Interventional Bronchoscopy

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Abstract

For over 150 years, bronchoscopy, especially flexible bronchoscopy, has been a mainstay for airway inspection, the diagnosis of airway lesions, therapeutic aspiration of airway secretions, and transbronchial biopsy to diagnose parenchymal lung disorders. Its utility for the diagnosis of peripheral pulmonary nodules and therapeutic treatments besides aspiration of airway secretions, however, has been limited. Challenges to the wider use of flexible bronchoscopy have included difficulty in navigating to the lung periphery, the avoidance of vasculature structures when performing diagnostic biopsies, and the ability to biopsy a lesion under direct visualization. The last 10–15 years have seen major advances in thoracic imaging, navigational platforms to direct the bronchoscopist to lung lesions, and the ability to visualize lesions during biopsy. Moreover, multiple new techniques have either become recently available or are currently being investigated to treat a broad range of airway and lung parenchymal diseases, such as asthma, emphysema, and chronic bronchitis, or to alleviate recurrent exacerbations. New bronchoscopic therapies are also being investigated to not only diagnose, but possibly treat, malignant peripheral lung nodules. As a result, flexible bronchoscopy is now able to provide a new and expanding armamentarium of diagnostic and therapeutic tools to treat patients with a variety of lung diseases. This State-of-the-Art review succinctly reviews these techniques and provides clinicians an organized approach to their role in the diagnosis and treatment of a range of lung diseases.

Keywords: emphysema; lung cancer; chronic bronchitis; bronchoscopy

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For over 150 years, bronchoscopy has been instrumental in the inspection and diagnosis of airway and parenchymal lung diseases (1). Recently, the capabilities of bronchoscopy to diagnose and treat a variety of lung diseases has expanded. Bronchoscope designs with enhanced optics, greater resolution, flexibility, and smaller size, but with functional working channels, are key to these advances.

High-resolution chest computed tomography (HRCT) imaging provides enhanced structural detail of lung lesions and, coupled with navigational technology, provides endoscopic roadmaps to small distal lesions. HRCT imaging can construct pulmonary vasculature maps and provide virtual avascular paths to lesions that lack a leading bronchus. Incorporation of real-time imaging during bronchoscopy can provide precision location of difficult-to-reach targets.

Simultaneously, advances in endobronchial ultrasound (EBUS) coupled with instruments that can aspirate, biopsy, cut, brush, freeze, ablate, and vaporize tissue provides an array of modalities to diagnose and treat many lung diseases. (Table 1)

Bronchoscopic interventions in selected patients with asthma and emphysema provide new treatment options. Current research focused on treating chronic bronchitis, fixed airflow obstruction, and lung cancer offer the possibility of less-invasive, but effective, therapies. (Table 2)

Herein, we review recent advances in the diagnostic and therapeutic applications of bronchoscopy.

Interventional Bronchoscopy for Lung Cancer Diagnosis and Treatment

Modalities That Enhance Imaging and Provide Bronchoscopic Navigation to Lung Lesions

Several imaging modalities can improve access to peripheral lesions. Some modalities provide real-time imaging during navigation (convex EBUS, radial EBUS [rEBUS], fluoroscopy, and CT imaging modalities); others use planning HRCTs to create navigational paths. A patient's condition during planning HRCT is different compared with the procedure; spontaneous respiration versus intubation plus mechanical ventilation, anesthesia and paralysis, and higher inspired O_2, respectively. The latter results in atelectasis and creates CT-to-body divergence. CT-to-body divergence describes differences in targeted lesion locations identified preprocedurally by HRCT and its location during bronchoscopy. CT-to-body divergence is more important than nodule size in adversely affecting diagnostic yield and a crucial barrier to ablation (2). The following modalities have been developed to address this obstacle; however, none of the technologies have been directly compared for diagnostic yields or cost effectiveness.

Imaging Techniques

rEBUS. Launched in 1999, rEBUS (Olympus Corp.), which uses a flexible catheter and rotating ultrasound transducer to produce 360° ultrasound images, was first used to guide transbronchial lung biopsy (3). During bronchoscopy, the 20-MHz mechanical probe is inserted through a guide sheath into the lung periphery. Figure 1 shows a typical ultrasonographic image.

rEBUS is the most commonly used real-time technique to confirm a lesion during diagnosis and probe placement during therapeutic interventions. However, discordance has been reported for diagnostic yields among studies.

Steinfort and colleagues (4) evaluated over 1,400 patients with rEBUS-guided transbronchial biopsy and showed a specificity of 1.00 and a sensitivity of 0.73 for lung cancer diagnoses. Variations in diagnostic sensitivities were attributed to the prevalence of malignancy, lesion size, probe position, and use of fluoroscopy. In a multicentered controlled trial, the diagnostic yield of thin bronchoscope plus rEBUS was compared with standard bronchoscopy and fluoroscopy; average lesion size was 31.2 (±10.8) mm (5). Diagnostic yield was higher with thin bronchoscope–rEBUS compared with standard bronchoscopy and fluoroscopy (49% vs. 37%) but was not statistically significant.

Several reasons may explain differences in diagnostic yield bedside lesion characteristics. rEBUS probes are not steerable; navigation support might be useful, especially in lesions <2 cm. Eberhardt and colleagues (6) reported that EBUS with electromagnetic navigational bronchoscopy (ENB) beneficially combines real-time imaging with steerability. Diagnostic yields of the combined procedure are greater than rEBUS or ENB alone. Others have confirmed this finding (7). An opportunity exists to improve rEBUS imaging, especially semisolid lesions, to enhance diagnostic accuracy (8).

Navigational Techniques

ENB. ENB systems (Medtronic, Inc.) assist placing biopsy tools into lesions. It uses low-frequency electromagnetic waves emitted from an electromagnetic board placed under the patient. A sensor probe is mounted on a cable tip and a flexible catheter provides biopsy tool access (9).

Meta-analyses report diagnostic accuracies of 70–75% (10–12). Lesion location, nodule size, an existing bronchus sign, procedural error, and biopsy technique all affect diagnostic yield. A prospective multicenter study (NAVIGATE) evaluated ENB using the superDimension navigation system (Medtronic) in patients with a median nodule size of 20 mm (13). In 1,157 patients that underwent ENB, 94% had navigation completed; diagnostic yield was 73%. The system recently added tomosynthesis (serial X-ray images during c-arm rotation) to improve real-time fluoroscopic evaluation and address CT-to-body divergence.

The SPiN Thoracic Navigation System (Veran Medical Technologies, Inc.) is an ENB platform that uses respiratory gating technology to track moving nodules during endoscopic or transthoracic lung nodule biopsy (14). Biopsy instruments have electromagnetic sensors that guide and track the path to the target and also address CT-to-body divergence.

Virtual bronchoscopic navigation and augmented fluoroscopy. Virtual bronchoscopic images of the bronchial path to a peripheral lesion are generated by software using HRCT data. During bronchoscopy, the virtual navigational image is projected on a display screen and compared with real-time images. Eberhardt and colleagues (15) reported an 80% diagnostic yield in patients with solitary pulmonary nodules. Diagnostic yield with virtual bronchoscopic navigation (VBN) depended upon lesion size, lobar location, and bronchus sign presence.

Visual guidance to targeted lesion is superimposed onto the endoscopic image (LungPoint; Broncus Medical). An image-

Table 1. Overview of Bronchoscopic Diagnostic Tools with Advantages and Disadvantages

Navigational Techniques		Imaging Assessment of Lung Lesions		Accessing Lung Lesions		Inspection of Lymph Nodes		Assessment of Mucosal Lesions	
Technique	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**	**Technique**	**Pro/Con**
ENB	Navigation aid	HRCT	Enhanced imaging	Transbronchial needle aspirate	Readily available/ cost effective	EBUS	Readily available/ cost effective	OCT	*In vivo* cellular morphology
	Increased costs, special equipment, and training		Increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Equipment and disposable costs and training		Investigational, unclear benefit
VBN	Navigation aid	Radial EBUS	Noninvasive endobronchial imaging	Transbronchial lung biopsy	Readily available/ cost effective	EBUS with mini forceps	Greater tissue volume	CLE	*In vivo* cellular morphology
	Increased costs, special equipment, and training		Special training and equipment required		Insufficient DX tissue and complications of PTX and bleeding		Insufficient clinical data and disposable costs and training		Investigational, unclear benefit
Thin bronchoscopy with guide sheath	Peripheral access	Fused flouroscopy	Real-time visualization	Cryobiopsy	Greater tissue volume avoids crush artifact	Elastography	Noninvasive assessment of LN stiffness	Image enhancement	*In vivo* cellular morphology
	Insufficient DX tissue and special disposables and diagnostic tools		Special equipment and increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Insufficient clinical data and increased equipment costs		Investigational, unclear benefit
Ultrathin bronchoscopy	Peripheral access	CT bronchoscopy	Real-time visualization	TPNA	Access extraluminal lesions	CT bronchoscopy	Enhanced imaging	Radial EBUS	Noninvasive endobronchial imaging
	Insufficient DX tissue and special disposables and diagnostic tools		Limited access and increased cost and radiation exposure		Insufficient DX tissue and complications of PTX and bleeding		Limited access and increased cost and radiation exposure		Needs clinical data
Robotic bronchoscopy	Peripheral access/stability	CBCT + augmented flouroscopy	Real-time visualization	Thin-EBUS	Noninvasive lung imaging	Thin-EBUS	Interlobar LN real-time imaging	Thin-EBUS	Noninvasive endobronchial imaging
	Increased equipment costs and special disposables and diagnostic tools		Limited access and increased cost and radiation exposure		Investigational, unclear benefit		Investigational, unclear benefit		Investigational, unclear benefit

Definition of abbreviations: CBCT = cone beam computed tomography; CLE = confocal laser endomicroscopy; CT = computed tomography; DX = diagnostic; EBUS = endobronchial ultrasound; ENB = electromagnetic navigational bronchoscopy; HRCT = high-resolution chest computed tomography; LN = lymph node; OCT = optical coherence tomography; PTX = pneumothorax; TPNA = transparenchymal nodule access; VBN = virtual bronchoscopic navigation.

Table 2. Overview of Advantages and Disadvantages of Current and Potential Flexible Bronchoscopy Therapeutic Tools

Malignant Solitary Nodules and Lesions		Emphysema		Asthma		COPD: Chronic Bronchitis		COPD: Exacerbation		Large Airway Abnormalities: Expiratory Airway Collapse		Large Airway Abnormalities: Bronchial and Segmental Airway Stenosis	
Radiofrequency ablation	Treat cancerous SPN	Endobronchial valves	Lung volume reduction	Bronchial thermoplasty	Improve symptoms and reduce exacerbation	Rheoplasty	Improve symptoms and reduce exacerbation	Total lung denervation	Improve symptoms and reduce exacerbations	Tracheobronchomalacia	Tracheal patency		
	Under investigation		PTX and exacerbation		Multiple procedures, exacerbation, and PNA		Under investigation		Under investigation		Granulation tissue and increased secretions		
Microwave ablation	Treat cancerous SPN	Thermal vapor ablation	Lung volume reduction	Total lung denervation	Improve symptoms and reduce exacerbation	Liquid nitrogen metered cryospray	Improve symptoms and reduce exacerbation			Airway stenting	Tracheal patency		
	Under investigation		Exacerbation		Under investigation		Under investigation				Granulation tissue and increased secretions		
Thermal vapor ablation	Treat cancerous SPN	Lung coils	Lung volume reduction			Microdebrider	Improve symptoms and reduce exacerbation						
	Under investigation		Under investigation, exacerbation, and PNA				Under investigation						
Cryoablation	Treat cancerous SPN	Polymeric agents	Lung volume reduction										
	Under investigation		Under investigation, exacerbation, and PNA										
Debridement (laser, electrocautery, argon plasma coagulation, or microdebrider)	Treat cancerous lesions												
	Special hardware, disposables and training, bleeding, perforation, and airway fire												
Brachytherapy	Treat cancerous SPN											Bronchoplasty	Airway patency
	Need for trans-laryngeal catheter												Need for repeat procedures
Chemoinjection	Treat cancerous SPN											Airway stenting	Airway patency
	Under investigation												Granulation tissue and increased secretions
Photodynamic therapy	Treat cancerous lesions											Electrocautery	Airway patency
	Under investigation												Need for repeat procedures and cartilaginous injury
Airway stenting	Airway patency												
	Granulation tissue and increased secretions												

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PNA = pneumonia; PTX = pneumothorax; SPN = solitary pulmonary nodule.

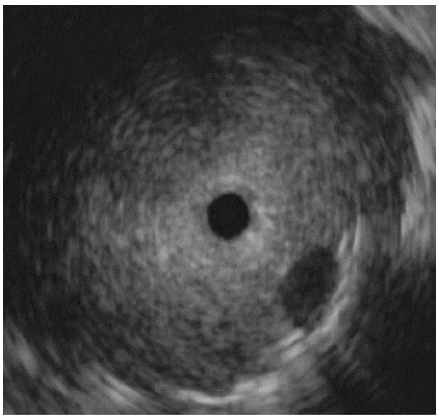

Figure 1. A radial endobronchial ultrasound probe in the center of a solitary pulmonary nodule.

based registration technique aligns virtual images with live bronchoscopic video. Once near the target, the lesion shape is overlaid onto the airway wall to provide biopsy guidance (Figure 2). Lesion shape is overlaid onto live fluoroscopic images (e.g., fused fluoroscopy or augmented fluoroscopy).

Another system uses real-time endobronchial augmented fluoroscopic navigation (BodyVision Medical Ltd.). This system enables lesion tracking during breathing movement and may improve lesion localization and diagnostic yield (16).

Others report that VBN-guided (Olympus Medical Systems) rEBUS–transbronchial diagnosis without fluoroscopy has equivalent diagnostic yield to fluoroscopy in nodules with a bronchus sign (17). Comparative evaluation of these techniques is required.

Transparenchymal nodule access. rEBUS, VBN, ultrathin scopes, and ENB improves diagnostic yield of pulmonary nodules compared with standard bronchoscopy; however, diagnostic yield still depends on lesion size, lesion location, and presence of a bronchus sign.

Some nodules lack a bronchus sign and are so distant from a bronchus that bronchoscopic sampling techniques fail. For these situations, transparenchymal nodule access was developed. The Archimedes Virtual Bronchoscopy Navigation System (Broncus Medical) reconstructs HRCT data into a three-dimensional (3D) model to provide virtual guidance of sheath placement through an airway wall and lung parenchyma into a lesion (18, 19).

A sheath with radiopaque marker bands is used to tunnel through lung parenchyma to the nodule, and samples are taken real-time under fused fluoroscopic guidance (Figure 3 A).

Herth and colleagues (20) presented a dataset at the European Respiratory Society conference showing that the yield of transparenchymal nodule access depends on lesion size.

The transbronchial access tool (TBAT; CrossCountry TBAT; Medtronic) biopsies peripheral lung nodules using rEBUS, ENB, or rEBUS plus ENB to diagnose peripheral lung nodules. (Figure 3B). TBAT with rEBUS and ENB plus cone beam CT (CBCT) may increase diagnostic yield close to 100% (21–23). Procedural time and radiation exposure is higher with use of CT. More data are needed to confirm the success of this technique.

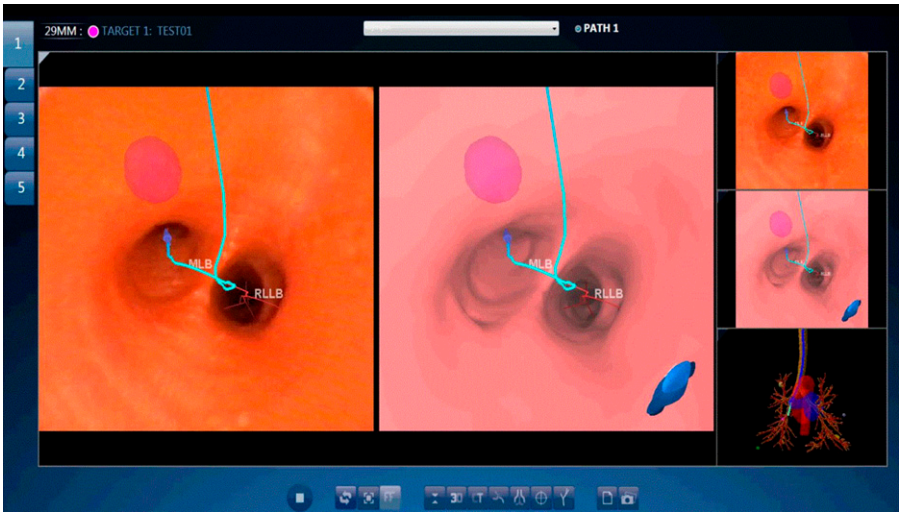

Figure 2. Overlaid track from the virtual bronchoscopic navigational pathway (right side) onto the bronchoscopic image (left side). MLB = middle lobe bronchus; RLLB = right lower lobe bronchus.

Imaging and Navigation

CT bronchoscopy. CT-guided biopsy helps the bronchoscopist biopsy fluoroscopically invisible lesions. Ultrathin bronchoscopy with CT guidance has 79% and 80% diagnostic sensitivities when a bronchus or artery, respectively, is at the center of the lesion (24). Combining VBN with CT-guided biopsy using an ultrathin bronchoscope may be helpful, especially left upper lobe lesions (24, 25). Others failed to increase diagnostic yield with CT guidance, suggesting that technical expertise may be crucial (26). Lesion location (superior segment of lower lobes), more distal navigation, and a CT bronchus or artery sign affects diagnostic yields (24). CBCT imaging to diagnose lung lesions is a modification of techniques used in digital angiography (27–29). With this technique, CBCT images are obtained and the target is overlaid on fluoroscopic images. Real-time multiplanar confirmation of lesion location in relationship to biopsy tools addresses CT-to-body divergence. A drawback is radiation bursts used to procure images during CBCT "spins." One report using CBCT with real-time ENB with or without rEBUS reported navigational and diagnostic yields of 91% and 70%, respectively (28). In malignant cases, diagnostic yield was 82% for lesions within 25 (±18) mm of the pleura (28). A study using CBCT with augmented fluoroscopy (Philips Allura Xper FD20 system with Oncosuite; PhilipsHealth) plus ENB reported a diagnostic yield of 83.7%; there was no relationship between diagnostic yield and lesion size, location, fluoroscopic visibility, or bronchus sign (30). CBCT with ENB and hook-wire localization enhances diagnosis and resection of lung lesions during the same session (27). Further investigation should compare CBCT diagnostic yield versus less costly modalities with lower radiation exposures.

Adjunctive bronchoscopic local imaging techniques. Lung cancer screening has precipitated a shift from central to more peripheral nodules for lung cancer evaluation. This has prompted development of new techniques based on sound optical,

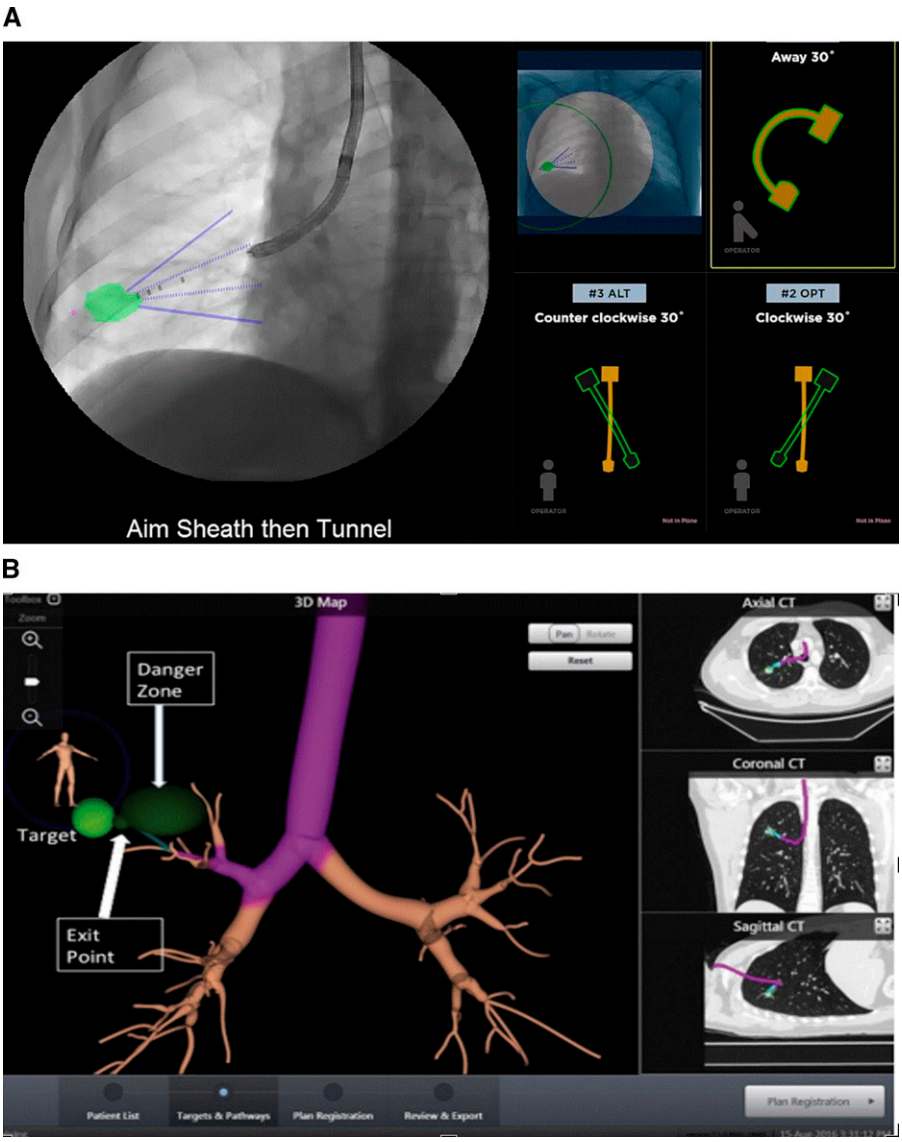

Figure 3. (*A*) View of transparenchymal nodule access on a solitary pulmonary nodule in the right lower lobe. Fused fluoroscopy is being used to create a fluoroscopically guided transparenchymal path to the superimposed target previously identified by planning high-resolution computed tomography. Purple dot represents virtual pleura. Multiple C-arm projections are used to confirm target location. (*B*) Three-dimensional (3D) map shows the danger zones and exit point, and the target lesion is demonstrated (23). CT = computed tomography.

biochemical, and physiological principles to provide greater *in vivo* guidance while biopsying small lung lesions. The clinical value of these techniques is currently unknown but has the potential to help diagnose peripheral lung cancers.

Optical coherence tomography. Optical coherence tomography (OCT) uses near-infrared light to create high-resolution images at a histology level with 10- to 15-μm resolution and 2- to 3-mm depth (31). It can identify and quantify changes in airway walls (32, 33), histologically examine lung parenchyma (34–36), and examine nodules and pulmonary vasculature. Images are captured using a 1-mm probe via the bronchoscope. OCT's clinical applications include identifying bronchial lesions (37–39), airway remodeling (40–43), subtyping interstitial lung diseases (44), and assessing vascular lesions due to pulmonary arterial hypertension (45, 46) or thromboembolic disease (47).

OCT has been used with other modalities to enhance diagnostic yield. Autofluorescence bronchoscopy (AFB)-guided OCT imaging provides *in vivo* imaging of preneoplastic bronchial lesions to study their natural history and the effects of chemopreventive intervention. In high-risk heavy smokers, Lam and colleagues (37) reported that dysplasia and carcinoma *in situ* (CIS) can be distinguished from lower-grade lesions. Polarization-sensitive OCT (PS-OCT) is another OCT imaging modality that is endoscope and/or needle compatible. It provides large volumetric views of lung tissue microstructure at high resolution (e.g., 10 mm) while simultaneously measuring birefringence of organized tissues like collagen or airway smooth muscle. In 64 lung nodule samples, PS-OCT accurately classified tumor regions with higher (>20%) from lower fibrosis, thus yielding higher tumor content with PS-OCT–directed biopsy (48).

Confocal laser endomicroscopy. Confocal laser endomicroscopy (CLE) uses low-power laser bundles to create real-time microscopic images at a cellular level. CLE has a resolution up to 3.5 μm, with a 240-μm maximum depth and 600-μm field of view (47). Contrast can enhance visualization of different cellular/tissue components. Images are captured using a probe-based CLE via bronchoscope or 19-G needle. It may help detect lung cancer (49–51), interstitial lung disease (52, 53), lung allograft rejection (54), and mediastinal lymph node pathology (55).

Image enhancement. AFB uses green- and red-spectrum light to detect mucosal alterations. Normal mucosa presents green color, whereas precancerous and cancerous lesions absorb the green spectrum and turn magenta. Narrow-band imaging removes all wavelengths except two that are absorbed by hemoglobin, thereby creating contrast between the vasculature (cyan) and surrounding mucosa (brown). AFB (56) and narrow-band imaging (57–60) are superior to white-light bronchoscopy in detecting dysplasia, CIS, or invasive carcinoma (61). Image enhancement has struggled for a role in bronchoscopy because no well-defined population exists for general use (62), poor standardization of pathological dysplastic criteria, and weak evidence for treatment of CIS (63). It may be useful in patients with abnormal sputum cytology or previous dysplasia to delineate tumor margins (64).

Thin convex probe EBUS. Convex probe EBUS is designed for mediastinal

and hilar lymph node staging and has limited size and flexibility to direct biopsy of lung lesions except those centrally located. Development of a thin convex probe EBUS scope that has smaller size and greater flexibility may improve smaller airway access (65). In *ex vivo* human lungs, it provides superior access to segmental and subsegmental bronchi (66). Thin convex probe EBUS could provide better access to interlobar lymph nodes and peripheral lung lesions.

Technological Changes in the Bronchoscope

Ultrathin bronchoscopy. The small size of the peripheral airways limits the ability of conventional bronchoscopes to navigate to peripheral lesions. The working channel of conventional pediatric bronchoscopes limits the size of the tools needed to diagnose peripheral nodules (67). Development of ultrathin bronchoscopes (~2.8–3.5 mm outer diameter) allows for greater maneuverability to traverse small airways. Although no strict definition of "ultrathin" exists, most have outer dimensions of 3.2 mm or less.
A retrospective analysis of 209 malignant lesions biopsied with an ultrathin bronchoscope reported diagnostic yields of 63% in lesions 2 cm or less (68).
A metanalysis of ultrathin bronchoscopy reported an overall diagnostic yield of 70% when combined with other modalities (e.g., VBN, rEBUS, and fluoroscopy) (69). A concern is that working channel size limits the size of collected specimens.
A multicentered trial reported that ultrathin bronchoscopy was superior to thin bronchoscopy to diagnose peripheral lung nodules of 30 mm or less (68). The ultrathin bronchoscope reached more distal bronchi (median fifth- vs. fourth-generation bronchi). Diagnosis of benign disorders was lower than malignant lesions, despite using the ultrathin bronchoscope (70). The type of image guidance (fluoroscopy vs. VBN vs. CT) used with the ultrathin bronchoscope and sampled lobe impacts diagnostic yields (24, 25, 71).

Robotic bronchoscopy. Robotic-assisted bronchoscope systems can navigate to small peripheral airways under continuous visualization while maintaining a static curved position. This advantage keeps biopsy tools and even ablation devices locked on the targeted lesion, despite flexed articulation (72–74). First use in humans has been reported in 15 patients (73). Biopsy samples were taken from 93% of subjects with lesions 2.6 mm in diameter; the closest edge was 0.6 mm from the pleura. Cancer was confirmed in 60% of lesions; time to biopsy was 45 minutes in the first five cases and 20 minutes in the last nine. Another robotic device (Ion Endoluminal System; www.intuitive.com/ion) received U.S. Food and Drug Administration (FDA) clearance in August 2019 (https://www.therobotreport.com/ion-lung-biopsy-intuitive-surgical-fda/). It has Fiber Optic RealShape technology with ultrathin and maneuverable catheters that navigate to the lung peripheral with maintenance of catheter stability. Fielding studied 29 subjects with mean lesion size of 12.2 (±4.2) mm; 41.4% had absent CT bronchus sign. In 96.6% of cases, target was reached and samples were obtained (75). An overall diagnostic yield of 79.3% was reported, with 88% yield for malignancy.

Malignant Solitary Pulmonary Nodule: Therapeutic Approaches

Solitary pulmonary nodule. Guidelines recommend surgical resection of early stage non–small-cell lung cancer (NSCLC) (76), but many patients are unsuitable (77). The only nonsurgical, nonpharmacological option is stereotaxic body radiation therapy, which is highly effective, but not without complications (78). The need exists for other nonpharmacological options that are similarly effective, but with fewer complications.

Advances in navigational bronchoscopy enable accessing a lung tumor and treating it. Various bronchoscopic ablation technologies might be possible: radiofrequency ablation (RFA), microwave ablation (MWA), photodynamic therapy (PDT), brachytherapy, cryoablation, vapor thermal ablation, or direct therapeutic injection. Most technologies are still in preclinical stages or undergoing small feasibility trials.

RFA. RFA uses high-frequency alternating current to deliver thermal injury with an electrode inserted into the tumor. RFA generates a tissue destruction zone around the electrode tip; treatment zone and tumor death may be affected by surrounding tissue. Damage to aerated lung surrounding a tumor is minimized by air's insulating effect (79, 80). Koizumi and colleagues (81) reported a local control rate of 83% using endoscopic RFA; median progression-free survival was 35 months, and overall 5-year survival was 61.5%.

MWA. MWA is a heat-based therapy that generates an elliptical-shaped electromagnetic field with microwave frequency ranges between 300 MHz and 300 GHz via a probe inserted into the lesion. Like RFA, MWA induces coagulation necrosis by heating target tissue to temperatures >60°C. An endoscopically directed, flexible, gas-cooled microwave antenna has been tested in a porcine model (82). Clinical trials with endoscopically delivered MWA are ongoing (clinicaltrials.gov identifiers: NCT03569111; NCT04005157; and NCT03769129).

Cryoablation. Cryoablation causes cell death using alternating freeze and thaw cycles. The exact lethal temperature threshold is unclear; some experiments suggest −20°C as a minimum threshold. Yamauchi and colleagues (83) reported that mean local tumor progression–free interval was 69 months and median survival was 62 months using percutaneous cryoablation in 22 patients with inoperable NSCLC. Zheng and colleagues (84) recently reported animal data using a flexible probe; human data are unavailable.

Bronchial thermal vapor ablation. Bronchial thermal vapor ablation (BTVA) has been used in bronchoscopic lung volume reduction and may have potential to treat focal cancers. An advantage of water vapor is rapid energy delivery. A porcine model demonstrated that uniform necrosis can be bronchoscopically delivered to a focal lung region (85). A first-in-human trial has begun (clinicaltrials.gov identifier: NCT03198468).

Brachytherapy. High-dose radiation therapy is used to palliate malignant central airway obstructions (CAOs). Experience for peripheral brachytherapy is limited, and only small case series are published (86, 87); most have used 5 Gy administered three times per week. The requirements for repeated applications and placement of a guide sheath are limitations.

PDT. PDT has been used for malignant CAOs and CISs. After administration of a photosensitizing agent with selective uptake by tumor cells, the photosensitizer is activated endoscopically by a specific laser light. The photosensitizer produces highly reactive oxygen species that cause cell death. Chen and colleagues (88) treated three patients with local control at 1 year.

A newly developed parallel-type ultrasmall composite optical fiberscope (Laser-eYe Ultrathin fiberscope) couples simultaneous imaging and phototherapy and was effective in preclinical lung cancer models (89). This new laser device has potential to treat peripheral lung cancers.

CAO. CAO is symptomatic obstruction of the trachea, mainstem bronchi, bronchus intermedius, or lobar bronchi (90, 91). Tracheal obstruction causes exertional symptoms when tracheal diameter is 8 mm or approximately 30% cross-sectional area, rest symptoms develop <5 mm or <20% cross-sectional area (92–94).

CAO can be divided into malignant or nonmalignant causes. Malignant disease is usually related to locally advanced thoracic malignancies. At presentation, approximately 10% of lung cancers have evidence of CAO (95). Tracheal invasion constitutes a T4 malignancy in the eighth Tumor Node Metastasis classification (96), tracheal invasion without metastasis constitutes stage 3A disease, with a median survival of 29.3 months, nearly double compared with prior years (97). Primary tracheal tumors are rare; in adults, these are mostly malignant and due to squamous cell carcinoma, adenoid cystic carcinoma, or carcinoid (98). Primary tracheal tumors should be treated with resection for most patients with benign lesions, tumors of intermediate aggressiveness, and localized malignant tumors (99).

Nonmalignant disease includes postintubation (100, 101), post-tracheostomy (93), infection-related (102), transplant airway disease (102), and autoimmune conditions.

CT imaging is essential to evaluate CAO; it provides insight into etiology, extent, morphology, and vascular involvement (103–106). Three-dimensional reconstructions with vascular and mediastinal anatomy assist with case planning and stent preparation.

Flexible bronchoscopy evaluates morphology and extent of CAO and can provide diagnostic specimens (107). Manipulation of CAO with a flexible can be dangerous; even minimal manipulation can cause edema or hemorrhage that precipitates airway compromise. Therapeutic instruments (laser, APC [Argon Plasma Coagulation], or stent deployment) can be used with a flexible bronchoscope (108). EBUS assesses invasion depth and vascular structures during therapeutic bronchoscopy (109).

Rigid bronchoscopy is the gold standard for CAO management (90, 110). It allows airway manipulation with the ability to ventilate, suction, and tamponade bleeding while debulking tumor (107). Its large working channel allows removal of large tumors and deployment of silicone stents but can also cause airway damage. A flexible bronchoscope can be inserted via the rigid bronchoscope to enhance maneuverability.

After appropriate patient selection (111, 112), therapeutic bronchoscopy for CAO can be performed with acceptable complications and mortality (113, 114). Therapeutic bronchoscopy improves quality of life (QoL) (114–116) and lung function (117), weans patients from ventilation (118), stabilizes patients before definitive therapy (119), and improves survival similar to comparable cancer-stage patients without CAO (120, 121).

CAO: treatment. Therapeutic destruction. Therapy for malignant CAO includes mechanical debridement with forceps, cutting tools, or mass coring with a rigid bronchoscope (107). Thermal therapies with laser, APC, and electrocautery can provide immediate relief. Depending on the laser and its settings, it can be a cutting tool or can coagulate and vaporize the tumor. There is a low rate of laser-related complications, but hemorrhage, airway fire, and fistula have been reported (122–125). APC is not ideal for large tumors but helps with mechanical debulking by coagulating the tumor and controlling bleeding (126). Electrocautery can be used but requires tissue debulking (127). Thermal therapies require reduced-oxygen environments, which limits use in patients with hypoxemia.

Pdt. PDT is indicated for nonoperable, malignant CAO (128). The effect is delayed and requires repeat bronchoscopy for airway clearance. Adverse reactions include photosensitive skin rash and hemoptysis (129).

Cryotherapy. Cryotherapy can be used as a spray (130) or a probe (131) for malignant and nonmalignant CAO. The cryoprobe requires removal from the airway between biopsies; serious hemorrhage has been reported.

Microdebrider. A microdebrider is a hollow suction tube with an internal rotary blade; the tissue is macerated by the blade and simultaneously removed by suction. This allows field visualization and rapid debridement without perforation (132, 133).

Airway dilation. Airway dilation uses high-pressure catheter balloons, bougie devices, or a rigid bronchoscope (134). Dilation is combined with other therapies: radial incisions for focal stenosis to prevent mucosal tear (135), debridement of tissue, and stent placement (136–138). Sustained airway patency after balloon dilation is variable (139, 140); the procedure usually needs repeating, surgery, or stenting for recalcitrant disease (141). Attempts to sustain benefit with drug-eluting balloons has been reported (142).

Chemoinjection. Direct injection of chemotherapeutic agents into CAO has been reported to be feasible (143–145).

Stents. When selecting a stent to manage CAO, one must consider the disease process, radial force required, duration of use, and insertion technique. The ideal stent should be *1*) easy to insert and remove, yet not migrate; *2*) of sufficient strength to support the airway, but flexible enough to promote secretion clearance; *3*) biologically inert to minimize granulation tissue; and *4*) available in multiple sizes (90).

Silicone stents developed (146) are inserted via a rigid bronchoscope; they are inexpensive and easy to modify and remove. The major issues are mucostasis (147) and migration. Silicone stents have reduced granulation tissue reaction (148), and the silicone Y stent is ideal for lesions at the carina or dynamic collapse of the distal trachea and mainstem bronchi (91).

Self-expandable metal stents are the most commonly used stents. They conform to the airway and have favorable internal-to-external diameters that aid mucus clearance. Indications include recurrent stenosis, malignant airway obstruction (9, 149–151), and transplant airway stenosis (152–154). They are used in expiratory central airway collapse to predict response to tracheoplasty (155).

Balloon-expandable metal stents are malleable and can be bent and perforated to aerate collateral bronchi. Currently, their limited diameters make them most useful in lobar airways (156, 157).

Patients with benign CAO survive longer than patients with malignant CAO, and thus experience more complications (150). Attempts to circumvent these issues have led to stents made with biodegradable polymers (158). Use of these stents is limited to reports in pediatric patients

and transplant airway disease (159–163). A pilot study in adults with transplant airway complications reported biodegradable stents to be effective, but they required repeated procedures (158, 161).

The tracheobronchial tree is well suited to 3D printing using multidetector CT data. Three-dimensional models have been used for procedure planning, stent design, and assessment of flow limitation (164–169).

Agents may be applied to stents that could retard bacterial colonization, granulation tissue formation, or malignant growth (29).

Mediastinal Lymph Node Staging

Real-time, EBUS-guided transbronchial needle aspiration (EBUS-TBNA) for lung cancer staging was introduced in 2003 (170). Since then, EBUS-TBNA has become essential for minimally invasive sampling of mediastinal lymph nodes for NSCLC (171, 172).

EBUS-TBNA is the initial modality for lung cancer staging for multiple reasons. The first is less-than-ideal assessment by staging modalities, such as positron emission tomography–CT. Next is its excellent safety profile. Complication rates from multiple databases reports EBUS associated complication rates at approximately 1%. Most complications are minor (cough and bleeding at puncture site), but more serious complications (pneumothorax, mediastinitis, pericarditis, and death) have been reported (171). The diagnostic accuracy of EBUS-TBNA is similar to mediastinoscopy (171–174). Compared with mediastinoscopy alone, when EBUS-TBNA and mediastinoscopy are used in conjunction, the sensitivity for detection of mediastinal metastasis improves from 79% to 94% (175). Follow-up data revealed similar 5-year survival between endoscopic- and surgical-staged groups (176).

Standard practices for EBUS-TBNA staging involves evaluation and sampling of nodal 3 (N3) stations, followed by N2 and N1 stations. Sampling all lymph nodes >5 mm in short axis is optimal to maximize procedure sensitivity (177). Stations traditionally accessible by EBUS-TBNA include 2 right (R)/2 left (L), 4R/4L, 7, 10R/10L, and 11R/11L. Stations 5 and 6 are inaccessible by EBUS-TBNA, unless a transvascular approach is employed. In place of bronchoscopic ultrasound, transesophageal and gastric use of the EBUS scope can be performed. It allows more complete staging of patients with lung cancer, including stations 8 and 9, and alternative access to stations 2L and 4L (178). EBUS can evaluate airway tumor infiltration better than CT imaging (179).

Technical aspects of EBUS-TBNA may maximize procedural yield. Aspiration needles come in 19-, 21-, 22-, and 25-G sizes. Trials comparing 21 to 22 g, as well as use of a 19-G needle, show improved sample volume with larger needle size, but larger needle size has not been shown to correlate with diagnostic yield (180, 181). Larger needles may be considered if lymphoma or sarcoidosis is suspected. Use of mini-forceps via EBUS may increase sample volume (182).

In the NSCLC era of tumor molecular analysis, sample adequacy is important in lung cancer staging. During node sampling, diagnostic yield plateaus after three passes (183). Rapid on-site evaluation ensures adequate sampling and reduces needle passes (184). EBUS-TBNA sampling is adequate for generation of molecular analysis, including ALK, EGFR mutations, and PDL1 expression (185, 186).

Ultrasound characteristics of lymph nodes provide insight into underlying pathology. Independent predictors of metastasis included rounded shape, distinct margins, heterogeneous echogenicity, and coagulation necrosis (187). An aggregate scoring system that uses the presence of matting, nonhilar vascular pattern perfusion, absence of central hilar structure, and rounded shape had a sensitivity of 93%, specificity of 55%, positive predictive value of 73%, and negative predictive value of 82% to predict malignancy if at least two factors were present (188).

Elastography

Elastography has been used in breast, thyroid, and hepatic diseases to measure elastic properties. It has also been used to evaluate mediastinal lymph nodes. The color map used with elastography includes red, yellow, green, and blue, corresponding, respectively, from least to most stiff. Elastogram colormetric patterns comprise three groups: type 1 homogeneous green (predominantly green with yellow and red areas); type 2 mixed (predominantly green with focal blue areas); or type 3 homogeneous blue (predominantly blue) (Figure 4).

Current data suggest that EBUS elastography is safe and may provide predictive information regarding malignant lymph node infiltration. Whether EBUS elastography precludes TBNA of lymph nodes is uncertain. A study using similar classification types found a sensitivity of 87%, a specificity of 68%, a positive predictive value of 80%, and a negative predictive value of 77% when type 1 was considered benign and type 3 malignant (189).

Obstructive Lung Diseases: Interventional Bronchoscopic Treatment

Asthma. Despite multiple inhaled therapies, patients with asthma may remain symptomatic and require chronic oral steroids or expensive biologics. Consequently, a need exists for other therapeutic options.

Bronchial thermoplasty. Bronchial thermoplasty is an effective bronchoscopic treatment for asthma. Smooth muscle hypertrophy is key in severe asthma, and its reduction may alleviate symptoms and downregulate airway inflammation. Bronchial thermoplasty is a catheter-based therapy that uses radio frequency energy to heat the airways. A thermocouple within the catheter detects temperature, and algorithms within the generator allow smooth muscle temperature to reach 65°C to induce permanent smooth muscle ablation (190). The mechanism of action was demonstrated by short- and long-term canine studies and has been confirmed in humans (191–195).

Clinical evidence. Two cohort and two randomized controlled trials (RCTs) have reported that bronchial thermoplasty is safe and effective in patients with mild to severe asthma. A study in patients with mild to moderate asthma demonstrated reductions in symptoms and reduced bronchial hyperresponsiveness (196). A subsequent study in patients with moderately severe disease (AIR [Asthma Intervention Research] Trial) confirmed improvements in QoL and symptom scores but no change in pulmonary function (197). An uncontrolled study in 30 patients with severe disease (RISA [Research in Severe Asthma] Study) reported benefits in asthma symptom scores and QoL (198). A 50% reduction in steroid dose has been reported after bronchial thermoplasty in steroid-dependent patients (198).

A sham-controlled study was performed in symptomatic patients with moderate to severe asthma on high-dose

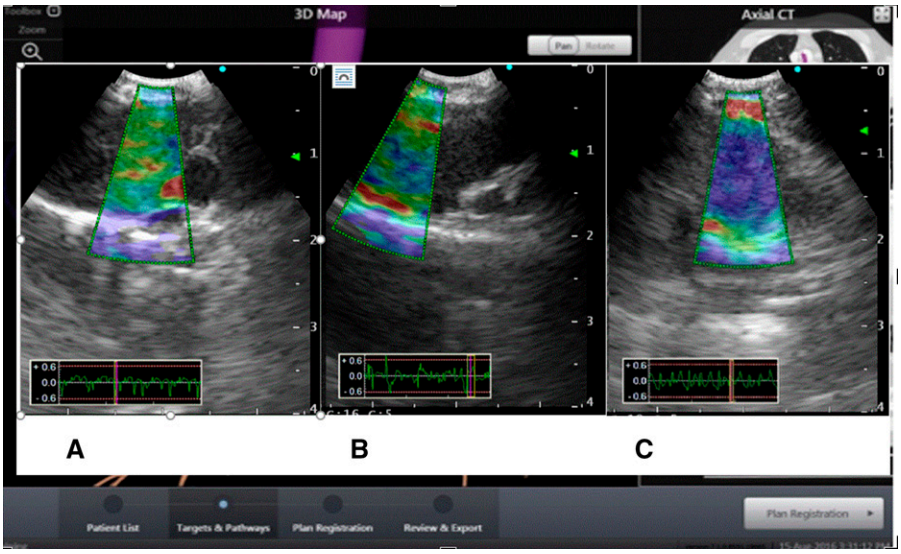

Figure 4. (*A*) Type 1 elastography pattern (homogenous green) in a patient with tuberculosis. (*B*) Type 2 elastography pattern (mixed color pattern) in a patient with sarcoidosis. (*C*) Type 3 elastography pattern (homogenous blue) in a patient with adenocarcinoma.

inhaled steroids (199). After bronchial thermoplasty, there were significant improvements in asthma QoL questionnaire measures and reduced exacerbations, healthcare utilization, and days lost from work or education. Reductions in exacerbations and hospitalizations were maintained long term (200).

Real-life treatment experience. The U.S. study (PAS2 Study [Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma]) collected registry data and demonstrated similar benefits to AIR2 (201). There was a 44% reduction in severe asthma exacerbations and a 55% decrease in emergency room attendance after bronchial thermoplasty.

Future endoscopic options. Historical studies suggest a role of the parasympathetic nervous system in hypersensitivity and benefit with denervation. Targeted lung denervation (TLD) has been studied in chronic obstructive pulmonary disease (COPD) but may also have a therapeutic role in severe, persistent asthma.

Bronchoscopic Treatment of Emphysema

Multiple interventional possibilities, both surgical and bronchscopic, exist for patients with advanced emphysema based on clinical, physiological, and radiological assessment. Figure 5 provides an overview of treatments based on clinical assessment.

Endoscopic valve placement. In patients with severe emphysema, destruction of the lung leads to both a reduction of gas exchange surface and static and dynamic hyperinflation. Therapeutic strategies aim to reduce air trapping to improve respiratory mechanics, physical activity, and even symptoms (202, 203).

Endoscopic valve placement via a flexible bronchoscope is a minimally invasive technique that mimics the benefits of lung volume reduction surgery. Two types of one-way valve are commercially available: intrabronchial valve (Spiration; Olympus) and endobronchial valve (EBV) (Zephyr; Pulmonx, Inc.). They have different shapes but similar function. Both block inspired air entry into the treated lobe, while air and secretions escape during expiration. Although intrabronchial valve was originally used for bilateral treatment with incomplete occlusion (204, 205), unilateral lobar occlusion of the most diseased lobe is the preferred technique for either valve (206) (Figure 6).

Valve treatment is suggested only in patients without collateral ventilation (CV) (207). Absent or low CV is presumed in cases with complete fissures on CT. However, CV can also be measured endoscopically with the Chartis system (Pulmonx, Inc.) (208). Using these criteria, RCTs show clinically meaningful improvements in pulmonary function testing, 6-minute-walk distance, and QoL. Mean changes in $FEV_1 \geqslant +20\%$ and an increase of 33–79 m in 6-minute-walk distance were reported. Although interindividual variability in response is high, 60% of treated patients achieve minimal clinically important difference in outcomes (209–211).

In approximately 20–30% of treated patients, a postinterventional pneumothorax is expected; it most frequently occurs in the first 3 days and can be life-threatening. Pneumothorax usually requires chest tube placement, valve removal, and, rarely, surgical intervention (212).

Patients who develop complete atelectasis after valve placement show improvements in lung function, exercise capacity, QoL, and survival (213).

Lung volume reduction coil treatment. Lung volume reduction coil treatment (LVRC; PneumRx/BTG) is a bronchoscopic treatment for patients with emphysema with severe hyperinflation (residual volume [RV] > 200% predicted) and absence of significant airway pathology (214), who are not candidates for EBV or lung volume reduction surgery (215). The LVRC is a shape-memory nitinol implant (Figure 7), of which 10–14 are fluoroscopically placed in the most diseased lobe of each lung during sequential bronchoscopic procedures (216). LVRC reduces static hyperinflation by improving airway resistance and from secondary inflammation due to mechanical tissue stress (217–220). Initial trials showed improved pulmonary function, QoL, and exercise performance (219, 221–224). A larger RCT failed to reproduce earlier trial results but still showed improved lung function and QoL (217). The benefits of LVRC treatment persist for up to 3 years (224) and can potentially be repeated; however, the benefit is not as robust as initial treatment (225). An FDA panel concluded that LVRC benefits did not outweigh risks, and it was denied clinical approval (226). A subanalysis of RENEW (Lung Volume Reduction Coil Treatment in Patients with Emphysema) suggests that patients with a RV > 200%, absence of airway disease, and coil placement in the lobe with most emphysema had better outcomes (214). These parameters are used for entry criteria in an ongoing trial (227).

BTVA/polymeric lung volume reduction. BTVA and polymeric lung volume reduction (PLVR) target hyperinflation in symptomatic patients with

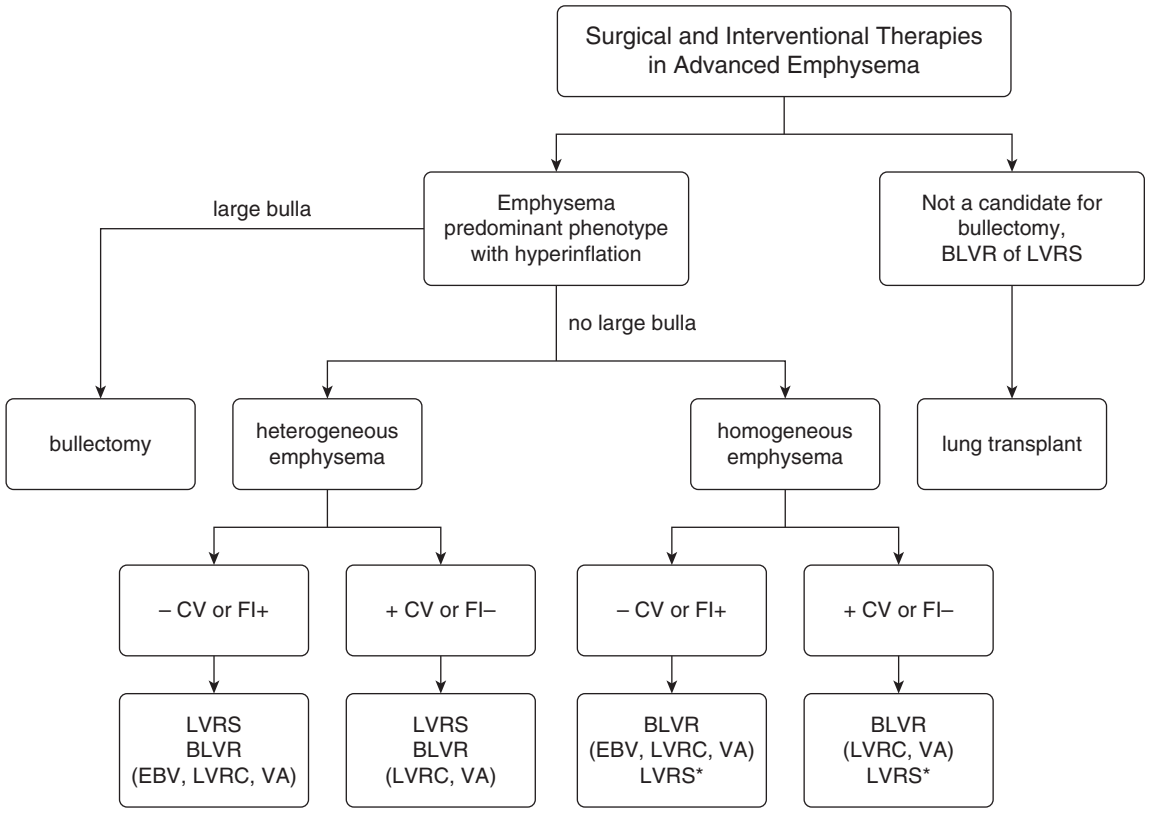

Figure 5. Overview of survival and interventional therapies for advanced emphysema. Adapted from Reference 232. BLVR = bronchoscopic lung volume reduction; CV = collateral ventilation measure by Chartis; EBV = endobronchial valve; FI+ = fissure integrity > 90% by HRCT; FI– = fissure integrity < 90% by HRCT; HRCT = high-resolution chest computed tomography; LVRC = lung volume reduction coil; LVRS = lung volume reduction surgery; VA = vapor ablation.

emphysema despite optimal pharmacological treatment. Both techniques incite inflammatory reactions to induce reduction of emphysematous areas. BTVA and PLVR treatments have some advantages over EBV: their efficacy does not depend on CV, and treatment occurs on a segmental, not lobar, level. Segmental treatment is important, as many patients have intralobar heterogeneity (228). The disadvantage of BTVA and PLVR is their irreversibility.

During BTVA, segmental application of 100°C-heated water vapor promotes inflammation to induce volume reduction of emphysematous segments (229). An RCT confirmed the efficacy of BTVA in 46 patients with upper lobe–predominant emphysema (230). At 6 months after bilateral treatment, significant improvements in FEV_1 and St. George's Respiratory Questionnaire occurred. BTVA is being evaluated for patients with homogeneous emphysema (clinicaltrials.gov identifier: NCT03670121).

PLVR deploys a synthetic polymer into emphysematous lung segments to induce inflammation and resultant volume reduction. An RCT evaluated the safety and efficacy of PLVR in 34 patients with upper lobe–predominant emphysema and showed significant improvement in lung function (231). However, the procedure had a high rate of adverse events. The results of another multicenter RCT are pending (clinicaltrials.gov identifier: NCT00884962).

Because both techniques induce inflammatory reactions, their most common adverse events are COPD exacerbations and pneumonitis/pneumonia. BTVA has limited clinical availability, and PLVR is currently under clinical trial investigation (STAGE [Clinical Investigation of a Modified Staged Treatment Algorithm Using the AeriSeal System], clinicaltrials.gov identifier: NCT02877459).

TLD. Reflex signaling via pulmonary branches of the vagus nerve is involved in the pathophysiology of COPD (232). Airway submucosal glands are innervated by pulmonary ganglion (233), and stimulation of parasympathetic efferent or sensory afferent (C fibers and stretch receptors) fibers initiate direct (efferent) (234) or reflex (afferent) (235, 236) mucus hypersecretion. Vagal nerve signaling facilitates disease-related airway hyperresponsiveness, and vagotomy abolishes the effect (237, 238). Cholingergic hyperactivity in COPD causes airway hyperresponsiveness, airflow limitation, gas trapping, mucus hypersecretion, and exacerbations. Blocking parasympathetic efferent lung signaling may complement bronchodilator therapies for COPD.

TLD targets parasympathetic branches of the vagus nerve that run alongside the mainstem bronchi (Figure 8). TLD directs radiofrequency energy to pulmonary branches of the vagus nerve to disrupt signaling to and from the lung. TLD uses

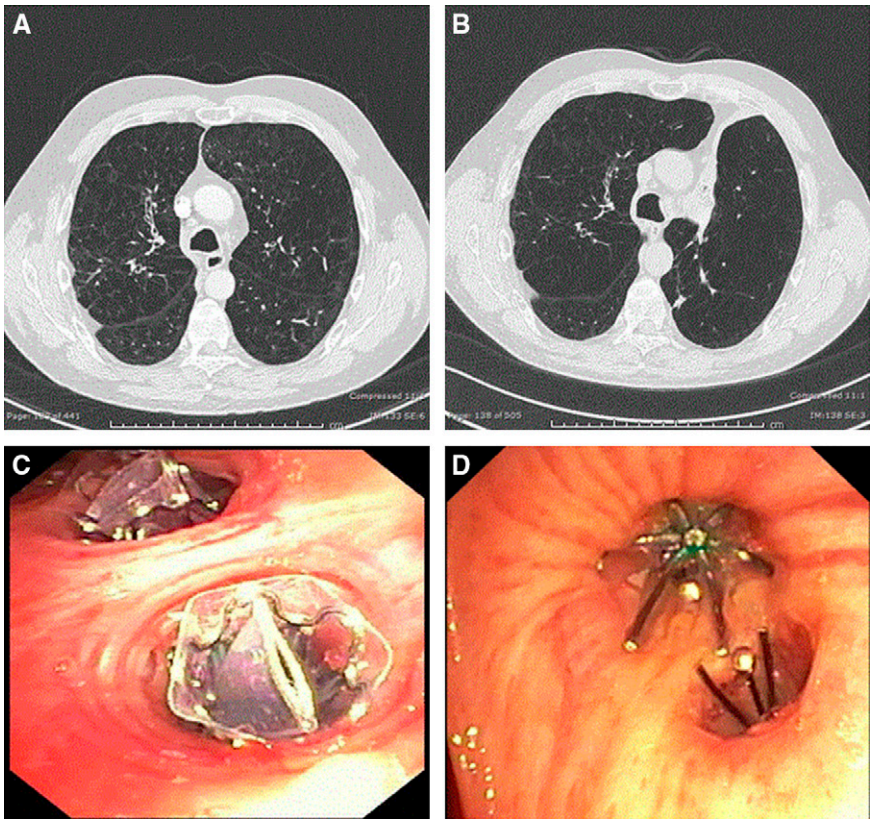

Figure 6. (*A* and *B*) Patient with advanced upper lobe emphysema before (*A*) and after (*B*) endobronchial valve placement in left upper lobe showing total lobar occlusion and complete atelectasis. (*C*) Valves are shown. (*D*) Another endobronchial valve option (SVS; Spiration, Inc) is shown.

dual-cooled technology to protect the airway epithelial surface, while delivering heat to a targeted depth where pulmonary vagus nerve branches reside. A preclinical study demonstrated that TLD disrupts vagal fibers histologically and produces physiologic changes associated with sensory/motor reflex signaling (239).

The first-in-man clinical study of TLD, IPS-I (Innovative Pulmonary Solutions), demonstrated that TLD provides a bronchodilator effect similar to anticholinergic therapy with a dose (power) dependency effect (240). TLD with an inhaled anticholinergic produced greater bronchodilator effect than either therapy alone (241). IPS-II demonstrated the feasibility and safety of a single whole-lung TLD procedure (242).

AIRFLOW (Targeted Lung Denervation for Patients with Moderate to Severe COPD) 1 confirmed safety and feasibility with a flexible bronchoscope, reduced gastrointestinal side effects associated with ablation near the esophagus, and the safety of TLD using a 32-W dose (243). AIRFLOW 2 demonstrated that TLD treatment produced fewer airway-related adverse events and fewer COPD hospitalizations (clinicaltrials.gov identifier: NCT02058459). An international, multicenter randomized sham-controlled TLD trial is evaluating if TLD reduces COPD exacerbations (clinicaltrials.gov identifier: NCT03639051).

Chronic bronchitis. Patients with chronic bronchitis have a poor QoL, increased hospitalizations, greater lung function decline, and increased mortality. It is characterized by excessive mucus hypersecretion by goblet cells predominantly located in the large airways. Treatments include smoking cessation, mucolytics, macrolides, anticholinergic agents, phosphodiesterase-4 inhibitors, glucocorticoids, and chest physiotherapy, but they are limited in treating symptoms or halting disease progression (244, 245).

Bronchial rheoplasty. Bronchial rheoplasty (RheOx System; Gala Therapeutics) delivers nonthermal energy to ablate airway mucosal cells and reduce goblet cell hyperplasia. The RheOx catheter is inserted via a bronchoscope from the subsegmental airways to the main carina, while energy is delivered during electrode expansion (Figure 9).

In a multicenter feasibility study, 25 patients with symptomatic chronic bronchitis underwent rheoplasty; procedure success was 100% (13). Two patients experienced serious device-related adverse event (pleural effusion and mucosal scarring); four patients had seven COPD hospitalizations. Most adverse events occurred within 30 days of bronchoscopy. Significant improvements in St. George's Respiratory Questionnaire and COPD Assessment Test scores were observed at 6 and 12 months. A reduction in goblet cell hyperplasia was observed. A U.S. clinical study is underway (clinicaltrials.gov identifier: NCT03631472).

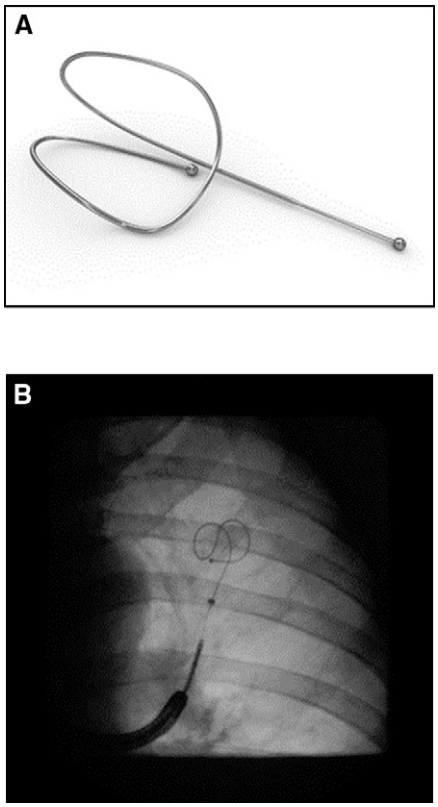

Figure 7. (*A*) Nitnol lung volume reduction coil. (*B*) Coil deployed in lung.

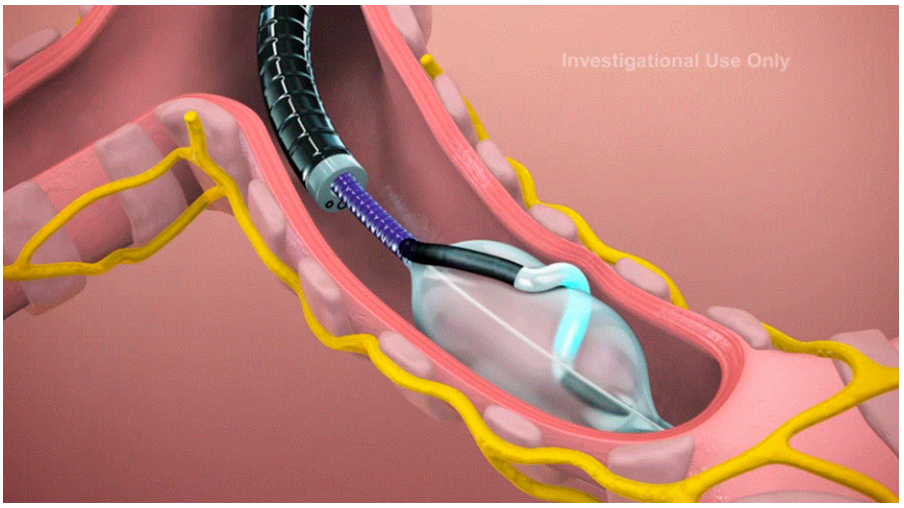

Figure 8. Total lung denervation. Electrode is positioned into the distal mainstem bronchi to deliver ablation treatment with thermal insulation provided to the airway wall by water-cooled jacket.

Liquid nitrogen metered cryospray. The Rejuvenair Liquid Nitrogen Metered Cryospray (CSA Medical) is another potential bronchoscopic treatment for chronic bronchitis (Figure 10). It ablates diseased airway epithelial using liquid nitrogen at −196°C, thereby inducing a nonscarring, noninflammatory healing process (246). The system delivers predetermined quantities of liquid nitrogen, depending on anatomic site and sex, and is locally controlled by thermocouple feedback. Treatment is performed in two sequential bronchoscopic procedures of approximately 45 minutes with intermittent airway circuit interruption to permit nitrogen gas egress. The Rejuvenair system was first tested in humans with sprays delivered into a resected lobe to demonstrate feasibility and safety (247). Its use for treatment of chronic bronchitis is under investigation (Rejuvenair study; clinicaltrials.gov identifier: NCT02483637).

Parenchymal Lung Diseases: Diagnosis

Diagnosis of diffuse parenchymal lung diseases relies on multidisciplinary evaluation (248). Histologic data contribute to the diagnosis (249–251). Surgical lung biopsies, the historical gold standard, are performed annually in 10,000 or more U.S. patients, and provide samples of size and quality generally sufficient for a diagnosis. However, surgery has increased risks; in-hospital mortality is 1.7% and 16% for elective and nonelective procedures, respectively (252). Accordingly, less-invasive alternatives are needed. Transbronchial forceps biopsies have a diagnostic yield of approximately 20% in diffuse parenchymal lung disease (253–255).

Transbronchial cryobiopsies have been proposed as a possible option. They are performed via either flexible or rigid bronchoscopy, using a cryoprobe advanced under fluoroscopy to the lung periphery, approximately 1 cm from the pleura. The probe is activated, releasing compressed gas (carbon dioxide or nitrous oxide) to the probe tip, which instantly freezes lung tissue that is extracted, *en bloc* with the bronchoscope (256). Biopsies typically measure 5 mm, are devoid of crush artifact, and have superior histopathologic quality to forceps biopsies. There are, however, major downsides. Biopsy size precludes extraction through the working channel of the flexible bronchoscope: both must be removed together, which exposes the patient to potentially severe endobronchial bleeding without maintaining a wedged position. Clinically significant bleeding occurs in 40% of patients. Cryobiopsies obtained at the lung periphery cause pneumothorax in 12% (257). Mortality after cryobiopsy remains substantial, estimated at around 0.3% (139).

Cryobiopsy techniques vary considerably, and the role of cryobiopsy remains controversial (258). Besides procedural risks, and critics highlight a lower diagnostic yield of cryobiopsies compared with surgical lung biopsies, estimated at 80% and 95%, respectively, and the lack of direct comparisons (139). Proponents of the procedure offer counter arguments: *1*) cryobiopsy and surgical lung biopsy offer comparable data to a multidisciplinary team (259); and *2*) head-to-head comparisons only address histologic sample quality, which needs to be balanced with the risks inherent to intervention. In that regard, cryobiopsies remain a promising alternative to the *status quo*. Detailed recommendations on effective and safe cryobiopsy practice provide guidance on patient selection, the need for multidisciplinary discussion, use

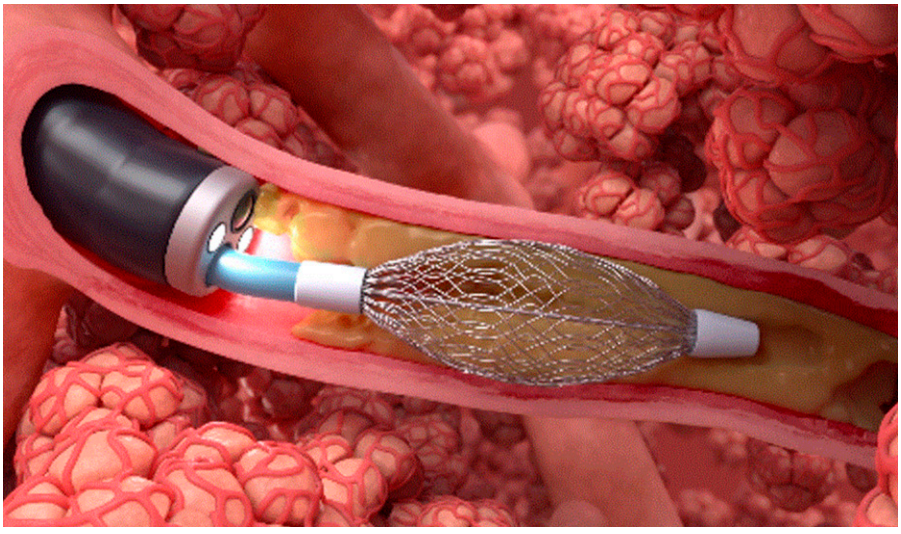

Figure 9. Rheoplasty. Expanded basket provides airway contact to deliver pulsed field energy to ablate airway epithelial goblet cells.

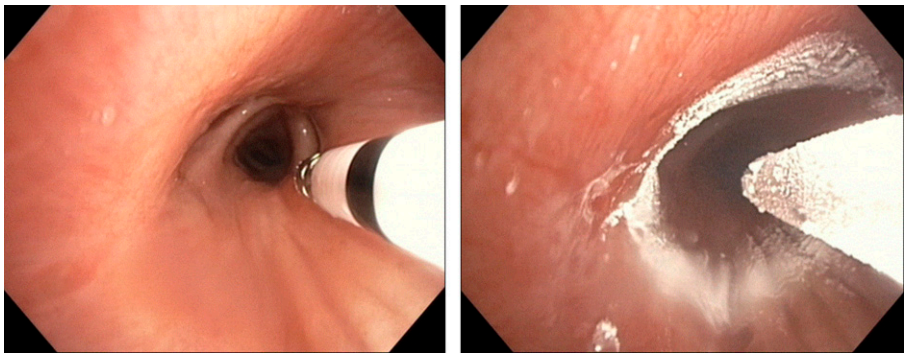

Figure 10. The Rejuvenair liquid nitrogen metered cryospray. (Left panel) Bronchus intermedius with Rejuvenair catheter *in situ* just before treatment. (Right panel) Liquid nitrogen metered cryospray in action at the same position showing the desired circular freezing pattern.

of an endobronchial blocker to mitigate bleeding, and the need for proper training and expertise (259).

Certification Training Issues

The time-honored apprenticeship model of "see one, learn one, teach one" is not acceptable. Its flaws include training on real patients in high-stress environments, inadequate preparation for uncommon events, and the absence of systemic and structured feedback (260).

For the cognitive component of procedural training, traditional tools, such as books and lectures, should be supplemented with newer approaches, such as interactive online learning and case-based discussion. Teaching should address all procedural aspects, including patient selection; preprocedural, procedural, and post-procedural care; and communication of results to patients and the care team. It is critical to educate proceduralists on when and how to decline a procedural request and the education of referring health care providers (261).

Simulation is an effective tool for teaching bronchoscopy skills and is available in two forms: low and high fidelity (262, 263). Low-fidelity simulation consists of molded models that offer realistic, airway-like structure or silicone-based lymph nodes, so learners can master anatomy and practice various sampling techniques. High-fidelity simulation consists of computer-generated 3D models of the airways, lymph nodes, and vessels with various iterations of anatomy, clinical situations, and even complications. High-fidelity simulation facilitates acquisition of bronchoscopy skills (262, 264).

Simulation models are available for basic bronchoscopy and EBUS skills. Explanted animal lungs or cadavers are effective in training for higher-risk procedures (e.g., cryobiopsy, ablation therapy, or stent placement).

Measuring competency in procedural performance is critical to assure best outcomes. Earlier guidelines published focused on procedural volume to determine competency (110, 265). However, this approach is less favorable, as learners acquire skills at different volume thresholds.

Newer guidelines emphasize the need to move to skill acquisition and knowledge-based assessments (266). Checklist-based assessment tools aid assessment of the learner performing the procedure and scores procedural steps based on objective criteria. These tools are validated and reliable in discriminating skill levels.

Optimal training in interventional bronchosopic procedures should incorporate traditional models (lecture and books) and newer approaches, including digital media platforms, case-based interaction, and simulation.

Interventional Bronchoscopy: the Future

In the near future, new approaches for many different lung diseases should become available: biodegradable stents, second- and -third-generation EBVs, better nonpharmacological treatments for chronic bronchitis and airflow obstruction, and new treatments in patients with emphysema who exhibit CV (267). Ablative procedures for early cancerous lesions will advance and clinical trials will determine their effectiveness.

To access small peripheral lesions precisely, navigational methods need further development. The advantages and disadvantages of ultrathin bronchoscopy, thin bronchoscopy with guided sheath catheters, and robotic-assisted bronchoscopy require comparative studies of diagnostic yields and cost effectiveness (73, 75). Imaging support during the procedures must be improved. Smaller EBUS bronchoscopes and rEBUS-tipped biopsy catheters should be compared with CBCT and augmented fluoroscopy in their abilities to provide real-time confirmation of lesion access during diagnostic and treatment interventions (268). This is especially true for semisolid lesions, where rEBUS currently has limitations.

The importance of training clinicians who perform bronchoscopy to be well versed in bronchial and lung anatomy is paramount and must be coupled with the skills needed to navigate the bronchoscope. In addition, although significant advances have been made to improve the technology of bronchial navigation devices and real-time imaging modalities, less-impressive advances have been made in developing new diagnostic tools.

To be able to improve our ability to diagnose and potentially treat small, peripheral, malignant lung nodules, tools that can maneuver in the close and more angulated environment of the small airways must be developed. Several new needles have been developed to provide enhanced flexible in the smaller airways during greater degrees of articulation. The PeriView FLEX TBNA 21-G (Olympus) and Arc point (Medtronic) 21- and 18-G needles are examples. The GenCut core biopsy system (Medtronic) is another example of a more flexible tool that may help provide higher diagnostic yield in the smaller airways. However, the clinical usefulness of these tools needs validation. Overall, our ability to treat a lesion depends on our ability to reach it and then fully access it. More tools that can allow us to achieve those goals are needed.

Navigational and biopsy tools must be studied in clinical settings to determine their effectiveness. The AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) program evaluated diagnostic yields of different types of bronchoscopy in clinical practice to identify factors that affect diagnostic yield (269). They found that peripheral TBNA improved diagnostic yield but was

underused, and diagnostic yields of ENB and rEBUS were lower than expected. Registry data can help prompt better bronchoscopic instruction and tools for community pulmonologists.

Another area with clear potential for development for minimally invasive procedures in the lung is natural orifice transluminal endoscopic surgery (NOTES). NOTES describes a wide spectrum of procedures that uses natural luminal access, such as transgastric or transvaginal routes, but could have applicability for other organs, such as the lung via the bronchoscope (270). Since Phillipe Mouret of France performed the first laparoscopic cholecystectomy in 1987 (271), NOTES has been studied in the mediastinum—predominately in porcine models. Concerns regarding complications of transtracheal or esophageal mediastinoscopy, such as infection and bleeding and healing of the esophageal incision, have limited progress. However, this technique could have potential for the diagnosis and treatment of select pulmonary lesions. Further study is required as NOTES techniques evolve.

Conclusions

A foreign body removed by G. Killian in 1896 was the first bronchoscopy and was subsequently followed by Chevalier Jackson, I. Kubo, and others, who further advanced bronchoscopic techniques. In the 1960s, S. Ikeda introduced the flexible bronchoscope as a diagnostic tool, and, in the 1970s, laser and stents fostered the growth of interventional bronchoscopy. With new options, new uses for interventional bronchoscopy are emerging, and it is plausible that interventional pulmonology has enormous potential to provide safe and effective diagnostic and therapeutic procedures at reduced costs for many patients with a variety of lung disorders. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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