

DEBATE

Should HGD or Degree of Villous Changes in Colon Polyps Be Reported?

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PRO: Villous Elements and High-Grade Dysplasia Help Guide Post-Polypectomy Colonoscopic Surveillance

COLONOSCOPY AND PATHOLOGIC EXAMINATION OF POLYPS ARE NOT PERFECT

Many aspects of medical practice are imperfect. Physicians use methods and technologies that are subject to operator dependency and interobserver variation. Colonoscopy itself is subject to these problems. That colonoscopy and polypectomy prevent colorectal cancer and death from colorectal cancer appears indisputable (1–5). Yet, colonoscopy is highly operator-dependent (6, 7), and several aspects of the procedure (*e.g.*, poor bowel preparation, areas hidden from view using current instruments, suboptimal technique, and ineffective polypectomy) can lead to diagnostic errors or an incomplete treatment (8). How should we respond to these imperfections in colonoscopy? The recent emphasis has been on the introduction of continuous quality improvement measures (9) and the development of advances in colonoscopic technology (8). Overall, colonoscopy does much good.

Similarly, the pathologic evaluation of colorectal adenomatous polyps is an imperfect exercise as there is undoubtedly significant interobserver variability in determining both the presence and extent of a villous component and the degree of dysplasia (10–13). While pathologists generally do not have difficulty distinguishing adenomatous polyps from hyperplastic polyps or separating a benign adenomatous polyp from a malignant colorectal polyp, it is clear that determining the villous elements and degree of dysplasia are more subjective and prone to interpretive differences (10–13). Acknowledging this is the case; the question remains whether it is futile to attempt to mention these features in the pathology report.

THE IMPORTANCE OF HIGH-GRADE DYSPLASIA AND VILLOUS FEATURES

Regardless of interobserver variation, which undoubtedly exists in the evaluation of these pathologic features, the literature does strongly support the contention that the villous elements and a high-grade dysplasia have predictive value in adenoma-bearing populations for the subsequent develop-

ment of advanced adenomas and cancer (14). For example, in a study of rigid sigmoidoscopy with polypectomy, villous histology in adenomas resected at a baseline procedure was associated with a standardized incidence ratio (SIR) of 5.0 (2.2–9.9) for the subsequent development of colon cancer. In the same study, the SIR of colon cancer when tubulovillous histology was found in baseline rectal adenomas was 3.8 (2.2–6.0), and when high-grade dysplasia was detected in a baseline adenoma, the SIR was 3.3 (1.1–8.0) (15). Yang *et al.* reported that villous elements in adenomas removed at a baseline sigmoidoscopy were associated with a relative risk (RR) of 8.1 (4.2–15.6) for the later appearance of advanced metachronous neoplasms (16). High-grade dysplasia in an adenoma at a baseline sigmoidoscopy was associated with an RR of 14.4 (5.0–41.3) of subsequent advanced neoplasia, including rectal cancer (16). Loeve *et al.* also identified villous elements and high-grade dysplasia as predictors of subsequent colon cancer (17). Lieberman *et al.* found that the RR of an advanced neoplasm within 5.5 yr of a baseline screening colonoscopy was 6.05 (2.48–14.71) if a baseline adenoma contained villous elements, and 6.87 (2.61–18.07) if a baseline adenoma had high-grade dysplasia (18). Certainly, not all studies have found that villous elements and high-grade dysplasia predict subsequent colorectal cancer or advanced adenomas. However, a recent detailed literature review concluded that patients with one or two tubular adenomas <1 cm in size with only a low-grade dysplasia were a distinct low-risk cohort, and that villous elements and high-grade dysplasia were independent predictors of subsequent advanced neoplasms (14).

CLINICAL RELEVANCE OF PATHOLOGY REPORTS

How do clinicians use the information from pathologists regarding tubular *versus* villous histology and low *versus* high-grade dysplasia? The primary use is to guide post-polypectomy surveillance colonoscopy intervals. The guidelines for post-polypectomy surveillance intervals have consistently relied on and endorsed reporting of villous elements and high-grade dysplasia (14, 19, 20). Post-polypectomy surveillance accounts for more than 20% of colonoscopic procedures, adds less to colorectal cancer prevention than do screening and diagnostic colonoscopies (14), and is often overused (21, 22). Recent guidelines (14) have set forth recommendations that delineate low-risk cohorts who can

undergo surveillance at 5–10 yr, substantially reducing the cost and risk of surveillance, with little concern about interval cancer. Villous elements and dysplasia grade are essential aspects of this risk stratification (14).

Colonoscopists must take care of their patients, and pathologists must help colonoscopists do their best. Colonoscopy is not perfect and neither is the pathologic interpretation of villous elements or high-grade dysplasia in colorectal adenomas. Should we throw out the baby with the bath water? That seems excessive. Should we look for better methods and systems? Of course! Colonoscopists must strive to improve the efficacy, safety, and tolerability of bowel preparation, reduce interobserver variation in adenoma detection, improve the safety and efficacy of polypectomy technique, and continue to improve the imaging technology (8, 9). Similarly, pathologists could (and should) seek consensus on definitions of high-grade dysplasia and terminology for pathologic description of adenomas. More quantitative and reproducible methods of interpreting villous elements and dysplasia grade should be developed.

CONCLUSION

While it is not a perfect world, clinicians still need pathologists to make their best educated effort to interpret villous elements and degree of dysplasia in colorectal adenomas. Without this information, clinicians cannot follow their own guidelines and may not be able to meet the standard of care in adenoma management. Because of interobserver variation and interpretation, errors will occur in the management of individual patients; but across populations, many patients at higher (and lower) risk will be correctly identified and appropriately guided to a more (or less) aggressive surveillance. At this time, pathologists should report on the presence of villous changes and high-grade dysplasia in colorectal adenomas.

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CON: High-Grade Dysplasia and Villous Features Should Not Be Part of the Routine Diagnosis of Colorectal Adenomas

The 2006 guidelines for post colectomy surveillance recommend that a patient with no more than two adenomas smaller than 1 cm should undergo the next colonoscopic examination in 5–10 yr, unless any of these small adenomas has microscopic “villous features” or “high-grade dysplasia,” in which case the interval should be 3 yr (1). We know that adenomas 1 cm or more across or with high-grade dysplasia (HGD) or that are villous are likely to contain carcinomas or to be surrogate markers for carcinoma risk. Such adenomas are called “advanced adenomas.” The guidelines offer no definitions of villous features or HGD, so pathologists have no criteria to identify characteristics critical for determining follow-up intervals. The authors of these guidelines refer to 15 studies with the best data. Only eight pathologists are coauthors of these studies, who are experienced gastrointestinal pathologists, but in most of the studies, either a single pathologist made the decisions about dysplasia and villi or the nonpathologist authors depended on diagnoses of groups of pathologists in various institutions. These pathologists did not compare their interpretations and did not define specific diagnostic criteria.

Size

The larger the adenoma, the more likely it will contain a carcinoma, and the more likely a carcinoma will develop within it (2). “Large” has been defined as 1 cm diameter based on an endoscopic measurement of the polyp; a 9-mm polyp has a different significance than a 10-mm (1 cm) polyp. Are endoscopic measurements reproducible among many endoscopists at the 1-mm level? What is measured is the polyp, not the adenoma. Pathologists know that the amount of adenoma in a polyp is commonly much less than the size of the polyp. A 1 cm polyp may contain only 3 mm of adenoma,

yet according to the guidelines, the amount of adenoma is not important while the size of the polyp is. No studies deal with the volume of the adenoma within the polyp. However, the determination of adenoma size is the endoscopist’s responsibility not the pathologist’s. The pathologist’s problems involve high-grade dysplasia and villous features.

High-Grade Dysplasia

An adenoma with HGD is more likely to contain a carcinoma than an adenoma without it, and the larger the adenoma, the more likely it will contain it. I looked for references by the giants in gastrointestinal pathology listing criteria for high-grade dysplasia. The atlases of tumor pathology put out by the Armed Forces Institute of Pathology are supposed to be the world’s best references to diagnosis of tumors by experts. In the Atlas on intestinal tumors, it is stated that “low- and high-grade (dysplasias) are artificial subdivisions of a spectrum,” but there is no definition of high-grade (3). In the World Health Organization (WHO) book on tumors of the digestive system, there is no list of criteria for HGD in adenomas. There are three photomicrographs labeled as HGD that have these features: loss of normal glandular architecture, hyperchromatic cells with multilayered irregular nuclei and loss of mucin, high nuclear/cytoplasmic ratio, and marked nuclear atypia with prominent nuclei, focal cribriform pattern. However, low-grade dysplasia has these features too, and this reference does not tell us what degree of these features moves a dysplasia from low-grade to high-grade (4). In an article, covering chronic colitis in the glossary, dysplasia is defined as “an unequivocal neoplastic epithelial proliferation. . . . Not all features are necessarily present to the same degree in all dysplastic epithelia. Low-grade dysplasia has these changes in lesser intensity. High-grade dysplasia has these changes in greater intensity and includes carcinoma in situ.” In the body of the article these features include architectural alteration often resembling the glandular arrangement of adenomas and cytologic abnormalities, principally cellular and nuclear pleomorphism, nuclear hyperchromatism, loss of nuclear polarity, and marked stratification of nuclei. “In contrast with low-grade dysplasia, in which fairly regular nuclei are confined largely to the basal halves of the cells, most cases of HGD show nuclear stratification that extends into the superficial (luminal) parts of the cells” (5). I tried to apply the same guidelines to adenomas, and I found that the epithelium in so many adenomas had colitic HGD features and that the designation became meaningless, so I stopped. In the Veterans Affairs (VA) Cooperative Study, about 11% of patients with HGD in adenomas of any size developed advanced neoplasia over the 5-yr surveillance period compared to less than 1% of those with less than 1 cm tubular adenomas (6). However, what should be compared are adenomas under 1 cm with and without HGD to exclude size, because size and increasing dysplasia are related. In the colitic dysplasia article, there is a recommendation that an HGD diagnosis be confirmed by a consultant pathologist, because of the risk of over-diagnosing high-grade dysplasia. However, in the adenoma guidelines

there is no mention of submitting an adenoma HGD diagnosis to a consultant, yet expensive colonoscopy intervals are based on this determination.

Villous Features

A villous adenoma is also more likely to contain a carcinoma, but villous characteristics are also not clearly independent of size. The consensus guidelines include in the definition of an advanced adenoma “any villous component (*i.e.*, nontubular),” suggesting that a single structure resembling a villus is enough to make even the tiniest adenoma an advanced adenoma. There are no data to prove that a 1-mm adenoma with a villus on the surface is more likely to require 3 yr instead of 5–10 yr surveillance. We know what a villus is in the small intestine, but what is it in an adenoma? The WHO book (4) mentions that in villous adenomas “leaf-like projections lined by dysplastic glandular epithelium comprise more than 80% of the luminal surface,” but there is no definition of a leaf-like projection. The discussion goes on to say, honestly, that the “distinction of villous structures from elongated, separated tubules is sometimes problematic. Villous architecture is defined arbitrarily by the length of the glands exceeding twice the thickness of normal colorectal mucosa.” This study deals with the definition of a villus, the others ignore it. In the Atlas of intestinal tumors, tubulovillous is said to have more than 20% villous component, and villous has more than 80%, but a villus is not defined. Therefore, by this definition, up to 20% villous surface is not an advanced adenoma, because such adenomas are designated as tubular. In one of the 15 studies used by the guideline authors, tubular adenomas were defined as those having up to 25% villous structure, so this adds more villous surface to the tubular adenoma (7). In the 2000 VA cooperative study, another of the criteria for an advanced adenoma, a villous adenoma, was a 25% or more villous component (8). Neither of the studies mentions how did the pathologists determine if there was a 25% villous component. Did they measure the total surface, or did they guess about the villous component? In a 2007 study from the VA group, there is no mention of the amount of villosity, but the authors still refer to villous adenoma as being part of the advanced neoplasia cohort. So presumably, the 25% level still applies (9). Nevertheless, in the 2006 AGA guidelines, only the term “villous features” is mentioned to be important in identifying an adenoma as advanced, not 25% or any other amount.

In the VA Cooperative Study in which the diagnosis of high-grade dysplasia is a strong predictor of advanced subsequent neoplasia, the HGD diagnosis was based on review of all diagnoses by the primary study pathologist, and in cases of disagreement, a second review conducted by pathologists at two other centers. These reviewers are not part of the family of general community pathologists, so the validity of this review for daily pathology practice is unclear. There are no studies indicating whether the determinations of villous features and HGD are reproducible among large numbers of pathologists. It is useless to use studies with diagnoses of dedicated gas-

trointestinal pathologists. Most adenomas are seen by general pathologists in community pathology practice. The decisions that pathologists make about villous features and HGD are, to some extent, dependent on the diagnoses of the pathologists who taught them during their residencies. My concept of HGD in an adenoma is epithelium that is identical to what is found in a typical invasive carcinoma, but others might find that requirement too restrictive. In order to test reproducibility, we sent 21 adenomas to 30 pathologists in six practices in five states, both general and academic GI pathologists, and asked them if these adenomas had HGD and villous features, using the nonexistent definitions in the guidelines. Reproducibility was poor for both determinations (10). We also asked them to determine the extent of villous surface; the reproducibility here was even worse.

CONCLUSION

In the absence of definitions of villous features and HGD and no large reproducibility studies, I cannot see how the length of surveillance intervals can depend on these determinations. Until pathologists have solid diagnostic criteria, and until we know that these criteria can be applied evenly by general surgical pathologists, I do not feel that villous features and HGD should be part of the routine diagnosis of colorectal adenomas. However, in the real world, pathologists recognize that some clinicians want this information, regardless of whether it is important or reproducible. So if they want HGD and villous features, we will try to diagnose them, although we should add a disclaimer about lack of criteria and reproducibility.

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CONFLICT OF INTEREST

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A BALANCING VIEW: Pathologist–Clinician Interaction Is Essential

The US Multi-Society Task Force on colorectal cancer and the American Cancer Society have recently revised their recommendations for surveillance colonoscopy in patients with adenoma(s) after polypectomy (1). Patients having one or two small (<1.0 cm) tubular adenomas with only low-grade dysplasia are recommended to have follow-up colonoscopy in 5–10 yr. In contrast, patients having three or more adenomas or with one or more “advanced” adenomas (adenoma that measures larger than 1 cm in greatest dimension, has villous features, or contains high-grade dysplasia) are recommended to undergo repeat colonoscopy in 3 yr provided that piecemeal polypectomy was not performed and that the adenoma was completely removed. These recommendations are based on the results of a variety of studies, both retrospective and prospective, which suggest that patients with an advanced adenoma have a higher risk of developing either further advanced adenomas or adenocarcinoma.

For better or worse, it seems that the concept of an advanced adenoma has taken on a life of its own and has led to the impression that these lesions may be biologically different from nonadvanced adenomas, or that only certain high-risk individuals with as yet undefined risk factors may be particularly prone to develop advanced neoplasia. Nevertheless, the current clinical issue is as follows: Do patients with one or more advanced adenomas represent a subset of individuals with a higher than usual risk of developing future, more severe, neoplastic alterations such as invasive carcinoma, and if so, should these people be surveyed at a higher frequency? In order to answer this question properly, a minimum of two factors must be met: (a) the criteria for an advanced adenoma need to be objective, consistent, and reproducible; and (b)

outcome studies that use cancer as the end point need to be performed. After reading the pro/con debate in this issue of the *Journal*, it seems that neither of these factors has been achieved. Nevertheless, at this point in time, utilizing less than perfect criteria for an advanced adenoma, Dr. Rex and Dr. Goldblum (pro) and Dr. Appelman (con) debate the value of reporting key pathologic features that, at least for the time being, comprise the criteria for advanced adenoma.

Strong arguments are made by both sets of authors, but there are limitations that are important for readers to be aware of prior to formulating their own judgment on this issue. In their article, Dr. Rex and Dr. Goldblum acknowledge the inherent variability and nonreproducibility of gauging the degree of villous elements and dysplasia in adenomatous polyps by pathologists. Nevertheless, these authors suggest that the literature strongly supports the contention that polyps with a prominent villous component and/or high-grade dysplasia have predictive value for the subsequent development of advanced adenomas or cancer. Although the results of some observational studies do provide data in support of this contention, there are limitations to these studies as outlined below.

As correctly pointed out by Dr. Rex and Dr. Goldblum, post-polypectomy surveillance colonoscopy accounts for 20% of all colonoscopies, but it is often overused. Thus, the aim is to reduce cost and to increase the efficiency of recognizing high-risk patients. Identifying clinical or pathologic biomarkers that may help predict an increased risk of neoplastic progression and thereby enable physicians to stratify patients into low- and high-risk groups is a good idea, but the impact of evaluating pathologic features that may not, in fact, show independent predictive ability may cause an unnecessary increase in the frequency of surveillance colonoscopies. For instance, if it is determined, reliably, that only adenomas with a significant (*e.g.*, >75%) villous component represent a marker of an increased risk of cancer development, then screening all patients who have “any” villous component may add unnecessarily to the pool of unneeded surveillance colonoscopies. Finally, although Drs Rex and Goldblum accurately point out that the results of several observational studies suggest a risk between the degree of villous elements and/or high-grade dysplasia and subsequent advanced neoplasia, these specific histologic features have never been shown to be a significant predictor of subsequent advanced neoplasia in randomized controlled trials.

As indicated by Dr. Appelman, the definition and criteria for advanced adenoma and its components (degree of villosity and features of high-grade dysplasia) and even the type of outcome, vary considerably among different studies. Unfortunately, there is a distinct lack of uniformity and consistency in the literature with regard to (a) categorization of an adenoma as “villous” or “tubulovillous” or “tubular” and (b) criteria for high-grade dysplasia. Furthermore, most studies do not control for adenoma size, so the independent importance of these aforementioned histologic variables is often quite difficult to assess. Some studies lack expert GI pathology review and others simply utilize information from pathology

reports. Finally, some studies use advanced adenoma as both a measured and outcome variable, instead of invasive carcinoma as the end point. Elimination of the latter is truly the ultimate goal of any viable cancer-prevention surveillance program. Although it seems inherently reasonable, from a biological point of view, that patients who have the capacity to develop “advanced” adenomas (ones that can grow to a large size or develop high-grade morphological aberrations) may have the biological make-up to develop more serious lesions, it remains unclear whether these pathologic features, in fact, simply represent surrogate morphologic markers of other clinical/susceptibility factors that render the patient at increased risk of carcinoma. In fact, other variables, such as age, multiplicity, etc., may be more reproducible and easy to measure, yet the independent value of these features, both clinical and pathologic, have been poorly defined.

Gastrointestinal pathologists have serious difficulty agreeing on the presence, absence, or degree of villous change and the degree of dysplasia. Can we really be confident of the results of outcome studies when the initial measured variables vary substantially among observers? In fact, even Basil Morrison, widely considered one of the groundbreaking forefathers of GI pathology, admits in his prior writings that “the perception of a villous is an artifact resulting from the two-dimensional view of a mucosal surface that is, in fact, thrown into folds or folio. In addition, the shaggy projections of villous adenomas seen macroscopically, and the delicate folia seen microscopically, are of quite different orders of magnitude.” (2) Interestingly, in his original description of the pathologic features of colonic adenomas, Basil Morrison applied the term “villous adenoma” only for lesions that showed greater than 80% villous components (3).

Nevertheless, the close relationship between high-grade dysplasia, degree of villous change, and size of adenomas is indisputable and has survived the test of time. However, analysis of the relative importance of each of these possible pathologic predictors is complicated by their close interrelationships, which have yet to be worked out satisfactorily at an investigational level. For instance, although it is clear that adenomas of larger size are more likely to harbor high-grade dysplasia, it is not clear whether the subsequent risk of advanced neoplasia in these patients is due to other factors, such as incomplete removal of (large) polyps. In fact, in the original national polyp study by O’Brien *et al.*, which systematically evaluated the pathologic features of adenomas, adenoma size, and extent of villous change, these characteristics were found to be independent polyp risk factors for high-grade dysplasia (4). Thus, perhaps high-risk patients may be best categorized on the basis of only one key pathologic feature, such as adenoma size or high-grade dysplasia. Does the degree of villous change alone, in a small (<1.0 cm) adenoma without high-grade dysplasia, portend an increased risk of colorectal cancer? The answer to this question is, at present, unknown. However, in O’Brien’s study, only seven of 1,093 (0.6%) small adenomas (<1.0 cm) with any villous component contained high-grade dysplasia (4). Furthermore,

the odds ratio for the risk of finding high-grade dysplasia in an adenoma was statistically similar in adenomas with less than 25% villous component compared to adenomas with 25–75% villous component. Thus, perhaps the degree of villous change is only a significant factor when it comprises virtually all of the adenoma, and even in this situation the vast majority of polyps are larger than 1 cm; so why bother including villous change in the definition of “advanced adenoma” at all? These and other independent pathologic features need to be assessed independently, accurately, and scientifically in future studies.

In conclusion, although it is clear that large adenomas or ones that are predominantly villous (whatever this means) or contain high-grade dysplasia correlate with an increased risk of carcinoma within the polyp itself, the jury is still out with regard to whether the finding of any of these variables in any one particular polyp independently predicts a true increased risk for subsequent cancer upon follow-up. Objective, consistent, and reproducible criteria for degree of villous change and high-grade dysplasia, in particular, need to be developed and tested independently and longitudinally in randomized controlled trials. In order for this to occur successfully, pathologists and clinicians need to work closely. In the consensus update reported in 2006 by Winawer *et al.* (1), it was suggested that the best study design to test these issues would be a randomized control trial, one that would take into account candidate risk factors, have sufficient follow-up time, have planned colonoscopic assessment for recurrence, have enough outcome events for reasonable statistical precision, and would utilize multivariate analysis. After evaluating the literature and having read carefully the pro/con arguments in this issue of the *Journal*, it is exceedingly clear that any type of “best study design” would also need to include clearly described, objective, and reproducible pathologic criteria. Until then, it is probably wise for pathologists to report the presence or absence of high-grade dysplasia and the degree of villous change (perhaps as a rough percentage, and particularly if it comprises either most or all the lesion) for future reference. We should include a cautionary note to emphasize that the biological significance of these variables, although potentially important, is in fact currently unknown.

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