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New Technologies for Examination of the Esophagus: Are They Really Better Than White-Light Endoscopy?

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G&H What are the most common indications for using white-light endoscopy to examine the esophagus?

MBW White-light endoscopy, whose name refers to the use of all colors of the visible spectrum, is the standard method for all indications of upper endoscopy. The most common indications for upper endoscopy include assessment of gastroesophageal reflux disease (GERD), complications of GERD such as Barrett esophagus, early esophageal cancer (involving either Barrett esophagus or early squamous-cell cancer of the esophagus), and early gastric cancer (which is a major problem in Eastern countries, particularly Japan and China, but is rare in Western countries).

G&H Given the widespread use of white-light endoscopy, why is there a need to develop other technologies for examination of the esophagus?

MBW Standard endoscopy is limited by the endoscope's resolution as well as its weak ability to produce contrast between normal and abnormal tissues. The resolution of a white-light endoscope depends on the model being used. As a general rule, most of the recent endoscope models have high resolutions, as there has been a trend over the history of endoscopy from low-resolution endoscopes to high-resolution endoscopes. This progression has allowed endoscopists to see abnormalities, boundaries, and small lesions more accurately.

Contrast refers to the difference between normal and abnormal tissues and is important for lesion detection. Contrast can come in various forms—for example, different colors. White-light endoscopes are typically capable of distinguishing only fairly crude contrast, such as a red lesion from a pale lesion. Newer endoscopes use various filtering methods or supplemental dyes, such as indigo carmine, to produce greater contrast between normal and abnormal tissues, ensuring that abnormalities stand out more significantly against a normal background.

Therefore, standard endoscopy limits the endoscopist's ability to make precise diagnoses in abnormal conditions (ie, inflammation, neoplasia, or atrophic conditions) and is generally used mainly for biopsy guidance. In most cases, white-light endoscopy cannot be used instead of a biopsy; endoscopists still have to rely almost completely on biopsy and microscopy to establish a specific diagnosis.

G&H What types of technologies have recently been developed for examining the esophagus?

MBW The new technologies can be divided into several different groups. One group consists of broad-field technologies, which are capable of imaging large surface areas and obtaining a more global view of the esophagus or upper gastrointestinal tract. At the other extreme are small-field technologies, which allow very precise imaging of very small areas. As a general rule, broad-field technologies have higher sensitivity rates, whereas small-field technologies have higher specificity rates for abnormal lesions. A few technologies can provide both broad-field and small-field imaging.

The other division separates image-based technologies (such as narrow-band imaging [Olympus], chromoendoscopy, and endomicroscopy) from spectroscopic technolo-

gies (such as light-scattering or fluorescent spectroscopy), which provide quantitative data regarding tissue obtained through the endoscope. A typical analogy of these 2 groups is the difference between visual flight navigation and instrument navigation: An image-based technology provides visualization of the esophagus, whereas spectroscopy provides instrument data to identify and diagnose abnormalities.

G&H How do these new technologies work, and how effective are they for examining the esophagus?

MBW Among the broad-field technologies that have been shown to be effective over the past 5 years, the most common is narrow-band imaging. Similar technologies available from other major endoscope manufacturers include Fujinon intelligent chromoendoscopy (Fujinon) and iScan (Pentax). These technologies optically filter the light used to illuminate the tissue or enhance the intensity of various wavelengths of light emitted or reflected off of tissue. These technologies tend to emphasize blue-light illumination or reflectance because blue light is heavily absorbed by blood cells, particularly hemoglobin. This absorption increases the contrast between normal and abnormal tissues, the ability to see individual small blood vessels and capillaries, and the ability to assess whether those blood vessels are abnormal (such as in early neoplasia or cancer). On the other hand, neoplastic or inflamed tissue typically appears reddish with white-light endoscopes and its contrast with normal tissue is not as significant.

Narrow-band imaging has undergone the most study in the detection of early neoplasia in Barrett esophagus and early squamous-cell neoplasia. Several trials, including one led by my colleague Herbert Wolfsen, have shown that, compared to standard white-light imaging, use of narrow-band imaging increases the detection rate of dysplasia in Barrett esophagus and allows the targeting of biopsies, which reduces the overall number of biopsies needed to detect dysplasia. Compared to white-light endoscopy, narrow-band imaging also enables detection of higher grades of dysplasia within a patient.

Also promising are spectroscopic technologies, which can assess the degree of nuclear enlargement and density, other tissue characteristics such as the organization of cells, and the extent of early increases in blood supply and vascularization that occur around neoplasms of the esophagus. There are several types of spectroscopy. Light-scattering spectroscopy measures nuclear size and diameter, while reflectance spectroscopy measures the light reflected off of tissue, particularly the amount of light absorbed by hemoglobin, which determines vasculature changes. Endomicroscopy is an emerging technology that is essentially a confocal endomicroscope that allows extremely high magnification and resolution imaging of tissue in a very small field of view; this technique has been shown to be very accurate for assessing tissue in this area. Lastly, optical coherence tomography and optical frequency domain imaging both produce very high-resolution and high-magnification views of esophageal tissue; in addition, they can assess broad fields of tissue (ie, they combine both broad-field and small-field imaging technologies). They can assess virtually the entire length of the esophagus within 5–10 minutes, which is the same amount of time needed for an upper endoscopy.

Confocal endomicroscopy, which has been quite extensively evaluated, is available in 2 forms: a confocal microscope integrated into a standard endoscope (Pentax) and a probe-based technology consisting of a catheter probe that can be placed through the working channel of any endoscope (Mauna Kea). Each system has pros and cons: The integrated system provides slightly higher lateral resolution and allows imaging to varying depths within the tissue, whereas the probe-based system is much more versatile because it can be used with any endoscope. The probe-based system also allows video-based imaging to monitor activity and motion (eg, blood cells flowing through small capillaries).

Both of these systems have been studied quite extensively in Barrett esophagus and, to a lesser extent, squamous-cell carcinoma. A large multicenter trial led by Prateek Sharma showed that the addition of confocal endomicroscopy to both white-light endoscopy and narrow-band imaging enabled increased detection of dysplasia in Barrett esophagus; the addition of confocal endomicroscopy enabled complete replacement of random biopsies, such that patients could be examined with white-light, narrow-band, and confocal views. Biopsies were only necessary in individuals in whom abnormalities were detected. Confocal endomicroscopy has the potential to significantly reduce the need for obtaining random biopsies in Barrett esophagus.

G&H Have any of these technologies been shown not to be effective for examining the esophagus?

MBW New technologies that have been used but appear to be less effective include chromoendoscopy and autofluorescence imaging. Chromoendoscopy has not been consistently effective in conditions such as GERD or Barrett esophagus, although this technology has been very useful in squamous-cell carcinoma of the esophagus. In particular, the use of Lugol's iodine with chromoendoscopy has been very effective at early detection and localization of early squamous-cell cancer. Autofluorescence imaging relies on the fact that the tissue emits a characteristic fluorescent light when illuminated with blue light from a narrow band or a

laser. Although this technique has been extensively evaluated, it has not been particularly effective for assessment of GERD, Barrett esophagus, or squamous-cell cancer.

G&H Is use of these new esophageal imaging technologies becoming mainstream, or do most physicians continue to use only white-light endoscopy?

MBW All physicians continue to use standard endoscopy, as it is our baseline examination. Technologies such as narrow-band imaging are certainly being used more frequently than 5 years ago, when they were largely being used only in academic referral centers. With the current generation of upper endoscopes, narrow-band imaging is becoming more accessible because 3 manufacturers now offer their own systems. Narrow-band imaging is routinely available to virtually any endoscopist who has modern equipment. The rate at which this technology is actually being used varies according to the level of the endoscopist's expertise. Narrow-band imaging has been studied in both academic centers and private practices, and good-quality studies have shown that it can be utilized in either setting.

G&H Is a significant learning curve associated with any of these technologies?

MBW As with all technologies, there is a learning curve, but it is relatively short. For example, my colleagues and I conducted a clinical trial to assess the learning curve for confocal endomicroscopy. After viewing 60–70 cases, which took approximately 2 hours of training, endoscopists were able to achieve accuracy levels similar to those of experts.

Nevertheless, there is a difference between learning the interpretation of an image and performing the procedure, particularly with confocal endomicroscopy. The acquisition of a stable image requires practice and training as well as the ability to hold the probe steady on the tissue. This is true for all endoscopic methods; the ability to perform a careful inspection, obtain good-quality still images, and interpret those images accurately all require learning. All of the technologies discussed above can be learned relatively quickly by dedicated endoscopists.

One of the important aspects of all these technologies, relative to learning, is the increasing availability of computer-aided diagnostic systems. Just like radiologists use quantitative information around an image (eg, the density on a computed tomography scan), endoscopists increasingly have tools that allow measurement and computer-aided diagnostics of endoscopic images. I predict that these aids will become more prevalent in the next 5–10 years, with technologies to detect lesions and quantitative measures to characterize and assist the endoscopist. For example, a computer-aided diagnostic algorithm was developed to analyze confocal images. This automated algorithm can distinguish a neoplastic site from a non-neoplastic site with the same level of accuracy as an expert in confocal imaging. The addition of such an algorithm can eliminate much of the learning curve, at least for the interpretational component of the esophageal examination.

G&H How safe are these new esophageal imaging technologies, compared to standard endoscopy?

MBW With the exception of confocal endomicroscopy, the technologies are not associated with any significant risk. For example, narrow-band imaging merely consists of the placement of a simple filter in front of the endoscope; because tissue is not altered in any way, there is no risk associated with the procedure. The same is true for the other 2 narrow-band imaging systems and for autofluorescence imaging.

Confocal endomicroscopy typically requires a contrast agent, the most common of which is an injectable agent called fluorescein. In collaboration with other centers worldwide, my colleagues and I published safety data from more than 2,000 cases and found no serious adverse events. The risk of minor adverse events such as nausea was approximately 1.4%. Overall, confocal endomicroscopy has been shown to be extremely safe.

G&H Has there been any cost-effectiveness analysis of these new technologies?

MBW There has been cost-effectiveness analysis specific to each field. For example, a recent trial led by Prateek Sharma showed that using all of the advanced imaging technologies, including narrow-band imaging and confocal microscopy, resulted in a reduction of approximately 39% in the number of patients who needed biopsy. Eliminating the need for biopsy reduces costs—both the cost of the procedure itself (because upper endoscopy is less expensive without a biopsy) and the cost of the pathology. (An exception to this conclusion is confocal imaging, which is relatively expensive.) Although the cost savings of avoiding biopsy may be offset by the cost of the technology, the procedure can be cost-effective if it reduces the number of biopsy samples required by at least 2 or 3; the cost of pathologic analysis of this number of samples is similar to that of the technology. In settings such as Barrett esophagus, particularly long-segment Barrett esophagus, which usually requires multiple jars of pathology, these imaging technologies are often cost-effective.

One advantage of narrow-band imaging is that the technology essentially has no added cost, as it is already built into the endoscope; thus, any reduction in the number of biopsy samples is a cost savings.

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

MBW Some of the key questions currently being faced in Barrett esophagus involve risk stratification. Since the vast majority of patients with Barrett esophagus do not develop dysplasia, technologies are needed that can assess which patients are at higher risk for this development so they can be identified for surveillance; simultaneously, the potentially large cohort of Barrett esophagus patients who do not need surveillance endoscopy could also be identified. This would require precise localization of early dysplasia. Spectroscopic technologies may be able to assess very early neoplastic changes that are not even visible.

Another key area for these technologies involves the guidance of endoscopic resection and ablation, particularly in patients with dysplastic lesions that have already been identified. These patients currently undergo endoscopic mucosal resection and ablation, with the endpoint of eradicating all of the patient's Barrett esophagus. However, there is no technology currently available that can accurately determine whether all of the Barrett esophagus has been eliminated; for confirmation, the patient has to be biopsied. Several of the new technologies discussed above are currently being studied to assess completeness of ablation. A recent trial that my colleagues and I conducted was presented in preliminary form at last year's Digestive Disease Week meeting. This study assessed the ability of confocal endomicroscopy and white-light endoscopy to assess complete response. The study showed that confocal endomicroscopy was no better than white-light imaging; the addition of confocal endomicroscopy did not increase the ability to detect residual Barrett esophagus after ablation, compared to white-light endoscopy alone. I think the more promising technology in this area is optical frequency domain imaging or optical coherence tomography. A study examining this hypothesis will soon be underway.

Suggested Reading

Sharma P, Meining AR, Coron E, et al. Real-time increased detection of neoplastic tissue in Barrett esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc.* 2011;74:465-472.

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