

## BARRETT'S DYSPLASIA

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Barrett's esophagus predisposes to the development of esophageal adenocarcinoma,<sup>1,2</sup> but the frequency with which it does so is not well established. Part of the difficulty in defining the cancer risk is that the prevalence of Barrett's esophagus itself is not well documented. Barrett's esophagus is present in about 10 to 12% of patients with symptomatic GERD disease who undergo endoscopy,<sup>1</sup> but an autopsy study has suggested that its true frequency may be as much as 20 times higher.<sup>3</sup> The reported *prevalence* of adenocarcinoma in Barrett's esophagus averages about 10%, i.e., at the time the initial diagnosis of Barrett's esophagus is made, about 10% of patients will have adenocarcinoma.<sup>1</sup> The estimated *incidence* of adenocarcinoma in Barrett's esophagus ranges from 1 in 52 to 1 in 441 patient years, representing an increased risk of 30 to 125-fold.<sup>1</sup> Adenocarcinoma of the esophagus appears to be limited to patients who have metaplastic epithelium. The length of the endoscopically visible columnar-lined segment does not seem to have a significant influence on cancer risk, as patients with even very short segments may develop cancer.<sup>4,5</sup> Cancer arises in Barrett's esophagus through a multi-step sequence of events that is initiated by chronic GERD, leading to metaplasia, then dysplasia, and finally adenocarcinoma.

### Definitions and Characteristics of Dysplasia

Dysplasia is defined as neoplastic epithelium that remains confined within the basement membrane of the epithelium within which it arises.<sup>6</sup> When the dysplastic epithelium proliferates to form a mass, the term adenoma may be applied, but this is uncommon in Barrett's esophagus.<sup>7</sup> Dysplasia in Barrett's esophagus is recognized histologically by a combination of architectural and cytologic abnormalities. Dysplastic glands may retain their normal configuration, but more often have irregular, crowded or even grossly distorted architecture. The glands are usually lined by cells with enlarged, irregular, hyperchromatic, crowded and stratified nuclei. In other examples, the nuclei are large, hyperchromatic, contain large nucleoli and have lost their polarity, but lack the crowding and stratification mentioned above. In all cases, the cytologic features extend from the glands onto the epithelial surface and this is perhaps the single most important criterion in the diagnosis of dysplasia. Slightly more baseline cytoarchitectural atypia develops in the absence of dysplasia directly at the SCJ.

For purposes of clinical utility, dysplasia in Barrett's esophagus has been subdivided into low-grade and high-grade categories. When no features of dysplasia are observed, the diagnosis of negative for dysplasia is rendered, and when the findings are uncertain, the category of indefinite for dysplasia is assigned. This grading scheme is directly analogous to that for dysplasia complicating idiopathic inflammatory bowel disease.<sup>1,6,8</sup> The criteria are as follows:

**Negative for dysplasia:** The glandular architecture and cellular morphology are free of neoplastic alterations, but may contain reactive or regenerative change. The glandular

architecture is orderly and not crowded. The regenerative basal glands characteristically display cytologic atypia in Barrett's intestinalized mucosa that is negative for dysplasia. This basal atypia includes nuclear enlargement, pleomorphism, outline irregularity, hyperchromasia and stratification, and is the baseline atypia of metaplastic epithelium that is negative for dysplasia. It may be particularly striking in comparison to frequently admixed non-metaplastic gastric glands that are usually quite bland. *Basal glandular atypia matures completely to the surface in epithelium that is negative for dysplasia.* Surface maturation refers to the nuclei becoming smaller (less than twice the size of stromal fibroblast nuclei and usually much less), less darkly staining, smoothly contoured, uniform, and non-stratified, as the cells extend from the basal glands and onto the mucosal surface. Care must be taken to not over interpret tangential sectioning artifact as surface nuclear stratification. Cytoplasmic elongation and stratification usually accompany tangential sectioning artifact and can be a helpful diagnostic clue.

Reactive cytologic alterations, in the presence of active inflammation, are also part of the spectrum of negative for dysplasia, as long as the cytologic changes still mature to the surface of the biopsy and the glandular architecture is intact. Reactive inflammatory change often produces a more open chromatin structure and some degree of cytoplasmic mucin depletion.

Regenerative cytoarchitectural alterations are also classified as negative for dysplasia. Regenerative change consists of a surface monolayer of cells, covering eroded or ulcerated mucosa that is usually devoid of glands or shows gland loss with replacement by granulation tissue. The surface regenerative cells may have variably atypical and even bizarre nuclei but they maintain a characteristic monolayer growth pattern and the cells generally have abundant cytoplasm.

**Indefinite for dysplasia:** The glandular architecture is intact or may exhibit mild crowding or mild loss of parallel architecture. The cytologic changes may be mild or focally markedly atypical and lack surface maturation in the presence of pronounced inflammation or erosion/ulceration. Numerous mitotic figures may be present. Marked crypt atypia that matures to the surface and mild atypia that mostly matures to the surface also fall into the indefinite for dysplasia category. Biopsies without intact surface to permit assessment of maturation to the surface may also be categorized as indefinite for dysplasia. The highly variable changes in this category are further discussed below.

**Low-grade dysplasia:** The crypt architecture is relatively preserved, and distortion, if present, is generally mild to moderate at the most. A villiform surface configuration may be present. The nuclei exhibit some combination of stratification, enlargement, hyperchromasia, pleomorphism and crowding. Abnormal mitotic figures may be present in the upper portion of the crypt. Goblet cell mucin is often diminished and may be absent. So called "dystrophic goblet cells" may be seen in which the mucin vacuole is located on the basal, rather than luminal side of the nucleus. The cytologic changes extend from the base of the crypts onto the surface epithelium. Nuclear polarity is preserved, whereby the long axes of the nuclei remain perpendicular to the basement membrane.

**High-grade dysplasia:** Distortion of crypt architecture is usually present and may be marked and consists of some combination of branching and lateral budding of crypts, marked glandular crowding, villiform surface configuration, or intraglandular bridging of epithelium to form a cribriform pattern or "back-to-back" gland patterns. Nuclear abnormalities are present as in low-grade dysplasia, but in addition, there is more marked nuclear enlargement,

more irregularity of nuclear membranes, and more hyperchromasia. These features are unfortunately subjective. Loss of nuclear polarity, however, is the most objective criterion to differentiate low and high-grade dysplasia. For this criterion, the long axes of the nuclei no longer remain perpendicular to the basement membrane. Loss of nuclear polarity also refers to the loss of an orderly arrangement of nuclei and the lack of orientation of nuclei to each other. The nuclei vary markedly in size, shape and staining characteristics. Cytoplasmic mucin is usually diminished or absent and dystrophic goblet cells (see above) may be present. The cytologic changes extend from the base of the crypts onto the surface epithelium. Due to the major consequences of a diagnosis of high-grade dysplasia, this author believes that it should not be established without 100% certainty on the part of the pathologist.

**Additional general comments on the grading of dysplasia:** Criteria applying to all grades of dysplasia are that biopsies that stand out as significantly different from others, such as those with mucin loss or hypermucinous change, dystrophic goblet cells and/or endocrine cell hyperplasia, or varying architecture or cytology, tend to associate with dysplasia but not always. In the case of discrepancy between cytology and architecture, cytology generally determines the grade. The one exception to this is when architecture is extremely abnormal. Dilated glands with necrotic luminal debris are another feature of markedly abnormal architecture that could in some cases determine the grade despite less abnormal cytology. In the presence of severe inflammation with or without erosion/ulceration, assignment of unequivocal dysplasia is done only in very rare circumstances. The overwhelming majority of such biopsies should be classified as indefinite for dysplasia but with commentary that they could be neoplastic. Recommendations that the patient be rebiopsied after aggressive medical management to induce remission of obscuring inflammation are entirely appropriate in this situation.

### **Problems in the Diagnosis of Dysplasia**

**Sampling:** Mapping studies of esophagectomy specimens containing adenocarcinoma that was not endoscopically visible show that dysplasia involves a highly variable amount of esophageal mucosa surrounding the invasive carcinoma.<sup>9</sup> The dysplastic mucosa may occupy most or the entire esophagus or it may be quite limited in extent.<sup>10</sup> Thus, the endoscopist must thoroughly sample the mucosa in order to avoid missing small areas of dysplasia or carcinoma. Four-quadrant, well-oriented jumbo biopsies taken at 2 cm intervals or less throughout the length of the Barrett's segment are recommended, combined with additional biopsies of any endoscopic lesions.<sup>11</sup> Shortening of the interval to every 1 cm is recommended for patients with high-grade dysplasia who are maintained in endoscopic surveillance.<sup>12</sup> Adherence to this or similar protocols produces excellent correlation between the pre-operative endoscopic diagnosis and the final diagnosis in the resected specimen.<sup>9-11</sup>

**Baseline Glandular Atypia of Barrett's Metaplastic Epithelium:** Metaplastic Barrett's epithelium that is negative for dysplasia consistently shows nuclear atypism when viewed in contrast to gastric epithelium. This is particularly true of the deepest metaplastic glands closest to the muscularis mucosae. This deep glandular nuclear atypia includes enlargement, hyperchromatism, crowding, irregular nuclear contours, and prominence of nucleoli and stratification. These changes may be marked and because of this these abnormalities may be confused with dysplasia. However, they are usually separable from dysplasia because they are confined to the deep glands, while the upper portions show less abnormality or are normal; this feature is best recognized in well-oriented biopsy specimens

and is termed maturation to the surface. *Thus, the diagnosis of dysplasia should be made with great caution, if ever, when the changes do not involve the mucosal surface.*

**Variations of Indefinite for Dysplasia:** When there is doubt as to the significance of the epithelial abnormalities in a biopsy, the diagnosis of “indefinite for dysplasia” should be made. Clinicians have the impression that there is only one type of indefinite for dysplasia. This is understandable because the diagnostic terminology in written pathology reports is always the same. In reality there may be hundreds or even thousands of variations on the cytoarchitectural changes in Barrett’s epithelium in this category. Pathologists strive to classify the vast array of alterations in this category into this single and utterly limited designation of indefinite for dysplasia. Understandably, this situation leads to inter and intra-observer diagnostic variability, which is highest in the indefinite category in the grading schema of Barrett’s esophagus.<sup>8</sup>

The differentiation of Barrett’s dysplasia from reactive or regenerative change caused by inflammation is difficult, and at times impossible. Reactive changes in biopsies from the edges of ulcers may be indistinguishable from dysplasia. In cases with marked inflammation or ulceration, the atypia may be so severe that not only is dysplasia in contention, but even carcinoma may be suspected. This is the first and most concerning type of change that is classified as indefinite for dysplasia. If inflammation or ulceration is present, repeat biopsies after intensive medical antireflux therapy will often show resolution of the abnormalities. Cases with reactive inflammatory change that are milder and are probably negative for dysplasia form the second major type of change that is classified as indefinite for dysplasia. The cytologic abnormalities do not entirely mature onto the surface, however, so that the diagnosis of indefinite for dysplasia is still warranted. The third major category of change that may be classified as indefinite for dysplasia is that of cytoarchitectural abnormalities in *uninflamed* Barrett’s epithelium that are not negative for dysplasia, but yet are insufficient for a diagnosis of low-grade dysplasia. A common issue is that the cytologic alterations mature partially but incompletely as the cells extend onto the surface of the biopsy. These are alterations that presumably are on the pathway of neoplastic progression, but have not yet crossed the threshold for low-grade dysplasia. Mechanical issues are one final category that may be diagnosed as indefinite for dysplasia, such as when the biopsy surface is denuded or the biopsy is maloriented and the surface is otherwise unavailable for evaluation.

**Variability in the Diagnosis of Dysplasia:** Because the epithelial abnormalities in dysplasia form a continuous morphologic spectrum, from relatively mild atypism to overt dysplasia, the boundaries between the grades cannot be sharply defined. Thus, observer variation exists in the diagnosis and grading of dysplasia, particularly at the indefinite/low-grade interface.<sup>8</sup> For this reason, the categories of indefinite for dysplasia and low-grade dysplasia are combined in most endoscopic protocols for practical clinical management purposes. Fortunately, at high end of the spectrum, namely high-grade dysplasia and intramucosal carcinoma, where the diagnosis may lead to invasive therapy, there is excellent agreement by GI pathologists within and between observers. Similarly, there is good reliability for the diagnosis of negative for dysplasia as well.<sup>8</sup> Of great concern, however is the lack of reproducibility beyond a diagnosis of high-grade dysplasia, that is regarding GI pathologists ability to distinguish high-grade dysplasia from intramucosal or submucosally invasive adenocarcinoma.<sup>13</sup> In a recent study of GI pathologists at the Cleveland Clinic Foundation, in the setting of high volume continual Barrett’s diagnoses, 168 preoperative

biopsies that were at least high grade dysplasia (Table 1) were reviewed. Observer variability was poor in general for distinguishing high-grade dysplasia from adenocarcinoma. This calls into question clinical management practices based on pathologists being able to differentiate these high end diagnoses accurately.

**TABLE 1. OBSERVER VARIABILITY IN BARRETT'S BIOPSIES WITH AT LEAST HIGH-GRADE DYSPLASIA**

Diagnosis	Overall Kappa	Kappa	P-value	95% CI	Interpretation
ALL	0.30		<0.001	0.28 - 0.32	Poor
HGD*		0.47	<0.001	0.44 - 0.51	Moderate
HGD-MAD**		0.21	<0.001	0.18 - 0.25	Poor
IMC <sup>^</sup>		0.30	<0.001	0.26 - 0.33	Poor
SMC <sup>#</sup>		0.17	<0.001	0.14 - 0.21	Poor

\*HGD=high-grade dysplasia; \*\*HGD-MAD=high-grade dysplasia with marked architectural distortion such that intramucosal carcinoma cannot be excluded; <sup>^</sup>IMC=intramucosal adenocarcinoma; <sup>#</sup>SMC=submucosally invasive adenocarcinoma

Thus, the problem of observer variability has probably been overstated in the literature,<sup>12</sup> for diagnosing negative for dysplasia through high-grade dysplasia, at least for experienced GI pathologists. Inter- and intra-observer diagnostic concordance can be excellent to outstanding through this part of the neoplastic spectrum. The caveat of course is that these pathologists see a high and continual volume of Barrett's esophagus. This is an important and probably critical factor in the accuracy of dysplasia grading in Barrett's esophagus. Nonetheless, histopathologic diagnosis can be highly reliable and accurate, especially regarding negative for dysplasia and high-grade dysplasia, the aspects of the spectrum where diagnostic management decisions are important. Expanding management options that now go beyond esophagectomy to include continued surveillance, ablative therapies and endoscopic mucosal resection (EMR), make differentiating high-grade dysplasia from carcinoma increasingly important. Unfortunately, even experienced GI pathologists have poor reproducibility at this diagnostic task (Table 1).<sup>13</sup>

**Over Diagnosis of High-Grade Dysplasia in Barrett's Esophagus:** Barrett's esophagus with high-grade dysplasia is a serious condition prone to over diagnosis by pathologists. Documentation of the magnitude of the problem of the over diagnosis of high-grade dysplasia is also provided by a multi-institutional and international trial of photodynamic therapy in over 200 patients with high-grade dysplasia in Barrett's esophagus. Prior to study enrollment, all potential patients carried a biopsy diagnosis from their local hospital of Barrett's esophagus with high-grade dysplasia. In order to identify the 208 patients with Barrett's with high-grade dysplasia who were ultimately randomized into the trial, at total of 485 patients had to be screened (Table 4-1). *There were an incredible 237 or 49% of patients who were thought to have high-grade dysplasia but ultimately did not.* This was uncovered by a rigorous endoscopic and pathologic screening biopsy protocol. The screening included review of the original pathology thought to have high-grade dysplasia by the referring pathologists, and a new protocol endoscopy by one of the trial investigators. This included 4-quadrant jumbo biopsies every 2 cm, beginning in the proximal gastric fundus, through the LES region and the entire visible columnar pink mucosa within the tubular esophagus to the proximally displaced Z-line and squamous mucosa. The 237 (49%)

patients who did not qualify for the trial had a variety of pathologies (Table 2), as interpreted by the three study pathologists at the University of Washington (unpublished data by the late Dr. Rodger Haggitt, Dr. Mary Bronner and Dr. Shari Taylor).

**TABLE 2: INCORRECT DIAGNOSIS OF HIGH-GRADE DYSPLASIA IN BARRETT'S ESOPHAGUS IN 237 OF 485 PATIENTS**

<i>Corrected Diagnoses</i>	<i>No.</i>	<i>%</i>
Gastric only	18	4%
Other, not Barrett's	1	<1%
Barrett's negative	35	7%
Barrett's indefinite for dysplasia	61	12%
Barrett's low-grade dysplasia	79	16%
Barrett's carcinoma	43	9%
<b>TOTAL</b>	<b>237</b>	<b>49%</b>

As shown in Table 2, many of the patients (18 or 4% in total) who failed to qualify for the trial did not even have Barrett's esophagus, much less Barrett's esophagus with high-grade dysplasia! These and the rest of a total of 194 patients who had less than Barrett's with high-grade dysplasia were all facing esophagectomy. This underscores the problem of the over diagnosis not only of Barrett's esophagus itself, but also Barrett's with high-grade dysplasia.

One of the more frequent errors in the over diagnosis of high-grade dysplasia in Barrett's esophagus is the misinterpretation of cardiac-type mucosa with reactive change. Such reactive change frequently develops in gastric mucosa in response to gastroesophageal reflux and gastritis involving the lower esophageal region and hiatal hernias. This is a particularly unfortunate misinterpretation, as it not only renders a false positive diagnosis of Barrett's, with all of its attendant problems as discussed above, but it may also cause the patient to undergo an unnecessary esophagectomy. The reasons for this error are at least 2-fold. First, damaged cardiac-type mucosa tends to develop reactive mucin depletion. Mucin depletion is also common in dysplastic Barrett's epithelium. Thus, both tend to lack goblet cells or much mucin in the remaining columnar epithelial cells, so that this potential differentiating cytoplasmic feature becomes confounding. Second, reactive cardiac-type mucosa may have marked cytologic atypia. The atypia of benign reactive gastric mucosa may in fact be *worse* than neoplastic atypia. Based on these issues, it is no surprise that reactive cardiac-type mucosa may be histologically treacherous and difficult to differentiate from Barrett's dysplastic epithelium.

A useful criterion to distinguish reactive cardiac-type mucosa from Barrett's dysplasia concerns the deeper glands. The deeper glands in reactive gastric mucosa tend to retain most and commonly all of their mucin. Further, the mucinous cells within the deep glands (and the surface for that matter) involve the entire gland or crypt in a linear continuous fashion, rather than as scattered goblet cells typical of metaplastic mucosa. The basal glands of cardiac or fundic-type mucosa are characteristically not mitotically active because the regenerative zone in these epithelia resides in the more superficial foveolar neck region, generally located in the upper mid-region of gastric-type mucosa, rather than within the deep glandular compartment. Parietal cells also indicate gastric-type mucosa. Reactive

cardiac-type mucosa may also retain some surface mucin in the form of markedly shortened but back-to-back foveolar mucin caps over the biopsy surfaces. These features in combination with bland mitotically inactive mucinous glands, that may be diffusely positive for Alcian blue at pH 2.5, are the best criteria for recognizing reactive cardiac-type mucosa and distinguishing it from Barrett's mucosa with dysplasia.

Dysplastic Barrett's epithelium typically also shows loss of goblet cell mucin, but the glandular compartment is characteristically *more* atypical than the surface. This is in sharp contrast to the opposite pattern in reactive cardiac-type mucosa, where the glands tend to be very bland and the surface markedly atypical, as described above. Mitotic activity is also highest in the regenerative glandular compartment of Barrett's metaplastic epithelium, akin to the regenerative compartment of intestinal epithelium elsewhere in the GI tract. This is quite different from the regenerative mitotic region of cardiac-type mucosa, located in the mid or neck region.

The cytologic atypia in reactive cardiac-type mucosa tends to be *uniform* across all of the affected nuclei, whereas dysplastic Barrett's nuclei tend to show more *pleomorphism*. Reactive cardiac-type nuclei usually are not as hyperchromatic as dysplastic Barrett's epithelium, but this often depends on the type of fixative and processing used and is therefore a somewhat less reliable criterion. As in all areas of diagnostic pathology, it is not always possible to distinguish reactive cardiac-type mucosa from Barrett's with dysplasia. In this case, a diagnosis of "atypical glandular epithelium of uncertain type with alterations indefinite for dysplasia" can be made, along with the request for additional biopsies following aggressive medical management to attempt to eliminate any obscuring reactive change.

**Baseline Atypia in Barrett's Regenerative Glands:** Another issue of great importance in the over diagnosis of dysplasia in Barrett's esophagus is that Barrett's metaplastic epithelium has a baseline and characteristic glandular atypia that is negative for dysplasia.<sup>64</sup> This is especially true when the metaplastic glands are viewed in comparison with the frequently admixed non-metaplastic cardiac or fundic glands. The pathologist needs to see enough cases of metaplastic Barrett's epithelium to gain an appreciation for the spectrum of this baseline glandular atypia that is negative for dysplasia. The major distinguishing factor between this and dysplastic Barrett's epithelium is maturation to the surface. This feature cannot be over emphasized.

**High-Grade Dysplasia versus Carcinoma:** When high-grade dysplasia develops, architectural distortion may reach a point at which the diagnosis of carcinoma is impossible to exclude with certainty on the basis of superficial biopsy samples. This occurs when glands grow in a cribriform or dense "back-to-back" pattern or when dilated glands with luminal necrotic debris are present. High-grade dysplasia in the setting of an ulcer is another significant risk factor for carcinoma. In such cases, a diagnosis along the lines of "high-grade dysplasia with marked distortion of glandular architecture, invasive adenocarcinoma cannot be excluded" is appropriate. When numerous individual invasive cells, or sheets of malignant cells, or angulated infiltrative and abortive glands infiltrate the lamina propria, a diagnosis of intramucosal adenocarcinoma can be made. If a well-defined desmoplastic stroma with infiltrating malignant glands can be identified and separated from inflammatory stromal change, the diagnosis of submucosally invasive adenocarcinoma can be made.

While these last two diagnostic categories (high-grade dysplasia and intramucosal adenocarcinoma) are easily defined on the printed page, distinction in practice can be quite

challenging, especially in endoscopic biopsies. Now that a few groups have published natural history data on dysplasia in Barrett's esophagus, and have shown that continued endoscopic surveillance can be a safe option for patients with high-grade dysplasia (see below), the precise distinction between high-grade dysplasia and intramucosal carcinoma is becoming ever more important. Inter- and intra-observer variability data did not exist regarding this distinction from mucosal biopsy material until our recent study at the Cleveland Clinic Foundation (Table 1 above). Unfortunately, these data document that accurate distinction of high-grade dysplasia from adenocarcinoma is probably not possible based on morphology from mucosal biopsies.

### **Brush Cytology**

Brush cytology may not be as sensitive or specific as histology in detecting Barrett's neoplastic epithelium. Although thought to be useful in detecting dysplasia in several studies,<sup>14,15</sup> others have found that its addition to histology increased the cost but not the diagnostic yield for dysplasia or cancer.<sup>16</sup> The use of brush cytology to diagnose Barrett's esophagus via non-endoscopic screening techniques may have more utility.<sup>17</sup>

### **Flow Cytometry**

DNA content flow cytometry has been extensively evaluated in the study of neoplastic progression in patients with Barrett's esophagus. The prevalence of DNA aneuploidy and /or increased 4N (G2/tetraploid) and S-phase fractions all increase with increasing histologic grade.<sup>12</sup> DNA aneuploidy can be detected in paraffin embedded mucosal biopsy specimens, and may help determine the significance of epithelial alterations in negative, indefinite and even possibly the low-grade dysplastic biopsy categories.<sup>11,12</sup> It appears to be adjunctive, but experts in this field do not recommend that it replace histology.<sup>12</sup> Once the histologic diagnosis of high-grade dysplasia has been made, DNA flow cytometry adds no additional prognostic information. The late Dr. Rodger Haggitt notes additional insights into neoplastic progression that are afforded by DNA flow cytometry in his excellent review on Barrett's esophagus.<sup>1</sup>

### **Specific Genetic Abnormalities in Barrett's Esophagus**

Although many genetic abnormalities have been documented in Barrett's esophagus, these tend to correlate with advancing histologic grades of neoplastic progression. However, to date, long-term, prospective studies are virtually non-existent to determine the potential clinical utility of these markers. No genetic marker has ever been shown to be a better predictor of cancer than histologic neoplastic progression, and in particular, high-grade dysplasia.<sup>1</sup> Reproducibility studies regarding genetic biomarkers of cancer risk are also very limited, and ease of extrapolation of these methods to routine use remains unknown. There has never been to date, to the knowledge of this author, a single patient who was referred for esophagectomy or any other high-risk therapy, for anything other than a histologic diagnosis of high-grade dysplasia or cancer in Barrett's esophagus. This may and hopefully will change in the future, but the current standard of care continues to rely upon histology.

### **Significance and Management of Barrett's Dysplasia**

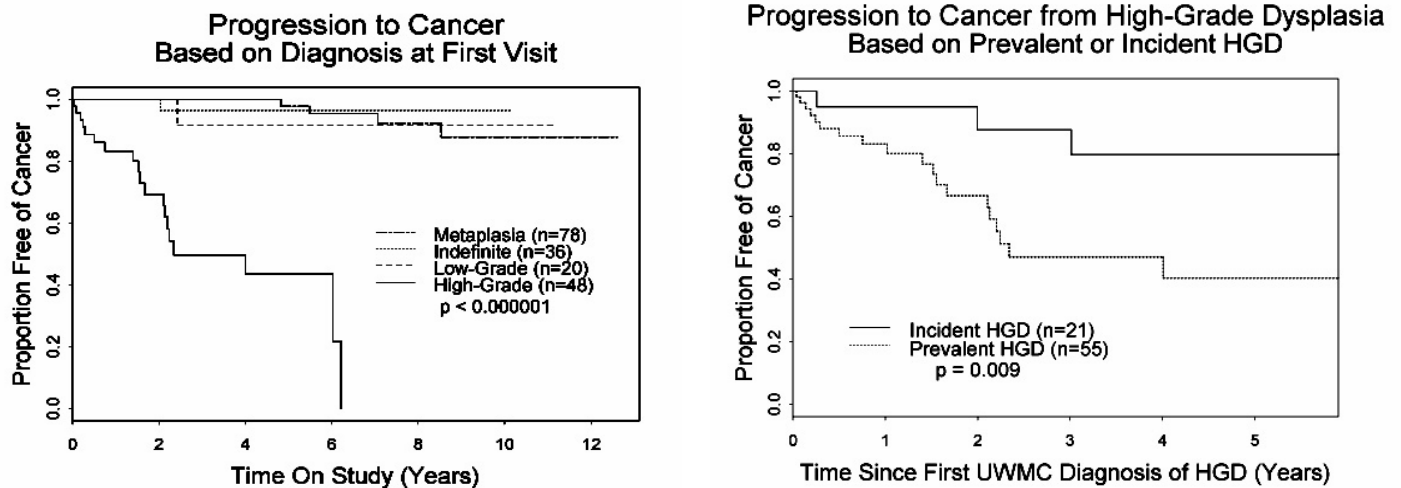
Management of the patient with dysplasia complicating Barrett's esophagus presents a difficult task. Until very recently, insufficient numbers of patients with dysplasia had been followed for a long enough period and using adequate numbers of biopsies to achieve a high degree of diagnostic confidence, to determine the natural history of dysplasia in Barrett's esophagus. Two large cohorts of patients with Barrett's esophagus have been followed

extensively using similar rigorous high-density surveillance biopsy protocols. One program is at the Hines VA Hospital in Chicago,<sup>18</sup> and the other is at the University of Washington in Seattle.<sup>12</sup>

At the Hines VA program,<sup>18</sup> a total of 1,099 patients were followed with Barrett's esophagus over a 20-year period. Of these, 79 (7.2%) patients had high-grade dysplasia, of which 34 had prevalent high-grade dysplasia (present at the first endoscopy) and 45 had incident high-grade dysplasia (detected during surveillance and therefore probably earlier in its natural history). Of the 75 who remained without detectable cancer during the first year of intensive biopsy surveillance, only 12 patients (16%) developed cancer over a mean of 7.3 years of surveillance. Further, 11 of the 12 who were compliant with the surveillance protocol were considered cured of their early cancers by surgical or ablative therapy. These findings support that high-grade dysplasia does not inexorably and rapidly progress to cancer, as previously feared. This previous unsubstantiated fear drove the standard of care over the past several decades that high-grade dysplasia was an indication for esophagectomy. The Hines VA data supports that it is much safer than previously thought to follow these patients, albeit with great vigilance.

In the 15-year prospective longitudinal study at the University of Washington,<sup>12</sup> a total of 327 patients were evaluated by rigorous surveillance endoscopy for progression from their baseline alterations. Median surveillance intervals were 24.4 months for baseline negative histology, 18.2 months for indefinite histology, 15.7 months for low-grade dysplasia, and 4.6 months for high-grade dysplasia. Mean and median follow-up periods were 3.9 and 2.4 years, respectively. Overall, a total of 42 patients developed cancer and 35 of these developed it within 5 years of their first endoscopy. No patient with negative, indefinite or low-grade dysplasia with normal flow cytometric studies developed cancer within 5 years; this patient comprised two-thirds of the entire cohort. This indicates that surveillance intervals could be lengthened to 5 years for this majority subset, using the intensive Seattle surveillance protocol, including baseline intensive biopsies and flow cytometry with expert preparation and interpretation of both. The benefits of extending the surveillance interval are manifold. No biomarkers were more powerful or diagnostically significant than the histologic detection of neoplastic progression and high-grade dysplasia in particular, which had a 5-year cancer incidence of 59%. Detailed information on the cancers that developed in this surveillance protocol and their curability were not provided by Reid and colleagues.

**TABLE 3. NATURAL HISTORY OF BARRETT'S NEOPLASTIC PROGRESSION:  
FROM THE SEATTLE COHORT AND DR. RODGER HAGGITT**



The above graphical data derive from the Seattle cohort (Table 3), and like the Hines VA data, show that lesions less than high-grade dysplasia (metaplasia, indefinite, and low-grade dysplasia) have a very low rate of progression over even greater than 10 years of follow-up, if they do so at all. The right hand graph above also shows that even high-grade dysplasia itself, as diagnosed by the late Dr. Rodger Haggitt, does not inexorably progress to cancer. In fact, one can increase the margin of safety if continued surveillance is performed for *incident rather than prevalent* high-grade dysplasia as shown. Specifically, incident high-grade dysplasia is discovered after the patient has been under surveillance with adequate biopsy sampling for some period of time. As shown, this type of high-grade dysplasia has only an ~20% progression rate to cancer after 6 years of follow-up. This is undoubtedly because incident high-grade dysplasia is diagnosed closer to the time at which it actually begins, and is therefore much more likely to be early in its progression. Prevalent high-grade dysplasia, on the other hand, is diagnosed at the patient's first endoscopy, when they are symptomatic in some way, and has therefore been present for an unknown and likely much longer period of time than incident high-grade dysplasia. Prevalent high-grade dysplasia would thus be expected to have a higher rate of progression to cancer, as it is further along in its neoplastic pathway than incident disease.

Based on these natural history data, we finally are beginning to form a rational basis for patient management. Especially in the setting of a patient who may be a poor surgical candidate, and in one who has incident high-grade dysplasia, continued intensive surveillance is now a more acceptable option. The reproducibility of the discussed Seattle and Chicago data, and the non-trivial issue of the transportability of this type of intensive surveillance from research settings into private practice both remain serious and important caveats at this time, however.

## **Squamous Overgrowth**

Successful antireflux therapy can eliminate or reduce the intensity of reactive changes secondary to inflammation that may be misinterpreted as dysplasia. Successful medical or surgical antireflux therapy may also be associated with some downward migration of the SCJ and with the development of squamous “islands” within the Barrett’s segment; however, complete regression of all Barrett’s epithelium rarely occurs. Prior biopsy sites, proton pump inhibitor therapy and ablative therapies are also associated with the development of squamous islands. Such squamous overgrowth may cause an underestimation of the endoscopic extent of Barrett’s mucosa, as metaplastic epithelium may persist beneath squamous re-epithelialized areas in Barrett’s esophagus.<sup>19,20</sup> The magnitude of this problem remains unknown.

The grading of dysplasia in metaplastic epithelium beneath squamous overgrowth remains uncharted territory. This author approaches it as follows: bland epithelium can be classified as negative for dysplasia and severely crowded and cytologically severely atypical glands with loss of nuclear polarity can be recognized as high-grade dysplasia or invasive carcinoma. However, because of the squamous overgrowth, maturation to the mucosal surface cannot be ascertained, so that the distinction between low-grade dysplasia and indefinite cannot be reliably made. This author classifies biopsies in this part of the spectrum beneath squamous mucosa as indefinite for dysplasia.

### **High-Grade Dysplasia as a Marker for Unsampled Carcinoma**

When high-grade dysplasia is detected for the first time in a patient with Barrett’s esophagus, early re-endoscopy with multiple biopsies should be done to rule out a coexisting early carcinoma.<sup>9,18</sup> Extensive sampling of the mucosa is essential, as early carcinomas may not be recognizable to the endoscopist. Accordingly, the sampling should be increased to 4 biopsies every 1 cm throughout the Barrett’s segment in patients with high-grade dysplasia. Because high-grade dysplasia is rare in unselected patients with Barrett’s esophagus, and because most pathologists therefore do not have the opportunity to study many examples of it, the general pathologist would be wise to seek a second opinion regarding the diagnosis of high-grade dysplasia before surgery is undertaken. The patient with early carcinoma, either intramucosal or submucosa and who has a reasonable estimated operative risk is a candidate for esophagectomy because these lesions have a low, but significant potential to metastasize (5% for intramucosal ca and 10-20% for submucosal invasion have positive nodes).<sup>21</sup> Resection of these early carcinomas provides the opportunity for cure.<sup>18,22,23</sup>

In patients with an endoscopic diagnosis of high-grade dysplasia, but not carcinoma, and who undergo esophagectomy, a relatively high prevalence of carcinoma in resected specimens has been reported.<sup>23</sup> This has led to the conclusion that high-grade dysplasia is a “marker” for coexisting adenocarcinoma, but this conclusion has been based on small numbers of patients, many of whom already had advanced disease because they had symptoms or endoscopic findings suggestive of carcinoma. When thorough endoscopic biopsy sampling is carried out according to the protocol outlined above, biopsies accurately determine whether or not a clinically unsuspected carcinoma accompanies the dysplasia.<sup>9,18</sup> Following such a policy has produced a high cure rate for early adenocarcinoma in Barrett’s esophagus, but at the same time, has avoided esophagectomy in patients with high-grade dysplasia who may never develop carcinoma (as many as ~41-84%).<sup>9,18</sup> However, given the

intensity of the biopsy protocols mentioned above, it is uncertain whether this information can be extrapolated to other centers.

### **Endoscopic Ablative Therapy in Barrett's Esophagus**

Non-surgical methods for the treatment of patients with high-grade dysplasia are being explored, and with very promising results. These include photodynamic therapy, multipolar electrocoagulation, heater probe, and argon plasma coagulation.<sup>24-30</sup> Photodynamic therapy (PDT), is now in completion of a phase III FDA controlled trial of over 200 patients for the treatment of Barrett's with high-grade dysplasia.<sup>24,28,29</sup> Interim results demonstrate that after a mean follow-up of one year (out of a total follow-up plan of 5 years that is nearly completed), 80% had complete ablation of all of their Barrett's epithelium, including their high-grade dysplasia. Further, these patients have a greater than 2-fold reduction in cancer development, compared to controls with high-grade dysplasia without PDT but under identical surveillance and selection conditions.<sup>28,29</sup>

### ESOPHAGUS REFERENCES

1. Haggitt RC. Barrett's esophagus, dysplasia and adenocarcinoma. *Hum Pathol* 25:982-993, 1994.
2. Antonioli DA, Wang HH. Morphology of Barrett's esophagus and Barrett's-associated dysplasia and adenocarcinoma. *Gastroenterol Clin N Am* 26:495-506, 1997.
3. Cameron AJ, Zinsmeister AR, Ballard DJ, et al. Prevalence of columnar-lined (Barrett's) esophagus: comparison of population-based and autopsy findings. *Gastroenterology* 99:918-922, 1990.
4. Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus – the need for standardization of the definition and of endoscopic criteria. *Am J Gastroenterol* 93:1033-1036 1998.
5. Nobukawa B, Abraham SC, Gill J, Heitmiller RF, et al. Clinicopathologic and molecular analysis of high-grade dysplasia and early adenocarcinoma in short- versus long-segment Barrett esophagus. *Hum Pathol* 32:447-545, 2001.
6. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 14:931-968, 1983.
7. Lee RG. Adenomas arising in Barrett's esophagus. *Am J Clin Pathol* 85:629-632, 1986.
8. Montgomery E, Bronner MP, Goldblum JR, et al: Reproducibility of the diagnosis of dysplasia in Barrett esophagus (BE): A reaffirmation. *Hum Pathol* 32:368-78, 2001.
9. Levine DS, Haggitt RC, Blount PL, et al. A systematic endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 105:40-50, 1993.
10. Cameron AJ, Carpenter HA. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: A pathological study. *Am J Gastroenterol* 92:586-591, 1997.
11. Reid BJ, Blount PL, Rubin CE, et al. Predictors of progression to malignancy in Barrett's esophagus: endoscopic, histologic and flow cytometric follow-up of a cohort. *Gastroenterology* 102:1212-1219, 1992.

12. Reid BJ, Levine DS, Longton G, et al. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. *Am J Gastroenterol* 95:1669-1676, 2000.
13. Mendelin JE, Bennett AE, Castilla E, Henricks WH, Schoenfield L, Skacel M, Yerian LM, Rice TW, Rybicki LA, Bronner MP, Goldblum JR. Interobserver agreement in the evaluation of pre-resection biopsies with at least high-grade dysplasia (HGD) in 163 Barrett's esophagus (BE) patients. *Mod Pathol* 18 (S-1): 112A, 2005.
14. Wang HH, Sovie S, Zeroogian JM, et al. Value of cytology in detecting intestinal metaplasia and associated dysplasia at the gastroesophageal junction. *Hum Pathol* 28:465-471, 1997.
15. Geisinger KR, Teot LA, Richter JE. A comparative cytopathologic and histologic study of atypia, dysplasia and adenocarcinoma in Barrett's esophagus. *Cancer* 69:8-16, 1992
16. Alexander JA, Jones SM, Smith CJ, et al. Usefulness of cytopathology and histology in the evaluation of Barrett's esophagus in a community hospital. *Gastrointest Endosc* 46:318-320, 1997.
17. Rader AE, Faigel DO, Ditomasso J, Magaret N, Burm M, Fennerty MB. Cytologic screening for Barrett's esophagus using a prototype flexible mesh catheter. *Diag Dis Sci* 46:2681-2686, 2001.
18. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 120:1607-1619, 2001.
19. Sharma P, Morales TG, Bhattacharyya A, et al. Squamous islands in Barrett's esophagus: what lies underneath? *Am J Gastroenterol* 93:332-335, 1998.
20. Biddlestone LR, Barham CP, Wilkinson SP, et al. The histopathology of treated Barrett's esophagus. *Am J Surg Pathol* 22:239-245, 1998.
21. Paraf F, Fléjou J-F, Pignon J-P, et al. Surgical pathology of adenocarcinoma arising in Barrett's esophagus: Analysis of 67 cases. *Am J Surg Pathol* 19:183-191, 1995.
22. Rusch VW, Levine DS, Haggitt RC, et al. The management of high-grade dysplasia and early cancer in Barrett's esophagus. *Cancer* 74:1225-1229, 1994.
23. Rice TW, Falk GW, Achkar E, et al. Surgical management of high-grade dysplasia in Barrett's esophagus. *Am J Gastroenterol* 88:1832-1836, 1993.
24. Overholt BF. Evaluating treatments of Barrett's esophagus that shows high-grade dysplasia. *Am J Manag Care* 6(16 Suppl):S903-8. Review, 2000.
25. Sampliner RE, Faigel D, Fennerty MR, et al. Effective and safe endoscopic reversal of nondysplastic Barrett's esophagus with thermal electrocoagulation combined with high-dose acid inhibition: a multicenter study. *Gastrointest Endosc* 53:554-558, 2001.
26. Van Laethem JL, Cremer M, Peny MO, et al. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. *Gut* 43:747-751, 1998.
27. Michopoulos S, Tsibouris P, Bouzakis H, et al. Complete regression of Barrett's esophagus with heat probe thermocoagulation: mid-term results. *Gastrointest Endosc* 50:165-172, 1999.

28. Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. *Gastrointest Endosc* 49:1-7, 1999.
29. Overholt BF, Haggitt RC, Bronner MP, et al. A multicenter, partially blinded, randomized study of the efficacy of photodynamic therapy (PDT) using porfimer sodium (PDR) for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE): results of 6-month follow-up. *Gastroenterology* (Suppl) 120:A79, 2001.
30. Lightdale CJ. Ablation therapy for Barrett's esophagus: is it time to chose our weapons? *Gastrointest Endosc* 49:122-125, 1999.