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Authors
Colt, Henri G
Murgu, Septimiu D
Jung, Bockhyun
et al.

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Multimodality Bronchoscopic Imaging of Recurrent Respiratory Papillomatosis

Henri G. Colt, MD[1], **Septimiu D. Murgu, M.D**[1], **Bockhyun Jung, MD**[2], **Yeh-Chan Ahn, PhD**[3], and **Matt Brenner, MD**[1,3]

[1]Pulmonary and Critical Care Medicine, Department of Medicine, University of California School of Medicine, Irvine, CA; 101 the City Drive South Bldg 53, Rm 119, Rt 81 Orange, CA 92868

[2]Department of Internal Medicine, Pulmonary and Critical Care Medicine, University of Ulsan, Gangneung Asan Hospital, Gangneung, Korea

[3]Beckman Laser Institute, University of California, Irvine; 1002 Health Sciences Road Irvine, CA 92612

Abstract

Objective/Hypothesis—Recurrent respiratory papillomatosis (RRP) of the central airways requires removal in order to potentially reduce recurrence and risk for malignant transformation. Analogous to the principles of treatment for early lung cancer, a precise determination of the extent of cartilage invasion could help guide therapeutic decisions and monitor response to treatment. The purpose of this study was to determine whether a bronchoscopy platform comprised of white light bronchoscopy (WLB), endobronchial ultrasound (EBUS), and optical coherence tomography (OCT) could identify layered microstructure of RRP and underlying cartilage.

Study Design—Case study

Methods—A bronchoscopy platform consisting of commercially available WLB, EBUS using a 7.5MHz convex probe (BF-UC 160F: Olympus Optical Co. Ltd, Tokyo, Japan) and a time-domain OCT with front-imaging and inside-actuation (Niris® Imaging system, Imalux® Corp, Cleveland, USA) was used in a patient with tracheal stenosis from RRP. Findings are compared with results of histology and the characteristics of imaging modalities are discussed.

Results—WLB revealed tracheal pedunculated lesions. EBUS showed a 1 cm hypoechogenic density corresponding to the papilloma, visualized above a hyperechogenic density corresponding to tracheal cartilage. There was no sonographic evidence of cartilage disruption or adjacent lymphadenopathy. OCT revealed a layer of heterogeneous light backscattering suggesting the mucosal papilloma, and a layer of high degree scattering, corresponding to the central fibrovascular core noted on histology.

Conclusions—Layered microstructures of RRP and underlying airway cartilage can be identified using a combination of acoustic and optical bronchoscopic imaging modalities with different resolution and depth of penetration characteristics.

Keywords

Bronchoscopy; Optical Coherence Tomography; Endoscopic Ultrasonography; Papillomatosis

Corresponding Author: Henri Colt, MD, UCI Medical Center, 101 the City Drive South, Bldg 53, Rm 119, Rt 81, Orange, CA 92868, hcolt@uci.edu, TEL: 714-456 5150 FAX: 714-456 8349.

Conflict of interest: None

Introduction

Recurrent Respiratory Papillomatosis (RRP) of the tracheobronchial tree is difficult to control, causes significant morbidity, and in almost 2 percent of cases may undergo malignant transformation[1]. Treatment includes palliative bronchoscopic resection, and potentially curative gene therapy (EGFR tyrosine kinase inhibitors), retinoids (oral metabolites or analogues of vitamin A), photodynamic therapy (PDT) and intra-lesional injection of antiviral agents in an attempt to induce growth arrest, apoptosis, inhibit the proliferation or promote normal differentiation of HPV- infected cells[2]. Malignant degeneration is aggressive and often rapidly fatal, albeit infrequent in the absence of prior radiation therapy [3]. While no treatment has consistently been shown to eradicate RRP, the removal of papilloma tissue as completely as possible without compromising normal airway wall structures may reduce recurrence and risk for malignant transformation. Analogous to the principles of treatment for early lung cancer [4], a precise determination of the extent of mucosal and cartilaginous wall invasion could, someday, help guide therapeutic decisions. If minimally invasive imaging technologies would identify the layered microstructure of papilloma, in-vivo changes in these structures might be noted in response to treatment.

The purpose of this study was to determine whether a multidimensional bronchoscopy platform comprised of white light bronchoscopy (WLB), conventional endobronchial ultrasound (EBUS) and optical coherence tomography (OCT) could identify layered microstructure of RRP and the underlying cartilage. The pathophysiologic features of RRP potentially relevant to these imaging modalities are described, and the advantages and disadvantages of this multimodality bronchoscopic imaging platform are presented.

Materials and Methods

A patient with a history of RRP presented with increased cough, shortness of breath and hoarseness. Computed tomography of the neck revealed stenosis from intraluminal abnormalities in the upper third of the trachea (Figure 1A). Multimodality imaging using commercially available EBUS with a 7.5MHz convex probe (BF-UC 160F: Olympus Optical Co. Ltd, Tokyo, Japan) (Figure 1B), white light bronchoscopy (Figure 2A and 2B), and two dimensional, time-domain OCT (Niris® Imaging system, Imalux® Corp, Cleveland, USA) (Figure 2C and 2D) was performed in order to identify features potentially suggestive of cartilage disruption as well as to visualize the layered microstructures of the lesion as compared with normal airway wall. Rigid bronchoscopy with Nd:YAG laser resection was performed in order to restore airway patency (Figure 3).

Results

WLB revealed two pedunculated cauliflower-like lesions in the upper trachea (Figure 2A). EBUS showed a 1 cm hypoechogenic density corresponding to the papilloma lesion which was visualized above the hyperechogenic density corresponding to the tracheal cartilaginous ring at the level of left upper tracheal lesion. There was no sonographic evidence of cartilage disruption (hypoechoic signal within the hyperechoic cartilaginous layer) and no evidence of paratracheal lymphadenopathy around the lesion (Figure 1B). Due to its limited resolution, EBUS did not reveal layered microstructures of the papilloma. The OCT system (Niris® Imaging system, Imalux® corp, Cleveland, USA) with frontal imaging flexible probe and higher resolution was then used (Figure 2). Comparative images were first obtained of normal appearing tracheal mucosa and underlying cartilage. Examining the papilloma, two-dimensional OCT imaging revealed a layer of heterogeneous light backscattering suggestive of the mucosal tumor. Also seen was a layer of high degree scattering, subsequently shown

to possibly correlate with the central fibrovascular core of the papilloma noted on the histologic section of the endotracheal biopsy taken from the same region. The loss of distinct multilayered architecture was seen in the papilloma as compared with distinct layering of normal mucosa (Figure 2C & 2D). Histology revealed papilloma with features of koilocytic atypia and squamous metaplasia without evidence of malignant transformation (Figure 3A), and the fibrovascular core possibly corresponding with the OCT image (Figure 3B). In-situ hybridization analysis was positive for human papilloma virus (HPV) subtypes 6 and 11.

Discussion

Overview of recurrent respiratory papillomatosis

RRP is caused by stem cell infection within the basal layer of airway mucosa by human papilloma virus (HPV) types 6 and 11 [1]. HPV activates the epidermal growth factor receptor (EGFR) pathway and results in abnormal cellular proliferation and defective epithelial differentiation as demonstrated by absent or reduced levels of keratin 13 expression [5]. These processes result in the formation of macroscopically visible “cauliflower-like” exophytic lesions often responsible for symptoms of central airway obstruction[1]. Although histologically benign, RRP is difficult to control, has a high recurrence rate, causes severe morbidity, and may undergo malignant transformation[1]. HPV is often present in macroscopically unaffected airway mucosa, and currently, it is not possible to distinguish with certainty the degree of involvement based solely on white light examination [1]. Proliferation of HPV within the mucosa results in multiple finger-like projections (aka fronds) with a central fibrovascular core covered by stratified squamous epithelium with koilocytic atypia (Figure 3A).

Overall, therapeutic goals are to reduce tumor burden, restore airway patency, improve symptoms, decrease spread of disease, and increase the time interval between endoscopic interventions[1]. While no therapy has consistently been shown to eradicate RRP, the removal of HPV-involved tissues as completely as possible, and without compromising normal airway structures, appears necessary to reduce recurrence. Analogous to the field of early lung cancer, an accurate evaluation of the depth of invasion into the airway wall may one day help choose among various therapeutic alternatives as well as monitor response to treatment.

Multimodality Imaging: Potential Clinical Applications

The premise for a multimodality bronchoscopic imaging platform is that the combination of different technologies with various resolution and depth of penetration characteristics will enhance the characterization of benign and malignant processes [6- 8]. Investigators are already proposing the use of EBUS in addition to WLB, for example, to document minimal depth of tumor invasion and total integrity of airway cartilage as prerequisites for choosing photodynamic therapy as a treatment for early lung cancer [4]. Eventually, the use of multidimensional imaging modalities might also identify tissue and cellular alterations in-vivo without resorting to biopsy in order to monitor response to therapy.

For RRP in particular, the current standard of care is complete surgical resection of papillomas while preserving normal structures. Adjuvant modalities such as PDT, intra-lesional injection of antiviral agents, retinoids and gene therapies, however, are also recommended in approximately 20 % of patients suffering from this disease[1]. Considering advances being made in other fields, one might speculate on the potential future applications of a multimodality diagnostic platform in RRP. Assessing the depth of invasion and cartilage integrity by EBUS, for example, might identify indications for PDT. This application has already been proposed in treatment planning for early lung cancer where, if

tumor invades into or beyond the cartilaginous layer, PDT might not be warranted because of its limited penetration [4].

In regards to the use of high resolution OCT, HPV-induced epithelial cellular proliferation might be identified in otherwise normal-appearing mucosa. By precisely assessing the extent of abnormalities not identified by WLB, one could potentially select a more appropriate diffuser length for PDT, or more accurately determine sites for intra-lesional application of antiviral agents. Furthermore, the differentiation of RRP epithelium induced by antiviral agents, retinoids and gene therapies[1, 2, 5] might be dynamically monitored in-vivo, thereby advancing science and providing greater insight into the reasons for therapeutic success or failure.

The multimodality diagnostic platform used in this study combined white light bronchoscopy, convex low-resolution endobronchial ultrasound, and a commercially available time-domain higher resolution optical coherence tomography system. Conventional bronchoscopy uses a white light source and endoscope with a distal lens that provides forward visualization and a large field of view. Subtle surface abnormalities are easily overlooked, and because there is no depth of penetration, subsurface lesions are readily missed [9]. WLB is neither sensitive nor specific for superficial or infiltrating mucosal abnormalities, has no cross-sectional imaging capabilities, and makes biopsy unavoidable for studies of tissue architecture.

EBUS, on the other hand, allows acoustic cross sectional imaging and identification of the structural layers of the airway walls. EBUS has been shown to be clinically useful in diagnosing mediastinal lymphadenopathy and staging lung cancer and in early lung cancer, can help therapeutic decision-making based on presence of cartilaginous wall involvement [10]. The commercially available conventional convex EBUS probe such as that used in this study has a frequency of 7.5 MHz, allowing for deep penetration but with a relatively low spatial resolution. Acoustic coupling is enhanced by using a water-filled balloon surrounding the transducer tip. Individual airway wall layers may be difficult to identify but the cartilage is visualized [7].

OCT is an evolving optical imaging modality based on the detection of reflected light waves. Unlike ultrasound, light waves do not require a liquid-based coupling medium and thus are more compatible with airway imaging. For example, while performing EBUS, the need to closely apply an inflated water-filled balloon probe to the airway surface can adversely affect the accurate evaluation of bronchial wall invasion. Using OCT, however, because the velocity of light is 200,000 times faster than that of sound, a technique known as low coherence interferometry is necessary for image construction [11]. In order to realize more practical real-time imaging of larger areas, even higher speed scanning capabilities are required than were obtained using this commercial time domain OCT system. This may include a high speed swept laser source or spectral domain systems that capture the interference pattern of the low coherence interferometer. OCT allows a resolution in the range of 1-10 μm. With its high tissue resolution, compact, portable and relatively inexpensive optical components, OCT can employ small diameter flexible non-contact probes which do not influence spatial resolution, and can provide optical image acquisition without morphologic tissue distortion. The depth range of OCT is limited to 2-3 mm below the airway surface, where many airway cancers and premalignant lesions originate [11]. OCT clearly identifies basement membrane violation from cancer and can identify transition zones at the cancer margin [12]. Because of its ability to discern the layered microstructure of the airways, OCT might also be useful in quantitatively assessing and guiding local therapy for airway processes [13].

In this study of a single patient with RRP, we were able to identify differences in the way these three imaging modalities characterize papilloma tissue and underlying airway cartilage. Our study has several limitations, however, in part relating to our choice of technical platforms. For example, further studies are warranted using an endobronchial ultrasound system with different acoustic properties. The commercially available, but currently infrequently used EBUS radial probe has a frequency of 20 MHz and resolution of less than 1 mm. Despite its limited depth of penetration this device has been used to distinguish central airway wall structural abnormalities in patients with benign airway disorders such as malacia caused by tuberculosis, relapsing polychondritis, and extrinsic compression by vascular rings, as well as to visualize structural differences in the membranous and cartilaginous portions of the central airways in patients with expiratory central airway collapse and the extent of intramural endobronchial tumor invasion in patients with early lung cancer [8].

In regards to the high resolution optical imaging platform, we used a commercially available, compact time-domain OCT system (Niris® Imaging system, Imalux® Corp, Cleveland, USA) with a frontal viewing flexible probe. This probe's diameter (2.7 mm) is unfortunately too large to fit through the 2.8 mm working channel of a flexible bronchoscope, and thereby requires rigid bronchoscopic application. Recently, the use of a single-mode fiber for light delivery as well as OCT signal acquisition has facilitated the development of very small diameter and potentially more flexible endoscopic probes. To our knowledge, the smallest currently available probes have a diameter of approximately 0.4 mm, which could be used in more peripheral airways through a flexible bronchoscope. The Niris® OCT system has approximately 15 μm resolution in the 'z" or depth direction and 25 μm of lateral resolution. It utilizes a magnetic actuation method which is capable of linear scanning only and time-domain technology, but is limited to 0.7 kHz A-scan rate capabilities. A three dimensional tomographic image cannot be constructed using this probe actuator design. Other probe designs have been developed that allow 3-dimensional scanning image acquisition.

Because there is tradeoff between sensitivity, speed and resolution, we believe it is important to develop OCT systems with performance characteristics conducive to real-time bronchoscopic applications. The highest axial resolution demonstrated so far is 0.5 μm, and high speed swept-source OCT utilizing buffered Fourier domain mode locking, for example, has been demonstrated at speeds of up to 370,000 axial scans per second, which allow three dimensional imaging within a few seconds. Recently, other OCT system designs were shown to detect airway wall thickness in obstructive ventilatory disorders, and to be able to generate macroscopic cross-sectional views of the tracheobronchial tree to around 36 mm, allowing visualization of the entire inner perimeter of a large airway in conditions such as obstructive sleep apnea, tracheal stenosis or tracheobronchomalacia [14]. Finally, we must recognize the potential future applications of other imaging technologies with submicron level resolution such as confocal endomicroscopy, which has already been shown to provide alveolar wall detail, macrophages, and basement membrane alterations associated with premalignant bronchial lesions [15]. It is possible that in the future, a multi-dimensional imaging platform using evolving technologies such as confocal endomicroscopy, higher resolution endobronchial ultrasound (30MHz) and frequency-domain OCT will provide a window onto tissue structure and function in-vivo. Potentially, this may one day replace the in vitro analysis of conventional biopsy specimens, and facilitate the dynamic study of benign and malignant processes to monitor targeted therapy.

Conclusion

To our knowledge, this is the first report of the use of a multimodality bronchoscopic imaging platform using WLB, EBUS and OCT to study tracheal RRP. Identification of the underlying airway cartilage and layered microstructures in RRP is indeed feasible, and likely to improve considering future advances in optical and acoustic technologies.

Acknowledgments

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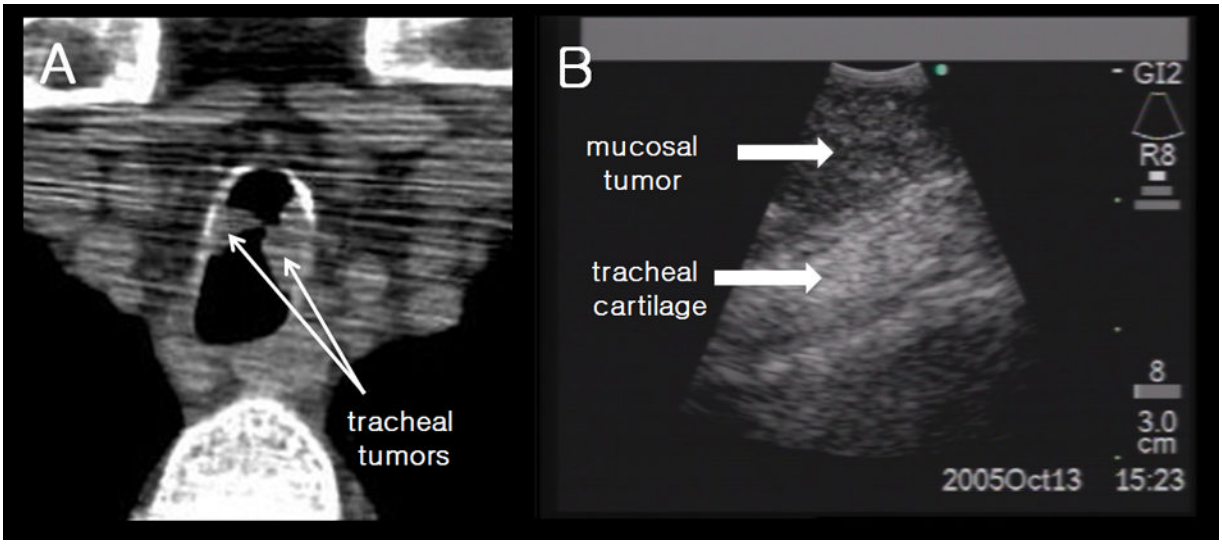

Figure 1.

A. Computed tomography shows stenosis from endoluminal masses in the upper trachea. B. Endobronchial ultrasound imaging using convex probe of 7.5 MHz shows hypoechoic density of mucosal papilloma above the hyperechoic density corresponding to tracheal cartilage.

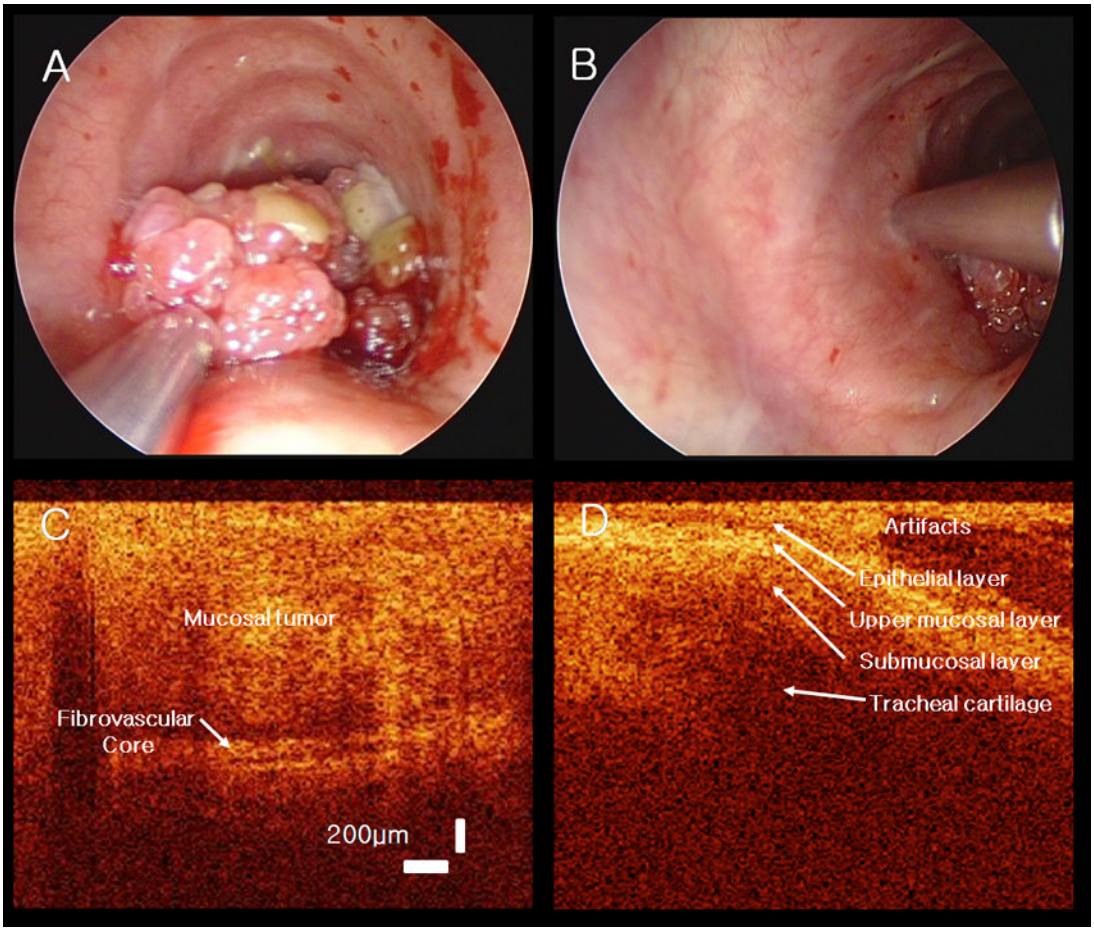

Figure 2.
Bronchoscopy shows the OCT probe overlying the pedunculated upper tracheal papilloma (A) and the normal tracheal wall (B). Two dimensional OCT images reveal the papilloma tissue with central fibrovascular core (C) and the normal mucosal structural layers (D). OCT image size is 2 mm horizontal and 2.2 mm (in air, vertical).

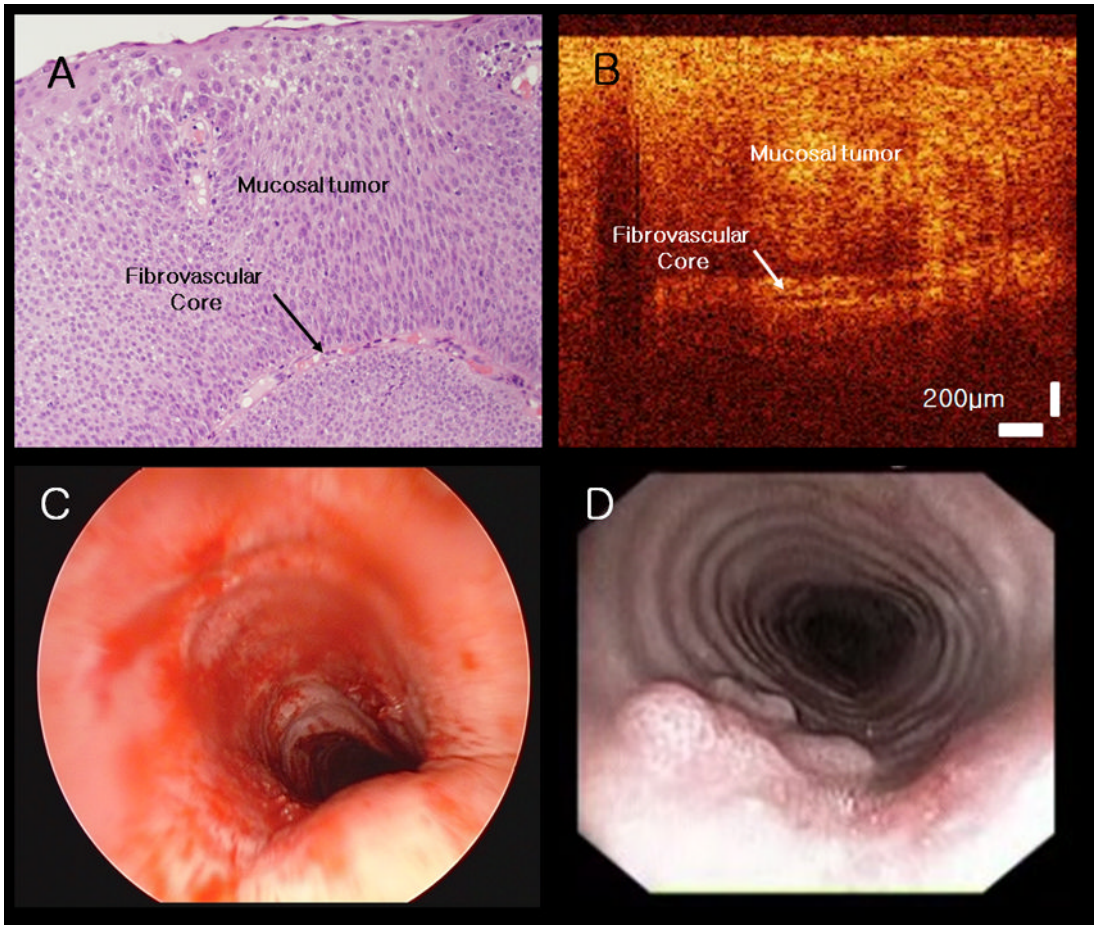

Figure 3.

A The papilloma tissue consists of stratified squamous cells with koilocytic atypia and a central fibrovascular core (magnification 20×, H&E). B. Corresponding OCT reveals heterogeneous light backscattering layer suggesting the mucosal abnormality and a high degree scattering layer suggesting the central fibrovascular core. C. Bronchoscopy immediately after laser treatment shows restored airway patency. D. Bronchoscopy four weeks later reveals velvety mucosal abnormality but no airway obstruction.