Grading colorectal adenomas needs more markers of dysplasia

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EDITORIAL

High-grade dysplasia (HGD) in colorectal adenomas is nowadays recognized as a risk factor for malignant transformation (1). In addition, the presence of high-grade dysplasia or villous component delineates an advanced adenoma, and imposes more intense endoscopic follow-up (2). The current histopathological criteria for grading colorectal adenomas are based on Vienna revised classification, which considers precise cyto-architectural parameters shown in Table 1 (3).

TABLE 1

Morphological criteria for dysplasia grading (modified from: Vieth M et al.)

Variables	Low-grade mucosal/ intraepithelial neoplasia (LGMN)	High-grade mucosal/ intraepithelial neoplasia (HGMN)
Glands	Villous	branching, cribriform, irregular, solid
Expansion	till surface	till surface
Epithelial differentation	top-down and exceptional down-top	no maturation towards surface
Goblet cells	(+)	–/(+) retronuclear, atypic
Nuclear rows	02-Mar	02-May
Nuclear size	Palisading	Enlarged
Chromatin	+	++
Nucleoli	None	Few small

Recent works stressed that, although high grade dysplasia is universally considered a risk factor for the development of invasive lesions, this is not included in the Dutch guidelines for endoscopic surveillance due to its inter-observer variability (3,4).

In particular, Kuijpers et al. (5), when comparing the results of 37 different laboratories, observed a considerable inter-laboratory variability and concluded with the need for a better standardization of the grading criteria for these lesions.

Histopathology diagnosis based on biopsy underestimates colorectal dysplasia in approximately 10% of the cases compared with complete resected specimens and advanced neoplasia has been underestimated in over 60% of the cases (6).

What can be done to improve and standardize the assessment of the degree of dysplasia in these lesions?

In my opinion, morphology obviously has to guide the pathologist in the evaluation of colorectal adenomas, and the criteria illustrated in Table 1 are current and must be considered.

Clearly low or high case cases should not require further investigation for their definition, but lesions with an ambiguous degree dysplasia (the old "moderate grade dysplasia") may be present, and it is in these cases that the need for further tools besides pure morphology becomes evident.

Literature studies always focused on identifying markers predicting the development of intraepithelial or infiltrating neoplasm from non-malignant adenomatous lesions, but no study is available regarding the identification of markers for the distinction between low and high-grade dysplasia.

Starting from histochemical techniques, just one study focused on the evaluation of mucins in advanced carcinomas and in adenomas with different degrees of dysplasia using simply Periodic Acid Schiff (PAS) staining.

The results of this study highlighted that the higher the grade of atypia of adenomas, the fewer the lesions of which goblet cell mucus and the mucus at the luminal surface or that in the luminal accumulation stained red (7).

Using immunohistochemistry, the expression of nuclear beta-catenine correlates with the presence of intraepithelial cancerization in the polyps and exposes its role in colorectal carcinogenesis.

The expression of E-cadherin and P-cadherin in adenomas suggests that these molecules may play a role in the formation of adenoma, although not necessarily involved in neoplastic progression. No information is given about the expression in the different grades of dysplasia (8).

Moreover, adenomas with high grade dysplasia and intramucous carcinoma can be correctly differentiated by MMP3 and CXCL1 stromal expression, MMP3 immunohistochemical expression in lamina propria appears to be highly specific for the detection of the malignant component in sporadic carcinomas. Also in this case, no information is given about the expression in the different grades of dysplasia (9).

Insulin-like mRNA binding protein 3 (IMP3) expression has been evaluated in adenomas and in colorectal carcinoma, demonstrating that its expression is a reliable marker for the diagnosis in endoscopic biopsies (10).

It would be interesting the evaluation of this marker in different grades of dyplasia, as it has been demonstrated that IMP3 expression could vary in low- and high grade intraepithelial lesions or in reactive atypical lesions in many organs (11,12).

Finally, many molecular markers have been identified in the adenoma-carcinoma transition, starting from APC and p53 to the more recent BRAF, SKA3 and DSN1, but no investigations have been conducted considering different grades of dysplasia (13-15).

In conclusion, the assessment of dysplasia in colorectal adenomas requires careful evaluation from the morphological point of view, which in most cases appears to be sufficient for proper classification.

In doubtful cases, where diagnostic orientation is uncertain, there is a need to identify new histochemical, immunohistochemical or molecular markers that could allow to categorize the dysplasia in the more appropriate way, because the biologic and surveillance implications are relevant and should condition the clinical approach.

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CONFLICT OF INTEREST

None.

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