Dysphagia drives doctors to diagnose a disease: pitfalls in interpreting observational studies

Dysphagia is a common presenting GI complaint, prevalent among 6% to 7% of the adult population.1 Causes of dysphagia are diverse and range from functional disease to lethal cancers. Traditionally, a barium esophagram has been the recommended initial diagnostic test for dysphagia, because it can assess subtle structural abnormalities, as well as motility.2 However, endoscopy provides the additional capability of sampling mucosa for histologic diagnosis and simultaneous therapeutic intervention for mechanical obstruction. Therefore, some gastroenterologists have come to recommend endoscopy as the initial diagnostic test for dysphagia; in fact, the Yamada Textbook of Gastroenterology2,3 changed its recommendations from barium esophagram to endoscopy between the 3rd and 4th editions.

In this issue of Gastrointestinal Endoscopy, Varadarajulu et al.4 have performed a retrospective analysis of patients with dysphagia to determine the yield of endoscopy that is performed as the initial diagnostic test. The investigators searched the databases of 6 endoscopy units over a 5-year time span and identified over 1500 patients who met the inclusion criteria. Of these patients, 54% had “major pathology” diagnosed by endoscopy, and cancer was suspected by endoscopic appearance in 4%. The investigators found that male gender, age greater than 40 years, and weight loss independently predicted the presence of cancer on endoscopy, whereas female gender and no concomitant heartburn were independent predictors of a normal endoscopy.

Do these results support the use of endoscopy as the initial diagnostic test for dysphagia? The fact that endoscopy identified major pathology in a majority of these patients might support that contention. But, as the investigators admit, no criterion standard or comparative strategy was provided, so the test characteristics (sensitivity, specificity, and positive and negative predictive value) of endoscopy cannot be determined. A prospective trial that compares barium swallow with endoscopy as the initial test in an unselected group of patients with dysphagia is still required to determine which strategy is optimal given particular patient characteristics. A prospective study comparing barium swallow to endoscopy as the initial test in unselected patients with dysphagia is still required to determine which strategy is optimal given particular patient characteristics.

The study by Varadarajulu et al.4 does not analyze the proportion of patients in whom medical management was altered by the results of the endoscopy. For instance, patients with untreated mild esophagitis would be likely to receive initial therapy with proton pump inhibitors regardless of the findings on endoscopy. The database likely precluded the investigators from reporting what prior

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management had been used. Young women with heartburn and dysphagia but with no other alarm symptoms might be best managed initially with empiric treatment, reserving diagnostic testing for those who fail the initial therapy. A prospective study of such a strategy would be warranted.

One of the most interesting findings in this study was the relatively high prevalence of suspected Barrett’s esophagus in this population. Previous studies have found that approximately 10% of patients with symptoms of GERD have Barrett’s esophagus. In this study, 18% of patients were listed as having heartburn as an indication for their procedure, but 5% were suspected to have Barrett’s esophagus based on endoscopic appearance. Based on the prevalence in other studies, we might expect only 1.8% of patients to have Barrett’s esophagus. What could be the reason for this discrepancy? One potential reason could be misclassification of GERD; more patients may have had GERD, but they had other symptoms that were listed as the indication for the procedure instead of heartburn. There also could have been a misclassification of Barrett’s esophagus. Because there was no histopathologic confirmation in this study, many of those patients categorized as having Barrett’s esophagus based on endoscopic appearance may not have truly harbored Barrett’s esophagus. A more intriguing possibility is selection bias; there may be some characteristic of these patients who presented for endoscopy that put them at higher risk for Barrett’s esophagus than would be expected based on heartburn alone. Barrett’s esophagus is not known to be a cause of dysphagia, but there may be common factors that predispose to development of both Barrett’s esophagus and dysphagia. Patients with Barrett’s esophagus can have decreased amplitudes of the esophageal body contractions and frequent nonperistaltic contractions. This may be either a cause or an effect of the poor clearance of refluxate, whose presence likely induces Barrett’s metaplasia. The dysmotility also could lead to the presenting symptom of dysphagia that defined this study population and, therefore, enrich the population with a higher proportion of patients with Barrett’s esophagus than would be expected for patients with heartburn alone. Therefore, it would be inappropriate to generalize the results from this study of a population of patients with dysphagia and heartburn to a population of patients with heartburn alone.

An additional caveat that may be gleaned from this study provides insight to understanding the natural history of Barrett’s esophagus. Most studies of “screening” for Barrett’s esophagus are not true population-based screening studies; instead, physicians referred those patients to endoscopists for what was probably a variety of reasons. Those physicians likely used some clinical judgment, either explicitly or subconsciously, to select which patients to refer for endoscopy. Some patients may have only had heartburn, but many likely had dysphagia, weight loss, or some other undefined factor that the physicians identified as indicating an increased risk for serious pathology. Such selection bias could explain the curious finding that the prevalence of esophageal adenocarcinoma at the initial “screening” endoscopy is relatively higher than the subsequent cumulative annual incidence of esophageal adenocarcinoma found on surveillance endoscopy. The prevalence of esophageal adenocarcinoma among patients at their initial diagnosis of Barrett’s esophagus has been reported to range between 4% and 27%. The best estimate for the annual incidence of esophageal adenocarcinoma among patients with Barrett’s esophagus is 0.5%, meaning it would require 8 to 54 years to accrue the same number of cancers after the initial diagnosis of Barrett’s esophagus as the number found at the initial “screening” endoscopy. In contrast, two prospective studies of the prevalence of Barrett’s esophagus among unselected populations (patients presenting for colon cancer screening who also agreed to undergo upper endoscopy) found zero prevalent cancers and zero prevalent cases of high-grade dysplasia among 92 patients diagnosed with Barrett’s esophagus. The discrepancy likely relates to differences in study populations among the various studies, based on inclusion criteria and whether patients underwent endoscopy to evaluate symptoms or for purely screening purposes.

The study by Varadarajulu et al. highlights the limitations of studies aimed at determining the epidemiology of conditions without attentively defining the study population in a generalizable manner. Most of the literature describing the natural history of Barrett’s esophagus, as well as the effect of surveillance endoscopy for Barrett’s esophagus, is hampered by the same limitation, and so our ability to make rational management decisions is likewise impaired. The most cost-effective surveillance interval depends on the relative prevalence and incidence of cancer in patients with Barrett’s esophagus. Additional large studies of the natural history of Barrett’s esophagus among truly unselected populations are sorely needed to help guide the prevention of mortality from esophageal adenocarcinoma.

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