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Position Paper

Pathology of the malignant colorectal polyp: Issues in morphologic criteria and recommendations from the Italian Group of Gastrointestinal Pathologists

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ABSTRACT

Malignant colorectal polyps (MCPs) are early-stage colorectal cancers (CRC) generally diagnosed following endoscopic removal of otherwise bland lesions. Due to nodal metastatic potential and risk of residual disease, diagnosis and risk stratification of MCPs are critical for determining appropriate clinical management, which can range from clinical/endoscopic/imaging follow-up to radical surgery with locoregional lymphadenectomy. Although a dedicated multidisciplinary team should discuss this decision, the MCP histopathologic assessment is crucial and raises several issues.

Following productive discussions that occurred in dedicated meetings and educational activities, the Italian Group of Gastrointestinal Pathologists have developed these recommendations for the histopathologic assessment and multidisciplinary management of MCPs, addressing diagnostic challenges and proposing standardized criteria.

This document is based on a comprehensive review of the literature and opinions from pathologists with dedicated gastrointestinal experience. Key topics include pre-analytical specimen handling, histopathologic criteria for MCP diagnosis, and assessment of histopathologic features associated with MCP high-risk behavior. The role and integration of features inferred from advanced CRCs, such as mismatch repair protein status testing, are also addressed and discussed.

The proposed recommendations aim to improve MCP risk stratification by structuring and standardizing the histopathologic approach. The adoption of a multidisciplinary team discussion remains crucial for MCP patient management.

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1. Introduction

Diagnosing a malignant colorectal polyp (MCP), and subsequent patient clinical management, are primarily based on a thorough histopathologic assessment and related multidisciplinary discussion. MCP is a locally colorectal cancer (CRC) that invades the submucosa through the muscularis mucosae, thus qualifying as pT1 in the current TNM classification [1]. The overall MCP prevalence is low (range: 0.2–5 %) but increasing worldwide due to more diffuse CRC screening programs [2–4].

The presence of loco-regional lymph node metastases in patients with CRC significantly increases the likelihood of distant metastases, leading to worse outcomes in terms of both morbidity and mortality. Although nodal metastases occur in a small percentage of MCP cases — approximately 6–16 % — identifying those at highest risk is crucial for determining the best course of treatment [5–12]. In particular, assessing whether patients with locally excised MCP should undergo surgical bowel resection is essential, as this procedure provides the opportunity to examine regional lymph nodes histologically thereby identifying patients with nodal metastases who will likely require adjuvant treatment with chemotherapy. While surgical resection of the colon can be beneficial, it carries a measurable risk of morbidity, low but present risk of mortality and requires considerable resources. In contrast, endoscopic resection is a less invasive and more cost-effective option, and is often sufficient for patient treatment [13,14]. Consequently, accurately evaluating histopathological indicators of lymph node metastases is key to optimizing treatment decisions and avoiding unnecessary major surgeries [4].

The best approach is decided by a dedicated multidisciplinary team (MDT) that discuss patients with MCP from multiple perspectives, including presence of histopathological features associated with a high risk of residual disease and/or nodal metastasis. These features include: (I) tumor grade and poorly differentiated clusters (PDC), (II) lymphovascular invasion (LVI), (III) tumor budding, (IV) depth of submucosal invasion and related microstaging (MS), and (V) resection margin status [4,15–24]. Despite accurately estimating MCP aggressiveness, histopathologic analysis alone cannot be the sole parameter to determine MCP-patient treatment and it should always be integrated with additional data (such as lesion location, endoscopic appearance, and patient age and status) and discussed at the MDT meeting [16–18,20,25]. Pathologists face significant difficulties, including procedural issues, when evaluating these features, especially if dealing with biopsy specimens with limited diagnostic material [26]. In the ideal world, colorectal lesions are perfectly sampled, oriented, and sectioned, thus providing all the above-mentioned histopathological metrics readily available for pathologists' evaluation. Alas, this is not always the case.

In this paper, the Italian Group of Gastrointestinal Pathologists (GIPAD) aims to (I) discuss real-world issues of MCP histopathological evaluation, (II) propose solutions combining literature evidence with opinions from pathologists with dedicated gastrointestinal training (i.e., examining at least 500 polypectomies annually), and (III) provide a document that supports MCP multidisciplinary team diagnostic and clinical practice.

These recommendations originated from discussions that emerged from meetings and educational activities promoted and organized by GIPAD, on the challenges pathologists face in this setting. The first part of the recommendations is dedicated to general concepts on specimen sampling and grossing, and tissue sample handling. Then, the recommendations address two aspects of MCP histopathological workup: the diagnostic phase, and the risk assessment. Each section is addressed and subdivided into specific topics and issues that pathologists face daily. Questions and related answers collected during the GIPAD meetings are also included.

We conclude these recommendations by describing recent acquisitions and putative new features for risk assessment of MCPs, and reporting our opinion on how we expect the field will move forward.

2. The pre-analytical phase

The best assessment of histopathological features is obtained when pre-analytical steps are optimized, and specimens are accurately oriented and prepared. This principle holds particularly true for MCPs. Here, we report some general concepts for optimal specimen handling, and how they apply in the MCP scenario.

2.1. MCP removal

Several procedures can be performed to excise a colorectal polyp. The goal is to completely remove the lesion and prevent potential progression to CRC, while minimizing procedure aggressiveness and side effects. The strategy can vary based on the dimensions and endoscopic appearance of the lesion, but it should also be tailored on a case-by-case basis.

There are two major approaches: endoscopic excision (either conventional or advanced techniques), and surgical resection. Endoscopic excision can provide complete removal of the lesion while avoiding surgical resection drawbacks (e.g., increased morbidity and mortality, and higher cost) [27]. Up to 80–90 % of colorectal polyps are <10 mm pedunculated lesions and can be completely excised with conventional endoscopic snare polypectomy [27]. If non-pedunculated, snare polypectomy (with or without submucosal injection) can also be used to remove lesions that are up to 20 mm. The resection site should be tattooed to facilitate subsequent follow-up [12].

Additional endoscopic approaches are (I) piecemeal biopsies with inking of biopsied mucosa (to facilitate subsequent surgery if necessary) [12], and (II) use of advanced techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [27]. Piecemeal biopsies are typically performed for right-sided lesions, while both EMR and ESD permit *en bloc* removal of the lesion, and are generally preferred for >20 mm non-pedunculated lesions. The advantages of EMR and ESD are the ability to obtain a large and preserved piece of tissue and avoid lesion fragmentation, but they are usually available only in specialized centers.

Apart from size and shape, lesion surface is also considered. The Narrow Band Imaging International Colorectal Endoscopic classification (NICE) [28] and the Kudo [29] classification further stratified MCP based on lesional color, vessel, and surface pattern (NICE classification) or pit pattern (Kudo classification). Based on these features, highly suspicious MCPs (i.e., NICE Type 3, or Kudo Type V_N and V_I) should be considered for immediate surgical resection (i.e., colectomy with locoregional lymph node dissection). Apart from this specific scenario, surgical resection is reserved for diagnosed MCP cases following MDT discussion [30,31]. A less invasive surgical approach is represented by transanal endoscopic microsurgery (TEM) [32,33]. TEM is considered for lesions up to the recto-sigmoid junction. It is mostly used for lateral spreading tumors (LST)/large adenomas, but also for MCP radical resection [34–36]. As for EMR and ESD, TEM is available in specialized institutions [32,36].

This paragraph aims to introduce pathologists to MCP resection and sampling procedures. More thorough and detailed analyses of these endoscopic and surgical techniques are the topics of excellent recent reviews [30,31,37–41], and will not be further discussed here.

2.2. Type of specimen, tissue handling and grossing

Different sampling/excision approaches equals different specimen types, and pathologists may be required to evaluate MCPs either as piecemeal biopsy fragments or the whole lesion with a variable amount of nearby normal mucosa. From a purely histopathologic perspective, piecemeal biopsy fragments of a potentially malignant lesion are highly discouraged due to the well-known caveats, including lack of orientation, equivocal submucosal representation, unavailability of resection margins, and overall impairment of histopathological assessment. In this unfortunate scenario, the endoscopist should orient fragments to favor diagnostic evaluation. When dealing with a putative MCP on a piecemeal fragmented biopsy, we recommend clearly indicating the limitations of this type of specimen in the diagnostic report. Further details (in particular, when the boundary between mucosa and submucosa is not readily assessable due to the fragmented, partial, or superficial nature of the sample) are detailed in a subsequent paragraph (i.e., "***3.1 Making the diagnosis***–*Submucosal invasion*").

In the Pathology Unit, the first step toward an optimal histopathologic diagnosis is adequate formalin fixation. The minimum fixation time required for colorectal lesions is five hours, but it depends on specimen dimensions. Lesions > 15 mm should be fixed overnight to minimize poor fixation risk and tissue fragmentation [42]. Over-fixation can equally harm tissue samples, especially in terms of tissue antigenicity for immunohistochemistry (IHC) [43,44].

Following fixation, grossing starts with recording sample dimensions, specifying the length, width, and height. Before proceeding with sectioning, the resection margin (both vertical and lateral) has to be identified (and potentially inked). If resection margins cannot be recognized (e.g., due to the retraction of the implant base or sample fragmentation), we recommend specifically indicating it in the diagnostic report. These procedures apply to endoscopically removed specimens. MCPs removed with segmental colorectal surgical resection are grossed following standard protocols.

Sectioning of the lesion depends on its gross appearance (pedunculated/semi-pedunculated/sessile) and dimensions [42,45,46].

- Semi-pedunculated or sessile lesions should be serially sectioned at 3-mm intervals, perpendicular to the resection basal margin.
- Sectioning of pedunculated lesions depends on dimensions:
  - Sectioning is not recommended for pedunculated lesions that are less than five mm or lesions with a narrow stalk.
  - If the pedunculated lesion measures between five to nine mm, it should be bisected and the halves included separately.
  - Pedunculated lesions measuring 10-to-19 mm should be sectioned serially and perpendicularly to the resection margin to permit complete visualization of the stalk. The tissue sections passing through the middle of the stalk should be included separately and differentiated from those composed of the apical part alone.
  - For larger lesions (≥20 mm), sections comprising the head of the polyp and the upper third of the stalk should be included separately from the remaining part of the stalk.

In all cases, if the dimension allows, a tissue section including the whole lesion (from the apical part to the deep resection margin) should be collected for accurate assessment of mucosa and submucosa. Furthermore, the whole lesional tissue should be processed for histologic evaluation regardless of dimensions and shape [42,45,46].

Accurate diagnosis and clinical management of MCPs start with optimal tissue handling and grossing. If this cannot be achieved, putative causes should be addressed at MDT meetings to identify solutions.

3. The histopathological assessment

A standardized histological approach should be adopted to grant optimal diagnostic yield. Here, we provide recommendations for the development of this standardized approach, focusing on both the diagnostic phase and the assessment of MCP aggressiveness. At the end of each paragraph, we report questions and doubts related to MCP evaluation that emerged during GIPAD educational meetings, and the related answers based on literature evidence and opinions from pathologists with dedicated expertise. The last paragraph of this section provides a template of an MCP pathology report that incorporates the GIPAD recommendations.

3.1. Making the diagnosis

Submucosal invasion

The defining feature of MCP is the presence of submucosal invasion without involvement of the muscularis propria. MCP can develop within various types of colorectal polyps, including adenomatous (tubular, tubule-villous, or villous), serrated (sessile serrated lesions – SSLs), and hamartomatous polyps, though rare [47–51]. In well-oriented histological sections, malignant glands invading submucosa can be readily identified, showing high-grade cytological atypia, irregular and haphazard growth pattern, single-cell infiltration, and desmoplastic stroma.

Significant caveats for MCP diagnosis are histological mimics of submucosa invasion, including (I) misplaced dysplastic epithelium within the submucosa (i.e., "pseudoinvasion"), and (II) adenocarcinoma limited to the mucosa/muscularis mucosae with suspected microinfiltration into the submucosa. Pseudoinvasion is characterized by a well-defined dysplastic lesion without evidence of an invasive component into the lamina propria. The misplaced glands generally exhibit mild cytologic atypia, regular margins, larger diameters compared to upper compartment, and luminal ectasia with mucin accumulation. These dysplastic glands are generally continuous with the upper compartment, whereas desmoplastic stromal reaction—a hallmark of true invasion—is absent. In general, pseudoinvasion is mostly observed in pedunculated polyps of the distal colon due to increased mechanical stress favoring ischemic discontinuation of muscularis mucosae and gland misplacement. Indeed, a key distinguishing feature of pseudoinvasion is the presence of hemosiderin-laden macrophages in the stroma, suggestive of prior chronic injury, as well as dilated large submucosal vessels, the presence of lamina propria-like stroma around misplaced glands, lobulated glandular pattern, and roundish, not angled dissociation attitude within the submucosa layer (Fig. 1) [45,46,52,53].

Putative or focal submucosal infiltration in adenomatous polyps with intramucosal adenocarcinoma can pose significant diagnostic challenges. In these cases, atypical glands can be located within the muscularis mucosae and/or side-by-side within the upper limit of the submucosa, thus making a reliable assessment of "true" submucosal extension demanding. Furthermore, the muscularis mucosae is frequently disrupted, attenuated, or fragmented, making it additionally challenging to distinguish intramucosal neoplasia and submucosal invasion [45,52,54]. If the invasion is equivocal, we recommend prioritizing the assessment of the following histopathological features: desmoplastic stroma, poorly differentiated morphology, and dubious lymphovascular invasion. If only these indirect features of MCP are present, we recommend conveying suspicion of MCP rather than providing a definitive diagnosis in the pathology report.

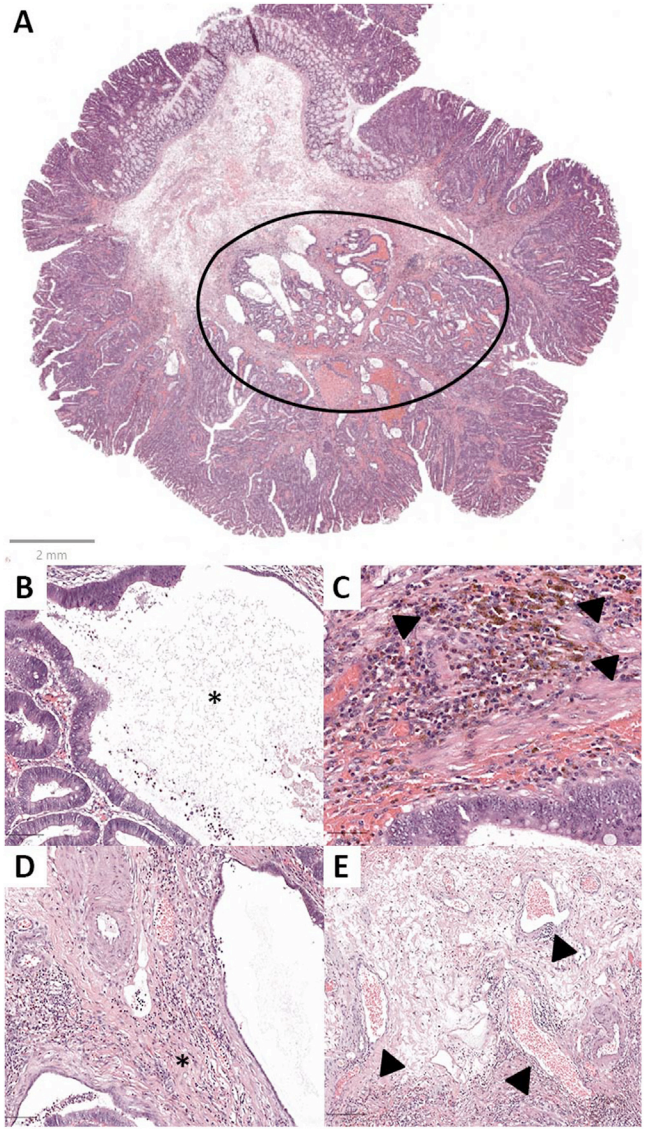

Fig. 1. Representative image of pseudoinvasion. A) Low-power image of an area of pseudoinvasion (black line). B) Dysplastic glands of the pseudoinvasion area showing luminal ectasia (asterisk). C) Presence of hemosiderin-laden macrophages in the stroma (black arrows). D) Lamina propria-like stroma around misplaced glands (asterisk). E) Dilated large submucosal vessels (black arrows).

Lesions with high-grade dysplasia, a villous component, and large dimension are more frequently associated with invasive adenocarcinoma and should be looked at with care [55,56].

Infiltration solely of the lamina propria with no deeper invasion deserves a specific comment (Fig. 2). This event can be rarely identified in colorectal specimens, and it is generally referred to as intramucosal colorectal carcinoma in the literature [54,57,58]. Association of lamina propria infiltration and increased risk of lymph node metastasis is still debated and generally absent [57,58]. Therefore, it is worth stressing that lamina propria infiltration alone, with no deeper invasion, does not qualify for a diagnosis of MCP. However, recent evidence has suggested a strong correlation between lamina propria invasion and an increased association with colorectal cancer risk factors, represented either by inflammatory bowel disease or hereditary syndromes [54]. Pending further analysis and validation, it may be appropriate to report lamina propria invasion and the association of this finding in patients at increased colorectal cancer risk.

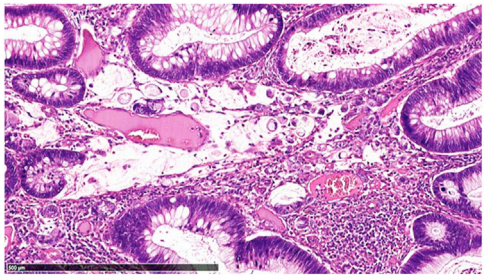

Fig. 2. Representative image of lamina propria invasion. Dysplastic glands surrounding a focal area of lamina propria invasion where tumor cells present mucinous/signet ring features.

As no definite criteria exist to solve cases with equivocal submucosal invasion, this diagnostic conundrum exemplifies the benefit of having two pathologists reviewing and confirming the MCP diagnosis. Indeed, we highly recommend having the diagnostic report of all putative MCPs signed out by two pathologists. This latter recommendation is especially relevant in a specific scenario, specifically whenever a polypoid lesion is superficially/partially biopsied and fragmented (thus precluding clear assessment of mucosa-submucosa boundary), but presents morphological features of an MCP/adenocarcinoma. In this setting, pathologists may struggle between a straightforward malignant diagnosis, or a more cautious yet formal approach that requires direct evidence of invasion to make a definitive diagnosis of malignancy. Here, we recommend sharing the case with a colleague pathologist. If the malignant nature is confirmed by both pathologists, then it is crucial to (I) provide a descriptive diagnosis, specifically reporting the features favoring the malignant nature of the lesion, but also the limitations (especially those related to sample fragmentation) that preclude a definitive diagnosis, (II) stressing the requirement of a thorough MDT discussion, and (III) have the diagnostic report signed by both evaluators. This approach has dual benefits: it strengthens the need of MDT discussion, and it favors the identification by all MDT participants of potential solutions to prevent the reiteration of this event.

Practical questions and solutions related to MCP diagnostic approaches are addressed in the following Q&A session.

Q: How many serial sections per tissue block should be performed if a lesion is between 10 and 20 mm*? What if between 20 and 30* mm*?*

GIPAD recommendations: A recommended number of serial sections per tissue block is not explicitly defined in the literature, and specific data based on lesion dimensions is not available. In general, we recommend preparing one slide per tissue block, containing as many serial sections as feasible.

Q: How many sections do we have to examine to assess submucosal invasion in equivocal cases?

GIPAD recommendations: Few specific scenarios may benefit from deeper levels, including equivocal submucosal invasion or uncertain presence of high-risk features. There is no recommended number, but we suggest performing no more than three additional deeper levels . In general, support from a colleague pathologist holds more value than producing deeper levels and additional serial sections.

Q: Are pedunculated lesions showing lamina propria invasion MCPs?

GIPAD recommendations: No, an invasion confined to the lamina propria does not meet the criteria for MCP diagnosis, as the presence of invasive neoplastic glands in the submucosa is required. If there are only indirect histologic features (e.g., desmoplastic stroma, poorly differentiated morphology, and dubious lymphovascular invasion), the pathology report should convey

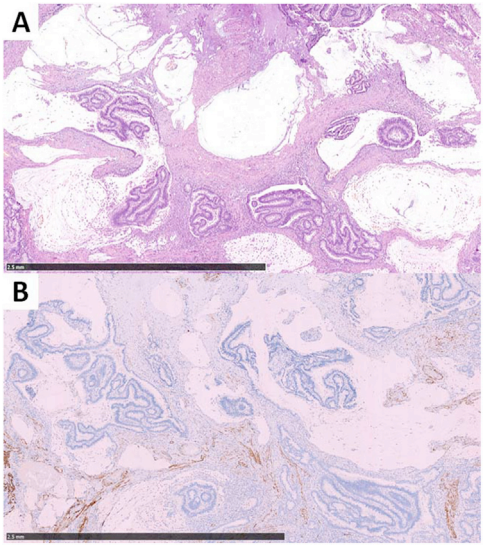

Fig. 3. Immunohistochemical stain for smooth muscle actin can support identification of muscularis mucosae disruption and neoplastic gland invasion if doubtful. A) An area of neoplastic invasion with malignant glands and acellular mucin pools infiltrating the muscularis mucosae. B) Smooth muscle actin IHC stain (brown stain) further highlight muscularis mucosae disruption, thus confirming the invasive nature of the lesion.

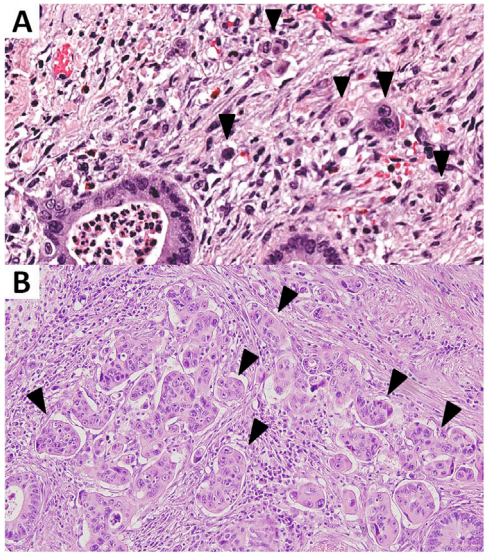

Fig. 4. Representative images of tumor budding and PDCs at the tumor invasive front. The number of tumor cells composing the aggregate is key to distinguish tumor buds (<5 tumor cells; A, black arrows) from PDC (>5 tumor cells; B, black arrows).

suspicion of MCP. Identification and reporting of invasion of the lamina propria alone (i.e., intramucosal colorectal carcinoma) may be relevant for its association with colorectal cancer risk factors (e.g., inflammatory bowel disease and hereditary syndromes).

Q: Should the percentage of invasive component over dysplasia be detailed in the diagnostic report?

GIPAD recommendations: No, it is not necessary to explicitly this percentage. Quantifying the exact proportion of each components does not provide additional prognostic value and is not required in routine reporting.

*Q: Should IHC for muscularis mucosae (*i.e.*, desmin) or adenocarcinoma (*i.e.*, cytokeratins) identification always be performed?*

GIPAD Recommendations: Performing IHC to highlight muscularis mucosae or adenocarcinoma is not required or recommended. It can be performed selectively on the tissue block with the most suspicious area to clearly define true submucosal invasion. However, this should not be considered as part of MCP diagnostic routine (Fig. 3).

Q: How should we report polypoid lesions that were superficially/partially biopsied, thus precluding clear assessment of the mucosa-submucosa boundary and invasion? Can we use the term "adenocarcinoma" in this setting?

GIPAD Recommendations: A two-step approach is recommended when diagnosing fragmented colorectal polypoid lesions with suspected malignancy: (I) consulting a second pathologist and (II) providing a descriptive diagnosis that highlights both malignant features and diagnostic limitations. In this context the presence of unequivocal desmoplasia is a crucial finding. As detailed above, this strategy strengthens the need for MDT discussions for optimal patient management, and helps identify solutions to prevent similar diagnostic challenges in the future.

3.2. Assessing the risk factors

Once an MCP is diagnosed, pathologists provide a comprehensive histopathological evaluation of risk factors associated with lymph node metastases or local recurrence/residual disease. In the following paragraphs, we will address established (lymphovascular invasion, tumor budding, tumor grade, and resection margins), innovative (mismatch repair protein status), and recently questioned (depth of invasion and microstaging) histopathological features of high risk MCP. As for the previous paragraph, a Q&A session will highlight major assessment caveats.

Grading and histotype

Histologic grading is an independent risk factor associated with poor prognosis in MCPs [57–59]. Unfortunately, grading assessment is subject to significant interobserver variability due to the lack of standardized quantification methods. In particular, a critical aspect is the minimum percentage of poorly differentiated component required to grade the whole lesion. Traditionally and according to the American Joint Committee on Cancer [60], tumor differentiation and grading are defined architecturally—whether the tumor forms glandular structures. If the glandular component is <50 % of the tumor, it is classified as poorly differentiated (high-grade). However, the literature indicates that even a small proportion (as little as 5 %) of poorly differentiated areas significantly increases the risk of lymph node metastases [61,62].

A caveat of tumor grade assessment is related to the grading system used. To improve inter-observer reproducibility, the latest WHO Classification of Gastrointestinal Tumors recommends a simplified two-tiered grading system: low-grade (G1-G2) and high-grade (G3) [63]. This classification is applied to not otherwise specified and mucinous adenocarcinomas. Remarkably, WHO grading system is based on the least differentiated component rather than the most represented. We recommend using the two-tiered grading system (low-grade vs. high-grade) in the diagnostic report, as it is more reproducible and prognostically relevant.

In addition, poorly differentiated clusters (PDCs) should be carefully evaluated. PDC are aggregates of at least five neoplastic cells lacking glandular formation and located at the tumor invasive front (Fig. 4). PDC presence is relevant in MCPs and pT1 CRCs, as they are strongly associated with nodal involvement [57,58]. However, there is no standardized consensus regarding PDC reporting to date. Therefore, we recommend (I) considering any quantity of tumor poor differentiation for the tumor grading, thus avoiding the need for specific percentages, and (II) specifically reporting whether there are PDCs and reporting them as present or absent (without further quantification). This information will be then presented in the MDT discussion for clinical

interpretation. The rationale for this approach is that, given the available monitoring tools, an isolated finding of poor differentiation area/PDC alone does not necessarily justify radical surgical intervention.

In addition to grade, certain histologic subtypes of MCPs exhibit distinctly aggressive behavior. Three histotypes are associated with a putative increased risk of nodal metastases: (I) mucinous subtype (at least 50 % of the tumor present mucinous features), particularly those in the rectum [64,65], (II) micropapillary subtype (micropapillae in ≥5 % of the total tumor component) [66,67], and (III) signet-ring cell subtype (signet ring required in at least 50 % of the tumor) [68]. Consensus on greater clinical aggressiveness has been established for the signet-ring cell subtype only. Other subtypes, such as adenosquamous carcinoma, also show aggressive behavior but are rare and have been anecdotally reported in MCPs [69,70]. While specific large-scale studies are lacking – mostly due to the rarity of these subtypes - the Japanese Society for Cancer of the Colon and Rectum (JSCCR) 2019 guidelines recommend surgical resection with lymph node dissection for MCPs exhibiting mucinous or signet-ring cell carcinoma histology [16].

Based on these considerations, we recommend specifying the tumor histotype in the diagnostic report. This information should be further highlighted by pathologists during MDT discussions.

Q: When a MCP qualifies for a high-grade adenocarcinoma diagnosis? Is there a cut-off or minimal percentage?

GIPAD Recommendations: 50 % is the usual percentage required for grade assessment [60]. However, evidence from the literature demonstrated that the high-grade component of MCP drives the risk of nodal metastasis regardless of its percentage. Therefore, we recommend considering any unequivocal poorly differentiated components of MCP, and grade the tumor accordingly.

Q: Should we always report PDCs in MCP? If so, how?

GIPAD Recommendations: The presence of PDCs, irrespective of their quantity, holds independent prognostic significance. Therefore, we recommend reporting whether PDCs are present or absent. No specific quantification is required.

Q: Should we specify MCP histotype?

GIPAD Recommendations: we recommend providing information on adenocarcinoma subtyping according to the WHO classification. Although the prevalence and prognostic significance of micropapillary, mucinous, and signet ring histotypes in MCP have not been fully investigated and validated, we suggest adding a comment about their worse prognosis in the pathologic report for MDT discussion. This consideration is especially relevant for the mucinous adenocarcinoma of the rectum.

Lymphovascular invasion

Lymphovascular invasion (LVI) is unanimously recognized as a crucial risk factor of lymph node metastasis in MCPs, with an overall risk ranging between 6 % and 16 % [71]. Furthermore, LVI is strongly correlated with poorly differentiated histology and tumor budding. Due to its relevance, we recommend always evaluating LVI, and reporting it as present or absent.

As advocated by the International Collaboration on Cancer Reporting [72], significant efforts are being made to distinguish between small vessel invasion (including lymphatics, capillaries, and venules) and large vessel invasion (veins), as well as to differentiate between lymphatic and venous invasion. If this differentiation is readily available on the tissue sample, we support its implementation.

*Q: Should IHC be performed to detect LVI (*i.e., *D2–40 and CD34, both as single-plex or combined with cytokeratins)?*

GIPAD Recommendations: IHC staining can enhance LVI evaluation [73], but performing it on all MCP cases is not feasible and rarely required. We recommend performing IHC staining for LVI detection only in selected cases where analysis of conventional hematoxylin-eosin staining fails to provide a definitive conclusion, as LVI is generally either clearly visible or absent. Ambiguous cases are rare.

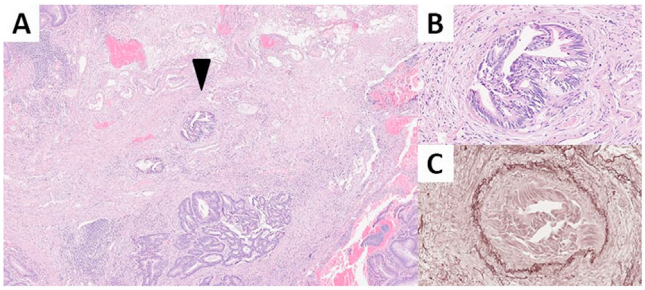

Fig. 5. LVI should be readily identifiable on morphology or with orcein stain. A) MCP showing equivocal areas of LVI on morphology. B) High-power detail of the area with equivocal LVI. C) Orcein stain highlights elastic fibers and confirms equivocal LVI.

Q: Should we differentiate lymphatic from venous invasion? What about small vessels from large vessels?

GIPAD Recommendations: These distinctions are not mandatory, but we support their implementation if it can be reliably made based on morphology alone [74]. Use of elastic fiber stains (such as Weigert's or orcein) to evaluate elastic fibers and facilitate assessment in doubtful cases can be performed, but we do not recommend the use of immunohistochemical staining for this purpose (Fig. 5).

Tumor Budding

Tumor budding refers to the presence of tumor cells organized as single elements or small groups (<5 tumor cells) and located at the invasive front of the lesion (Fig. 4). Small clusters of tumor cells with ≥5 cells lacking a glandular formation qualify as poorly differentiated clusters – PDC - and are discussed separately in the dedicated section ("*Grading and histotype*"). Nowadays, tumor budding is crucial for MCP clinical management. In 2016, recommendations from the International Tumor Budding Consensus Conference (ITBCC) [74] introduced a three-tier tumor budding scoring system, based on a 0.785 mm^2 field area at 20x magnification:

- Bd1: 0–4 buds
- Bd2: 5–9 buds
- Bd3: ≥10 buds

Remarkably, the actual clinical relevance of each score depends on the stage of the tumor. Regarding MCP and pT1 CRC, ≥5 buds per hotspot (i.e., Bd2 and Bd3) exhibit an increased risk of lymph node metastasis. We recommend reporting the specific number of buds and related score (Bd1, Bd2, or Bd3). We discourage reporting tumor budding as present/absent, or high/low tumor budding (unless contextually specifying the related scoring system and specific number).

Q: Should IHC be performed to assess tumor budding? How many deeper levels should be analyzed?

GIPAD Recommendations: Tumor budding assessment can be challenging especially in cases with tumor fragmentation, peritumoral inflammation, or difficulty distinguishing malignant epithelial cells from inflammatory cells/fibroblasts. However, conflicting data exist regarding the added value of IHC for this purpose [75]. Both the ITBCC and the Royal College of Pathologists guidelines recommend evaluating tumor budding on hematoxylin and eosin sections, reserving IHC to identify hot-spots for calculation [74,76]. In line with our overall perspective regarding IHC use in the MCP scenario, we recommend evaluating tumor budding on H&E. Deeper levels should be reserved for poor-quality sections.

Microstaging and depth of invasion

Microstaging refers to the direct measurement of tumor cell invasion within the submucosa. Microstaging has historically been considered a crucial feature for MCP [77], but more recent studies have questioned its relevance: in the absence of other high-risk features, microstaging alone was one of the most relevant causes of surgical overtreatment of otherwise low-risk MCP cases [78–80]. As detailed below, part of this issue is related to sample conditions, lesional morphology, and the measurement procedure itself.

The classification of submucosal invasion in **sessile** MCPs has been historically defined by the Kudo system [29] subsequently updated by Kikuchi [81]. The Kudo system categorizes submucosal invasion into three levels:

- SM1: Invasion into the upper third of the submucosa.
- SM2: Invasion into the middle third of the submucosa.
- SM3: Invasion into the lower third of the submucosa.

The revised Kikuchi system further specifies these classes as follows:

- SM1: invasion from the muscularis mucosa to the depth of maximum of 300 μm.
- SM2: intermediate between SM1 and SM3.
- SM3: carcinoma invasion near the inner surface of the muscularis propria.

According to this system, the SM1 and SM2 classes are associated with a low risk of nodal metastases (0 % and 10 %, respectively), whereas SM3 harbors the highest risk (up to 25 %) [29,82]. Unfortunately, the applicability of both systems is often limited in clinical practice as full-thickness submucosa and muscularis propria are not frequently available. If anything, both the Kudo and Kikuchi systems can be used with samples obtained via advanced endoscopic resection techniques (ESD, EID) or surgical approaches (TEM, colectomy).

A different classification system has been proposed by Ueno and colleagues [6]. This system requires the direct measurement in μm of the depth and width of the invasive component beyond the muscularis mucosae. The original study identified a depth of 2000 μm and a width of 4000 μm as the best cut-off for MCP risk assessment. MCP with a depth $\geq$ 2000 μm had a higher risk (17.1 %) of lymph node metastases compared to lesions with a depth $<$ 2000 μm (3.9 %). Similarly, invasion width $\geq$ 4000 μm implicated a higher risk (18.2 %) compared to $<$ 4000 μm (2.5 %) [6]. Subsequent studies identified 1000 μm as the best cut-off to stratify MCP aggressiveness, as lesions with $<$ 1000 μm depth had virtually no risk of lymph node metastasis [83]. In sessile lesions, we recommend reporting both the width and the absolute depth of invasion beyond the muscularis mucosae. The exact measurement (the actual micron-/millimeters) rather than semiquantitative cut-offs ($<$1000 um or $>$1000 um) should be used. The absolute depth of invasion refers to the depth measured from the deepest layer of the muscularis mucosae to the deepest aspect of invasion. If the muscularis mucosae is completely disrupted by malignant glands, pathologists should either attempt to approximate its presence and location (but this approximation is challenging and may introduce significant inter-observer variability) or, if this is not possible, measure up to the surface of the lesion (introducing, however, a non-negligible risk of over measurement).

Microstaging and invasion measurement are particularly challenging in **pedunculated** lesions, as traditional assessments often overestimate the risk by extrapolating criteria derived from sessile lesions. In pedunculated malignant polyps, the extent of submucosal invasion is better represented by the Haggitt classification system [84]. The Haggitt system stratifies invasion into five levels:

- Level 0: No invasion of the muscularis mucosae.
- Level 1: Invasion into the submucosa confined to the head of the pedunculated polyp.
- Level 2: Invasion extending into the neck of the pedunculated polyp.
- Level 3: Invasion reaching the stalk of the pedunculated polyp.
- Level 4: Invasion extending beyond the stalk.

Levels 1 to 3 are associated with a low risk of lymph node metastases ($<$1 %), while Level 4 carries the highest risk (up to 27 %) [84]. The Haggitt classification system also requires well-oriented whole-section specimens. Fragmentation can conceal the polyp topography (the head, neck, and stalk structural relationship), limiting the utility of the classification.

A caveat for invasion measurement is represented by lesion surface ulceration. In this setting, the measurement should start from the base of the ulcer, and not from the surface, to prevent measurement overestimation. While some studies attempted to standardize measurement techniques [85–87], precise microstaging can often be impractical, regardless of the lesion morphology. Due to this reason, we would like to stress that microstaging alone should not justify MCP surgical resection.

*Q: What system should be preferred for MCP microstaging? What about "**semi-pedunculated**" polyps?*

GIPAD Recommendations: Unfortunately, most specimens may not present the required conditions (i.e., specimen orientation) for appropriate microstaging. If "forced", microstaging systems are the major culprit of MCP overtreatment. If all conditions are met, we recommend using the direct measurement (mm or μm) of depth and width for sessile MCPs, and Haggitt levels for pedunculated lesions. The definition of "semi-pedunculated" lesion is not standardized, but generally refer to lesions with a very short stalk, making them morphologically intermediate between sessile and pedunculated lesions. The limited data available in the literature using the "semi-pedunculated" terminology has not demonstrated a superior system for microstaging [88]. However, since the definition implies the presence of a stalk, the Haggitt levels should be used for microstaging. It is important to emphasize that the term "semi-pedunculated" has not been standardized, and it is neither widely accepted nor consistently implemented in the literature. Therefore, we discourage its use.

Q. How many sections/deeper levels should be performed and analyzed for MCP microstaging?

GIPAD Recommendations: There are no data supporting the need of additional sections for MCP microstaging. We recommend performing microstaging evaluation on the tissue section with both the most representative area of tumor infiltration and preserved anatomic topography required for measurement. Deeper levels should be reserved for poor-quality sections.

Margins of resection

The presence of invasive tumor cells on the resection margin raises concerns about residual disease. Remarkably, the definition of tumor cell margins involvement varies across guidelines. The ESGE guidelines consider the resection margin as positive if tumor cells are identified within 1 mm from it [89], whereas the Japanese guidelines consider a margin positive if any infiltrating tumor cells are observed at the submucosal margin of the resected specimen [16]. We endorse the direct measurement and recommend reporting the exact distance of tumor cells from the margin (in mm or μm) rather than using semiquantitative categories ($<$1 mm and $\geq$1). Furthermore, we recommend specifying whether tumor cells show or are located in an area with diathermy effect, especially if $\leq$1 mm from the resection margin (Fig. 6). Indeed, diathermy per se can have a "therapeutic" effect on the residual tumor cell thus sparing the need for radicalization surgery. If the positive resection margin is the only risk factor of the MCP,

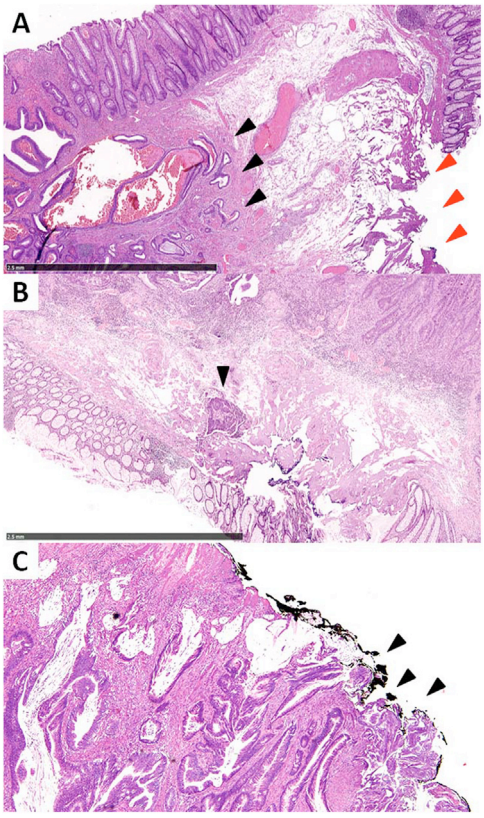

Fig. 6. Evaluation of resection margin. A) Representation of an ideal scenario for tumor cells-margin measurement, where tumor cells invasion is clearly evaluable (black arrows) as well as the distance and limit of resection margin (red arrows). B) In this case, artifactual involvement of the resection margins (black arrow) is due to free-floating tumor cells/ loose tumor fragments that were mostly likely misplaced during tissue handling. C) An example of positive margin where tumor cells with black ink and diathermic effects are located at the margin (black arrows).

especially if tumor cells are located in the diathermy area, the potential benefit of surgical resection should be thoroughly evaluated.

Q: How should we report the resection margin? Should we use a cut-off-based approach (<1 mm or >1 mm)?

GIPAD recommendations: A comment on the resection margin should always be present in the diagnostic report. Firstly, the report should clearly state whether any issue occurred (i.e., fragmented sample, stalk retraction). If none exist and margin evaluation is feasible, the exact distance between the deepest neoplastic gland and the margin should be reported. While using cut-offs is not formally wrong, we recommend providing the exact measurement (in mm or µm).

Innovative features: mismatch repair proteins and molecular pathways

Testing microsatellite instability/mismatch repair (MMR) protein status is crucial in several malignances, especially CRC [90–98]. While several studies have evaluated MMR role in stage II and III CRC [90–92,99,100], no guidelines specifically recommend testing in MCP. However, a recent study reported that MCPs with deficient MMR profile were associated with a lower risk of nodal metastases compared to proficient MMR profile MCPs [101].

Molecular profiling has improved our understanding of CRC and mutation-specific therapeutic targeting [102]. In the setting of MCP, it hints at significant clinical implications, including identification of patients with familial polyposis [2,25,45,103–110]. Despite these potential benefits, the impact of molecular profiling on MCP risk aggressiveness assessment is yet to be evaluated.

Q: Do we have to test MMR in all MCPs?

GIPAD Recommendations: we suggest integrating MMR protein status assessment into the routine MCP evaluation. In addition to the suggested prognostic potential, MMR evaluation of MCP supports Lynch syndrome algorithm assessment [111]. Therefore, testing for *BRAF V600E* mutation and/or *MLH1* promoter methylation in case of MMR deficiency (*MLH1/PMS2* loss) is also recommended.

We recognize that this statement may pose some concerns and expose pathologists to practical issues in their daily routine. Lynch syndrome universal screening and reflex testing for patients with CRC are recommended by multiple medical societies, but their regulation and implementation can vary locally and depending on the single institution's practice [112]. The role of the pathologist in guiding additional testing and supporting timely clinical decision-making is becoming increasingly central. As they are embracing their evolving responsibility within MCP multidisciplinary care pathways, we believe pathologists should encourage the appropriate but early consideration of these biomarkers within the diagnostic workflow [113].

3.3. Standardized MCP diagnostic report

As part of these recommendations, we produced a standardized report template for MCP diagnosis to provide a "checklist" that incorporates all the topics examined here (Supplementary Material). We here report some additional questions regarding how to sign out the MCP pathology report.

Q: Should the final diagnostic report include the MCP risk of metastases/recurrence? Should we make a final diagnosis of low- or high-risk MCP?

GIPAD Recommendations: No, we discourage specifying the MCP risk in the diagnostic report. Two arguments justify this choice: (I) there are other characteristics (including patient age and clinical status, lesion location, and endoscopic features) that contribute to patients clinical management and should be considered when deciding the most appropriate and patient-specific therapeutic approach; (II) avoiding such definitive risk categorization in the pathology report makes MDT discussion of each case mandatory. To this end, we additionally recommend specifying that MDT discussion is required. This remark serves to ensure that all relevant histopathological and clinical factors are considered and discussed.

Q: How many pathologists should sign out the pathology report?

GIPAD Recommendations: The MCP diagnosis presents several issues which may challenge pathologists with dedicated expertise. Therefore, we recommend that all MCP cases should be evaluated and diagnosed by two pathologists, in particular, if equivocal features are observed.

4. Conclusions

In these recommendations, GIPAD aimed to answer major dilemmas and drawbacks faced by pathologists in real-world MCP diagnosis. We collected the most recent literature evidence that formed the main structure and source for the recommendations. Still, several areas presented no specific data or clear indications. Considering the increasing global incidence and relevance of MCPs, these aspects of ambiguity require more granular and MCP-dedicated evidence. The present recommendations harness literature data and the experience of dedicated pathologists to provide a complete and detailed perspective with the ultimate goal of improving multidisciplinary discussion and patient clinical management.

A key challenge in the study of MCPs is the difficulty of applying findings derived from pT1 CRC surgical resection specimens, to cases diagnosed via endoscopic removal and polypectomy. Most studies assessing risk factors for lymph node metastases and residual/recurrent disease have relied on surgical specimens, which may

not accurately represent the risks associated with lesions considered suitable for endoscopic resection. Given the peculiar characteristics of polypectomy specimens, there is a critical need for dedicated studies focusing solely on this setting. The few data available suggest that the actual rate of lymph node metastases in polypectomy cases is significantly lower than previously reported, highlighting the importance of distinguishing between these two settings when interpreting findings [101].

As pathology-driven innovation continues to refine classification systems, the MCP diagnostic process still needs to integrate more innovative data, such as MMR testing. The little evidence available for MCP/pT1 is promising and in line with stage II and III CRC, but robust data is still lacking. Nonetheless, we have opted to include MMR testing as part of the diagnostic workup of all MCP cases to foster its adoption and underline its importance. Promising evidence is emerging from the literature for other features, such as tumor-infiltrating lymphocytes, PD-L1 testing, and molecular profiling [22,25,104–107,112–114]. We expect that MCP assessment via these new approaches will soon become part of the routine diagnostic evaluation.

We would like to conclude these recommendations by emphasizing the importance of incorporating the pathology report in the MDT discussion. MCPs represent a unique diagnostic entity requiring the combination of precise evaluation from different perspectives. To this end, regardless of whether high- or low-risk histopathologic features are evident, all cases of MCPs should be discussed in a multidisciplinary setting to determine the optimal therapeutic strategy. Instead of evaluating risk on isolated parameters, efforts should be directed to develop a composite assessment that integrates multiple factors. Enhanced risk stratification via this combined approach harbors the potential to maximize oncologic safety while minimizing unnecessary surgery.

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Declaration of competing interest

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Supplementary materials

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