

Barrett's esophagus: A review of diagnostic criteria, clinical surveillance practices and new developments

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Abstract: Barrett's esophagus is defined by metaplastic glandular changes to the distal esophagus and is linked to an increased risk of esophageal adenocarcinoma. Controversy exists whether the definition should be limited to intestinal type glands with goblet cells or should be expanded to include non-goblet cell columnar epithelium. Barrett's esophagus may be asymptomatic in a large proportion of the population but screening should be considered for those with certain clinical findings. The diagnosis of Barrett's should be based on the combination of careful endoscopic evaluation and histologic review of the biopsy material. Continued surveillance biopsies may be necessary in cases of indeterminate or low grade dysplasia. Clinical follow-up of patients with high grade dysplasia should be tailored to the individual patient. Development of newer endoscopy techniques including chemoendoscopy, chromoendoscopy and use of biomarkers on frozen tissue have shown some promise of identifying patients at risk for malignancy.

Key Words: Barrett's; intestinal metaplasia; surveillance; endoscopy



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The current definition for Barrett's esophagus (BE) proposed by the American Gastroenterological Association (AGA) is "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus (1)". Three types of columnar epithelium are seen in the setting of BE: (I) gastric-fundic type, (II) cardia-type, and (III) intestinal-type including goblet cells. However, only the last type has been clearly linked to an increased risk of malignant progression, with a reported annual risk of esophageal adenocarcinoma (EAC) of about 0.5% per year in patients with intestinal metaplasia of the esophagus (1-3). For this reason both the AGA and the American College of Gastroenterology (ACG) currently recommend that although columnar-type mucosa can be recognized during endoscopy, the presence of intestinal metaplasia must be confirmed by biopsy before rendering a diagnosis of BE (1,4).

Controversies regarding intestinal metaplasia

The American definition is used in most parts of the world,

however, Great Britain and Japan allow the diagnosis of BE to be assigned if only cardiac-type metaplasia is seen on biopsy (5,6). While some advocate the universal adoption of the less stringent criteria (7), the evidence to do so is controversial. Gatenby *et al.* and Kelty *et al.* each conducted studies that showed a similar risk of EAC in patients having columnar metaplasia of the esophagus with and without goblet cells (8,9). In contrast, two large population studies from Northern Ireland showed a clear increased risk of cancer when intestinal metaplasia was present versus when only columnar cell change was identified (10,11).

A study by Takubo *et al.* which examined the mucosa adjacent to EAC treated with endoscopic mucosal resection found that most (>70%) were bordered by cardiac-type mucosa rather than intestinal-type mucosa and that 56% had no intestinal-type mucosa in any areas of the resection specimens. They concluded that there is a relationship between EAC and cardiac-type mucosa and that a background of intestinal metaplasia may not be a necessary pre-requisite to EAC (6).

Two similar studies by Chandrasoma and colleagues had different findings. The first, which examined

esophagogastrectomy specimens resected due to adenocarcinoma, showed cardiac mucosa adjacent to all tumors but also showed residual intestinal metaplasia in 65% of cases overall and in 100% of intramucosal tumors as well as those less than 1 cm in diameter (12). The second study reviewed two groups: (I) cases with visible columnar metaplasia of the esophagus which underwent systematic 4-quadrant biopsies every 1 to 2 cm and (II) cases of dysplasia or EAC which did not receive systematic biopsy. They found that when systematic biopsy was performed, intestinal metaplasia was identified in >87% of cases including all cases with dysplasia or EAC. None of the cases with cardiac type epithelium alone had dysplasia or EAC. In the group which did not receive systematic biopsy but did have dysplasia or EAC, many showed only tumor on biopsy. However, slightly more than half (56%) of those with non-tumor mucosa had residual intestinal-type metaplasia (13). They hypothesize that the absence of residual intestinal metaplasia immediately adjacent to many cases of EAC is due to tumor overgrowth and inadequate sampling rather than a true absence (12,13). They also propose that when metaplastic columnar epithelium is adequately and systematically biopsied, patients without intestinal metaplasia have a negligible risk of dysplasia and cancer (13).

Recent data shows that columnar cell epithelium may have an intestinal-type immunohistochemical profile even when goblet cells are not identified. Various studies have shown significantly increased positivity for intestinal markers such as DAS-1 (14-16), CDX-2 (14,17,18), and HepPar1 (19) as well as a similar cytokeratin (16,20) and mucin (20) expression profile in both goblet cell and non-goblet cell columnar epithelia, which suggests a similar origin. There have also been studies showing similar molecular alterations in both non-goblet cell and intestinal-type metaplasia including chromosomal instability (21,22), microsatellite instability (22), and similar DNA content abnormalities (23). Despite the similar phenotypic and molecular profiles, the natural history of columnar cells and goblet cells is not always the same (24) suggesting that additional factors are required for progression toward dysplasia and cancer.

Expanding the definition of BE to include all patients with columnar metaplasia of the esophagus would have substantial societal and personal economic impact. Studies from both the United States and Sweden show that the population of patients with columnar metaplasia of the esophagus without goblet cells is significantly greater than the population with intestinal metaplasia (25,26). Conducting surveillance on all of these patients has the potential to overwhelm healthcare resources and greatly increase treatment costs. Also, despite data which

demonstrate a normal life expectancy in patients with BE, the cost of life insurance is substantially increased and availability of health insurance is decreased in patients with this diagnosis (27). Until such a time as columnar cell metaplasia of the esophagus without goblet cells is clearly shown to convey increased risk of EAC, it seems appropriate to hold back from labeling these patients with BE (1,4).

Screening

Endoscopic screening for BE is widely practiced and patients are often selected for screening based on the presence of multiple well-established risk factors for BE including: chronic gastroesophageal reflux disease (GERD), older age (>50 years), male sex, white race, elevated body mass index, intra-abdominal fat distribution, and hiatal hernia (1,4).

While the presence of GERD symptoms was one of the first recognized and strongest risk factors identified for BE, the presence of GERD alone is not sufficient to recommend screening. Up to 40% of US adults experience GERD on a monthly basis (28), yet despite the increasing incidence of EAC there are still fewer than 10,000 new cases of EAC diagnosed per year (29). Up to 40% of patients who have adenocarcinoma of the esophagus report no history of chronic GERD (30). Eliminating patients from screening based on a lack of symptoms could exclude a large portion of those who might have their cancers detected at an early, presymptomatic stage. Additionally, difficulties recognizing mucosal lesions (31), sampling error (32), and disagreement over pathologic interpretation (33) can decrease the effectiveness of endoscopic screening. For these reasons, the decision of who and when to screen should be individualized (1,4).

Endoscopic diagnosis

Barrett's esophagus (BE) presents on endoscopy as characteristic salmon-pink colored extensions (or "tongues") of mucosa that grow into the esophagus above the esophageal gastric junction (EGJ). For screening and surveillance, four quadrant biopsies are taken along every 2 cm of the BE type mucosa and submitted to pathology in separate containers. While this approach samples only a small fraction of the affected lining, it allows the opportunity to recognize dysplasia and focus subsequent biopsies on the appropriate area if dysplasia is identified (4). Traditionally, BE is termed long segment if the tongues are 3 cm or more in length, short segment BE when less than 3 cm, and ultra-short segment BE when less than 1 cm (34). The exact location of the biopsy relative to the Z-line and

EGJ is important to know, as ultra-short BE can be difficult to differentiate from an irregular EGJ and is thought to carry significantly less risk of cancer development than traditional BE (34-38). Additionally, intestinal metaplasia below the EGJ should not be diagnosed as BE. The changes are thought to have a different etiology, often arising secondary to *Helicobacter pylori* infection, and the significance as a precursor to EAC is uncertain (35,39-41). For these reasons, changes in this region should be given a descriptive diagnosis of intestinal metaplasia.

Accurate assessment of the extent of BE on endoscopy is clinically important because more extensive BE carries a higher risk of cancer development (42,43), however there is a high degree of inter- and intraobserver variation (44-46). The Prague C&M Criteria (47) is a consensus-driven, validated system which utilizes standardized landmarks - the squamocolumnar junction, the EGJ, the extent of circumferential columnar lining, and the proximal extension of the columnar mucosa - to determine the length of BE. This system has an overall reliability coefficient (RC) of 0.72 in recognition of BE ≥ 1 cm, however the RC dropped to 0.22 when less than 1 cm of columnar-lining was present. This is the endoscopic classification system currently suggested by the American College of Gastroenterology (4). A recent small study by Kinjo *et al.* (48) suggests that recognition of ultra-short segment BE may be improved using the Japanese EGJ reference point (the distal end of the palisade-shaped longitudinal vessels) rather than the traditional proximal limit of the linear gastric mucosal folds currently utilized in the Prague C&M criteria, but more information is needed to determine if these results are reproducible and applicable outside of the Japanese population.

Histologic features of Barrett's esophagus and dysplasia

Clinicians and pathologists have defined BE to include not only a characteristic endoscopic appearance to the esophagus but also histologically confirmed intestinal metaplasia consisting of columnar epithelium with well-formed goblet cells (1). Goblet cells are recognized by a large cytoplasmic vacuole filled with blue-tinted mucin. During carcinogenesis, the tissue develops morphologic changes related to unregulated cell growth that can be recognized as dysplasia on microscopic examination (49). The spectrum of changes is subdivided into four clinically significant groups: negative for dysplasia, indefinite for dysplasia, low grade dysplasia, and high grade dysplasia. Patients with histologically confirmed dysplasia have been shown to have significantly increased risk of progression to EAC (33,50-52). Despite concerns over adequate sampling

and imperfect intra- and interobserver reproducibility (particularly at the low end of the dysplasia spectrum), histologic evaluation for dysplasia retains a key role in the surveillance of patients with BE (4,33,53).

Due to the significance of identifying dysplasia, much work has gone into clarifying and refining the criteria used to interpret biopsies (33,54-57). The degree of dysplasia is determined by evaluating the cytology (nuclear and cytoplasmic features), architecture (relationship of glands and lamina propria), and degree of surface maturation (comparison of nuclear size within crypts to nuclear size at the mucosal surface) and interpreting these findings in conjunction with the amount of background inflammation. Features of each category of dysplasia are described below and summarized in *Table 1*.

Negative for dysplasia – These biopsies can have a minimal amount of cytologic atypia but retain normal architecture, abundant lamina propria between glands, and appropriate maturation with a low nuclear:cytoplasmic ratio at the mucosal surface. The nuclei are regular, have smooth membranes, and are basally situated. If mitoses are present they are within the basal compartment. In the presence of inflammation, increased cytologic atypia is allowed (*Figure 1A*).

Indefinite for dysplasia – This category is applied to biopsies where the changes seen cannot be definitively described as reactive or neoplastic. It is most often used in the presence of pronounced inflammation or the loss of surface epithelium. Cytologic atypia characterized by hyperchromasia, overlapping nuclei, irregular nuclear borders, and nuclear stratification can be seen in the deep glands or the sides of villiform structures while the surface epithelium is free of atypia. The architecture should be largely normal with, at the most, minimal gland crowding. Surface maturation is present (*Figure 1B*).

Low grade dysplasia – The most important feature of low grade dysplasia is cytologic atypia extending to the mucosal surface and either minimal or absent surface maturation. Severe architectural distortion is not a feature, though mild gland crowding with decreased intervening lamina propria can be seen. Mitoses may be increased but no atypical forms should be seen. Inflammation is usually minimal. One important note: although cytologic atypia is a key finding, nuclear polarity is preserved. Loss of polarity - where the nucleus is tilted, rounded, or horizontal to the basement membrane - is associated with higher grade lesions (*Figure 1C*).

High grade dysplasia – The cytologic changes are severe with markedly enlarged nuclei at the surface, pronounced pleomorphism, and at least focal loss of nuclear polarity. Surface maturation is lost. Mild to marked architectural distortion is a frequent finding, with crowded glands, loss of lamina propria, focal budding, and/or cribriform glands.

Table 1 Categories of dysplasia: Histologic features and suggested endoscopic surveillance (4,33,53)

Category	Histology		Follow Up
Negative for dysplasia	Architecture	Normal with well-spaced glands	Repeat EGD* within 1 year EGD every 3 years
	Cytology	Regular nuclei Smooth membranes	
	Maturation	Complete	
Indefinite for dysplasia	Architecture	Normal to mild distortion, often inflamed	Repeat EGD within 6 months Follow-up as indicated by results PPI** prior to repeat biopsy if significant inflammation present
	Cytology	Hyperchromasia Overlapping nuclei Irregular nuclear borders	
	Maturation	Complete when intact surface epithelium is present	
Low grade dysplasia	Architecture	Normal to mild distortion Gland crowding	Repeat EGD within 6 months to rule out high grade Expert pathologist confirmation Yearly EGD until no dysplasia
	Cytology	Minimal pleomorphism Maintained polarity Increased mitotic activity	
	Maturation	Minimal to none	
High grade dysplasia	Architecture	Mild to marked distortion Crowded glands Cribriform or budding glands	Repeat EGD within 3 months to rule out cancer Expert pathologist confirmation Mucosal irregularity – EMR*** Individualized surveillance or treatment plan
	Cytology	Loss of polarity Markedly enlarged nuclei Prominent pleomorphism Atypical mitoses	
	Maturation	None	

*EGD – esophagogastroduodenoscopy; **PPI – proton pump inhibitor; ***EMR – endoscopic mucosal resection

There should be no evidence of invasion into the lamina propria. Mitoses are increased and atypical mitoses may be seen. Ideally inflammation is minimal or absent. If either the cytologic or architectural changes are severe and extensive, the diagnosis of high grade dysplasia can be made even if other features are only low grade in severity (*Figure 1D*).

Whenever high grade dysplasia is diagnosed the biopsy should also be evaluated for the presence of co-existing EAC. This may be difficult or impossible to exclude on biopsy, but suspicious or suggestive architectural changes include single cells in the lamina propria, desmoplasia, cribriform or solid tubular architecture, dilated tubules filled with necrotic debris, extensive neutrophilic infiltrate within the epithelium, ulcerated high grade dysplasia, and neoplastic tubules incorporated into the overlying squamous epithelium (57).

Surveillance of Barrett's esophagus

Although there is a lack of randomized trials that support the value of endoscopic surveillance in BE, indirect evidence from multiple retrospective studies indicates a statistically significant improvement in survival for cancers that are detected endoscopically versus those that present with symptoms (58-64). In light of this evidence and the poor 5 year survival for EAC, surveillance endoscopy is widely practiced (65,66).

Ideally surveillance endoscopy is performed in patients

whose reflux symptoms are controlled, reducing the chance of inflammatory or reactive changes interfering with pathologic interpretation (67). Four quadrant biopsies should be obtained at a minimum of every 2 cm and submitted to pathology in separate containers. The surveillance intervals suggested by the 2008 ACG Guidelines (4) are dependent on the pathology results (*Table 1*).

If the initial biopsy diagnostic of BE is negative for dysplasia, a repeat endoscopic exam with biopsy is recommended within a year. If the second study is also negative for dysplasia then follow-up at 3 year intervals is suggested. If low grade dysplasia is identified it is suggested that the diagnosis be confirmed by second opinion from an expert pathologist and a repeat exam take place within 6 months to ensure no higher grade of dysplasia is identified. If no higher grade lesion is found, yearly follow up is suggested until two consecutive exams are negative for dysplasia. Biopsies interpreted as indefinite for dysplasia should be managed similarly to those with low grade dysplasia. A diagnosis of high grade dysplasia should also be confirmed by an expert pathologist but repeat exam should take place within 3 months. Biopsies should be taken at smaller, 1 cm intervals. It is also suggested that any mucosal irregularities be treated with endoscopic mucosal resection to obtain enough tissue for accurate diagnosis. Beyond these suggestions, treatment options for high-grade dysplasia include careful surveillance, a variety of ablative therapies, and surgical resection. Treatment should be

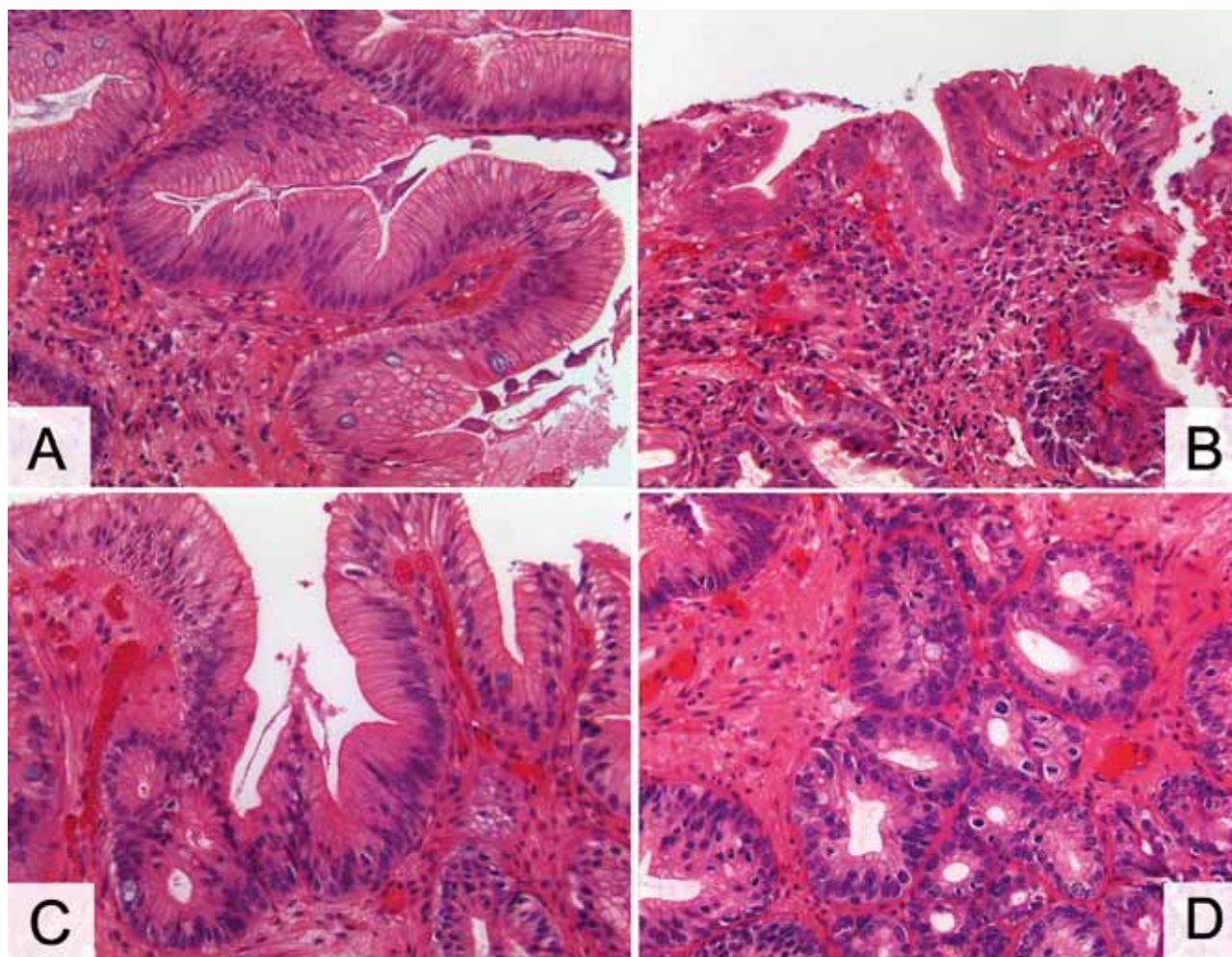


Figure 1 A. Negative for dysplasia - There is columnar cell metaplasia including mucin-filled, blue-tinted goblet cells. The glands are well spaced with abundant intervening lamina propria and the nuclei are regular, smooth, and basally aligned [hematoxylin and eosin stain (H&E), 200×]; B. Indefinite for dysplasia - Increased inflammation is seen in the lamina propria and the epithelium. Nuclei are enlarged with some overlap and nuclear stratification can be seen. There is mild crowding of glands (lower right) but the architecture is largely normal (H&E, 200×); C. Low grade dysplasia - There is increased nuclear atypia with hyperchromasia, increased pleomorphism, and nuclear overlap. These features approach the surface. Mitoses are increased. The architectural changes are distinct in this case with increased gland crowding (H&E, 200×); D. High grade dysplasia - The cytologic changes are distinct, with obvious nuclear enlargement, pleomorphism, hyperchromasia, and overlap. Frequent mitoses, including some at the surface, are seen. The glands are crowded with a near absence of intervening lamina propria (H&E, 200×)

tailored for individual patients based on their preferences, their appropriateness for each option, and the experience of the treating physician (4).

Developments in the diagnosis and surveillance of Barrett's esophagus

Controversies over the best methods to diagnosis and monitor BE exist, largely because the current process involves many variables that are subjective and therefore difficult to standardize: selection of patients for screening, recognition of landmarks and BE-type changes on endoscopy, sampling

variation, histologic grading of dysplasia, and the timing and type of intervention. The ultimate goal is to detect cancers that develop in the setting of BE at a curable stage. Advances in techniques are being explored, with most of the emphasis placed either on increasing the recognition of suspicious lesions for biopsy during endoscopy or objectively identifying which cases of dysplasia are likely to progress to carcinoma using biomarkers.

Enhanced endoscopy

High-resolution white light endoscopy combines

endoscopes with large numbers of pixels (600,000 to 1,000,000), magnification devices, and high-definition screens to optimize visualization of the esophageal mucosa (68). It has shown greater sensitivity in the detection of early neoplastic lesions when compared to standard endoscopy (69).

Chemoendoscopy involves the application of chemicals that selectively react with and highlight various mucosal features, theoretically improving the detection of abnormalities (70-76). Methylene blue is absorbed by non-dysplastic intestinal-type epithelial cells theoretically helping to detect BE and target biopsies. However, meta-analysis found no significant difference in the detection rates of BE or dysplasia between methylene blue directed biopsy and a standard 4-quadrant approach (74). Additionally, there is some evidence that methylene blue induces DNA damage in BE (77,78). Lugol's solution is absorbed by glycogen-containing squamous epithelial cells and helps identify the squamocolumnar junction after eradication therapy, which is helpful in the recognition of residual columnar-cell islands (75). Indigo carmine dye is combined with magnification endoscopy to distinguish mucosal pit patterns - round, reticular, villous, and ridged (68). While there is good association of certain patterns with intestinal metaplasia (76), it has not been shown to increase the detection of dysplasia beyond that of high-resolution endoscopy (69).

Electronic chromoendoscopy includes optimal band imaging which involves postprocessing to accentuate the contrast between columnar and squamous epithelia (79) and narrow band imaging (NBI) which uses optical filters to highlight vascular patterns on the mucosal surface (80). While studies show good correlation of vascular patterns identified by magnified NBI with BE and high grade dysplasia (80,81), prospective studies comparing the actual diagnostic yield of NBI to standard endoscopy have had mixed results (82-84). A comparison of NBI to high resolution white light endoscopy showed no significant difference in the detection of BE or dysplasia (84).

Autofluorescence imaging utilizes differences in the endogenous fluorophores found in normal and neoplastic epithelia (68). While the technique has good sensitivity for the detection of high grade dysplasia, studies have shown poor specificity with false positive rates up to 81% (85-87). An analogous process recently described by Bird-Lieberman *et al.* utilizes a fluorescently labeled wheat germ derived lectin that binds to surface glycans of normal esophageal epithelial cells. Expression of these glycans is decreased or lost during neoplastic progression, so potentially pre-malignant or malignant regions are highlighted by a negative staining pattern (88). The potential applications are intriguing, but it has yet to be applied *in vivo* or prospective clinical trial.

Magnifications exceeding 1,000 \times can be achieved in real time using confocal laser endomicroscopy, allowing for analysis of the crypt architecture and capillaries during endoscopic examination. A few initial studies have shown accuracy rates above 85% in detecting high-grade dysplasia (89,90), fused glands indicating neoplasia with a sensitivity of 80%, and good interobserver agreement (91).

Light scattering spectroscopy and diffuse reflectance spectroscopy use algorithms to analyze light scattered back to the sensing device by the tissue. This spectroscopic information has been able to distinguish neoplastic from non-neoplastic tissue with both good sensitivity and specificity (92,93) in a few small trials. Optical coherence tomography uses variations in the reflectance of near-infrared light from different tissues to create a high-resolution cross-sectional image of the mucosa (94). One study has shown excellent sensitivity (97%) and specificity (92%) in the recognition of BE without dysplasia (95) while another showed good sensitivity (83%) and specificity (75%) in identifying high grade dysplasia (96).

While many of these endoscopic techniques show promise, there is currently no definitive evidence that they provide additional information beyond careful examination using high-resolution white light endoscopy. Also, most require specialized equipment and/or training that may not currently be available outside of specialty centers.

Biomarkers

The grading of dysplasia currently guides surveillance and treatment decisions; however it is an imperfect predictor of cancer risk. Several biomarkers have shown promise as objective adjunct tests to improve risk stratification of patients with BE. Panels of immunohistochemical stains including α -methylacyl-CoA racemase (AMACR), β -catenin, cyclin D1, and p53 show promise in separating grades of dysplasia and in distinguishing true neoplastic progression from reactive changes (97-99).

Other biomarkers which test for DNA abnormalities have been evaluated in cross-sectional or retrospective studies. The detection of aneuploidy, increased tetraploidy, and loss of heterozygosity (LOH) for chromosome 17p in patients with no dysplasia or low grade dysplasia on biopsy has been shown to have good predictive value for neoplastic progression, but added little information when high grade dysplasia was detected (100-104). These studies utilized flow cytometry to detect DNA content abnormalities in fresh frozen tissue, which may not be practical in clinical practice. Fluorescence in situ hybridization can theoretically be used to detect these same abnormalities in fixed tissue and most initial studies show promising results (104-108).

Biomarker panels - including detection of chromosomal abnormalities (aneuploidy/tetraploidy, 17p LOH, 9p LOH) or tumor-suppressor gene-methylation patterns - have also been good indicators of progression risk in initial studies (109-111). One methylation-based panel, applied retrospectively, even identified patients who progressed to high grade dysplasia two years before histologic changes were seen (111).

Biomarkers may prove to be the best predictors of cancer progression, however much of the work done with them to-date has involved freshly frozen tissue (which may not always be available) and none have been validated in prospective controlled clinical trials. While promising, they should not replace grading dysplasia for risk stratification in routine clinical practice at this time (68).

Conclusions

Although newer techniques are being studied, at this time none have definitively been shown to be more cost effective than careful clinical evaluations and systematic biopsy screening. Good patient care includes coordination of careful microscopic study with patient clinical history. The findings of both the endoscopist and the pathologist are critical.

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