

Dysplasia can be a pain in the gut
Barbara J. McKenna

University of Michigan
barbmcke@umich.edu

Introduction

Over the past 20 years or so, we have been bombarded with dysplasia: biopsies looking for dysplasia from patients with ulcerative colitis, Barrett's esophagus, atrophic gastritis; and thousands and thousands of adenomas. We have read and heard myriad discussions about definitions, clinical implications, lack of interobserver agreement, histologic features. Clearly the diagnosis of dysplasia in the gastrointestinal tract is an area of major concern.

What makes the diagnosis of dysplasia such an area of concern? Perhaps it is because most examples of dysplasia in the setting of Barrett's esophagus or ulcerative colitis have no helpful endoscopic features, so that the diagnosis depends solely on histology. Perhaps it is because the implications for these diagnoses are significant, including follow-up endoscopic examinations that are expensive and unpleasant. Perhaps it is because most pathologists' experience in this area is limited and nearly devoid of follow up correlation to tell them how they are doing. All of these factors likely contribute to anxiety over diagnosing dysplasia in these settings. However, the most likely cause of angst is the fact that the features of neoplasia may be only subtly different from those of regeneration, and the distinction maddeningly difficult. An attractive solution would be to define precancerous epithelium by its molecular changes, but this is not yet practical. At present, we must still do the best we can with morphology.

Definitions and terminology:

The term "dysplasia" generically means an abnormality in growth. In adults, "dysplasia" generally refers to epithelial alterations that are steps in the transition from normal to malignancy. In 1983 Riddell and a group of gastrointestinal pathologists published the paper that established the term "dysplasia" to describe premalignant lesions in ulcerative colitis (15). In this paper dysplasia is defined as "an unequivocal neoplastic epithelial proliferation." Thus, the ability to diagnose dysplasia is the ability to distinguish what is definitely neoplastic from what is not, certainly not an easy task. Some pathologists seem not to understand the fact that the diagnosis of "dysplasia" is synonymous with the diagnosis of neoplasia. Thus, they may use terms such as "atypia" for lesions that are truly dysplastic, while others are likely to use the same "atypia" to diagnose reactive or regenerative epithelium, creating confusion among the clinicians who read their reports.

The Riddell paper also established the nomenclature for GI dysplasias—low grade and high grade. It is expected that all pathologists will comply with this two tier system for diagnosing gastrointestinal dysplasias. Many pathologists have persisted in using the now-outdated three-tier system, once used for uterine cervical biopsies, grading dysplasias as mild, moderate, or severe, instead of low and high-grade. This three-grade system for dysplasia causes difficulty for the gastroenterologist in deciding management when the term "moderate dysplasia" is used, since the management recommendations do not include

that term. Furthermore, some pathologists are not aware that “carcinoma in situ” and “intramucosal carcinoma” are diagnoses that have been omitted from most classification schemes and, as a result, they have no specific management implications.

The Riddell paper was based on a study involving several exchanges of microscopic slides from chronic colitis cases, mainly ulcerative colitis, among eleven specialized gastrointestinal pathologists. They recognized that there were some epithelia with histologic features that were not clearly dysplastic, yet they also were not clearly regenerative. These were designated as “indefinite for dysplasia.” Initially, the indefinite category was divided into 3 subcategories based on the participants’ histologic suspicions. Most gastrointestinal pathologists now have a single category of indefinite for dysplasia which includes all epithelia that they cannot confidently classify as either regenerative or dysplastic.

Criteria for low-grade and high-grade dysplasia:

The histologic features of dysplasia are the classic cytologic and architectural changes of malignancy that are taught in introductory pathology classes in medical school and relied upon throughout surgical pathology and cytopathology. Dysplasias are often taught as specific entities with clear-cut histologic and cytologic criteria that separate low-grade from high-grade. The histologic features are generally described as follows:

- Cytologic:
 - Nuclear enlargement, hyperchromasia, and pleomorphism
 - Increased numbers of mitoses, especially near or on the surface
 - Loss of cytoplasmic maturation, including decrease or loss of mucin
- Architectural
 - Nuclear crowding and stratification, loss of polarity
 - Complex arrangements and crowding of tubules
 - Abnormal surface contours—often villiform rather than flat

Then, the distinction between low-grade, high-grade and indefinite are often listed as follows:

- Low grade:
 - Mild, if any architectural abnormalities
 - A combination of nuclear stratification, enlargement, hyperchromasia, and pleomorphism, that extends onto the surface, but with preservation of nuclear polarity
- High-grade:
 - Architectural distortion is present and may be marked
 - Nuclear abnormalities are more pronounced than in low grade dysplasia
 - Loss of nuclear polarity
- Indefinite for dysplasia. Criteria not definable—published criteria include
 - marked nuclear atypia in deep mucosa, with surface maturation, or nuclear atypia that “mostly matures”
 - Biopsies with disturbing cytologic/architectural changes, with significant inflammation or lack of evaluable surface

Most pathologists realize that there is no specific histologic point that separates low-grade from high-grade dysplasia, making this cut-off highly subjective. In addition, although the terminology is the same, and published histologic features are similar, dysplasias occurring in different settings, such as in colonic adenomas, ulcerative colitis, Barrett's esophagus and atrophic gastritis, have different appearances, and perhaps different thresholds for separating low- from high-grade dysplasia. Thus, despite the fact that there is an accepted terminology and a set of histologic criteria, the task of diagnosing dysplasia is anything but straightforward.

Clinical implications of the diagnoses

Adding to the anxiety of pathologists dealing with these biopsies is awareness of the implications of their diagnoses. The diagnoses of both low-grade dysplasia and indefinite for dysplasia in ulcerative colitis and Barrett's mucosa mean more stringent surveillance with more frequent endoscopies and more fastidious biopsy sampling. Thus, the category of indefinite for dysplasia should not be indiscriminately used for biopsies that are most likely regenerative rather than neoplastic. Certainly, the diagnosis of high-grade dysplasia in any setting has significant management implications, often immediate resection. It is not surprising that pathologists who have limited experience in this difficult and important area are increasingly seeking consultation from specialized gastrointestinal pathologists. It is also not surprising that one recommendation for dealing with a biopsy diagnosed as high-grade dysplasia is to ask for verification from a consultant.

The Problem Areas

There are two principle areas of difficulty in diagnosing and reporting gastrointestinal dysplasias, and these relate to two important management thresholds. The first is in distinguishing mucosa with regenerative epithelial changes from something that deserves to be called either indefinite or low grade. The second is deciding when mucosa with high-grade dysplasia also harbors carcinoma.

Is it regenerative or low-grade dysplasia?

The most daunting challenge that pathologists face in evaluating biopsies from patients with Barrett's or ulcerative colitis is the diagnosis of low-grade dysplasia in the setting of chronic epithelial injury. It is challenging because the features used to diagnose low-grade dysplasia are also features commonly present in regenerative epithelium, and regenerative epithelium is a regular component of such mucosae. Both dysplasia and regenerative epithelium have cytologic features that include nuclear enlargement, hyperchromasia, stratification, and increased numbers of mitoses. In fact, in a single high power microscopic field, the two may be indistinguishable. For the most part, it is the *distribution* of these changes that serve to distinguish regenerative from low-grade dysplastic epithelium. Regenerative changes tend to be most marked in the normal proliferative zone of the mucosa—that is, deep to the surface—with maturation toward the surface. In contrast, dysplastic epithelium, being neoplastic, doesn't follow such rules and is often most evident at or near the surface. But these are not always easy patterns to appreciate, especially in small and randomly oriented biopsies.

Some examples of regeneration that may resemble low grade dysplasia:

- The basal regeneration that is common in Barrett's mucosa can look exactly like low-grade dysplasia, but it is accompanied by gradual loss of atypical features with maturation toward the surface. Thus, many experienced GI pathologists find it virtually impossible to diagnose low-grade dysplasia in Barrett's epithelium unless there is surface epithelial involvement.
- In reactive or chemical gastropathy, an intense neck and pit proliferation in response to surface epithelial injury may be confused with dysplasia. In this condition, the necks and pits are elongated and lined by an epithelium that is commonly more cuboidal than columnar, and has enlarged, often hyperchromatic nuclei, and mitoses in cells close to the surface. Because the normal proliferative zone of the gastric mucosa is the neck region, and because this region is close to the surface, this neck and pit expansion and proliferation mimics dysplasia.
- Finally, in any colitis, especially in the active phases, the epithelium proliferates in response to the injury, resulting in crypts lined by cells with enlarged, hyperchromatic nuclei and frequent mitoses. This regenerative epithelium may even stratify, so that it truly looks dysplastic. It is this epithelium that has led experienced pathologists to recognize that the diagnosis of low-grade colitic dysplasia in the face of active inflammation may be impossible. This resemblance between neoplastic and non-neoplastic proliferative epithelia is not limited to inflammations. In hyperplastic colonic polyps, proliferation of epithelium in the basal crypts may look exactly like low-grade dysplasia.

It is important for pathologists and the clinicians with whom they deal to recognize that all low-grade dysplasias do not look alike. All have epithelium that is neoplastic, but some have pronounced cytologic changes with few architectural abnormalities, while in others the nuclei are quite abnormal, but are only slightly stratified. In yet others, the biopsy captures dysplastic-looking epithelium that underlies a normal surface. Because of this heterogeneity, and because of the overlap of features with regenerative epithelium, it is at this low end of the dysplasia spectrum that most of the diagnostic difficulties exist, even among the most experienced pathologists. (25-32)

When does Dysplastic Mucosa also Contain Carcinoma?

There are two issues related to diagnosing carcinoma in the setting of dysplasia. The first is the use of the term "carcinoma in situ", and the other relates to the diagnosis of invasive carcinoma. In the Riddell, et al paper in which the definition of dysplasia appears, that definition also states that high-grade dysplasia includes something previously referred to as "carcinoma in situ." (15) Thus, the diagnosis of "carcinoma in situ" is not to be used, and any epithelial changes that formerly led to that diagnosis in ulcerative colitis are to be called "high-grade dysplasia."

The term "carcinoma", then, refers to invasive carcinoma. The point at which this term is appropriate differs based on the site within the gut, because of the differences in distribution of lymphatics. We assume that carcinomas of the GI tract, with rare exceptions, have no metastatic potential unless they have access to lymphatics. Thus, carcinoma is diagnosed when the neoplastic cells invade tissue in which lymphatics are present. In the esophagus, stomach, and small intestine, lymphatics are present in the lamina propria. In

contrast, the colonic lamina propria has virtually no lymphatics; they only begin to appear in the superficial submucosa and muscularis mucosae. Therefore, in the esophagus, stomach and small bowel, anything that invades the lamina propria is a carcinoma with metastatic potential, whereas in the colon and rectum, only invasion of the superficial submucosa implies metastatic potential. As a result, invasion only of lamina propria in the colorectum can be considered to be clinically the same as high-grade dysplasia, and most GI pathologists have adopted this approach. There are gut pathologists who still make the diagnosis of “intramucosal adenocarcinoma”, but usually add a comment that this carcinoma will not metastasize.

How does one identify invasive carcinoma in an endoscopic biopsy? Submucosal invasion is generally readily identified by the desmoplasia that carcinomas throughout the gut commonly stimulate. This desmoplasia is the fibrotic and sometimes inflamed stroma that surrounds neoplastic tubules, and only seems to occur when the invasion has reached the submucosa; it almost never occurs when the invasion is confined to the lamina propria. Thus, the finding of desmoplasia is marvelous evidence that invasive carcinoma has occurred, and it is especially useful for the colon and rectum where carcinoma is not diagnosed until the invasion has reached the submucosa. In contrast, in the esophagus and stomach, invasion of the lamina propria satisfies the definition of carcinoma. It is in these sites where we have the greatest difficulty recognizing the subtlest signs of lamina propria invasion. Even the most experienced pathologists have trouble identifying the first evidence of invasion of the lamina propria in a biopsy. There are no set criteria for making this decision. In general, since we cannot rely on desmoplasia, we hope to find small clusters of neoplastic cells or single cells in the lamina propria, separated from the adjacent dysplastic tubules, but this is not terribly reproducible. Another criterion used is architectural complexity more striking than expected in even very high grade dysplasia, forming confluent cribriform arrangements of cells—again, not a reproducible criterion. Other features that raise suspicion for invasive carcinoma include the presence necrotic debris within dysplastic tubules and ulceration of the dysplastic mucosa, since dysplasias without cancer rarely undergo necrosis and do not ulcerate. These latter features are especially helpful in biopsies of dysplastic Barrett’s mucosa. (33) Very often, the diagnosis of incipient invasion is a matter of gestalt and is based on the experience of the observer and his or her visual and probably emotional, response to the microscopic appearance of the biopsy.

The Reproducibility Problem

It has been proven in several studies that even the most experienced gastrointestinal pathologists who deal with these types of biopsies have difficulty agreeing on which epithelia are low-grade dysplasia or indefinite for dysplasia. They also have difficulty agreeing on when carcinoma is present in mucosae with high grade dysplasia, particularly in Barrett’s biopsies. In contrast, they are much more likely to agree on what is non-dysplastic and what is high-grade dysplasia. Such studies indicate that equally experienced pathologists are likely to include different epithelial changes in the categories of indefinite for dysplasia or low-grade dysplasia; thus, these diagnoses are not reproducible among pathologists. A recently published study of reproducibility in the diagnosis of epithelial

changes in Barrett's mucosa by 12 GI pathologists found that reproducibility was good if all categories that did not require intervention (negative, indefinite and low-grade dysplasia) were compared with the categories that required intervention (high-grade dysplasia and carcinoma). (29) However, the reproducibility among the group for individual categories was not nearly as good. It was best for carcinoma, slightly less for high-grade dysplasia and negative, considerably less for low-grade dysplasia and much less for the indefinite category. This is much the same as the result of the study of chronic colitis that led to the Riddell et al paper. (15) Haggitt acknowledged that in Barrett's mucosa the distinction between indefinite for dysplasia and low grade dysplasia was often impossible, and since the management implication for both diagnoses was the same, he suggested that there be a single category combining the two diagnoses for more effective endoscopic and biopsy surveillance. (30)

What should pathologists do?

The ability to make these diagnoses with comfort and confidence requires not only frequent exposure to these problem biopsies, but clinical correlation and follow up. Detailed and consistent communication between endoscopist and pathologist is essential, so that pathologists learn of the clinical circumstances in which the biopsies were taken, the actions instituted based on their diagnoses, and, perhaps most critically, the resultant patient outcomes

What can pathologists do to assure that we are giving the most accurate diagnosis possible in surveillance biopsies of the gastrointestinal tract? First, we must comply with the accepted two-tier system of nomenclature, using the terms "low grade dysplasia" and "high grade dysplasia", rather than "mild, moderate, and severe dysplasia." The term "carcinoma in situ" has no place in the lexicon. The terms "atypia" and "intramucosal carcinoma" may communicate different messages than intended, so it may be advisable to avoid their use, as well. Classifying a biopsy as "indefinite for dysplasia" is appropriate in some cases, but we should resist overuse of the category, and be aware that such a diagnosis may have the same management implication as a diagnosis of low-grade dysplasia.

Pathologists will need to familiarize themselves, as much as possible, with the spectrum of appearances that comprise the low grade and high-grade dysplasias. For pathologists who see small numbers of such cases, this is easier said than done. Review of cases among members of a pathology group or department may expand the experience of each member and promote consistency within the group. However, as with all groups that tried in the past, one cannot expect uniform agreement, especially among the more difficult cases—those in which the differential is between regenerative changes and low-grade dysplasia. In selected cases it may be appropriate to seek expert consultation; examples might include those cases in which one is unsure of a diagnosis that will have significant consequences, such as a diagnosis of high grade dysplasia in a biopsy from a patient with Barrett's esophagus.

In an ideal world pathologists and gastroenterologists would establish excellent lines of communication about all kinds of cases. We know, of course, that this does not always happen. We pathologists may need to seek out follow up information to assess the accuracy of our diagnoses, not only for surveillance biopsies, but for inflammatory diseases

too. In the end, surveillance biopsies from patients with chronic colitis, Barrett's esophagus, or atrophic gastritis will remain challenging, frustrating, and frequently anxiety-producing cases. On the other hand, these are the cases in which the gastroenterologists, and, therefore patients, rely heavily upon our diagnoses to decide on management, perhaps more than for any other types of gastrointestinal biopsies, and so it is with these cases that we have one of our best opportunities to serve patients.

References

Parts of the above text are abridged and rearranged components of a review article written by McKenna and Appelman (McKenna BJ, Appelman HA. Dysplasia can be a pain in the gut. *Pathology*. 2002 Dec;34(6):518-28). Rather than delete and re-number the references, all of the references from that paper are listed below.

1. Warren S, Sommers SC. Pathogenesis of ulcerative colitis. *Am J Pathol* 1949;25:657-679
2. Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967;8:423-434
3. Evans DJ, Pollock DJ. In-situ and invasive carcinoma of the colon in patients with ulcerative colitis. *Gut* 1972;13:566-570
4. Hulten L, Kewenter J, Ahren C. Precancer and carcinoma in chronic ulcerative colitis. A histopathological and clinical investigation. *Scand J Gastroent* 1972;7:663-669
5. Fenoglio CM, Pascal RR. Adenomatous epithelium, intraepithelial anaplasia, and invasive carcinoma in ulcerative colitis. *Am J Dig Dis* 1973;18:556-562
6. Yardley JH, Keren DF. "Precancerous" lesions in ulcerative colitis. A retrospective study of rectal biopsy and colectomy specimens. *Cancer* 1974;34:835-844
7. Gewertz BL, Dent TL, Appelman HD. Implications of precancerous rectal biopsy in patients with inflammatory bowel disease. *Arch Surg* 1976;111:326-329
8. Lennard-Jones JE, Misiewicz JJ, Parrish JA, et al. Prospective study of outpatients with extensive colitis. *Lancet* 1974;1:1065-1067
9. Cook MG, Goligher JC. Carcinoma and epithelial dysplasia complicating ulcerative colitis. *Gastroenterol* 1975;68:1127-1136
10. Riddell RH. *The Gastrointestinal Tract*. Baltimore: Williams & Wilkins Co, 1977; Chapter 8, The precancerous lesion of ulcerative colitis
11. Nugent FW, Haggitt RC, Colcher H, Kutteruf GC. Malignant potential of chronic ulcerative colitis. *Gastroenterol* 1979;76:1-5
12. Ekelund G, Lindstrom C. Histopathological analysis of benign polyps in patients with carcinoma of the colon and rectum. *Gut* 1974;15:654-663
13. Morson BC. Evolution of cancer of the colon and rectum. *Cancer* 1974;34:845-849
14. Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;36:2251-2270
15. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983;14:931-968

16. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia. A new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25:579-586
17. Jass JR, Sobin LH. *Histologic Typing of Oesophageal and Gastric Tumours*. 2nd edn. Berlin, Springer-Verlag, 1990;19-20, 38-39
18. Watanabe H, Jass JR, Sobin LH. *Histologic Typing of Intestinal Tumours*. 2nd edn. Berlin, Springer-Verlag, 1989;32
19. Schlemper RJ, Itabashi M, Kato Y, et al. Differences in diagnostic criteria for gastric carcinoma between Japanese and Western pathologists. *Lancet* 1997;349:1725-1739
20. Schlemper RJ, Itabashi M, Kato Y, et al. Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. *Cancer* 1998;82:60-69
21. Appelman HD, McKenna BJ. A “rose is a rose is a rose,” but exactly what is a gastric adenocarcinoma? Guest Editorial, *J Surg Oncology* 1998;68:141-143
22. Rugge M, Correa P, Dixon MF, et al. Gastric dysplasia. The Padova international classification. *Am J Surg Pathol* 2000;24:167-176
23. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251-255
24. Lauwers GY, Riddell RH. Review: Gastric epithelial dysplasia. *Gut*. 1999;45:784-790
25. Reid BJ, Haggitt RC, Rubin CE, et al. Observer variation in the diagnosis of dysplasia in Barrett’s esophagus. *Hum Pathol* 1988;19:166-178
26. Dixon MF, Brown LJR, Gilmour HM, et al. Observer variation in the assessment of dysplasia in ulcerative colitis. *Histopathol* 1988;13:385-398
27. Melville DM, Jass JR, Morson BC, et al. Observer study of the grading of dysplasia in ulcerative colitis: comparison with clinical outcome. *Hum Pathol* 1998;20:1008-1014
28. Filipe MI. Borderline lesions of the gastric epithelium: new indicators of cancer risk and clinical implications. In: Fenoglio-Preiser CM, Wolff M, Rilke F, editors. *Progress in Surgical Pathology*, volume XII, New York, Field & Wood, 1992:269-290
29. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett’s esophagus: a reaffirmation. *Hum Pathol* 2001;32:368-378
30. Haggitt RC. Barrett’s esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;25:982-993
31. Skacel M, Petras RE, Gramlich TL, et al. The diagnosis of low-grade dysplasia in Barrett’s esophagus and its implications for disease progression. *Am J Gastroenterol* 2000;95:3383-3387
32. Geboes K, Van Eyken P. The diagnosis of dysplasia and malignancy in Barrett’s oesophagus. *Histopathol* 2000;37:99-107
33. Montgomery E, Bronner MP, Greenson JK, et al. Are ulcers a marker for invasive carcinoma in Barrett’s esophagus? Data from a diagnostic variability study with clinical follow-up. *Am J Gastroenterol* 2002;97:27-31
34. Hamilton SR, Aaltonen LA. Pathology and Genetics of Tumours of the Digestive System. World Health Organization Classification of Tumours. Lyon. International Agency for Research on Cancer Press, 2000;8