Guidelines for an optimal management of a malignant colorectal polyp. What is essential in a pathology report ?

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Abstract

Colorectal cancer (CRC) has become the most common malignancy in our country. Routine screening colonoscopy is on the rise. With the recent advances in endoscopic treatment, many T1 colorectal carcinomas are now found and their percentage amenable to endoscopic resection has increased. Endoscopists and pathologists dealing with the steadily increasing number of excised colorectal polyps have to collaborate closely to optimize patient care. Therapeutic management of patients after endoscopic resection is based on precise histological criteria that determine the risk of metastasis and the need for complementary surgery. This paper summarizes the procedures for the macroscopic management of endoscopic excisions and presents the identified risk factors which should be included in a standardized pathology report. (Acta gastroenterol. belg., **2020**, 83, **53-59**).

Key words : malignant polyp, risk factors, tumour budding, micro-papillary, degree of invasion, lymphovascular permeation, depth invasion.

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide. Detection at an early stage improves its curability. Diagnosis of a malignant colorectal polyp requires the presence of neoplastic cells infiltrating beyond the muscular mucosae into the submucosa (pT1) (1,2,3). In European national screening programs, 17 % of CRCs are detected at the pT1 stage and the risk of developing advanced cancer after polypectomy is estimated at 0.6% (4). The sigmoid colon and rectum are by far the most common sites where malignant polyps are detected and excised (5).

Malignant polyps can be pedunculated or sessile and this feature on itself is associated with a significant difference in the prevalence of lymph node metastasis (6). It needs therefore to be included in the protocol. Pedunculated polyps can be removed relatively easily with a very low risk of incomplete resection (7).

The therapeutic management of malignant colorectal polyps by endoscopic resection and the follow up after resection are mainly based on specific histopathological criteria predicting tumour aggressiveness, risk of recurrence or lymph node and distant metastasis. These are : depth of submucosal invasion, lymphovascular and venous permeation, differentiation grade and status of the resection margins (8,9,10,11). In the recent literature, other potential risk factors have been proposed, such as tumour budding, histological subtype, status of the muscularis mucosae (12,13,14,15,16,17). All these risk factors are summarized in Table 1. Moreover, for a rigorous histological diagnosis, several criteria must be satisfied including optimal technical processing of the specimen.

The aim of this paper is to review all of these items in order to propose a complete standardized pathology report for the management of endoscopically resected pedunculated or sessile/flat polyps. This review is based on the TNM AJCC classification (8th edition), the 2019 WHO classification, the international consensus for prognostic criteria and the synthesis of the recent literature (1,12,18).

Table 1. — **Histological risk factors of a malignant polyp**

- Macroscopic features
- Size of the tumour
- Status of resection margin
- Degree of invasion
- Histological grade
- Lymphovascular infiltration
- Tumour budding
- Subtype adenocarcinoma (micropapillary, mucinous component...)
- Status of muscularis mucosae

Definition

pTis : polyp that contains either carcinoma *in situ* or intramucosal carcinoma without evidence of submucosal infiltration. Normally, lymphatics do not penetrate much beyond the muscularis mucosae; so, intramucosal carcinoma appears to present little or no risk of spread to lymph nodes

pT1 : penetration of cancer cells beyond the muscularis mucosae into the submucosa of the head or stalk of a pedunculated polyp or into the submucosa in a sessile lesion. Invasion of the submucosa increases the risk for metastasis via the lymphatic and blood vessels.

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Macroscopic handling

Good collaboration between clinicians and pathologists is essential for optimal management of the specimens. Localisation, size, configuration of the polyp (pedunculated or sessile according to the Paris classification (19), resection technique (one piece or piecemeal resection) and type of excision (polypectomy, endoscopic mucosal resection) (EMR), endoscopic submucosal dissection (ESD) are very important features. They are essential for the realisation of a complete report and for a fruitful discussion during the multidisciplinary meeting.

Optimal management of a malignant polyp requires an adequate handling of the specimen. Histological analysis depends on the way the lesion was removed by the endoscopist, the orientation of the specimen and the ability to view the mucosal / submucosal interface and the fixation of the specimen. One piece-resection is the only one that enables correct interpretation of the resection margins by pathologists (20).

Pedunculated and sessile or flat malignant polyps need to be handled differently. As described in the PARIS classification, a sessile lesion is defined as a lesion growing more than 2.5 mm above the surrounding mucosa (19). A flat lesion is defined as a lesion with a height that is no more than twice the height of the adjacent normal mucosa corresponding to less than 2.5mm above the surrounding mucosa. Its technical approach is similar as a sessile lesion.

A pedunculated polyp should be oriented by the endoscopist by inking the stalk or placing an hypodermic needle in the stalk (Fig. 1a). It can be sectioned in a plane parallel to the long axis of the stalk (Fig. 1b). It is important to assess the relation of the irregular front line of the cancer with the endoscopic cut line to determine whether the cancer is fully excised. The polyp should be embedded completely for histologic examination.

Flat and sessile polyps removed by ESD or EMR should be spread flat, pinned on a styrofoam board, oriented and immediately placed in a 4% formaldehyde solution by the endoscopist. These modalities make it possible to orient optimally the samples after fixation. The deep margins should be inked. After the description of the macroscopical aspects (homogeneous mucosal surface or heterogeneous with nodularities, erosions, ulcerations), major and minor axis dimensions are measured and the specimen is serially breadloafed at 2 to 3 mm intervals and entirely included in paraffin.

Two different macroscopic approaches are proposed for assessment of the lateral margins on peripheral slices:

- The “parallel technique” consists of sectioning the entire specimen into parallel slices at 2-mm intervals and including all sections.
- The “perpendicular technique” is used for specimens with a major axis of 3cm or more. This technique involves first cutting a 1-cm-wide strip of tissue at both ends of the major axis. Both strips are then subsequently sliced perpendicular at 2-mm intervals (Fig.2). The rest of the specimen is included with parallel section at 2-mm intervals. Using this method, the complete peripheral circumference can be examined perpendicular to the resection margin reducing significantly the proportion of cases with a false positive lateral margin (21).

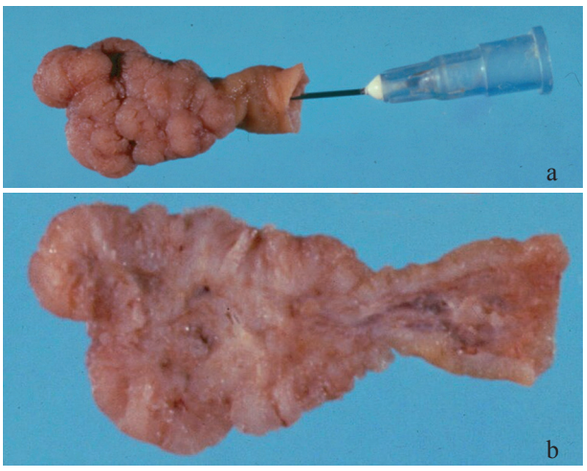

Figure 1. — Placing a needle in the center of the stalk (1a) optimizes the cut for a careful study to determine the depth of tumour invasion (1b).

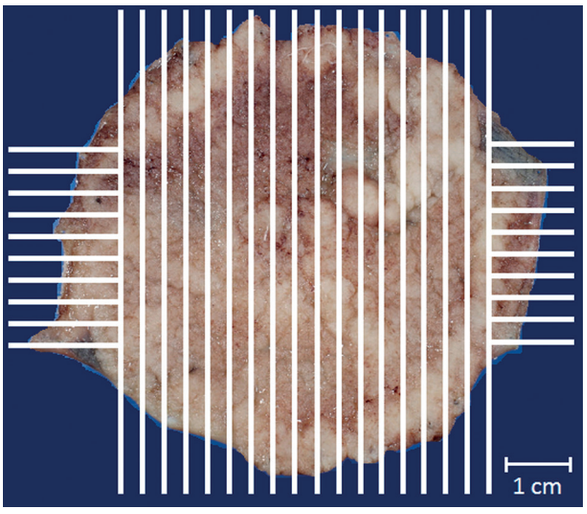

Figure 2. — Illustration of the perpendicular margin section technique : first cuta 1cm wide strip of tissue at both ends of the major axis and secondarily slice perpendicular at 2mm intervals (21).

Morphological risk factors

With recent advances in endoscopic treatments (ESD), many pT1 CRCs can be resected endoscopically with negative margins. However, lymph node metastases for which an additional oncological resection is required, are present in up to 17% of pT1 CRCs as described in a systematic review and meta-analyse published in 2013 by Beaton C. et al. (10). Identification of associated histopathological criteria would enable counselling of patients regarding this risk.

Current guidelines published by the European Society for Medical Oncology (ESMO) as well as a lot of papers in the literature show that several histopathological factors have an influence on the risk or presence of lymph node metastasis (11,13,22,24).

Polyp margins

It is widely accepted that resection margin status is a reliable prognostic factor in predicting adverse outcomes in resected malignant polyps. The deep resection margin can be easier analysed in specimens obtained by one piece resection. It corresponds to the distance between the deepest invasion front (including vascular invasion, mucin pools with malignant cells) and the deep inked margin (25). In the literature, most authors recommend a deep margin of more than 1mm (including the electrocoagulation zone) as a healthy margin. A deep resection margin of less than 1mm should be considered as an involved margin.This has been a strong predictor, when associated with other risk factors, for adverse outcomes in terms of residual tumour, tumour recurrence or lymph node metastasis (8,26).When the deep resection margin is involved or less than 1 mm from the tumour front, the percentage of local relapse ranges between 21 and 33%, while the risk of relapse ranges from 0% to 2% in malignant polyps with a distance to the resection margin greater than 1mm (26). By far, one of the high-risk feature after polypectomy is a non-radical or undeterminable deep resection margin (27).

Positive lateral margins can also cause recurrence but these margins can be treated more easily by a complementary endoscopic treatment if necessary. Lateral margins can be analysed only in one piece resection and it is recommended to specify whether a lateral positive margin contains adenomatous tissue or passes through malignant tissue.

Degree of invasion

The role of the depth of invasion in increasing the risk of nodal metastasis in CRC has been well known for a long time and is published in all the textbooks on digestive pathology. Haggitt level is used for pedunculated polyps (11,28). Its application is dependent on the orientation of the pedunculated polyp and the presence of a clearly defined stalk.

The Haggitt system corresponds to four levels of tumour cell invasion:

Level 0 : tumour has not extended below the muscularis mucosae

Level 1 : Tumour cells invading within the head of the polyp

Level 2 : Tumour cells invading the level of the neck of the polyp

Level 3 : Tumour cells invading the stalk

Level 4 : Tumour cells invading into the bowel wall below the stalk

The incidence of lymph node metastasis is virtually 0,0% in pedunculated polyps with polyp head invasion (defined as the upper limit of Haggitt level 2) without other high-risk criteria as compared to 6.2% in cases with polyp stalk invasion (29).

For flat and sessile polyps, some authors use the Kikuchi-sm grade (30) to measure the submucosal invasion dividing the submucosal layer into three levels : sm1 indicating infiltration into the upper third of the submucosa, sm2 the middle third and sm3 the lower third. The prevalence of lymph node metastases in accordance with these different levels is respectively 2%, 8% and 23% (31). The problem with this system is however that the polypectomy or mucosectomy specimens contain only a limited part of the submucosa without the muscularis propria.

To overcome these limitations, it is easier to use for flat and sessile polyps the UENO proposition published in 2004 (8). The depth of submucosal invasion is measured from the deep part of the muscularis mucosae to the invasion front of the tumour. If the muscularis mucosae is focally destroyed by tumour, the proposition is to draw a horizontal line following the residual muscularis mucosae persistent on both sides and measure the tumour thickness from this line to the deepest point of invasion.

In the literature, it has been suggested that a sub-mucosal invasion depth of more than 1000 microns is significantly associated with an increased risk of lymph node metastasis (32). Nodal involvement risk for a cancer with a submucosal depth of invasion between 1000 to 2000 microns is about 1.3 to 4% while in case of submucosal invasion depth of more than 2000microns, lymph node metastasis occurs in 12 to 18% of cases (10).

Histological differentiation

Poorly differentiated tumours (<50% of glandular features) are significantly associated with a higher risk of lymph node metastasis when compared with well (>95% of glandular features) or moderately (50 to 95% of glandular features) differentiated tumours in a meta-analysis of 13 studies (10).

Some subtypes of CRCshave been recently described as high-grade carcinoma:

Micropapillary carcinoma (MC) is a recently described subtype of CRC. In the WHO 2019 definition : MC is a carcinoma composed of small clusters of inversed tumor cells within stromal spaces that mimic vascular channels (1) (Fig.3). By immunohistochemistry, the negativity of D2-40 for these stromal spaces excludes lymphatic emboli. The «inside-out» pattern can be detected by EMA and MUC1 immunohistochemistry. The inverted polarity of the tumoral cells disturbs the epithelial adhesion and might explain the aggressive behaviour of this type of tumour (33). A component of MC is more frequent than pure MC and correspond from 4.3 to 27.8 % of CRC (34). Verdu noted that malignant polyps with MC are associated with the worst prognosis whatever the percentage of the

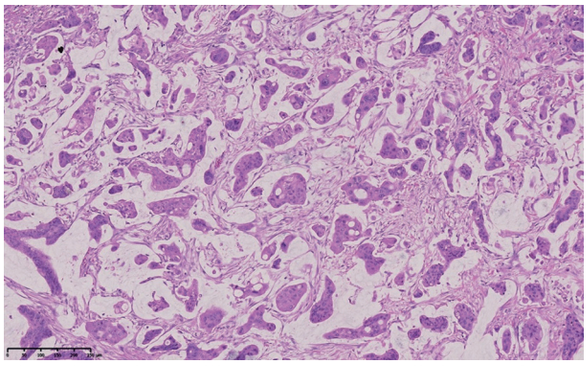

Figure 3 — Micropapillary component : small clusters of tumor cells within stromal spaces (x10).

component (17). In the literature it is stated that this type of carcinoma is more often found in an advanced stage of the disease, which, in turn, increases the rate of lymph nodes metastasis (34,35). MC shows *BRAF* and *KRAS* mutations, and almost all cases are microsatellite stable. Thereby, it is important to always report the presence of MC in the pathological report

Mucinous carcinoma. As described in the WHO 2019 classification, pure mucinous adenocarcinoma (MAC) is a subtype of carcinoma composed of > 50% of pools of extracellular mucin that contain malignant epithelium. When it represents <50% of the total lesion, it is considered as an adenocarcinoma with a mucinous component. MAC represents 5-15% of all primary CRC and more often originates from the right colon. It affects more women than men. It is associated with a high risk of peritoneal metastases that can be explained by the production of mucus which, under pressure, allows cancer cells to gain access to the peritoneal cavity (36*)*. Pure MAC has a distinct molecular profile compared to classical adenocarcinoma, with a higher incidence of *KRAS* and *BRAF* mutations and microsatellite instability (MSI) or Mismach repair deficiency (MMRd) (37) .Andrici stated that MMRd is a powerful prognostic factor in pure MAC, although in addition histological grade remains prognostically important (38). Pure MMRp (Mismach repair proficient – MSS or MSI-L) MAC is associated with a worse prognosis. Although these findings are not clearly established for adenocarcinomas with a mucinous component and moreover for stage 1 adenocarcinoma, it is important to perform MMR status for all new CRCs as recommended by the Belgian Commission of Personalized Medecine (Com Per Med) (39).

Signet ring cell carcinoma is a variant of adeno-carcinoma defined by the presence of >50% of tumour cells with prominent intracytoplasmic mucin, displacing the nucleus aside (1). This carcinoma shares some molecular features with MAC. MMRp signet ring cell carcinoma for instance is associated with a worse prognosis (40).

Lymphovascular permeation

Lymphovascular permeation, observed in up to 17% of all malignant polyps is significantly associated with lymph node metastasis (10). It is thus useful , when a doubt persists with regard to a possible lymphatic permeation, to perform D2-40 immunostaining, which is specific for lymphatic endothelium.

Normally, lymphatics do not penetrate much beyond the muscularis mucosae, and intramucosal carcinoma (pTis) appears to present little or no risk of lymph node spread. This theory has been challenged by recent studies which have shown that lymphatics are present within the lamina propria or with rare extension into the lamina propria limited to the region at the base of the crypts (41,42). Moreover, recently, cases of intramucosal CRC with lymphatic permeation have been reported (43). It is therefore useful to specify the tumoral component even when it is restricted to intramucosal infiltration and to check lymphatic pemeation even in cases of intramucosal carcinoma

Tumour budding

Tumour budding (TB) is an important additional prognostic factor for patients with malignant polyps. The international tumour budding consensus (ITBCC) defines tumour budding as a single tumour cell or a cluster consisting of four tumour cells or less observed in the front of invasion. TB must be distinguished from a poorly differentiated cluster (PDC), which is defined as five or more cells (12). TB is now recognized as a robust independent predictor of lymph node metastases in pT1 colorectal cancer - malignant polyps (12) It is also associated with lymphovascular permeation (44,45). Therefore patients with tumour budding may benefit from oncological resection (10,46,47). Standardization of scoring is crucial in clinical practice.

The ITBCC recommends to score only on haemato-xylin-eosin stained slides (12). Sometimes tumour buds may be obscured by inflammatory infiltrates or may be difficult to distinguish from stromal cells. In these cases, pankeratin immunohistochemistry can help to visualize and confirm that the cells are tumour buds. The procedure proposed for reporting tumour budding in daily practice was published by the ITBCC in 2017 (12).

They recommend :

1. To score in a single field with the highest density of tumour buds (hotspot method) at the front of invasion
2. To count tumours buds in the selected “hotspot”
3. To use a three-tier system :

a. 0-4 buds : low budding (Bd 1)
b. 5-9 buds : intermediate budding (Bd2)
c. 10 buds : high budding (Bd3)

4. To report the score per field area. The proposed field area is 0.785mm^2 which corresponds to the field area adopted by the Japanese society and by the ITBCC. A conversion table is developed to normalize bud counts to

Table 2. — **Conversion table to normalize the bud count for different microscope types (12)**

Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
18	0.636	0.810
19	0.709	0.903
20	0.785	1.000
21	0.866	1.103
22	0.950	1.210
23	1.039	1.323
24	1.131	1.440
25	1.227	1.563
26	1.327	1.690

0.785 mm^2 for microscopes with ocular lenses with other fields of vision and has been published by ITBCC(Table 2) (12).

Bd 2 and Bd 3 are associated with an increased risk of lymph node metastasis (46,48,49).

Status of muscularis mucosae

According to the recent literature, the muscularis mucosae status (MM) in pT1 CRCs after endoscopic treatment is associated with nodal metastasis (6,50). The authors classify the status of the muscularis mucosae using desmin immunostaining as either MM grade 1 or MM grade 2. MM1 is noted when the muscular fibers of the muscularis mucosae are still maintained (they maintain their original direction and continuity with disappearance of only a small part – within 3 to 4 normal glands wide (because of carcinoma invasion)). The cases fall into MM grade 2 if the muscular fibers of the muscularis mucosae are fragmented and have lost their original alignment or show wider disappearance. The rate of lymphovascular infiltration and lymph node metastasis appears higher (up to 20% when associated with lymphovascular invasion, budding and poor differentiation) in patients with MM grade 2 (6,50).

Conclusion

Endoscopists encounter malignant polyps with increasing frequency. After endoscopic treatment, however, if there is a risk of lymph node metastasis, additional surgery with lymph node dissection should be considered and discussed in a multidisciplinary approach. The decision to perform a surgical resection rests mainly on the assessment of histological features associated with an increased risk of lymph node metastases (LNM). In the literature, risk factors for LNM in a malignant polyp are well identified and include: poor differentiation, presence of lymphovascular or venous permeation, depth of submucosal invasion more than 1000 microns, involvement of the deep margin, presence of budding and grade 2 status of the muscularis mucosae. If no risk factors are present, the probability of LNM is almost zero rendering complementary oncological surgery unnecessary. Of course, this decision must be made in careful consultation between the treating physician and the patient.

Accurate assessment of these factors is essential for correct identification of at-risk patients while avoiding

Table 3. — **Standardized report of malignant colorectal polyp (pTis /pT1)**

Malignant polypectomy including intramucosal carcinoma (pTis)
Site : ___ Specimen Integrity : One piece ___ Fragmented ___ ____
Polyp : Size : ___ cm non evaluable___
Polyp Configuration : Pedunculated ____ Stalk length: ___ cm non evaluable ____
Sessile ____ Flat ___ ____ ____ ____ _
Type of Polyp in which invasive carcinoma crose : Tubular adenoma ___ Villous adenoma ___ Tubulovillous adenoma *___ TSA___ SSA/P
Others :___
Histologic Type : Adenocarcinoma : LG (well, moderately differentiated) :____
HG (poorly differentiated) :____
Adenocarcinoma with HG component : Mucinous, Micropapillary ___ Signet-ring cell ___,
Other : ___
Immunophenotype : MMRp ___ ; MMRd___ ; non evaluable___
Microscopic Tumor Extension : Invasion (deepest) : ___
- Flat/ Sessile polyp (UENO classification) : Depth : ___ µm
- Pedunculated polyp (Haggitt classification) : Level 1 ___ level 2__
level 3___ level 4____ non evaluable___

Margins :
- Deep Margin : Distance of invasive carcinoma from margin: ___ mm, non evaluable ___
- Lateral mucosal Margin : ___ non evaluable ___ Uninvolved by invasive carcinoma ___ Involved by invasive carcinoma ___ Involved by adenoma___

Lymph-Vascular permeation : non identified ____ present : lymphatic ____ venous ____
Perineural Invasion : non identified ____ present
Tumor budding : absent____
present ____ Number of buds/0,785 mm^2___ Bd1___Bd2___Bd3___
non evaluable ____
Status of muscularis mucosae : MM1 (maintenance), MM2 (fragmented or disappeared)
Additional Pathologic Findings : ___
pTNM (8th Edition) : pTis___ pT1___

overtreatment. Pathologists have to specify these risk factors in their report.

To facilitate the communication between gastro-enterologists and pathologists we propose to standardize the pathology report including all risk factors described in the literature in the form of a standardized report as presented in Table 3.

Conflict of interest : none.

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