500-1000 adenomas and/or a germline mutation on the *APC* gene between codon 1250–1450 associated with a severe phenotype in FAP may also be indications to remove the rectum, since these patients are at highest risk of developing rectal cancer or undergoing secondary proctectomy [37,45].

Now that patients with FAP have a longer lifespan, subsequent abdominal surgical interventions may be needed by time. Sinha et al. found that half of FAP patients with IRA had undergone secondary proctectomy at age 60 due to rectal polyposis or cancer [37]. Although the exact risk is unknown, gradually more patients undergo pouch excision after IPAA mostly due to pouch polyposis not amenable to endoscopic management and rarely due to cancer [46]. This risk might increase over the forthcoming years since pouches get older overall and more patients present with extensive pouch polyposis. In these patients sometimes a new IPAA can be constructed but when there is insufficient small bowel length or poor sphincter function, patients will end up having a conventional end ileostomy or continent ileostomy.

Besides the risk of cancer and re-operation after colectomy, also other long-term outcome parameters should be taken into account when deciding on the type of surgery. An important aspect is the consequence on bowel function, urological function, sexual function, fertility and overall quality of life. A meta-analysis by Aziz et al. showed that patients with an IPAA have a higher daily stool frequency (3.8–8 versus 2–6.1), increased need for night defecation (44.1% versus 8.2) and higher risk of incontinence and use of incontinence pads than patients with an IRA. Contrarily, fecal urgency was reduced in patients with an IPAA [47]. Both procedures do not seem to induce urinary or sexual dysfunction [48–50]. One study showed that the fecundity of female FAP patients dropped significantly after IPAA while undergoing IRA did not influence fecundity [51]. Studies on the influence of both types of surgery on the overall quality of life report contrary results varying from studies showing no difference and studies showing that patients with IRA experience a better quality of life [50,52–55].

Abdominal surgery increases the risk of desmoids [56]. A meta-analysis by Xie et al. showed that the overall risk of developing desmoid tumours is not significantly different after IRA versus IPAA (9 versus 12%) [57]. However, most included studies did not adjust for known confounders such as mutation site, sex and family history. Both Vitellaro et al. and Saito et al. adjusted for confounders and found IPAA to be a risk factor for desmoid formation in multivariable analysis [58,59]. Moreover patients who underwent laparoscopic surgery were less likely to develop desmoid tumours [58]. Therefore, laparoscopic surgery for FAP might not only result in fewer complications and shorter hospital stay but it might also result in a lower risk of desmoid tumours, potentially due to less surgical trauma.

1.3. Endoscopic surveillance after colectomy

After colectomy, patients will have a gradually increasing burden of polyps in the retained rectum after IRA/ISA and in the pouch after IPAA, and thus remain at risk of developing cancer. As expected, the risk of developing adenomas is greater after rectum-sparing surgery. Whereas all patients after IRA will have rectal polyps, the 5, 10 and 15 year risks of developing adenomas in the pouch after IPAA are 7–16%, 35–42% and 75%, respectively [4,60]. Lifelong endoscopic surveillance remains of utmost importance to monitor disease progression, to resect lesions before they progress to cancer and to prevent more surgery. International guidelines recommend to perform half to three yearly surveillance depending on severity of polyposis of the rectum or pouch (Table 1) [26–28]. No clear indications are provided on choosing the right surveillance interval, potentially leading to over-as well as undertreatment. In general, polypectomy is performed for lesion greater than 5 mm. However, it might be preferred to resect smaller lesions located on places that are difficult to approach endoscopically, such as the remnant rectal cuff in patients with a pouch. Although pouch cancers are rare, a review on all reported carcinomas after IPAA showed that 75% of cases the cancer developed in the rectal cuff and in 25% in the pouch body itself, highlighting the importance of retroflexion and adequate assessment of this high risk area [61]. As in pre-colectomy endoscopic surveillance, cold snare polypectomy or EMR should be performed in the rectal remnant after IRA and in the pouch and rectal cuff after IPAA. Currently the use of a personalized endoscopic surveillance and intervention protocol for patients with FAP and IRA/ISA or IPAA is studied in a multi-center prospective study (NCT04678011). Albeit studies on the use of advanced imaging techniques after colectomy are scarce, the use of virtual or dye chromoendoscopy next to white light endoscopy seems to result in a more accurate assessment than the use of white light endoscopy alone [41].

1.4. Endoscopic surveillance of the duodenum

The life-time risk of developing duodenal adenomas approaches 100% in FAP compared to lower rates reported at 21% in MAP [62–64]. The prevalence of duodenal cancer is much lower however at 4–10% in FAP and 1% in MAP [64–68]. However, duodenal cancer has a poor

prognosis and it is one of the most important FAP-related causes of death [7]. Life-long endoscopic surveillance is recommended from age 20–25 years in FAP and 30–35 years in MAP and guided by Spigelman stage (Table 1) [26–28,63]. The goal is to prevent duodenal cancer and duodenal surgery. The Spigelman stage reflects the severity of duodenal polyposis and ranges from stage 0 to IV. The stage is based on both endoscopy as well as histopathology and includes the number, size and grade of dysplasia and villosity of adenomas. The Spigelman stage correlates with the risk of duodenal cancer with a risk up to 36% in patients with the most advanced Spigelman stage IV [62,69]. Over the past years, concerns are rising on the accuracy of the Spigelman staging system as a predictor for duodenal and especially ampullary cancer. Latchford et al. showed that in 11 patients with ampullary cancer, the mean Spigelman stage was II [70]. Another study by Thiruvengadam et al. showed that a Spigelman score of IV was found in 7 out of 9 patients with duodenal cancers and 2 out of 8 patients with ampullary cancer [71]. Identified risk factors for duodenal and ampullary cancer included a polyp or ampulla greater than 10 mm and high-grade dysplasia but not number of polyps or villosity. The aspect of the ampulla was not included in the original Spigelman staging system and therefore guidelines recommend an additional assessment of the ampulla [26–28]. To be able to calculate the Spigelman stage, histopathology is needed either gathered after polypectomy or biopsy. Taking biopsies of polyps can cause fibrosis potentially resulting in an inaccurate optical diagnosis and more difficult polypectomy in the future. Besides, gastric findings are not part of the current system while gastric adenomas are an increasing concern in patients with FAP. Currently, a newly developed personalized endoscopic surveillance and intervention protocol for duodenal and gastric polyposis in FAP is being studied prospectively (NCT04677998). The duodenal polyps in MAP do not seem to have the same genetic profile as in FAP: cancers may occur isolated or in a context of very low polyp burden (and consequently with a low Spigelman stage), with high-grade dysplasia encountered even in adenomas <10 mm [64]. In fact duodenal polyps in MAP have a higher rate of somatic mutations and may have a higher risk of cancer, independently of Spigelman stage [19]. These features clearly make the Spigelman staging system less useful in MAP and implies research to develop new scores and surveillance techniques to improve duodenal management in these patients.

Dye-spray chromoendoscopy has been proposed by some authors as a tool for improving the diagnostic yield in FAP and MAP patients, leading to an upstaging of the Spigelman stage but without known clinical outcomes [72–74]. Due to this lack of strong evidence, current guidelines do not suggest its routine use in endoscopic surveillance [72–74]. Virtual chromoendoscopy techniques such as narrow band imaging (NBI) might be a more accessible advanced imaging method and are widely used during endoscopic detection and characterization of polyps in FAP and MAP.

Patients with advanced duodenal polyposis are advised radical duodenal surgery to timely prevent duodenal cancer. However, nowadays the attention has shifted to prophylactic endoscopic polypectomies of duodenal polyps aiming to postpone or even prevent extensive surgery. Guidelines recommend to resect duodenal and ampullary adenomas when larger than 10 mm. Two studies showed that endoscopic duodenal polypectomy is effective for downstaging of the severity of duodenal polyposis, as incidence of cancer and duodenal surgery after polypectomies was low. The recurrence rate after duodenal polypectomy is substantial at 23% [75] thus surveillance is indicated. The complication risks of duodenal polypectomy are considerable: the risk of perforation is 2–3% and risk of delayed hemorrhage 13–20% [75,76]. In the study of Roos et al., delayed bleedings only occurred after resection of polyps greater than 20 mm. The cold snare EMR technique might result in reduced complication risks. In an exploratory study, ten patients underwent a total of 332 cold snare polypectomies of duodenal polyps ranging from 1 to 30 mm. One patient had an arterial bleeding during the procedure. No severe adverse events occurred [77]. However, this study mostly included small duodenal adenomas and did not report on the recurrence rate. Currently, two prospective studies investigate the outcomes after cold snare polypectomy in the duodenum in patients with FAP (NCT03471403, NCT04677998). Endoscopic papillectomy as a treatment of ampullary adenomas comes with even higher complication risks. Ramai et al. performed a meta-analysis of studies reporting on endoscopic papillectomy in FAP and found a perforation risk of 4% and bleeding risk of 9%. Furthermore, papillectomy results in a substantial (15%) risk of acute pancreatitis, although in 68% of procedures a prophylactic pancreatic stent was placed. Moreover, in 25% of those patients a recurrence was found during follow-up endoscopy [78]. A meta-analysis by Mendonca et al. compared endoscopic treatment of ampullary adenomas with surgical treatment in the sporadic setting and showed that recurrences were significantly more often found after endoscopic treatment (19% versus 6%). Complications occurred (non-significantly) more often after surgery (21% versus 43%) [79]. Management of ampullary adenomas should be carefully discussed within a multidisciplinary evaluation.

Sometimes large duodenal adenomas or adenomas with high-grade dysplasia are not amenable to endoscopic resection, for example due to their size or due to a difficult location. Thus, duodenal surgery should be considered for these cases. For single adenomas or when only one duodenal segment is affected, transduodenal excision of the lesion or segmental duodenal resection could be performed in which the ampullary area is preserved [80]. In case of diffuse duodenal polyposis, a total duodenectomy should be performed either by pancreas-preserving total duodenectomy (PPTD) including re-insertion of a single 'neo-ampulla' in the jejunum or pancreatoduodenectomy with separately hepatojejunostomy and pancreatojejunostomy. The clear advantage of PPTD is the preservation of the endocrine and exocrine pancreatic function on the long-term [81–83]. Severe post-operative complications are common, mainly due to pancreatic fistulas occurring in 14–40% of patients after PPTD [81,82,84–88]. Complications do not seem to occur more frequently after PPTD compared to pancreatoduodenectomy [81–83]. For duodenal or ampullary cancer, pancreatoduodenectomy should be performed providing an oncologic resection including adequate removal of lymph nodes.

1.5. Endoscopic surveillance of the stomach

The most commonly observed gastric lesions in FAP during endoscopy are fundic gland polyps which are found in 65–88% of patients. The risk of malignant transformation of these lesions seems to be very low. However, two reports showed fundic gland polyps contain low-grade dysplasia in 36–38% and high-grade dysplasia in 3%, and one case-reports described a gastric adenocarcinoma arising from a fundic gland polyp [89–91]. Probably clinically more relevant is the prevalence of gastric adenomas which may develop in the antrum as well as in the fundus and corpus. In a recent study in 726 patients with FAP, gastric adenomas were detected in 14% of patients with a median age at diagnosis of 47 [5]. In patients with MAP, gastric polyps are less common compared to FAP and found in 11% of patients 14]. Most of the gastric polyps encountered in MAP are fundic gland polyps (52.4%) and fewer are adenomas (24%).

In the past, western patients with FAP were not considered to be at an increased risk of developing gastric cancer [92,93]. In patients with MAP, a slightly higher rate of gastric cancer (2%) was observed compared to the general population, but this data was not statistically significant [94].

Mankaney et al. recently described a concerning increase in the number of FAP patients with gastric cancer [6]. In all the cases described, gastric cancer arose in the proximal stomach and within area of carpeting fundic gland polyposis. These polyps might lead to difficult identification of gastric cancer and the precursor lesions during endoscopy, highlighted by the worrisome fact that only 2/10 gastric cancers were endoscopically visualised [95]. Proximal gastric adenomas are mostly seen on top of fundic gland polyps and have a slightly lighter

colour and different pit pattern. Whether these adenomas can arise from fundic gland polyps or they develop in normal mucosa and grow on top of the surrounding fundic gland polyps, is something that needs to be further investigated. Narrow band imaging seems to help distinguishing adenomas from fundic gland polyps as the polyps become more white then the fundic gland polyps (Fig. 2) [96].

Histologically, gastric adenomas are divided into different types. The most common gastric adenomas in FAP are foveolar-type adenomas which seem to be solitary low risk lesions developing superficially on a normal background of gastric mucosa. Less commonly found are pyloric gland adenomas which develop from the glandular compartment in the corpus and fundus of the stomach and these lesions seem to be at higher risk of progressing into cancer [97]. Of 67 pyloric gland adenomas studied by Choi et al. 25% contained high-grade dysplasia, 7.5% intramucosal adenocarcinoma and 9% invasive adenocarcinoma [98]. Although never reported before in MAP, a pyloric gland adenoma has recently been described for the first time at the gastric body of a 59-year old MAP patient [99].

To date, there are no clear recommendations on when to resect gastric adenomas in FAP and the preferred technique. Martin et al. reported on 63 patients undergoing endoscopic resection of gastric adenomas and showed it was relatively safe with a 5% complication rate [5]. The recurrence rate was 3%, remarkably lower than the 23% recurrence rate after duodenal polypectomy [75]. In 5–14% of gastric adenomas, high-grade dysplasia is found and the median size of these lesions is 25 mm (range 7–50) [5,93]. Martin et al. advise to resect gastric adenomas when they are greater than 5 mm and the preferred endoscopic resection techniques in the stomach are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [5]. ESD could also be considered as non-invasive treatment for early gastric cancer demonstrating high R0 resection rates [100]. Gastric surgery is reserved for patients with more advanced gastric cancer or patients with too large or too many gastric adenomas not amenable to endoscopic treatment, or after (multiple) incomplete endoscopic resection(s).

1.6. Chemoprevention

As already stated, currently the gold standard for cancer prevention in FAP is prophylactic colectomy and endoscopic surveillance. In the last thirty years great attention has been raised by researchers on finding drugs capable of preventing CRC. Chemopreventive agents are natural or synthetic drugs that aim at reducing or delaying the risk of cancer by targeting cancer-development mechanisms. Hereditary syndromes are the ideal context for chemoprevention, because chemopreventive effects could have a greater impact in high-risk settings. Many clinically-relevant endpoints for chemoprevention in FAP have been indicated over the years: number of polypectomies, number of patients undergoing surgery, cumulative number of polyps >10 mm removed, duodenal cancer, decrease in the number of surveillance colonoscopies and number of patients needing polypectomies for polyps >10 mm [101]. Hereby we will discuss the studies reporting the chemopreventive agents tested so far in FAP.

1.6.1. Aspirin

Most recent ACG clinical guidelines on CRC screening suggest the use of aspirin for chemoprevention in the average risk population between 50 and 69 years old [102]. Unfortunately, large clinical trials on the use of aspirin in FAP are lacking. The largest one is the CAPP-1 study, in which 227 patients with intact colon were randomized to aspirin, aspirin plus resistant starch, resistant starch alone and placebo: there were no significant differences between the four groups in the number of polyps but a low significant difference ($p = 0.02$) was found in size reduction of the largest polyp among patients taking aspirin for more than 1 year [103]. Recently a new randomized controlled clinical trial (J-FAPP IV study) has enrolled 104 FAP patients with intact colon to test aspirin/mesalazine, aspirin/mesalazine placebo, mesalazine/aspirin placebo and placebo/placebo: low-dose aspirin reduced significantly the recurrence of polyps greater than 5 mm [104]. However, at the moment there is no sufficient evidence to recommend aspirin as a chemopreventive agent for FAP.

1.6.2. Selective Cox-2 inhibitors

Celecoxib and rofecoxib are the two most studied COX-2 inhibitors in FAP. The rationale of use is that the COX-2 enzyme has strong relationship with *APC* and wnt/β-catenin signaling and is upregulated in colonic cells in patients with polyposis syndromes: by inhibiting this pathway in *APC* knockout mice a reduction in polyp number was observed [105]. The use of celecoxib in FAP was firstly approved by EMA in 2000, following a clinical trial in which 77 FAP patients were administered celecoxib with a significant reduction in polyp number in a tattooed area of the colon [106]. Another trial evaluated the efficacy of celecoxib in FAP pediatric patients with a significant reduction in polyp number [107]. More recently, researchers have tested the association of celecoxib and eflornithine or difluoromethylornitine (DFMO). DFMO is a drug that irreversibly inhibits ornithine decarboxylase (ODC), an enzyme that is involved in the polyamine pathways and is overexpressed in adenomas and CRC. Combination between celecoxib and DFMO was tested in a randomized controlled trial. The trial terminated prematurely due to low recruitment. Unfortunately no significant differences were seen in polyp count (the primary endpoint) between the two arms, while the authors found a significant reduction of colonic polyp burden (a secondary endpoint), weighted by polyp's diameter, in the celecoxib plus DFMO arm [108]. Celecoxib was withdrawn in 2011 as chemopreventive agent for FAP due to cardiovascular safety concerns.

1.6.3. Sulindac

Sulindac is a NSAID with inhibitory effects on both COX-1 and COX-2 enzymes, and was one of the first chemopreventive agents tested in FAP. One of the first randomized placebo-controlled trials published in 1993 showed a reduction in polyp number and size after sulindac administration in FAP patients [109] but further trials failed to demonstrate a statistically significant benefit [110]. Because of unsuccessful results, researchers started to test combinations between Sulindac and other compounds. Erlonitib is an *anti*-EGFR drug approved for lung cancer and, since several studies have demonstrated that the *APC*$^{Min\ \pm}$ mice have upregulation of the EGFR signaling in colonic crypts, researchers

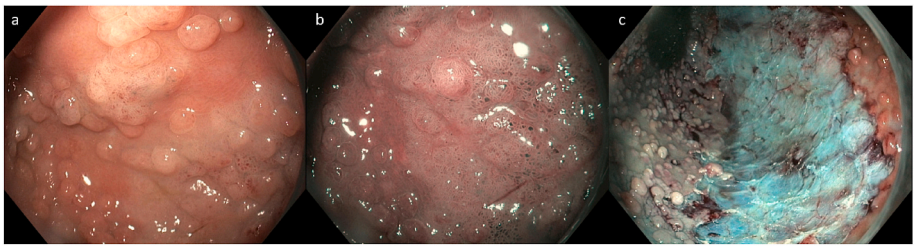

Fig. 2. A gastric adenoma in the corpus of the stomach carpeted with fundic gland polyps (a), best identified with narrow band imaging (b), resected with piecemeal EMR (c).

have introduced its use in FAP clinical trials in association with sulindac [111]. In the FAPEST trial 91 FAP patients were randomized to sulindac plus low-dose erlotinib versus placebo in order to assess differences in duodenal polyp burden at 6 months. The sulindac plus erlotinib arm showed a reduced duodenal burden and the post-hoc analysis showed a reduction in colorectal and pouch burden as well [112,113]. Unfortunately the study had several limitations: no information about the prevention of new adenomas was provided since the main outcome was to measure regression of already existing duodenal polyps; moreover no information about therapy durability or drug-resistance was provided since there was no long-term follow-up; finally the number of participants was limited and several adverse events were reported, notably an erlotinib-induced acneiform rash in 87% of patients and oral mucositis in 39.1%.

DFMO was firstly tested in association with Sulindac on 375 patients with sporadic colorectal polyps: the study showed a reduction in the recurrence of adenomas [114]. This association was tested for the first time in FAP in a recent randomized double-blind trial. The results showed that there was no significant difference in preventing upper and lower disease progression (defined as a composite of major surgery, endoscopic excision of advanced adenomas, diagnosis of high-grade dysplasia in the rectum or pouch, or progression of duodenal disease) between sulindac plus DFMO, sulindac alone and DFMO alone [115]. Following this trial, a post-hoc analysis was carried out in order to assess the efficacy of the sulindac plus DFMO combination in delaying disease progression in the lower gastrointestinal tract: an 80% risk reduction for disease progression was estimated in the combination therapy arm compared to monotherapy, while a 100% risk reduction was obtained only after censoring patients who underwent major polypectomies (>10 mm) [116].

1.6.4. Eicosapentaenoic acid (EPA)

The omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA), commonly found in fish oil, has resulted to have a great anti-tumorigenic activity in vitro due to its capacity of modulating colonic crypt cells turnover: EPA competitively binds to COX-2 enzyme producing pro-apoptotic and anti-inflammatory prostaglandins (notably PGE_3), thus reducing arachidonic acid metabolism, that it is supposed to have a pro-tumorigenic and pro-inflammatory activity [117]. Pre-clinical studies have demonstrated that an high purified form of EPA as free fatty acid (EPA-FFA) can lead to a dramatic reduction in polyp number in *APC*$^{Min/+}$ mice [118]. EPA-FFA 2 g/day has been tested for 6 months in patients with FAP and ileorectal anastomosis. A statistically significant reduction in number of polyps and polyp burden was found between the treatment and the placebo group within a specific target area of the rectum [119]. An ongoing randomized, double-blind, placebo-controlled trial is now testing 2 g EPA-FFA on FAP patients with ileorectal anastomosis for a longer period (24 months) (NCT03806426).

1.6.5. Rapamycin

Rapamycin (known as sirolimus) is a drug extensively used in transplant medicine as an immunosuppressor and has an inhibitory activity on mTOR (mammalian target of rapamycin). mTOR pathway is deeply involved in regulating cell division and cell proliferation and thus has a playing role in cancer development and progression [120]. Rapamycin has recently gained great attention for its immunomodulating activity at low dosage, that could be of interest for chemoprevention of patients with hereditary syndromes. In a case report two children with FAP and unwilling to undergo surgery for rectal bleeding were treated with low dosage of rapamycin obtaining reduction in size and grade of dysplasia of duodenal and colonic polyps, without reported side effects [121]. A recent pilot study on four FAP patients with ileorectal anastomosis and ileal pouch demonstrated a reduction in polyp number but was hampered by adverse events (notably diarrhea, fatigue, dyspnea, sexual disfunction and insomnia) [122].

1.6.6. Curcumin

Curcumin is a polyphenol compound derived from turmeric, a spice widely employed in traditional Asian medicine, with well-known antioxidant, anti-inflammatory and antiapoptotic effect. Furthermore, like DFMO, curcumin has the capacity of inhibiting the polyamine metabolism, thus potentially playing a role in slowing cancer development and progression [123]. In a pilot study, 5 FAP patients with ileorectal anastomosis and ileal pouch were treated with curcumin plus quercetin. Since curcumin is poorly absorbed in the gut, quercetin was used in order to increase curcumin absorption. After the treatment period all patients had a significant reduction in polyp number (−51%) and size (−60%) [124]. In a recent randomized, double-blind, placebo-controlled trial 44 FAP patients with either intact colon, ileorectal anastomosis and ileal pouch were randomized to a 12-months administration of 100% pure curcumin versus placebo. The authors found no significant differences in mean polyp number and size between the two groups [125].

Based on the available scientific literature, although in vitro and pre-clinical studies have shown a promising and convincing role of chemoprevention in FAP management, strong clinical results are still lacking. Therefore no recommendations on chemoprevention can be provided to FAP and MAP patients. Further large trials, with well-predefined outcomes, must be conducted in order to gain more clinical evidence.

1.7. Practice points

- The combination of prophylactic colectomy and frequent life-long endoscopic surveillance of the lower and upper gastrointestinal tract is the cornerstone in the management of familial adenomatous polyposis (FAP)
- Compared to FAP, *MUTYH*-associated polyposis (MAP) is characterized by a low polyp burden, right-sided disease, later onset of CRC, isolated CRC and occurrence of hyperplastic/serrated polyps as well as adenomas. Surveillance and preventive polypectomies are indicated; colectomy is not always necessary.
- For patients with FAP and MAP with rectum-sparing disease, a (sub) total colectomy with ileorectal or ileosigmoidal anastomosis followed by aggressive endoscopic surveillance is the procedure of choice resulting in favorable bowel function.
- The Spigelman staging system is not a very accurate predictor for duodenal and ampullary cancer and has several other limitations. Surveillance intervals for upper gastrointestinal disease should be determined based on severity of both duodenal and gastric polyposis. During surveillance endoscopies, polypectomy should be performed of relevant lesions to prevent cancer and surgery.
- Gastric adenomas and gastric cancer are increasingly diagnosed in patients with FAP, highlighting the importance of meticulous endoscopic inspection of the stomach including the use of advanced imaging techniques such as narrow band imaging to identify dysplastic lesions.
- In MAP, metachronous lesions of colorectum and duodenum, driven by a potentially accelerated carcinogenesis and a high mutational burden, are not uncommon and post-surgery endoscopic surveillance must be careful.
- There is no robust evidence that currently available chemoprevention agents are able to significantly reduce polyp burden.

1.8. Research agenda

- Large multicenter studies on the long-term outcomes after different types of colectomy and the influence of minimally invasive surgery to better guide surgical decision making.
- Large multicenter study investigating the efficacy and safety of an up-to-date surveillance protocol for the lower as well as upper gastrointestinal tract.

- Studies on the efficacy and safety of different endoscopic resection techniques in the duodenum and stomach.
- Studies on identifying the precursor lesions of gastric cancer in FAP.
- Studies on new chemopreventive agents with the goal of reducing polyp burden and polypectomies, delaying surgical interventions and increasing the quality of life.

2. Summary

Although developments in endoscopic surveillance and chemoprevention, prophylactic colectomy remains necessary in FAP and sometimes in MAP to prevent colorectal cancer. It remains challenging to decide on the right timing and type of colectomy. Whereas in the past proctocolectomy was the preferred procedure for FAP in most centers, there seems to be a shift towards a preference for rectum sparing surgery (as usually performed in MAP) followed by aggressive endoscopic surveillance to maintain acceptable bowel function. This organ-sparing approach is also applicable for upper GI management in which endoscopic polypectomy seems promising for postponing or preventing cancer and surgery. In line with this development, chemoprevention might help in reducing interventions. Although some agents showed slightly promising results, the quest for an effective medical therapy is going on.

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