ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Esophageal Cancer Prevention

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G&H How prevalent is esophageal cancer in the United States?

KW Esophageal cancer is not a very common cancer in the United States. Overall numbers are relatively static, although adenocarcinomas are currently increasing while squamous cell cancers are decreasing. Data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, which monitors incidence and survival rates of cancer in the United States, estimate an incidence rate of approximately 13,000 to 14,000 new cases of esophageal cancer per year, or 4 per 100,000 persons. To put this number in perspective, it is approximately one-tenth the number of expected new colon cancers in a year.

G&H What are the most common risk factors for esophageal cancer?

KW The main risk factor for esophageal cancer is a history of chronic gastroesophageal reflux disease. Male sex is a common risk factor for esophageal adenocarcinoma and slightly less so for squamous cell carcinoma. Other risk factors include age greater than 50 years, white race, central obesity (as cytokines generated from the pannus produce an inflammatory state), a family history of Barrett esophagus or adenocarcinoma, and large hiatal hernias. Alcohol and tobacco use are risk factors for squamous cell carcinoma, and tobacco use plays a role in esophageal adenocarcinoma. Genomic risk factors, such as aneuploidy or genomic instability in the mucosa, also place patients at a higher risk of progression.

G&H How often do patients with Barrett esophagus progress to esophageal adenocarcinoma?

KW The progression rate to cancer has been debated in the literature; however, progression is fairly uncommon overall. A population-based study conducted by Dr Frederik Hvid-Jensen and colleagues that was published in the *New England Journal of Medicine* reported a progression rate of 1.2 per 1000 person-years, although the progression rate to various degrees of dysplasia was much higher.

G&H What procedures are available to reduce or prevent the risk of progression, and how effective are they?

KW The standard procedure is currently ablation therapy, in which the Barrett mucosa is destroyed. For high-grade dysplasia, radiofrequency ablation has an efficacy of slightly more than 80% in completely removing the mucosa and regenerating normal tissue. Its efficacy in low-grade dysplasia is approximately 90%. Cryotherapy, which freezes the tissue to destroy abnormal mucosa, has reported similar success rates of 80% to 90% for low- and high-grade dysplasia.

Esophagectomy, or the surgical treatment of Barrett esophagus in which the esophagus is removed, can

be performed minimally invasively. There are different approaches to surgically removing the esophagus; however, they all have similar complication rates and are associated with several months off of work to recover and a weight loss of at least 20 pounds, which can take a toll on patients.

G&H What role do aspirin and nonsteroidal anti-inflammatory drugs play in reducing the risk of progression to cancer?

KW There is a fair amount of evidence that suggests that aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, COX-2 inhibitors) may decrease inflammation in reflux esophagitis. Epidemiologic studies have reported a reduced risk of developing esophageal adenocarcinoma in patients on aspirin compared to those who were not. In animal models, aspirin and NSAIDs have demonstrated an effect on decreasing the development of neoplasia. However, results from a prospective, clinical trial reported no effect on regression or progression rates in patients with high-grade dysplasia.

Although plenty of epidemiologic and animal studies have been conducted, there is a lack of human correlates in terms of well-controlled, prospective studies that demonstrate a reduced risk of progression to cancer. It has been established that aspirin and NSAIDs decrease inflammation in the esophagus and secondary markers of neoplasia such as COX-2 expression; therefore, they should have an effect on cancer progression. However, there is currently no conclusive evidence to support this idea.

G&H Are proton pump inhibitors effective or recommended for reducing the risk of cancer progression?

KW There are several large epidemiologic trials that suggest that proton pump inhibitors (PPIs), which are recommended primarily for control of symptoms, have a protective effect by decreasing the incidence of cancer development. Unfortunately, similar to the role of aspirin and NSAIDs, we lack prospective trials that demonstrate that PPIs will be effective. It could be that the effect is seen only during the development of Barrett esophagus, as once it is present, PPIs do not seem to be able to cause regression.

G&H Which patients would most benefit from undergoing screening?

KW The most recent guidelines published by the American College of Gastroenterology, the American Gastroenterological Association, and the British Society of Gastroenterology advocate selective screening, which had not previously been recommended. The problem is that there are no data that suggest that selective screening actually works and has any effect on the overall incidence of esophageal cancer. However, the societies have recommended that people at higher risk (ie, obese patients, male patients >50 years, patients with symptomatic heartburn, patients with family histories) should undergo screening. The BEACON (International Barrett's and Esophageal Adenocarcinoma Consortium) has a calculator for predicting adenocarcinoma risk, and Dr Joel Rubenstein at the University of Michigan developed the M-BERET (Michigan Barrett's Esophagus Prediction Tool) score, which is a composite of endoscopic findings, symptoms, and patient demographics. Both of these calculators are used to predict cancer risk, which allows for more objective evidence of how to identify patients at risk.

G&H How often should patients undergo surveillance endoscopy with biopsies?

KW The guidelines usually recommend surveillance endoscopy every 3 to 5 years, with 3 years being the most common interval for patients with nondysplastic Barrett esophagus. Patients with low-grade dysplasia are advised to undergo surveillance every year, with some societies suggesting follow-up endoscopy after 6 months and at 1 year to ensure that a sampling error did not occur or that a more severe lesion was not missed. With high-grade dysplasia, intervention is usually recommended.

G&H How effective is treatment for early- and late-stage esophageal cancer?

KW Mucosal resection techniques, in which the tissue is cut or shaved off, are very effective for early-stage cancer (≤T1a) when performed in experienced centers. Endoscopic mucosal resection and endoscopic submucosal dissection are performed primarily for large lesions. If the cancer is confined in a mucosa, cure rates with resection are well over 90% for both esophageal adenocarcinoma and squamous cell carcinoma. Late-stage cancer is a little more difficult to treat, although there have been advances in chemotherapy. The FOLFOX (folinic acid, fluorouracil, and oxaliplatin) regimen and its FOLFIRINOX (folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin) variation have been shown to work well in columnar neoplasia in the gastrointestinal tract. Both standard and modified FOLFIRINOX based upon UGT1A1*28 genotyping are recommended. The likelihood of longer-term survival of patients with esophageal adenocarcinoma (and a mean cancer-free survival of 8 months) is up to approximately 20% with these chemotherapy regimens.

G&H How significant of a concern is recurrence of esophageal cancer?

KW Recurrence is a major concern if the cancer was deep. For superficial cancers (eg, T1a), recurrence rates are relatively low, at less than 1% to 2%. Deeper cancers have recurrence rates up to 20%, and more advanced cancers, even locally advanced cancers, have recurrence rates over 80%.

G&H What are the optimal follow-up intervals for monitoring patients with esophageal cancer?

KW Follow-up intervals are dependent upon which treatment a patient received. For definitive therapy (ie, chemotherapy and radiation followed by surgery in 1 month) with clear surgical margins, patients should typically be followed-up at 6 months. Patients with more advanced disease should be followed-up sooner. It is important to note that there is no evidence to suggest that a metastasis found earlier should be treated any differently or will respond any better.

G&H What are the priorities for research in this field?

KW There are several areas that need to be improved in order for clinicians to control esophageal cancer. One of the top priorities is to develop an effective screening program. Oftentimes, physicians do not take into account patient preferences. An example is seen with colonoscopy, which is known to be effective in reducing colon cancer risk and cancer-related mortality. Despite the knowledge that colonoscopy works, only approximately 60% of the US population participates in colon cancer screening due to its invasive nature, its use of sedation, the need to take a day off of work, and the need to have a friend or family member available to drive the patient to and from the procedure, all of which make the procedure less palatable to the at-risk population. Therefore, we need tests that are much simpler than what we currently have, that can be administered almost anywhere, and that provide real-time feedback so patients know immediately whether further evaluation is needed. There are 2 screening devices that the Mayo Clinic has been evaluating. The Cytosponge (University of Cambridge), pioneered in England by Dr Rebecca Fitzgerald, is a sponge capsule that, once swallowed, dissolves in the stomach and exposes a sponge that is drawn out through the esophagus to sample the esophageal lining. The second device is a tool that the Mayo Clinic has developed that is similar to a breathalyzer, which we are hopeful can find a signature for Barrett esophagus. We have used this tool in approximately 80 patients with an accuracy of a little less than 80%. This is a test that could be administered anywhere and provides real-time results.

We also need better research to help define the patient populations that require therapy. Randomized, controlled trials have reported that approximately one-third of patients with high-grade dysplasia progress to cancer, which means that two-thirds of patients are being treated unnecessarily. It would be beneficial to evolve therapies to precision medicine and treat only the patients who are going to progress. This would decrease costs as well as avoid discomfort or complications in patients who do not need treatment. We have effective therapies, but treating only those who are at risk of progression would help manage costs. Stratifying patients by those who require therapy will also help to determine which therapy might be the most effective. Patients who are going to develop cancer rapidly need a more aggressive therapy than ablation, such as mucosal resection.

Dr Wang has no relevant conflicts of interest to disclose.

Suggested Reading

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