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Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure

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Here we introduce tethered capsule endomicroscopy, which involves swallowing an optomechanically engineered pill that captures cross-sectional microscopic images of the gut wall at 30 μm (lateral) × 7 μm (axial) resolution as it travels through the digestive tract. Results in human subjects show that this technique rapidly provides three-dimensional, microstructural images of the upper gastrointestinal tract in a simple and painless procedure, opening up new opportunities for screening for internal diseases.

Diseases of the gastrointestinal tract are commonly diagnosed by endoscopy, where a flexible video-imaging probe is advanced through a natural orifice into the luminal digestive organs. If an abnormal region is identified, endoscopic biopsy forceps are used to extract a small amount of tissue from the area. The biopsy is then processed and reviewed under a microscope by a pathologist who renders the final diagnosis. It is estimated that approximately 15 million such biopsies are excised and analyzed every year in the United States[1].

Although endoscopy has substantially improved health outcomes, it has certain inefficiencies that limit its impact. For most endoscopic procedures, subjects are sedated, requiring specialized settings, equipment and medical staff to monitor for adverse reactions. Transnasal endoscopy, which has been gaining in popularity in some endoscopy communities[2], does not require sedation yet necessitates a trained endoscopist to conduct the procedure. Endoscopy is therefore time consuming and costly, making population-based screening for most conditions difficult to justify. Some gastrointestinal diseases involve microscopic features that manifest below the tissue surface. Because video imaging only provides information about the superficial mucosal structures, these features cannot be seen with

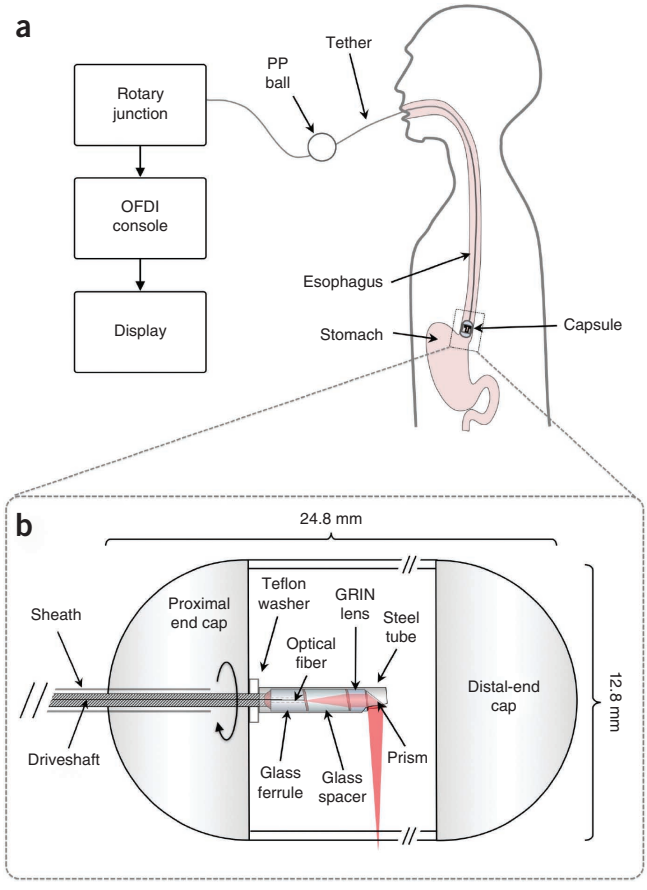

Figure 1 Tethered capsule endomicroscopy schematics. (**a**) Overview of the tethered capsule endomicroscopy device. The capsule is attached to a tether. A polypropylene (PP) ball handle is affixed to the tether 60 cm from the capsule. The tether terminates at the rotary junction, which is connected to the imaging console that generates OFDI images for display. Together, the ball and tether allow control of the pill's location and provide a means for extracting the capsule from the subject when the procedure is complete. (**b**) Expanded schematic of the capsule. The tether is comprised of a sheath surrounding a driveshaft that encloses an optical fiber. Within the capsule, the driveshaft is connected to a steel tube that contains the miniature imaging optics, including a ferrule, spacer, gradient index (GRIN) lens and 45° reflecting prism. Proximal rotational motion of the driveshaft and fiber at the rotary junction is transduced to the distal steel tube and optics in the capsule, causing the focused beam to rotate around the outer circumference of the capsule. The Teflon washer acts as a bearing to reduce friction between the steel tube and the proximal end cap.

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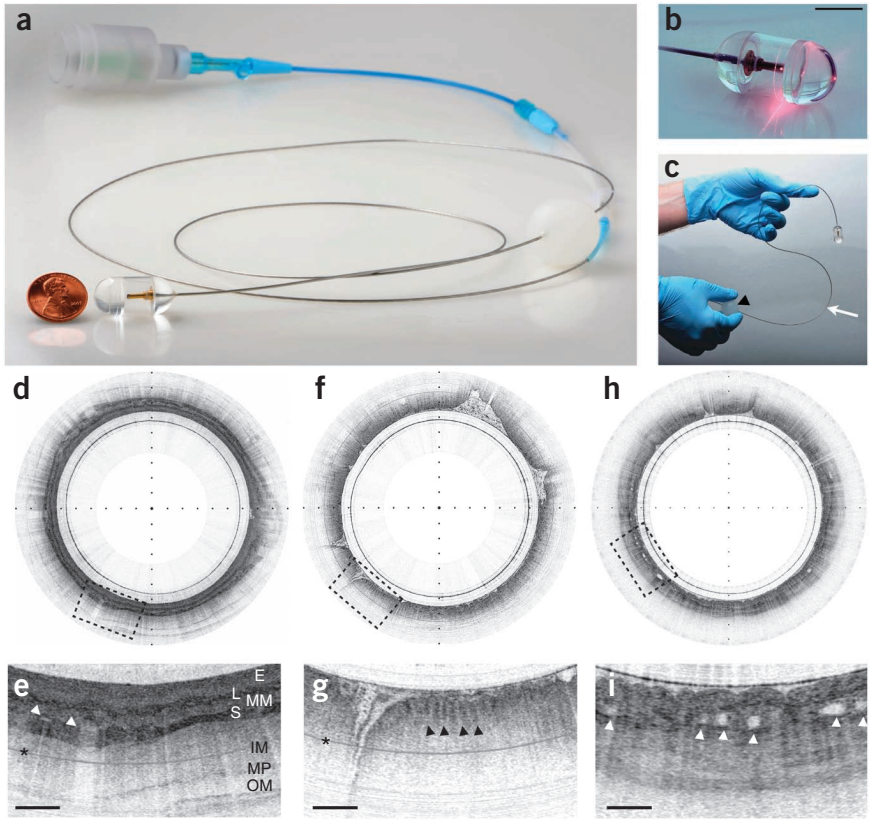

Figure 2 Tethered capsule endomicroscopy. (**a**) Photograph of the entire tethered capsule endomicroscopy device showing the capsule portion adjacent to a penny for scale. (**b**) Close-up, time-integrated photograph of the tethered capsule endomicroscope transmitting red light as the internal optics rotate. (**c**) The tether (arrow) is very flexible, and a plastic ball attached to the tether (arrowhead) facilitates manipulation of the device. (**d**,**e**) Tethered capsule endomicroscopy image of the normal esophagus obtained from a healthy volunteer *in vivo*, with an expanded view (3×) (**e**) showing the architectural morphology of the normal esophageal wall, including the squamous epithelium (E), muscularis mucosa (MM), lamina propria (L), submucosa (S) containing blood vessels (arrowheads), inner muscularis (IM), outer muscularis (OM) and myenteric plexus (MP). The asterisk indicates a multiple reflection artifact. (**f**,**g**) Tethered capsule endomicroscopy cross-sectional image of the stomach obtained from a healthy volunteer *in vivo*, with an expanded view (3×) (**g**) showing characteristic glandular 'pits' (arrowheads). The asterisk indicates a multiple reflection artifact. (**h**,**i**) Tethered capsule endomicroscopy image obtained from a patient with histopathologically confirmed Barrett's esophagus *in vivo*, with an expanded view (3×) (**i**) showing an irregular luminal surface, heterogeneous backscattering and glands within the mucosa (arrowheads). Tick marks, (**d**,**f**,**h**) 1 mm; scale bars, (**e**,**g**,**i**) 0.5 mm.

conventional endoscopy or even higher-resolution forms of endoscopy such as high-definition magnification endoscopy[3]. In these instances, the physician must randomly biopsy multiple portions of the organ with the hope of sampling the correct spot, which, unfortunately, is often missed.

We have created a new, tethered optomechanical pill[4] (**Figs. 1** and **2a–c**) that captures three-dimensional microscopic images of the digestive organs after it has been swallowed. The tethered capsule uses optical frequency domain imaging (OFDI)[5] technology to provide cross-sectional architectural morphologic data that has been previously shown to enable the diagnosis of Barrett's esophagus and high-grade neoplastic changes in the esophagus[6–8]. The capsule portion of the device is connected to a thin, string-like tether (**Figs. 1** and **2a–c**)

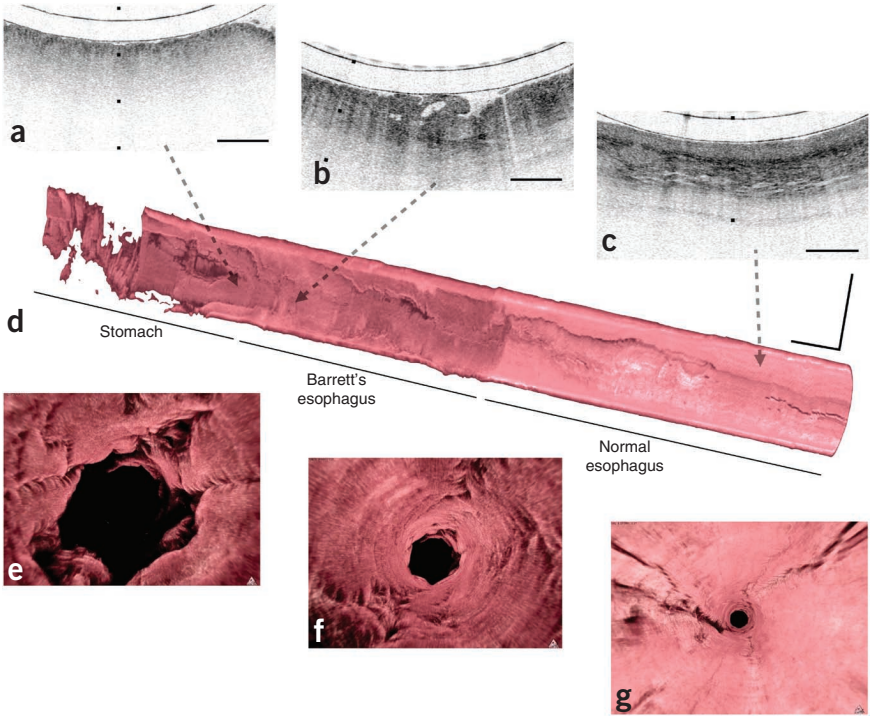

Figure 3 Tethered capsule endomicroscopy data from a patient with a diagnosis of Barrett's esophagus and high-grade dysplasia, and intramucosal carcinoma. (**a–c**) Portion of a cross-sectional tethered capsule microscopy image of the stomach (**a**), Barrett's esophagus mucosa with architectural atypia suggestive of high-grade dysplasia (**b**) and squamous mucosa (**c**) at the distal, mid and proximal ends of the esophagus, respectively. (**d**) A three-dimensional representation of the tethered capsule endomicroscopy data showing a 4 cm segment of Barrett's esophagus with multiple raised plaques and nodules, one of which corresponds to the features in **b**. (**e–g**) Three-dimensional flythrough views of the stomach (**e**), Barrett's segment (**f**) and squamous mucosa (**g**) showing a clear difference between the superficial appearance of the rugal folds of the stomach, the crypt pattern of Barrett's esophagus and the smooth surface of the squamous mucosa. Tick marks and scale bars, (**a–c**) 1 mm; scale bars, (**d**) 1 cm.

that allows the operator to control the position of the capsule in the gastrointestinal tract[9], effectuates a circumferential scan of the miniature focusing optics in the pill and transceives light to and from the capsule. Once swallowed, the luminal organs constrict around the pill and gradually push it down the gastrointestinal tract under the natural propulsion force of peristalsis. After the capsule has reached the distal-most region of interest, it is pulled back using the tether, again while imaging. During its transit, multiple OFDI cross-sections of the luminal organ are acquired at 30 µm (lateral) × 7 µm (axial) resolution, enabling the visualization of normal squamous mucosa, stomach and Barrett's mucosa (**Figs. 2d–i**, **3a–c** and **Supplementary Videos 1** and **2**). Sequential cross-sections may also be compiled to reconstruct a three-dimensional microscopic representation of the entire luminal organ (**Fig. 3d–g** and **Supplementary Video 3**). After the procedure, the capsule is withdrawn through the mouth and disinfected for reuse. In a study of 13 subjects (healthy volunteers (n = 7) and volunteers with known Barrett's esophagus (n = 6)), we found that the mean transit time for imaging an ~15 cm length of esophagus was only 58 s. For four imaging passes (two up and two down), resulting in four complete data sets, the entire procedure lasted an average of approximately 6 min (6 min, 18 s) from capsule insertion to extraction. There were no complications of tethered capsule endomicroscopy. After the procedure, the majority (12/13) of the subjects reported that they would prefer tethered capsule endomicroscopy to conventional endoscopy. The Partners HealthCare Institutional Review Board approved the study (protocol #2011P002619).

Tethered capsule endomicroscopy has the opportunity to open up new possibilities for medical screening and diagnosis of organs in the gastrointestinal tract. Because these images are obtained from singly scattered light rather than the multiply scattered color reflectance of endoscopy, they carry architectural microscopic image information that is spatially correlated with the histopathology from corresponding locations[6–8]. The device also acquires three-dimensional microscopic image data from large segments of luminal tissues, enabling the comprehensive assessment of subsurface microstructures that are not evident and can be missed by endoscopy. Because the tethered endomicroscopy pill traverses the gastrointestinal tract without visual guidance, the training required to conduct the procedure is minimal. This fact, combined with the brevity and ease with which the procedure is performed, will enable internal microscopic imaging in almost any health care setting, including in the office of the primary care physician. In addition, because the device can be retrieved and disinfected, tethered capsule endomicroscopy has the potential to be inexpensive[9], making it feasible to screen large populations for upper digestive diseases. A somewhat surprising finding of this first foray into capsule endomicroscopy was the degree to which the esophagus remained close to the outer surface of the pill, enabling the production of high-quality images (an average of 94.5% of all frames were high quality). This result indicates that other *in vivo* endomicroscopy technologies, such as confocal microscopy[10,11], could also be effective when implemented using a capsule. Looking toward the future, the full potential of capsule endomicroscopy will truly come to light through the implementation of tether-free pills, the addition of video imaging for guidance, the incorporation of externally controlled locomotion[12,13] and concomitant biopsy and therapy[14] functionalities.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

M.J.G., R.W.C., K.A.G., M.J.S., B.E.B., M.R. and G.J.T. designed the devices used. J.S.S., M.J.G., M.R., L.E.K. and G.J.T. designed the study. J.S.S., N.S.N., L.E.K., K.A.G., M.J.G. and G.J.T. conducted the study. G.J.T., M.J.G. and K.A.G. processed the data. G.J.T. and M.J.G. wrote the manuscript, and all authors contributed to the review and editing of the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

OFDI technology. OFDI is a cross-sectional, interferometric microscopic imaging technique that records light reflected as a function of depth within tissue[15], information that may be used to accurately render pathologic diagnoses in digestive tract tissues such as the esophagus[6]. The OFDI system used in this study illuminated tissue using near-infrared wavelengths sweeping from 1,250 nm to 1,380 nm. We acquired circumferential, cross-sectional images at 20 frames s^{-1} using a total of 2,048 axial (depth) scans per image. The axial resolution was 7 μm in tissue (estimated refractive index, $n = 1.4$), and the sensitivity was ~110 dB. During the procedure, we recorded all raw data in real time and also displayed subsampled versions of the images in real time. Immediately after the imaging session, we reconstructed the images at full resolution (2,900 × 2,900 pixels) and displayed them using an inverse gray scale lookup table. We automatically aligned frames and rotationally registered them using cross-correlation in ImageJ. We removed signals from the capsule's inner and outer surfaces before three-dimensional volume rendering (Osirix 4.0). We measured the percentage of frames in which the capsule was in proximity to the esophagus by dividing the number of frames in which the esophageal wall was clearly visible for greater than 50% of its circumference by the total number of frames.

Tethered capsule endomicroscope device. The capsule comprises a 12.8 mm (diameter) × 24.8 mm (length) transparent, cylindrical shell bounded by hemispherical end caps (**Fig. 1**). The shell encloses miniature optics that redirect focused (full width at half maximum diameter, 30 μm) light outside the capsule. The capsule is connected to a flexible, 0.96 mm diameter sheath, which serves as a tether[9] (**Fig. 1**). The sheath encloses a driveshaft and an optical fiber; the fiber transmits light to and receives light from the miniature optics inside the capsule. The driveshaft conveys rotational torque from the system's optical rotary junction to the capsule's optics (**Fig. 1**). Circumferential, cross-sectional images are acquired as the rotary junction, and thus the optical beam in the capsule, continuously spins. Three-dimensional images are obtained while acquiring cross-sectional images as the tethered capsule moves up and down the digestive tract.

Imaging procedure. Healthy volunteers and volunteers with known Barrett's esophagus were enrolled in the study. After informed consent, the unsedated subjects were asked to swallow the capsule endomicroscope and then take a sip of water. While the operator held the tether, the capsule was gently allowed to descend through the esophagus to the stomach. The distance between the capsule and the incisors was recorded using marks on the tether spaced 5 cm apart. We visualized images in real time to determine when the capsule had reached the stomach. Once in the stomach, we gradually pulled back the pill up through the esophagus to the mouth while imaging. We performed a total of four imaging passes (two up and two down) in each subject. After imaging, we removed the tethered capsule and disinfected it for reuse in accordance with the standard procedure for the disinfection of gastrointestinal endoscopes (submersion in Cidex OPA for 12 min). Immediately after the pill was withdrawn, we asked each subject whether the procedure was preferable to endoscopy. We used REDCap electronic data capture tools hosted at Massachusetts General Hospital to collect and manage study data. The Partners HealthCare Institutional Review Board approved the study (protocol #2011P002619).

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