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Feasibility of optical coherence tomography for high-resolution imaging of human gastrointestinal tract malignancies

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Abstract: Optical coherence tomography (OCT) is a new imaging technology which can perform high-resolution, cross-sectional imaging of the internal microstructure of biological tissues. OCT is analogous to ultrasound, except that it measures the intensity of back-reflected infrared light rather than sound waves. OCT performs two- and three-dimensional imaging of tissue microstructure in situ and in real time. It can achieve image resolutions approaching the cellular level over approximately the same imaging depths as a conventional biopsy. In this article we examine the feasibility of OCT for high-resolution imaging of gastrointestinal malignancies with ex-vivo imaging of normal and pathologic microstructures. Tissue, both normal and neoplastic, was obtained from patients undergoing surgical resection after an initial diagnosis of a gastrointestinal malignancy. The tissue samples were imaged prior to fixation using a laboratory OCT system. The OCT system consists of a fiber optic-based Michelson interferometer, a commercially available amplified superluminscent light source, and a computer for data acquisition. The images were subsequently compared with histological cross-sections corresponding to the imaged areas. The stratified squamous epithelium of the normal esophagus was clearly visible in the OCT images and contrasted to the disorganized and non-uniform nature of the mucosal layers of Barrett's esophagus and squamous carcinoma. The columnar epithelial morphology as well as other mucosal structures in normal colon were distinctly visible using OCT. In contrast, disorganization of the normal mucosal layers and ulcerative lesions were identified in tissues from ulcerative colitis and adenocarcinoma of the colon. The ability of OCT to image tissue microstructure at high resolutions makes it a potentially powerful technology for minimally invasive assessment of the gastrointestinal tract and the evaluation of early neoplastic changes.

Key words: optical coherence tomography adenocarcinoma, gastrointestinal cancer, endoscopic ultrasound, Barrett's esophagus

Introduction

The endoscopic diagnosis and management of gastrointestinal malignancies has advanced considerably over the past two decades, offering patients better management and more treatment alternatives.[1] High-resolution video endoscopy using distal charge coupled devices provides image resolutions that are impossible or prohibitively expensive to achieve using fiber bundle endoscopes.[2] Endoscopic ultrasonography provides information on tissue structure and pathology complementary to endoscopic image information.[3–5] However, many diseases, such as early neoplastic changes, remain beyond the resolution limit of these approaches. The dysplasia associated with esophageal columnar metaplasia (Barrett's esophagus) for example, can go undetected with conventional endoscopy and ultrasonography.[4] The early stages of colon adenocarcinoma can also present with microstructural changes below the resolution limit of these imaging modalities.[5] A technology capable of imaging the gastrointestinal tract, at or near the cellular level, could lead to the detection of pathology at earlier stages than is currently possible. The current clinical technology with the greatest resolution is high-frequency ultrasound (20 MHz) with a resolution of approximately 110 μm. Impressive results have

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been obtained with high-frequency ultrasound imaging demonstrating an ability to differentiate mucosal from submucosal invasion.[6,7] However, image resolutions are not high enough to identify epithelial or other microstructural morphology. Optical coherence tomography (OCT), a recently developed imaging technology which has been shown to achieve resolutions approaching the cellular range (4–20 μm), with imaging depths which are comparable to conventional biopsy (2–3 mm), could improve the diagnostic capability of clinical imaging procedures.[8,9]

OCT is analogous to ultrasound, except that it measures the intensity of back-reflected infrared light rather than sound waves. OCT was first applied to image optically transparent structures such as the anterior eye and retina.[10,11] Subsequent advances have enabled high-resolution imaging in nontransparent tissue, including the identification of pathology in the cardiovascular system, gastrointestinal tract, skin, and nervous system.[12–14] Recently, in-vivo endoscope/catheter-based imaging has been performed (at 4–8 frames/s) of the rabbit gastrointestinal tract, respiratory tract, and circulatory system.[16,17] In addition to its high resolution, several features of OCT suggest that it will be a powerful imaging technology for the diagnosis of a wide range of gastrointestinal pathologies. First, imaging can be performed in situ and in real time in conjunction with endoscopy, allowing pathology of the gastrointestinal tract to be monitored on screen and stored on high-resolution videotape. Second, OCT is compact and portable, an important consideration for a clinically viable device. Third, unlike ultrasound, imaging with OCT can be performed directly through air without requiring direct contact with the tissue or a transducing medium, and contrast-enhancing agents are not required. Finally, OCT is fiber optic-based, allowing imaging to be performed using small OCT endoscopic accessories (approximately 1-mm diameter) which fit through the biopsy channel of a standard endoscope.

In this article we examine the feasibility of OCT for high-resolution imaging of gastrointestinal malignancies. In addition to normal tissue, we examined pathologic microstructures ex-vivo at a resolution higher than that with any currently available, non-invasive clinical, imaging technology. OCT images were correlated with histopathology to confirm tissue identity.

Methods

The principles behind OCT have been previously described.[8,17] Imaging is performed by directing low-coherence light at the sample and detecting reflections from various internal structures, in analogy to ultrasound. However, unlike ultrasound, the speed of light is very high, making direct electronic measurement of the echo delay time of the reflected light impossible. Therefore, a technique known as low-coherence interferometry is used to measure the intensity of light backscattered from within the tissue. The origin of the backscattered light is localized by measuring the interference pattern of that light with light that has traveled the same distance in a reference arm. Two- or three-dimensional images are produced by scanning the beam across the sample and recording the optical backscattering versus depth at different transverse positions. A laboratory system, similar to the one shown in Fig. 1, was used for the acquisition of the images presented.

The axial resolution of OCT is determined by the coherence length, a statistical property of the light source. The coherence length of the light, and therefore the axial resolution, is also inversely proportional to the bandwidth, or distribution of wavelengths of the light. The images presented here were obtained using a commercially available amplified superluminescent light source (AFC Technologies, Hull, PQ, Canada) which had a center wavelength of 1310 nm and a bandwidth of 50 nm, resulting in a 15-μm axial image resolution. This wavelength in the near-infrared is close to a minimum in tissue absorption and scattering and enables image penetration depths of 2–3 mm. The transverse resolution is limited by the optical focussing characteristics of the delivery system on the specimen. More specifically, the transverse resolution is determined by the wavelength and the numerical aperture of the focussing of the incident light, as in conventional microscopy. The combination of focussing optics and beam size used for the experiments reported here resulted in a 30-μm transverse resolution.

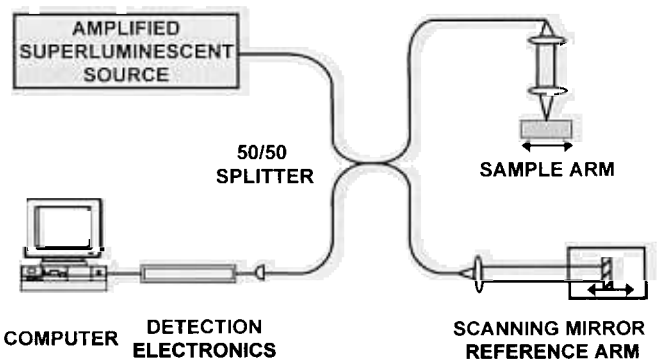

Fig. 1. Schematic of the fiber optic implementation of the optical coherence tomography (OCT) system. High-resolution measurements of intensity of backscattered light are performed using a low-coherence length light source and fiber optic intereferometer. Two-dimensional cross-sectional images are generated by scanning the light beam in the transverse direction while measuring backscattering intensity versus delay (distance)

Tissue, both normal and neoplastic, was obtained from surgically excised specimens and was imaged fresh, prior to fixation, which might change optical properties. Samples were obtained from 14 patients and included tissue from normal (3 samples), Barrett's (2 samples), and squamous carcinoma (2 samples) of the esophagus, as well as normal colon (2 samples), ulcerative colitis (1 samples), and adenocarcinoma of the colon (4 samples). The specimens were placed in a Petri dish and irrigated with isotonic saline to prevent dehydration during imaging. Imaging was performed using a laboratory system similar to the one shown in Fig. 1. The acquisition of each image required between 10 and 30s depending on the size (number of pixel elements) of the image. Since the OCT beam is invisible, tissue registration was performed using a coincident, visible-light, guiding beam. The orientation of the OCT imaging scan was marked on the specimen, using a micro-application of India ink. The slight mismatch between histology and OCT imaging planes, as well as changes in physical dimensions of the tissue associated with fixation and sectioning, account for the minor differences which were observed between the OCT images and histology. After the OCT imaging, samples then underwent routine histologic processing. Specimens were immersed in 10% buffered formalin for 48h. The tissues were then processed for standard paraffin embedding. Five-micron-thick sections were cut at the marked imaging sites and stained with hematoxylin and eosin. The stained histologic sections enabled verification of tissue identity and allowed identification of sources of tissue contrast in the OCT images.

Results

The stratified squamous epithelium of the normal esophagus is clearly visible in the OCT images. It presents as a uniform, highly backscattering layer, as would be expected for that epithelial structure. The lamina propria appears loose and less optically backscattering. Blood vessels in the lamina propria are also identified in the OCT images (Fig. 2A). In the tissue of esophageal metaplasia (Barrett's esophagus), the uniformly layered structure is destroyed and is instead replaced by columnar epithelium (Fig. 2B). OCT images of Barrett's esophagus clearly demonstrate the disorganized and non-uniform nature of the mucosal layers. Lymphoid aggregates are also visible. Squamous cell carcinoma of the esophagus can also be visualized using OCT. The tumors appear as abnormal growths that interrupt the normal structure of the esophageal layers. The formation of malignant cell nodules is evident in the OCT images (Fig. 2C).

Imaging of the colon produced distinct images of the layers characteristic of the colonic microstructure. The mucosa of the normal colon is clearly visible. Ordered, narrow crypts and villi are present, as expected and confirmed by histology. The submucosa appears as a loose, less optically backscattering layer (Fig. 3A). In contrast, destruction of the normal mucosal layers and ulcerative lesions were identified in ulcerative colitis (Fig. 3B). In early cancer, OCT was able to detect changes in the mucosal/submucosal microstructure. The crypts were more dilated and disorganized, sharply contrasting to the appearance of normal colon described previously (Fig. 3C).

Discussion

This study suggests the feasibility of OCT for imaging neoplasias of the gastrointestinal tract. Significant differentiation of structures, including the epithelium, crypts, supportive tissue, and tumors was observed. The demonstration of fiber optic, endoscope-based real-time OCT in vivo in an animal model suggests the feasibility of applying this technique to the human gastrointestinal tract.[17] By integrating OCT with endoscopes, the gastrointestinal surface could be scanned and pathology imaged in situ at high resolution and in real time.

OCT could be used to provide adjunct diagnostic information to conventional endoscopy by imaging the internal microstructure to assess dysplasia in lesions identified endoscopically. It is unclear if an imaging technology such as OCT would be cost-effective for screening the general patient population for early neoplasias. However, future applications of OCT might be identified in screening high-risk patient populations. Such target populations could be patients who have been diagnosed with esophageal metaplasia. These patients have at least a 30-fold increased chance of developing adenocarcinoma of the esophagus compared with the general population.[18] By using OCT to guide conventional biopsy, sampling errors can be reduced, and higher sensitivity may be achieved using fewer biopsies to identify areas of dysplasia, thus increasing the diagnostic yield of endoscopy and histology.[19] Furthermore, in analogy with endoscopic ultrasound, OCT could aid in identifying the invasion depth of early neoplasias and in monitoring response to therapy.

Improvements in endoscope design, acquisition rates, and resolution are necessary to transform the current OCT system into a viable clinical device. The prototype catheter/endoscope used in previous in-vivo animal studies is 1mm or 2.9-French in diameter. This is small enough so that it may be inserted through the 2.8-mm biopsy channel of conventional flexible endoscopes,

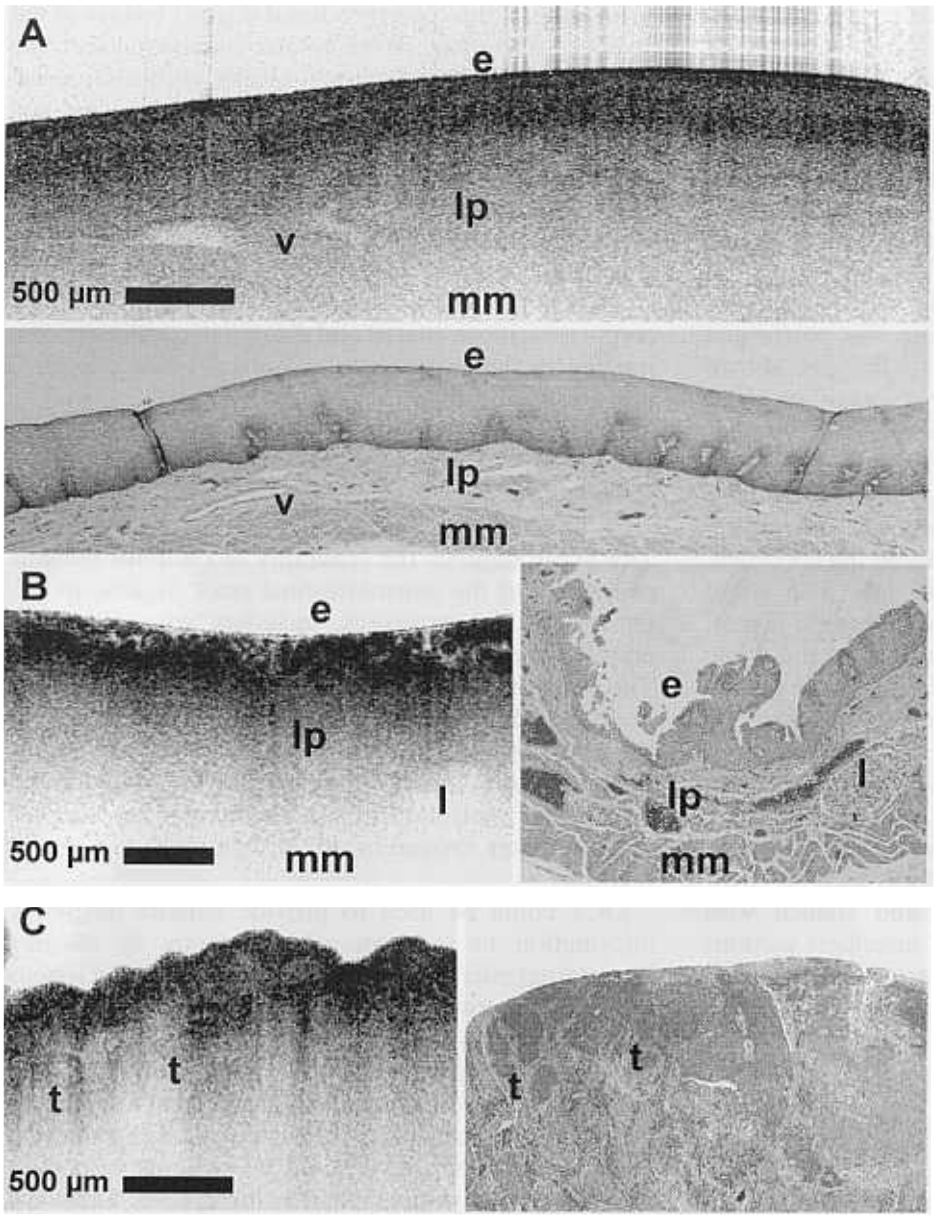

Fig. 2A–C. OCT images and associated histology of **A** normal esophagus, **B** Barrett's esophagus, and **C** esophageal cancer. The epithelium (*e*), lamina propria (*lp*) and muscularis mucosae layers (*mm*) are visible in **A** and **B**. Vessels (*v*), lymphoid aggregates (*l*), as well as tumor nodules (*t*) are also present. Resolution, 15-μm axial × 30-μm transverse

thus permitting imaging without modification of endoscope design. Transverse scanning, as well as linear scanning devices, can be developed, in analogy with endoscopic ultrasound.[7] Used as an accessory, the OCT device requires only an optical fiber and passive light-directing elements, making it relatively inexpensive. The optical delivery and scanning system may also be integrated directly into the endoscope in a manner analogous to endoscopic ultrasound. Finally, in contrast to ultrasound, OCT imaging is performed with light instead of sound, so direct contact of the tissue or fluid filling of the lumen is not required.

While the images presented here were performed with a laboratory OCT system with image acquisition times of several seconds, OCT imaging at acquisition rates of 4–8 frames per s for 256 to 512 transverse pixel images has been demonstrated.[12] These imaging speeds are comparable to those in conventional endoscopic ultrasound and should be sufficient to minimize motion artifacts in-vivo. Higher acquisition rates approaching video rates can be achieved with engineering modifications to the system. The 15-μm resolution of images used in this study allows imaging of tissue microstructure but does not allow subcellular imaging to be performed. The ability to identify individual cells and to assess subcellular structures such as the nuclei would be useful in the assessment of a wide range of neoplastic disorders. Recently, in-vivo cellular level OCT imaging

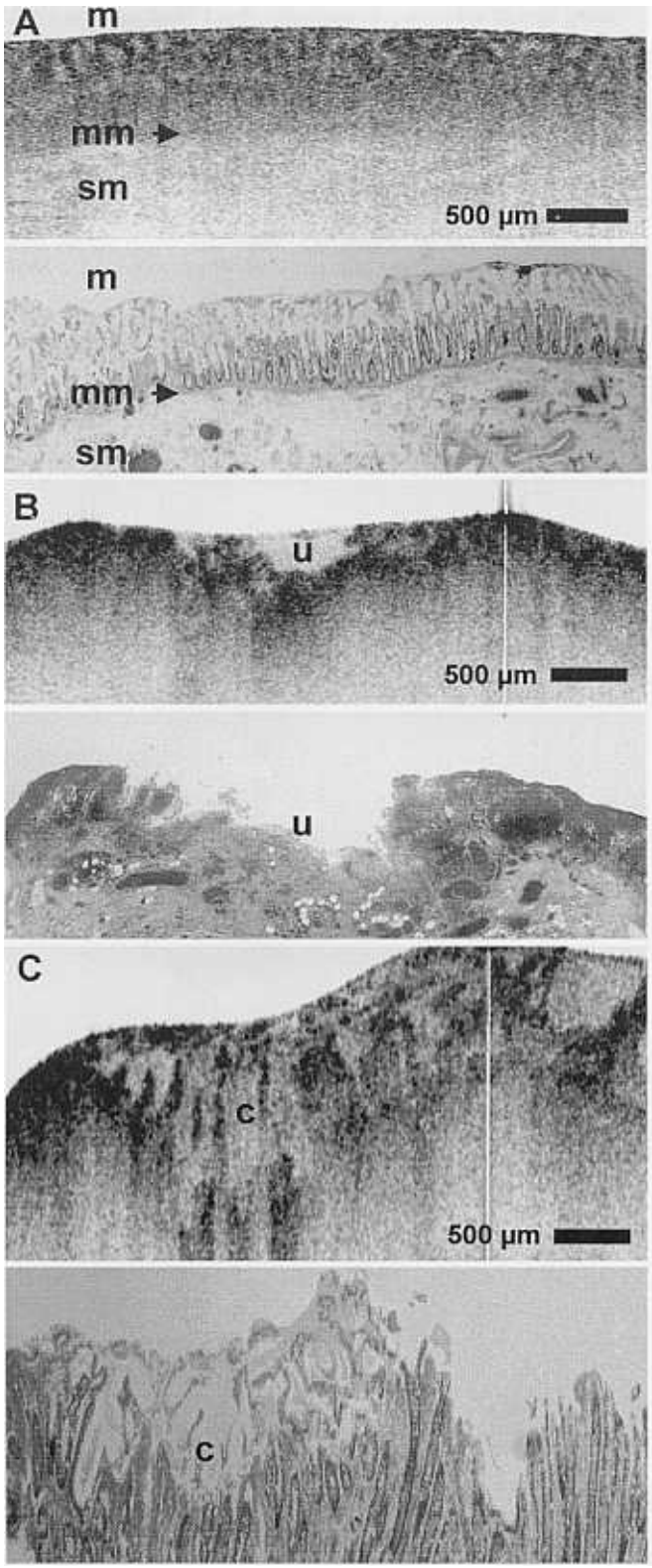

Fig. 3A–C. OCT images and associated histology of **A** normal colon, **B** ulcerative colitis, and **C** adenocarcinoma of the colon. The mucosal (*m*), muscularis mucosal (*mm*), and submucosal (*sm*) layers of the normal colon are identifiable in the OCT images. Ulcerative lesions (*u*) were identified in specimens of ulcerative colitis. Dilated and disorganized crypts (*c*) are present in specimen of colon carcinoma. Resolution, 15 × 30 μm

in developmental biology specimens has been demonstrated, using a solid-state laser light source.[9] Although additional advances are required to demonstrate cellular level imaging in humans, further improvements in technology and performance may be expected in the future.

The ability of OCT to image tissue microstructure in situ and in real time makes it a potentially powerful technology for minimally invasive assessment of the gastrointestinal tract. The image resolution of OCT, which is greater than that of current clinical imaging modalities, suggests that this technology will be attractive for the assessment of early neoplastic changes.

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