ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Update on Barrett Esophagus Diagnosis and Management

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G&H What has recent research revealed about the rise in esophageal adenocarcinoma despite screening and surveillance for Barrett esophagus?

AC Esophageal adenocarcinoma (EAC) has been increasing for several decades, and no one understands exactly what changed in our environment to cause the rise. There are etiologies one can speculate on. Obesity has increased and along with it, gastroesophageal reflux disease (GERD) has increased, although neither risk factor can entirely explain the rise in incidence. Obesity and GERD are known independent risk factors for EAC, but the odds ratios would only explain a fraction of the increasing incidence. We do not know what in obesity causes Barrett esophagus or cancer. Diet and lifestyle may be part of it. *Helicobacter pylori* also protects against EAC. Eradication of *H pylori* or alterations in the human gut microbiome, where *H pylori* may just be a surrogate marker for another microbe, may be contributing to the rise in cancer. However, the environmental change that has led to this dramatic increase has not been identified.

Modeling studies suggest that something happened around the time of the World Wars that led to a change in the environment and the development of EAC. Its incidence started to rise in the 1960s. Since then, rates of EAC have continued to rise despite endoscopic screening efforts and new techniques for preventing cancer and despite all the focus on them. In addition, survival rates have not significantly improved. EAC has become more of a public health problem and like other cancers is increasingly affecting younger adults.

G&H What are the challenges of endoscopic screening of Barrett esophagus?

AC Endoscopic screening of Barrett esophagus has not had an impact on EAC prevention, and it is time for gastroenterologists to recognize that we have failed. We have tried to recommend endoscopy in patients with heartburn symptoms caused by GERD and patients with risk factors. However, endoscopy is expensive, and it only can be performed in a select group of patients. Our primary care colleagues do not necessarily send all their patients for endoscopy, especially if they can control GERD with proton pump inhibitor medications. The screening strategy recommended by the national societies was already limited to those with GERD; however, only approximately 60% of patients with EAC have a history of GERD. Because the goal has been to look at a high-risk group, most patients with GERD are not being screened, and screening is not even recommended in the 40% who do not have GERD.

G&H Do you see a potential future role for nonendoscopic methods of screening?

AC Great advances have been made in EAC prevention owing to development of methods for identifying and ablating Barrett esophagus. Patients who are diagnosed with dysplasia or early cancer can be managed with endoscopy, and they no longer require surgery. However, gastroenterologists cannot prevent cancer or impact it early unless better, more patient-friendly, and less costly methods for screening are available. Among the research efforts to try to develop nonendoscopic screening is one com-

mercial technology my colleagues and I developed that is licensed for use in this country (EsoCheck/EsoGuard, Lucid Diagnostics). In this method, the patient swallows a capsule holding a silicone balloon that when inflated collects esophageal cell samples from the lower esophagus, which are then analyzed for methylated biomarkers. The balloon is attached to a catheter that is placed at the back of the throat, which is how the balloon is inflated, deflated, and removed from the patient. The technology received a Breakthrough Device Designation from the US Food and Drug Administration, and its efficacy and safety in the diagnosis of Barrett esophagus are currently being evaluated in a few clinical trials.

Other groups have been trying to develop nonendoscopic methods for screening. Dr Rebecca Fitzgerald and colleagues in the United Kingdom championed the development of the sponge capsule (Cytosponge, Medtronic) to provide screening with immunohistochemistry marker technology to assess patient samples. Numerous studies on this technology have been published dating back to 2010. Recent data have evaluated the sponge capsule with testing for trefoil factor 3 (TFF3) in identifying Barrett esophagus. Fitzgerald and her team, through a population screening program in the United Kingdom, have shown that this technology can identify Barrett esophagus, high-grade dysplasia, and early cancer. This technology is not available in the United States.

Both the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) have updated their guidelines to include consideration of nonendoscopic cell-collection devices as an alternative option to screening for Barrett esophagus. I am hoping that nonendoscopic methods will be used to screen many people and identify Barrett esophagus.

G&H What are key new developments in the endoscopic diagnosis of Barrett esophagus?

AC Endoscopic identification with biopsy confirmation is still the gold standard for Barrett esophagus diagnosis. The new developments are in nonendoscopic screening, which then prompts an endoscopy. If someone at higher risk for Barrett esophagus is identified by nonendoscopic methods, then endoscopy can be used much more effectively. The goal is to find a group of patients in whom endoscopy will have a higher yield than the current national society screening strategy.

The ACG is considering expanding the population to be screened. According to the AGA, screening may be considered in individuals with at least 3 established risk factors, which may include people who do not have GERD but have, for example, obesity, smoking, and a family history of Barrett esophagus or EAC.

G&H What are the latest recommendations regarding endoscopic biopsies?

AC The ACG guidelines recommend obtaining at least 8 endoscopic biopsies in screening examinations. The more biopsies obtained, the more likely it is to diagnose Barrett esophagus. One of the reasons for lack of a diagnosis was found to be an insufficient number of biopsy samples. Personally, I tend to obtain 6 to 8 biopsies every 2 centimeters to ensure that the biopsy sizes are adequate and acceptable for the pathologist to look at.

G&H What progress has been made in identifying genes that may contribute to the development of Barrett esophagus?

AC I became interested in the disease primarily because we found that Barrett esophagus ran in families. The best marker for genetic risk is still simply obtaining a good family history. Family history is now one of the risk factors used to help define screening. Families with 2 or more members with Barrett esophagus or cancer should be considered for screening at about age 50 or 10 years younger than the individual with cancer.

In terms of identifying specific genes, that has been a lot more challenging. Through the combined effort of many partners, basic science collaborators, and research coordinators from several institutions, we have identified 2 genes from rare gene families that have helped us understand the pathophysiology of Barrett esophagus and what causes it. One of the genes has a role in maintaining the integrity of the normal esophagus, and a mutation in the gene makes the esophagus more susceptible to injury and to developing Barrett esophagus. The other gene is still under investigation, although we think it is involved in the ability to respond to injury from GERD and then repair the esophagus. Persons with these genes may have a genetic predisposition to developing Barrett esophagus. We may have identified a third gene that may someday become a blood test. There is currently no genetic test like there is for *BRCA1* or *BRCA2,* but we are still working on trying to identify the genetic basis. The current standard of care is to obtain a family history and be more alert about having families screened when multiple family members have Barrett esophagus or cancer.

G&H What is new in endoscopic therapy for Barrett esophagus?

AC Endoscopic therapy for patients with high-grade dysplasia has become an accepted practice. In these patients, there is no doubt that endoscopic therapy should be the standard of care. Of all endoscopic eradication therapies

for treatment of flat dysplastic Barrett esophagus and flat dysplasia, the standard therapy with the most evidence is radiofrequency ablation. However, cryotherapy, which has been around for many years, keeps improving and is starting to find a niche, certainly as an alternative when radiofrequency fails and as a primary modality in some patients. Other modalities that are not as well developed or studied yet are mucosal resection for modular Barrett esophagus or early cancers and argon plasma coagulation.

In the guidelines, the most controversial subject is how to manage low-grade dysplasia, which could be with endoscopic therapy or continued surveillance. Remember, in a substantial proportion, low-grade dysplasia can disappear without any intervention. If it could be identified which low-grade dysplasia is not going to progress, then ablation would not have to be performed. It is important to confirm with the pathologist first if the patient even has low-grade dysplasia. How endoscopic therapy should be used for management of low-grade dysplasia is not resolved. There are complications associated with endoscopic therapy for this use. Although it has been validated in some studies, there is not enough evidence to recommend it. A multicenter randomized controlled trial has started recruiting nationally to determine whether low-grade dysplasia should be ablated or surveyed. This new study will hopefully help answer that question.

G&H What are future therapeutic targets for Barrett esophagus and esophageal cancer?

AC On the other end of the spectrum from low-grade dysplasia are the more-advanced cancers or slightly more-advanced cancers. In early intramucosal cancer, endoscopic therapy is the best standard of care over surgery. Beyond that, when can we push the envelope more? Could some patients with minimally invasive cancers (T1B cancers) or cancer with risk for nodal metastases be managed with endoscopy or with endoscopy and an adjunct therapy? Researchers could look at how to make endoscopic therapy a little more effective or curative, how to reduce the stricture rate, or whether there is an adjunct therapy that can reduce recurrence and the need for repeat ablation. They could then consider how these new techniques can be applied to low-grade dysplasia. Perhaps someday there will be an easier way, whether endoscopic or not, to manage even nondysplastic Barrett esophagus. Certainly, this would be a direction to head in now that endoscopic therapy has advanced to the point where gastrointestinal endoscopists are comfortable using ablative therapy to manage high-grade dysplasia. The fact that it is being practiced to a large extent around the country has pushed us toward considering ablation of low-grade dysplasia.

G&H How might testing of esophageal samples change in the future?

AC The biomarker TFF3 in the United Kingdom and methylated vimentin and methylated cyclin A1 in the United States are being evaluated for nonendoscopic detection of Barrett esophagus. It would be ideal if nonendoscopic screening could be combined with a test that predicted high risk for progression by identifying dysplasia in the cells of nonendoscopic samples. The sampling technique of nonendoscopic devices could be improved to prevent dilution of samples or more selectively sample the lower esophagus. However, a molecular method to help prognosticate is still needed. Liquid-biopsy technology to detect cancer in blood is one potential method developed by Dr Bert Vogelstein's group at Johns Hopkins. The problem with the blood test is finding 1 abnormal cell in millions of cells. Using the liquid-biopsy method, my colleagues and I found that the technology can indeed detect cancers in high-grade dysplasia in a wide-area brush sample of Barrett esophagus. Migration of this technology to nonendoscopic devices (eg, EsoCheck, EsophaCap, or Cytosponge) has the potential to detect dysplastic cells in esophageal samples. However, this type of testing is not sensitive or specific enough yet for clinical use.

Disclosures

Dr Chak has founders shares and stock options in Lucid Diagnostics, for which he serves as a consultant, has sponsored research, and has a royalty interest in licensed patents. He also was a consultant in the past for Interpace Diagnostics, CDX, and Cernostics, and receives research support from C2 Therapeutics/Pentax Inc. He is supported by National Institutes of Health grants U54CA163060 and P50CA150964.

Suggested Reading

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