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Chromoendoscopy and magnification endoscopy for diagnosing esophageal cancer and dysplasia

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Early detection and classification of esophageal cancer is an important task for the gastrointestinal endoscopist. Two primary subtypes of esophageal carcinoma are commonly seen in the esophagus: squamous cell carcinoma and adenocarcinoma. The majority of esophageal malignancies are detected by endoscopy at a late stage and are therefore cannot be resected for cure. No obvious, endoscopically visible premalignant stage exists for squamous cell carcinoma of the esophagus; however, Barrett's esophagus is now recognized as an important risk factor for the development of esophageal and esophagogastric junction adenocarcinoma.

Squamous cell carcinoma is the most common esophageal malignancy in the world. Multiple environmental and other factors have been shown to be important in the pathogenesis of this carcinoma. In industrialized countries, smoking, heavy alcohol ingestion, and achalasia are established risk factors. Esophageal squamous cell carcinoma has also been associated with head and neck cancer. Synchronous or metachronous esophageal squamous cell carcinoma has been reported in up to 15% of patients who have head and neck carcinoma [1]. Widespread screening for squamous cell carcinoma has been attempted in Far Eastern and South American countries, primarily using exfoliative cytology methods, although the sensitivity and specificity of these techniques are questionable. Identification of a target population that would benefit from screening in the United States is an important step in reducing morbidity and mortality caused by this malignancy.

Barrett's esophagus is defined as columnar-appearing mucosa of any length within the tubular esophagus, with the histologic finding of intestinal metaplasia [2]. The columnar-lined distal esophageal mucosa can potentially contain three subtypes of epithelium, including intestinal metaplasia, fundic, and junctional. It has become clear that intestinal metaplasia, with the presence of goblet cells by histology, is the predominant premalignant epithelium associated with dysplasia and adenocarcinoma. Currently, endoscopy with biopsy remains the gold standard for diagnosing Barrett's esophagus. Standard endoscopic techniques have been shown to be inaccurate, with biopsies from short segments of columnar-appearing mucosa generally revealing intestinal metaplasia in only 40% to 60% of patients [3]. When Barrett's esophagus has been diagnosed, patients are advised to enroll in a surveillance program. Current guidelines suggest obtaining systematic four-quadrant biopsies at 2 cm intervals from columnar-appearing mucosa in the distal esophagus for the detection of dysplasia or cancer [4]. Similar to the distribution of metaplastic tissue, the presence of dysplasia or early adenocarcinoma within a segment of Barrett's esophagus is patchy and focal. Standard endoscopy and random biopsies might fail to detect these lesions [5]. Foci of unsuspected carcinoma have been found in up to 73% of resected specimens when esophagectomy is performed for high-grade dysplasia [6].

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In squamous cell dysplasia, no visible endoscopic lesions such as plaques, nodules, or ulcers are seen regularly. Because of the patchy occurrence of dysplastic and cancerous lesions within the esophagus, the sensitivity of standard biopsy techniques is low. Because of these limitations, new techniques have been used in an attempt to maximize the sensitivity and overall accuracy of endoscopy and biopsy for the diagnosis of squamous dysplasia, squamous cell carcinoma, Barrett's esophagus, and associated dysplasia/early cancer. Chromoendoscopy and magnification endoscopy stand at the forefront of these modalities because of their availability, ease of use, and low cost. This article summarizes the basic chromoendoscopic and magnification techniques used for the detection of metaplastic, dysplastic, and malignant tissue in the esophagus and examines the current literature regarding this subject.

Chromoendoscopy

Chromoendoscopy employs chemical staining agents applied to the gastrointestinal mucosa to identify specific subtypes of epithelia or to highlight surface characteristics of the epithelium. Chromoendoscopy has been used in several regions of the gastrointestinal tract including the esophagus, stomach, duodenum, and colon to aid the characterization of multiple disease states. Recently, the use of methylene blue-assisted chromoendoscopy was shown to increase the yield of detecting dysplasia and cancer in patients undergoing surveillance colonoscopy for inflammatory bowel disease [7].

For squamous cell carcinoma, chromoendoscopy is used to detect metachronous or synchronous lesions and to define the extent of dysplasia or cancer. In the setting of Barrett's esophagus, chromoendoscopy is performed to allow targeting of biopsies to increase the accuracy of detecting intestinal metaplasia and dysplasia. Two types of tissue staining are used in the esophagus. Vital (absorptive) stains such as Lugol's solution and methylene blue are taken up by esophageal mucosa actively. Contrast stains are not absorbed, but they highlight the surface of the mucosa, allowing for the identification of minute lesions and subtle patterns. Contrast stains currently used in the esophagus include indigo carmine, toluidine blue, and dilute acetic acid solution.

Tissue staining is performed using multiple steps with the goal of removing surface mucous and other material before staining, which allows for maximal contact of the agent with the epithelium. Tissue stains are typically applied directly onto the mucosal surface during endoscopy using a spray catheter [8]. After the stain is applied, water rinses are performed to remove excess stain and allow for the most accurate visualization of the mucosa.

Lugol's solution

Lugol's solution is an inexpensive, widely available solution comprising a mixture of iodine and potassium iodide. This vital stain is absorbed by glycogen-containing, nonkeratinized squamous epithelium, the normal tissue type in the esophagus. Lugol's-stained tissue will characteristically turn green–brown. The intensity is partly dependent upon the amount of glycogen present within the epithelium. This stain is used as a 1% or 2% solution in a volume of 20 to 50 mL sprayed through endoscopic catheters. Inflammatory or dysplastic squamous epithelium, squamous cell carcinoma, and columnar epithelium will not stain with Lugol's solution. The most widely accepted use of Lugol's solution currently involves screening for squamous cell carcinoma of the esophagus in high-risk patients and in patients who have documented squamous cell dysplasia/cancer to rule out synchronous lesions (Fig. 1A, B).

Many investigators have used Lugol's solution in an attempt to identify early, treatable squamous cell carcinomas of the esophagus. Muto et al used Lugol's chromoendoscopy of the esophagus in 389 patients who had newly diagnosed squamous cell carcinoma of the head and neck. In this population 54 patients (14%) had synchronous squamous cell carcinoma of the esophagus. Fifty-five percent of the patients who had irregular, multiform regions of Lugol's-voiding mucosa had squamous cell carcinoma [1]. Fagunda et al identified 190 asymptomatic patients who had multiple risk factors (eg, prior head and neck carcinoma, alcohol abuse, dietary factors, tobacco use) for the development of squamous cell carcinoma of the esophagus, then performed Lugol's chromoendoscopy. They found a higher rate of dysplastic mucosa in biopsies taken from unstained areas than stained areas, with a sensitivity of 46% and a specificity of 90%; however, the positive predictive value was only 26% [9]. Mori et al applied Lugol's solution to 24 specimens of resected esophagus and attempted to grade staining patterns into four types: (1) grade I, hyperstaining; (2) grade II, normal green–brown staining; (3) grade III, less intense staining; and (4) grade IV, unstained. The authors established that cancers and high-grade dysplasia tended to exhibit the grade IV pattern, whereas low-grade dysplasia tended to exhibit the grade III pattern. Margins between normal squamous mucosa and carcinoma

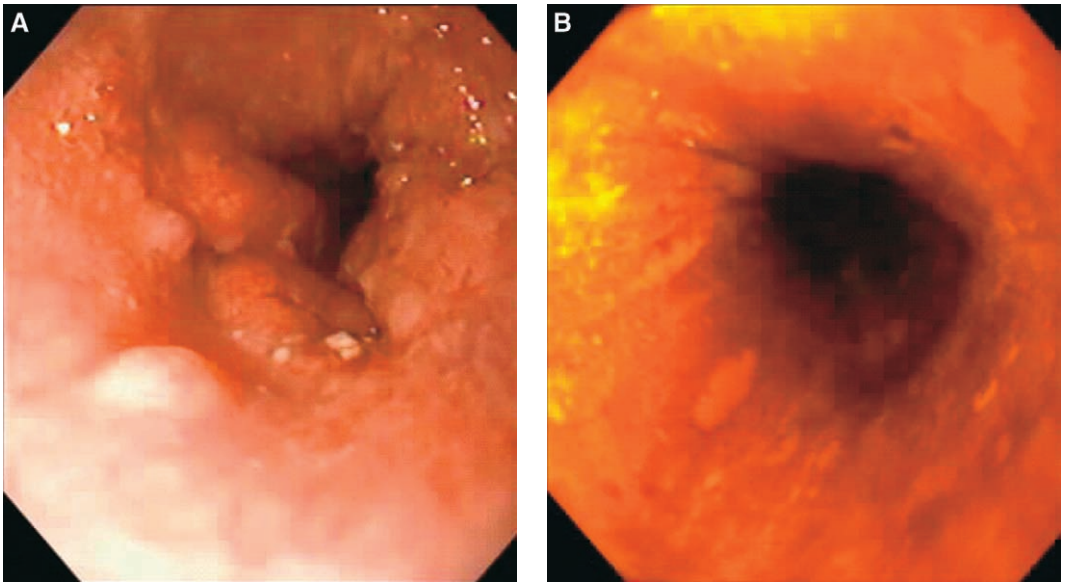

Fig. 1. (*A*) Squamous cell carcinoma diagnosed in patient who had recent dysphagia and weight loss. (*B*) Use of Lugol's solution to highlight unstained areas in same patient representing flat dysplastic/cancerous lesions.

tended to be sharp, whereas margins between normal mucosa and low-grade dysplasia tended to be less well demarcated [10]. Although some studies have suggested low accuracy rates for screening, Lugol's solution appears to be a simple-to-perform, inexpensive method of improving the endoscopic detection and delineation of esophageal squamous cell dysplasia and cancer in high-risk groups and defining the extent and margin of the tumor in patients who have known squamous cell cancer.

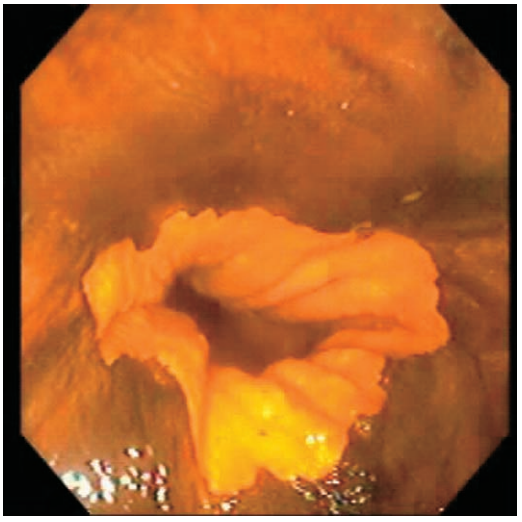

Fig. 2. Endoscopic picture of distal esophagus stained with Lugol's solution, highlighting the squamo–columnar junction. (*From* Conner MJ, Sharma P. Chromoendoscopy and magnification endoscopy in Barrett's esophagus. Tech Gastrointest Endosc 2003;5:89–93; with permission.)

Because of the stain's ability to differentiate esophageal from gastric mucosa, Lugol's solution can also be a valuable aid for identifying and highlighting the squamo–columnar junction (Fig. 2) because columnar mucosa will not absorb the stain. Stevens et al used Lugol's solution with indigo carmine and 35 × magnification endoscopy to identify Barrett's esophagus in 13 of 46 patients who had gastroesophageal reflux symptoms. In this study Lugol's solution was used to identify the squamo–columnar junction precisely, allowing for more accurate biopsies [11]. Several investigators have also used Lugol's solution to identify islands of residual columnar epithelium after endoscopic ablation therapy has been performed in patients who have Barrett's esophagus [12].

Methylene blue

Methylene blue is a vital stain that is readily taken up by absorptive epithelium, primarily that of the small bowel and colon, but is not absorbed by normal squamous or gastric epithelium. Metaplastic epithelium, including intestinal metaplasia of the stomach and esophagus, also absorb methylene blue. Methyl-

ene blue has been used successfully to aid in the identification of gastric intestinal metaplasia and dysplasia [13]. Because of these properties, this stain can be potentially beneficial in the distal esophagus. Before applying the stain, surface mucous must be removed to expose as much surface area as possible for staining. N-acetylcysteine solution is generally used for this purpose. Next, depending on the length of Barrett's esophagus, 10 to 20 mL of 0.5% methylene blue solution is sprayed onto the mucosa. The stained area is then irrigated vigorously with water. Staining becomes apparent within 2 to 3 minutes and generally fades within 15 to 20 minutes (Fig. 3A, B) [14].

Several studies have evaluated the usefulness of methylene blue staining for the identification of intestinal metaplasia in the esophagus. Canto et al compared methylene blue-directed biopsies with random biopsies in 43 patients who had Barrett's esophagus. Intestinal metaplasia was found in 91% of methylene blue-targeted biopsies versus 69% of random biopsies ($P = 0.0001$). Using methylene blue-targeted biopsies also enabled the endoscopist to identify intestinal metaplasia using fewer overall biopsies per patient (9.5 versus 14.1; $P = 0.0001$) [15]. Sharma et al performed methylene blue-guided target biopsies in 75 patients who had endoscopically suspected short-segment Barrett's esophagus. This group was compared with a control group of 83 patients who had short-segment Barrett's esophagus who had undergone standard endoscopic random biopsies. Intestinal metaplasia was detected in 61% of the methylene blue group versus 42% of the control group ($P = 0.016$), and fewer biopsy specimens were required in the methylene blue group [16]. This study highlighted that methylene blue-targeted biopsies might increase the diagnosis of short segments of intestinal metaplasia in the distal esophagus.

Other studies have not demonstrated a significant benefit of methylene blue staining in the identification of intestinal metaplasia or dysplasia. In a nonblinded study Dave et al performed methylene blue staining with biopsies on nine patients who had Barrett's esophagus. Methylene blue staining was found to have only 57% sensitivity and 32% specificity for the detection of specialized intestinal metaplasia. Furthermore, procedure times were longer and more patient discomfort was recorded compared with standard upper endoscopy [17]. Wo et al studied 47 patients who had columnar-lined esophagus in a prospective, randomized crossover trial. They found that the sensitivity and specificity of methylene blue for the detection of specialized intestinal metaplasia were 53% and 51%, respectively. No significant differences were found in the detection of intestinal metaplasia and dysplasia between methylene blue-directed and standard biopsy methods [18]. Thus, use

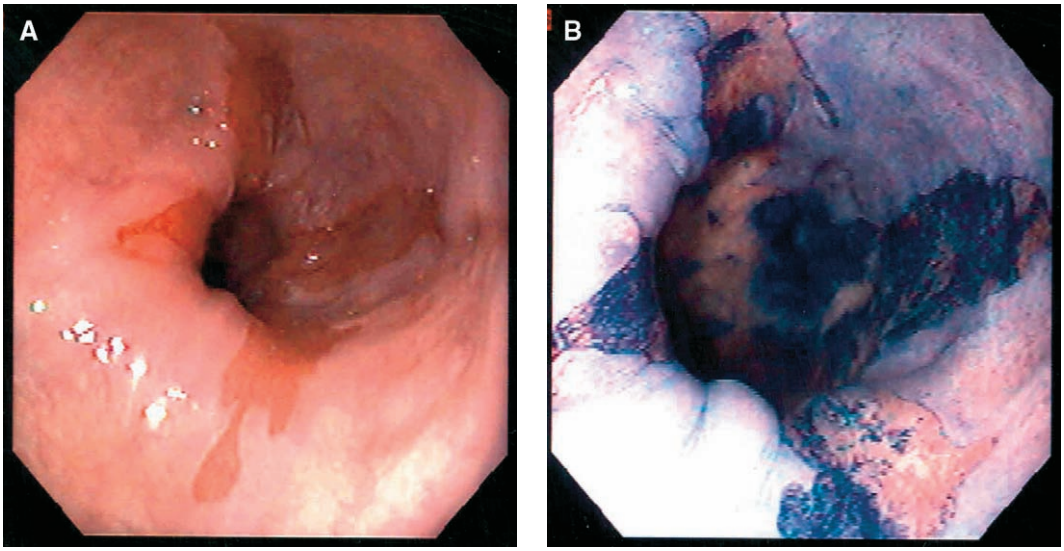

Fig. 3. (*A*) Short segment of columnar mucosa in the distal esophagus in the form of multiple tongue-like projections. (*B*) Areas of methylene blue staining within the columnar mucosa after washing the distal esophagus with water; target biopsies from the blue-stained areas revealed intestinal metaplasia. (*From* Sharma P, Topalovski M, Mayo M, Weston A. Methylene blue chromoendoscopy for detection of short-segment Barrett's esophagus. Gastrointest Endosc 2001;54(3):289–93; with permission.)

of methylene blue in patients who have Barrett's esophagus has yielded conflicting results, and its general use remains controversial.

The use of methylene blue staining in surveillance protocols to identify dysplasia also is controversial. In a single-center study, Canto et al were able to diagnose dysplasia and adenocarcinoma more accurately with methylene blue-directed biopsies than with random biopsies. The authors classified the degree tissue staining according to pattern, intensity, and heterogeneity. High grades of dysplasia stained less intensely with methylene blue, presumably because of the decreased number of goblet cells and the higher nuclear-to-cytoplasmic ratio. Dysplastic regions also tended to display a higher degree of stain heterogeneity than nondysplastic regions [19]. Use of methylene blue in this situation (ie, for detection of neoplastic lesions) needs to be studied further.

High-resolution/high-magnification endoscopy

High-resolution imaging improves the ability of the endoscopist to discriminate between two closely approximated points. High-resolution endoscopes provide magnified views of the gastrointestinal tract with greater mucosal detail. These instruments are capable of discriminating lesions 10 to 71 microns apart, compared with the naked eye, which is only capable of discriminating lesions 125 to 165 microns apart. The technique of magnification is relatively simple. A cap is fitted onto the distal tip of the endoscope, allowing the mucosa in contact with the cap to be magnified without the motility of the esophagus affecting visualization. Magnification is performed by using a lever located next to the up/down knob of the endoscope. When the lever is depressed fully, magnification of up to 115 × can be achieved (Olympus GIF-Q160Z Olympus, Melville, New York) [20].

Use of magnification endoscopy in Barrett's esophagus and dysplasia

The combination of chromoendoscopy with magnification endoscopy has been used for more accurate identification of Barrett's esophagus and dysplasia. Endo et al used 80 × magnification endoscopy with methylene blue staining in 30 patients who had a columnar-lined distal esophagus. Five discreet staining patterns were identified: (1) small/round (21 segments), (2) straight (8 segments); (3) long oval (26 segments), (4) tubular (10 segments), and (5) villous (2 segments). The percentage of biopsy specimens containing specialized columnar epithelium from the long oval, tubular, and villous types were 40%, 100%, and 100%, respectively. Intestinal metaplasia was detected infrequently in specimens taken from mucosa exhibiting the small/round or straight-type patterns, but specimens from tubular and villous patterns contained predominantly intestinal-type epithelium [21]. This study showed that specific patterns (ie, tubular and villous) observed under magnification might help in identifying intestinal metaplasia.

Indigo carmine is a contrast stain that has been shown to be useful in the detection and differentiation of colon polyps. It has also been used in conjunction with magnification endoscopy to identify areas of intestinal metaplasia and dysplasia within columnar-lined esophageal mucosa. Sharma et al studied 80 patients who had columnar-lined distal esophagus using indigo carmine dye and 115 × magnification endoscopy. Three mucosal patterns were identified: (1) ridged/villous, (2) circular, and (3) irregular/distorted (Fig. 4A–C). Regions exhibiting the ridged/villous pattern were found to have the highest yield of intestinal metaplasia (97%) versus regions exhibiting the circular pattern (17%). Six patients had the irregular/distorted pattern, and all of these patients were found to have histologic findings of high-grade dysplasia. Low-grade dysplasia was detected in 18 patients, all of whom exhibited the ridged/villous pattern. This technique proved useful for detecting intestinal metaplasia and high-grade dysplastic lesions; however, it was unable to differentiate between low-grade dysplastic lesions and nondysplastic epithelium [22]. Stevens et al also used indigo carmine with 35 × magnification endoscopy to identify short segments of intestinal metaplasia. Identification of a raised, villiform surface pattern correlated well with the histologic finding of intestinal metaplasia in 13 of 46 patients who had gastroesophageal reflux disease [23].

By using magnification endoscopy with a contrast stain such as indigo carmine, patterns are detected that might suggest the presence of intestinal metaplasia or dysplasia. Based on these studies, enhanced magnification endoscopy appears to be a useful surveillance tool for the detection of unsuspected dysplasia or cancer and for screening for intestinal metaplasia of the esophagus.

Acetic acid, another contrast agent, has been studied extensively as an aid in the detection of small lesions in the uterine cervical mucosa during colposcopy. It has recently been used in conjunction with magnification endoscopy to improve screening for Barrett's esophagus. Five to 10 mL of 1.5% acetic acid solution is sprayed onto the distal esophagus using a spray catheter. Following application, the

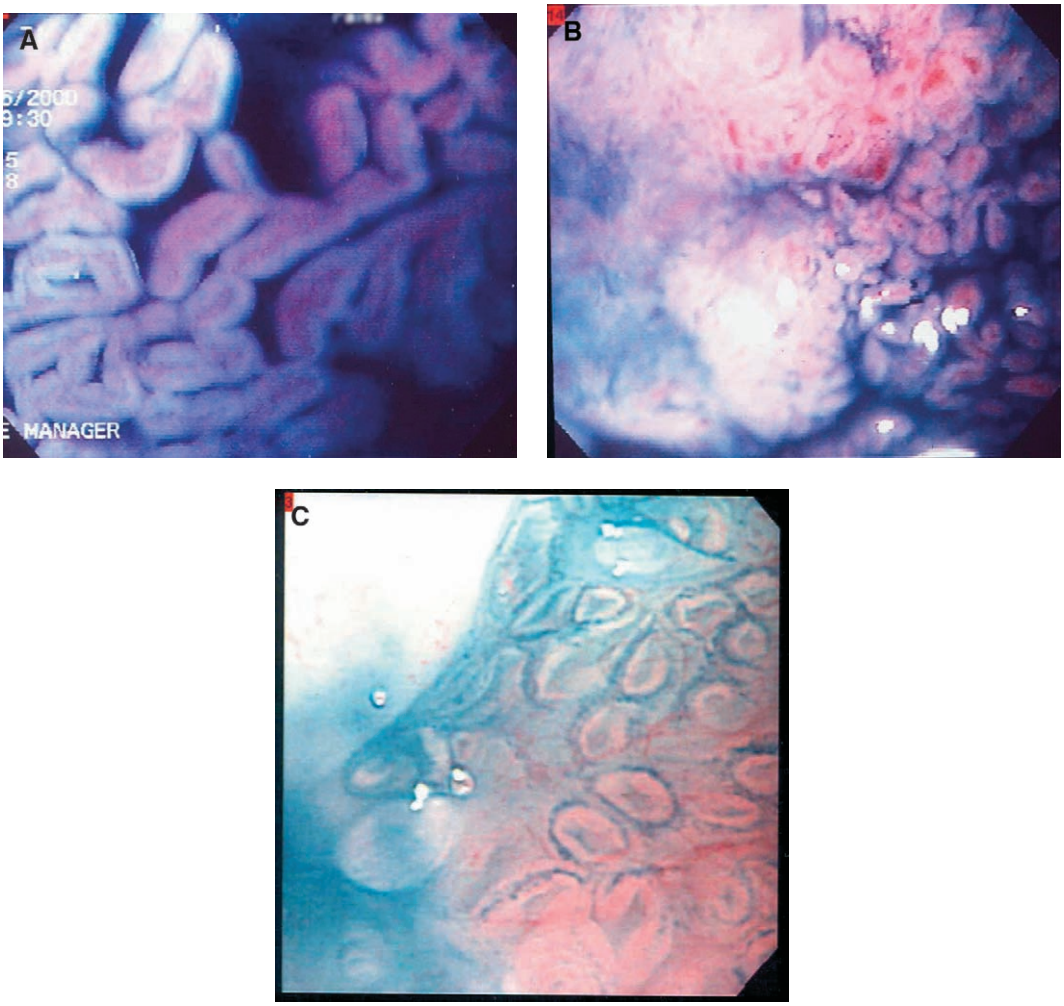

Fig. 4. Three distinct patterns observed under magnification (115 ×) after spraying indigo carmine in patients who had Barrett's esophagus. (*A*) Ridged villous. (*B*) Irregular/distorted. (*C*) Circular. (*From* Sharma P, Weston A, Topalovski M, et al. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's esophagus. Gut 2003;52:24–7; with permission.)

esophageal and gastric mucosa turn white. Within 2 to 3 minutes the esophagus remains white and the columnar epithelium turns reddish. Guelrud et al used acetic acid to improve detection of residual islands of Barrett's esophagus after endoscopic ablation therapy in 21 patients. In 11 patients, acetic acid demonstrated small remnant islands of columnar epithelium that were not visualized before acetic acid instillation [24]. The authors later used acetic acid in conjunction with magnification endoscopy to identify intestinal metaplasia in 49 patients who had suspected short-segment Barrett's esophagus. In this study four mucosal patterns were identified: (1) round, (2) reticular, (3) villous, and (4) ridged. Mucosa exhibiting the villous and ridged patterns yielded intestinal metaplasia in 87% and 100% of biopsy specimens, respectively [25].

Summary

Based on preliminary reports, the use of chromoendoscopy and magnification endoscopy appears to be a valuable adjunct to standard endoscopy for the detection and classification of metaplastic and dysplastic lesions of the esophagus. Ideally, the use of this technique would enable the endoscopist to rule in or out the presence of intestinal metaplasia and

dysplastic/cancerous epithelium by obtaining only a minimal number of targeted biopsy specimens—or potentially taking no biopsies at all, which could transform upper endoscopy into a much more effective screening and surveillance tool.

There are several problems with the use of chromoendoscopy and magnification endoscopy in the esophagus. This technique is operator-dependent (ie, dependent on the skill and experience of the endoscopist). Studies reporting the accuracy of chromoendoscopy remain mixed, especially for Barrett's esophagus and dysplasia, which is likely explained by differences in techniques and materials used in the investigations. Staining within the esophagus is often patchy and uneven. Poor spraying technique can exaggerate irregular uptake by the mucosa. There is a high false-positive rate when staining gastric-type epithelium or in the setting of inflammation. Areas of dysplasia or cancer might take up stain in an irregular manner or might not stain at all. Magnification only allows the endoscopist to observe small areas of mucosa at a time, increasing the overall difficulty of the procedure and procedure length.

Currently, the greatest body of literature exists concerning the use of Lugol's solution for the diagnosis of squamous cell dysplasia/carcinoma of the esophagus and methylene blue for diagnosing Barrett's esophagus. If used consistently by practicing physicians, the accuracy of biopsies could be improved. If endoscopic ablative therapy for high-grade dysplasia and early carcinoma (eg, photodynamic therapy and endoscopic mucosal resection) becomes accepted, sensitive methods of detecting residual metaplastic or dysplastic epithelium after ablation will be needed to help guide additional endoscopic therapy. Chromoendoscopy and magnification endoscopy could prove helpful in this setting.

Further research in this field needs to be performed. As a first step, a uniform classification system for staining and magnification patterns should be devised. Future studies could then be performed using consistent terminologies. More controlled investigations with larger numbers of patients must be performed before tissue staining and magnification endoscopy become a part of day-to-day endoscopic practice. Lugol's chromoendoscopy is a simple technique for the detection of synchronous squamous dysplasia and cancer, but a substantial amount of work remains to be performed for the validation of chromoendoscopy for the detection of Barrett's esophagus and dysplasia. The ultimate aim of chromoendoscopy and magnification endoscopy in the esophagus is to show improved outcomes (ie, early detection of cancer and improved survival). These goals have not yet been realized and will require well-designed studies in the future.

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