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## Advances in Barrett's Esophagus



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**Esophageal adenocarcinoma is increasing in frequency in the United States. Barrett's esophagus is the strongest risk factor for esophageal adenocarcinoma making evaluation for Barrett's esophagus of utmost importance. Currently screening and surveillance are accomplished with regular white light endoscopy; however, new advances in both population screening and surveillance are being developed. This review will cover selecting the appropriate patient population for Barrett's esophagus screening, available and upcoming technologies for screening and surveillance, and lastly treatment of Barrett's esophagus.**

### BACKGROUND

**E**sophageal cancer is increasing in frequency and is the sixth leading cause of cancer death in the world.<sup>1,2</sup> While squamous cell carcinoma is more common in the developing world, adenocarcinoma is more common in the United States. Esophageal adenocarcinoma carries a poor prognosis, making it imperative to diagnose it early. The strongest risk factor for esophageal adenocarcinoma is Barrett's esophagus, which increases the risk of esophageal adenocarcinoma 30-50 fold.<sup>3,4</sup>

Barrett's esophagus is defined as the replacement of squamous epithelium by intestinal epithelium.

Diagnosis requires endoscopic evidence of columnar mucosa in the esophagus with histologic confirmation of intestinal metaplasia with goblet cells. The Prague classification system is used to systematically describe a segment of Barrett's esophagus. The classification system assesses the circumferential and maximal extent of an endoscopically visualized Barrett's esophagus segment to help facilitate diagnosis and treatment.<sup>5</sup> Barrett's esophagus has been divided into long segment ( $\geq 3$  cm in length), short segment ( $< 3$  cm in length), and very short segment ( $< 1$  cm in length).<sup>5,6</sup> Increasing length of Barrett's segment is associated with increased risk of dysplasia.<sup>7</sup>

Very short segment Barrett's esophagus remains controversial as the most recent guidelines from the American College of Gastroenterology (ACG) and British Society of Gastroenterology require at

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least 1 cm of columnar mucosa for the diagnosis of Barrett's esophagus, while the American Gastroenterological Association does not have a similar restriction.<sup>6,8</sup> This controversy stems from previous studies showing that very short segment Barrett's esophagus, otherwise known as an irregular Z line, does not have the same association with high-grade dysplasia or adenocarcinoma.<sup>9</sup> A recently published paper performed a prospective, multicenter cohort study of patients who underwent endoscopic examination for Barrett's esophagus in the United States and Europe and found that none of the patients with irregular Z line developed high-grade dysplasia or esophageal adenocarcinoma within a median follow-up period of 4.8 years.<sup>10</sup>

Risk factors for Barrett's esophagus include age over 50, male sex, chronic reflux disease, white ethnicity, smoking, and obesity.<sup>11,12</sup> Roughly 5-15% of patient with chronic gastroesophageal reflux disease have Barrett's esophagus.<sup>13</sup>

## Screening

Despite retrospective studies showing that adenocarcinomas diagnosed in screening programs tend to be earlier stage, screening for Barrett's esophagus remains controversial. The main questions revolve around whom to screen, as symptomatic gastroesophageal reflux disease remains a poor predictor of Barrett's esophagus on endoscopy. The most recent guidelines by the ACG published in 2016 recommend screening for Barrett's esophagus be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux and two or more risk factors for Barrett's esophagus including age >50, Caucasian race, presence of central obesity, history of smoking, or a family history of Barrett's or esophageal adenocarcinoma.<sup>6</sup>

Conventional endoscopy remains the gold standard for screening for Barrett's esophagus. This involves using standard white light endoscopy with collection of biopsy specimens from any suspicious lesions as well as random four quadrant biopsies of endoscopically visible columnar tissue. The examination should be conducted carefully with a high-definition endoscope. Longer Barrett's inspection time significantly increases high-grade dysplasia and adenocarcinoma detection rates.<sup>14</sup> Special attention needs to be paid to the right

hemisphere of the Barrett's segment as early adenocarcinomas have a predilection to develop in this area.<sup>15</sup> If initial endoscopy does not show Barrett's esophagus, society guidelines do not recommend repeating future endoscopies.<sup>6</sup>

Given the costs and specialist expertise associated with upper endoscopy, investigators have studied other techniques for Barrett's detection. Transnasal endoscopy involves using a smaller caliber endoscope that is inserted nasally without the need for sedation. It has been shown to have similar efficacy compared to standard endoscopy.<sup>16</sup> Non-endoscopic techniques have also been developed. The cytosponge is a gelatin-coated sponge attached to a string that is swallowed and collects cytology specimens when withdrawn. Cells are retrieved from the cytosponge and analyzed for expression of markers specific to Barrett's esophagus. Trefoil factor 3 is a marker that distinguishes the columnar cells in Barrett's esophagus cells from columnar cells in the rest of the gastrointestinal and upper airway tracts. Studies with cytosponge have shown 73% to 90% sensitivity for detecting Barrett's esophagus, however, the diagnostic accuracy is still being determined.<sup>17,18</sup>

Biomarkers have been investigated extensively and the most promising of these include P53, copy number alterations and methylation panels. However, as of now no single biomarker is adequate for risk stratification. Though, when coupled with the cytosponge, biomarkers could potentially provide a cost-effective method for community based screening for Barrett's esophagus by risk stratifying patient's risk of progression to dysplasia and adenocarcinoma. The recently done BEST2 multicenter cohort study showed that the Cytosponge could be coupled with biomarkers (P53, c-Myc, Aurora kinase A, and methylation markers) to identify a cohort of patients at low risk of progression of Barrett's esophagus who may be suitable for non-endoscopic follow-up.<sup>19</sup> However, more studies are needed, especially randomized control trials to address accuracy and long-term follow-up.

A new screening technique under development for the identification of Barrett's esophagus is breath testing. Breath testing uses an electronic nose device to measure subtle volatile organic compounds (VOC). A group from Mayo Clinic

performed a cross-sectional study and evaluated the breath VOCs of a cohort of patients with a history of dysplastic Barrett's esophagus for the presence or absence of Barrett's esophagus.<sup>20</sup> They were able to detect Barrett's esophagus with 82% sensitivity and 80% sensitivity. More data will be needed on testing healthy subjects, but if successful may potentially become an important non-invasive community screening technique for Barrett's esophagus.

### Surveillance

Early detection of esophageal adenocarcinoma improves survival. Several studies have demonstrated that adenocarcinomas detected in surveillance programs are detected in earlier stages thus suggesting a potential improvement in survival.<sup>21,22</sup> While there is no prospective data proving this concept, a large population based cohort study found that patients with adenocarcinoma who had undergone endoscopic surveillance had increased survival compared to patients who had not undergone surveillance.<sup>23</sup>

Surveillance is aimed at detecting dysplasia, which can be categorized as indeterminate, low-grade, high-grade, or adenocarcinoma. The degree of dysplasia dictates recommended surveillance intervals. Similar to screening, surveillance endoscopy is accomplished with high definition white light endoscopy. According to the Seattle protocol, random four quadrant biopsies are taken every 2 cm.<sup>24</sup> However, adherence to the Seattle protocol in the community is low and non-adherence is associated with decreased dysplasia detection.<sup>25</sup> The Seattle protocol is also time-intensive, labor-intensive, expensive and fraught with sampling error. Subsequently, new imaging techniques for Barrett's surveillance have been developed.

Advanced imaging modalities include narrow band imaging (NBI), chromoendoscopy with acetic acid, and confocal laser endoscopy (CLE). NBI allows for enhanced visualization of subtle mucosal and vascular changes thus allowing for targeted biopsies. Using the Barrett's international NBI group (BING) criteria, a newly validated NBI classification system, NBI can identify dysplasia in patients with Barrett's esophagus with 80% sensitivity and 88% specificity.<sup>26</sup> Chromoendoscopy

uses dye to highlight irregular areas for biopsy. CLE provides up to 1000-fold magnification of the esophageal mucosa as well as real-time histologic evaluation of esophageal mucosa.

The American Society of Gastroenterology (ASGE) created the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative to establish diagnostic and therapeutic thresholds for endoscopic technologies. The committee established that imaging technology for targeted biopsy should have a per-patient sensitivity of  $\geq 90\%$ , a negative predictive value of  $\geq 98\%$  for the detection of high-grade dysplasia and/or esophageal adenocarcinoma, and a specificity of 80% compared to the gold standard. Only NBI, acetic acid chromoendoscopy and CLE currently meet these criteria.<sup>27</sup> However, most of the studies examined in the meta-analysis were performed by experts at referral centers. Since community centers have not been adequately studied, the PIVI guidelines only recommend the use of advanced imaging techniques by endoscopists proficient in these modalities.

Wide-area transepithelial sampling (WATS) is a new brush sampling technique that can provide extensive as well as full thickness sampling results. Analysis is complemented by a computer scan that identifies potentially abnormal cells. A recent multicenter, prospective randomized trial showed that the use of WATS in addition to standard four quadrant biopsies increased the detection of high-grade dysplasia and esophageal adenocarcinoma compared to biopsy sampling alone.<sup>28</sup> However, this modality adds extra time to an already time intensive procedure. It has also not been studied with other advanced imaging techniques or in the community setting.

### Treatment

Proton pump inhibitors (PPI) remain the mainstay of medical treatment even in patients without reflux symptoms. A meta-analysis in patients with Barrett's esophagus showed a 71% decrease in the risk of progression to esophageal adenocarcinoma and/or high-grade dysplasia. This effect was seen independent of the presence of erosive esophagitis.<sup>29</sup>

Endoscopic treatment for Barrett's esophagus depends on confirmation of dysplasia on biopsy

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samples. This is in itself controversial as there is significant inter-observer variability between pathologists in the interpretation of dysplasia. Current guidelines subsequently recommend the confirmation of dysplasia by a second experienced pathologist.<sup>6</sup>

Per recent society guidelines, flat mucosal non-dysplastic Barrett's lesions should have repeat endoscopic surveillance in 3-5 years. Indefinite lesions should be optimized with PPI therapy and have repeat endoscopy in one year. Low-grade or high-grade dysplasia in both flat and nodular lesions merits endoscopic ablative therapy.<sup>6</sup> Treatment of low-grade dysplasia with ablative endoscopic therapy was once disputed. However, recent data shows that presence of low-grade dysplasia along with Barrett segment length, and nodularity were independent predictors for progression to high-grade dysplasia and adenocarcinoma.<sup>7</sup> Furthermore, other studies demonstrate that ablative therapy for low-grade dysplasia significantly reduces progression to high-grade dysplasia and adenocarcinoma.<sup>30</sup> Endoscopic treatment for low-grade dysplasia has now become commonplace.

## CONCLUSION

Barrett's esophagus is highly prevalent among the United States population. It is an established risk factor for esophageal adenocarcinoma and follows a direct sequence from metaplasia, to low-grade dysplasia, to high grade-dysplasia, and eventually adenocarcinoma. Given esophageal cancer's poor survival rate and association with Barrett's esophagus, screening and surveillance are important. This is currently an exciting field with advances in population screening and surveillance technology. However, risk of progression to adenocarcinoma will have to be balanced with cost-effectiveness and patient tolerability as we continue to explore new technology. ■

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## POSITION AVAILABLE

Johns Hopkins University School of Medicine, Division of Gastroenterology is looking for a gastroenterology hospitalist with experience in ERCP, EUS, and enteroscopy. Applicants should have at least five years of post fellowship experience in gastroenterology and have completed a two year advanced interventional endoscopy fellowship. Experience in motility and fluency in Spanish helpful.

For further information please contact:

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