

## Enhanced imaging in the GI tract: spectroscopy and optical coherence tomography

*The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of new or emerging endoscopic technologies that have the potential to have an impact on the practice of GI endoscopy. Evidence-based methodology is used, using a MEDLINE literature search to identify pertinent preclinical and clinical studies on the topic, and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. For this review, the MEDLINE database was searched through February 2013 by using the keywords spectroscopy, optical coherence tomography, Raman spectroscopy, gastrointestinal, Barrett's esophagus, pancreas, bile ducts, and colon.*

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Conventional white-light endoscopy enables examination of the GI tract mucosa. Biopsy with histologic examination is necessary to examine tissue at a microscopic level. The ability to examine microscopic characteristics of tissue (optical biopsy) during endoscopy is a desirable goal. Enhanced imaging techniques have been developed with the goal of providing additional real-time diagnostic information about target tissue.

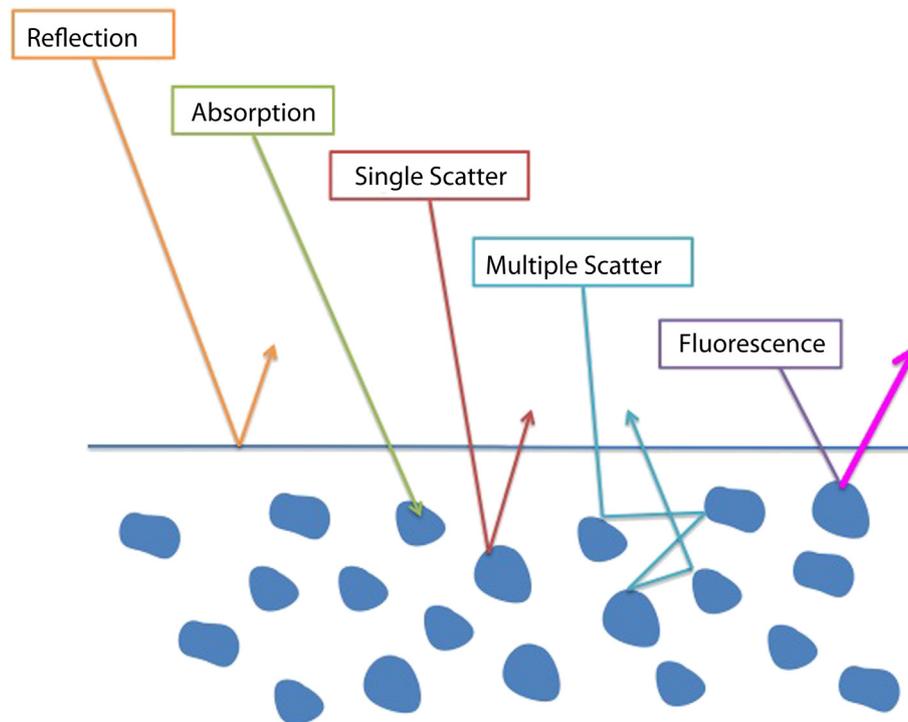
Light may interact with tissue in various ways that can be measured and analyzed. These interactions may provide information about tissue type, hemoglobin content, microstructure, or molecular characteristics. The scope of this review includes spectroscopic methods (elastic scattering spectroscopy and inelastic spectroscopy) and optical coherence tomography (OCT).

### EMERGING TECHNOLOGY

#### Spectroscopy

Spectroscopy is based on light interaction with tissue. The incident light directed on the tissue may be reflected in different patterns called scattering events (Fig. 1). Light may be also be absorbed and re-emitted at longer wavelengths, or it may be shifted slightly to a different wavelength. These characterizations may correlate with histopathology, subcellular architecture (eg, enlarged nuclei), specific molecular bonds, or differing tissue absorptions of light driven by exogenous or endogenous fluorescent compounds (fluorophores). Properties of these spectroscopic methods are explained in the following, with examples shown in Table 1.

*Elastic scattering spectroscopy* refers to the way that light is reflected from the tissue after scattering events. Light may reflect back from tissue 1 time (single scatter) or may ricochet within the cellular components of tissue multiple times before reflecting back toward the source (multiple scatter). Elastic scattering spectroscopy exploits the fact that light scatters differently in normal tissue compared with neoplastic tissue, and it measures the scatter characteristics to examine tissue microarchitecture. Many elastic scattering spectroscopy systems use white light as the incident light. There is no change in wavelength or energy in the reflected light with respect to the incident light. Several probe-based elastic scattering spectroscopy systems have been designed<sup>1-3</sup> that have differing parameters such as depth of penetration or size of the field that is targeted. One example is the endoscopic polarized scanning spectroscopy system. This endoscope-compatible probe rotates, scans, and withdraws, sequentially capturing information throughout the esophagus and providing information in nearly real time.<sup>4</sup> This system is being evaluated for the detection of Barrett's associated neoplasia. Another example is low-coherence enhanced backscattering spectroscopy. This system has been



**Figure 1.** Scattering events.

designed to be depth selective. Trials using this system to detect field effect changes in the periampullary region of the duodenum for pancreatic cancer detection and in the rectum for colorectal cancer are ongoing.<sup>3</sup> Additional technology variations and systems have been described, including diffuse reflectance spectroscopy, light scattering spectroscopy, polarized gated spectroscopy, partial wave spectroscopy, nanocytology, and angle-resolved low coherence interferometry.<sup>5-7</sup>

*Inelastic (Raman) scattering spectroscopy* measures the signals obtained when the incident light undergoes wavelength shifts caused by energy transfer in the tissue. The shifts in light wavelength are caused by vibrations of common molecular bonds found in the tissue. Different types of tissue (eg, neoplastic vs normal) have different vibrations, producing different shifts in light wavelength. The light wavelength shifts are relatively rare events, and therefore the signal is weak and difficult to measure. Some related technologies (eg, coherent anti-Stokes Raman scattering spectroscopy<sup>8</sup> and surface-enhanced Raman spectroscopy<sup>9</sup>) may have the ability to amplify the signal, allowing for easier differentiation between desired signal and background noise, although these have not been studied in humans. Raman probe-based systems have been developed and are currently being studied for detection of esophageal neoplasia.<sup>10</sup>

*Fluorescence spectroscopy* is based on the principle that when incident light is absorbed by a target fluorophore, it increases in energy, causing fluorescence to occur. The target emits this energy as light with longer wavelength

than the incident light, yielding an optical fingerprint based on the relationship between wavelength (color) and intensity of the emitted fluorescence. The incident light is often a monochromatic laser. A fluorophore is the substance that produces the fluorescence signal and may be either endogenous (ie, collagen, flavins) or exogenous (ie, Porfimer sodium or aminolevulinic acid-induced protoporphyrin IX).

The basic equipment for spectroscopy includes a light source with laser or filtered light, a fiberoptic device that delivers light to the tissue, and a component that captures the signal from the target tissue. An optical analyzer or spectrograph then determines the signal intensity as a function of wavelength. The spectroscopic raw data are further processed into diagnostic information that may be quantitative or visual. This must be further interpreted by the user to infer tissue characteristics. These systems have been developed as ex vivo systems where tissue or cells are interrogated by spectroscopy systems and as in vivo systems. In the in vivo systems, a fiberoptic device may be inserted in the working channel of the endoscope, may be incorporated into the endoscope itself, or may work independently of the endoscope either with direct insertion or by using a tethered capsule system.<sup>11</sup> In vivo systems may focus on point-based measurements on the order of 1 to 2 mm<sup>2</sup> volume of tissue or incorporate a wider field microscopy approach.

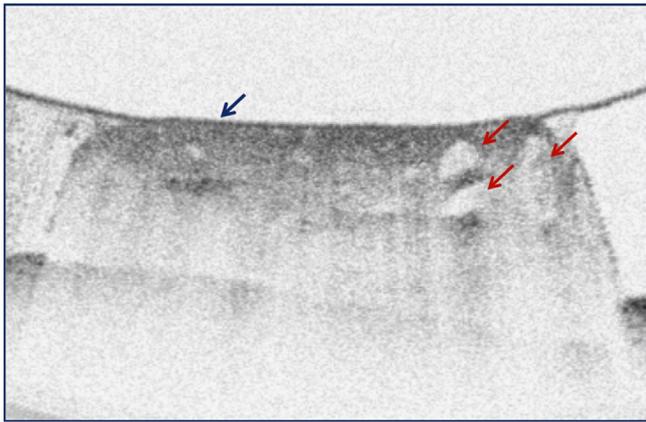
The different types of spectroscopy are listed in Table 1.

### Optical coherence tomography

OCT is a technology that obtains cross-sectional images of target tissue with high resolution on the order of a

**TABLE 1. Spectroscopic methods and their properties**

	Light–target interaction	Impact on light	Incident light example	Possible tissue determinants
Elastic	Multiple scattering events	No change in wavelength	White light	Microarchitecture, subcellular components, hemoglobin content
Fluorescence	Absorption and re-emission	Longer wavelength	Monochromatic	Collagen structure, flavins, porphyrins
Raman	Rare energy shifts by vibrations in molecular bonds	Slight wavelength shifts	Near-infrared	Covalent bonds



**Figure 2.** A volumetric laser endomicroscopy image of an EMR specimen demonstrating the loss of layered architecture (*blue arrow*) and the presence of atypical glands (*red arrows*) concerning for Barrett's esophagus with dysplasia.

low-power microscope. Interferometry is the technique used in OCT that measures the path length of reflected light and processes the information for image generation. OCT is similar to ultrasound but uses light as the signal instead of an acoustic signal. Compared with endosonography, OCT offers a higher spatial resolution on the order of 1 to 15  $\mu\text{m}$ , but less depth of penetration. OCT can operate with air or water interface. The images generated by OCT correlate with the subsurface of tissue (Fig. 2). The original iteration of OCT was conventional time domain OCT.<sup>12,13</sup> Frequency domain OCT has been developed to provide faster real-time imaging with high resolution.<sup>14</sup> A system based on frequency domain OCT (volumetric laser endomicroscopy; Ninepoint Medical, Cambridge, Mass) has been cleared by the U.S. Food and Drug Administration. Volumetric laser endomicroscopy provides resolution to 10  $\mu\text{m}$  and imaging depth down to 3 mm scanning over a 6-cm length of esophagus over a period of 90 seconds. Some probe-based systems are being developed to be compatible with needles or catheters to access the pancreaticobiliary system.<sup>15</sup>

Multiple modalities within a single system have been described, such as confocal light absorption and scattering

spectroscopic microscopy<sup>16</sup> or the combined OCT–laser-induced fluorescence system.<sup>17</sup> Some point measurement systems are also being designed to include an integrated snare or biopsy forceps, allowing for immediate management of targeted tissue (eg, biopsy, retrieve, discard, or not sample) based on the enhanced imaging information.

## POTENTIAL APPLICATIONS

One of the most enticing applications of using spectroscopy and OCT in the GI tract is to help distinguish malignant or dysplastic tissue from benign. This would be particularly useful in settings such as Barrett's esophagus (BE) and inflammatory bowel disease surveillance, differentiating between hyperplastic and adenomatous colon polyps, or where tissue is difficult or challenging to obtain such as in the pancreaticobiliary system. The field effect of carcinogenesis is a theory that normal tissue from organs with neoplasia (eg, the colon) also has genetic or molecular changes that may not yet be evident on histology. Spectroscopy examining the field effects of carcinogenesis may be helpful in screening or risk stratification of patients. Many ex vivo and in vivo studies have been performed, focusing on feasibility and determination of performance characteristics of these technologies compared with existing methods of diagnosis (eg, histology).

### Barrett's esophagus

Several investigators have focused on using spectroscopy and OCT to identify dysplasia in BE without the need for biopsy (optical biopsy). Early studies using probe-based light-scattering spectroscopy systems to take point measurements in vivo matched with biopsy specimens demonstrated the ability to detect dysplasia with 90% to 92% sensitivity.<sup>4,16,18</sup> One preliminary study demonstrated quantitatively detectable levels of nicotinamide adenine dinucleotide phosphate). Nicotinamide adenine dinucleotide phosphate fluorescence in vivo in dysplastic tissue in the esophagus.<sup>19</sup> In an ex vivo study of 87 samples of BE (acquired from 44 patients), Raman spectroscopy demonstrated sensitivities for dysplasia

between 73% and 100% and specificities of 90% to 100%.<sup>20</sup> An in vivo study of 54 patients evaluated different parameters of dual diffuse reflectance spectroscopy in combination with autofluorescence endoscopy in a training set and obtained a sensitivity and specificity of 0.67 and 0.85, respectively, to distinguish dysplasia in the setting of BE in a testing set.<sup>21</sup>

OCT has also been used to characterize in vivo histopathology and differentiate high-grade dysplasia in BE.<sup>22-25</sup> A sensitivity of 68% and specificity of 82% for dysplasia were reported in a prospective, double-blind study of 33 patients.<sup>26</sup> Another study developed a scoring system for OCT and reported a sensitivity of 83% and specificity of 75% in the detection of high-grade dysplasia and intramucosal carcinoma.<sup>23</sup> OCT has been described to reveal subepithelial glands in naive and in post-radiofrequency ablation (RFA) settings.<sup>27,28</sup> It has also been used to characterize structural markers such as Barrett's epithelial thickness and to evaluate for residual glands after RFA that may predict ablative treatment response.<sup>29</sup> Three-dimensional OCT was performed in 27 patients with BE who had undergone RFA (n = 18 with complete eradication and n = 16 before complete eradication). OCT was able to detect subsquamous residual intestinal metaplasia (buried glands) in 63% of patients who had achieved complete eradication and 72% before complete eradication.<sup>30</sup>

## Colon

In a preliminary study, elastic scattering spectroscopy was found to have 84% sensitivity and 84% specificity for differentiating hyperplastic from adenomatous tissue in the colon.<sup>31</sup> Initial ex vivo studies evaluating the use of Raman spectroscopy<sup>32-36</sup> and coherent anti-Stokes Raman scattering spectroscopy<sup>37</sup> in the colon have been performed as well. One study demonstrated that Raman spectroscopy could differentiate between malignant and normal mucosa with up to 81% accuracy.<sup>32</sup> A pilot study characterized the findings of OCT in normal colon and a variety of disease states (eg, radiation proctitis, neoplasia).<sup>38</sup> OCT was used to evaluate the imaging characteristics in adenomatous tissue versus hyperplastic tissue in an exploratory study.<sup>39</sup>

The possibility of a field effect of carcinogenesis in the colon has been studied using spectroscopy to characterize optical signatures from normal-appearing rectum that might predict the presence of more proximal adenomas or cancer. These preliminary studies used elastic scattering spectroscopy to interrogate the microvascular blood supply content,<sup>40</sup> tissue microarchitecture,<sup>41</sup> or the nanoarchitecture of the cells.<sup>42</sup> For example, in a study of 216 patients, an increase in microvascular rectal blood supply with a probe-based polarized gated spectroscopy system provided a sensitivity of 83%, specificity of 82%, and an area under the receiver-operating characteristic curve of 0.88 for the detection of advanced adenomas more proximally.<sup>43</sup>

## Pancreaticobiliary applications

OCT has also been used in the pancreaticobiliary system.<sup>44,45</sup> In an ex vivo pilot study, OCT was able to characterize features of mucinous cystic lesions with over 95% sensitivity.<sup>46</sup> A pilot study (n = 11) evaluated the use of an OCT probe passed through an ERCP catheter in the pancreatic duct and demonstrated 100% sensitivity and specificity for neoplastic or non-neoplastic pancreatic strictures.<sup>47</sup> Similarly, OCT was used to characterize features of malignancy in biliary strictures at ERCP.<sup>48</sup> Optical signatures from the periampullary duodenal mucosa have been studied in an attempt stratify patients who may be harboring pancreatic neoplasia.<sup>49,50</sup>

## AREAS FOR FUTURE RESEARCH

Further developments are under way for probe-based systems for clinical integration into endoscopy. Larger, prospective trials determining and validating performance characteristics of spectroscopy and OCT compared with histology need to be performed. Other applications of these technologies should be explored, including their use in chronic inflammatory states, detection of ischemia, and specific drug or receptor monitoring.<sup>51,52</sup> Assessments of field carcinogenesis by spectroscopy of the rectum may support a simple office-based, nonendoscopic screening test to identify which patients would benefit most from a diagnostic colonoscopy.<sup>6</sup>

Methods for teaching endoscopists how to use the technology and interpret the information need to be developed. The learning curves need to be defined. The performance characteristics of the technology with widespread use also need to be elucidated.

## SUMMARY

Initial investigations of OCT and spectroscopy are promising. Further characterization of normal and pathologic findings is required. Larger clinical trials for validation are under way for areas such as BE. The concept of exploiting the field effect for risk stratification may also be able transform current screening paradigms.

## DISCLOSURE

*The following author disclosed a financial relationship relevant to this publication: Dr Tokar received an honorarium from Olympus for participating in a conference. All other authors disclosed no financial relationships relevant to this publication.*

*Abbreviations: BE, Barrett's esophagus; OCT, optical coherence tomography; RFA, radiofrequency ablation.*

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