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Recent advances in optical coherence tomography for the diagnoses of lung disorders

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Abstract

There have been many advances in the field of diagnostic and therapeutic pulmonary medicine in the past several years, with major progress in the field of imaging. Optical coherence tomography (OCT) is a high-resolution (micron level) imaging modality currently being advanced with the potential to image airway wall structures in real time and at higher resolution than previously possible. OCT has the potential to increase the sensitivity and specificity of biopsies, create 3D images of the airway to guide diagnostics, and may have a future role in diverse areas such as the evaluation and treatment of patients with obstructive sleep apnea, tracheal stenosis, airway remodeling and inhalation injury. OCT has recently been investigated to monitor airway compliance in chronic obstructive pulmonary disease and asthma patients as well as differentiate causes of pulmonary hypertension. In future clinical and research applications, OCT will likely be combined with other endoscopic based modalities such as ultrasound, spectroscopy, confocal, and/or photoacoustic tomography to determine functional and biomolecular properties. This article discusses the current uses of OCT, its potential applications, as it relates to specific pulmonary diseases, and the future directions for OCT.

Keywords

imaging; multimodal; OCT; optical coherence tomography; optics; pulmonary advances; spectroscopy

The world of pulmonary imaging has advanced dramatically over the past decade. Flexible bronchoscopy as a minimally invasive technique allows examination of the trachea, bronchi and subsegmental bronchi to the level of fourth to fifth order but new technologies are necessary because conventional white light bronchoscopy (WLB) is of limited use for detecting mucosal changes that might be just a few cells thick or below the tissue surface [1]. The future of flexible bronchoscopy is in optical diagnostics that go beyond gross visualization. In fact, rates for diagnosing even visible lesions in patients with endobronchial tumors using WLB have been reported as between 75–98% with an overall specificity of 64–96% and pathologic diagnostic error rates of 1.5–3%. For central tumors (i.e., those

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visible during bronchoscopy), diagnostic yield increases with increasing numbers of biopsy samples, with the highest success reported at around four biopsies [2].

Selection of biopsy site is prone to sampling error and biopsies may be associated with complications including bleeding with pneumothorax or persistent air-leak. Therefore, improved guidance for airway biopsy would increase yield and decrease risks associated with the large number of biopsies currently necessary for diagnosis. When we apply these imaging modalities in practice we need to keep in mind their potential and predicted role. In general, systems with good depth of penetration have lower resolution and cover larger areas, while systems with shallow depth of penetration can have higher resolution and cover smaller areas (Figure 1). For example, the resolution of clinical ultrasound is typically 0.1–1 mm and depends on the sound wave frequency (3–40 MHz) used for imaging. Optical coherence tomography (OCT) resolution is 1–15 μm and imaging depth is 2–4 mm, while with confocal endomicroscopy (CFM), the depth of focus is on the order of 50 μm and the lateral resolution of <1–3 μm. New optical diagnostic technologies are being developed and they continue to improve for surface, and deeper tissue diagnostics (i.e., visualizing the normal airway layered microstructures or their disruption in various disease processes). Since the depth of penetration and resolution varies greatly among different optical and acoustic techniques, the future of pulmonary imaging will likely consist of a multimodality approach using a combination of technologies able to visualize deeper structures such as cartilage and potential invasion (e.g., high-frequency endobronchial ultrasound [EBUS]), complemented with higher-resolution technologies that reveal alterations in the microstructures (i.e., CFM and OCT).

Optical coherence tomography is an optical signal acquisition and processing method based on measurement of the reflected light from tissue optical interfaces, and uses the principles of optical interferometry. This optical technology has been shown to be capable of imaging the surface and sub-surface airway wall layers at near microscopic resolution, with good correlation with histology specimens.

Optical coherence tomography fulfills a niche in pulmonary imaging not previously available: real time, minimally invasive imaging of subsurface mucosa at virtually histologic-level resolution [3]. Advantages of OCT over conventional computed tomography (CT) are the ultrahigh resolution capabilities and no exposure to ionizing radiation. There are no contraindications for patients who have metallic implants or patients who cannot tolerate maintaining a supine position for a significant time, as currently limited with MRI. OCT can penetrate approximately three-times deeper into tissues than CFM. In addition, OCT is less susceptible to motion artifact from movements such as cardiac pulsation and respirations compared with CFM. On the other hand, high-frequency EBUS, is able to visualize the airway wall layers in various benign and malignant central airway processes but at much lower resolution levels than OCT. In addition, unlike sound waves, light waves do not require a liquid-based coupling medium (i.e., can be used in noncontact modes) and thus are well suited for use inside the air-filled lumen of the tracheobronchial tree [4].

Optical coherence tomography technology and clinical applications have advanced significantly over the past decade. The purpose of this article, in the perspective of the overall role of OCT in airway imaging presented above, is to provide a brief background in OCT technique, a synopsis of the current areas of research and clinical application, and an extended look into the future of OCT for clinical application in pulmonary medicine.

Basic principles of optical coherence tomography

Optical coherence tomography obtains imaging of subsurface mucosa with a resolution on the order of a low power microscope with a depth of penetration of 2–4 mm. It accomplishes

this by directing a beam of near-infrared light from a broadband coherent light source, (e.g., a superluminescent diode) at target tissue, and capturing light that is back-scattered from that tissue. This phenomenon is similar to ultrasound imaging, only using light rather than sound (the time delay difference from light reflected from different tissue onto a detector cannot be quantified by directly measuring these time delays, but this problem is overcome by the use of interferometry as further discussed in the text). Different tissues have different qualities that influence the back-reflectance (the degree of intensity which that tissue reflects light). These qualities then allow the OCT image to differentiate layers of tissue based on the relative differences in the back-reflectance of the tissue composites. The longer the distance traveled, the longer the delay in returning to a detector. The delay in the returning light from deeper structures compared with shallow structures is used to reconstruct images in a 'time domain' OCT system (Figure 2A) (for light in the near-infrared region, the maximal resolution is around 2–10 μm currently, which would mean 10–50-fold greater resolution than ultrasound). The delay time of the reflected signal is equal to the distance the beam travels divided by the velocity. Since the echo delay time is proportional to the distance traveled, the detector has to be capable of resolving time delays equal to the time it takes light to travel a distance of approximately 1 μm, with an approximate time scale of femtoseconds. This problem has been overcome by the use of interferometry techniques to detect such small delays in a reflected signal.

Interferometry

The technique to resolve the back-scattered light signals using interferometry employs the use of a reference arm, which utilizes a laser light beam split from source with a beam splitter (a partially reflecting mirror), sending some to the target tissue (target arm), and the remaining portion sent to a reference mirror (reference arm) (Figure 2). Both beams are then reflected back to the beam splitter (from the sample and reference mirror, respectively) and directed back together to a detector. Only that reflected within the coherence pathlength of the laser light provide interference that is detected (i.e., when the distance to the reference mirror in the reference arm is equal to the distance to the reflecting target within the tissue). Therefore, by moving the reference mirror closer and farther from the beam splitter in a time domain system, a depth scan of reflecting targets within the tissue can be obtained. The area of interest is scanned to create cross-sectional images and stacked to create a 3D composite image.

There have been two main probe designs for OCT. One is a direct forward scanning, or translational probe, while the other utilizes a rotating motor and a 45° angled mirror to produce a radial probe that scans 360° at a 90° angle to the probe [5]. There are several different systems that utilizes a different process and have different advantages and applications.

Time domain OCT

In time domain OCT, the reference arm is moved to different distances from the beam source, allowing sampling of the target at different depths. In time domain OCT, the speed at which the reference arm can be moved limits the axial (depth) scanning speed (Figure 2A). While axial resolution is governed by OCT interference patterns, the lateral resolution in endoscopic and fiber-based OCT imaging is limited by the numerical aperture of the optical lens system and tends to run in the 15–30-μm deliverable range with small fiber endoscopic systems currently being employed [6].

Frequency domain OCT

More recently, spectral domain OCT systems have been developed that have the potential for much more rapid axial (depth) scanning capabilities. In spatially-encoded frequency

domain (SEFD)-OCT, also known as Fourier domain OCT, the depth scan is obtained by analyzing the interference signal based on the wavelength of light. This eliminates the need for moving reference mirrors, and the entire axial depth scan is obtained for each point essentially 'simultaneously'. This enables many orders of magnitude higher scanning rates. A number of approaches to spectral domain OCT have been developed. The most commonly used spectral domain OCT systems at this time involve either a dispersive detector, used to break up the optical beam into light beams of different wavelengths at the detector region (SEFD-OCT) (Figure 2B), or a 'swept source laser' (SS-OCT) that rapidly sweeps the source laser across wavelengths (Figure 2C). Advantages of SS-OCT over SEFD-OCT include simpler setup, higher resolutions and improved signal-to-noise ratio (signal-to-noise ratio is the ratio of signal power to noise power. It is used to quantify how much of the signal is being distorted by the noise) [3,7]. Compared to SEFD-OCT, the detection system for SS-OCT is simpler and cheaper because, a high performance spectrometer and charged couple device camera are not required. Spectral domain OCT technology has been demonstrated to comprehensively image the entire distal esophagus in a time (<2 min, 50 μm pitch) that is acceptable for an endoscopic procedures, and could be applied to airway pathology detection [8]. The faster axial scanning capabilities allow for improved *in vivo* application, higher resolution images enabling 3D reconstruction (fourier domain OCT has been demonstrated to provide higher acquisition speed and better signal-to-noise ratio than OCT with time domain detection), and reducing motion artifact.

Long-range OCT

One significant limitation in conventional OCT is the axial (depth) scanning range. Typical scanning range is to the order of several millimeters. This does not pose a problem when scanning portions of mucosa in which the probe is placed near or on the surface, or when performing radial scans of a small lumen, such as the distal airways or small caliber blood vessels. However, when attempting to radially scan large hollow organs such as the upper airway, large central airways or GI tract, the short scanning range is often insufficient. Several methods have been implemented to overcome short scanning range limitations for specific pulmonary application needs (such as when seeking dynamic assessment of airway caliber changes during respiration). These approaches include manipulation of the optical delay line, known as rapid-scanning frequency domain optical delay line (FDODL), shown to increase the scanning range to as high as 26 mm [9]. More recently, through the use of recirculation loops in both sample and reference arms, scanning ranges of up to 40 mm have been produced with a fast-scanning SS-OCT system. Each arm incorporates a separate optical ring with an adjustable path length allowing for a longer axial image depth. Investigators have also reported incorporating an acousto–optic frequency shifter and a semiconductor optical amplifier, allowing for multiple depths to be scanned simultaneously [10]. Images can be obtained in two distinct ways: by maintaining the rotational probe at a certain location and scanning that area continuously over a period of time, or by advancing the probe beyond the area of interest, and retracting the probe as it is actively scanning, the so-called 'pullback' method. This can generate a 3D image of the region of interest. The pullback method is also useful for identifying specific anatomical areas of interest that can later be analyzed over time using the first method. The purpose of long-range OCT (anatomical [a]OCT) is to evaluate the gross anatomical features of the tissue surface, and thus subsurface high resolution images are not required and typically not available with this technique. This aOCT approach can also be used for studying the dynamics and changes in cross sectional area in various upper and central airway processes.

Current applications in OCT

Optimal computed tomography has been utilized successfully in clinical practice in non-pulmonary fields of medicine, such as dermatology and ophthalmology. These fields have

pioneered the use of OCT because the tissue in question is more easily accessible. In dermatology, OCT has been used to distinguish inflammatory and blistering skin conditions, and skin tumors with resolution of approximately 10 μm. With improving technology, resolution levels down to 1 μm may allow us to analyze tissue on the cellular level [11]. OCT has been utilized in the field of ophthalmology to image multiple structures of the eye including the cornea, macula and retina and diagnose a variety of ophthalmologic disorders, and is rapidly becoming standard clinical practice in retinal ophthalmology [12–14]. As OCT technology improves and systems are miniaturized, other fields of medicine follow, including otolaryngology, gastroenterology and cardiology. OCT has been utilized to evaluate laryngeal tumors, diagnose Barrett's esophagus *in vivo*, and distinguish characteristics of a vulnerable atherosclerotic plaque [15–17].

Applying OCT to the field of pulmonary medicine requires overcoming several challenges. The tracheobronchial tree is small, branching and convoluted, and only accessible in large part via flexible bronchoscopy. Therefore, the OCT probe must be small enough to be passed through the working channel of a standard bronchoscope, which ranges from 1.2 to 2.8 mm in diameter. In addition, this imaging technology must be able to overcome the motion artifact that will invariably be present secondary to cardiac pulsations and respiratory movements.

Diagnostic applications

The gold standard for thoracic imaging has been CT which currently allows high image resolution (~0.5 mm) to be readily available [18]. However, even the most advanced CT scanner does not resolve the small airways reliably, which, in fact, may approach the size of individual voxels. In a recent study, OCT was able to obtain airway wall dimensions of medium to large airways that correlated well with CT and obtain very clear images of small airways [18] and, therefore, may be appropriate to diagnose and study airway wall changes including remodeling in asthma and chronic obstructive pulmonary disease (COPD).

Obstructive lung diseases

Despite the prevalence of obstructive lung diseases such as asthma, COPD and bronchiectasis, little is known about airway remodeling and how it affects the elastic properties of the airway. In a controlled study, healthy subjects and subjects with a known history of asthma, COPD or bronchiectasis were evaluated with OCT. In asthma patients, the airway lumen was narrower and showed greater distention at a given airway pressure compared with control. Bronchiectasis patients showed a similar pattern, with a greater range of airway lumen area measurements, which may to some degree contribute to the propensity of bronchiectatic airways to collapsibility. It was postulated that these findings may be a result of chronic inflammation causing decreased effect of the radial distending force of the lung parenchyma on the airway, resulting in a narrower airway lumen at baseline which distends more easily with application of intraluminal airway pressure. There was no statistically significant difference in the OCT diameter measurements of the airways in COPD compared with controls. However, there was a strong trend towards greater compliance. This greater compliance can explain airway narrowing in COPD by decreasing the force necessary for the airway smooth muscle to exert on the airway to cause narrowing [19]. This study used measurements of airway compliance derived from simultaneous measurements of airway pressure with cross-sectional airway area obtained using anatomical OCT.

In the study described above, OCT was more sensitive than CT at detecting lung function changes in the smaller airways. Using measured luminal area and wall area as measured by OCT and CT, when compared with a patient's predicted forced expiratory volume in one

second, it was found that while there was no correlation at the third-generation level, there was a negative correlation at the fifth-generation airway [18]. This suggests that a primary site of obstruction in COPD is in the peripheral airway and raises the possibility that OCT may become a tool in evaluating small airway changes associated with COPD [18,20]. The implications of this study are that OCT provides a way to evaluate regional airway properties not previously available, and this information may provide new insight into the mechanisms of obstructive lung diseases, which may in turn help guide treatment, provide an *in vivo* tool to longitudinally follow changes in airway to assess treatment efficacy and to study disease progression over time.

Lung cancer

Thus far, routine screening for lung cancer is still controversial [21]. Therefore, there is still a need of newer techniques that can potentially assist in the early detection of lung cancer. In a pilot study enrolling five patients, a forward-scanning OCT probe was employed via a flexible bronchoscope and OCT images of endobronchial lesions, as well as normal mucosa were obtained, and these areas were biopsied as well [22]. These subjects were chosen because they had imaging studies that suggested the presence of an endobronchial lesion. Each patient had a single endobronchial mass that was visualized with WLB. The bronchoscopies were performed under moderate sedation, lasted an average of 29 min, and there were no related complications. Four of the five endobronchial lesions revealed various forms of lung cancer by histopathology, and none of the biopsies of normal mucosa revealed cancer. When comparing the OCT images of the malignant and benign regions of airway, there were clear differences. The malignant OCT images had lost some of the contrast and layering seen in benign images. This pilot study showed that OCT can be safely employed through a flexible bronchoscope with minimal additional risk or burden to the patient, and produce images that clearly show a difference between malignant and normal tissue *in vivo*, and in real time. The main limitation of OCT in this study was that other nonmalignant pathologic changes were not compared with malignant pathology. Therefore, while OCT could distinguish malignant from normal tissue, it remains to be seen if OCT can distinguish malignant from nonmalignant pathologic changes (such as granulation, strictures or other inflammatory pathology). In addition, the OCT probe had a rigid tip that could not be passed through the working channel of the bronchoscope, and therefore had to be attached to the bronchoscope's exterior. This made navigation of the bronchoscope more difficult [22].

In a separate study, both *in vivo* and *ex vivo* analysis of bronchial mucosa were performed using a radial OCT probe in seven patients [23]. Both benign and malignant airway mucosa were examined. Again, when comparing normal to abnormal mucosa, there was a loss of the distinct layering structure in the abnormal tissue [23].

In a study comprised of 15 patients already diagnosed with lung cancer awaiting curative surgery, OCT was employed through a flexible bronchoscope and airway mucosa of excised lung lobes were imaged immediately following the lobectomy surgeries [6]. Images with a depth of penetration of 2–3 mm and a spatial resolution of 10 μm were achieved. There was a strong correlation between OCT and histology. In addition, inflammatory infiltrates, squamous metaplasia and tumor was able to be identified on the OCT images, when analyzed with the corresponding histologic images [6]. Therefore, with both forward-scanning and radial OCT probes, a distinct difference can be seen in the OCT images of benign and malignant mucosa from normal mucosa. However, its utility to differentiate various airway pathologies (benign from malignant) remains to be established. These studies suggest that OCT has potential to be a powerful diagnostic tool for airway malignancies. In the future, it may be possible to utilize OCT in conjunction with other pulmonary imaging modalities such as EBUS and autoflourescence bronchoscopy to provide biopsy guidance and increased diagnostic yield.

Sepsis & smoke inhalation airway wall injury

The ability of OCT to distinguish histologic properties of tracheal mucosa was demonstrated in excised rabbit tracheas. The OCT images were compared with histologic preparations of the same tissues and the results were found to be similar [24]. In later studies, a sepsis/pneumonia model was applied to rabbits, and the excised tracheas were again analyzed by both OCT and conventional histology. OCT was able to detect airway wall thickening consistent with tracheal edema, as well as epithelial denuding and mucosal sloughing [25].

Airway injury from inhalation of smoke is a major source of morbidity and mortality in fire victims. The difficulty in treating victims of smoke inhalation is that there is currently no means by which to anticipate respiratory compromise with precision. There are several animal studies in which the airway was imaged with OCT following uniform exposure to smoke [26–28]. After just 15 min post-smoke exposure, there was evidence of increased thickness of the airway wall on OCT, with a maximum increase in airway wall thickness of 120% after 5 h [26]. In a subsequent study, it was also noted that the lower trachea experienced more swelling than the upper trachea. It was proposed that perhaps the lower trachea is inherently more sensitive to smoke, or that the position of the lower trachea/main bronchi creates more smoke particle deposition than the upper trachea [27]. In a follow-up study, a new, swept-source radial OCT probe was used to produce 3D images of the trachea during smoke exposure, which may provide further insight into the degree and pattern of smoke-related acute airway injury [28]. Using OCT, one could not only determine the extent of the injury but could also potentially be able to predict impending obstruction which could be used to guide treatment choices. In addition, it would provide a good tool to monitor for recovery, looking at changes both at the structural and cellular level.

Chronic pulmonary embolism & pulmonary hypertension

There are currently different sub-groups of patients with pulmonary hypertension, among which chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) are quite common. These two groups often present in similar fashion and have similar effects on the pulmonary circulation, but have different pathophysiology and require different treatment. In one study, normal patients, patients with CTEPH and patients with PAH underwent right heart catheterization and OCT of the pulmonary arteries [29]. The method of intravascular OCT was not explained in the cited reference. However, data from cardiovascular OCT reviews describe the technique in some detail. Blood absorbs light and will interfere with the capture of vessel wall anatomy. The conventional technique to solve this issue is by instilling either normal saline or lactated Ringer solution, which allows penetration of light, with or without proximal balloon occlusion of the vessel. Newer frequency domain OCT systems are able to capture images faster, thus allowing for the use of power injection of contrast medium and obviating the need for proximal balloon occlusion, and decreasing the risk of ischemic complications [30].

The OCT images from these three groups were significantly different. Compared to the control group, the media and intima of the pulmonary arteries were much thicker in PAH patients. In CTEPH patients, the pulmonary arteries were either occluded presumably with thrombus, and/or contained flaps within the lumen [29]. This study provides evidence that OCT can potentially distinguish CTEPH from PAH. If OCT is further validated in larger studies for the purpose of diagnosing CTEPH, it holds potential as a confirmatory test for securing the diagnosis of CTEPH, especially if a strong diagnosis of CTEPH will change management significantly, such as in the case of a patient who is being considered for surgery. Therefore, on the initial diagnosis of pulmonary hypertension with right heart catheterization, OCT can potentially be performed at that time to assist with the diagnosis of CTEPH.

Pleural disease

Current research in OCT imaging of the pleura is limited to animal studies. Such studies demonstrated that fine structures such as the visceral pleura and alveoli were able to be visualized with OCT at high resolution. In addition, empysema and metastatic cancer animal models showed that OCT was able to detect characteristic changes in the pleura and lung as a result of infection or malignancy, as well as areas of malignancy in the sub-pleural region 2–3 mm below the surface [31]. OCT was able to provide high-resolution detail about the pleura depending on the disease. Structural changes such as mucosal wall thickening, as seen in infection, could be seen. Pleural based nodules and lung tumors as small as 500 μm were also visualized using OCT. When comparing extensive disease such as induced empyema and metastatic disease in animals, distinguishable structures such as alveoli and visceral pleura are lost because of compression by tumor and filling of alveoli with purulent material [31]. While OCT can clearly distinguish normal from abnormal pleural and surface parenchymal disease, it is remains to be determined whether OCT is capable of differentiating between benign and malignant pathologies.

In a subsequent study, using a prototype SS-OCT system, high-resolution (10 μm) 3D OCT images were obtained with a multi-modal approach in conjunction with thoracoscopy [32]. A series of rabbits were inoculated with tumor cells in the pleural space. After an incubation period, a video-assisted thoracoscopic surgery was performed. The areas of tumor growth were visualized initially with white-light thoracoscopy. A rigid OCT probe was then inserted through a trocar at a separate incision site and OCT images of the same area were obtained during direct thoracoscopic visualization. The areas where this process was performed included the parietal and visceral pleura, as well as the pericardium. The rabbits were then euthanized, and histologic preparations of the areas of tumor were made. 3D reconstructions of the OCT images were obtained at high resolution, in the order of approximately 10 μm, and were comparable to the histologic preparations [32]. OCT may be particularly useful in guiding the location of thoracoscopic biopsy, if areas of tumor can be distinguished from nonmalignant irregularities. Future human studies will be needed to confirm the above findings.

One such example is identifying lesions with irregular blood vessels to biopsy using the combination of video pleuroscope and narrow band imaging performed during pleuroscopy. NBI enhances blood vessels by taking advantage of the absorption spectrum of hemoglobin. In one study, pleuroscopy was performed on 45 patients with pleural effusion of unknown etiology. Pleuroscopy with white light and NBI was performed. Blood vessels were then sub-classified based on physical characteristics and of those that were identified as irregular (type III) by NBI, 85% of them were found to be malignant. When compared with white light, it was found that the accuracy, sensitivity, and specificity was improved for detection of malignant lesions. The combination of OCT with other imaging modalities may also be helpful, but future human studies will be needed to address such questions [33].

Obstructive sleep apnea

Potential use of OCT for imaging the upper airway (defined as the airway from the nares to the glottis) includes the ability to quantitatively evaluate the dynamics of the upper airway over a significant period of time, such as during an overnight polysomnogram. Through the technological advancement of aOCT, large hollow organs such as the upper airway are now able to be visualized in such a manner [9]. A series of studies by the same research group reveals the usefulness of OCT in the evaluation of obstructive sleep apnea (OSA). In one study employing FDODL (FDODL is a device that creates an optical delay in an interferometer, and allows the amount of delay to be scanned at a high speed) aOCT, the upper airway was visualized dynamically by passing an introducer sheath through the nares

into the esophagus. The OCT probe was passed through this sheath and OCT analysis of the upper airway was performed, both at specific anatomical sites over a period of time, along with the 'pullback' method that allowed 3D reconstruction of the upper airway [9].

In a validation study, aOCT imaging of the upper airway was compared with conventional CT imaging, and demonstrated that the cross-sectional area and luminal dimensions were comparable to values obtained via CT [34]. In one controlled study, OCT was used to image the upper airway of both subjects with OSA and BMI-, gender- and age-matched control subjects in the awake state. It was noted that the velopharynx was the portion of the upper airway in both groups with the smallest cross-sectional area, and that subjects with OSA had a smaller velopharyngeal area than the control subjects. OSA subjects also had longer uvulae. It appears from this study that the size, specifically of the velopharynx, and not the shape, of the upper airway determines risk for OSA [35]. In another study by the same group, a respiratory-gated aOCT system was used in OSA patients undergoing sleep studies. The system was able to assess upper airway changes associated with the use of continuous positive airway pressure at increasing pressures. An apnea event was also recorded on OCT, where the airway was shown to completely collapse for a period of 11 s, then recover patency after the patient experienced a post-apnea arousal [36].

Based on current research publications, OCT holds significant potential for clinical application in OSA, both in diagnosis, as well as titration of continuous positive airway pressure. It may even provide information that can guide surgical procedures to reverse OSA (such as targeting the velopharynx for patients with similar findings in the previous study), and improve the outcomes for uvulopalatopharyngeoplasty and other OSA-related operations by accurately delineating the sites of airway obstruction. Further research and analysis of upper airway OCT images will be needed to shape the way that OCT will be applied to the clinical management of OSA [36–38].

Central airway obstruction

Anatomic or long range OCT has been used to study central airway diseases such as tracheobronchomalacia and tracheal stenosis. Conventional OCT provides high resolution images at a depth of 1–3 mm. With aOCT, the focus is on luminal size and shape using low coherence interferomometry by passing a fiber optic probe through the bronchoscope. It has the added advantage of creating a 3D image with rotation and retraction of the probe. This can be done *in vivo* providing good characterization of the airway in these diseases as well as providing real time data that may guide immediate treatment such as stent deployment for tracheal stenosis [39].

One study performed used aOCT to measure airway dimensions on three subjects: one with subglottic tracheal stenosis; one with malignant left main bronchus obstruction; and another with severe tracheomalacia. aOCT was employed to quantify the degree of severity and can provide real time imaging to evaluate stenosis and the dynamic changes associated with malacia [40].

These studies suggest that aOCT has many advantages in diseases such as tracheal stenosis and tracheobroncomalacia. It is comparable to CT in measuring the size and shape of stenotic lesions, but provides the added advantage of real time imaging at the time of stent deployment. This could allow the operator to decide what method of treatment to use at the time of imaging. In addition, aOCT can provide quantitative measurements of airway collapse in bronchomalacia and allow for longitudinal follow-up to follow-up treatment efficacy, as well as guide new treatments in the future.

Therapeutic applications

Optimal computed tomography is a diagnostic modality, and in itself is not a therapeutic device. However, its ability to create ultrahigh resolution images in real time enables OCT to potentially be used in conjunction with therapeutic procedures as a guidance tool.

A case study was presented of a patient with severe, symptomatic tracheal stenosis. Multimodality imaging was used to assist in the endotracheal excision and dilation of the stenotic region, including rigid bronchoscopy utilizing conventional WLB high-frequency endobronchial ultrasound and OCT. Both endobronchial ultrasound and OCT were able to provide real time images differentiating normal tissue from hypertrophic and fibrotic tissue as well as cartilage. In this case, OCT was able to provide margins for the area of stenosis, and possibly prevent both excessive unresected hypertrophic and fibrotic tissue as well as excessive destruction of normal tissue [41].

In a case series, patients with early-stage laryngeal cancer underwent minimally invasive laser surgery. Again, OCT was employed to obtain real time ultrahigh-resolution images of the larynx, and OCT was able to distinguish normal tissue from malignant tissue. With real time confirmation of tumor borders, OCT provided the surgeon with intraoperative guidance of the resection procedure. Follow-up of these patients showed good preservation of laryngeal structure and function, and the authors concluded that OCT was useful in minimizing collateral damage. It was also suggested that OCT could be useful in guiding the area of surgical biopsy in making the initial diagnosis of laryngeal cancer, although it is unclear if this technique was used in this study [15]. There are substantial limitations to the above research. The small size and lack of control groups limits the usefulness of these studies. Larger randomized control studies are needed to further validate the usefulness of OCT in guidance of therapeutic procedures.

Future directions

New pulmonary applications

Airway compliance—Airway compliance is a key factor in peripheral and central obstructive lung diseases such as asthma, COPD and tracheobronchomalacia, respectively. New research is being developed using OCT to analyze strains during breathing and provides estimates of the elastic properties of the airway. In experimental models, these techniques were used to assess the compliance of rabbit trachea *in vivo*, in its normal state as well as in a wound-healing model [42]. This information could be clinically useful for identifying the collapsible airway segments that limit airflow (also known as ‘choke points’) in patients with dynamic central airway obstruction who may require stabilizing procedures such as stent insertion or tracheoplasty [43,44].

Doppler OCT—The interaction between the lungs and the pulmonary vasculature is extremely dynamic, with disorder in the lung significantly affecting the structure and function of the vasculature. Doppler OCT is being investigated as a means to provide imaging of the pulmonary vessels, and has been shown to be able to visualize even small bronchial vasculature *in vivo* [45]. The basic principle of Doppler OCT is that the broadband laser signals will be Doppler shifted when reflecting off of moving surfaces, resulting in shifts in the interference pattern. These shifts provide the information on highly specific, spatially localized velocities of the target tissues involved. This information is potentially useful for calculating resistance indices in the mediastinal lymph nodes thus potentially facilitating differentiation between benign and malignant lymphadenopathy as has already been suggested by application of color Doppler ultrasonography [46].

Alveolar imaging—The dynamics of the alveoli are insufficiently studied since there has been no previous method able to provide real time dynamic imaging of such a minute structure. New research has been able to provide 3D images of *in vivo* murine subpleural alveoli during the inspiratory phase utilizing a triggered SS-OCT system. The ability to capture alveoli dynamics can provide valuable insight into the pathophysiology of lung injury states such as ventilator-associated lung injury, acute lung injury and acute respiratory distress syndrome, and inspire new therapeutic options for an illness that carries a very high mortality rate [47]. There are several limitations of alveolar OCT studies at this time and, therefore, it is unlikely that this technology will be clinically valuable in the very near future. Owing to the major changes in refractive index between air filled alveoli and alveolar walls/interstitium, only a few alveolar layers can be visualized. In addition, these tend to be adjacent to the probe (or window to lung surface). Thus, questions remain over sampling error bias, and potential differences between function of surface or probe adjacent alveolar function compared with other alveolar sites. Use of index matching fluid filling has been described to improve depths of penetration for OCT, but the additional penetration benefits are modest and effects on alveolar properties from fluid filling must be considered.

Needle-based OCT—Although OCT excels in providing high resolution images at very high speeds, a major limitation of OCT is its depth of penetration, which in most cases does not exceed 2–4 mm. One way to overcome this barrier, which is currently being investigated is the use of needle-based OCT platforms. A frequency-domain OCT probe was miniaturized and placed inside a 23-gauge hypodermic needle. Fresh, *ex vivo* sheep lungs were analyzed using this needle probe, and 3D images of individual alveoli and small respiratory bronchioles several centimeters below the surface were captured using this approach [48].

Sampling of lymph nodes can sometimes prove difficult, depending on the location and size and often requires invasive methods, which carry significant morbidity risks. In an *ex vivo* animal model, tumor cells were injected into the lymphatic system, and excised popliteal lymph nodes were examined with OCT. OCT was able to capture images of the capsule, precortical regions, follicles and germinal centers. The findings were compared with OCT images of normal lymph nodes, as well as histopathological preparations of the same lymph nodes. OCT images correlated well with the histologic findings in showing the inflammatory and immunologic changes of the malignant lymph nodes [49]. In a different study, OCT imaging of the *ex vivo* lymph node specimens demonstrated a clear correlation with histology. OCT was shown to enable differentiation of lymph node tissue from surrounding adipose tissue, reveal nodal structures such as germinal centers and intranodal vessels, and show both diffuse and well circumscribed patterns of metastatic node involvement [50]. The potential to image metastatic deposits using OCT opens the possibility of new *in vivo* techniques for the assessment of lymph node involvement. While biopsy may still be necessary, OCT can be used as a guide to aim for the intranodal areas involved with tumor, thus increasing the yield of the procedure. Therefore, needle-based OCT holds potential to be utilized in combination with many other modalities to guide needle biopsies. While a true ‘optical biopsy’ in clinical practice may be years away from becoming a reality (if ever) owing to the inability to provide vital information from special stains, immunohistochemical assays, culture, sensitivity and genotyping information, OCT-guided needle biopsies have the potential to become integrated into clinical practice in the relatively near future.

Another aspect of the airway that has not been well studied *in vivo* is the ciliary system, which serves to clear excess mucus and other foreign bodies out of the airway. No previous method has been able to capture ciliary motion and its changes in response to mucus *in vivo* and in 3D. In a novel research endeavor, OCT was used to visualize active cilia, and characterize the beating motion into resting, recovery and effective phases. OCT was also

able to monitor ciliary motion in response to a heavy mucus load. The ciliary system was seen to both recruit more cilia, and increase the beat frequency by up to 50% in response to increased mucus. This new insight into ciliary mechanisms can potentially be utilized in the clinical application of various diseases such as cystic fibrosis, bronchiectasis of other etiologies, and diseases such as Kartagener's syndrome [51].

Advancing OCT technology

Many optical and bioengineering groups are currently developing novel systems that are performing OCT with faster and better results. These systems are scanning at much higher speeds and producing images with much higher spatial resolution than before. Some groups are reporting four-times the scanning speed of any prior system (approaching MHz axial scanning rates), and spatial resolutions of 6 μm to as low as 2.1 μm have been reported as well. These are accomplished through a variety of new systems such as polarization-sensitive OCT, the use of new and modified light sources, and novel contrast agents such as gold nanoparticles and glucose clearance [52–57]. Although some of these research projects are performed on *in vivo* lung tissue, many of these research projects use *ex vivo* tissue or ophthalmologic animal models as, intuitively, these mediums are easier to access with no space restriction. Further validation studies for clinical application of these novel systems, as well as technological advancements to miniaturize these systems, will be needed before these advancements can be applied to *in vivo* pulmonary medicine.

Multimodality imaging

Alongside OCT, there are a number of other novel imaging techniques that have their advantages and limitations. One way to capitalize on the best aspects of each technology is to use multiple complementary techniques concurrently in the same clinical application. This multimodality approach using OCT is an area of active research.

With the advent of OCT needle probes, it is feasible to envision a multimodal approach to sampling of mediastinal and hilar lymph nodes with the combination of WLB EBUS [58] and needle-based OCT [48]. In this regard, OCT has been shown in previous studies to effectively image the lymph node and may be able to distinguish the changes characteristic for malignancy that correlate well with histology [49]. This multimodal approach may further improve the diagnostic yield of EBUS-transbronchial needle aspiration by guiding the needle to areas of lymph node tissue that are highly suspicious for malignancy or other abnormality. In addition, OCT may also provide a higher index of suspicion for malignancy if the OCT images are consistent with cancer but the biopsy is negative, providing further justification for proceeding with a more definitive diagnostic procedure such as a mediastinoscopy.

Electromagnetic navigation bronchoscopy (ENB) is a bronchoscopic technique that uses an electromagnetic field and a 3D CT reconstruction of a patient's airways to guide a catheter through the small airways and direct it to a peripheral nodule for sampling. The locating catheter has a sheath around it that is left in place while the catheter is retrieved and a needle or biopsy forceps is inserted through the sheath [59]. It would be relatively seamless to utilize an OCT needle probe instead of a standard biopsy needle. Similar to the current needle EBUS systems for this purpose, OCT could then be used to confirm that the needle is indeed in the lesion of interest; in addition OCT could potentially provide information on its likelihood of being malignant or benign. In the future, if an OCT needle probe could be designed so that the probe could be removed while the needle is left in (or concurrently with the probe OCT fiber in place), then an aspiration of tissue could be obtained without removal of the needle, which would further simplify the procedure and likely lead to increased diagnostic yield.

Confocal endoscopy, based on CFM principles, provides image of a thin section within a biological sample, where the microscope's objective is replaced by a flexible fiberoptic miniprobe and provides images of nuclear and cellular morphology: en face section, parallel to surface with a lateral resolution of 0.2–2 μm; and section thickness of 1–5 μm. Compared with the other optical technologies, CFM has the highest resolution (1 μm), but shallow depth of penetration and covers a small area. For the lung, the commercially available system is currently provided by Manu Kea from France, the Cellvizio system. The respiratory probes are devoid of distal optics and have a depth of focus of 0–50 μm, lateral resolution of 3 μm for a field of view of 600 × 600 μm with a 9–12-frames/s image acquisition. Two wavelengths are available: 488 (for autofluorescence) and 660 nm (for exogenous fluorophores). This system has been used for *in vivo* autofluorescence of the proximal bronchial wall; the probe is placed over the mucosa, the basement membrane is clearly visualized. The pattern is that of large fibers oriented along the longitudinal axis of the airway with cross-linked small fibers; and large opening of 100–200 μm, corresponding to the openings of the mucosal glands. It can provide near-histologic level images of the mucosal surface, with a depth of penetration of less than 1 mm [60]. Its obvious limitation is the shallow penetration. New probes have been developed that combine confocal microscopy and OCT together for concurrent use in the same clinical application. One study utilized this multimodal approach in analyzing the morphological changes and compliance of alveoli in an *ex vivo* acute lung injury model. Another group modified a fluorescence confocal microendoscope to accommodate a spectral-domain OCT fiber, thus creating a device capable of simultaneous confocal and OCT imaging [61,62].

Photoacoustic tomography (PAT) is another new imaging modality that combines optical, thermal and ultrasonic properties of tissue to produce high-resolution images. Essentially, tissue is irradiated with a short-pulsed laser beam, which causes a small rise in temperature, resulting in thermal expansion of the tissue, creating a rise in pressure. This pressure is propagated as an ultrasonic wave, which is the information medium that is collected and processed to produce a photoacoustic image. PAT provides information not available through OCT, including an increased depth range (3–30 mm), as well as functional, molecular and genetic imaging. Endogenous contrast is used to image physiologic changes tissue/organ systems. Molecular imaging uses exogenous contrast to stain biomarkers and provide information on processes occurring at the molecular level. For example, molecular imaging probes can be designed to specifically target biomarkers on tumor cell surfaces. Genetic imaging can be based on fusion of a reporter gene to another segment of interest. This leads to protein expression that can either be imaged directly or is involved in enzymatic reactions that lead to imageable substrates [63]. Current research endeavors are combining OCT and PAT in a multimodal system that can provide advantages of both technologies in one application. One such study utilized OCT as a guidance system in correlation with PAT as the main imaging modality in an ophthalmological study. The increased depth range as well as the capability to provide functional imaging could be useful in pulmonary application in a variety of settings, including imaging of mediastinal structures and lung parenchymal lesions that are not in close proximity to either the airways or the visceral pleura [64], as well as a clear high resolution visualization of the layers of the entire airway. To our knowledge, there are no reports of the use of this technology for pulmonary application. While PAT can be an excellent addition to the multimodal airway imaging armamentarium, miniaturization of the probes is necessary for bronchoscopic applications.

Positron detection has been utilized in cancer detection, most widely in the technique of PET scanning. In one study, a novel probe was designed that could detect positron emissions as well as produce OCT images. Normal, precancer, and malignant ovarian tissues were analyzed *ex vivo* using this combined positron–OCT probe. Positron counts in malignant tissue were 3–30-fold higher than in normal tissues. OCT images were able to distinguish

changes consistent with malignancy that correlated well with histology preparations. This technique is unique in that it enables both functional and morphologic detection of malignancy [65]. Although this study used *ex vivo* ovarian cancer as the model, this combination probe could feasibly be used in pulmonary application as well. If the probe was sufficiently small enough to be passed through the working channel of a flexible bronchoscope, it could be used to further confirm areas of malignancy within the thoracic lymph node system when used in conjunction with EBUS, or in the lung parenchyma when used in conjunction with ENB. Its application would be even more powerful if the probe could be miniaturized into a needle-based system.

Identification of tumor boundaries—Optical coherence tomography may have a role in identification of tumor boundaries in the mucosa and submucosa of airways. Multimodality bronchoscopic imaging including EBUS, OCT and WLB was used in recurrent respiratory papillomatosis. Determining the exact extent of the lesion requires precise delineation of the proximal and distal boundaries of airway involvement. This is an important step in determining operability, extent of resection and resection margins [66].

Because thermal injury disrupts the normal optical properties of tissues, OCT is capable of visualizing architectural features of the airway wall. It is well suited to defining therapeutic target volumes *in situ* and to monitoring tissue coagulation, cutting and ablation intraoperatively. This may result in subsequent reduction in iatrogenic collateral airway wall injury which is well described in experimental studies. Furthermore, the use of targeted laser energy to induce localized zones of thermal coagulation and necrosis has been investigated *ex vivo* and *in vivo* in animal studies. The effects of laser assisted mechanical dilation in tracheal stenosis were recently investigated and it was noticed that there were clear differences in the OCT imaging at the level of stenosis, in comparison with the normal airway wall structures, and that the charred tissue absorbs the light, the penetration is reduced and the OCT imaging is compromised (Figure 3) [41]. If these findings are validated in larger studies, then real time OCT imaging feedback during laser application could soon become applicable in clinical practice.

Fiber optic ref lectance spectroscopy may improve the identification of malignant regions in lymph nodes and improve sampling selection and decrease the false negative rates seen with the current endobronchial ultrasound needle aspiration techniques [67]. In one study, this was accomplished by extending the probe through the sampling needle. When a lesion is identified, the needle is deployed and a sample taken. Normal and metastatic lymph nodes were differentiated by analysis of the single fiber reflectance spectra. Microvascular hemoglobin oxygen saturation and blood volume fraction were found to be lower in metastatic nodes in comparison with normal lymph nodes. As tumor burden worsened, the vasculature inside the node may be destroyed or replaced by tumor cells as well as necrosis and keratinization within the node. Using OCT, one may be able to image lymph nodes and discern surrounding structures and aid in sampling choices *in vivo* [67].

Optical coherence tomography can also be used to monitor real time effects and treatment efficacy. One such novel treatment for severely asthmatic patients that has just been approved by the US FDA is bronchial thermoplasty. Asthma is a chronic inflammatory disease that may lead to remodeling, with changes in the airway smooth muscle bundle, cellular hyperplasia and hypertrophy [68]. Hyperplasia and hypertrophy of certain cells/tissues including the airway smooth muscle can lead to decreased airway compliance, changes to the extra and cartilage can decrease elasticity causing flaccidity and malacia. As described before, using aOCT, the elastic properties such as luminal area, airway compliance and specific compliance have been measured and derived [19]. Bronchial thermoplasty is a novel technique designed to reduce the number of airway smooth muscle

bundles for patients with chronic severe asthma, thus decreasing the contractility. Using a specially designed bronchial catheter and radiofrequency generator, the airway wall is heated with radiofrequency energy using a flexible bronchoscopic approach [69]. Although this treatment has recently been approved in the USA, there is no method for real time assessment of anatomic effects or dosimetry. OCT could potentially address this need but clinical studies would be required to assess such feasibility in asthmatic patients.

Conclusion

Optical coherence tomography is an imaging technique that has been used with significant success in fields such as dermatology, ophthalmology and otolaryngology, but only recently has the technology advanced enough to allow for pulmonary applications.

Research in the pulmonary application of OCT has involved nearly every realm of the field, from obstructive central and peripheral airway disease and lung cancer to CTEPH and OSA. Some studies have evaluated pathology of human subjects and are awaiting larger studies for validation of promising results while other studies are only in the preliminary stages utilizing animal and/or *ex vivo* models. The cutting edge of pulmonary OCT research includes detailed analysis of airway elastic properties, imaging alveoli dynamics, needle-based OCT probes, and *in vivo* examination of active ciliary beating and interaction with mucus. Many optical bioengineering groups are developing advanced OCT systems that are producing OCT images with even higher resolution as low as 2.1 μm and many times faster scanning speeds. The future of endoscopic pulmonary imaging is likely to be a multimodality approach involving probe-based techniques such as OCT. Multimodality imaging involving OCT is an area of active research, and OCT holds significant potential for successful integration into other proven techniques such as EBUS-transbronchial needle aspiration, spectroscopy, ENB, CFM, high-frequency EBUS and potentially PAT. Although larger trials are needed before OCT can be brought into routine clinical practice, this optical imaging carries strong potential for improving both diagnostic and therapeutic options in the field of pulmonary medicine.

Expert commentary

Tremendous strides have been made in OCT in recent years and this technology continues to evolve rapidly. However, at this time, OCT remains primarily a research tool in pulmonary medicine due primarily to limitations in depth of penetration and inherent tissue subcellular contrast that would be necessary for definitively distinguishing benign from malignant pathology (Figure 4). In the relatively near term, the high-resolution, nonradiating, minimally invasive, noncontact properties of OCT provide potential for future advances that will increase clinical utility for airway/pulmonary OCT imaging. OCT may become very useful for precise quantitative determination of change in surface and sub-surface characteristics for following regression of disease processes and response to interventions. aOCT may become a valuable tool assessment of OSA and upper airway obstruction, as well as lower airway dynamics.

Five-year view

Optical coherence tomography will likely progress in a number of directions over the next 5 years, including dramatically increased sampling acquisition rates, development of ultrafast and aOCT, and most importantly, multimodality imaging. Through the use of multimodality imaging, the inherent limitations of individual optical technologies and regimes can be overcome by use of complementary technologies. Such approaches are likely to involve combined modality imaging with such technologies as ultrasound, reflectance spectroscopy, diffuse optical spectroscopy, optoacoustics, as well as confocal, nonlinear and multiphoton

endoscopy. Methods for increasing endogenous and exogenous contrast, coupled with the technology advances will likely position OCT into clinically valuable roles in airway and pulmonary research and diagnostics.

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Key issues

- Optical coherence tomography (OCT) is an optical signal acquisition and processing method based on measurement of reflected light from tissue optical interfaces and uses the principles of optical interferometry capable of imaging tissue at micron-level resolution to a depth of 2–4 mm thick.
- In obstructive lung diseases, OCT has been reported to not only measure airway wall dimensions comparable to computed tomography, but was also more sensitive than computed tomography at detecting lung function changes in the smaller airways.
- OCT could potentially be used to improve upon biopsy sensitivity and specificity of airway lesions.
- OCT has been explored as a potential method to distinguish pulmonary hypertension caused by chronic pulmonary embolism from pulmonary arterial hypertension.
- OCT can be used to examine the pleura with ability to detect characteristic changes as a result of infection or malignancy, as well as areas of malignancy in the sub-pleural region 2–3 mm below the surface.
- With probe rotation or ‘pull back’, 3D images can be created with OCT, which can be useful for evaluating airway obstruction as in obstructive sleep apnea, tracheal stenosis or tracheobronchomalacia.
- Advancements in OCT technology should one day allow for faster processing and improved imaging that will allow us to visualize bronchial vasculature, monitor airway compliance in diseases and improve on lymph node sampling.
- OCT has the potential to be combined with other modalities such as photoacoustic tomography or confocal endoscopy that can improve our understanding of airway physiology and disease pathophysiology.
- OCT is minimally invasive, can provide real time imaging over a prolonged period of time, can be correlated to other imaging modalities, offers no ionizing radiation exposure and is safe for patients with metal implants.

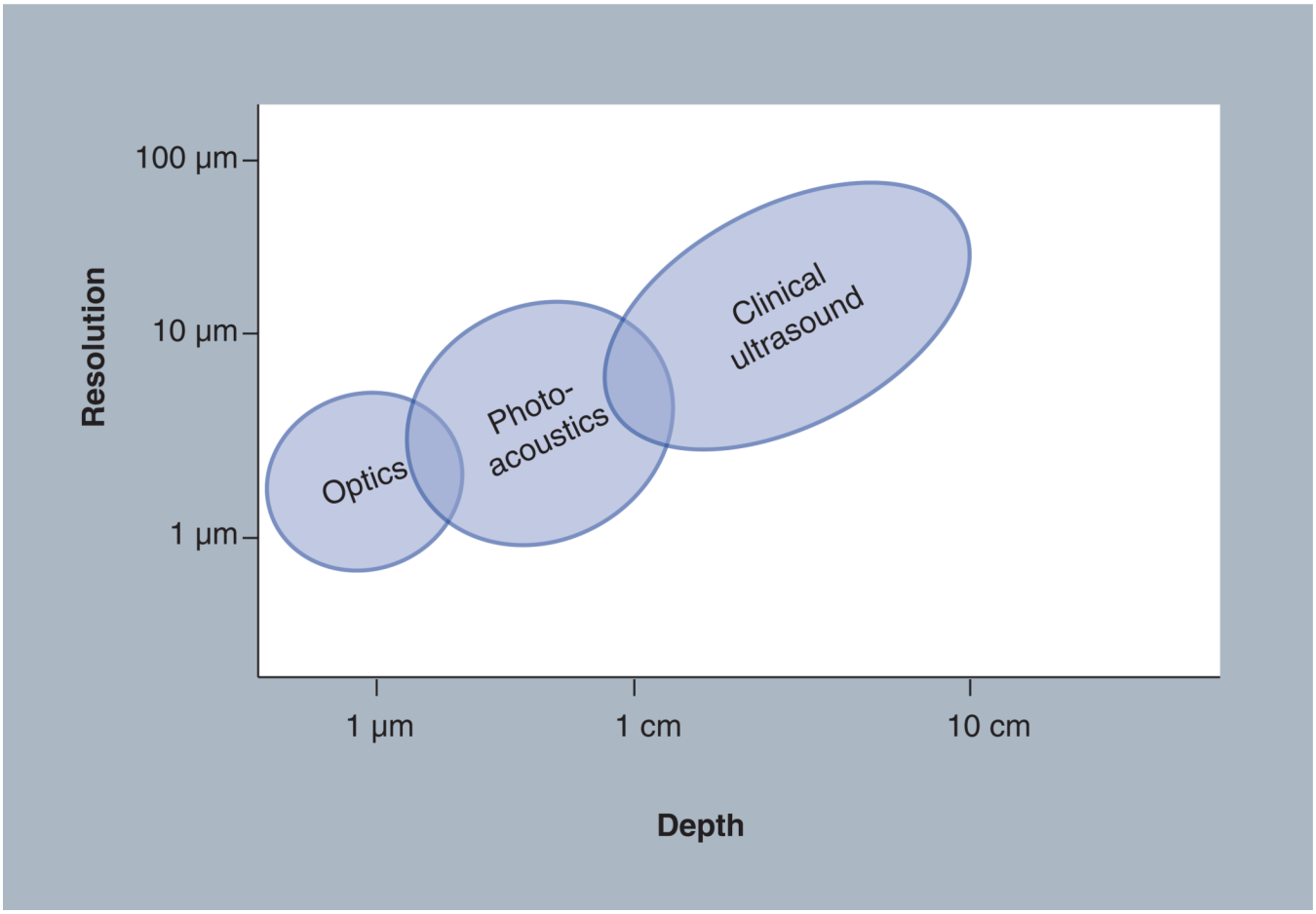

Figure 1. Technologies with greater depth of penetration have lower resolution and cover larger interrogation regions, while systems with higher resolution have shallower depth of penetration and cover small regions

For example, the resolution of clinical ultrasound is typically 0.1–1 mm and depends on the sound wave frequency (3–40 MHz). The resolution of optical computed tomography is 1–15 µm and imaging depth is 2–3 mm. Photoacoustic tomography is a hybrid imaging technique that converts optical illumination into acoustic waves to produce high-resolution images with a depth range of 3–30 mm; for example, a 50 MHz ultrasound transducer provides 15-µm axial and 45-µm lateral resolution with approximately 3-mm imaging depth.

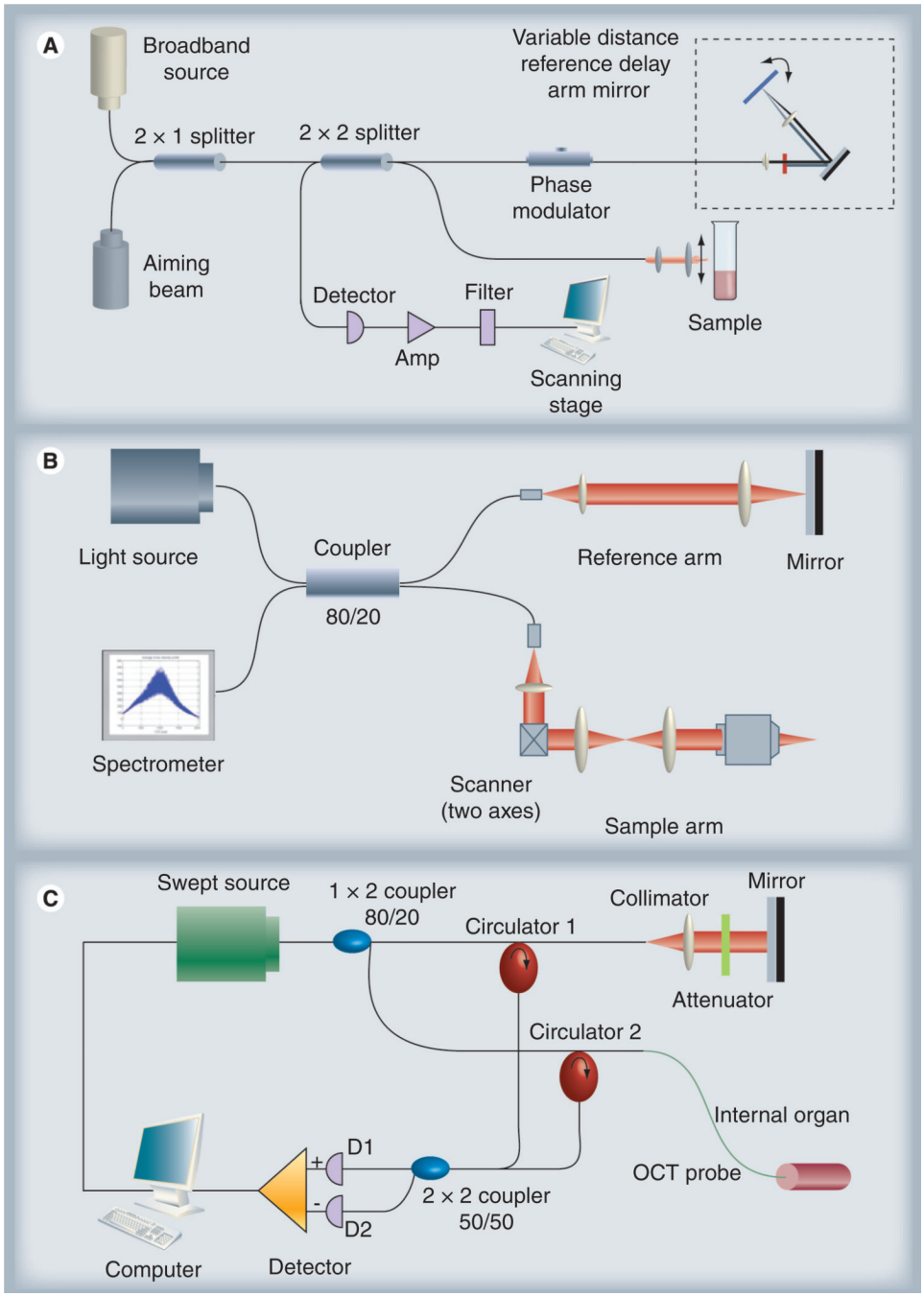

Figure 2. Optical coherence tomography system designs

(A) Time domain OCT system: the reference arm mirror moves closer and further from the beam splitter in order to obtain the axial (depth) scan. A broadband laser light source is directed to the beam splitter, where one beam goes to the reference mirror, and the other to the sample. Reflected signals return from both arms where they are recombined at the beam splitter and directed toward the detector. An axial scan is made by the sweep distance of the reference arm mirror. The sample beam is then moved in a linear pattern to obtain a 2D scan and moved to cover a surface array to develop a 3D scan. **(B)** Spectrally encoded Fourier domain OCT system: the broadband laser source is directed to the beam splitter with a fixed

distance reference arm. When reflected signals from the sample and reference are recombined at the beam splitter and directed toward a spectrophotometer, the spectrally encoded information in the interference signal provides the axial depth scan reflectance information. **(C)** Swept source OCT system: the source laser rapidly sweeps across the spectral frequency band. As the reflected signals from the sample and fixed reference arm are combined at the beam splitter and directed towards the detector, an axial scan is constructed from the depth resolved spectral interference signals.
OCT: Optical coherence tomography
Composite figure adapted with permission from: **(A)** [70], **(B)** [101] and **(C)** [28].

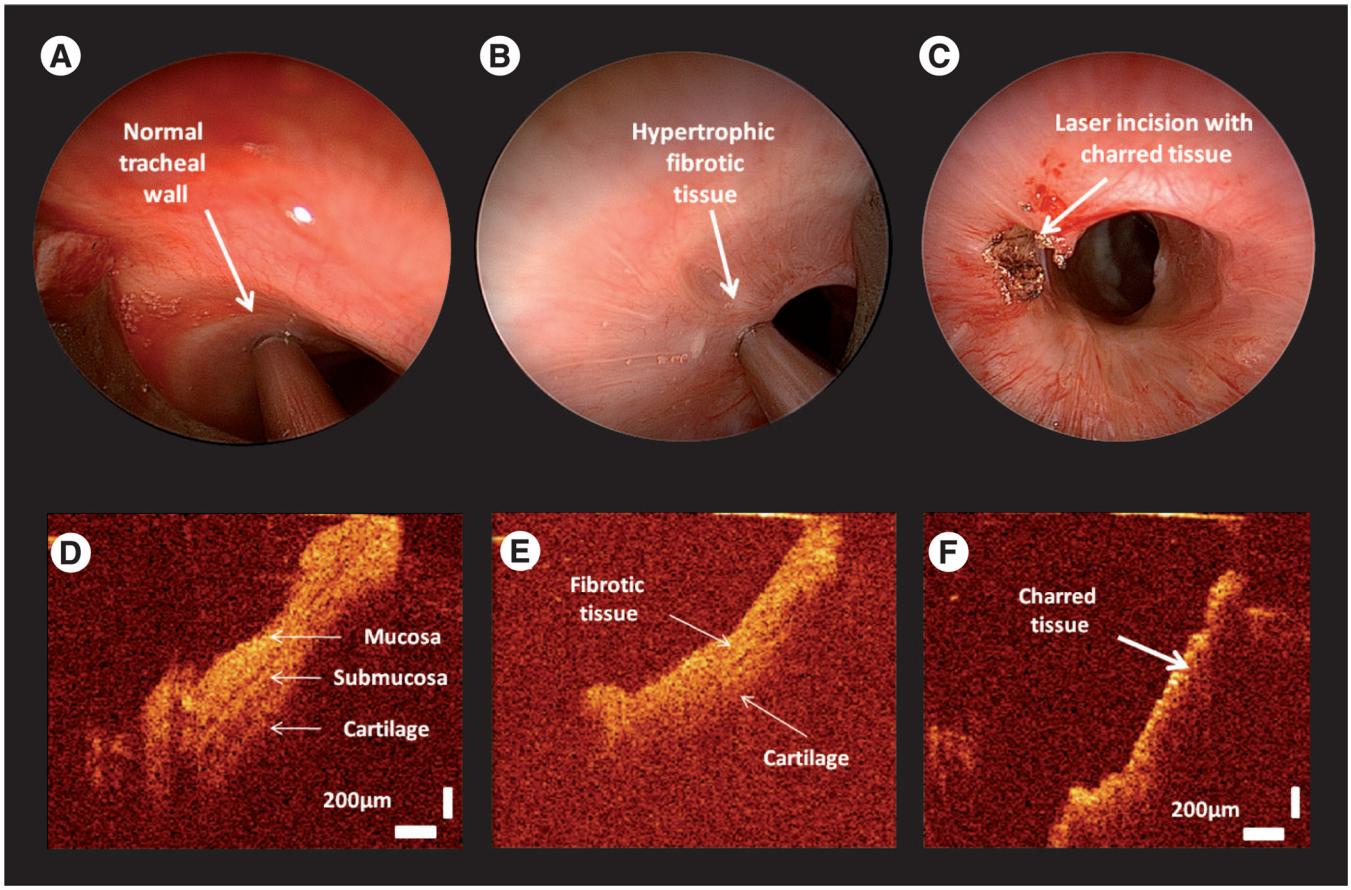

Figure 3. Optical coherence tomography findings before and after laser treatment of tracheal stenosis

(A) Optical coherence tomography (OCT) probe overlying the normal tracheal wall. **(B)** OCT probe at the laser incision site before laser ablation. **(C)** Laser incision site shows charring. **(D)** OCT tomogram reveals the normal airway wall layers: mucosa has enhanced reflectivity compared with the underlying submucosa; the extracellular matrix of cartilage decreases scattering of incident light and reflects as a dark region on the OCT image. **(E)** OCT imaging of the left incision site before laser: the homogeneous light backscattering layer and resultant loss of layer structures is visible. **(F)** OCT of the charred fibrotic tissue post laser shows a high backscattering layer; the carbonized layer at the surface absorbs and scatters the incident OCT beam resulting in reduced OCT imaging penetration. OCT image size is 2 mm horizontal and 2.2 mm vertical. OCT was performed using a commercial 2D, time-domain system (Niris® Imaging system, Imalux Corp, Cleveland, OH, USA).

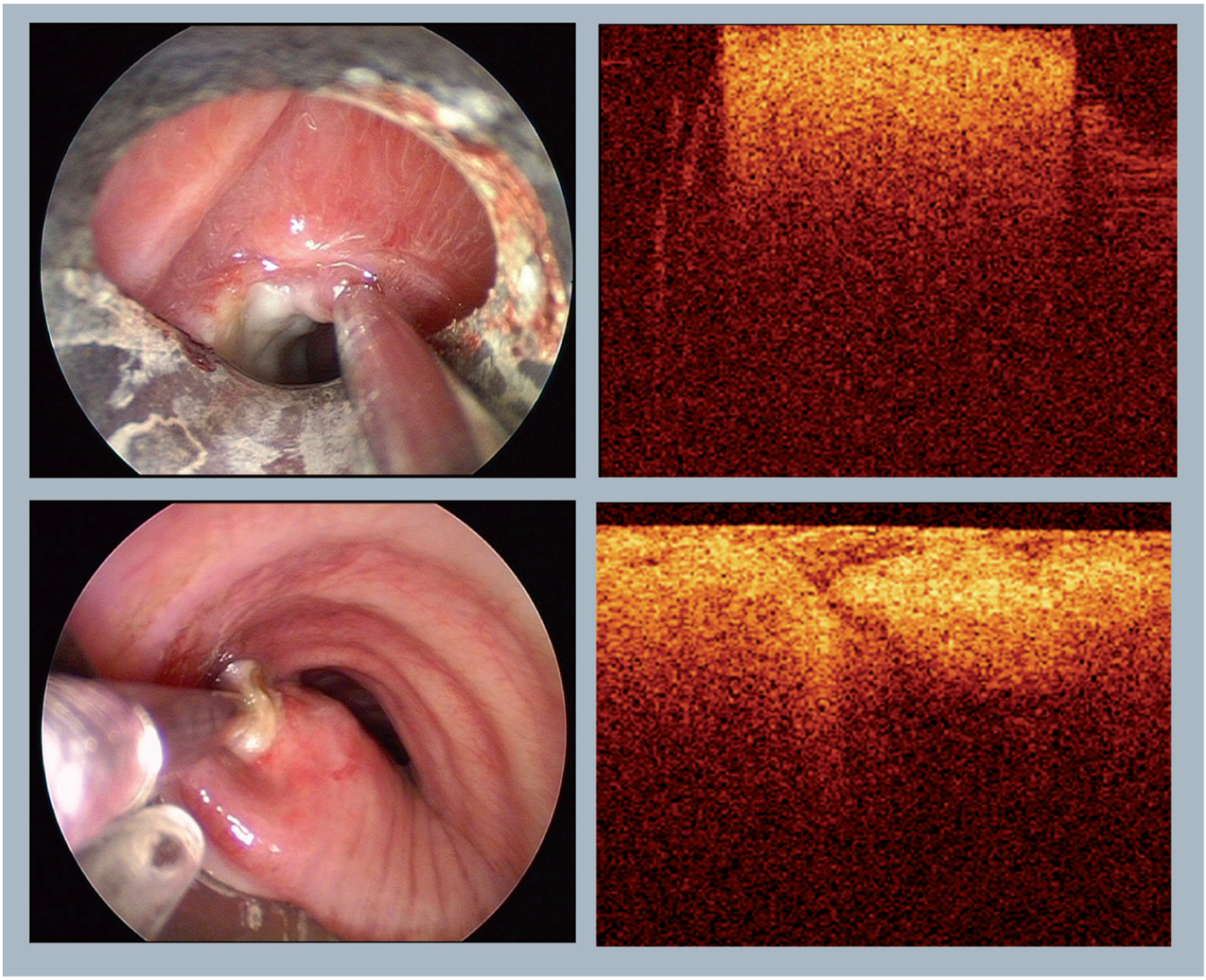

Figure 4. Optical coherence tomography imaging of malignant and benign airway processes

White light bronchoscopy and the corresponding optical computed tomography tomograms from a patient with necrotizing tracheatis and severe mucosal inflammation (top panel) and from a patient with squamous cell carcinoma and complete left main bronchial obstruction. Both white light bronchoscopy images show the optical computed tomography probe overlying the abnormality. Note the similarity between the two optical computed tomography tomograms showing a blend image and lack of normal layered airway wall microstructures.