ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Management of Esophageal Cancer

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

SD There are 2 types of esophageal cancer: adenocarcinoma and squamous cell carcinoma. In the United States, adenocarcinoma is the more common type, and the biggest risk factor for adenocarcinoma is gastroesophageal reflux disease (GERD). GERD is most commonly found in white men and can lead to Barrett esophagus, which is the precursor to esophageal adenocarcinoma. Therefore, in the United States, esophageal cancer is most prevalent in white men with GERD and Barrett esophagus.

An important consideration to keep in mind when managing at-risk patients is that GERD does not generally disappear on its own. In other words, lifelong therapy is required to address the typical GERD symptoms of heartburn and regurgitation. These symptoms may disappear or improve in some patients over time, but it is a mistake to think that their GERD has magically gone away. In fact, this change in symptoms may be a warning sign that something else is going on, such as the development of Barrett esophagus. Because Barrett esophagus is less sensitive to acid, symptoms of GERD may improve, but the disease might actually have taken a turn for the worse, and, unfortunately, most patients are unaware of this development.

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

SD Once a patient is confirmed to have Barrett esophagus, the risk of progression to esophageal cancer is estimated to be around 0.5% per year. Recently, 2 studies have suggested that this number may be a little lower, perhaps in the range of 0.2% per year, but there are significant fallacies with these studies, which likely underestimate the true risk of progression. In one of the studies, patients without intestinal metaplasia were included. In the United States, these patients would not be considered to have Barrett esophagus, so inclusion of patients at little to no risk of cancer dilutes the true risk of progression in that study. The second study excluded patients with adenocarcinoma of the gastroesophageal junction. Adenocarcinoma at this location typically develops from short-segment Barrett esophagus, which is the most common type of Barrett esophagus, so exclusion of these cancers likely diluted or artificially reduced the risk of progression that the authors reported.

G&H Is it possible to prevent Barrett cells from developing into cancer?

SD Complete eradication of the entire Barrett esophagus is the only definitive way to eliminate the risk of progression to cancer; however, short of esophagectomy, complete eradication is difficult to achieve during a patient's lifetime, and Barrett esophagus has been shown to recur even after an esophagectomy. Consequently, most efforts focus on reducing the risk of progression, and ablation is an option. There is a positive relationship between the extent of Barrett esophagus and the risk of cancer, but the presence of any Barrett cells can lead to cancer. Thus, for ablation to prevent cancer, every Barrett cell would need to be permanently destroyed. No study has yet shown this to be possible. Most commonly, the Barrett esophagus

is surveyed with regular endoscopy and biopsy. Factors such as the use of aspirin, nonsteroidal anti-inflammatory drugs, or statins may play a role in reducing the risk of progression, but perhaps most important is control of the inciting problem—GERD. Recent studies have suggested that effective acid suppression (ie, proton pump inhibitor therapy) may reduce the risk of progression, although other studies have failed to find a benefit. Furthermore, there is a growing body of literature suggesting that effective antireflux surgery may induce quiescence in the Barrett esophagus and reduce the risk of progression to cancer. In my opinion, the best thing that a person with Barrett esophagus can do is undergo annual surveillance endoscopy with biopsies. The current guidelines suggest that surveillance endoscopy be performed every 3 to 5 years, but this recommendation is outdated, as infrequent surveillance has been shown to be ineffective at detecting progression in time to cure patients of their disease.

G&H Should any patient groups undergo screening for esophageal cancer?

SD I think that white men with GERD should undergo screening upper endoscopy. The problem is that patients often manage their symptoms on their own or have relatively few symptoms, so they might not be captured in a screening program unless it is structured like colonoscopy, which is recommended in all people at a certain age. To make a major dent in the explosive increase in esophageal cancer, screening programs need to be developed. New options in the pipeline (such as unsedated transnasal endoscopy and the cytosponge) may offer opportunities to begin screening on a larger scale. Once Barrett esophagus is found in persons being screened, it will be important to enter these persons into an effective surveillance program, so, in a sense, screening and surveillance will have to go hand-in-hand to decrease the incidence of esophageal cancer.

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

SD This is a critical issue. When discovered early, either as high-grade dysplasia or intramucosal adenocarcinoma, this disease is curable in nearly all patients. In many centers, the most common treatment for early-stage esophageal cancer is still esophagectomy, but, increasingly, there has been a shift toward endoscopic therapies, usually consisting of a combination of endoscopic resection and ablation. These techniques allow preservation of the esophagus with curative endoscopic therapy of the mucosal disease in most patients.

More advanced disease is much more difficult and expensive to cure. Advanced stages of esophageal cancer are usually treated with a combination of chemotherapy and radiation plus surgery, and survival in these patients depends on factors such as how well the patients respond to the therapy and the amount of disease left at the time of surgery. Furthermore, the type of esophagectomy and the experience of the surgeon and the center all factor into the survival and cure rates of this disease. My advice to patients with any stage of esophageal cancer is to find a center and surgeon with extensive experience with this disease, including the treatment options. With all of the information that is currently available on the Internet, it is not difficult to find experienced surgeons and centers nowadays, but patients may have to travel. Some countries, such as Canada, even require that esophagectomy be performed in regional centers because of the evidence that outcomes improve with experienced surgeons and centers.

G&H How does a physician decide which treatment to use?

SD Not every physician is comfortable with all of the treatment options, and not every center offers all of them, so those factors certainly affect the treatment decision. The first critical step is to stage the disease. The staging should be specific to the extent of disease present on endoscopy. For example, in a patient with a 1-cm nodule on endoscopy, staging will be different than in a patient with a large circumferential mass occupying 6 cm of the lower esophagus. For small lesions, the critical staging step is an endoscopic resection to pathologically determine the depth of invasion and characteristics of the tumor. Subsequent treatment decisions all stem from the endoscopic resection findings. In patients with larger lesions, staging usually includes endoscopic ultrasound, computed tomography (CT) scans, and positron emission tomography (PET) scans. The stage of the tumor will guide subsequent strategies for therapy, which can range from purely endoscopic treatment to a combination of chemotherapy, radiation, and esophagectomy or, in the most advanced stages, perhaps only palliative therapy.

G&H Is minimally invasive esophagectomy more effective than open esophagectomy?

SD I think that minimally invasive esophagectomy, like other therapies, has a role. I do not believe that a single therapy is best for all patients, so, in my opinion, the esophagectomy should be tailored to the individual patient. There are pros and cons to all therapies, and esophagectomy is no different. A minimally invasive esophagectomy may offer some advantages, but an esophagectomy is such a significant operation that the magnitude of the benefits is not anywhere near that seen with other minimally invasive operations (eg, as in a laparoscopic cholecystectomy com-

pared with an open cholecystectomy). In my opinion, the extent of the lymph node dissection and the experience of the surgeon and the center (which can minimize complications and maximize survival) are more important than the type of approach (open vs minimally invasive or robotic).

G&H Should esophagectomy therefore be performed only in specialized centers?

SD Esophagectomy in the United States is currently being performed in almost all centers, but there is debate over whether this should continue. It is well established that this procedure is one of the most complex and physiologically demanding operations, and a number of studies have shown that experienced surgeons who perform the surgery in high-volume centers have better outcomes. As mentioned above, in some countries, an esophagectomy can be performed only in regional high-volume centers. I am not sure that the United States is ready for this step, but from the standpoint of costs and outcomes, it makes sense to direct patients to centers of excellence for this disease.

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

SD There are 2 types of recurrence. Local recurrence is when the tumor recurs locally in lymph nodes or within the esophagus, and distant recurrence is when the tumor recurs in other organs, such as the liver or lungs. Both types of recurrence can occur, and the risk of each type depends on the stage of the initial tumor and how it was treated. The biggest risk with endoscopic therapy for early-stage lesions is local recurrence in the esophagus, and both the patient and the physician have to be vigilant and aggressively eradicate any recurrent Barrett esophagus cells to prevent cancer recurrence. In patients with more advanced stages of disease, systemic recurrence is the major concern, and this is where effective chemotherapeutic agents that can eradicate micrometastatic disease are needed.

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

SD The optimal interval and type of follow-up will vary depending on the stage of the tumor. Several years ago, my colleagues and I looked at this issue in our center to characterize when most recurrences occur and the best techniques to watch for recurrence. In general, we use blood work, CT scans, and PET scans to follow patients after esophagectomy, typically every 3 months for the first several years and then at longer intervals. Patients with superficial tumors that were treated endoscopically should undergo endoscopic follow-up usually every 2 to 3 months and then once a year after 1 or 2 years.

G&H What has been the focus of recent research on esophageal cancer treatment?

SD There have been several recent studies suggesting that the outcomes associated with endoscopic therapy are similar to those of esophagectomy in patients with high-grade dysplasia or intramucosal adenocarcinoma. In patients with more advanced disease, recent studies have shown that the use of chemotherapy and radiation plus surgery is better than surgery alone. Furthermore, there is increasing evidence that survival is improved when esophagectomy removes more than just the most immediate lymph nodes around the tumor. In other words, to provide the best chance for cure, the esophagectomy should include an extensive node dissection in the areas where the cancer tends to spread.

G&H What are the next steps in research in this area?

SD There are 2 areas in which I believe we can make a push to substantially reduce mortality from esophageal adenocarcinoma. The first is in the prevention of the development of Barrett esophagus, since this condition is the major risk factor for esophageal cancer. Recent reports from the long-term ProGERD study of patients with reflux disease showed that within 5 years, nearly 10% of reflux patients developed a columnar-lined or Barrett esophagus. On multivariate analysis, one of the major risk factors for progression to Barrett esophagus was the presence of esophagitis at baseline endoscopy. I believe that if we target these patients for antireflux surgery or new antireflux options such as the esophageal sphincter device (Linx Reflux Management System, Torax Medical) and effectively control reflux disease, we will likely prevent the development of Barrett esophagus and esophageal adenocarcinoma. After all, as far as we know, if we can prevent Barrett esophagus from developing, the patient is not at risk for esophageal adenocarcinoma. Thus, the first step toward reducing this deadly disease is to identify those patients with GERD who have risk factors for progression and then to rethink how these patients should be managed.

Secondly, widespread screening for Barrett esophagus, effective surveillance in those with Barrett esophagus, and timely intervention in those who progress to dysplasia are the other key steps to halting the increase in esophageal adenocarcinoma. If we can treat esophageal cancer early, most patients can be cured and usually can keep their esophagus; however, if esophageal cancer is detected at a later stage, it is difficult to cure, and survival rates are low.

Thus, screening is a critical issue, and there are several new technologies in development to help screen patients. One such device, called the cytosponge, is a small pill with a string. After being swallowed, the pill dissolves in the stomach and forms a little brush-sponge that is pulled out by the string, bringing up scrapings of the lining of the esophagus. These scrapings can be analyzed for the presence of Barrett esophagus. Once Barrett esophagus is found, effective surveillance is needed, which probably means annual endoscopy with biopsies. Progression to dysplasia needs to be treated with endoscopic resection and/or ablation to prevent adenocarcinoma from developing.

Preventing Barrett esophagus, finding it in people who already have it, and appropriately surveying those with it such that timely interventions can be performed in those who progress will have a major impact on esophageal adenocarcinoma and save thousands of lives each year.

Dr DeMeester has no relevant conflicts of interest to disclose.

Suggested Reading

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