

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2023 November 15; 15(11): 1835-2048



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- 1951** Identification of necroptosis-related lncRNAs for prognosis prediction and screening of potential drugs in patients with colorectal cancer  
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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

**INDEXING/ABSTRACTING**

The WJGO is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJGO as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Oncology*

**ISSN**

ISSN 1948-5204 (online)

**LAUNCH DATE**

February 15, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Monjur Ahmed, Florin Burada

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

**PUBLICATION DATE**

November 15, 2023

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

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Retrospective Study

# MUTYH-associated polyposis: Is it time to change upper gastrointestinal surveillance? A single-center case series and a literature overview

Lupe Sanchez-Mete, Lorenzo Mosciatti, Marco Casadio, Luigi Vittori, Aline Martayan, Vittoria Stigliano

**Specialty type:** Oncology

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Serban ED, Romania;  
Yuan Y, China

**Received:** February 13, 2023

**Peer-review started:** February 13, 2023

**First decision:** April 25, 2023

**Revised:** May 28, 2023

**Accepted:** June 13, 2023

**Article in press:** June 13, 2023

**Published online:** November 15, 2023



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## Abstract

### BACKGROUND

The presence of Spigelman stage (SS) IV duodenal polyposis is considered the most significant risk factor for duodenal cancer in patients with *MUTYH*-associated polyposis (MAP). However, advanced SS disease is rarely reported in MAP patients, and no clear recommendations on small bowel (SB) surveillance have been proposed in this patient setting.

### AIM

To research more because that case reports of duodenal cancers in MAP suggest that they may develop in the absence of advanced benign SS disease and often involve the distal portion of the duodenum.

### METHODS

We describe a series of MAP patients followed up at the Regina Elena National Cancer Institute of Rome (Italy). A literature overview on previously reported SB cancers in MAP is also provided.

### RESULTS

We identified two (6%) SB adenocarcinomas with no previous history of duodenal polyposis. Our observations, supported by literature evidence, suggest that the formula for staging duodenal polyposis and predicting risk factors for distal duodenum and jejunal cancer may need to be adjusted to take this into account rather than focusing solely on the presence or absence of SS IV disease.

## CONCLUSION

Our study emphasizes the need for further studies to define appropriate upper gastrointestinal surveillance programs in MAP patients.

**Key Words:** *MUTYH*-associated polyposis; Duodenal adenomatosis; Duodenal cancer; Endoscopic management; Case report

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**Core Tip:** Case reports of duodenal cancers in *MUTYH*-associated polyposis suggest that they may develop in the absence of advanced Spigelman stage (SS) benign disease and often involve the distal portion of the duodenum. In our case series, we identified two (6%) small-bowel adenocarcinomas with no previous history of duodenal polyposis. Our observations, supported by literature evidence, suggest that the formula for staging duodenal polyposis and predicting risk factors for distal duodenum and jejunal cancer should be adjusted to take into consideration the presence of SS IV disease, rather than focusing only on this feature.

**Citation:** Sanchez-Mete L, Mosciatti L, Casadio M, Vittori L, Martayan A, Stigliano V. *MUTYH*-associated polyposis: Is it time to change upper gastrointestinal surveillance? A single-center case series and a literature overview. *World J Gastrointest Oncol* 2023; 15(11): 1891-1899

**URL:** <https://www.wjgnet.com/1948-5204/full/v15/i11/1891.htm>

**DOI:** <https://dx.doi.org/10.4251/wjgo.v15.i11.1891>

## INTRODUCTION

*MUTYH*-associated polyposis (MAP) is an autosomal recessive inherited disease caused by a biallelic pathogenic germline variant in the *MUTYH* gene. It was first described in 2002 in patients who presented clinical features similar to familial adenomatous polyposis/attenuated FAP (FAP/AFAP) but without *APC* gene mutation, with lesser polyps, later onset and a lower cancer lifetime risk[1,2]. MAP is typically associated with a dozen to a few hundred colonic adenomatous polyps, most frequently located in the right colon. However, colorectal cancer (CRC) can develop in some individuals in the absence of polyposis. Serrated adenomas, hyperplastic/sessile serrated polyps, and mixed (hyperplastic and adenomatous) polyps can also occur[3]. The lifetime risk of CRC in patients with MAP without surveillance is 80%-90% at a median age of onset of 48 years[3,4]. Given this substantial risk, MAP patients are advised to receive intensive colonoscopy surveillance every 1-2 years depending on the polyp burden, beginning at 25-30 years, and/or prophylactic surgery if the burden polyps are not manageable endoscopically[5-7].

Like FAP/AFAP, patients with MAP present an increased risk of extra-intestinal manifestations[8]. Among them, a frequent extra-colonic manifestation is a duodenal polyposis[9]. Even if duodenal polyposis develops less frequently than in FAP (14%-34% *versus* 65%-90%, respectively) and at a later age[9], the risk of developing duodenal cancer is comparable between the two conditions[5,9-11].

The Spigelman five-stage (0-IV) system (SS) is traditionally used to classify the duodenal polyposis severity, predict the risk of duodenal cancer, define the frequency of endoscopic surveillance and the timing of prophylactic duodenectomy. Equal relevance is given to each of the criteria considered in calculating the SS score and stage - size, number, histology, and degree of dysplasia[12]. Histological evaluation of duodenal polyps is required to obtain all criteria of the SS score. However, the biopsy is not performed routinely because it could interfere with the optical diagnosis using narrow-band imaging or create fibrosis that interferes with subsequent endoscopic resection.

When endoscopic removal is not performed (*i.e.*, small adenomas < 10 mm), SS could be determined by using optical diagnosis like narrow-band imaging[13,14]. The occurrence of SS IV duodenal polyposis is reported as the main risk factor for duodenal cancer[5,15]. However, advanced SS disease is rarely reported in MAP patients, and adenomas and adenocarcinoma beyond Treitz's ligament are described anecdotally[9]. Consequently, no clear recommendations on SB surveillance in MAP patients have been proposed (Table 1). The frequency of surveillance is mostly determined by the SS classification, with increasing frequency only if advanced-stage polyps are discovered[5].

Notably, case reports of duodenal cancers in MAP suggest that they may develop in the absence of advanced benign SS disease, even without coexisting adenomas, and often involve the distal portion of the duodenum, out of the reach of conventional esophagogastroduodenoscopy[9,11].

To increase our knowledge regarding MAP and its associated duodenal polyposis, in light of recent literature evidence, this paper describes a series of MAP patients followed up at the Regina Elena National Cancer Institute of Rome, Italy. In particular, the presence of SB cancers was assessed in relation to the history of duodenal polyposis. In addition, a literature overview on previously reported SB cancers in MAP is provided.



**Table 1 Comparison of international guidelines for small bowel surveillance in familial polyposis**

Surveillance interval (yr/mo)					
SS	ESGE[13,14] 2022, 2019	EMG[35] 2008	ESMO[36] 2019	ASGE[5] 2020	NCCN[7] (v. 2.2022)
<b>Duodenum</b>					
0	5 yr	5 yr	5 yr	5 yr	3-5 yr
I	5 yr	5 yr	5 yr	5 yr	2-3 yr
II	3 yr	3 yr	3 yr	3 yr	1-2 yr
III	1 yr	1-2 yr	1-2 yr	6-12 mo	6-12 mo
IV	6 mo, consider treatment	Surgical evaluation	6 mo or consider prophylactic surgery	3-6 mo, surgical evaluation	Expert surveillance 3-6 mo
<b>Rest of SB</b>					
	ESGE 2019 do not mention SB. ESGE 2022: CE and/or cross-sectional imaging techniques may be considered when an investigation of the mid-distal small bowel is clinically indicated	Not mentioned	Carry out a first endoscopy at 25-30 yr and continue depending on the SS. In FAP, the risk of cancer in the jejunum and ileum is extremely low; therefore, routine surveillance is not recommended	Suggested in SS IV with CE or MRE. Enteroscopy is not recommended routinely but only in positive CE or MRE and pre-duodenal surgery to avoid reconstruction with an SB segment with a high-density adenoma	High evidence supporting SB screening distal to the duodenum is lacking. Consider it, especially if advanced duodenal polyposis

ESGE: European Society of Gastrointestinal endoscopy; EMG: European Mallorca Group; ESMO: European Society of Medical Oncology; ASGE: American Society of Gastrointestinal Endoscopy; NCCN: National Comprehensive Cancer Network; CE: Capsule endoscopy; MRE: Magnetic resonance enteroscopy; SB: Small bowel; SS: Spigelman stage; FAP: Familial adenomatous polyposis.

## MATERIALS AND METHODS

Clinical records of thirty-eight MAP patients followed up at the Regina Elena National Cancer Institute between 2003 and 2021 were considered. In addition, a literature revision by a PubMed search was carried out on previously reported SB cancers in MAP, without any limitations in terms of publication date and language.

## RESULTS

### Case series

The baseline characteristics of patients are summarized in Table 2. The missense pathogenic variant c.452A>G;p.Tyr151Cys (NM\_001048174.2)[16] (previously known as c.536A>G;p.Tyr179Cys, NM\_001128425.1) was the most reported one ( $n = 13$ ; 33%). Upper gastrointestinal endoscopy was performed in 33 out of 38 patients (87%); the median age (SD) at first duodenoscopy was 49 (10) years. The first and last duodenoscopy showed a similar endoscopic feature: In 30 out of 33 patients (90%), no polyps were found, whereas a SS grade I polyposis was found in two patients (6%), and a SS II polyposis in one patient (3%).

SB cancer was found in two out of 33 patients (6%) with no previous history of duodenal polyposis. The first patient, a 54-year-old man, was a compound heterozygote for the *MUTYH* pathogenic variants c.452A>G;p.Tyr151Cys (previously known as c.536A>G;p.Tyr179Cys) and c.849+3A>C;p.? (previously known as c.933+3A>C;p.?). During routine surveillance, an advanced, metastatic adenocarcinoma of the distal duodenum was found (Figures 1A, 1C and 1E).

The second patient, a 58-year-old man, was homozygote for the *MUTYH* pathogenic variant c.452A>G;p.Tyr151Cys (previously known as c.536A>G;p.Tyr179Cys). He underwent capsule endoscopy and subsequent push enteroscopy for anemia. A proximal jejunal adenocarcinoma was found and treated with surgery. In his anamnestic history, this patient presented a papillary tumor of the thyroid gland, adrenal adenoma, and a duodenal ampullary adenoma, diagnosed after surgery during a subsequent duodenoscopy (Figures 1B, 1D and 1E).

### Duodenal cancers in MAP

After the first description of MAP as an adenomatous colorectal polyposis in 2002, several extracolonic manifestations, particularly duodenal polyposis, have been reported in MAP patients[8,17,18]. Although different studies suggested that SS IV disease strongly predicts future cancer[15], duodenal cancers lacking prior stage IV disease have been reported in MAP patients[9-11,19].

Large cohort studies can be useful in describing features and frequency of duodenal cancers in MAP (Table 3). In a cohort of 276 MAP patients recruited from a European multicenter study, duodenal polyposis occurred in 26 out of 150 patients (17%) who underwent esophagogastroduodenoscopy. SS classification was not presented. Among this cohort, two duodenal cancers were reported (about 1%)[10].

**Table 2 Baseline characteristics of *MUTYH*-associated polyposis patients (*n* = 38)**

Characteristics	<i>n</i> (%)
Male	28 (74)
Age at diagnosis (yr), mean ± SD	48 ± 10
Pathogenic <i>MUTYH</i> variants	
Homozygotes	7 (18)
Compound heterozygotes	31 (82)
Most reported variant <sup>1</sup>	c.452A>G;p.Tyr151Cys
Colectomy	
No	11 (29)
Total	14 (37)
Subtotal	13 (34)
Colorectal cancer	18 (47)
Duodenal adenomas	3 <sup>2</sup> (9)
Spigelman stage I	2 (6)
Spigelman stage II	1 (3)
Spigelman stage III	0
Spigelman stage IV	0
Extracolonic tumors	11 (29)
Thyroid carcinoma/papillary thyroid carcinoma	4 (36)
Breast cancer	2 (18)
Small bowel cancer	2 (18)
Bladder cancer	1 (9)
Desmoid tumor	1 (9)
Kidney tumor	1 (9)

<sup>1</sup>This variant was detected in both patients with small bowel cancer.

<sup>2</sup>Upper gastrointestinal endoscopy was performed in 33 out of 38 patients (87%).

**Table 3 Literature review of duodenal cancers in *MUTYH*-associated polyposis**

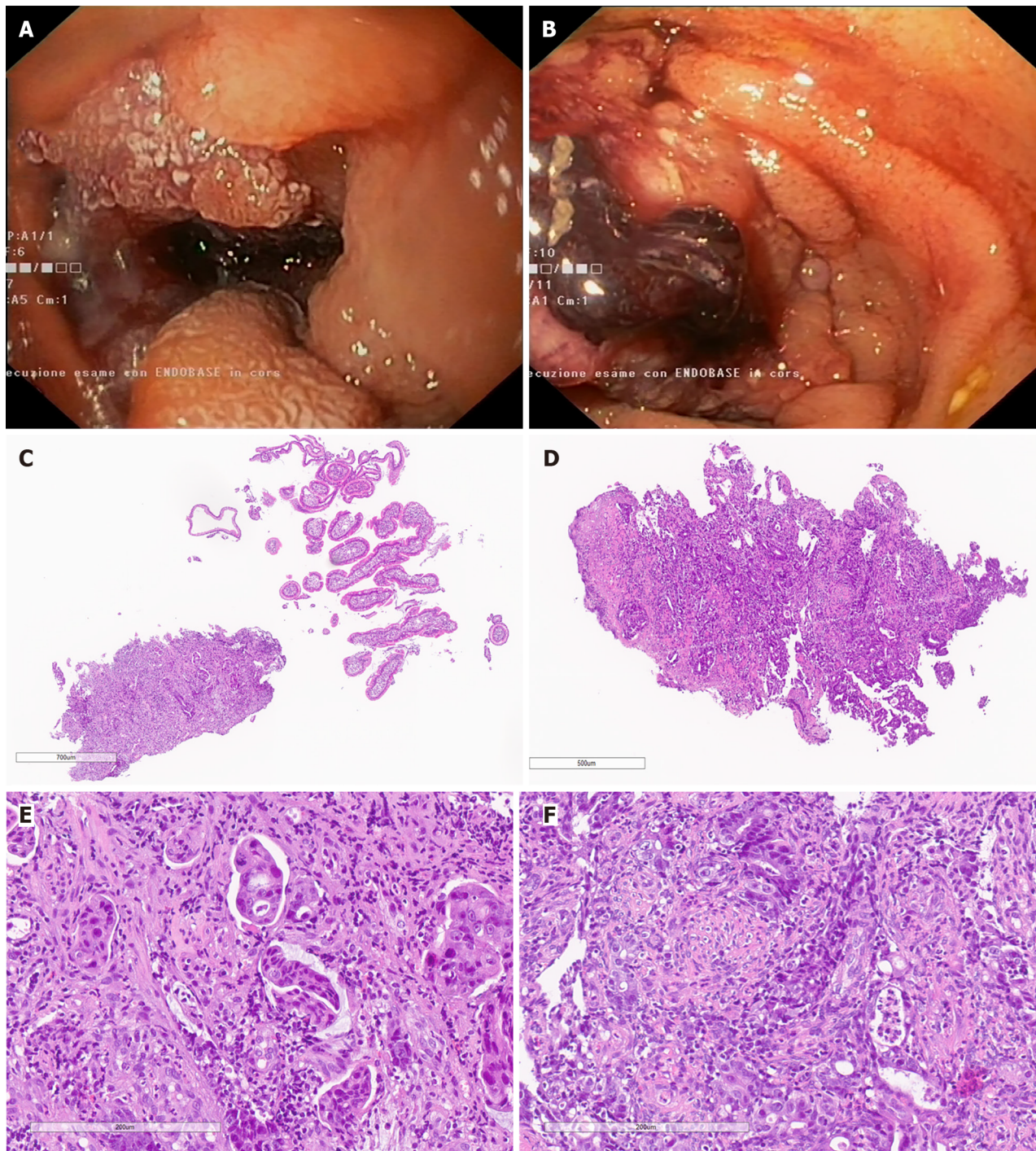
Study design	Number of MAP patients	Main findings	Ref.
Cohort study	394	None of the four MAP-associated duodenal cancers (about 1%) reported in this cohort study developed in the context of prior stage IV disease. Three of them involved the distal duodenum	[11]
Retrospective study	92	One duodenal and one ampullary cancer occurred in this cohort (about 2%), none in the context of prior stage IV disease	[9]
European multicenter study	276	Duodenal polyposis occurred in 17% of patients who underwent esophagogastroduodenoscopy. SS classification was not presented. Two duodenal cancers were reported (about 1%)	[10]

MAP: *MUTYH*-associated polyposis; SS: Spigelman stage.

In a retrospective study on 92 MAP patients undergoing surveillance esophagogastroduodenoscopy, 34% (*n* = 31) reported duodenal polyposis. Of them, 29 (32%) developed SS I-III disease and only 2 (2%) SS IV disease. One duodenal and one ampullary cancer occurred in this cohort (about 2%), none in the context of prior stage IV disease[9].

In a recent cohort study on 394 MAP patients, 21% of patients had duodenal polyposis, and the incidence of SS IV duodenal polyposis was 1.5%[11]. None of the four MAP-associated duodenal cancers (about 1%) reported in this cohort study developed in the context of prior stage IV disease, and three of four duodenal cancers involved the distal duodenum[11].





DOI: 10.4251/wjgo.v15.i11.1891 Copyright ©The Author(s) 2023.

**Figure 1** Endoscopic and histopathological features of the two cases of small bowel cancer identified. A: Upper push-enteroscopy in the first patient showed a vegetate-ulcerative lesion located 100-105 cm from the incisors, involving at least three-quarters of the luminal circumference, that causes partial stenosis of the lumen that could be passed through, anyway. There was a small clot in the distal portion, but the lesion was not actively bleeding. Multiple biopsies were taken, and the diagnosis was adenocarcinoma of the distal duodenum; B: Upper push-enteroscopy in the second patient showed an ulcerative lesion located 120-130 cm from the incisors, actively bleeding, involving at least two-thirds of the luminal circumference, with a clot in the mid portion. Multiple biopsies were taken and after clot removal, hemospray was applied to the tumor surface and complete hemostasis was obtained. Tattooing was then performed. The diagnosis was adenocarcinoma of the proximal jejunum; C: Hematoxylin-eosin staining in the first patient, 5 ×. Low magnification reveals two biopsic fragments. The first, on the right, of normal small intestine and the second, on the left, of fibrous/granulation tissue, show variably sized glands and desmoplasia, indicative of adenocarcinoma; D: Hematoxylin-eosin staining in the second patient, 5 ×. Low magnification reveals a single biopsic fragment of fibrous tissue showing variably sized glands with moderate/severe atypia (loss of normal glandular architecture) and desmoplasia, indicative of adenocarcinoma; E: Hematoxylin-eosin staining in the first patient, 20 ×. On higher magnification, solid nests and sheets and few and small poorly-formed glands contain enlarged, hyperchromatic cells with loss of mucin, nuclei with prominent eosinophilic nucleoli and irregular nuclear membranes in a desmoplastic stroma, diagnostic of invasive adenocarcinoma; F: Hematoxylin-eosin staining in the second patient, 20 ×. High magnification shows marked cytological atypia (the cells are hyperchromatic with loss of mucin and contain nuclei with prominent eosinophilic nucleoli and irregular nuclear membranes) forming marked atypical glands with intraluminal apoptotic and inflammatory debris in a desmoplastic stroma,

suggestive of invasive adenocarcinoma.

## DISCUSSION

In our series, we identified two (6%) SB adenocarcinomas with no previous history of duodenal polyposis. Both cancer patients carried the most reported pathogenic variant (c.452A>G;p.Tyr151Cys; NM\_001048174.2), known to be associated with more aggressive disease[20]. Prior studies on larger series reported a lower percentage (about 1%) of duodenal cancers. Nonetheless, in most of them, no previous history of SS IV duodenal polyposis was reported; the distal duodenum/jejunum was mostly involved, as we observed in our series[9-11]. This suggests that SS can fail in identifying patients with MAP at risk of future cancer.

It is still unclear if SS should also be considered a duodenal cancer predictor in FAP. Although several studies have shown a good correlation between these two parameters[21], a recent systematic review assessing the risk factors for non-ampullary duodenal carcinoma in FAP patients reported three cohort studies characterized by an increased incidence in SS[22]; in only one case-control study, the inconsistency of SS as a duodenal cancer prediction risk indicator was suggested since more than half of FAP patients diagnosed with duodenal cancer lacked SS IV duodenal polyposis[23]. The authors found that only two out of four SS components (large duodenal polyp size and degree of dysplasia) were positively associated with duodenal cancer and reported advanced papilla pathology as an important feature[23].

Of note, duodenal adenomas in MAP appear to display a more aggressive molecular pattern. Recent molecular analyses suggest they have a high mutational burden and likely harbor oncogenic driver mutations, such as those in *KRAS*[24]. These features of the biology and natural history of duodenal polyposis in MAP, together with the debate over the utility of all the SS components, challenge the current upper gastrointestinal tract surveillance guidelines in this patient setting, as recently observed[25].

Current International guidelines do not suggest any specific surveillance of small bowel (SB) in MAP for FAP. More recent guidelines suggest performing an SB study with capsule endoscopy or magnetic resonance enterography only in cases of advanced duodenal polyposis and limiting device-assisted enteroscopy to pre-duodenal surgery[5,26]. As a matter of fact, capsule endoscopy has shown better diagnostic yield for detecting smaller jejunum-ileal polyps than other imaging modalities; therefore, when indicated, it should be the first-choice examination. Moreover, it has a similar detection rate to device-assisted enteroscopy but a lower diagnostic yield for SB tumors/polyps located in the first tract of the SB, especially the periampullary area and the proximal jejunum. This could probably be due to the rapid transit[27-33].

In our MAP series, the SB cancer identified were both in the distal duodenum/jejunum, within reach of push enteroscopy. According to international guidelines, MAP patients regularly undergo front and side view upper endoscopy, so deeper exploration of the proximal jejunum, using push enteroscopy, could be considered instead of conventional gastroscopy.

This study presents some limitations, such as the small sample and the retrospective analysis. However, some strengths can be described, such as the focus on some peculiar features of MAP which emerged in the last years, that consider MAP a distinct clinical entity characterized by a higher susceptibility to extra-colonic malignancies than APC-associated polyposis, with a different and more aggressive behavior[8,25,34]. However, taken together, our observations and literature evidence suggest that further studies are needed to define appropriate upper gastrointestinal surveillance programs in MAP patients.

## CONCLUSION

Although larger studies are needed to validate the overall findings, our observations suggest that the formula for staging duodenal polyposis and predicting risk factors for distal duodenum and jejunal cancer may need to be adjusted to take this into account rather than focusing solely on the presence or absence of SS IV disease. Moreover, the biological pattern and behavior of SB adenomas in MAP compared with FAP ones should be investigated. Push enteroscopy and side view upper endoscopy could be considered/hypothesized to better examine the proximal SB. In conclusion, a revision of upper gastrointestinal/SB surveillance guidelines may be required to better prevent SB cancer in MAP.

## ARTICLE HIGHLIGHTS

### Research background

Patients with *MUTYH*-associated polyposis (MAP) present an increased risk of extra-intestinal manifestations. Among them, a frequent extra-colonic manifestation is duodenal polyposis, which severity is traditionally classified with the Spigelman five-stage system (SS). The occurrence of SS IV duodenal polyposis is reported as the main risk factor for duodenal cancer. However, case reports of duodenal cancers in MAP suggest that they may develop in the absence of advanced benign SS disease, even without coexisting adenomas, and often involve the distal portion of the duodenum, out of the reach of conventional esophagogastroduodenoscopy.



**Research motivation**

Further studies are needed to define appropriate upper gastrointestinal surveillance programs in MAP patients.

**Research objectives**

To increase the knowledge regarding MAP and its associated duodenal polyposis, in light of recent literature evidence, we describe a series of MAP patients followed up at the Regina Elena National Cancer Institute of Rome, Italy. In addition, a literature revision on previously reported small bowel (SB) cancers in MAP was carried out.

**Research methods**

Clinical records of thirty-eight MAP patients followed up at the Regina Elena National Cancer Institute between 2003 and 2021 were considered. A literature revision by a PubMed search was carried out on previously reported SB cancers in MAP, without any limitations in terms of publication date and language.

**Research results**

In our case series, we identified two (6%) SB adenocarcinomas with no previous history of duodenal polyposis.

**Research conclusions**

Our observations suggest that the formula for staging duodenal polyposis and predicting risk factors for distal duodenum and jejunal cancer should be adjusted to take in consideration the presence of SS IV disease, rather than focusing only on this feature.

**Research perspectives**

A revision of upper gastrointestinal/SB surveillance guidelines may be required to better prevent SB cancer in MAP.

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**ACKNOWLEDGEMENTS**

Editorial and graphical assistance was provided by Simonetta Papa, PhD, Massimiliano Pianta, Valentina Attanasio, and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by internal funds.

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**FOOTNOTES**

**Author contributions:** Sanchez-Mete L and Mosciatti L contributed to the literature research and wrote the first draft; all authors critically contributed to the analysis of evidence and provided major intellectual input to the paper, and commented on previous versions of the manuscript; and all authors read and approved the final manuscript.

**Institutional review board statement:** This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

**Informed consent statement:** All the participants signed an informed consent form.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**S-Editor:** Wang JJ

**L-Editor:** A

**P-Editor:** Yu HG

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