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Guidelines

Definition and management of colorectal polyposis not associated with *APC/MUTYH* germline pathogenic variants: AIFEG consensus statement

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ABSTRACT

An expert consensus panel convened by the Italian Association for Inherited and Familial Gastrointestinal Tumors (*Associazione Italiana per lo Studio della Familiarità ed Ereditarietà dei Tumori Gastrointestinali*, AIFEG) reviewed the literature and agreed on a number of position statements regarding the definition and management of polyposis coli without an identified pathogenic mutation on the *APC* or *MUTYH* genes, defined in the document as NAMP (non-*APC/MUTYH* polyposis).

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1. Introduction

Hereditary colorectal cancer (CRC) syndromes are characterized by a lifetime increased risk of developing colorectal tumors. These syndromes are classified into polyposis and non-polyposis variants according to the number and histology of the colorectal polyps. Familial adenomatous polyposis (FAP) is a polyposis syndrome characterized by the early onset of hundreds to thousands of colon adenomas. Patients have *a* >90% lifetime risk of developing CRC associated with less frequent duodenal adenomas, desmoid tumors and other extracolonic manifestations. The majority of patients showing this "classic" phenotype carry germline pathogenic variants (GPVs) on the *APC* gene.

APC is a tumor fackrowor gene located on chromosome 5q22; it encodes a protein that negatively regulates the expression of beta-catenin. *APC*-associated polyposis is inherited in a dominant manner, with virtually complete penetrance [1–4].

Around 10% of polyposis cases with no identified mutation in *APC* carry biallelic GPVs in *MUTYH*. The MUTYH protein is a base excision repair protein that corrects oxidative DNA damage. *MUTYH*-associated polyposis (MAP) is an autosomal-recessive disorder characterized by a lower polyp burden, rarely exceeding 100 polyps [5,6].

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Some polyposis syndrome cases remain genetically unexplained despite increasing knowledge of the syndromes and advanced molecular diagnostics (gene sequencing, multiplex ligation-dependent probe amplification [MLPA], multigene panel testing and tissue analysis for mosaicism assessment). These unclassified cases lead to uncertainties in establishing proper clinical management and risk evaluation for family members. This is especially true for the attenuated forms of polyposis [7–9].

Recently a polyposis coli milder than classical FAP is being observed with increasing frequency. It is characterized by the presence of 10 or more (but fewer than 100) colorectal polyps, mostly in middle-aged individuals. The polyps tend to occur in a single segment of the large bowel, often the proximal colon. This form is associated with an increased – though not yet fully quantified – risk of CRC [10–12].

At the moment there is a lack of epidemiological data on milder polyposis forms. However, a recent CRC screening study in the UK reported that 1% of colonoscopies show 10 or more synchronous polyps [13]. According to this study, attenuated polyposis could be a major clinical condition predisposing to CRC with a greater incidence than other known forms of polyposis. This is of great clinical relevance. However, the heterogeneity of clinical, endoscopic, histological and biological criteria used for the diagnosis of milder polyposis has resulted in impractical and complex classifications that prevent shared clinical practice, surveillance and treatment.

Moreover, in only a small fraction of patients with mild polyposis was an association found with GPVs in *APC* or *MUTYH*, and the detection rate of these GPVs was directly related to the number of polyps and inversely related to the age of disease onset [14].

The attenuated form of polyposis associated with pathogenic *APC* variants is defined as A-FAP, while the form associated with pathogenic biallelic *MUTYH* variants is defined as MAP.

Moreover, GPVs of recently discovered CRC genes (*POLE*, *POLD1*, *NTHL1*, *MSH3* and *GREM1*) account for very rare cancer families and are unlikely to significantly contribute to attenuated polyposis cases [15–18]. Most *APC*/*MUTYH* mutation carriers with attenuated polyposis do not differ from individuals with genetically unexplained attenuated forms in terms of clinical features (symptoms, polyp localization, development of malignant tumors and surgical treatment). However, in some surveys, patients with identified genetic lesions, especially on *APC*, have been reported to have an earlier age at diagnosis [10,14,19–21].

The aim of this consensus document is to standardize the definition, diagnosis and treatment strategy of the attenuated forms of adenomatous polyposis coli with no identified *APC*/*MUTYH* pathogenic variants (NAMP).

2. Methods

The Italian Association for Inherited and Familial Gastrointestinal Tumors (*Associazione Italiana per lo Studio della Familiarità ed Ereditarietà dei Tumori Gastrointestinali*, AIFEG) is a multidisciplinary association of professionals who study inherited conditions at high risk for the development of gastrointestinal tumors. AIFEG is composed of molecular biologists, pathologists, geneticists, gastroenterologists, oncologists, surgeons, psychologists and nurse researchers.

The advisory board of the association commissioned a panel of 7 experts in different specialties (the NAMP Committee) to perform a comprehensive literature search and review the most relevant publications in order to clarify the biological and clinical definition, diagnosis and management of polyposis coli without *APC* and *MUTYH* pathogenic variants. The NAMP Committee reviewed the literature published before May 31st 2019 and drafted a document on the state of the art as a collection of statements.

International guidelines were consulted in the development process of this position paper [22–24]. If no publications on a specific topic were available, a statement reflecting an expert opinion was drafted. Levels of evidence and grades were assigned to the recommendations according to internal validity protocols (such as the National Program of Guidelines of the Italian Institute of Health [25]) and external validity protocols [26–28] (Table 1). After the paper was revised and approved by the NAMP Committee, it was emailed to all AIFEG members before the association's annual meeting held in October 2019 in Padua (Italy). The paper was presented to the audience and amended, if needed, based on the audience's suggestions. A statement was approved when consent was achieved by more than 70% of the voting members (77 in total).

The recommendations were formulated in order to provide grades and levels of evidence on NAMP for the following aspects: 1) definition; 2) genetic counseling; 3) genetic-molecular definition of NAMP; 4) cases of uncertainty; 5) genetic heterogeneity of NAMP; 6) endoscopic diagnosis; 7) risk of invasive carcinoma; 8) management; 9) endoscopic management/follow up; 10) surveillance of the proband; 11) chemoprevention; 12) lifestyle; 13) surgery; 14) surveillance of first-degree relatives (father, mother, siblings, children) of a patient with NAMP; 15) revision of the document.

3. Results

3.1. Definition

This paper focused on colorectal polyposis with conventional adenoma as the prevalent histological type. Cases with a total number of synchronous polyps greater than 10 and without GPVs on *APC* or *MUTYH* were included. Serrated polyposis and hamartomatous polyposis were excluded. Polyposis without an identified pathogenic mutation on *APC* or *MUTYH* was defined as non-*APC*/*MUTYH* polyposis or NAMP.

Level 6, Grade A [*Statement voted*]

3.2. Genetic counseling

Genetic counseling should be offered to all patients with more than 10 synchronous adenomas.

Level 2, Grade A

3.3. Genetic-molecular definition of NAMP

APC and *MUTYH* pathogenic variants, independent of family history (negative or positive for polyposis; dominant or recessive inheritance), should be excluded using 1) complete sequencing testing of the exons and splicing sites, possibly with next-generation sequencing (NGS) or other validated methods; 2) testing for deletion/duplication (e.g. MLPA assay or NGS-validated methods for copy number variation detection in the coding and promoter sequence).

Level 2, Grade A

In sporadic cases of suspected FAP, the possibility of an *APC* somatic mosaicism should be evaluated through the analysis of DNA extracted from the polyps and the adjacent intestinal mucosa.

[*Sentence voted for the necessity of including the evaluation of somatic mosaicism.*]

All cases that are not solved/confirmed by the above analyses should be defined as NAMP.

Level 6, Grade A

3.4. Cases of uncertainty

The definition of NAMP has limits because of the limited knowledge of this type of polyposis. It is still debated how we should

Table 1
Level of evidence and grade of recommendations (adapted from the Italian Program of Guidelines of the Istituto Superiore di Sanità in accordance with international guidelines).

Level of evidence	
Level 1	Data derived from meta-analyses or systematic reviews or from (multiple) randomized controlled trials with high quality
Level 2	Data derived from a single randomized controlled trial
Level 3	Data derived from multiple non-randomized studies
Level 4	Data derived from retrospective observational studies or case–control studies
Level 5	Data derived from case series studies without control groups
Level 6	Data derived from expert opinions or consensus conference
Grade of recommendations	
A (strong)	Strong recommendation: factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes and cost
B (weak)	Weaker recommendation: variability in preferences and values, or more uncertainty
C	The existing evidence is conflicting and does not allow a recommendation to be made for or against the use of the action; however, other factors may influence decision-making
D	There is fair evidence to recommend against the action
E	There is good evidence to recommend against the action

consider and treat patients with *APC* variants of uncertain significance (VUS) or carriers of 2 *MUTYH* variants (one pathogenic and one VUS) where NAMP cannot be formally diagnosed. Moreover, in the case of a monoallelic *MUTYH* variant (i.e. only one heterozygous pathogenic or likely pathogenic variant) it cannot be excluded that the second pathogenic variant was missed by the analysis because it was not detectable by the performed tests.

Level 6, Grade A

3.5. Genetic heterogeneity of NAMP

Besides *APC* and *MUTYH*, other genes are known to have high/medium penetrance for adenomatous or mixed polyposis. The mutation frequency of these genes is low (around 2%) but not negligible [15,17,18,29].

The known/validated genes and associated phenotypes are:

- *POLE* (heterozygous mutation in proofreading domain): attenuated or oligoadenomatous polyposis and CRC
- *POLD1* (heterozygous mutation in proofreading domain): attenuated or oligoadenomatous polyposis and CRC
- *NTHL1* (biallelic mutation): attenuated adenomatous or mixed polyposis and CRC and extracolonic malignancies
- *MSH3* (biallelic mutation; very rare): adenomatous polyposis and CRC; elevated microsatellite alterations at selected tetranucleotide repeats-EMAST phenotype
- *GREM1* (heterozygous promoter duplication): adenomatous, hyperplastic and juvenile polyps
- Mismatch repair (MMR) genes (*MSH6*, *PMS2*, *MLH1*, *MSH2*; biallelic mutations; MSI phenotype): young age, oligoadenomatous polyposis and tumor spectrum of constitutional MMR-deficiency syndrome.

Analysis of these genes, singularly or in a gene panel, should not be considered standard management in NAMP patients.

Level 6, Grade A [*Statement voted*]

However, analysis of *POLE, POLD1, NTHL1, MSH3* and *GREM1* is beneficial and may become a clinical standard in the management of NAMP in the near future.

Level 6, Grade B

3.6. Endoscopic diagnosis

Endoscopic procedures for the diagnosis of colorectal adenomatous polyposis should include the following:

- High-definition endoscopy, with the possibility of electronic chromoendoscopy
- Good intestinal preparation: Boston Bowel Preparation Scale (BBPS) score >2 in all segments (proximal, transverse and distal colon) [30]
- Highly accurate polyp counting, dividing the colon into the following segments: cecum, ascending colon (from cecum to hepatic flexure); transverse colon; distal colon (from splenic flexure to upper rectum); rectum (15 cm from the anal verge)

Level 2, Grade A

A recorded video or thorough collection of electronic images of the whole colonoscopy should be available [31].

Level 5, Grade A

If no adequate video or images from the colonoscopy are available, it may be useful to repeat the colonoscopy at a secondary center of digestive endoscopy within 6 months of the first diagnosis.

Level 6, Grade B [*Statement voted*]

Polyps greater than 5 mm should be removed and analyzed in one or more endoscopic sessions until surgical resection is planned.

Level 2, Grade A

3.7. Risk of invasive carcinoma

The risk of CRC is high, even if not measurable. The high risk of invasive carcinoma should be taken into account in the clinical decision.

Level 6, Grade A

3.8. Management

After NAMP is diagnosed, the decision towards endoscopic versus surgical treatment should be made after multidisciplinary evaluation of the case. The multidisciplinary group should include at least geneticists, gastroenterologists/endoscopists and surgeons. Chromoendoscopy with indigo-carmine dye may be carried out before completing the decision process to quantify the extent of polyposis throughout the colon [32].

Level 6, Grade A [*Statement voted*]

Treatment decision-making should consider the following criteria:

- Number of polyps
- Size and location of the largest polyps
- Number of colon segments involved by polyposis
- Grade of dysplasia in the polypectomy specimen
- Family history of CRC
- Patient's age
- Patient's health status

- Patient's compliance with multiple operative endoscopic sessions
- Patient's awareness of high CRC risk

Level 6, Grade A

The multidisciplinary evaluation should have a formal setting: the involved specialists and the final decision should be clearly identified on an electronic (digitally signed) or paper document.

Level 6, Grade A

3.9. Endoscopic management/follow-up

If the multidisciplinary team decides on an endoscopic approach, resection of all non-diminutive polyps (≥5 mm) should be planned in one or more endoscopic sessions.

Level 3, Grade A

The need for several colonoscopies at intervals of 6 months or less could indicate a low efficacy of the endoscopic approach.

Level 6, Grade A

3.10. Surveillance of the proband

After resection of all non-diminutive polyps, annual colonoscopy may be planned. Chromoendoscopy with indigocarmine dye may be performed to improve the detection of non-diminutive polyps [32].

Level 6, Grade B

The interval between 2 colonoscopies should not exceed 3 years even when a clear colon has been achieved.

Level 6, Grade A

Esophagogastroduodenoscopy (EGD) may be planned at the time of polyposis diagnosis and should be repeated every 5 years if no gastroduodenal polyps are found at the first examination. A side-view upper endoscopy may be planned to exclude a misdiagnosis of ampullomas if gastroduodenal polyps are found at the first EGD. Endoscopic resection should be performed in the case of duodenal adenomas/ampullomas, and follow-up should be planned according to Spigelman's classification [33].

Level 5, Grade B

Surveillance should be stopped at the most advanced age possible, taking into account such factors as a family history of CRC, comorbidities and compliance with endoscopic follow-up.

Level 6, Grade A

3.11. Chemoprevention

Acetylsalicylic acid or celecoxib may be considered as part of NAMP treatment (in the absence of contraindications; Level 6, Grade B) but their use should not represent an alternative to standard endoscopic/surgical management.

Level 6, Grade A [*Statement voted*]

3.12. Lifestyle

Patients may be invited to observe the WCRF/AICR recommendations for cancer prevention (https://www.wcrf.org/dietandcancer/cancer-prevention-recommendations). These include:

- Have a healthy weight
- Be physically active
- Eat wholegrains, vegetables, fruit and beans
- Limit "fast foods"
- Limit red and processed meat
- Limit sugar-sweetened drinks
- Limit alcohol consumption
- Do not rely on oral supplements for cancer prevention

Level 1, Grade B

3.13. Surgery

Surgery should be considered in case of a diagnosis of invasive carcinoma or in the presence of diffuse polyposis or non-diminutive polyps during endoscopic follow-up.

Level 3, Grade A

Surgery may be considered in case of a diagnosis of high-grade dysplasia in small polyps without alarming endoscopic features.

Level 6, Grade B [*Statement voted*]

Endoscopic management of polyposis requires frequently repeated colonoscopies (every 3/6 months).

Level 6, Grade B [*Statement voted*]

The surgical procedures include:

- Proctocolectomy with ileal pouch-rectal anastomosis (above the anal canal) when a carcinoma is diagnosed in the rectum (in which case neoadjuvant radiotherapy and/or chemotherapy can be considered for locally advanced rectal cancer) or when the polyposis develops in both colon and rectum.
- Rectum-sparing total colectomy when there is no evidence of carcinoma in the rectum and the polyps cannot be removed in all colon segments. Non-diminutive rectal polyps must be endoscopically removed for histological evaluation before a colectomy with ileorectal anastomosis is planned.
- Segmental colectomy (e.g. right hemicolectomy, transverse colon resection, left hemicolectomy, sigmoidectomy) maybe considered in the presence of polyps and/or carcinoma concentrated in a single colon segment, especially in patients at an advanced age or with comorbidities that could be harmful in the case of a total colectomy.

The patient should be adequately informed about the risk of developing polyposis and metachronous carcinoma in the preserved colon segments.

Minimally invasive surgery (laparoscopic or robotic resection) should be planned whenever possible.

Level 6, Grade A [*Statement voted*]

3.14. Surveillance of first-degree relatives (father, mother, siblings, children) of a patient with NAMP

Endoscopic surveillance of first-degree relatives must fulfill high-quality endoscopic criteria including complete large bowel visualization, high-definition endoscopy with the possibility of electronic chromoendoscopy, and good intestinal preparation (BBPS score >2 in all colon segments) [10].

First-degree relatives of patients with NAMP and a FAP-like phenotype should be followed up with colonoscopy at 14 years of age, repeated every 5 years if no polyps are found [22].

The surveillance of first-degree relatives of patients with mild forms of NAMP should be as follows:

- The first colonoscopy should be suggested around age 35, or 10 years earlier than the age of polyp appearance in the proband.
- The interval time between 2 colonoscopies mustnot exceed 5 years in the case of a clear colon (optimal range 3–5 years).
- EGD should be suggested at age 40 and could be repeated every 5 years if there is a history of gastric/duodenal carcinoma or polyposis in the family.
- Surveillance should be stopped at the most advanced age possible, taking into account such factors as a family history of CRC, comorbidities and compliance with colonoscopy.

Level 6, Grade A [*Statement voted*]

3.15. Revision of the document

The consensus document should be revised after 2 years.

Level 6, Grade A

4. Discussion

Non-*APC/MUTYH* polyposis, especially with fewer than 100 polyps and a late age of onset, is becoming an entity of great clinical interest. Despite the frequency of this form, few data are available on its genetic background, surveillance protocols for the proband and family members, and optimal treatment. After an extensive review of the literature, AIFEG has drawn up a systematic road map, discussed by a multidisciplinary team of experts, to create a solid base for the definition and standardization of NAMP. The aim of the present paper is to provide sound, homogeneous definitions and surveillance/treatment protocols in order to improve the treatment of NAMP.

The British Society of Gastroenterology (BSG) together with the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the United Kingdom Cancer Genetics Group (UKCGG) recently published guidelines for the management of hereditary CRC [22]. One chapter discusses NAMP, defining it as "multiple colorectal adenomas". The document served as a cornerstone for the present consensus because it showed the necessity to clarify definitions and standardize the surveillance and treatment of NAMP. Moreover, the UK guidelines did not consider many aspects of NAMP, hence the need for detailed statements on this entity as provided by the present consensus.

4.1. Definition

The number of 10 polyps, even though arbitrary, is a widely accepted cut-off in the literature [34]; however, there is discussion as to whether it should be considered synchronous or metachronous. The majority of AIFEG members agreed that including in the definition of NAMP cases of 10 or more polyps detected in consecutive colonoscopies was not cost-effective and not practical for standardizing a NAMP protocol.

Considering that in polyposis coli not all polyps are removed (e.g. diminutive polyps may be left behind), it seemed more practical and clinically useful to refer to NAMP as "polyposis with mainly adenomas" rather than define an adenoma/non-adenoma ratio. It is important to exclude criteria for serrated polyposis (in which synchronous adenomas can be seen), even if a number of 10 synchronous adenomas is very rare in this condition [35].

The name to be given to the polyposis was long discussed before a shared definition was achieved. Non-*APC/MUTYH* polyposis was chosen because "multiple colorectal adenomas" is a merely phenotypic definition that does not exclude patients with *APC* and *MUTYH* pathogenic variants.

4.2. Genetic counseling

Our research had a dual aim: 1) to help clinicians in the management of NAMP and, 2) to be a starting point for future improvements.

In a large US study [14] the incidence of *APC* and *MUTYH* pathogenic variants was reported to be 9% in the group with 10–19 polyps and 17% in the group with 20–99 polyps, while in a recent Dutch study the overall detection rate was above 10% for patients with >10 adenomas aged <60 years [36].

The AIFEG members agreed that at the moment a low mutation detection rate is acceptable when defining a NAMP, especially in cases with few polyps. Much work needs to be done to collect information on pathogenic variant types, genotype/phenotype correlations and cancer risk, especially in patients with mild polyposis and late age at onset compared to classic FAP.

4.3. Molecular definition of NAMP

This is considered the core of the consensus, because it states for the first time the minimum analyses required to exclude an *APC* or *MUTYH* pathogenic variant to define NAMP. There was discussion regarding the need to check for somatic *APC* mosaicism in specific cases such as sporadic younger patients or those with a high polyp count.

The requirement of good-quality DNA from multiple biopsies may limit the implementation of this testing strategy because of the difficulty in retrieving biological samples of more than one polyp and of non-polyposis mucosa, along with the complexity and low reproducibility of the analytical method. However, the literature provides several examples indicating the relevance of mosaicism in patients with unexplained polyposis coli.

A weak positive recommendation was agreed on, considering the few cases concerned, the few well-equipped and experienced laboratories capable of analyzing somatic *APC* mosaicism, and the accuracy of available tests in excluding *APC* involvement [37–39].

4.4. Genetic heterogeneity of NAMP

Deficiencies in the *POLE, POLD1, NTHL1* and *GREM1* genes are causes of polyposis coli and CRC, although their GPV rate, both in diffuse polyposis and oligopolyposis, is very low. The literature on clinical management is sparse. A weak recommendation was agreed upon to consider the analysis of these genes as standard clinical practice at the moment. The genetic paneling that was suggested as good clinical practice by the UK guidelines [22] cannot be considered essential in the standard of care of polyposis patients.

There was also discussion about the role of immunohistochemical (IHC) staining for MMR proteins (MLH1, PMS2, MSH2 and MSH6) in retrieved adenomatous polyps. Although the general consensus is in favor of universal screening of CRC with MMR IHC examination, its value in colorectal adenomas, even in Lynch syndrome families, is still uncertain. The AIFEG members agreed that the low sensitivity of IHC staining in adenomatous tissue, in particular with low dysplasia, can lead to misdiagnosis, and IHC examination should therefore not be considered a standard for NAMP patients. In addition, some sporadic adenomas may occur in patients with Lynch syndrome. For these reasons, universal IHC screening of adenomas in patients <50 years may not be an effective strategy for detecting potential Lynch syndrome [40–43].

4.5. Risk of colorectal cancer

The risk of CRC for NAMP patients is high but difficult to assess because of the different inclusion criteria in the few available studies. With the exception of Tieu et al., who reported only 2 CRC cases among 27 NAMP patients in their series [20], CRC rates have been found to exceed 40% of NAMP patients [10,21].

4.6. Endoscopy

The best treatment for NAMP patients with a FAP-like phenotype and a good health status is surgery. Treatment of NAMP with a mild phenotype can be either endoscopic or surgical depending on several factors. Less invasive treatment should always be preferred, with surgery being indicated only when the CRC risk cannot be managed by the endoscopic approach. Every NAMP patient with a mild phenotype should undergo a multidisciplinary evaluation so that the best treatment strategy can be chosen on the basis of the estimated CRC risk. The formal setting of a multidisciplinary approach is preferred because it confers reliability and traceability on the decision process.

Because of the need for a multidisciplinary evaluation and because the findings of the index colonoscopy are the cornerstone of the first treatment decision, a precise description of the polyposis and a complete image collection or film of the examination should be obtained. If images or film are not available or not exhaustive for the multidisciplinary consultation, colonoscopy should be repeated after a short interval, preferably in an endoscopy referral center. This indication was included as a weak recommendation because it is known that colonoscopy is invasive and time-consuming for patients and caregivers, with expenses for the health care system.

The primary aim of the endoscopic approach is to clear the colon of polyps larger than 5 mm. The rationale is that larger polyps are associated with a higher probability of high-grade dysplasia [44] and the risk of CRC is very low in diminutive polyps [45]. This goal can generally be reached with several consecutive endoscopy sessions. The total number of non-diminutive polyps following these polypectomies has to decrease significantly after every intervention. Surgery should be indicated if no trend toward a clear colon is observed.

When endoscopy is successful in managing the CRC risk and all non-diminutive polyps are removed, caution is warranted because follow-up data on NAMP are currently lacking. Since NAMP is a clinically heterogeneous condition at a high risk of CRC, we consider yearly colonoscopy a cautious recommendation. An interval between colonoscopies exceeding 3 years was strongly advised against. It is reasonable to expect that further data can be collected in the future to allow stratification of NAMP patients according to the CRC risk for follow-up optimization.

EGD is indicated for NAMP probands because of the evidence of a higher rate of duodenal adenomas and fundic gland polyps in these patients [20] like in those with *APC* and *MUTYH*-mutation-related polyposis. However, considering the small risk reported for advanced upper gastrointestinal tumors and the absence of robust data, the suggested follow-up interval is longer than for FAP or MAP.

A recommendation to stop endoscopic surveillance the latest possible was assessed for both probands and family members. Even if the median age of NAMP patients is in the 5th decade, cases >70 years with CRC have been reported [10,21,46], the CRC risk increasing with age.

4.7. Chemoprevention

Although no chemoprevention studies have been carried out in NAMP patients, it was assumed that the results obtained for FAP are adequate for a weak positive recommendation in favor of chemoprevention [47] if there are no contraindications to NSAIDs. The consensus was for a strong recommendation to not consider chemoprevention as an alternative to endoscopic surgical management.

4.8. Surgery

Surgery is the most important treatment for patients with polyposis coli, whether the classic FAP phenotype or mild forms. The majority of cases in reported NAMP series underwent segmental or extended surgical resection [10,20,21].

AIFEG emphasizes that only invasive CRC and diffuse polyposis are strong indications for surgery. In cases of mild phenotypes the surgical indication should be assessed after a new endoscopic evaluation at an experienced center and on the basis of multidisciplinary consensus. The AIFEG forum introduced 2 weak positive recommendations for surgery: 1) an unexpected diagnosis of high-grade dysplasia after excision of small polyps without critical features, and 2) the failure of several endoscopic sessions to control non-diminutive adenomas.

AIFEG agreed that the type and extension of surgery should be tailored to the individual patient in order to limit the extent of resection and invasiveness as much as possible. Therefore, a proctocolectomy is recommended only in case of diffuse polyposis in the colon and rectum, or rectal cancer and diffuse polyposis in the colon. Resection of the rectum may be avoided by means of endoscopic removal of non-diminutive rectal adenomas before surgery. As already reported in some series of mild polyposis coli [10,11,21], a segmental resection can be considered adequate if the polyposis is concentrated in one colonic segment and the remaining colon can be managed endoscopically.

It is very important to involve NAMP patients in the decision-making process and to make them aware of the pros and cons of endoscopic and surgical management, as in the case of segmental versus extended resection. In particular, NAMP patients must fully understand the need for continuous surveillance of the spared rectum or colon for invasive CRC.

The strong recommendation for minimally invasive surgery was prompted by the evidence that laparoscopic resections are oncologically as adequate as open surgery [48] and that minimally invasive surgery for polyposis is associated with better short-term outcomes and fewer complications [49,50].

4.9. Surveillance of first-degree relatives of a patient with NAMP

The recommendations were grounded in these considerations:

- NAMP is a condition at high risk of CRC with an unknown genetic cause, and surveillance of first-degree relatives cannot be optimized by the result of genetic testing in the proband.
- The median age at diagnosis of probands is in the 5th decade, but many NAMP patients are diagnosed before age 40.
- The primary aim of surveillance is early recognition and treatment of an at-risk condition.
- In patients at high risk of CRC without an identified disease-causing mutation (e.g. families that fulfill the Amsterdam criteria with cancer probands that are wild type for MMR genes), relatives of probands undergo follow-up every 5 years starting at 40 years of age [22].

AIFEG considered it reasonable to suggest that colonoscopy for first-degree relatives of NAMP patients be started at 35 years of age, or 10 years before the diagnosis of polyposis in the proband, with follow-up intervals not exceeding 5 years. Upper gastrointestinal tract surveillance was suggested by analogy with other types of polyposis coli, with a weak recommendation that is reinforced in the case of familiarity for upper gastrointestinal polyps or cancer.

4.10. Future planning

This consensus document is a starting point for standardized data collection on NAMP. AIFEG will shortly provide its centers with a centralized database for NAMP. Data collected in the next 2 years, taking this consensus document as a template, will be used to revise these recommendations.

Declaration of Competing Interest

None declared

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