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REVIEW ARTICLE

Diagnostic Fiber-based Optical Imaging Catheters

Jun Young Kim, Min Woo Lee and Hongki Yoo

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Abstract
Fiber optics miniaturization and advances in signal acquisition and processing have allowed the development of fiber-based optical imaging catheters that permit instantaneous luminal organ imaging. This technique is applicable in clinical settings for diagnosing various diseases. Intravascular optical coherence tomography (IV-OCT), a catheter-based optical imaging technique, acquires high-resolution cross-sectional human coronary arterial wall imaging, enabling precise assessment of coronary atherosclerosis. OCT with a balloon-centering catheter or a tethered capsule acquires comprehensive three-dimensional images of the distal esophagus for diagnostic imaging in patients with esophageal diseases, including Barrett's esophagus. Spectrally encoded confocal microscopy (SECM), an advanced type of confocal microscopy that uses diffraction grating and a broadband laser source to laterally scan the sample without mechanical motion, has been developed as a tethered confocal endomicroscopy capsule to diagnose and monitor eosinophilic esophagitis, an allergic condition in the esophageal wall. In this review, the authors describe the recent development of fiber-based imaging catheters with rotary scanning for diagnosing various diseases in luminal organs, including the coronary artery and esophagus. Further developments, including miniaturization of optics, increased speed, and multimodal acquisition, could significantly improve diagnostic capability to improve patient care.

Keywords Optical imaging catheters, Rotary scanner, Optical diagnosis, Fiber optics

Jun Young Kim, Min Woo Lee, Hongki Yoo (✉)
Biomedical Optics and Photomedicine Lab, Department of Biomedical Engineering, Hanyang University, Seoul, South Korea
Tel : +82-2-2220-2323 / Fax : +82-2-2296-5943
E-mail : hyoo@hanyang.ac.kr

INTRODUCTION

Medical optical imaging has emerged as an effective diagnostic tool and provides many advantages over traditional radiological imaging [1]. First, optical imaging is non-ionizing, which significantly reduces safety issues for patients and physicians as well as researchers and allows for multiple serial imaging acquisitions over time [1]. This non- or minimally-invasive feature is very important for diagnostic or monitoring applications. Second, optical imaging can provide both structural and functional information with a high spatio-temporal resolution. In fact, numerous optical imaging modalities with unique functionalities are becoming available for various clinical applications [2-7]. Since each tissue has different absorption, emission, and scattering, light extracts rich information by interacting with the tissue, using broadband spectrum [8]. Third, optical imaging can provide microscopic information, which allows diagnosis and monitoring of various diseases at a cellular-level. This microscopic information can be quantified for objective analysis [2].

One fundamental limitation of optical imaging is tissue penetration depth, which can range from tens of micrometers to several centimeters depending on the imaging modality and the type of tissue, due to the strong scattering and absorption of light [9-11]. Although some researches have focused on extending the penetration depth of optical imaging, the entire human body is difficult to image and the depth is limited to the surface layers. Due to the relative difficulty of accessing the internal organs, the eyes and skin have been primary targets of various optical imaging methods [5-7, 12-14]. Endoscopy is one of the most successful internal optical imaging techniques and is widely used in clinic to diagnose gastrointestinal diseases and aid in surgical procedures. Recently, novel endoscopic imaging techniques have been developed for patient diagnosis, monitoring, and treatment, based on advances in fiber optics and lasers, development of image processing devices, and optic component miniaturization [15, 16].

Endoscopic optical coherence tomography (OCT) and confocal endomicroscopy have emerged as a clinical diagnostic tool and provide real-time optical tissue biopsy within the internal organs, such as the esophagus and coronary artery, in the procedure room [3, 4, 17-19]. Specifically, the fast imaging speed and spiral scanning that use a rotary scanner allowed full three-dimensional imaging of luminal organs, which was previously impossible due to the limited field of view of transverse scanning. Endoscopic OCT and confocal endomicroscopy with a fiber-based imaging probe, using rotary scanner, has become an important application for diagnosis, monitoring, and screening of luminal organs. In this review, fiber-based imaging catheters with rotary scanning for luminal organs will be discussed. We will specifically focus on technical advances and medical applications in cardiology and gastroenterology.

IMAGING CATHETERS IN CARDIOLOGY

Optical coherence tomography

OCT is an optical imaging technique that allows noninvasive cross-sectional imaging of internal structures in biological samples using the interference nature of light [20]. OCT is one of the most successful optical imaging techniques and is applied as a clinical diagnostic tool as well as a research technique [14, 21-23]. The early version of OCT, often referred to as time-domain OCT (TD-OCT), used mechanical scanning of the reference mirror to acquire depth information [20]. Due to this mechanical scanning, the imaging speed and the sensitivity were limited. There have been many studies focused on improving the speed of mechanical scanning, for example, using a piezo-electric crystal [24] or galvano mirror [25]. Despite these efforts, the imaging speed of TD-OCT has limited usability in various clinical applications. Fourier-domain OCT (FD-OCT), which was developed in the early 2000s, has overcome these problems. FD-OCT achieves a depth profile of the biological tissue using frequency variation of the interference spectrum that is proportional to the optical path difference instead of mechanical scanning of the reference mirror [26, 27].

OCT imaging catheters

OCT is particularly appealing for clinical imaging because it provides three-dimensional tomographic images of semi-transparent biological tissue with a high spatial resolution as well as a fast imaging speed. Combined with a fiber optics and a rotary scanning method, an OCT imaging catheter can depict the inside of luminal organs, such as the coronary artery and esophagus, thus making the OCT catheter very useful in cardiology and gastroenterology. In 1996, Tearney *et al*. developed a catheter-endoscope for OCT, which combined OCT with a miniaturized imaging catheter to image luminal organs [28]. The imaging probe was fabricated with a Gradient Index (GRIN) lens, then combined with TD-OCT by a rotary fiber scanner (Fig. 1) [25] . In the following study, *in vivo* imaging of rabbit esophagus and trachea were successfully acquired, demonstrating the feasibility of this technique in clinical applications (Fig. 2) [25].

Intravascular OCT

It was not long before the OCT catheter was applied in interventional cardiology [18, 29-32]. The first human intravascular OCT (IV-OCT) visualized coronary atherosclerotic plaques in living patients [18, 29]. Compared to intravascular ultrasound (IVUS), OCT showed significantly improved spatial resolution of approximately 10 μm [18]. In a comparison study of OCT and histology, it was demonstrated that OCT is feasible and reliable for visualizing atherosclerotic plaque morphology with a high resolution, which was sufficient for characterizing different types of plaques [30].

Intravascular optical imaging is particularly challenging

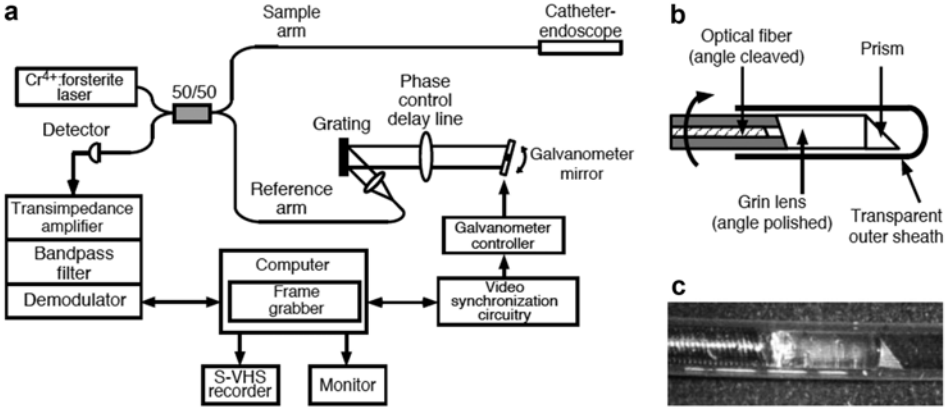

Fig. 1. (a) Schematic of the endoscopic OCT system. (b) Schematic of the OCT catheter-endoscope. (c) Photograph of the catheter-endoscope (From Tearney *et al*. [25]; with permission).

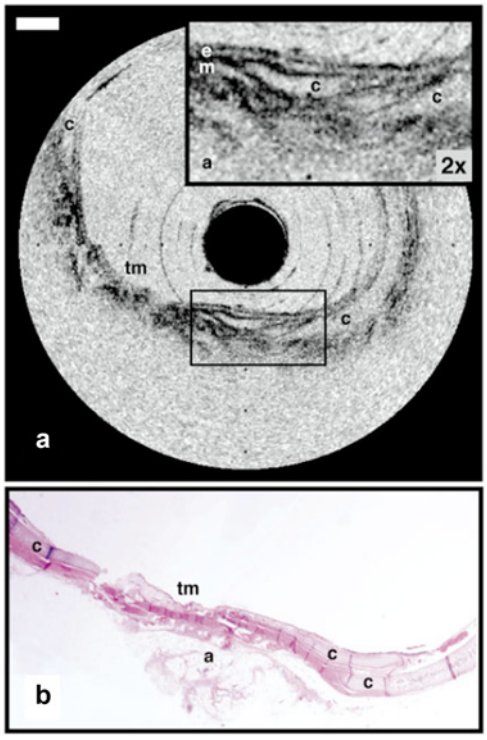

Fig. 2. (a) OCT image of a rabbit trachea. (b) Corresponding histology (From Tearney *et al*. [25]; with permission).

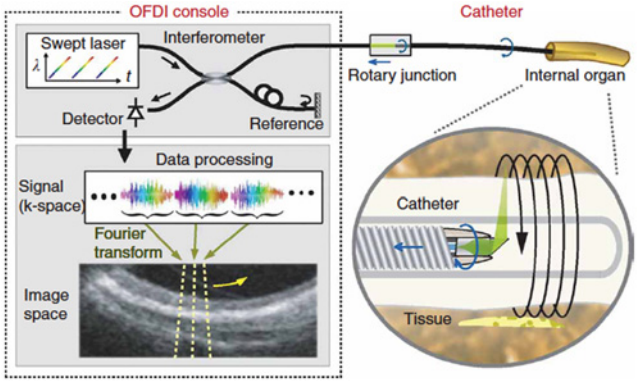

Fig. 3. Schematic of the endoscopic OFDI system. (From Yun *et al*. [33]; with permission).

because blood in the vessel causes light to scatter and degrades coherence. The solution to this problem is temporarily removing blood from the imaging region by injecting saline or a contrast agent [18]. However, due to the low imaging speed of TD-OCT (4 to 8 frames per second), imaging long vessel segments was very challenging. Endoscopic FD-OCT with a faster imaging speed resolved this problem and enabled comprehensive volumetric imaging [33]. With a 90-fold increase in imaging speed, an approximately 30-fold increase in A-line acquisition rate and a 3-fold increase in ranging depth compared to conventional TD-OCT, this IV-

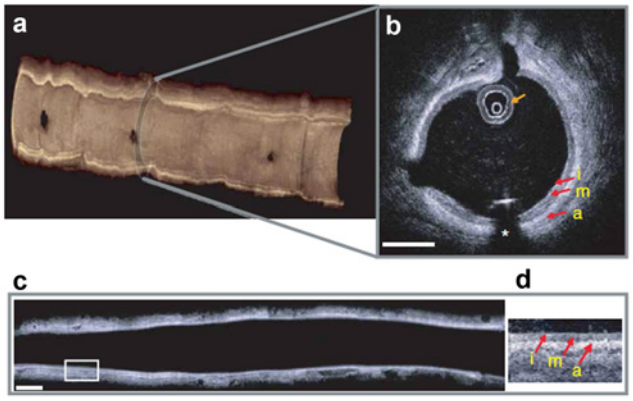

Fig. 4. OFDI image of a porcine coronary artery *in vivo* (a) Volumetric cut-away of the right coronary artery. (b) Cross-sectional imaging at the denoted area. (c) A longitudinal section of volumetric imaging. (d) Magnification of the boxed area in c (From Yun *et al*. [33]; with permission).

OCT system used helical scanning to acquire three-dimensional microscopic images of swine coronary arteries *in vivo* (Figs. 3 and 4) [33]. The first trial in human patient using this technology demonstrated volumetric imaging of coronary wall microstructures, including stent struts and lipid core, without balloon occlusion and was completed within a few seconds [3]. IV-OCT has emerged as a useful clinical diagnostic tool and has enabled numerous clinical research approaches in interventional cardiology [19, 34-36].

Recent technical advances in IV-OCT

There have been many technical advances for improving IV-OCT performance, such as improving the image acquisition rate [37, 38], reducing motion artifacts [39], and three-dimensional visualizing technique [40]. The IV-OCT imaging rate has been improved by up to 350 frames per second, using a high-speed wavelength-swept laser and a high-speed fiber optic rotary junction, either to shorten the imaging time, which maintains longitudinal resolution, or to improve the longitudinal imaging pitch with a given imaging time (Fig. 5) [38]. Combining a micro-motor with the imaging probe is a good approach for helical scanning, because it could solve some technical difficulties in the rotary junction system, such as non-uniform rotational distortion and insertion loss, and it can also significantly increase the scan speed [37, 41-43]. Shadow artifacts due to electrical wires are problems that remain unresolved [37]. In addition to image acquisition speed improvement, there was a study on motion compensation utilizing the Doppler Effect by integrating wavelength division multiplexed monochromatic beams with an IVOCT imaging catheter to compensate for a distortion caused by cardiac motion [39]. Three-dimensional rendering of OCT data could allow clear visualization of complex vessel anatomy, such as stent fracture [40] and spontaneous coronary artery

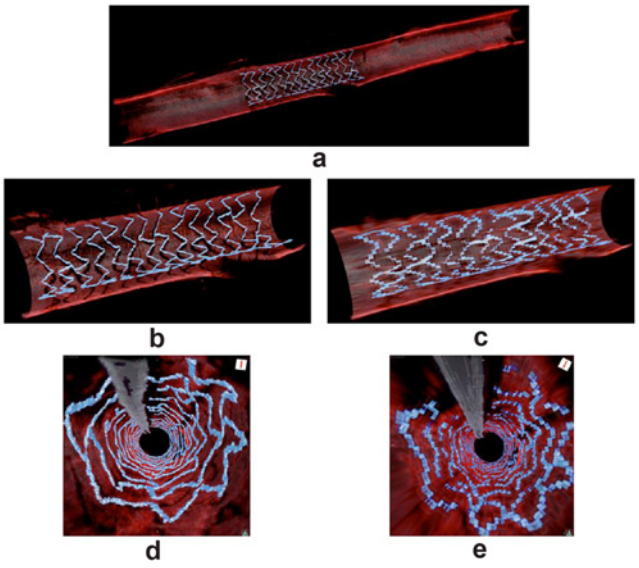

Fig. 5. Three-dimensional, volume-rendered intravascular OFDI images. (a) Longitudinal cutaway view of a 45-mm-long rabbit aorta. (b) Longitudinal cutaway view with 34-μm longitudinal pitches with a high frame rate system. (c) 200-μm longitudinal pitches with a conventional frame rate system. (d) Fly-through view with 34-μm longitudinal pitches (d) 200-μm longitudinal pitches (From Cho *et al*. [38]; with permission).

dissection [44]. An image processing algorithm for OCT to automatically detect stent struts and vessel lumen, or to assess stent coverage may provide useful information for understanding stent pathology [45-47].

Multimodalities in IV-OCT

OCT acquires microstructural information from blood vessels, such as thin fibrous cap, lipid pool and macrophage accumulation [3]. Although OCT provides morphological information required for diagnosing coronary artery disease (CAD), stand-alone OCT is limited for complete assessment of plaque [48-50]. To accurately understand progression and pathophysiology of CAD, it is necessary to determine not only morphological information, but also molecular information, which cannot be acquired by OCT alone [48, 49]. There are also some morphological ambiguities in OCT images, which cause difficulties in interpretation [50]. Also, OCT has limited penetration depth due to the strong scattering and absorption. To compensate the OCT limitations, complementary imaging modalities are needed [50-55].

Near infra-red fluorescence (NIRF) imaging can provide molecular or compositional information of atherosclerotic plaque, such as macrophage activation and necrotic lipid core presence [48, 49, 56]. Yoo and Kim *et al*. [48] reported an integrated OCT-NIRF catheter system comprising a double-clad fiber (DCF), dichroic mirror and optical filters (Fig. 6). Intravascular imaging was conducted on a rabbit atherosclerosis model with a cysteine protease-activatable NIRF agent *in vivo*. The integrated system simultaneously showed microstructure and inflammatory enzyme activity. In another study, OCT was integrated with NIRF using a wavelength division multiplexer (WDM) and a DCF combiner [43]. They performed *ex vivo* imaging on atherosclerotic rabbit aortas with Annexin V-conjugated Cy 5.5, which targets macrophage accumulation, and simultaneously showed blood vessel microstructure and macrophage activation. Recently, Lee, *et al*. [49] reported an integrated OCT-NIRF imaging technique *in vivo* with indocyanine green (ICG), which is the only FDA-approved NIRF dye and specifically bonded to lipids and macrophages [57]. *In vivo* structural/molecular imaging of lipid-rich inflamed plaque has been demonstrated using ICG (Fig. 7), bringing the multimodal intra-vascular imaging technique one step closer to clinical applications.

Near infra-red spectroscopy (NIRS) acquires molecular

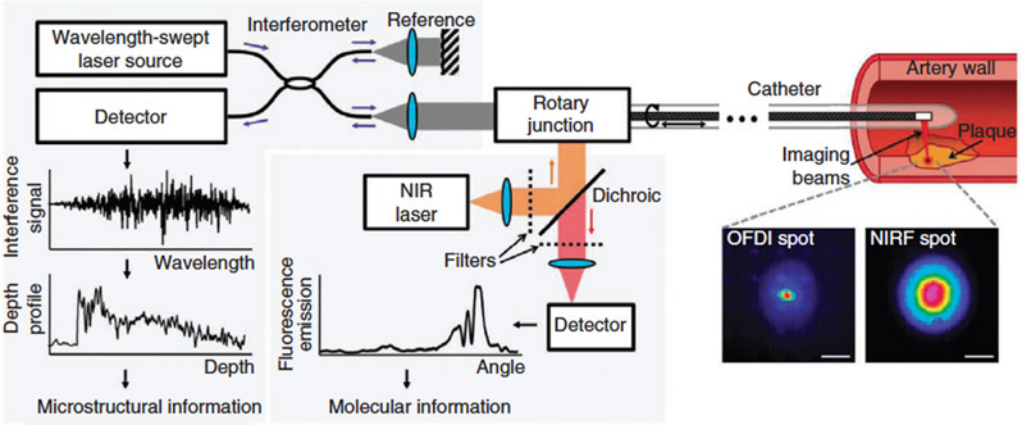

Fig. 6. Schematic of the integrated OFDI-NIRF catheter for microstructural and molecular imaging. OFDI and NIRF systems are combined in one system by a dual-modality rotary junction that contains a dichroic mirror and optical filter (From Yoo *et al*. [48]; with permission).

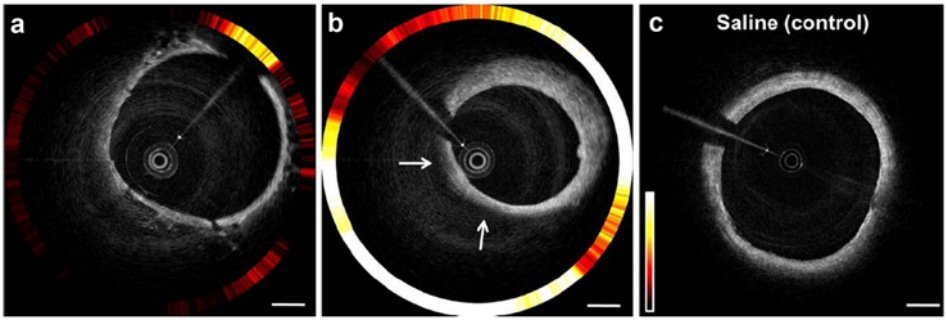

Fig. 7. Structural/molecular cross-sectional images of an atherosclerotic rabbit artery *in vivo*. OCT/NIRF cross-sectional images of the aorta (a) at a normal portion with ICG, (b) at a plaque portion with ICG, (c) at a plaque portion with saline (From Lee *et al*. [49]; with permission).

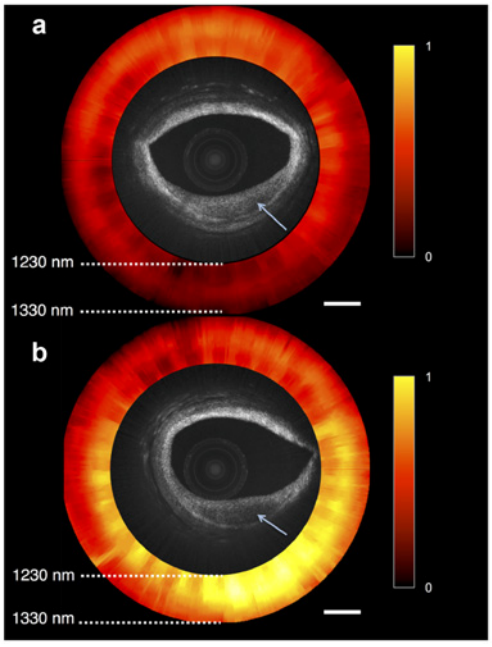

Fig. 8. Structural-compositional cross-sectional images of cadaver coronary artery *ex vivo*. Although both OCT images seem similar, they show different NIRS signals. (b) indicates the presence of high lipid; however, (a) does not (From Fard *et al*. [50]; with permission).

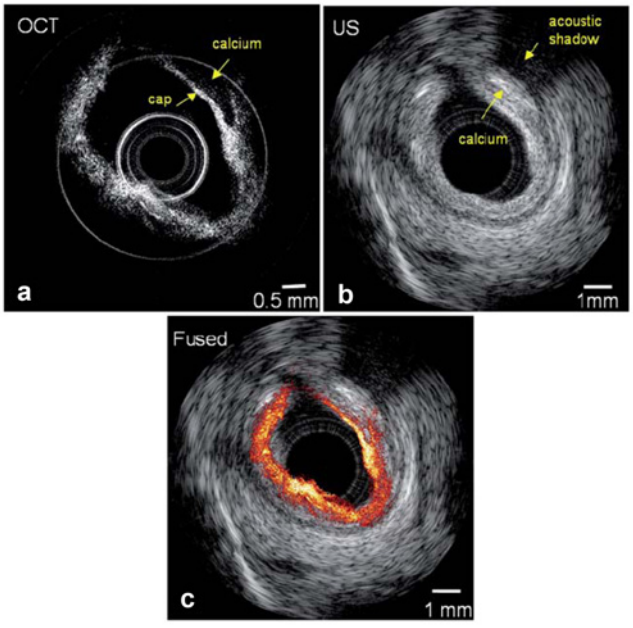

Fig. 9. Cross-sectional images of (a) OCT, (b) IVUS, and (c) integrated OCT-IVUS on a human coronary artery *ex vivo* (From Yin *et al*. [60]; with permission).

and compositional information by analyzing the spectrum that returns from the tissue. NIRS combined with intravascular ultrasound (IVUS) has been successfully translated into clinical applications to image high-risk plaques [58]. A combined OCT-NIRS system was designed by Fard *et al*., using a double clad fiber coupler (DCFC) and a separated collection part of NIRS from OCT using a DCF combiner to enable deeper imaging [50]. They carried out cross-sectional imaging on human coronary arteries *ex vivo*, demonstrating that portions showing similar morphologic features in OCT images are distinguished by NIRS, which provides information about the presence of lipids (Fig. 8). This deep penetration of NIRS could overcome the OCT penetration issue by providing lipid information from deeper tissue portions.

Fluorescence lifetime imaging microscopy (FLIM) provides biochemical tissue information by measuring the fluorescence temporal decay. An integrated OCT-multispectral FLIM system was reported by Park *et al*. [55]. They performed microstructure and biochemical B-scan imaging *ex vivo* on a longitudinally opened human coronary artery. Collagen and lipid were distinguished by FLIM and a lifetime map was overlaid on 3D OCT rendering images. Also, an intravascular catheter that combines multispectral FLIM and IVUS has been reported to show the feasibility of mapping biochemical features provided by FLIM on structural features provided by IVUS [59].

Although IVUS and OCT both provide structural information about tissue, they are complementary because IVUS has a

deep penetration with a poor resolution and OCT has excellent resolution with limited penetration; therefore, IVUS combined with OCT could provide complementary information for diagnosing CAD. Yin *et al*. reported the first integrated intravascular OCT-IVUS system [51]. Simultaneous cross-sectional OCT-IVUS images of rabbit arteries *in vitro* demonstrated both micro-scale and deep tissue imaging via an integrated OCT-IVUS system [51-53]. Additional studies have demonstrated OCT-IVUS imaging of rabbit abdominal aorta *in vivo* and human coronary arteries *in vitro* [54, 60] (Fig. 9).

IMAGING CATHETERS IN GASTROENTEROLOGY

Upper endoscopy

The current standard of care includes endogastroduodenoscopy (EGD), also called upper endoscopy, and pinch biopsy of at-risk tissue for upper gastrointestinal (GI) disease screening, diagnosis, and monitoring. This includes the esophagus, stomach, and duodenum. However, biopsy incorporates significant random error since the samples are taken without knowledge of the presence of disease and the whole affected area cannot be examined [61, 62]. To minimize random error and the risk of missing a lesion, a systematic approach is used to diagnose GI disease that involves multiple excessive biopsies [63]. Because a high number of repeated endoscopes and biopsies are often used to manage GI diseases, less invasive and more cost-effective methods could significantly improve patient care.

OCT imaging catheters in gastroenterology

Since the first invention of the *in vivo* OCT catheter-endoscope [25] and the application for human patients (Fig. 10) [23, 64], the technology has been extensively developed for diagnosing esophageal tissues, including developing an algorithm for image analysis [65], adapting the FD-OCT for faster and more sensitive imaging [33], and combining a balloon-centering catheter for comprehensive imaging [66]. Because the clinical study has successfully shown that the comprehensive microscopic imaging of the whole distal esophagus can be performed safely with a balloon catheter-based OCT (Fig. 11) [67-69], this technology has become a strong candidate for monitoring and screening Barrett's esophagus. Recently, NinePoint Medical has launched an OCT balloon-based imaging catheter to evaluate esophageal tissue microstructure (www.ninepointmedical.com/).

To incorporate the large diameter of esophagus, which is approximately 20 mm, a balloon-centering sheath has been used in many studies to maintain the luminal tissue within the imaging range (Fig. 12) [33, 66, 67, 70-72]. Additionally, GRIN lens-based fiber-optics with a micro-prism has been used to fabricate the imaging core (Fig. 13) [23, 25, 33, 66,

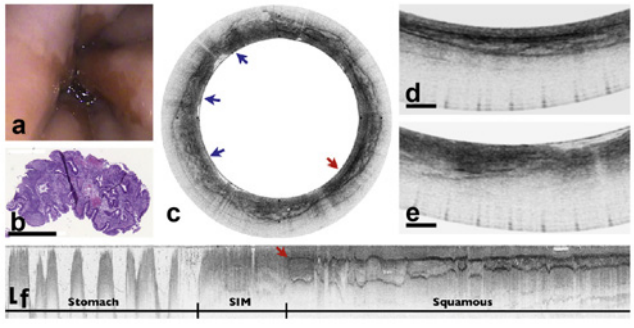

Fig. 10. Barrett's esophagus. (a) Endoscopic view demonstrating irregular squamocolumnar junction. (b) H&E section of a biopsy demonstrates Barrett's esophagus. (c-e) Cross-sectional OCT image shows normal squamous mucosa (red arrow, expanded in d) and Barrett's esophagus (blue arrows, expanded in e). (f) Longitudinal section across the gastroesophageal junction showing the stomach, Barrett's and normal squamous mucosa. Scale bars, 1 mm (From Suter *et al*. [67]; with permission).

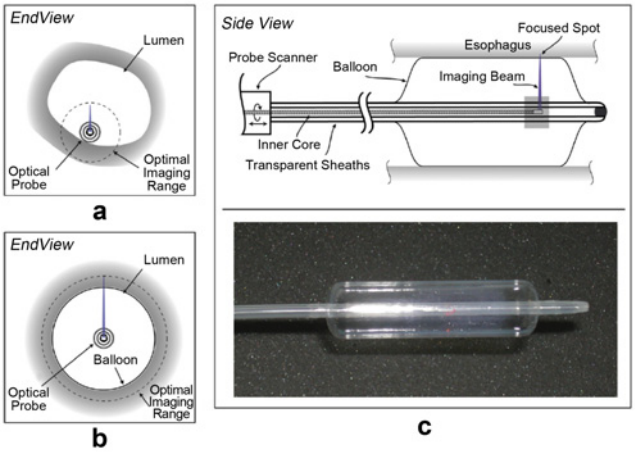

Fig. 11. The balloon-centering imaging catheter. (a) Field of view is limited due to centering offset and irregular lumen shape. (b) A balloon-centering catheter allows full circumferential imaging of the esophagus. (c) Schematic and picture of the balloon catheter (From Vakoc *et al*. [66]; with permission).

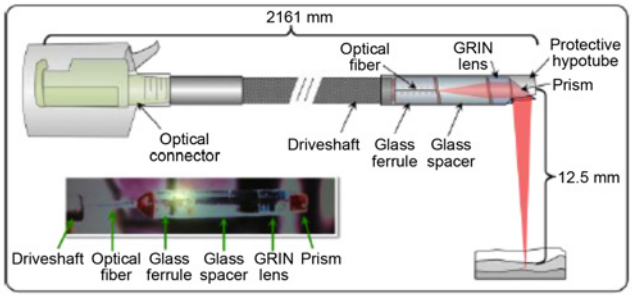

Fig. 12. Schematic and a picture of the optical imaging core for OCT (From Gora *et al*. [71]; with permission).

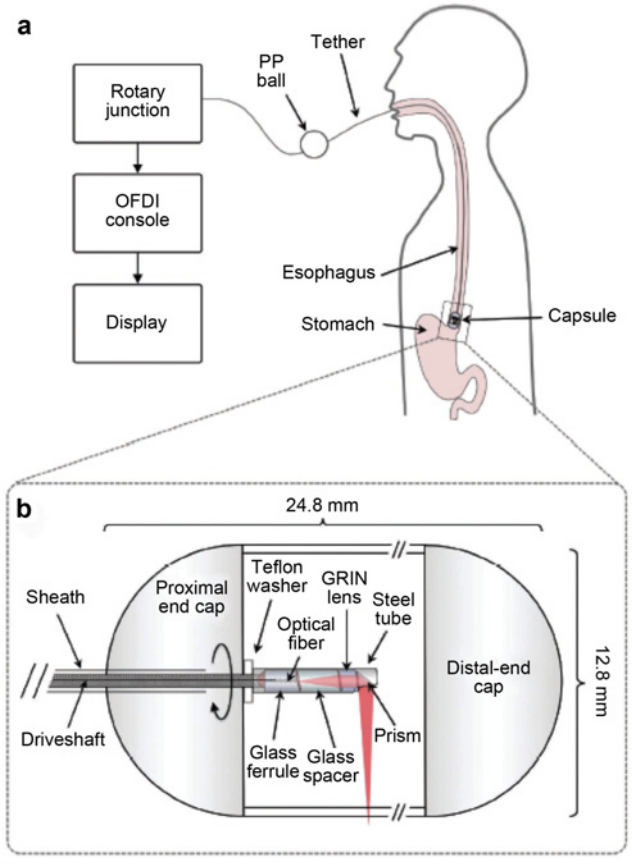

Fig. 13. Tethered capsule endomicroscopy for OCT. (a) The capsule is attached to a tether that contains an optical fiber. The capsule is swallowed by a patient and the capsule's location is controlled by the tether. The OCT image of the esophageal wall is collected by the OCT system. (b) Schematic of the imaging capsule. Imaging core containing a GRIN lens and a prism acquires three-dimensional volumetric images with helical scanning provided by a driveshaft (From Gora *et al*. [80]; with permission).

67, 71], which provides a long working distance compared to ball lens-based imaging probes. To minimize the influence of astigmatism induced by the sheaths, a cylindrical lens was used to correct aberrations [66, 73-75].

One concern regarding imaging through the balloon sheath is the influence of pressure on tissue morphology. To study this issue, a double-balloon endoscopic OCT catheter has been developed and tested in human patients [73]. During the image acquisition, there is significant motion interference due to the physiology, including respiration and heart beats. An automated registration algorithm improved the visualization by suppressing image distortion [76]. Additionally, ultrahigh speed imaging is appealing because it reduces imaging time and motion artifacts. Recent development of VCSEL technology combined with a micro-motor was applied *in vivo* 3D-OCT imaging in the rabbit gastrointestinal tract and has demonstrated a frame rate of 400 fps [72]. These technical advances could promote a wide range of clinical

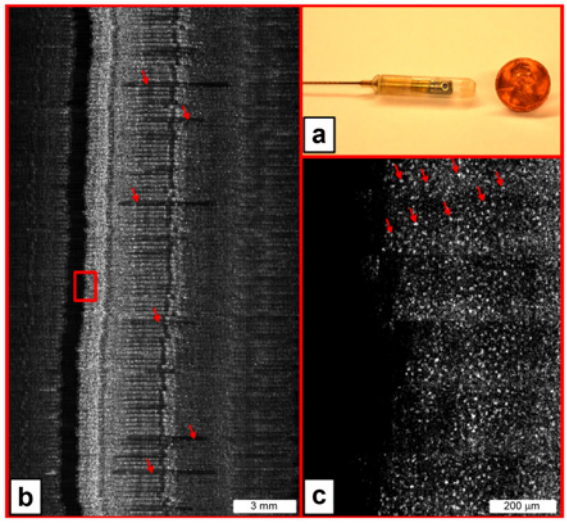

Fig. 14. (a) Photograph of the SECM tethered capsule. (b) Large-area SECM image of swine esophagus *in vivo*. (c) Magnified image of the red rectangular area in the panel. (b) Nuclei of epithelial cells (arrows) (From Tabatabaei *et al*. [88]; with permission)

applications. In a clinical pilot study, the 3-D endoscopic OCT successfully acquired microstructural images of colon tissue and showed an ability to distinguish normal from pathologic colorectal tissue [77]. In a pre-clinical study using a murine model, OCT was utilized to obtain esophageal images for differentiating esophageal sub-layers and monitoring structural changes, which could potentially be applied to eosinophilic esophagus, an allergic disorder in the esophagus [78].

More recently, tethered capsule endomicroscope that incorporates high-speed OCT has been developed [79, 80]. Tethered capsule endoscopy, which consists of an easy-to-swallow capsule and a cable that contains optic fibers and electric wires, is an attractive alternative technology for esophageal disease screening because of its performance and cost-effectiveness [81]. The tethered capsule endomicroscope with an OCT imaging core can be easily swallowed to provide rapid microstructural tissue images of the upper GI tract in a simple procedure and does not require sedation (Fig. 14) [80].

Imaging catheter for microendoscopy

A major drawback of OCT in GI imaging is low-spatial resolution on the order of 10 μm, which is not sufficient for detecting cellular and sub-cellular changes, crucial aspects of accurate diagnosis. Confocal microendoscopy is an attractive tool for sub-cellular imaging of GI tissue, since it generates micron-resolution images [17, 82, 83]. However, this optical-biopsy technology is subject to random sampling error, similar to the EGD followed by pinch biopsies [84]. Spectrally encoded confocal microscopy (SECM) has been

introduced to overcome this problem [84, 85]. SECM is a type of confocal microscopy that uses a diffraction grating to simultaneously detect multiple reflection signals from the tissue along a transverse line by laterally dispersing broadband light [85]. Since mechanical scanning, which limits the imaging speed, can be eliminated in one direction, image acquisition is much faster than conventional confocal imaging method. This feature enables comprehensive large-area imaging of biological tissue with microscopic resolution [62, 84, 86]. Endoscopic SECM probes have been developed for imaging large areas of the esophagus *ex vivo* and *in vivo* at the cellular scale [61, 87], demonstrating the feasibility of comprehensive microscopic imaging of a large area esophageal tissue. In this study, helical scanning, similar to IV-OCT, was adopted to scan the esophagus. Recently, an SECM capsule has been developed for diagnosing and monitoring eosinophilic esophagitis (EoE) in unsedated patients [88]. In this study, eosinophils were clearly visualized from a biopsy sample taken from an EoE patient, and microscopic cellular features were clearly delineated in SECM images of swine esophagus mucosa *in vivo* [88].

CONCLUSIONS

Optical biopsy, enabled by miniaturized endoscopic imaging of tissue at a cellular resolution, could impact and improve patient care strategies. We have discussed high resolution imaging techniques, including OCT and SECM, combined with helical scanning, which have emerged as diagnostic tools for luminal organ imaging, such as the coronary artery and esophagus. By providing cellular-resolution images from intact tissue *in vivo*, optical imaging catheters acquire valuable information regarding disease diagnosis, particularly in cases where biopsies are impossible or very risky. Additionally, comprehensive imaging within a short time enables entire luminal organ scanning, thus eliminating the sampling error associated with random biopsies. Several aspects of these optical imaging catheters are still being developed. A higher imaging speed is needed for screening entire organs and further miniaturization of imaging optics helps minimally invasive diagnosis. Multimodal imaging for complete lesion assessment might provide a better understanding of disease. Finally, more clinical data should be assessed and updated to support the clinical benefits of using these novel diagnostic tools, which could greatly impact clinical practice.

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CONFLICT OF INTEREST STATEMENTS

Kim JY declares that s/he has no conflict of interest in relation to the work in this article. Lee MW declares that s/he has no conflict of interest in relation to the work in this article. Yoo H declares that s/he has no conflict of interest in relation to the work in this article.

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