The Relationship Between Columnar Epithelial Dysplasia and Invasive Adenocarcinoma Arising in Barrett's Esophagus

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The authors assessed the relationship between dysplasia in Barrett's esophagus and invasive adenocarcinoma in a study of both endoscopic biopsy specimens and esophagectomy specimens. They reviewed the pathologic findings and clinical follow-up of 14 patients with dysplasia in Barrett's mucosa in endoscopic biopsy specimens. They also studied systematically the histopathologic features of the Barrett's mucosa in 43 esophagectomy specimens resected for Barrett's carcinoma. In the biopsy specimens, dysplasia occurred in distinctive-type Barrett's mucosa of 13 patients (93%) but in cardiac-type mucosa of only 3 (21%). Six patients had high-grade dysplasia; five underwent esophagectomy and three of these were found to have superficially invasive adenocarcinoma. The other patient with high-grade dysplasia as well as eight patients with intermediate- or low-grade dysplasia are not known to have carcinoma on available follow-up. In the study of resection specimens, high-grade dysplasia was strongly associated with adjoining invasive adenocarcinoma, because 84% of areas with invasion had high-grade dysplasia and 92% of areas with high-grade dysplasia showed invasion. The authors' findings suggest that (1) the dysplasia-carcinoma sequence most commonly occurs in Barrett's mucosa of the distinctive type; (2) high-grade dysplasia in Barrett's mucosa is a marker indicating high probability of invasive carcinoma; (3) the presence of high-grade dysplasia in biopsy specimens of Barrett's mucosa is an indication for esophagectomy in suitable surgical candidates. (Key words: Barrett's esophagus; Dysplasia; Adenocarcinoma; Esophageal neoplasms; Gastroesophageal reflux)

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Introduction

BARRETT'S ESOPHAGUS is the eponym for the columnar epithelial-lined lower esophagus that is acquired as a consequence of chronic gastroesophageal reflux. Adenocarcinoma is a well-known complication of Barrett's esophagus with a frequency of about 8-15% in large series of patients. When patients present with symptoms resulting from carcinoma arising in Barrett's esophagus, survival is generally poor, e.g., five-year survival of 22% in the series of Skinner and associates and median survival of 23 ± 5 months in our series. As a result of the relatively high frequency of carcinoma and the poor survival, surveillance by serial endoscopic examinations with esophageal biopsies and/or cytologic examination is recommended currently for patients with Barrett's esophagus. The finding of invasive carcinoma during surveillance is clearly an indication for esophagectomy. However, dysplasia without demonstrable invasive carcinoma in a biopsy specimen poses a dilemma in patient management. Prophylactic esophagectomy is recommended by some authors because dysplasia is found frequently in Barrett's mucosa of patients with invasive carcinoma and a dysplasia-carcinoma sequence has been proposed. On the other hand, esophagectomy itself results in substantial morbidity and mortality. As a result, additional data on the relationship between columnar epithelial dysplasia in Barrett's mucosa and the occurrence of invasive carcinoma are needed as a basis for patient management.

We, therefore, reviewed the pathologic findings and clinical follow-up of 14 patients with dysplasia in Barrett's mucosa in prospectively accumulated esophageal mucosal biopsy specimens. Because biopsies have inherent sampling error due to their small size, we also studied the histopathologic features of the Barrett's mucosa in 43 esophagectomy specimens resected for Barrett's carcinoma. The studies were designed to answer two questions: (1) What types of Barrett's mucosa are predisposed to dysplasia? (2) What grade of dysplasia is a marker indicating high probability of invasive adenocarcinoma and thus provides an indication for esophagectomy in suitable surgical candidates?

Materials and Methods

The specimens studied were of two types: endoscopic esophageal mucosal biopsy specimens and esophagectomy specimens. All specimens were from the Surgical Pathology files of The Johns Hopkins Hospital.
Table 1. Nomenclature for Classification of Columnar Epithelial Dysplasia in Barrett Esophagus

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for dysplasia</td>
<td></td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>Probably negative</td>
</tr>
<tr>
<td></td>
<td>Of unknown significance</td>
</tr>
<tr>
<td></td>
<td>Probably positive</td>
</tr>
<tr>
<td>Positive for dysplasia</td>
<td>Low grade</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade</td>
</tr>
<tr>
<td></td>
<td>High grade</td>
</tr>
</tbody>
</table>

Study of Endoscopic Biopsy Specimens with Dysplasia in Barrett Mucosa

Case Identification. All esophageal biopsy specimens from 14 patients who had dysplasia in Barrett’s mucosa without demonstrable invasive carcinoma in initial biopsies were studied. Other patients with invasive carcinoma in addition to dysplasia in initial biopsies were excluded. The specimens with dysplasia were accumulated prospectively by one of the authors (S.R.H.) from January 1981 through February 1986. Review of the Surgical Pathology index for these years revealed no additional cases.

Histopathologic Study Methods. The clinical records, pathology reports, and histopathologic slides of the 14 patients were reviewed. The specimens were fixed in either Hollande (modified Bouin) fixative or formalin and processed for paraffin embedding. Six-micron-thick sections were stained with hematoxylin and eosin or periodic acid-Schiff (PAS) and Alcian blue, pH 2.5. Positive mucin was termed gastric type and Alcian blue-positive mucin was called intestinal type. Five patients with high-grade dysplasia by biopsy subsequently underwent esophagectomy; their resection specimens were fixed in formalin, photographed, and embedded in their entirety for histopathologic examination.

Classification of Types of Barrett’s Mucosa. Barrett mucosa was classified based on criteria modified from Paul and co-workers. The categories were distinctive type (“specialized” type); cardiac type; fundic type; and unclassified type (characterized by epithelial dedifferentiation due to high-grade dysplasia, which precluded further classification).

Classification of Dysplasia in Barrett’s Mucosa. “Dysplasia” was used to describe histopathologic epithelial abnormalities that were regarded as unequivocally neoplastic. The term was not used descriptively for reactive atypical epithelium. Mucosal architecture, epithelial morphology, and cytology of individual epithelial cells were used as the basis for identification and classification of dysplasia. The nomenclature of “negative for dysplasia,” “indefinite for dysplasia,” and “positive for dysplasia” was used (Table 1). The positive category was subdivided into high-grade, intermediate-grade, and low-grade dysplasia. The use of three grades was based on the international classification of gastric dysplasia and on our initial findings on the relationship between the grades of dysplasia in Barrett’s mucosa and the presence of invasive carcinoma.

A spectrum of histopathologic features of dysplasia was evident, and this spectrum complicated classification. High-grade dysplasia was distinguished by markedly abnormal mucosal architecture, epithelial morphology, and cytology that were often equivalent to the morphology described as “carcinoma in situ” (see Figs. 1–3 for examples). We have restricted “high-grade dysplasia” to lesions in which no infiltration through the epithelial basement membrane into the lamina propria or muscularis mucosae was recognizable. Lesions with recognizable infiltration were termed “invasive carcinoma.” Intermediate-grade dysplasia and low-grade dysplasia showed lesser degrees of abnormality (see Figs. 4 and 5 for examples), analogous to moderate and mild dysplasia in the international classification of gastric dysplasia.

Study of Resection Specimens

Case Identification. All resection specimens indexed as adenocarcinoma of the esophagus or gastric cardia in the Surgical Pathology files of The Johns Hopkins Hospital in 1951 through 1984 were reviewed. Forty-three cases with invasive carcinoma arising in Barrett’s esophagus were identified. Twenty-six of the 43 cases were included in our previous study. One of the resection specimens was from a patient included in the study of biopsy specimens (case 2).

Histopathologic Study Methods. The pathology reports, gross photographs, and histopathologic sections of the 43 resection specimens were reviewed. Specimens were fixed in formalin or Zenker’s fixative and processed for routine paraffin embedding and sectioning. In 16 specimens, the entire columnar-lined esophagus had been embedded for histopathologic examination.

The histopathologic sections were evaluated for inclusion in two study groups. The first group consisted of those sections showing Barrett’s mucosa from which microscopic invasive carcinoma originated, as illustrated in Figures 3 and 4. These sections generally were of Barrett’s mucosa that did not adjoin the main tumor mass; rather, the sections for study were chosen to include other microscopic foci of invasive carcinoma so that intact Barrett’s mucosa giving rise to invasive carcinoma could be examined. The second group of histopathologic sections consisted of those slides showing intact Barrett’s mucosa without adjoining invasive carcinoma, as illustrated in Figure 5. For purposes of analysis, histologic sections from adjacent blocks of tissue that showed similar findings were
Fig. 1. Biopsy specimen study: case 1 with high-grade dysplasia. A. Unclassified-type Barrett's mucosa with high-grade dysplasia. The villous architecture, although bizarre, suggests antecedent distinctive-type mucosa. Hematoxylin and eosin (X55). B. The epithelium is hypercellular, with stratified abnormal nuclei showing loss of polarity. Hematoxylin and eosin (X550). C. Barrett's mucosa of the distinctive type with high-grade dysplasia (arrow). The architectural abnormalities are less striking than in A. (X85). D. High-power view of epithelium in area indicated by arrow in C. (Hematoxylin and eosin (X550).
FIG. 2. Biopsy specimen study: esophagectomy specimen from case 1 (see Fig. 1 for illustrations of biopsy specimens). A. Gross photograph of esophagectomy specimen. The nodule (arrowhead; see B and C for histopathology) was seen endoscopically. Although no invasive carcinoma was found in the nodule, the granular mucosa indicated by the long arrow showed foci of intramucosal invasive adenocarcinoma (see D and E for histopathology). In addition, adenocarcinoma infiltrated into the submucosa beneath another granular area of high-grade dysplasia, indicated by the short arrow. The specimen thus illustrates the multifocal nature of carcinoma arising in Barrett's esophagus (×1.3).

B. Histopathologic section of the nodule indicated by arrowhead in A shows polypoid high-grade dysplasia occurring in the midst of distinctive-type Barrett's mucosa. Prominent glandular dilatation is evident in the nodule, but no invasive carcinoma was identified. Hematoxylin and eosin (×11).

C. High-power view of nodule in B. Full-thickness stratification of nuclei is present. Hematoxylin and eosin (×600).

D. Intramucosal invasive adenocarcinoma in one focus indicated by long arrow in A. Invasion was confined to the lamina propria and spared the muscularis mucosae (MM). Hematoxylin and eosin (×140).

E. Intramucosal invasive adenocarcinoma infiltrates through the superficial layer of the muscularis mucosae (MM) beneath an area of high-grade dysplasia in another focus indicated by long arrow in A. Hematoxylin and eosin (×100).
Fig. 3. Resection specimen study: high-grade dysplasia in Barrett's mucosa giving rise to superficially invasive adenocarcinoma. A. Moderately differentiated gland-forming adenocarcinoma invades through the muscularis mucosae into the submucosa (long arrows) beneath an area of high-grade dysplasia. Intramucosal invasive mucinous adenocarcinoma (short arrow) is present within the area of high-grade dysplasia. Hematoxylin and eosin (×24). B. The Barrett's mucosa with high-grade dysplasia is of unclassified type, but the villous architecture suggests antecedent distinctive-type mucosa. Hematoxylin and eosin (×100). C. This example of Barrett's epithelium with high-grade dysplasia shows little nuclear stratification but prominent loss of nuclear polarity and cytologic abnormalities. Hematoxylin and eosin (×675).
Fig. 4. Resection specimen study: intermediate-grade dysplasia in Barrett's mucosa giving rise to superficially invasive adenocarcinoma. A. Well-differentiated gland-forming adenocarcinoma infiltrates through the muscularis mucosae (arrow) beneath an area of intermediate-grade dysplasia in distinctive-type Barrett's mucosa. Hematoxylin and eosin (×19). B. Area of intermediate-grade dysplasia shows abnormal mucosal architecture characterized by distorted, irregular glands. Hematoxylin and eosin (×100). C. The epithelium of the glands with intermediate-grade dysplasia shows nuclear stratification, loss of nuclear polarity, and cytologic abnormalities. Hematoxylin and eosin (×900).

considered to constitute an “area.” Representative slides were selected specifically to include the spectrum of areas with and without invasive carcinoma in each case. Serial sections from the selected blocks were stained with either hematoxylin and eosin or PAS and Alcian blue, pH 2.5.

Classification of Types of Barrett's Mucosa and Grades of Dysplasia. These evaluations were carried out as for the biopsy specimens.

Results

Study of Endoscopic Biopsy Specimens with Dysplasia in Barrett's Mucosa

Grades of Dysplasia (Table 2). Among 14 patients with biopsy specimens showing dysplasia without invasive carcinoma, 6 had high-grade dysplasia (43%), 3 had inter-
FIG. 5. Resection specimen study: low-grade dysplasia in Barrett's mucosa distant from invasive carcinoma.  
A. Cardiac-type Barrett's mucosa (C-T) with low-grade dysplasia adjoins distinctive-type mucosa (D-T) that is negative for dysplasia. Hematoxylin and eosin (×60).  
B. The cardiac-type epithelium with low-grade dysplasia shows columnar mucous cells with nuclear stratification and loss of polarity, increased nuclear-to-cytoplasmic ratio, hyperchromatism, prominent nucleoli, and decreased cytoplasmic mucin content. Hematoxylin and eosin (×900).  
C. The epithelial morphology and cytology of the distinctive-type epithelium that is negative for dysplasia contrasts with the cardiac-type epithelium showing low-grade dysplasia in B. Hematoxylin and eosin (×900).
mediate-grade dysplasia (21%), and five had low-grade dysplasia (36%). One of the patients with high-grade dysplasia (case 1) is illustrated in Figures 1 and 2.

Types of Barrett’s Mucosa (Table 2). Distinctive-type mucosa was found most frequently (13 of 14 patients, 93%). Cardiac-type mucosa was present in ten patients (71%) and fundic-type mucosa in three (21%). Barrett’s mucosa that was of unclassified type because of the presence of high-grade dysplasia was found in five patients (36%). The unclassified-type mucosa in all five had villous configuration and/or intestinal-type mucin favoring antecedent distinctive-type mucosa.

Types of Barrett’s Mucosa with Dysplasia (Table 2). The tissue fragments showing dysplasia in the six patients with high-grade dysplasia included distinctive-type mucosa in all, unclassified-type mucosa in five, and cardiac-type mucosa in two. In seven of the eight patients with intermediate- and low-grade dysplasia, the tissue fragments with dysplasia consisted of distinctive-type Barrett’s mucosa. Cardiac-type mucosa showed dysplasia in one patient with low-grade dysplasia. No fundic-type mucosa with dysplasia was found in the 14 patients.

Relationship Between High-Grade Dysplasia and Invasive Carcinoma. The clinical and pathologic findings in the five patients with high-grade dysplasia who were treated by esophagectomy are summarized in Table 3. Invasive carcinoma was known to be present at the time of operation in only one patient (patient 3: demonstrated by a second set of preoperative biopsies). However, three of the five patients had invasive adenocarcinoma in their esophagectomy specimens. Of note, the invasive carcinoma had not been demonstrated by repeat biopsies in two of the three patients with invasion. The three carcinomas were only superficially invasive; two of the patients had submucosal invasion and one had intramusosal invasive adenocarcinoma involving, but not penetrating, the muscularis mucosae. The fourth and fifth patients had extensive high-grade dysplasia without demonstrable invasive carcinoma, despite histopathologic examination of tissue blocks constituting the entire columnar-lined esophagus.

The sixth patient with high-grade dysplasia had the finding confirmed in a second set of biopsies taken one month after initial endoscopic examination. Radiographic evaluation and surgical exploration at another hospital showed no tumor mass, and fundoplication was performed. Follow-up biopsies three months later again showed high-grade dysplasia.

Of the three patients with intermediate-grade dysplasia in their biopsy specimens, two showed epithelial changes indefinite for dysplasia in repeat biopsies (three sets of repeat biopsies over a two-year period in one patient and one set one month later in the other). The third patient has not returned for follow-up examination.

Of the five patients with low-grade dysplasia, repeat biopsies in two were negative for dysplasia one to two years later. The third had epithelial changes indefinite for dysplasia two years later, after two intervening sets of biopsies were negative for dysplasia. The other two patients have not returned for follow-up examination.

In summary, this study showed that high-grade dysplasia in endoscopic biopsy specimens of Barrett’s mucosa was associated with the presence of invasive carcinoma (three of five patients), even when the invasive carcinoma could not be demonstrated in the biopsy specimens. Of particular importance, the carcinomas showed only superficial invasion. This finding is consistent with good prognosis, but longer follow-up of these patients and additional cases are needed to allow meaningful assessment of outcome.

Study of Resection Specimens

Types of Barrett’s Mucosa. Of the 90 areas of Barrett’s mucosa evaluated in our study of resection specimens, 36
### Table 3. Summary of Patients with High-Grade Dysplasia by Biopsy Who Were Treated with Esophagectomy

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of dysplasia, race, sex</td>
<td>56WM</td>
<td>60WM</td>
<td>51WM</td>
<td>73WM</td>
</tr>
<tr>
<td>Duration of diagnosis of Barrett’s esophagus</td>
<td>Initial</td>
<td>Initial</td>
<td>Initial</td>
<td>Initial</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Mild dysphagia 6 years after subtotal gastrectomy and Billroth II for ulcer</td>
<td>Nausea, dysphagia, and epigastric pain for 3 months</td>
<td>Nausea and vague epigastric pain for 6 months; long history of heartburn</td>
<td>None; upper GI bleeding</td>
</tr>
<tr>
<td>Endoscopic description of Barrett’s mucosa</td>
<td>Irregularity with 3-cm soft friable exophytic mass</td>
<td>Erosion; no mass or ulcer</td>
<td>Erythema; no mass or ulcer</td>
<td>Erythema; no mass or ulcer</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Yes (esophagectomy; repeat biopsies showed dysplasia only)</td>
<td>Yes (esophagectomy; repeat biopsies showed dysplasia only)</td>
<td>Yes (repeat biopsy and esophagectomy)</td>
<td>No: high-grade dysplasia only</td>
</tr>
<tr>
<td>Interval between diagnosis of high-grade dysplasia and invasive carcinoma</td>
<td>1 month</td>
<td>3 months</td>
<td>3 weeks</td>
<td>Not applicable (22 months until esophagectomy)</td>
</tr>
<tr>
<td>Deepest invasion</td>
<td>Submucosa</td>
<td>Submucosa, with venous invasion</td>
<td>Muscularis mucosae (intramucosal)</td>
<td>None</td>
</tr>
<tr>
<td>Follow-up status</td>
<td>No evidence of tumor</td>
<td>No evidence of tumor</td>
<td>No evidence of tumor</td>
<td>No evidence of tumor</td>
</tr>
<tr>
<td>Length of follow-up since esophagectomy</td>
<td>4 months</td>
<td>1.5 years</td>
<td>8 months</td>
<td>2.5 years</td>
</tr>
</tbody>
</table>

(40%) were of the unclassified type. As in the biopsy study, the unclassified-type Barrett’s mucosa was usually villous, villiform or papillary (32 of 36 areas, 89%) and had intestinal-type mucin (27 of 36 areas, 75%), findings that suggested antecedent distinctive-type mucosa (Fig. 3). In the 54 areas in which the type of Barrett’s mucosa could be identified, the distinctive type was by far the most common (37 of 54, 69%), while cardiac-type mucosa was found in the other 17 areas (31%). No areas of fundic-type Barrett’s mucosa were identified, although clusters of glands containing parietal cells were often found within areas of predominantly cardiac-type mucosa.

**Types of Barrett’s Mucosa with Dysplasia (Table 4).** By definition, unclassified-type mucosa always showed high-grade dysplasia. Among the other types of Barrett’s mucosa, only the distinctive type was found to have high-grade dysplasia. In addition, there was a suggestion of higher frequency of high- and intermediate-grade dysplasia in distinctive-type mucosa than in the cardiac type, although the difference was not statistically significant ($P = 0.08$ by Fisher’s exact test).

**Grades of Dysplasia in Barrett’s Mucosa Without Ad-**
joining Invasive Carcinoma. Forty-seven areas without invasion were included in the study. High-grade dysplasia was identified in 3 (6%), intermediate-grade dysplasia in 18 (38%), and low-grade dysplasia in 15 areas (32%). Eleven areas negative for dysplasia were included in the study (23%).

Relationship Between High-Grade Dysplasia and Invasive Carcinoma. As in the biopsy study, high-grade dysplasia was strongly associated with invasive carcinoma, as shown in Table 5. By contrast, if high- and intermediate-grade dysplasia were considered together, the strength of the relationship to invasive carcinoma was less: the percentage of areas with either high- or intermediate-grade dysplasia that showed invasion was only 67% (42 of 63) as compared with 92% for high-grade dysplasia alone.

Discussion

The results of our study have implications for both the pathogenesis of adenocarcinoma arising in Barrett’s esophagus and the management of patients with dysplasia in Barrett’s mucosa. From a pathogenetic standpoint, the association between dysplasia and carcinoma in both biopsy and esophagectomy specimens supports the occurrence of a Barrett’s mucosa-columnar epithelial dysplasia–invasive carcinoma sequence. From the standpoint of patient management, our study also provides data on the type of Barrett’s mucosa that appears to be at risk, as well as the relationship between grade of dysplasia and occurrence of invasion.

We found that the type of Barrett’s mucosa that appears to be at greatest risk for the dysplasia–carcinoma sequence was the distinctive-type mucosa, in agreement with previous reports. This conclusion was based on two findings: (1) Barrett’s mucosa exhibiting dysplasia was usually of the distinctive type; and (2) Barrett’s mucosa of unclassified-type because of the presence of high-grade dysplasia frequently had villous architecture and intestinal-type mucin by histochemistry, thereby favoring distinctive-type mucosa as the predecessor. Cardiac-type Barrett’s mucosa also showed dysplasia, in agreement with previous reports, but the grades of dysplasia tended to be lower than in distinctive-type mucosa. The possibility remains, however, that the distinctive-type mucosa most commonly shows dysplasia simply because it is the most common and extensive type of Barrett’s mucosa in adults. If the risk of dysplasia in the various types of Barrett’s mucosa was similar, the association between dysplasia and the distinctive-type mucosa could result from the greater surface area at risk, rather than inherent susceptibility. Thus, additional studies of the various types of Barrett’s mucosa for markers of increased susceptibility to malignancy are needed.

Our systematic study of the relationship between grade of dysplasia and presence of invasive carcinoma showed that high-grade dysplasia is the usual finding associated with invasion. Thus, high-grade dysplasia appears to be a marker indicating high probability of invasive carcinoma. Of particular note, the three patients with carcinoma identified consequent to biopsy demonstration of high-grade dysplasia had small and only superficially invasive carcinomas (two into the submucosa and one intramucosal into the muscularis mucosae). In addition, two patients had high-grade dysplasia in their biopsy specimens and subsequent esophagectomy specimens but no invasive carcinoma (cases 4 and 5 in Table 3). These latter cases provide circumstantial evidence that high-grade dysplasia can be a precursor to, as well as a concomitant of, invasive carcinoma.

Intermediate-grade dysplasia did adjoin microscopic invasive carcinoma in some areas in our resection specimen study, but this was rarely the case for low-grade dysplasia. On the other hand, neither intermediate-nor low-grade dysplasia in the biopsy specimens of eight patients was found to be associated with invasive carcinoma. However, the results of prospective biopsy studies with large numbers of patients, which are in progress at several institutions, are needed to determine the natural history of the dysplasia–carcinoma sequence. Whether or not antireflux surgery can modify the natural history is also uncertain at present.

No universally accepted classification of dysplasia in Barrett mucosa exists as yet. Recently proposed grading schemes have included both two grades and three grades of dysplasia. Intermediate-grade dysplasia in our study would be included in the category of high-grade dysplasia in the two-grade classification schemes, which are based on the criteria used for dysplasia in chronic

### Table 5. Relationship between High-Grade Dysplasia and Invasive Carcinoma in Resection Specimens

<table>
<thead>
<tr>
<th>High-Grade Dysplasia</th>
<th>Areas from which Invasion Occurred (n = 43)</th>
<th>Areas Without Adjoining Invasion (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (n = 39)</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Absent* (n = 51)</td>
<td>7</td>
<td>44</td>
</tr>
</tbody>
</table>

Percentage of areas with invasion that showed high-grade dysplasia = 84% (36/43).† Percentage of areas without invasion that did not show high-grade dysplasia = 94% (44/47).‡ Percentage of areas with high-grade dysplasia that showed invasion = 92% (36/39).§ Percentage of areas without high-grade dysplasia that did not show invasion = 86% (44/51).¶

* Includes intermediate-grade dysplasia, low-grade dysplasia, and negative for dysplasia.
† Analogous to sensitivity.
‡ Analogous to specificity.
§ Analogous to predictive value of positive.
¶ Analogous to predictive value of negative.
inflammatory bowel disease. Our study has practical implications for the histopathologic diagnosis of high-grade dysplasia and for the management of patients with this finding on esophageal biopsy.

As regards diagnosis, we found that mucosal thickening and marked abnormalities of villous and gland architecture as compared with non-dysplastic Barrett's mucosa were important histopathologic characteristics of high-grade dysplasia. These abnormalities were sometimes accompanied by relatively bland epithelial morphologic and cytologic findings, even in areas of high-grade dysplasia adjoining microscopic invasive carcinoma. Thus, architectural features on low-power examination of a histopathologic section appear to be an important diagnostic criterion for high-grade dysplasia. In addition, the diagnosis of high-grade dysplasia should not depend on the presence of endoscopic abnormalities. In our study, high-grade dysplasia in biopsy specimens from Barrett's mucosa with no apparent mass or nodularity on endoscopic examination was associated with invasive carcinoma in two patients (cases 2 and 3 in Table 3). Furthermore, in the other patient with invasive adenocarcinoma (case 1), invasion was not found in the nodular area seen endoscopically but rather in flat mucosa (see Figure 2). Some authors have used “adenoma” to refer to polypoid areas of dysplasia in Barrett's mucosa. Based on our findings, we recommend that “adenoma” not be used because it has unfortunate connotations of benignity and potential for local removal by polypectomy, as in the large bowel.

As regards patient management, surveillance for dysplasia and carcinoma in patients with Barrett's esophagus has many issues in common with surveillance of patients with another well-known predisposing (premalignant) condition, i.e., chronic inflammatory bowel disease in the form of ulcerative colitis and Crohn's disease involving the colon. Recent studies have shown that the incidence of carcinoma arising in Barrett's esophagus is relatively low (1 of 175 to 1 of 441 cases per patient year) as contrasted with the relatively high prevalence (8–15%). As a result, studies of cost and benefit are needed to determine what, if any, surveillance protocols should be followed. Nonetheless, many patients with Barrett's esophagus follow current management recommendations for periodic endoscopic examination with biopsies and brush cytology. In our study, high-grade dysplasia was found to be a marker indicating high probability of invasive carcinoma. We, therefore, support the provisional recommendation that prophylactic esophagectomy is indicated in a patient with persistent high-grade dysplasia in esophageal biopsy specimens of Barrett's mucosa if the patient is likely to tolerate the resection.

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