Optical Coherence Tomography for Retinal Surgery: Perioperative Analysis to Real-Time Four-Dimensional Image-Guided Surgery

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Magnification of the surgical field using the operating microscope facilitated profound innovations in retinal surgery in the 1970s, as pars plana vitrectomy. Although surgical instrumentation and illumination techniques are continually developing, the operating microscope for vitreoretinal procedures has remained essentially unchanged and currently limits the surgeon’s depth perception and assessment of subtle microanatomy. Optical coherence tomography (OCT) has revolutionized clinical management of retinal pathology, and its introduction into the operating suite may have a similar impact on surgical visualization and treatment. In this article, we review the evolution of OCT for retinal surgery, from perioperative analysis to live volumetric (four-dimensional, 4D) image-guided surgery. We begin by briefly addressing the benefits and limitations of the operating microscope, the progression of OCT technology, and OCT applications in clinical/perioperative retinal imaging. Next, we review intraoperative OCT (iOCT) applications using handheld probes during surgical pauses, two-dimensional (2D) microscope-integrated OCT (MIOCT) of live surgery, and volumetric MIOCT of live surgery. The iOCT discussion focuses on technological advancements, applications during human retinal surgery, translational difficulties and limitations, and future directions.

Keywords: intraoperative imaging, optical coherence tomography, vitreoretinal surgery

Optical Coherence Tomography in Ophthalmology

Optical coherence tomography (OCT) is a noncontact tomographic imaging modality that achieves micrometer-scale axial resolution via interferometric detection of backscattered near-infrared light. Optical coherence tomography technology has dramatically improved since its inception in 1991,12 and imaging speeds have progressed from real-time A-scans, to real-time B-scans,15,16 to real-time volumes.15,16 The advent of Fourier-domain OCT technology—in the form of spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT)—resulted in improved sensitivity17 and increased system robustness, which facilitated commercialization and led to widespread clinical adoption.

The imaging depth, resolution, and sensitivity of OCT are ideal for imaging transparent ocular structures and provide diagnostic potential similar to that of histologic analysis.18,19 In vivo OCT retinal imaging was first demonstrated in 199320 and led to a revolution in the diagnosis and monitoring of many retinal pathologies,21–24 Since then, OCT has been extended to a wide variety of applications, including specific retinal layer thickness analysis to derive disease indicators,25–29 wide field-of-view imaging for evaluation of the retinal periphery,30,31 motion-compensated in vivo imaging,32,33 and retinal angiography without the need for exogenous contrast agents.34–39
PERIOPERATIVE OCT

Motivated by its diagnostic potential, ophthalmic surgeons implemented OCT for perioperative analysis of retinal surgery in the mid-1990s. Optical coherence tomography has since become an irreplaceable tool in preoperative surgical planning and postoperative monitoring of recovery, primarily because of its ability to image pathologic structures and surgically induced alterations that are difficult to detect with fundus photography. Applications of perioperative OCT include localization and characterization of epiretinal membranes (ERM) during surgical planning, and confirmation of their removal or discovery of persistent ERM postoperatively. Optical coherence tomography also enhanced monitoring of macular hole closure in the early postoperative period, during which fundus photography was limited by opacity secondary to intravitreal gas and/or postvitrectomy debris. Additionally, OCT allowed correlation of macular hole size to closure rate, as well as monitoring of ellipsoid zone (inner segment–outer segment [IS/OS] junction) deformation due to surgery.

While OCT has clearly improved pre- and postoperative analysis, absence of this enhanced feedback during surgery limits the determination of surgical endpoints that may be visible on OCT. As a result, additional surgery is often required to repair persistent lesions or remove persisting tissue identified on postoperative OCT. Because multiple surgical interventions are expensive and increase the patient’s risk for adverse events, the next logical evolution in OCT management of retinal surgery was intraoperative OCT (iOCT). Early attempts to translate OCT into the operating suite demonstrated successful imaging of excised tumors and postmortem specimens, in vitro human arteries and nerves, and structural alterations due to laser surgery. Nevertheless, these early applications were confounded by time-domain technology—resulting in suboptimal imaging speeds and sensitivity—and their inability to image in vivo human surgery.

HANDHELD OCT DURING SURGICAL PAUSES

Technological Development

Retinal iOCT was first accomplished using handheld OCT (HHOCT) probes during pauses in surgery. Handheld OCT technology was developed around the turn of the century and successfully applied for pediatric imaging using a commercial handheld SD-OCT system introduced in 2007 (Bioptigen, Inc., Research Triangle Park, NC, USA). The Bioptigen HHOCT featured a compact handheld imaging probe connected via flexible optical fiber to a portable cart (Fig. 1). The SD-OCT engine operated at 840 nm to produce tomograms with 5 μm axial resolution at 17k A-scans per second, and could readily achieve video-rate B-scans with minimal motion artifacts. This imaging speed represented a substantial improvement over time-domain OCT but still limited the volumetric acquisition time to several seconds. To acquire retinal images, the probe was positioned ~2 cm away from the patient’s cornea and could be angled to center the scans on the site of interest. Optical coherence tomography data were visualized intraoperatively as B-scans and en face retinal images (also known as summed voxel projections [SVPI]) displayed on a computer screen. Most importantly, unlike conventional tabletop scanners that required an upright and cooperative patient, HHOCT enabled imaging of supine patients and was readily applicable for intraoperative imaging during surgical pauses. Similar HHOCT systems from other vendors have since been developed and applied during macular surgery.

Intraoperative Applications

Dayani et al. at the Duke University Medical Center first demonstrated retinal iOCT imaging with HHOCT during surgical pauses in 2009. Indications for PPV in this study included macular hole, ERM, and vitreomacular traction (VMT). Static imaging was performed preincision and intraoperatively. Preincision iOCT images confirmed the disease of interest in all tested cases, while intraoperative images acquired immediately after ERM and internal limiting membrane (ILM) peeling revealed alterations in the retinal contour and decrease in macular hole size compared to the preincision images. Moreover, residual ILM was discovered with HHOCT intraoperatively, confirming to the surgeons the need for additional peeling. Despite its small sample size, this seminal study demonstrated the feasibility of iOCT with HHOCT to alter surgical decision making. Subsequent studies used intraoperative HHOCT to assess macular hole closure after ILM peeling in a pediatric case and to evaluate retinoschisis during treatment of optic pit–related maculopathies. Handheld OCT systems were also employed to differentiate Coat’s disease from diffuse retinoblastoma intraoperatively, and to study the inner retinal surface after peeling of ERM “with connecting strands” and their correlation to outcomes following ILM peeling.

To increase imaging stability, Ray et al. secured an HHOCT probe to the operating microscope using a custom mount and successfully imaged 25 consecutive eyes undergoing retinal surgery. The microscope-mounted approach was also adopted by the Cleveland Clinic Cole Eye Institute for the 2-year PIONEER study. This study comprised 256 eyes undergoing retinal surgery for a variety of indications, making it the largest evaluation of intraoperative HHOCT to date. The most common indications for surgery were ERM and macular hole. The authors reported that in 63 out of 146 procedures involving ERM peeling, iOCT impacted surgical decision making, with confirmation of peeling completion being the most commonly reported impact. Other results from the PIONEER study included quantification of macular hole volumetric alterations before and after ILM peeling in 21 consecutive eyes, in which increased macular hole volume and increased height between the ellipsoid zone (IS/OS junction) and RPE were reported. The latter finding in particular was interpreted by the authors as potentially implying that photoreceptor stretching had occurred during surgery. In the same study, iOCT also revealed full-thickness macular hole development after hyaloid elevation during surgeries for VMT, persistent subretinal fluid and significant alterations to foveal architecture during surgeries for rhegmatogenous retinal detachment, and significant membrane peeling-induced retinal alterations with both intraocular forces and membrane scrapers.

Translational Difficulties and Limitations

As originally reported in 2009 by Dayani et al., intraoperative HHOCT imaging was performed by placing several fingers on the patient’s forehead to stabilize the probe. A learning curve for localizing regions of interest and obtaining high-quality images was noted due to challenges in manual alignment and potential instability of the imager’s hand. The custom mount developed by Ray et al. exploited the microscope’s motorized X/Y/Z translation to facilitate alignment of the HHOCT
probe to the patient. However, in the microscope-mounted approach, the probe could not be offset angularly relative to the ocular pupil to image the retinal periphery. More importantly, the primary drawback of intraoperative HH-OCT—in both the handheld and microscope-mounted approaches—was its restriction to surgical pauses since the microscope must be displaced away from the patient during imaging. Although these pauses could be relatively short—Dayani et al.\textsuperscript{70} reported 4 to 5 minutes per imaging session and Ehlers et al.\textsuperscript{76} reported 3.4 minutes per session—intraoperative HH-OCT could not image the live instrument–tissue interactions that resulted in the structural alterations described above.

**LIVE TWO-DIMENSIONAL (2D) OCT IMAGING OF SURGERY**

**Technological Development**

The first demonstration of microscope-integrated OCT (MIOCT) to achieve concurrent microscope and OCT imaging of human retina was published by Tao et al. in 2010\textsuperscript{81} at Duke University. The authors constructed custom optomechanics that allowed integration of a research OCT sample arm into a commercial operating microscope. The two modalities were coaligned with a dichroic mirror prior to the microscope objective to keep the microscope’s working distance and surgeon’s view unobstructed. Moreover, the coalignment allowed the microscope and OCT to focus at the same plane so that high-quality OCT images of structures in the focal plane of the operating microscope could be readily acquired. The MIOCT system was also compatible with the binocular indirect ophthalmic microscope (BIOM; Oculus Surgical, Inc., Port St. Lucie, FL, USA) for wide-field imaging of retinal surgery. The OCT beam was magnified prior to the microscope objective and BIOM to achieve a 2.5-mm beam diameter prior to cornea and 10-\textmu m lateral resolution at the retina. Acquired OCT images were displayed on a computer monitor or wall-mounted display for surgical feedback.

Alternative MIOCT approaches include integration of the OCT sample arm at the microscope’s surgical camera port to minimize microscope height,\textsuperscript{82,83} the use of reflective ele-
ments and a tunable-focus lens to optimize OCT image quality,83 and the incorporation of a microscope-integrated monocular heads-up display unit (HUD).84-85 The latter development was particularly important since it allowed concurrent OCT and operating microscope visualization through the microscope oculars to facilitate real-time feedback to the surgeon.

All aforementioned MIOCT systems employed commercially available SD-OCT technology for intraoperative data acquisition and visualization.86,87 While volumetric OCT data could technically be acquired with these systems, volume acquisition was slow (2-10 seconds) and rendering was restricted to post-processing. Real-time volumetric imaging of retinal surgery was thus unfeasible and iOCT feedback was limited to 2D formats (B-scan and SVP).

We note that early MIOCT publications used the term “microscope-mounted OCT” to describe their systems.90,91 This nomenclature was subsequently modified to MIOCT to better reflect the incorporation of the OCT into the operating microscope, and to differentiate it from microscope-mounted HH-OCT devices described previously.

Surgical Applications

Comprehensive studies were first conducted to assess MIOCT image quality in healthy volunteers in a nonoperative setting and MIOCT visualization of instruments and maneuvers during ex vivo porcine eye surgery.88-90 This work was fundamental to facilitate the translation of MIOCT into the human operating suite and to ensure that integration of OCT into the microscope did not negatively impact the surgeon’s view. Binder et al.95 first demonstrated intraoperative MIOCT human imaging in between surgical steps and before/after surgery using a Cirrus HD-OCT (Carl Zeiss Meditec, Oberkochen, Germany) adapted to the surgical microscope. Advantages of MIOCT outlined in that report included its ability to evaluate the completeness of ERM/ILM peeling, macular anatomy immediately after peeling, and the presence or absence of subretinal fluid. A subsequent study by Hahn et al.91 compared intraoperative MIOCT and HHOCT imaging and confirmed that the two systems achieved comparable image quality and feedback to the surgeon during surgical pauses. Although a learning curve was noted, MIOCT maintained the advantages of HH-OCT but without the need to displace the microscope away from the patient.

Intraoperative MIOCT rapidly progressed to imaging of live surgery and evaluation of instrument-retina interactions, as demonstrated in three studies published in quick succession92-94 (Fig. 2). Falkner-Radler et al.93 investigated the ability of MIOCT to guide ERM/ILM peeling in 70 surgical cases. Imaging was performed before, during, and after membrane peeling, and the surgeon analyzed B-scans and SVPs displayed on a monitor adjacent to the operating microscope. The authors reported that MIOCT facilitated peeling without membrane staining, and that the structural alterations due to ERM/ILM peeling detected by MIOCT—such as photoreceptor disruption and enlargement of the macular hole base—were similar to those detected in HH-OCT studies previously discussed.77 In a separate study, Hahn et al.91 incorporated a tracking device that allowed the OCT operator to manually track the moving instrument and keep the scan centered on the region of interest. Manual tracking facilitated MIOCT imaging of surgical maneuvers such as retinal scraping during ERM removal (Fig. 2C).

Recently published studies95-97 evaluated the performance of the RESCAN 700 (Carl Zeiss Meditec), a commercially available MIOCT system that incorporates SD-OCT technology and a monocular microscope-integrated HUD for real-time feedback to the surgeon (Figs. 3A, 3B). In the DISCOVER study,95 the authors performed MIOCT imaging in 136 eyes undergoing posterior segment surgery for ERM, macular hole, retinal detachment, proliferative diabetic retinopathy, panuvei-tis, and traction retinal detachment. Key results included the demonstration of OCT impact on surgical decision making in 19% of ERM/ILM peeling cases. In such instances, MIOCT feedback was discordant with the surgeon’s impression of the completeness of peel and revealed occult membrane or lack of residual membrane. Additionally, MIOCT provided feedback that impacted surgical decision making in 21% of retinal detachment cases, such as the identification of a macular hole under perfluorocarbon liquid.96 In another MIOCT study, Pfau et al.96 demonstrated similar results with the RESCAN 700 in 40 surgeries. Such results included improved visual feedback of MIOCT compared to the operating microscope in 74.1% of cases, and MIOCT altering surgical decision making in 41.9% of cases. The component of MIOCT feedback that appeared to have the most impact on surgical decision making in this study was identification of ILM/ERM cleavage sites.

Translational Difficulties and Limitations

The introduction of MIOCT transformed the paradigm of live vitreoretinal surgical visualization by extending the en face view through operating microscope to high-resolution OCT tomograms. With the integration of HUD technology into MIOCT, surgeons were offered an alternative imaging modality to guide their surgeries for the first time since the 1960s. Although its advantages were demonstrated in the studies discussed above, MIOCT is still a nascent technology with important limitations.

Microscope-integrated OCT imaging of live surgery introduces confounding factors that are not present in iOCT imaging during pauses in surgery. Namely, intraocular instruments present during live surgery often cast “shadows” on underlying tissue in the B-scans. This shadowing effect was characterized during ex vivo porcine eye surgeries89 and found to vary with instrument material, thickness, and orientation relative to the OCT optical axis. Unfortunately, instrument shadowing may preclude OCT visualization of vital instrument-retina areas of contact. Solutions to mitigate these effects include the spatial compounding of B-scans to enhance tissue visualization underneath instruments,99 and custom instrument development to optimize OCT visibility.100 Regarding real-time feedback, several authors noted the need to optimize the location, size, and type of OCT images displayed in the surgical oculars via the HUD.95-96 The surgical oculars constrain the surgeon’s visual field and limit the size of OCT images displayed with the HUD. Presenting OCT images on an external monitor instead could be advantageous in select scenarios due to their superior resolution and contrast compared to HUD displays.

A significant limitation of the previously described MIOCT systems is the inability to image continuous and complete instrument motion. Intraoperative real-time visualization was limited to B-scans; therefore, the maneuver of interest must be coaligned with the B-scan axis for comprehensive imaging. Since restricting surgical motion to the B-scan imaging axis is unfeasible, several authors noted the need for OCT instrument tracking. Potential solutions proposed include a manual tracking device to allow the OCT operator to target the scan location in real time,94 and automatic instrument tracking using a stereo camera pair—albeit the latter approach is currently limited to anterior segment surgery.101 Additionally, Hahn et al.94 and Falkner-Radler et al.93 discussed the potential advantages of real-time volumetric OCT acquisition to facilitate imaging of live surgery, although both noted that this approach...
was unfeasible with SD-MIOCT systems discussed thus far. In both studies, intraoperative volumetric acquisition was possible (fig. 3), but volume rendering and visualization required intensive postprocessing.

**LIVE THREE-DIMENSIONAL OCT IMAGING OF SURGERY**

**Technological Development**

Real-time intraoperative imaging with all previously discussed MIOCT devices was limited to live B-scans due to the relatively slow A-scan rates of the SD-OCT systems they were based upon. Real-time volumetric MIOCT imaging could achieve more efficient assessment of live surgery and allow guidance of maneuvers with four-dimensional (4D) (volumes through time) visual feedback to the surgeon. Volumetric iOCT imaging of live model eye surgery was first demonstrated by Carrasco-Zevallos et al. in 2014 at Duke University (IOVS 2014;55:ARVO E-Abstract 1633). The authors constructed a custom ultrafast SS-OCT system that operated at 100-kHz A-scan rate, which was three to five times faster than previous MIOCT implementations. Custom graphic processing unit (GPU) software was also developed to acquire, process, and render volumes in real time. The MIOCT mechanical interface reported by Tao et al. was used to integrate the research OCT system into a commercial operating microscope (Leica Microsystems, Inc., Buffalo Grove, IL, USA). Additionally, the authors constructed a custom microscope-integrated HUD for stereoscopic visualization of OCT volumes through the microscope oculars. The integrated system (SS-MIOCT and stereoscopic HUD) was termed 4D MIOCT.

**Surgical Applications**

The image quality of 4D MIOCT was shown to be comparable to that of intraoperative HHOCT during surgical pauses in six eyes undergoing macular hole surgery (Seider MI, et al. IOVS 2015;56:ARVO E-Abstract 4084). Four-dimensional MIOCT provided feedback similar to that of HHOCT to assess completeness of ERM/ILM peeling and ERM/ILM cleavage points. Additionally, 4D MIOCT provided substantially enhanced visualization of volumetric tissue deformation, which facilitated recognition of changes in 3D macular structures after surgical intervention compared to the HHOCT.

Four-dimensional MIOCT imaging of live retinal surgery has been performed in vitrectomies for cases of macular hole, ERM, myopic foveal schisis, diabetic macular edema, or retinal detachment in over 100 cases to date. A substantial advantage of 4D MIOCT over previous MIOCT systems was its ability to image and record the progression of surgical maneuvers with volumetric imaging, including retinal scraping during peel initiation and membrane peeling with intraocular forceps (Figs. 4, 5). The 4D MIOCT volumes and B-scans were relayed to the surgeon via the stereoscopic HUD and provided enhanced context that augmented information obtained from human retinal surgery with 4D MIOCT was demonstrated in 2015 (Carrasco-Zevallos OM, et al. IOVS 2015;56:ARVO E-Abstract 4085). In this study, the overall volumetric frame rate depended on A-scan sampling density and varied between 3, 3 and 10 volumes per second. Each OCT volume was saved immediately after acquisition in “stream saving” mode that enabled continuous volumetric recording of surgery. A dedicated operator controlled the MIOCT data acquisition parameters during surgery and was able to target the OCT scan using a manual tracking system similar to that developed by Hahn et al. Volumetric data were displayed in three formats during surgery: B-scans, SVPs, and stereo volumetric renderings. The surgeon visualized the stereoscopic OCT volumes via the HUD and controlled the volumerendering perspective with a foot-operated joystick.
B-scan imaging alone. Key results have included enhanced visualization (compared to that with the operating microscope) of membrane elevation relative to the retinal surface over time, precise determination of instrument distance from retinal surface, and detailed visualization of retinal contour deformation during and following instrument contact (Fig. 5). Moreover, the ability to control the volume-rendering orientation allowed the surgeon to inspect maneuvers from different visual perspectives (Supplementary Movie S2).

**Translational Difficulties and Limitations**

The extension of MIOCT to real-time volumetric imaging during live surgery overcame many of the limitations that confounded previous MIOCT implementations. Namely, live 4D visualization relaxed the constraint for constant tracking of the OCT scan to moving targets of interest. Using the stereo HUD for real-time intraoperative visualization, the surgeon could use the 4D data available to assess the surgical field and guide maneuvers in a more efficient manner compared to B-scan visualization only. However, high-quality 4D MIOCT B-scans could also be displayed via the HUD and were particularly useful for analyzing subtle structures such as ILM.

The primary limitation of this technology may be its inability to achieve volumetric frame rates that surpass the human flicker fusion rate (16 Hz). In its current iteration, even 4D MIOCT at 10 volumes per second requires sparsely distributed A-scans that result in suboptimal lateral resolution of the displayed volumes. However, recently commercialized OCT laser sources that operate at hundreds of kHz and MHz A-scans...
scan rates could be readily implemented to overcome this limitation in the near future. Additionally, instrument shadowing first encountered in SD-MIOCT applications still presents a substantial limitation for 4D MIOCT. Volumetric imaging provides the surgeon with more context than B-scans and could facilitate surgical interpretation of the shadowed regions, but previously proposed solutions for instrument shadowing in 2D MIOCT could be applied for 4D MIOCT as well.\(^9^9,1^0^0\) Finally, OCT data visualization via the stereo HUD presents limitations similar to those of the monocular HUDs in live 2D MIOCT. Specifically, concurrent OCT and microscope viewing through the oculars limits the size and resolution of the OCT images.

**DISCUSSION AND FUTURE DIRECTIONS**

The ongoing development and commercialization of HH-OCT probes and more recently MIOCT devices may be pivotal toward the widespread clinical adoption of iOCT. This section compares currently available research-grade and commercial iOCT technology, discusses current iOCT limitations, and addresses how ongoing and future OCT technological innovations may help overcome some of these challenges.

To our knowledge, two commercial HH-OCT systems have been employed in human retinal surgery to date, the Bioptigen Envisu and the Optovue iVue (Fremont, CA, USA). The Bioptigen probe is compact and lightweight and can be
Both the membrane scraper (red asterisk) and ERM (yellow arrow) are clearly visualized in the volumes and B-scans. The volumes show retinal contour deformation during instrument contact and three-dimensional ERM structural alterations during and after brushing. Increased retinal surface tension is particularly prominent in (A2) and (A3). Scale bars: 1 mm.

Table 2 lists all commercial and research-grade MIOCT devices that have been employed in human retinal surgery to date (to the best of our knowledge). All commercial MIOCT systems utilize SD-OCT technology and are restricted to A-scan rates between 10 and 68 kHz, while the Duke 4D MIOCT system operated at 100 kHz. However, recent interest in high-speed OCT resulted in SD-OCT and SS-OCT prototype systems that operated at >100 kHz \(^{107-109}\) and at >1 MHz \(^{16,110,111}\) A-scan rates, respectively. In their current iterations, these research prototypes were not suitable for use in large-scale clinical trials, but ongoing commercialization of SS laser technology and ultrafast line scan cameras for SD may accelerate the introduction of faster OCT systems in the operating suite. Additionally, MIOCT systems operating at ~850 nm have superior resolution compared to the Duke 4D MIOCT system that operated at 1040 nm. Optical coherence tomography imaging at ~1040 nm, however, is not degraded by indocyanine green dye (absorption maximum at ~800 nm) staining of tissue, and achieves enhanced imaging of the choroid\(^{112}\) and improved visibility through cataracts\(^{113}\) and corneal edema.\(^{114}\) This enhanced visibility can be valuable in complex and lengthy ocular surgeries.

Real-time MIOCT visualization of live surgery requires HUD technology to relay the images directly into the surgeon’s oculars, and optimizing OCT feedback without altering the surgeon’s view through the operating microscope can be challenging. Current MIOCT HUDs use microdisplays to project the OCT images into a small portion of the surgeon’s visual field through the oculars to avoid obstructing the surgery view. Microdisplays are compact and can help reduce the footprint of the HUD to facilitate their integration into the microscope. However, the limited resolution of current microdisplays may restrict the size and resolution of the displayed OCT images, and multiple microdisplays could be required for a binocular HUD. Alternatively, the Duke MIOCT HUD employed a spatial multiplexing scheme to achieve a binocular stereo presentation of OCT volumes with only one microdisplay.\(^{103}\) The Zeiss RESCAN 700 also uses the HUD to display cross-hairs over the fundus view to denote the OCT scan location to the surgeon.

Most MIOCT systems also allow the surgeon to control aspects of the OCT acquisition and/or visualization in real time. The Zeiss RESCAN 700 allows the surgeon to control the lateral OCT scan location with a foot pedal,\(^{95}\) while the Haag-Streit Surgical system allows the surgeon to turn the OCT display on and off with a foot-activated switch.\(^{83}\) In the Duke 4D MIOCT system, the foot pedal allowed the surgeon to alter the rendering perspective of the stereo volumes displayed via the HUD.\(^{104}\) Control of the surgical viewpoint empowers the surgeon to examine tissue beneath and around a complex surgical site, for example, the surgeon can examine a retinal break from a viewpoint beneath an elevated membrane. Visualization of the retinal surface from alternative viewpoints has been previously demonstrated with an intraocular monocular endoscope\(^{115}\); however, the endoscopic approach was limited to surface imaging only and would require excision of tissue for submembrane viewing, rendering this technique unfeasible for intraretinal viewing. In contrast, 4D MIOCT volumetric visualization allows the surgeon to inspect both epiretinal and intraretinal structures noninvasively from arbitrary perspectives.
All MIOCT systems, except the Zeiss RESCAN 700, utilize a modular MIOCT scanner that is not permanently attached to the operating microscope. The modular design allows the MIOCT scanner to be used with multiple microscopes and facilitates MIOCT imaging in multiple operating suites with one system. The MIOCT attachment point on the microscope varies between systems; most MIOCT scanners are attached prior to the microscope objective and after the zoom optics, while the Haag-Streit iOCT is mounted onto the camera port of the microscope and the OCT beam is projected through the microscope zoom optics. As a result, the lateral resolution of the Haag-Streit iOCT system can be controlled using the microscope’s optical zoom, while the lateral resolution of the other modular MIOCT scanners is independent of the microscope objective and after the zoom optics.

### Table 1. System Specifications and Features of Commercial HHOCT Systems Used in Human Retinal Surgery to Date

<table>
<thead>
<tr>
<th>System</th>
<th>OCT Technology</th>
<th>Speed, Resolution, Wavelength</th>
<th>Primary Visualization Modes</th>
<th>Modes of Operation</th>
<th>Commercial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioptigen Envisu</td>
<td>Spectral domain</td>
<td>17k–32k†, 3–5† μm, 870 nm</td>
<td>B-scans, en face on external monitor</td>
<td>Handheld, mounted onto microscope</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Optovue iVue</td>
<td>Spectral domain</td>
<td>26K, 5 μm, 840 nm</td>
<td>B-scans, volumes, en face on external monitor</td>
<td>Mounted onto stabilizing arm</td>
<td>FDA approved</td>
</tr>
</tbody>
</table>

* Speed is listed in terms of A-scans/second; resolution refers to axial resolution; wavelength refers to the central wavelength of the source. † Not specified in publications. Range provided by manufacturer.

### Table 2. System Specifications and Features of All Research-Grade and Commercial MIOCT Systems Used in Human Retinal Surgery to Date

<table>
<thead>
<tr>
<th>System</th>
<th>OCT Technology</th>
<th>Speed, Resolution, Wavelength</th>
<th>Primary Visualization Modes</th>
<th>OCT Acquisition and Features</th>
<th>OCT Scanner Design</th>
<th>Commercial Status</th>
</tr>
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<tbody>
<tr>
<td>Live 2D MIOCT</td>
<td></td>
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<tr>
<td>Duke 2010,81,110 Biop.</td>
<td>Spectral domain</td>
<td>20k, 5 μm, 840 nm</td>
<td>Live B-scans, static en face on external monitor</td>
<td>OCT operator control with manual tracking</td>
<td>Modular</td>
<td>Research prototype</td>
</tr>
<tr>
<td>Vienna 2011,85,93,116 Zeiss</td>
<td>Spectral domain</td>
<td>27k–68k†, 5 μm, 840 nm</td>
<td>Live B-scans, static en face on external monitor</td>
<td>OCT operator control</td>
<td>Modular</td>
<td>Research prototype</td>
</tr>
<tr>
<td>Cleveland Clinic 2015,84</td>
<td>Spectral domain</td>
<td>36k, 5.2 μm, 870 nm</td>
<td>Live B-scans on monocular, monoscopic HUD</td>
<td>OCT operator control with tunable focus lens</td>
<td>Modular</td>
<td>Research prototype</td>
</tr>
<tr>
<td>Zeiss RESCAN 700,96,98,117</td>
<td>Spectral domain</td>
<td>27k, 5.5 μm, 840 nm</td>
<td>Live B-scans on monocular, monoscopic HUD</td>
<td>OCT operator control with z-tracking, surgeon control of OCT scan location via foot pedal</td>
<td>Permanently integrated</td>
<td></td>
</tr>
<tr>
<td>HaagStreit Surgical iOCT93,118,119</td>
<td>Spectral domain</td>
<td>10k, 10 μm, 840 nm</td>
<td>Live B-scans on binocular, monoscopic HUD</td>
<td>OCT operator control, surgeon control of OCT display via foot pedal, optical zoom</td>
<td>Modular</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Bioptigen EnFocus120</td>
<td>Spectral domain</td>
<td>32k, 4 μm, 860 nm</td>
<td>Live B-scans, static en face on external monitor</td>
<td>OCT operator control, surgeon control via foot pedal</td>
<td>Modular</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Live 3D MIOCT</td>
<td>Swept source</td>
<td>100k, 7.8 μm, 1040 nm</td>
<td>Live B-scan and live stereo volumes on binocular stereo HUD</td>
<td>OCT operator control with manual tracking, surgeon control of volume-rendering perspective via foot pedal</td>
<td>Modular</td>
<td>Research prototype</td>
</tr>
</tbody>
</table>

* Speed is listed in terms of A-scans/second; resolution refers to axial resolution; wavelength refers to the central wavelength of the source. † Not specified in publications. Range provided by manufacturer.
microscope’s optical zoom. In contrast to the modular design, the Zeiss RESCAN 700 employs a fully integrated design in which the MI OCT scanner is permanently attached to the operating microscope. The primary benefit of this approach is that the mechanical and optical integration of the two modalities can be optimized such that the overall footprint and physical appearance of the microscope is minimally altered.55

Imaging of live surgery with MI OCT presents unique challenges compared to imaging at surgical pauses with handheld probes. In particular, the introduction of intraocular instruments causes shadowing that may result in suboptimal visualization of underlying retinal tissue. Smaller-gauge instruments were found to shadow less in general, but shadowing also varied due to instrument material, design, and orientation relative to the OCT imaging axis.30 Optical coherence tomography-compatible instrument prototypes composed of semitransparent material in the near-infrared have been demonstrated100 and allowed OCT visualization with significantly reduced shadowing, but the surgical functionality of these instruments has yet to be rigorously evaluated. The recent commercialization of MI OCT devices, however, may catalyze the further development and commercialization of such instruments as MI OCT systems become more commonplace in operating suites worldwide. A second factor that may degrade MI OCT live surgical imaging is eye motion due to the voluntary patient motion and/or surgical maneuvers. In both cases, retinal tracking may be desired to generate IOCT images with minimal motion artifacts. The Zeiss RESCAN 700 MI OCT utilizes “z-tracking” to automatically adjust the reference arm delay to compensate for axial motion. This technique may be particularly useful in surgical cases involving large axial motion, such as retinal detachment repairs. Previously demonstrated implementations of real-time retinal tracking22,121,122 to compensate for lateral motion require additional hardware that could increase the size of the MI OCT scanners, but the benefits of motion-compensated MI OCT, especially during volumetric imaging, may justify these hardware additions. Furthermore, automated surgical instrument tracking could also help center the IOCT scans on the region of interest in the presence of motion. Several previous instrument tracking implementations used a fundus camera123,124 for tracking, and another implementation employed a stereo camera pair to localize and track the instrument.101 However, the former technique has not been integrated with IOCT, and the latter is currently limited to IOCT imaging in anterior eye surgery.

Qualitative visual assessment of the surgical field is the primary intraoperative feedback mechanism allowed by current IOCT technology. Retinal OCT image-processing techniques, such as retinal layer segmentation,29 are now commonplace and can provide to the clinician quantitative metrics to assess pathology. Such algorithms have been applied to IOCT data postoperatively to analyze anatomical alterations that occurred during surgical repair,72,77 but their intraoperative application could provide quantitative feedback to surgeons about the impact of their maneuvers in real time. Additional surgery-specific algorithms, such as real-time calculation of the retina-instrument distance based on OCT data, could help increase the precision and repeatability of maneuvers by providing quantitative metrics. Secondary forms of feedback to the surgeon, such as auditory signals indicating the instrument distance to the retinal surface, could also be facilitated by these quantitative metrics.

Due to its versatility and historical importance, the operating microscope is an irreplaceable instrument for current retinal surgery. Yet IOCT systems can provide unique feedback regarding the retinal anatomy and retina-instrument interactions, which in select scenarios results in superior visualization compared to the operating microscope. Therefore, it is not unreasonable to posit that IOCT image guidance as the primary (or only) mode of visualization may be desirable in select surgical scenarios, although significant testing and development would be required before such alternate visualization modes are used routinely in human surgery. The feasibility of 4D MI OCT imaged-guided retinal surgery without the operating microscope view has been evaluated in an ex vivo pilot study by Toth et al. (IOVS 2015;56:ARVO E-Abstract 3512). Surgical maneuvers in porcine eyes were initially performed with the operating microscope view augmented by 4D MI OCT (as performed during human surgery imaging). The surgeons then operated under 4D MI OCT guidance alone (without the fiberoptic illumination) using either the stereoscopic HUD or an external 3D monitor with viewing eyewear (Nvidia Corporation, Santa Clara, CA, USA). The surgeons performed simulated membrane peeling, retinal surface scraping, and intra- and subretinal placement of instruments and delivery of subretinal materials. Four-dimensional MI OCT provided sufficient orientation, context, and structural detail of the retinal surface to perform accurate and smooth maneuvers, albeit at a slow pace due to the limited volumetric frame rate. Unique advantages of exclusive 4D MI OCT guidance included the ability to perform bimanual maneuvers without the need for intraocular visible light illumination, and the ability to reorient the volume to view intra- and subretinal structures and instruments during surgical manipulation.

**Conclusions**

Retinal surgery visualization with the operating microscope, while revolutionary when first introduced, currently limits the surgeon’s depth perception and assessment of subtle microanatomy. The development of retinal IOCT has dramatically enhanced intraoperative feedback to the surgeon. As IOCT applications evolve from imaging during surgical pauses to 4D image-guided surgery, the improved visualization afforded by these systems may lead to refinement of surgical techniques and development of novel procedures enabled by real-time tomographic and volumetric visualization.

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The intraoperative OCT systems at Duke University are nonsignificant risk investigational devices as defined in Food and Drug Administration (FDA) guidelines 21 CFR 812. These devices are used in minimal risk studies under a Duke University Health System (DUHS) Institutional Review Board (IRB)-approved research protocol, Pro00016827.

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**References**

Evolution of OCT for Retinal Surgery


Evolution of OCT for Retinal Surgery

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Evolution of OCT for Retinal Surgery


