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Optical Coherence Tomography as an Adjunct to Flexible Bronchoscopy in the Diagnosis of Lung Cancer: A Pilot Study

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ABSTRACT

Background: Lung cancer is the leading cause of cancer-related deaths in the United States and the second most common type of cancer in both men and women. Optical coherence tomography (OCT) can generate high resolution cross-sectional images of complex, living tissues in real time. The objectives of this study were to determine the feasibility of using OCT during flexible bronchoscopy, and to preliminarily assess the ability of OCT to distinguish an endobronchial malignancy from normal endobronchial mucosa.

Methods: A Niris™ OCT probe was introduced into the airways of patients with an endobronchial mass during flexible bronchoscopy. An investigational device exemption was approved by the FDA for the use of the OCT system in this study. Conventional OCT scans of an endobronchial mass and a control area of normal bronchial mucosa were done to generate real time images in each patient. Following OCT imaging, the same sites were biopsied for pathologic correlation.

Results: We report on the first 5 patients enrolled. A total of 60 OCT images with corresponding endobronchial biopsies were obtained. The average procedure time was 29 minutes. The histopathologic diagnoses of the endobronchial masses included 2 small cell carcinomas, 1 squamous cell carcinoma, 1 adenocarcinoma, and 1 endobronchial schwannoma. Microstructures of normal bronchial mucosa, including epithelium and lamina propria, were identified with OCT. OCT features of malignancy included loss of normal, identifiable microstructures and subepithelial “optical fracture” of tissues. All patients tolerated the endobronchial imaging well without complications.
Conclusions: Preliminary results suggest that OCT is a technically feasible adjunct to flexible bronchoscopy in the diagnosis of lung cancer. This is the first reported use of OCT to generate images of endobronchial neoplasms during flexible bronchoscopy in the United States. This technology may in the future provide a non-invasive “optical biopsy”, which could potentially guide the bronchoscopist to areas for biopsy or even obviate the need for conventional lung biopsies.

Trial Registration: ClinicalTrials.gov Identifier: NCT01039311

Abbreviations: OCT = Optical coherence tomography
INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the United States and the second most common type of cancer in both men and women. Over 85% of lung tumors originate in the bronchial epithelium with multi-stage cellular changes advancing over a relatively long period of time before their first presentation of invasive cancer. Endobronchial samples are obtained when suspected mucosal abnormalities or visible endobronchial masses are identified, most commonly by chest x-ray, spiral computed tomography, and positron emission tomography. Sometimes, it is difficult to identify subtle mucosal changes that may be a precursor or a harbor of a malignant process. Several endobronchial techniques, such as autofluorescence bronchoscopy and endobronchial ultrasound, have been investigated to better identify areas in need of biopsy. Autofluorescence bronchoscopy enhances identification of in situ mucosal abnormalities, but this method is limited by inadequate image resolution and tissue depth penetration. High-frequency endobronchial ultrasonography (EBUS) achieves deeper penetration of airway tissue, but offers insufficient spatial resolution for clear demarcation of the microstructural profile and morphologic changes.

Optical coherence tomography (OCT) is a rapidly evolving imaging technology capable of generating real time, high resolution, cross sectional images of complex, living tissues. OCT is similar to ultrasound in that it measures phase and intensity differences of reflected or backscattered wave signals from tissues. Unlike ultrasound which uses sound waves, OCT analyzes interference patterns from low-power, near-infrared light to generate topographical images. Compared to ultrasound, OCT systems used in prior clinical studies demonstrate greater
sensitivity and much higher resolution (approximately 10-20 micrometers with a depth of penetration at 2 millimeters) of tissues in the lower respiratory tract. The objectives of this pilot study were to determine the feasibility of conventional OCT during flexible bronchoscopy and to preliminarily assess its ability to distinguish an endobronchial neoplasm from normal endobronchial mucosa. To our knowledge, this is the first reported use of OCT as an adjunct to diagnostic flexible bronchoscopy in the United States.

METHODS AND MATERIALS

Study population

Subjects were enrolled at the University of Oklahoma Health Sciences Center from June 2009 to December 2009. Study inclusion criteria included subjects 18-99 years of age with the presence of an endobronchial mass seen on chest imaging and the need for flexible bronchoscopy with endobronchial biopsies. An arterial blood gas was obtained pre-procedurally on all patients. Exclusion criteria included a PaCO2 > 47 mm Hg, long term oxygen therapy, unwillingness to undergo flexible bronchoscopy, coagulopathy (defined as a platelet count < 100,000/mm3, or an INR> 1.4, or known clinical bleeding disorder), or current therapy with an anticoagulant (including warfarin and clopidogrel). Additional exclusion criteria included renal dysfunction (defined as a creatinine > 2 mg/dl), life-threatening arrhythmias, history of myocardial infarction or cerebrovascular accident within the preceding 6 months, facial abnormalities preventing safe introduction of the bronchoscope, uncontrolled hypertension, active liver disease, pregnancy, breastfeeding, or inability to give informed consent. The study was approved by the Institutional
Review Board at the University of Oklahoma Health Sciences Center and informed consent was obtained for all subjects.

Optical Coherence Tomography

Conventional OCT was performed using a commercially available system (Niris® Imaging System, Imalux® Corp., Cleveland, Ohio). This system is cleared by the Food and Drug Administration for use as an imaging tool in the evaluation of human tissue microstructure (FDA 510(k) Number K042894). An investigational device exemption for the use of this OCT system during flexible bronchoscopy for lung masses was approved by the FDA. (IDE G080136/S002).

The Niris™ is a compact, time-domain OCT system comprised of an imaging console and a flexible, forward facing, magnetically actuating probe. This system uses near infrared, back-scattered light to generate two-dimensional images with a depth resolution of 10–20 micrometers and a lateral resolution of 20-25 micrometers. Spatial information is determined from the time delay of reflected signals according to the formula $Z = \Delta T \times v$, where $Z$ is the distance the signal travels, $T$ is the time, and $v$ is the light wave propagation velocity (Figure 1). The lateral scanning range is 2.0 mm with an image depth of 2.2 mm (Figure 2). These imaging capabilities allow penetration through the upper layers of exposed tissues on airway surfaces where many airway neoplasms may present, and are equivalent to the tissue sampling depth of conventional endobronchial forceps.


Procedure

All procedures were conducted in a bronchoscopy suite at the University of Oklahoma Health Sciences Center. After informed consents were obtained, patients were sedated using midazolam and meperidine. The upper airways were anesthetized with topical lidocaine. Using trans-nasal flexible bronchoscopy, a complete airway exam was performed. Upon identification of an endobronchial mass, a saline wash of the mass was obtained for cytology. The bronchoscope was then removed, and a second flexible bronchoscope pre-loaded with the OCT probe (Figure 3) was introduced trans-nasally into the lower airways. Since the re-usable OCT probe (outer diameter of 2.7 mm) does not fit through the working channel of a conventional flexible bronchoscope, the probe tip was attached to the exterior of the scope using a size 28 Fr Rusch™ PVC nasal airway. The flexible bronchoscope was then used to guide the OCT probe tip to the endobronchial mass under direct visualization.

Once mucosal contact was made with the OCT probe tip, an imaging console was used to generate and save a total of 6 real time OCT images of the mass. The bronchoscope and attached OCT probe were then moved to an area of normal appearing bronchial mucosa, and 6 additional OCT images of the normal appearing mucosa were generated. Upon completion of the imaging, 6 corresponding biopsies of the endobronchial mass and 6 control biopsies of the imaged normal appearing area were done. Brushings of the endobronchial masses were then done and sent for analysis.

Patients were monitored for any immediate post-procedure complications. A Steris™ sterilization system was used to sterilize both the OCT probe and the bronchoscopes. All OCT images from this study were reviewed by the investigators. Collected data included subject’s
demographics, smoking history, comorbid pulmonary conditions, tumor size, biopsy site locations, and total procedure time.

**Histologic Analysis**

Biopsy specimens were processed by the Department of Pathology of the University of Oklahoma Health Sciences Center. Formalin fixed, paraffin embedded sections were cut at a thickness of 5 micrometers for both normal control and tumor biopsy samples. The tumor biopsy specimens were examined and reported upon in routine fashion. These samples were further examined with their corresponding normal control samples by an experienced pulmonary pathologist (KMF). Immunohistochemistry for S100 was performed with a rabbit polyclonal antibody using an automated immunohistochemistry system (Ventana BenchMark® ULTRA, Ventana® Medical Systems, Tuscon, AZ) with dianminobenzidine as chromogen and lightly counter-stained by hematoxylin. Immunohistochemistry was performed with adequate positive and negative controls.
RESULTS

Eight patients with endobronchial masses on chest imaging were screened during the study period. Five patients were found to be eligible and participated in the study. A single endobronchial mass was identified in each subject during flexible bronchoscopy. A total of 60 endobronchial OCT images and corresponding biopsies were obtained from the 5 subjects - 30 from an endobronchial mass and 30 from areas of normal appearing bronchial mucosa. A library of OCT images with their corresponding histology was constructed. (Figures 1, 2, and 3 of the online supplement).

Clinical characteristics of all 5 patients are summarized in table 1. The histopathologic diagnoses of the endobronchial masses included 2 small cell carcinomas, 1 squamous cell carcinoma, 1 adenocarcinoma, and 1 endobronchial schwannoma. These tumors all displayed classic histopathologic features of their respective types. There was no histopathologic evidence of neoplastic or other abnormal changes in the control biopsies from areas of normal appearing bronchial mucosa. All 4 patients with carcinomas were smokers with a history of COPD. The single benign tumor was an endobronchial schwannoma which was found in the left lower lobe bronchus of our youngest, and only non-smoking subject. The average procedure length was 29 minutes. All subjects tolerated the procedure well without any immediate complications.

OCT images showed differences between neoplasms and normal bronchial mucosa. Images from normal areas displayed defined layers of epithelium, basement membrane and lamina propria (Figure 4A). Subepithelial areas in normal tissues had a variety of polymorphic light and dark areas which were likely produced by microscopic structures including seromucinous glands, fibroconnective tissues, and cartilage. Malignant tumors in the first 4
patients had loss of normal, identifiable microstructures (Figure 4B). The thickness of surface
epithelium in OCT images ranged from 20-50 micrometers and corresponded to the thickness of
the lining epithelium in the histologic sections. OCT images from neoplastic lesions displayed
irregular, ragged, dark lines between two light areas that had the appearance of a fracture in the
subepithelium. We termed these dark lines “optical fractures” (Figure 5) and postulate that they
represent an OCT feature of neoplasm.

DISCUSSION

The objective of this pilot study was to determine if it is feasible to use conventional
OCT as an adjunct to flexible bronchoscopy in the evaluation of patients with suspected lung
cancer. Although the use of OCT during rigid bronchoscopy for tracheal lesions has been
reported \(^8,^9\), this is the first reported use of OCT in the United States during flexible
bronchoscopy for bronchial lesions. Our data show that OCT can be used during flexible
bronchoscopy to provide images of endobronchial tumors in large airways with a relatively short
total procedure time. As none of our patients experienced any complications during or following
the procedure, we believe that the use of OCT likely adds minimal risk to conventional flexible
bronchoscopy in selected patients.

The earliest and most extensive clinical use of OCT has been in ophthalmology for retinal
imaging in patients with macular degeneration \(^10,^11\). This technology has been used by
otolaryngologists and has been shown to be a feasible adjunct to awake trans-nasal laryngoscopy
\(^12\). OCT can clearly identify basement membrane violation and transition zones at cancer
margins in patients with laryngeal cancer \(^13\). Gastroenterologists have found that \textit{in vivo} OCT
correctly detected disease features of ulcerative colitis in endoscopically affected colon segments with high sensitivity. OCT has been studied for use by dermatologists for monitoring cutaneous inflammation and hyperkeratotic conditions. In the field of cardiology, OCT is being compared to intravascular ultrasound for characterization of coronary artery disease. Anatomical OCT (aOCT), a variant of conventional OCT, has been show to be helpful for real-time large diameter airway measurements.

Although using OCT during flexible bronchoscopy appears to be feasible, it remains technically difficult. The Niris™ is the only OCT imaging system with a flexible probe that is approved by the FDA for use in the United States. Currently, no commercially available flexible bronchoscope can accommodate the Niris™ probe, as the rigid probe tip will not pass through the working channel. Using the OCT probe on the exterior of the bronchoscope resulted in limited scope flexion, causing a somewhat difficult passage of the bronchoscope through the upper and lower airways. FDA clearance of an OCT probe that fits down the working channel of a standard flexible bronchoscope is needed for practical use of this technology in the U.S.

Interpretation of the OCT images in the lung is an evolving field of study. OCT is capable of generating images of epithelium, mucosa, cartilage and subepithelial structures in animal and human trachea, and has been shown to identify morphologic changes associated with inflammatory infiltrates, squamous metaplasia, and tumor presence in resected lung specimens. In a recent study by Lam et al using radial scanning endobronchial OCT, bronchial epithelial thickness of invasive lung carcinoma was significantly greater than that of carcinoma in situ. Investigators from that study used a radially scanning OCT probe which generates different views of bronchial mucosa than the forward scanning probe utilized in our study. In our study, no areas of carcinoma in situ were identified and there was no significant
difference in epithelial thickness from benign mucosa and the malignant tumors that had an identifiable epithelial layer. Although increased epithelial thickness may be an important feature of lung malignancies, we feel that other OCT architectural features may be equally important in distinguishing lung malignancies from normal bronchial mucosa.

A goal of our pilot study was to generate a library of OCT images with corresponding pathology findings to preliminarily determine if OCT can distinguish malignancies from normal bronchial mucosa. We feel that we may have identified some OCT characteristics of malignancy, including the loss of normal, identifiable epithelial and subepithelial microstructures and possibly subepithelial “optical fracture”. The mechanism of optical fracture is uncertain. As infiltrative carcinomatous tissue tends to be more fibrotic than the surrounding normal tissue, we postulate that optical fracture is due to the interference pattern of backscattered light from an interface between two distinct tissue densities which are found in tumors. To further characterize OCT features of malignancy, we intend to continue our current recruitment. Once we identify these features, we plan to validate our findings prospectively in a separate, larger group of patients.

Limitations of this pilot study include a small sample size and an inherent inability to precisely biopsy the exact sites from which the OCT images were obtained. In addition to our ongoing trial, further studies are needed to determine the sensitivity and specificity of this evolving technology in identifying lung cancer during routine diagnostic flexible bronchoscopy.

OCT could become a powerful tool in diagnostic pulmonary medicine, not only in the early recognition of lung cancer, but also in the evaluation and monitoring of microstructures in the lower respiratory tract that are affected by other inflammatory or invasive disease processes. It could potentially be used in conjunction with endobronchial ultrasound, autofluorescence...
bronchoscopy, or narrow band imaging to guide the location of biopsies. Using a combination of multiple imaging modalities may provide increased diagnostic yield during bronchoscopy. This technology may provide a non-invasive “optical biopsy”, which could potentially obviate the need for conventional biopsies, particularly in patients with high risks for biopsy-related complications, such as bleeding.

CONCLUSION

Conventional OCT during flexible bronchoscopy appears to be feasible in patients with endobronchial tumors. This is the first reported use of this technology during flexible bronchoscopy in the United States. OCT features of malignancy may include loss of normal landmarks in the bronchial epithelium and lamina propria. Further studies are needed to determine the diagnostic yield of OCT in the evaluation of endobronchial lesions.

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REFERENCES


FIGURE LEGENDS

Figure 1: OCT principles of operation. Spatial information is determined from the time delay of reflected light signals according to the formula $z = \Delta T \times v$, where $Z$ is the distance the light signal travels, $T$ is time, and $v$ is the light wave propagation velocity. Republished with permission from Imalux.

Figure 2: Light signal intensity diminishes at increased tissue depth. Lateral scanning range is 2 mm. For reference, the white horizontal scale bar is 1 mm. Republished with permission from Imalux.

Figure 3: Flexible bronchoscope with the OCT imaging probe attached to the scope exterior using a size 28 Fr Rusch™ PVC nasal airway.

Figure 4: (A) OCT images from normal bronchial mucosa in patient 1, showing normal layers of epithelium (white arrow) and lamina propria (black arrow). (B) OCT image from the tumor area in the same patient, showing loss of identifiable microstructures.

Figure 5: “Optical fracture” in an OCT image of small cell carcinoma from patient 2. This ragged, irregular, dark line between two light areas in the subepithelium was seen in OCT images of neoplastic lesions.
Table 1 - Clinical Characteristics of the 5 patients

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* C: Caucasian; AA: African American; LUL: Left Upper Lobe; RUL: Right Upper Lobe.
\[ z = \Delta T \cdot v \]
Online supplement figure legends: Library of OCT images

**Figure 1:** Small Cell Carcinoma (Patients 1 & 2). Histologic and OCT images from the normal carina (A, A1-A6) and left upper lobe tumor (B, B1-B6) in Patient 1. High magnification of the normal epithelial cells and tumor cells are illustrated in the insets respectively. Similar images from the normal carina (C, C1-C6) and left upper lobe tumor (D, D1-D6) in Patient 2. In the histologic images, the epithelia are highlighted by black arrows. Geographic, ragged dark lines or gaps (optical fractures) are present in OCT images from tumor areas but not in normal control tissue. Original magnification of the histologic pictures is 10x and 60x for the insets. The white horizontal scale bars in the OCT images correspond to 1 mm.

**Figure 2:** Non-Small Cell Carcinoma (Patients 3 & 4). Histologic and OCT images from the normal left upper lobe (A, A1-A6) and right upper lobe tumor (B, B1-B6) in Patient 3 with poorly differentiated adenocarcinoma. High magnification of the normal epithelial cells and tumor cells are illustrated in the insets respectively. Note the intracellular mucin illustrated in the inset (B). Similar images from the normal carina and right upper lobe tumor in Patient 4 with squamous cell carcinoma are illustrated in (C, C1-C6) and (D, D1-D6) respectively. In the histologic images, the epithelia are highlighted by black arrows. No normal surface epithelium is present in the biopsy material of the tumor in patient 4. The OCT images show geographic, ragged, dark lines or gaps (optical fractures) in the tumor areas but not in normal control tissue. Original magnification of histologic pictures is 10x and the insets is 60x. The white horizontal scale bars in the OCT images correspond to 1 mm.
**Figure 3:** Schwannoma (Patient 5). The histologic (A) and OCT images (A1-A6) of normal mucosa are illustrated. Panoramic views of the biopsy material stained with hematoxylin and eosin stain (B) and immunohistochemistry for S100 (C). Note that the tumor is submucosal and stained brown (C). Subepithelial non-neoplastic area (1) and tumor (2) which display different cell densities in additional histology images (D, E). This tumor has classic palisading spindle cell morphology (F) and is strongly positive for S100. OCT images of the tumor are illustrated (B1-B6). Note that the irregular optical fracture lines are also present. In addition, there are areas with smooth streaming of dark and light areas in the tumor but not in the normal areas. These areas may be due to the change in cellular density of the tumor and connective tissue. The surface epithelium is highlighted by black arrows in A, B and E. Original magnification is is 10x (A,F), 4x (B, C), 60x (D, E, inset F). The white horizontal scale bars in the OCT images correspond to 1 mm.
Optical Coherence Tomography as an Adjunct to Flexible Bronchoscopy in the Diagnosis of Lung Cancer

A Pilot Study

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e-Figure 1.
e-Figure 2.
Figure 3.
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