Advances in bronchoscopic optical coherence tomography and confocal laser endomicroscopy in pulmonary diseases

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Purpose of review
Imaging techniques play a crucial role in the diagnostic work-up of pulmonary diseases but generally lack detailed information on a microscopic level. Optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE) are imaging techniques which provide microscopic images in vivo during bronchoscopy. The purpose of this review is to describe recent advancements in the use of bronchoscopic OCT- and CLE-imaging in pulmonary medicine.

Recent findings
In recent years, OCT- and CLE-imaging have been evaluated in a wide variety of pulmonary diseases and demonstrated to be complementary to bronchoscopy for real-time, near-histological imaging. Several pulmonary compartments were visualized and characteristic patterns for disease were identified. In thoracic malignancy, OCT- and CLE-imaging can provide characterization of malignant tissue with the ability to identify the optimal sampling area. In interstitial lung disease (ILD), fibrotic patterns were detected by both (PS-) OCT and CLE, complementary to current HRCT-imaging. For obstructive lung diseases, (PS-) OCT enables to detect airway wall structures and remodelling, including changes in the airway smooth muscle and extracellular matrix.

Summary
Bronchoscopic OCT- and CLE-imaging allow high resolution imaging of airways, lung parenchyma, pleura, lung tumours and mediastinal lymph nodes. Although investigational at the moment, promising clinical applications are on the horizon.

Keywords
bronchoscopy, confocal laser endomicroscopy, diagnostics, imaging, optical coherence tomography

INTRODUCTION
Imaging techniques such as (high-resolution) computed tomography (HRCT), X-ray, trans-thoracic ultrasound, PET and MRI are cornerstones in diagnosing a wide variety of pulmonary diseases [1]. Although these techniques provide important clinical insights, they are limited in resolution and unable to provide near-histological information. Therefore, regularly additional tissue sampling is needed for pathologic evaluation to establish a precise diagnosis. Although tissue biopsies are often regarded as the gold standard, they are invasive, only provide focal information of sampling location and are subject to sampling errors.

Optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE) are imaging techniques compatible with conventional bronchoscopy for (near-)microscopic scanning. Several studies have evaluated OCT- and CLE-imaging of the airway wall, lung tumours, lung parenchyma, mediastinal lymph nodes and pleura to improve the diagnosis and understanding of pulmonary diseases [2]. In 2017, Wijmans et al. [3] published a review article about OCT- and CLE-imaging in pulmonary diseases in this journal. In the last 5 years, new developments have been reported including potential clinical applications.
The aim of this review article is to provide an update on OCT- and CLE-imaging in pulmonary medicine and to discuss future clinical perspectives.

OPTICAL COHERENCE TOMOGRAPHY

Technical background

OCT is a near-infrared light-based imaging technique, which obtains high resolution images from tissues of interest [4]. As there are variances in time of light backscattering from different tissue structures, OCT is able to generate images with a resolution of ±10 μm and imaging depth of 2–3 mm [5]. In clinical practice, OCT has been used in ophthalmology to assess the retina and in vascular disease to assess chronic thromboembolic pulmonary hypertension, coronary artery stenosis and stent placement [6–9]. In pulmonology, this imaging technique has been applied in several pulmonary diseases, but so far in research settings only [2]. During bronchoscopy, an OCT probe is inserted through the working channel of the bronchoscope and real-time imaging of the lung parenchyma and airways is performed by generating pullbacks from distal to proximal (Fig. 1). Circumferential
two-dimensional images can be reconstructed into a three-dimensional overview. A different approach is OCT-imaging through a biopsy needle (needle-based OCT) to guide needle tissue sampling. The latest advancement includes polarization sensitive OCT (PS-OCT), which enables the detection of pulmonary tissues with birefringence properties [10,11]. This review summarizes OCT results in malignancy, interstitial and obstrunctive lung diseases.

**Lung cancer**

In 2005, the first report on bronchoscopic OCT-imaging in five patients with endobronchial lung tumours was published. OCT-imaging of the tumour area found dispersed distribution of high backscattering areas and loss of the normal airway wall layer architecture (Table 1) [12]. Thereafter, OCT-imaging of endobronchial lesions has demonstrated to provide additional value in the identification and characterization of premalignant bronchial lesions as compared to white-light evaluation [13,14]. Furthermore, Hariri et al. [15] performed ex-vivo OCT-imaging on 82 fresh lung tumour specimens and reported distinguishing criteria for primary lung adenocarcinoma, squamous cell carcinoma and poorly differentiated carcinoma. Although encouraging, the authors concluded that OCT-imaging cannot replace histological evaluation to distinguish different tumour types [15]. A potential application of OCT-imaging in lung cancer diagnosis, might be to provide feedback on the optimal biopsy needle positioning [16–19]. For this purpose, several needle-based OCT catheters have been investigated by multiple groups [18,20–25]. Hariri et al. [17] performed needle-based OCT-imaging in 26 thoracic lymph nodes and identified malignant lymph nodes with irregular architecture and variations in signal intensity and attenuation (Table 1). In addition, necrosis was identified as nested structures with a signal-intense periphery and central signal-poor homogeneous tissue [17]. Furthermore, in ex-vivo experiments, PS-OCT-imaging was able to accurately differentiate tumours with high from low fibrosis content, which can potentially impact diagnostic yield [26,27]. To date, no study has evaluated the use of needle based and PS-OCT-imaging in lung cancer patients in vivo, which deserves further studies.

**Interstitial lung diseases**

Diagnosing ILD is challenging and currently no gold standard single test is available to diagnose and differentiate different subtypes of ILD [28]. Histological evaluation by surgical lung biopsies or bronchoscopic cryobiopsies may be indicated, but are invasive, associated with significant morbidity and are not useful for (longitudinal) measurements [29]. Hence, minimally invasive bronchoscopic OCT-imaging could be of added value. The alveolar compartment can be visualized in high detail by OCT-imaging, allowing the detection of microscopic honeycombing undetectable by HRCT [30]. Nandy et al. [31] demonstrated that OCT can differentiate between an usual interstitial pneumonia (UIP) and a non-UIP histopathological pattern in fibrotic lung disease. In this study, 27 patients were evaluated and OCT outcomes were compared with histology from surgical lung biopsies, demonstrating a 100% sensitivity and specificity for diagnosing a UIP histopathological pattern (Table 1). The potential to differentiate between UIP and non-UIP by adding OCT to standard bronchoscopic bronchoalveolar lavage might impact the diagnostic workup of patients with ILD and may overcome the need for surgical or cryobiopsies in selected cases. Although conventional OCT has successfully identified anatomical structures and characteristics compatible with subsets of ILD, PS-OCT enhances the ability to visualize fibrosis by detecting birefringence tissue properties (Fig. 2). Two study groups are currently working on endobronchial PS-OCT (EB-PS-OCT) in the field of fibrotic ILD. Recently, Nandy et al. [32] reported the feasibility of EB-PS-OCT for microscopic assessment of fibrosis. Furthermore, a recent abstract reported the possibility to quantify the amount of fibrosis by birefringence structures using histology as the reference standard [33]. Whether EB-PS-OCT allows improved regional identification of (early) fibrotic tissue in comparison to standard HRCT imaging, is currently under investigation.

**Obstructive lung disease**

Airway remodelling is a pathological feature of obstructive lung disease in asthma and chronic obstructive pulmonary disease (COPD). Airway remodelling is characterized by changes in the airway wall including alterations in the airway smooth muscle (ASM) and extracellular matrix (ECM) [34]. The current imaging standard for airway remodelling detection is HRCT, which has limited resolution and coincides with radiation exposure. Alternatively, histological evaluation of airway biopsies can be used to assess airway remodelling, but these are invasive and provide only focal airway wall information. OCT has the potential to overcome these limitations and several study groups have reported on OCT for this clinical purpose (Table 1). First, conventional OCT-imaging was compared with HRCT to identify and quantify airway wall...
Table 1. Bronchoscopic optical coherence tomography imaging in lung cancer, interstitial lung disease and obstructive lung disease

| Application | Identified patterns | Clinical perspectives | Stage of innovation |
|-------------|-------------------|----------------------|---------------------|
| Lung cancer | Identification of malignant lesions using OCT-imaging [13–17] | Endobronchial tumour: - high backscattering areas and loss of layered structure - ragged, irregular, dark line between light areas in the subepithelium | Endobronchial (pre) malignancy detection Molecular OCT-imaging for tumour detection | Development (2A) |
| Needle based OCT in lymph nodes (ex-vivo) [18–25] | Normal lymph nodes: - round structure, homogeneous with moderate signal intensity and minimal architectural variation Malignant lymph nodes: - irregular architecture and variation in signal intensity and attenuation | Needle based malignancy detection in-vivo Molecular OCT-imaging for tumour detection | Proof of concept (1) |
| Identification of malignant lesions using PS-OCT imaging (ex-vivo) [26,27] | Normal lung parenchyma: - lattice like alveolar structure - moderate birefringence Tumour area with low fibrosis: - low birefringence Tumour area with high fibrosis: - high birefringence | Lung cancer detection in-vivo Identification of tumour areas with high versus low fibrosis for intra-procedural tumour yield assessment | Proof of concept (1) |
| Interstitial lung disease | OCT-imaging of the lung parenchyma [30,31**] | Normal lung parenchyma: - thin, lattice-like alveoli and evenly sized. Fibrotic lung parenchyma: - Loss aeration - Microscopic honeycombing and traction bronchiectasis - irregularly shaped, with thickened alveoli | Diagnosing ILD (UIP versus non-UIP) ILD assessment and treatment effect evaluation | Development (2A) |
| Identification of fibrotic tissue using PS-OCT imaging [32*,33*] | Normal lung parenchyma: - thin, lattice-like alveoli with very little birefringence present. Destructive fibrosis: - tissue with destruction of underlying lung architecture with increased birefringence presence Nondestructive interstitial fibrosis: - thickening of alveolar walls with increased presence birefringence | Early and progressive fibrosis detection Differentiation of fibrotic tissue and other cause for loss of aerated lung tissue ILD assessment and treatment effect evaluation | Development (2A) |
| Obstructive lung disease | Identification airway wall layers using OCT-imaging [35,36,40*] | Airway wall layers and structures: - epithelium and basement membrane - lamina propria - submucosa - cartilage - collagen and elastin (ex-vivo) | Airway remodelling detection Evaluation of treatments targeting airway remodelling Molecular OCT-imaging for airway remodelling detection | Development (2A) |
| Quantification of airway dimensions [37,38,39*] | Dynamic changes in: - airway lumen - airway wall thickness | Evaluation of airway remodelling | Development (2A) |
| Identification airway wall layers using PS-OCT imaging [11*,35] | Airway wall layers - airway smooth muscle visualisation and quantification - cartilage | Detection of extra cellular matrix components Molecular OCT-imaging for airway remodelling detection | Development (2A) |

*Stage of innovation based on IDEAL guidelines for surgical interventions: Stage 1 Proof of concept, Stage 2a Development, Stage 2b Exploration, Stage 3 Assessment, Stage 4 Surveillance [69].
layers [35,36] and dimensions in both asthma and COPD [37,38]. Recently, Su et al. [39] reported airway lumen diameter changes measured by OCT after the application of bronchodilators in asthmatic patients in airways from the third till the ninth generation. Apart from these dynamic changes, OCT has the ability to directly visualize and quantify tissue compartments by the use of deep learning assistance in vivo [40] and is able to visualize specific ECM components by using a threshold technique on light scattering intensities (Fig. 1). In an ex-vivo study, the potential of this strategy to automatically identify and quantify ECM structures in the airway wall was demonstrated [41].

Next to conventional OCT, PS-OCT has shown promising results in visualization and quantification of ASM in the airways (Fig. 3) which is considered a key structure in bronchoconstriction and release of inflammatory mediators in asthma patients [32]. Moreover, two studies measured the ASM content after bronchial thermoplasty, an endoscopic treatment for severe asthma to decrease the ASM [11,38]. Taken together, (PS)-OCT enables near-histological investigation of complete airways and as such has the potential to assess changes in airway remodelling and might improve the understanding of the pathogenesis and treatment effects in obstructive lung diseases (Table 1).

For future research purposes, the combination of (PS)-OCT with the detection of fluorescently labelled antibodies (immune-OCT), for example biologicals used in asthma treatment, might be developed to elucidate cellular targets of the biologicals and the treatment effects on airway remodelling [42].

**CONFOCAL LASER ENDOMICROSCOPY**

**Technical background**

CLE is a laser-based imaging technique that allows the visualization of cells in vivo for a real-time microscopic evaluation of the tissue investigated. With an objective lens, the laser-light (most commonly 488 nm) is focused on the tissue wherein it strikes an autofluorescent structure (e.g. elastin) or fluorescent dye (e.g. fluorescein). Light is emitted back to the detector using a pin-hole to acquire high-resolution images with a resolution up to 3.5 μm, maximum imaging depth of 70 μm and maximum field of view of 600 μm [2,3]. In the field of gastro-enterology, CLE-imaging has been used in clinical practice for the diagnosis of Barret’s disease and pancreatic cysts [43–46]. In pulmonology, CLE-imaging is mainly investigational and further research is ongoing before implementation in clinical practice.

There are two different applications of CLE-imaging, namely probe-based CLE-imaging (pCLE), wherein the flexible CLE-probe is inserted through the working channel of the bronchoscope, and needle-based CLE-imaging (nCLE), wherein the probe is advanced through the lumen of a biopsy needle. The pCLE technique is frequently used for visualizing the autofluorescent elastin fibres of the alveoli and airways [47]. Although there are different CLE-probes, the Alveoflex CLE-probe (Mauna Kea Technologies, Paris, France) has the largest field of view (optic area of 1.13 mm² and image plane 50 μm) and is therefore most commonly used for pCLE-imaging.

nCLE-imaging is most commonly used for the evaluation of cellular structures in mediastinal lymph nodes and lung lesions [48,49]. The AQ-flex CLE
probe (Mauna Kea Technologies) is usually used for nCLE-imaging, as this smaller probe fits through the lumen of a biopsy needle. The AQ-flex probe has a smaller field of view with an optic area of 0.33 mm² and an image plane of 20 μm. As (tumour-)cells do not have autofluorescent properties, it is recommended to administer fluorescein intravenously to create a contrast between the cells and bright fluorescein-rich stromal background. In this review, we aim to describe current advancements of CLE-imaging in lung cancer, pleural malignancy and ILD.

**Lung cancer**

Initially, CLE-imaging for the diagnosis of lung cancer was performed by scanning the surface of the airways and lung tumours using the pCLE-technique. Although some indirect malignant patterns were identified, no clear delineation of tumour cells was visualized due to the limited penetration depth [50–55]. Another disadvantage of pCLE-imaging is that as the CLE probe occupies the working channel of the bronchoscope, the CLE probe has to be removed before taking a biopsy sample and subsequent biopsies are taken without CLE guidance.

With the development of the smaller AQ-flex probe, nCLE-imaging at the biopsy needle tip was introduced. Wijmans et al. [49,56] performed for the first time nCLE-imaging in central lung tumours and metastatic lymph nodes during endoscopic ultrasound procedures. Three nCLE criteria for lung cancer were identified (enlarged pleomorphic cells, dark clumps and directional streaming) and validated with 90% accuracy [49]. In a subsequent study, bronchoscopic nCLE-imaging was performed in 24 peripheral lung tumours (Fig. 4). The previous identified nCLE malignancy criteria were confirmed and novel criteria for airway and lung parenchyma (elastin fibres, alveoli, bronchial epithelium and still image) were identified (Table 2). Therefore, the authors hypothesized that nCLE-imaging can be used to fine-tune the optimal needle positioning [48**]. In a recent case report, this hypothesis was tested, and nCLE-imaging was combined with...
FIGURE 4. Bronchoscopic nCLE-imaging of a peripheral lung tumour. (a) Chest CT-scan with a lung tumour in the left lower lobe (circle). (b) nCLE-imaging of the lung lesion shows clusters of enlarged pleomorphic tumour cells. (c) Corresponding cytology representing a pulmonary metastasis of a urothelial carcinoma.

Table 2. Bronchoscopic confocal laser endomicroscopy imaging in lung cancer, pleural malignancy and interstitial lung disease

| Application | Identified patterns | Clinical perspectives | Stage of innovationa |
|-------------|--------------------|-----------------------|----------------------|
| Lung cancer | Identification of malignant lesions using needle-based CLE-imaging (nCLE) [47,48*,55,56] | Malignancy: - enlarged pleomorphic cells - dark clumps - directional streaming Normal airway/lung parenchyma: - elastin fibres - alveoli - still image - bronchial epithelium | Improve diagnostic yield by fine-tuning of sampling area Molecular CLE-imaging for in vivo analysis of different tumour types | Development (2A) |
| | | | | |
| Pleural malignancy | Identify malignant pleural disease during thorascopic procedures using probe-based CLE-imaging (pCLE) [60–63] | Malignant pleura: - enlarged pleomorphic cells - dysplastic vessels - abnormal architecture Benign pleura: - full chiasma sign - cell shape homogeneity | Improve thorascoscopic diagnostic yield by identifying optimal sampling area | Exploration (2B) |
| | Identification of malignant cells in pleural effusion using probe-based CLE-imaging (pCLE) [62*] | Malignant effusion: - variated cell size - enlarged nucleus - irregular nucleus and cell membranes | Improve pleural fluid malignancy detection | Proof of concept (1) |
| Interstitial lung disease | Identify ILD characteristics by probe-based CLE-imaging (pCLE) of the lung parenchyma [64,65,67–69] | Cellular ILD: - hypercellular patterns Fibrotic ILD: - disorganized elastin network - decreased alveolar openings - thickened septal fibres | Discriminate cellular ILD from fibrotic ILD Fibrosis detection | Development (2A) |
| | Assess optimal sampling area with probe-based CLE-guided (pCLE) cryobiopsies of the lung parenchyma [66] | Mild fibrosis: - mild increase of elastin fibres - preserved alveolar architecture Dense fibrosis: - dramatic increase of elastin fibres - destruction alveolar architecture Pleura: - dense cross-fibre pattern | Improve diagnostic yield of cryobiopsies in ILD patients Reduce pneumothorax complication rate | Development (2A) |

aStage of innovation based on IDEAL guidelines for surgical interventions: Stage 1 Proof of concept, Stage 2a Development, Stage 2b Exploration, Stage 3 Assessment, Stage 4 Surveillance [69].
Interventional pulmonology

robotic bronchoscopy in a small, partially cystic lesion to determine the exact sampling location [57*]. Whether nCLE-imaging in suspected lung lesions will eventually result in an improved diagnostic yield is under investigation. In a future concept, immediate tumour ablation can be performed after malignancy confirmation. Molecular nCLE-imaging with fluorescent malignant tracers can contribute to this concept. Recently, a study performed in vitro and ex vivo near-infrared CLE-imaging using a malignant molecular tracer. Blinded raters were able to accurately distinguish malignant tissue from healthy tissue [58**,59*]. Whether similar results can be achieved in vivo, including benign disease differentiation, should be evaluated.

Pleural malignancy
Several studies performed CLE-imaging for the diagnosis of pleural malignancies [60–63]. One study performed both pCLE and nCLE-imaging of the pleura during 20 diagnostic procedures, including thoracoscopy, surgical excision, ultrasound and endoscopic ultrasound [61]. In comparison with 105 pleural biopsies, distinctive CLE patterns for pleural tumour deposits, malignant infiltration in fat tissue and benign fibrotic pleural tissue were validated with moderate interobserver agreement [61]. The most extensive experience, however, was gained recently by performing pCLE-imaging during thoracoscopic procedures [62*]. Of the 62 included patients, 36 had benign and 26 had malignant pleural disease upon histological evaluation. On the basis of 310 CLE-videos, the criteria ‘abnormal tissue architecture with pleomorphic cells’ and ‘dysplastic vessels’ were significantly associated with malignancy, whereas the criteria ‘full chia seeds sign’ and ‘cell shape homogeneity’ were associated with benign pleura (Table 2). Whether CLE-guided pleura sampling will result in an improved diagnostic yield should be evaluated.

One ex-vivo study performed pCLE-imaging in pleural effusions and found high sensitivity and specificity for the detection of enlarged pleomorphic cells in cytological malignant pleural effusions (Table 2) [63]. However, as cytology of pleural effusions is associated with a sensitivity of approximately 60% [63], the added value of CLE-imaging in pleural effusions is unknown.

Interstitial lung disease
As ILD is a disease affecting the lung parenchyma, several studies have evaluated CLE-imaging of the alveolar compartment to improve the diagnosis of ILD [64–66]. Initial experience was gained by performing pCLE-imaging in patients with amiodarone related pneumonia, pulmonary alveolar proteinosis and alveolar microlithiasis. It was demonstrated that autofluorescent macrophages, calcispherites and complexes of granulated lipoproteinaeous substances can be identified on pCLE-imaging [67–69]. Meng et al. [65] performed pCLE-imaging in 27 patients with different subtypes of ILD and showed a significant correlation between hypercellular patterns on pCLE-imaging and inflammatory patterns on CT-scan (Table 2). Surprisingly, however, no significant correlation between densely packed elastin fibres on pCLE-imaging and fibrosing interstitial pneumonia was found [65]. In a subsequent study, Salaiń et al. [64] performed pCLE-imaging in 80 people, including 59 ILD patients and 21 healthy volunteers. Of the 14 pCLE patterns initially described, nine patterns were significantly more frequent in at least one of the ILD groups compared with healthy volunteers (Table 2). This included disorganized, dense septal alveolar fibres in patients with idiopathic pulmonary fibrosis [64]. Furthermore, Wijmans et al. [66] suggested the use of pCLE-imaging to guide transbronchial cryobiopsies to improve the diagnostic yield by differentiating normal from diseased lung parenchyma (Fig. 5). This application might also reduce the current pneumothorax complication rate by real-time identification of the conducting airways, parenchyma and pleura (Table 2) [66]. Whether CLE-imaging will actually improve the diagnostic yield and reduce complication rates, should be the subject of prospective comparative studies.

DISCUSSION
Both bronchoscopic OCT- and CLE-imaging have been applied for real-time, near-microscopic evaluation in vivo in a wide variety of pulmonary diseases and different anatomical compartments, including lung cancer, pleural malignancy, interstitial and obstructive lung diseases. For clinical application, clinical perspectives for (PS-)OCT imaging include assessment of airway remodelling in obstructive airway disease and differentiating (fibrotic) subtypes of ILD. CLE-imaging has shown promising results to improve the diagnosis of lung cancer and pleural malignancy. In a desirable future concept, immediate tumour ablation could be performed after (nCLE) malignancy confirmation. Molecular OCT- and CLE-imaging with labelled markers will be of great interest to assess tumour environment and the distribution of antibodies to evaluate treatment effects in pulmonary diseases. Furthermore, the development of automated image recognition software could contribute to an improved image interpretation and ease clinical application. However, as
most studies are still exploratory and performed in research settings, larger and comparative studies are needed before implementation in standard clinical care.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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This study shows OCT is a well tolerated, accurate method to differentiate UIP from non-UIP histopathological pattern using histology as the reference standard.

This study shows how OCT provides a unique ability to assess the small airways and to visualize and quantify tissue compartments in 3D.

This letter shows how changes of the airway structures can be assessed by the use of OCT.

This study shows OCT is a well tolerated, accurate method to differentiate UIP from non-UIP histopathological pattern using histology as the reference standard.

This study shows how OCT provides a unique ability to assess the small airways and to visualize and quantify tissue compartments in 3D.