Endoscopic Therapy for Barrett’s Esophagus

Edited by

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Preface

Endoscopic therapy for Barrett’s esophagus (BE) has come of age. This is documented by the publication of a randomized controlled trial of one modality and an abstract of a randomized sham-controlled trial of another. The goal of this book is to highlight and detail the differing techniques of ablation for the elimination of neoplasia and intestinal metaplasia in BE. The authors are all experts in the utilization of endoscopic therapy for BE. The latest developments in technology and the most recent clinical data are reviewed.

Additional chapters on endoscopic imaging modalities to detect dysplasia, decision making in the clinical arena, and cost-effectiveness of ablation round out this approach to the management of BE.

High-grade dysplasia and early (intramucosal) adenocarcinoma should not lead to automatic esophagectomy in the current era. Familiarity with the availability of ablation techniques is essential for every clinician dealing with patients with Barrett’s esophagus.

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New Technologies for Imaging of Barrett’s Esophagus

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Summary

Several important endoscopic imaging modalities have recently been approved for use and are commercially available. This chapter briefly reviews these developments and the implication for patients with Barrett’s esophagus, especially advanced dysplasia and mucosal carcinoma. Important developments in biophotonics have been moving from the experiment laboratory to the gastrointestinal endoscopy unit. Narrow band imaging, auto-fluorescence, confocal fluorescent microscopy, spectroscopy and optical coherence tomography are reviewed. Unresolved issues for most of these technologies include regulatory approval, commercial availability and demonstration of clinical utility. This chapter reviews recent developments in endoscopy-based imaging modalities in patients with Barrett’s esophagus.

Key Words: Narrow band imaging, Auto-fluorescence, Confocal microscopy, Spectroscopy, Optical coherence tomography

INTRODUCTION

Several important endoscopic imaging modalities have recently been approved for use and are commercially available. This chapter briefly reviews these developments and the implications for patients with Barrett’s disease, especially advanced dysplasia and mucosal carcinoma. The history of Barrett’s esophagus features several important milestones. Norman Barrett initially described a congenital short esophagus with ulcerations in the gastric cardia. Later, others determined that Barrett’s esophagus represented acquired glandular ulcerations of the distal esophagus [1, 2] related to severe gastroesophageal reflux disease [3], with increasing rates of dysplasia and adenocarcinoma [4]. Subsequently, much of the interest in Barrett’s esophagus has focused on the utility of standard resolution white light surveillance endoscopy, with random mucosal biopsies to detect dysplasia and early carcinoma [5]. Recently, important developments in biophotonics have been moving from the laboratory to the gastrointestinal endoscopy unit. Unresolved issues for most of these technologies include regulatory approval, commercial availability, demonstration of clinical utility, securing reimbursement for the required additional time and imaging equipment, as well clarifying the medical–legal issues associated with image interpretation and data storage. This chapter reviews recent developments in endoscopy-based imaging modalities in patients with Barrett’s esophagus.
WHITE LIGHT ENDOscOPIC IMAGING FOR Barrett’s ESOPHAGUS

Barrett’s disease is suspected when endoscopy detects salmon-colored mucosa in the distal esophagus. North American guidelines require mucosal biopsies to document the specialized intestinal metaplasia of Barrett’s disease and differentiation from fundic or cardiac forms of gastric metaplasia. Beyond the initial diagnosis, the role of surveillance endoscopy, using standard resolution white light surveillance endoscopy, has not proven reliable for the visualization of dysplasia and early neoplasia. Therefore, surveillance endoscopy biopsy protocols, dependent upon quadrantic mucosal biopsies, have been adopted despite their expense, time consumption, associated sampling error, and the high inter- and intra-observer variability found in the histologic analysis [5, 6]. In the recent past, video endoscopes have largely replaced the fiber optic instruments around the world. A video endoscope utilizes a charge-coupled device (CCD) – an integrated electrical circuit made of photosensitive silicone semiconductors. The CCD surface is made up of photosensitive elements (pixels) that generate an electrical charge in proportion to light exposure and then generate an analog signal that is digitalized by the computer video processor. CCDs in standard video endoscopes have 100,000–300,000 pixels, and the image resolution, the ability to discriminate between two adjacent points, varies accordingly (Fig. 1). These endoscopes have a focal distance of 1–9 cm, and images will appear out of focus if they are beyond this range. Endoscopes with high-density CCDs (600,000–1,000,000 pixels per CCD), referred to as high-resolution endoscopes (HRE),

Fig. 1. High-resolution white light imaging of the same nodule. Despite the improved image quality the fine mucosal details are somewhat obscured by the red light.
are capable of producing high-magnification images, with increased spatial resolution for the detection of microscopic abnormalities in mucosal glandular and vascular structures. In conjunction with a movable lens for magnification endoscopy, the focal distance may be controlled to allow detailed examination of the mucosal surface at close range (< 3 mm).

**CHROMOENDOSCOPY AND BARRETT’S ESOPHAGUS**

It is laborious and impractical to use high-resolution endoscopy with high-magnification endoscopy over a large mucosal surface area. Therefore, HRE and magnification endoscopy have been combined with the use of chromendoscopy (vital dye staining) in an attempt to improve detection of mucosal abnormalities. Researchers recently reviewed chromendoscopy (vital dye staining with agents such as Lugol’s iodine solution, methylene blue, indigo carmine, crystal violet, and acetic acid), for the enhanced detection of the specialized intestinal metaplasia of Barrett’s esophagus [7]. Lugol’s solution, a 0.5–3.0% aqueous solution of potassium iodide and iodine, has been used to improve the detection and delineation of the squamous cell carcinoma and dysplasia in the aerodigestive tract via absorption by glycogen-containing cells. Lugol’s is often used with endoscopy procedures in patients at an increased risk of squamous cell carcinoma (heavy smokers, alcoholics, and prior lye ingestion patients). Methylene blue, 0.1–1.0% solution after mucolysis, is used for the detection of Barrett’s esophagus as it is taken up by intestinalized mucosa, but not squamous or gastric mucosa. Methylene blue, indigo carmine, and acetic acid combined with magnification endoscopy have been found to identify mucosal glandular patterns. Guelrud et al. described four pit patterns using acetic acid and magnification endoscopy (round, reticular, villous, and ridged) and found ridged and villous to be associated with intestinal metaplasia [8]. Sharma et al. described three mucosal patterns visualized with indigo carmine in patients with Barrett’s esophagus (ridged/villous, circular, and irregular/distorted), with the ridged or villous patterns found to be associated with intestinal metaplasia, while the irregular or distorted pattern was noted with Barrett’s high-grade dysplasia or superficial adenocarcinoma [9]. A review of seven prospective and controlled studies using methylene blue-targeted biopsies found a higher yield for the detection of Barrett’s disease compared with a random biopsy protocol [8, 10–15]. Sharma et al. studied 80 Barrett’s esophagus patients using indigo carmine dye and determined the presence of the ridged or villous pattern which had high sensitivity, specificity, and positive predictive
value (97%, 76%, and 92%, respectively) [9]. The distorted or irregular glandular pattern was also detected in six patients with Barrett’s high-grade dysplasia. However, subsequent studies have failed to demonstrate a detection benefit for either Barrett’s metaplasia or dysplasia [16, 17]. There has also been a report that raises the issue of DNA damage resulting from methylene blue staining and white light illumination [18]. Similar conflicting results have been found with studies using acetic acid, a mucolytic agent that alters cellular protein structure, and crystal violet staining [19–21]. These initial enthusiastic results have subsequently been found to vary widely, perhaps because of differences in technique, operator experience, and a patient population with the prevalence of Barrett’s esophagus [22, 23]. Four expert gastrointestinal endoscopists in Europe analyzed blinded evaluations of magnification chromendoscopy images of Barrett’s esophagus, using acetic acid or methylene blue. The interobserver agreement was poor (kappa = 0.40) for all parameters studied including the mucosal patterns, methylene blue positive staining, and the presence of specialized intestinal metaplasia. These inconsistencies, along with safety issues, increased cost, and procedure time, have prevented the widespread use of vital dye-staining chromendoscopy techniques [24].

NARROW BAND IMAGING AND BARRETT’S ESOPHAGUS

Narrow band imaging (NBI) is currently the best studied advanced endoscopic imaging technique for the detection of Barrett’s dysplasia. In addition, NBI has received regulatory approval and is a commercially available method of optical chromendoscopy that improves detection of mucosal abnormalities, without the messy, time-consuming problems associated with vital dye-staining chromoendoscopy (Fig. 2). NBI was developed by Gono et al. in 1999 as a joint project of the Japanese National Cancer Center Hospital East and Olympus Corporation (Tokyo, Japan) [25]. Their team of bio-optical physicists studied variations of conventional endoscopy that potentially could visualize early changes of angiogenesis (increased density of microvessels), associated with the development of dysplasia and superficial neoplasia. Using light filters, the contribution of blue light is increased by narrowing the band widths of the red, green, and blue components of the excitation light, reducing the amount of green light, and eliminating the red light. The resulting “narrow band” blue-green light improves imaging of mucosal patterns because of the limited optical scattering and shallow penetration depth. This blue light is also absorbed by hemoglobin [since the
hemoglobin absorption band (Soret band) lies at 415 nm] for optimal detection of mucosal glandular, vascular patterns, and the presence of abnormal blood vessels that are associated with the development of dysplasia [26]. Olympus, Tokyo, Japan, produces two versions of the NBI system. The Evis Exera II system is available in North America, with a high-resolution white light endoscope and narrow band imaging using a color charge-coupled device to detect the reflected red, green, and blue light, with several diminutive band-pass color filters in each pixel for 530–550 nm green light and 390–445 blue light. The Lucera system uses a monochromatic CCD system and is available predominantly in Japan and Europe. Both of these systems feature an electronic switch on the handle of the endoscope to permit rapid switching between high-resolution white light and narrow band imaging modes. While these systems are technically distinct, they are functionally equivalent.

Several single center studies have correlated the appearance of mucosal glandular and vascular patterns with metaplasia. Kara et al. studied magnified images in Barrett’s esophagus patients and found that regular mucosal and vascular patterns were associated with intestinal metaplasia, whereas irregular mucosal and vascular patterns and the presence of abnormal blood vessels were associated with Barrett’s high-grade dysplasia [27, 28]. These mucosal and vascular patterns have been the basis of a series of studies from several advanced endoscopy centers, demonstrating the utility of NBI in evaluating Barrett’s dysplasia patients. Kara et al. compared HRE with indigo carmine chromendoscopy or NBI in 14 patients with Barrett’s high-grade dysplasia.

Fig. 2. This view of the same nodule with narrow band imaging allows better appreciation of mucosal glandular and vascular irregularities.
(HGD). The aim of the study was to test and compare these combinations for the detection of Barrett’s high-grade dysplasia or superficial carcinoma. HRE alone found HGD in 11 patients (79%), while NBI detected it in 12 patients (86%), and indigo carmine chromendoscopy detected it in 13 patients (93%). One patient had HGD that was not detected with any imaging modality, but it was found with random biopsies (7%). NBI found an additional four HGD lesions in three of these 12 patients. The efficacy of both techniques was found to be similar, and NBI was preferred over vital dye staining for its ease of use, although white light resolution endoscopy detected all cases of high-grade dysplasia, suggesting that NBI improved detailed inspection of suspicious lesions, rather than for their primary detection. As a historical comparison, a previous study performed by this group detected HGD in 62% of patients using targeted standard resolution endoscopy (SRE) biopsies, and in 85% of patients with SRE targeted plus random quadrant biopsies [29, 30]. Anagnostopoulos found similar results in a study of 344 lesions in 50 patients using magnified endoscopic microstructural and vascular features of Barrett’s disease. Regular microstructural patterns were associated with sensitivity, specificity, positive, and negative predictive values of 100%, 79%, 94%, and 100%, respectively, for intestinal metaplasia. The sensitivity, specificity, positive, and negative predictive values for patients with high-grade dysplasia was 90%, 100%, 99%, and 100%, respectively [28]. Interestingly, a recent publication from Curvers et al. studied the use of high-resolution endoscopy with vital dye-staining techniques, using acetic acid and indigo carmine as well as NBI, in 14 patients with 22 suspicious lesions, including 8 areas of high grade dysplasia, 1 area of low grade dysplasia, 1 area indefinite for dysplasia, and 12 areas of non-dysplastic Barrett’s disease. In a blinded study, seven community and five expert gastrointestinal endoscopists evaluated standard images from these lesions for glandular and vascular patterns, and any association with dysplasia. The yield for detecting dysplasia or neoplasia, with high-resolution white light endoscopy, was 86% overall (90% for experts and 84% for non-experts), and the addition of enhancement techniques (vital dye staining or NBI) did not improve the diagnostic yield [31].

A prospective, blinded, tandem endoscopy study from our group, in press at *Gastroenterology*, compared SRE and HRE-NBI in 65 patients referred for evaluation of Barrett’s dysplasia. As commercially available HRE-NBI systems in North America do not have high-magnification capability, the determination of areas suspicious for dysplasia or cancer was made with standard endoscopic techniques, in an attempt to reproduce a realistic clinical practice setting. This study
found that NBI-targeted biopsies found dysplasia in more patients (37 patients, 57%), compared with SRE with targeted plus random biopsies (28 patients, 43%; $p < 0.001$). NBI also found higher grades of dysplasia in 12 patients (18%), compared to zero cases where SRE, with targeted plus random biopsies, detected a high grade of histology (0%; $p < 0.001$). In addition, more biopsies were taken using SRE with targeted plus random biopsies (mean 8.5 biopsies per case), compared with NBI-directed biopsies (mean 4.7 biopsies per case; $p < 0.001$). The ability of HRE, combined with NBI to find dysplasia in significantly more patients with Barrett’s esophagus with greater efficiency, using significantly fewer biopsy samples, illustrates the importance of this technology for the surveillance evaluation of Barrett’s esophagus patients. Further studies, however, will be required to document this increased efficiency and cost savings for surveillance endoscopy and also to determine the impact of HRE-NBI on the results of endoscopic screening for BE and surveillance programs for dysplasia detection in BE [32, 33].

AUTO-FLUORESCENCE IMAGING, TRI-MODAL IMAGING, AND BARRETT’S ESOPHAGUS

Auto-fluorescence imaging (AFI) is a technique that differentiates tissue types based on their differences in fluorescence emission. When tissues are exposed to short wavelength light, endogenous biological substances (fluorophores) are excited, causing emission of fluorescent light of a longer wavelength (auto-fluorescence). The molecules responsible for tissue auto-fluorescence include collagen, NADH, elastin, flavin, porphyrins, and aromatic amino acids – each with a characteristic excitation and emission spectral pattern. AFI detects differences in the natural, endogenous fluorescence of normal, dysplastic, and neoplastic mucosa using blue light illumination, producing a low-intensity auto-fluorescence that is detected through highly sensitive CCDs, along with reflectance imaging detected through non-intensified CCD [34] (Fig. 3). The image processor incorporates the CCD signals into a real-time pseudo-color image of normal mucosa (green color) and dysplasia or neoplasia (varying tones of red/purple color). Previously, the use of AFI was with fiber optic endoscopes, which provided relatively poor white-light images. Early studies with this limited technology could prove no benefit for the use of AFI over white light endoscopy, including a randomized, crossover study from the Academic Medical Center in Amsterdam [29, 35, 36]. In a single center, uncontrolled study, Kara et al. evaluated using AFI after high-resolution white light
Fig. 3. Endoscopic tri-modal imaging utilizes an imaging system with auto-fluorescence imaging (AFI), high-resolution white light (HRE), and narrow band imaging (NBI). This image visualized a distal esophageal nodule with auto-fluorescence imaging where a pseudo-image is created based on the fluorescence spectrum with the dysplastic mucosa represented in purple color, in contrast to the normal mucosa that is green color.

endoscopy in 60 patients with Barrett’s esophagus. High-grade dysplasia was detected in 22 patients including 6 patients where white light endoscopy did not identify lesions, but were only found with AFI. Therefore, AFI detected a significant number of patients with high-grade dysplasia, who had no visible lesions on high-resolution white light endoscopy, increasing the target detection rate from 63 to 91%. However, the use of AFI was associated with a 51% false positive rate, as 41 of 81 suspicious areas by AFI did not have dysplasia at biopsy. AFI endoscopy, then, offers the promise of wide-area imaging for Barrett’s surveillance, but is associated with poor specificity [37].

Subsequently, tri-modal imaging endoscopes have been developed that combine the use of wide-field endoscopic imaging (high-resolution white light endoscopy), a wide-field sensitive method for the detection of dysplasia and carcinoma (so-called “red flag” technique; AFI), and a virtual chromendoscopy technique, to enhance and improve the combined accuracy of these techniques for the detection of mucosal dysplasia and neoplasia (NBI) [38]. Again, the initial single center study came from Bergman’s group in Amsterdam where 20 patients were evaluated for 47 suspicious areas found with AFI. Of these 47, 28 were found to be abnormal based on NBI, and subsequently, biopsy confirmed the diagnosis of high-grade dysplasia in each case. However,
14 of 19 areas detected with AFI appeared normal with NBI, thereby reducing the number of false positive lesions from 40 to 10% (of 47 lesions, total). The positive predictive value of AFI alone for Barrett’s disease with high-grade dysplasia was only 60%, but it improved to 85% when used in combination with NBI [39]. Curvers et al. published the results using tri-modal imaging in four expert endoscopy imaging centers in Europe and the United States, for the evaluation of 84 patients referred with Barrett’s dysplasia [31]. The study outcomes were the number of patients and lesions of HGD detected with HRE and AFI plus the reduction of false positive AFI findings after NBI. The AFI algorithm utilized total auto-fluorescence after blue light illumination and green reflectance. At endoscopy, HRE was first used to examine the Barrett’s segment for the presence of esophagitis or visible lesions. Then, AFI was used to identify areas suspicious for the presence of dysplasia (violet-purple pseudo-color). NBI was then used to describe the vascular and mucosal pattern of these suspicious lesions, in order to determine if they were suspicious for the presence of dysplasia or not. Random quadrantic biopsies were obtained after the image-targeted biopsies.

Overall, 30 patients were diagnosed with Barrett’s high-grade dysplasia, 16 were detected with HRE, 11 were detected only with AFI, and 3 were diagnosed only by random biopsies. The use of AFI, therefore, increased the number of patients found to have HGD from 53% (16/30 patients) to 90% (27/30 patients). The use of NBI reduced the false positive rate of AFI from 81 to 26%, and the false positive rate of HRE was reduced from 67 to 44%, but mis-classified two lesions that were found to contain HGD. The utility of random quadrantic biopsies in addition to HRE, AFI, and NBI is unknown. Thus far, the published experience with these prototype systems, combining the use of HRE, AFI, and NBI in one endoscope, has come from academic centers with expert endoscopists evaluating a highly selected group of Barrett’s patients with dysplasia and carcinoma. The application of this technology has not yet been studied in other practice settings, and these devices have not been approved for use in the United States.

CONFOCAL FLUORESCENT MICROSCOPY AND ENDOCYTOSCOPY FOR BARRETT’S ESOPHAGUS

The development of probe-based and endoscopic devices for real-time, in vivo microscopic imaging of Barrett’s mucosa represents another milestone in advanced imaging technology [40]. Confocal microscopy uses blue laser light to stimulate mucosal cells, which reflect back
through a pin-hole opening to eliminate out-of-focus light. Laser scanning with computer generated cross-sectional images permits real-time microscopic imaging of Barrett’s mucosa. The miniature confocal microscope, developed by OptiScan with Pentax, Japan, permits magnification beyond 1,000× with cellular and sub-cellular resolution of crypt and cellular architecture to a depth of 250 microns (level of the lamina propria). Improved images, however, require the use of a contrast agent, such as topical acriflavine or intravenous fluorescein sodium, for resolution of cellular structures and microvasculature. Image production tends to be relatively slow, one frame per second, creating lengthy procedure times. Initial studies using this system have reported very high accuracy (85–94%) for the detection of high-grade dysplasia in Barrett’s esophagus [41, 42]. However, these results reflect the expert use of this technology in a single referral center. Importantly, this microscopy analysis was performed in patients with visible lesions detected on white light endoscopy. It is unclear if this experience would produce similar results for lesions that were not visible with white light endoscopy, or if this technology could produce similar or significantly better results when compared with tri-modal imaging with HRE, AFI, and NBI.

The second approach to in vivo microscopic imaging involves a small confocal microscope probe developed by Mauna Kea Technologies, France, which can be used with any endoscope to provide real-time endoscopic microscopy to varying depths from 50 to 200 microns [43]. This system features post-procedure image reconstruction for video mosaicing, the combination of dynamic single-frame images into a static, mosaic image over a broad field, without reduction in image resolution [44]. Larger studies from more centers are awaited to determine the role and utility of confocal microendoscopy systems in the evaluation of patients with Barrett’s disease.

Endocytoscopy allows visualization of cells and nuclei using high-magnification probes or endoscopes for the detection of dysplasia, neoplasia, inflammation, and infection involving the gut mucosa, with initial reports describing findings in 12 esophageal squamous cell cancer patients [45]. For use in Barrett’s disease, this method requires a dye or contrast agent, such as methylene blue or NBI for cellular imaging to evaluate the cell size, shape, and nuclear characteristics. A recent ex vivo study of 166 biopsy sites from 16 patients with 450× and 1,125× magnification, with investigators blinded to endoscopic and histologic findings, found adenocarcinoma 4.2% of biopsy sites, high-grade intraepithelial neoplasia in 16.9% and low-grade intraepithelial neoplasia in 12.1%. However, adequate assessment of endocytoscopy images was not possible in 49% of the target areas at the
450× magnification, and in 22% of the target areas at 1,125× magnification. At most, 23% of images with lower magnification and 41% of higher magnification images could be interpreted in order to identify characteristics of dysplasia and neoplasia. Interobserver agreement was less than fair (kappa from < 0 to 0.45), with positive and negative predictive values for high-grade dysplasia or carcinoma of 0.29 and 0.87, respectively, for 450× magnification and 0.44 and 0.83, respectively, for 1,125× magnification [46]. The real-time, in vivo use of these systems is likely to be limited by image stabilization problems, with motion artifact and image distortion.

**SPECTROSCOPY**

Optical spectroscopy may provide the means to detect mucosal abnormalities in real-time, using molecular and microstructural information in light–tissue interactions such as fluorescence, reflectance, Elastic scattering, and Raman (inelastic scattering) [47]. The behavior of light provides information about tissue composition, oxygenation, degree of inflammation, and dysplasia for histological-like characterizations of gut mucosa. Different spectroscopic techniques can be used to provide information about tissue biochemistry and oxygenation. However, currently available clinical studies are limited to single center feasibility studies. Reflectance spectroscopy quantitatively measures the color and intensity of reflected light after tissue illumination, to discriminate normal, dysplastic, and neoplastic mucosa. Unlike autofluorescence spectroscopy, this reflected light maintains the same wavelength, although varying degrees of light wavelengths are absorbed and reflected. Hemoglobin is the primary molecule that absorbs light, providing a marker of angiogenesis and dysplasia based on tissue oxygenation. Light scattering spectroscopy is a type of reflectance spectroscopy that studies elastic scattering (light not changed by the tissue interaction). Each wavelength of light is scattered differently depending on the density of the mucosal and cellular structures it encounters. By measuring which light wavelengths are scattered, and which are not, the size and characteristics of the mucosal and cellular structures, such as the size and density of nuclei, may be determined. Since endogenous fluorophores produce weak fluorescence signals, exogenous fluorophores, such as porphyrin compounds, are used to enhance the fluorescence effect. Exogenous fluorophores are thought to be relatively specifically retained in dysplastic and neoplastic tissues, and they exhibit a much higher intensity-induced fluorescence signal. Among different sensitizers, porphyrins have been best studied for application.
New Technologies for Imaging of Barrett’s Esophagus

in fluorescence spectroscopy. Porphyrins are heme products associated with prolonged photosensitivity (porfimer sodium), or other potentially serious adverse events such as nausea and hypotension (aminolevulinic acid). The advantage of drug-induced fluorescence is that the fluorescent signal generated by these exogenous fluorophores is typically stronger than auto-fluorescence and can be detected by simpler and cheaper instruments. Among exogenous fluorophores, 5-aminolevulinic acid (5-ALA) is the best studied photosensitizer that converts intracellularly to the photoactive compound protoporphyrin IX (PPIX). PPIX is associated with a significantly higher tumor selectivity compared to other exogenous fluorophores used in fluorescence imaging [48]. Furthermore, compared to other exogenous fluorophores, skin sensitivity is reduced to 24–48 h, although cardio-vascular side effects including severe hypotension and sudden death have been reported [49, 50]. An issue in the measurement of fluorescence spectra is the background generated by scattering and absorption. In this case, the fluorescence spectra may be analyzed, with information from the corresponding reflectance spectra, to permit subtraction of this background and produce a measure of intrinsic fluorescence [51]. Different fluorophores are excited by different wavelengths of light, and the optimal excitation wavelength for detecting dysplasia is unknown. A significant technical advance in fluorescence spectroscopy was made with the development of a fast multiexcitation system, capable of rapid tissue excitation with up to 11 different wavelengths, providing information to optical probes and allowing collection of many different fluorescence spectra for the determination of the optimal excitation wavelength [51, 52]. In addition to specific excitation and emission wavelengths, different fluorophores fade or decay their fluorescence at different rates. This difference between normal and abnormal tissue can be enhanced by measuring stimulated fluorescence at different intervals. This technique, termed “time-resolved fluorescence,” has been used to increase the accuracy of dysplasia detection in patients with Barrett’s esophagus [53].

Light propagation in tissue is governed by scattering and absorption. Light-scattering spectroscopy measures the extent to which the angular path of photons of light is altered by the size and number of cellular components (scatterers) they encounter. The primary scatterers are collagen fibers in the extracellular matrix, mitochondria, cellular nuclei, and other intracellular structures. By mathematical modeling, the number, size, and optical density of cellular structures (such as nuclei), can be determined by measuring the diffuse reflected light from epithelial surfaces [54]. This phenomenon has been exploited during endoscopic procedures to determine the number of nuclei, the size of