

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Current Surveillance and Therapeutic Options for Barrett Esophagus

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G&H Could you describe the controversy surrounding the use of screening in reflux patients to detect Barrett esophagus and enroll them in surveillance programs?

DC The first issue is one of whether screening should be undertaken at all in the larger population with gastroesophageal reflux disease (GERD). I do not currently believe that evidence exists to implement this practice. Screening programs are currently justified by the belief that the vast majority of esophageal adenocarcinoma patients have Barrett esophagus (BE) before they develop cancer. However, less than 5% of people who have esophageal adenocarcinoma are identified as having BE before the cancer develops. Therefore, everything we do in terms of surveillance and treatment is aimed at this population of less than 5% of people with the cancer. Advocates of screening argue that if we are to serve our main goal of decreasing the number of cancer deaths, the percentage of detected BE cases needs to increase and that can be done through widespread screening programs. This concept generally makes sense, but there is currently no direct evidence to support it. Screening a large population, such as that of patients affected by GERD, increases the risk and inconvenience to an enormous number of people who will never develop BE or cancer. Thus we run the risk of doing, on average, more harm than good.

Further, medical interventions can have surprising effects. For example, study has shown that negative screening results can adversely impact patient behavior. A recent colon cancer screening trial in Scandinavia randomized patients to sigmoidoscopy or no screen-

ing and recorded a number of other risk factors (body mass index, smoking habits, dietary habits). Afterward, patients were followed for a number of years to determine the effects of screening. The researchers found that patients who were screened, but did not have any polyp or cancer identified, deteriorated in terms of high-risk behavior. After the screening, they were more likely to gain weight, more likely to smoke, and more likely to have poor diets than persons who were not screened at all. Essentially, it appeared they may have engaged in unhealthy behaviors because they believed, either consciously or subconsciously, that they were at lower risk. Thus, if screening is undertaken in a very large cohort of people who are at very low risk of dying from cancer, the psychological predisposition that encourages other unhealthy behaviors may have unanticipated adverse events that outweigh any benefit seen from screening.

The only way to evaluate whether screening would have more benefit than harm is to find more definitive evidence of overall benefit from screening protocols. As of yet, no randomized trials, cohort studies, or case-control studies have looked at whether screening a large group of GERD patients, who are very unlikely to develop cancer on average, would be of benefit.

G&H What is the current argument supporting the use of surveillance for dysplasia in patients with known BE?

DC Again, no trials have shown definitively that BE patients undergoing surveillance fair better on average than those who do not. However, a fair amount of evidence does support its use.

For either screening or surveillance to work in any cancer, several factors need to be in place. It must be possible to detect disease at a stage earlier than when it would present clinically. Treatment of that earlier disease must have better outcomes than later treatment. The surveillance needs to show an overall benefit in the population

when weighed against the complications, side effects, and other patient-related problems incurred among patients receiving surveillance who do not ever develop cancer. Finally, surveillance needs to be feasible, given the available resources that could potentially be devoted to it. All of these factors are, arguably, favorable in the case of surveillance of patients with known BE for esophageal adenocarcinoma as opposed to diseases such as lung cancer, where radiology can detect very early tumors but there is no benefit to surveillance because the disease metastasizes so quickly that early treatment from early detection has not yet been convincingly equated with better outcomes.

G&H What is the current protocol for BE surveillance?

DC There are currently two, very similar, protocols for BE surveillance, one issued by the American College of Gastroenterology (ACG) and the other by the American Gastroenterological Association (AGA). Both protocols emphasize that successful surveillance requires several different procedures. Both suggest that before patients are put into a long-term surveillance program with intermittent intervals of endoscopy, they undergo two initial endoscopies to definitively detect any extant cancer or dysplasia. The concern is that surveillance biopsies are not a perfect method of detection and, perhaps particularly in patients with a long BE segment, a single endoscopy may miss many dysplastic lesions. Therefore, two endoscopies are recommended in these guidelines to better establish a lack of dysplasia before long-interval surveillance is implemented.

After concurring on this initial recommendation, the protocols diverge somewhat. The ACG guidelines suggest endoscopy every 3 years whereas the AGA guidelines suggest every 5 years, in patients with no detected dysplasia. There is no hard evidence supporting the effectiveness of either method. It has been suggested that most of the benefit that patients get from these exams is similar to that from colonoscopy screening, where the initial examination provides the bulk of benefit in terms of detecting early cancer. Later examinations may be of much lower overall benefit.

G&H Are there ways to stratify GERD patients so that screening programs are more effective?

DC The patients most likely to benefit, if screening is shown to be helpful, are those who are at the highest risk of developing and dying from esophageal adenocarcinoma. Men are more likely to develop this cancer than women, as are Whites and, to some extent, Hispanics versus Asians and African-Americans. These ethnic differences may

change as the prevalence of GERD changes. Older GERD patients (>50 years), encompass a cohort in whom likelihood of developing esophageal adenocarcinoma begins to increase, as do patients with longstanding GERD symptoms. That said, there are controversies in attempting to target certain populations based on demographics, particularly race and gender. In addition, approximately half the people with cancer do not have GERD symptoms that would target them for stratification, again raising the question of how many cancers would be prevented by this strategy.

G&H How effective are current surveillance protocols in detecting treatable lesions?

DC Although current evidence is very indirect, it suggests that surveillance protocols are quite likely to detect a large proportion if not the majority of treatable lesions in BE. A study at our institution in a community-based cohort looked at every patient with BE who subsequently developed cancer. Among those with confirmed BE, who were in surveillance, none of the patients died from metastatic cancer. Some died from the surgery to treat a cancer but none from the cancer itself; in contrast, all of the patients who developed esophageal adenocarcinoma who were not in surveillance died from the cancer or its complications. Doubtless, there will be cases in which patients have lesions that are missed, but studies suggest that a large proportion, if not the majority, are fairly likely to be detected in a surveillance protocol.

G&H What new technologies are available to potentially improve the sensitivity of surveillance protocols?

DC There are several novel technologies with potential to both detect dysplasia and the extent of BE itself, including chromoendoscopy, confocal microscopy, and narrow-band imaging (NBI). Each of these methods, in studies, has shown an ability to increase the visibility of dysplastic or abnormal areas. The remaining question is one of whether they increase visibility sufficiently above what is detectable with white-light imaging in order to better reach our treatment goals. Whether the increased visibility will decrease the number of biopsies needed to detect cancer or allow us to detect abnormalities that are not at all visible with normal endoscopy will determine if they will ultimately affect the overall rate of cancer deaths or morbidity in the surveillance population.

Of these methods, chromoendoscopy has been studied the most thoroughly. Although unblinded studies suggest an increased ability to detect lesions; randomized, crossover studies have not supported the same conclu-

sions. These same rigorous standards need to be applied to studies of confocal microscopy and NBI. Unfortunately, preliminary results from other studies suggest that when considered in terms of actual effects on outcomes, these technologies do not significantly improve on what can be achieved with white-light imaging. It remains to be seen whether they can allow us to target and thus decrease the number of biopsies taken at each surveillance. Further, when considering that the vast majority of patients are screened and surveyed in community endoscopy settings, switching to these new technologies would require a substantial investment in new equipment, which would be difficult to adopt in a large number of centers.

G&H What surveillance findings are indicative of a need for treatment to avoid cancer?

DC Currently, there is insufficient agreement regarding the natural course of low-grade dysplasia findings and whether or not these patients require treatment. The same can be said for BE patients with findings of no dysplasia. Thus, there is no indication for treating or ablating BE patients who have low-grade dysplasia or no dysplasia.

Patients who have cancer are obviously at high risk and should be treated in some manner. The protocol for those with high-grade dysplasia is less clear. The natural history of high-grade dysplasia requires more intensive surveillance to ensure the detection of other malignant lesions but it appears many and perhaps a large majority of these patients will not go on to develop cancer. Thus, the question remains as to whether all should undergo a highly aggressive, possibly morbid treatment to prevent a moderate percentage of them from progressing to cancer.

G&H Is there a role for medical therapies in preventing or treating esophageal dysplasia?

DC There is currently no consistent evidence that proton-pump inhibitors (PPIs) or other acid-reducing therapies decrease the risk of cancer and neither medications nor surgery to reduce esophageal acid should be indicated as anticancer treatments. They should be advertised as antireflux or anti-esophagitis treatments only.

The most comprehensive study to date on medical treatment for GERD comes from a randomized trial by Dr. Stuart Spechler and colleagues, looking at patients undergoing fundoplication, the most potent anti-acid treatment available. In several hundred patients who received medical treatment versus fundoplication, there was no clear difference in terms of progression to cancer or dysplasia. Further, other studies in animal models of BE have suggested that the effects of acid inhibition are unpredictable; lower acid levels may actually increase the

proliferation and multiplication of precancerous changes. Currently, definitive data are not available to predict what happens when acid is suppressed and whether it will increase, decrease, or make no difference in the likelihood of a patient with BE going on to develop cancer.

G&H Can you describe the surgical options for treating dysplasia and cancer?

DC Surgical methods depend on the severity of the lesion. Patients with a substantial cancer require esophageal resection. This procedure provides a definitive resection for patients with moderate-to-large tumors and allows for sampling and examination of surrounding lymph nodes to determine the need for additional therapy. The disadvantage of esophageal resection is that it is fairly morbid. Patients can develop life-long problems with reflux, swallowing disorders, and other conditions that affect quality of life. There is also a risk of death from the surgery. In high-volume centers, that risk is less than 5% but a fair number of esophagectomies are not done in high-volume centers and are associated with a moderate risk of death. In addition, many cancer patients are older and have more difficulty undergoing morbid procedures due to other complicating health problems. In order to avoid these comorbidities, patients with high-grade dysplasia or smaller cancers may benefit from mucosal resection or ablation therapy.

G&H Can you describe the indications for the mucosal resection procedure?

DC Mucosal resection is a procedure in which sections of the mucosal lining are removed in patients with either high-grade dysplasia or very small, noninvasive cancers. Early studies suggest that it is effective in removing neoplastic areas with a low incidence of recurrence. When performed by experienced endoscopists, rates of morbidity are also very low. The risk associated with mucosal resection comes from the small number of patients who have undetected advanced cancer that has spread to lymph nodes, a condition which cannot be determined from this procedure and, as a result, may be allowed to progress unchecked.

G&H How does current research define the role of ablation therapies in preventing esophageal cancer?

DC There are two main ablation therapies for high-grade dysplasia that have undergone randomized studies: photodynamic therapy and radiofrequency ablation. An unblinded study suggested that photodynamic therapy

was very effective in decreasing cancer risk when administered to patients with BE and dysplasia. A subsequent randomized study showed that it was better than observation/surveillance alone though the difference was smaller and a moderate number of treated patients still developed cancers in follow-up. However, photodynamic therapy has significant side effects. Patients are required to take a photosensitizing agent that makes them very sensitive to light. Photofrin, the most widely used of these agents, has been associated with erythema, swelling, itching, burning sensations, blisters, and strictures, and patients must still continue to undergo endoscopic surveillance.

Radiofrequency ablation, under the proprietary trade name BarrX, is currently in clinical trials for dysplasia. Preliminary results suggest that it may be fairly effective in eliminating high-grade dysplasia without the side effects associated with photodynamic therapy. However, it should be noted that preliminary trials for almost every technique suggest positive efficacy and randomized trial results are necessary in order to recommend use in the clinical setting.

The main consideration in use of any of these therapies is whether they decrease the number of surgeries and the number of deaths from esophageal adenocarcinoma. In order to determine their true usefulness, we need to address questions of both efficacy in clinical trials and effectiveness in clinical practice. More time and study will be needed to determine the real impact of radiofrequency ablation and other therapeutic methods in the clinical setting.

G&H Do you foresee scenarios for the possible use of ablation and mucosal resection techniques in combination?

DC Some patients present on endoscopy with dysplastic nodules throughout their Barrett segment, which may harbor small cancers that are not detected on biopsy. These patients may be best treated with combination therapy consisting of mucosal resection of the highest-risk areas and some type of ablation therapy of the remainder of the dysplastic BE.

G&H What are the goals of future research in BE and the prevention and treatment of esophageal adenocarcinoma?

DC The primary goal is to decrease cancer morbidity and cancer death. Right now, our efforts are mainly focused on helping prevent the 5% of cancer deaths that occur in patients who have a pre-existing BE diagnosis. We need to show that the surveillance and treatments we are doing for these patients work, while enhancing our ability to target BE patients who need intensive surveillance or treatment and minimize interventions on those who are unlikely to benefit.

However, the most effective way to decrease cancer deaths will be to find proven ways to get to the other 95% before they develop cancer. The clinical behavior of that 95% might be different and some of those patients may not have BE at all. We must keep an open mind in terms of how these patients present and ways to change their risk, because they may be very different from the high-risk cohort that we are currently surveilling and treating.

Suggested Reading

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