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Interventional Pulmonology: Extending the Breadth of Thoracic Care

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Abstract

Interventional pulmonary medicine has developed as a subspecialty focused on the management of patients with complex thoracic disease. Leveraging minimally invasive techniques, interventional pulmonologists diagnose and treat pathologies that previously required more invasive options such as surgery. By mitigating procedural risk, interventional pulmonologists have extended the reach of care to a wider pool of vulnerable patients who require therapy. Endoscopic innovations, including endobronchial ultrasound and robotic and electromagnetic bronchoscopy, have enhanced the ability to perform diagnostic procedures on an ambulatory basis. Therapeutic procedures for patients with symptomatic airway disease, pleural disease, and severe emphysema have provided the ability to palliate symptoms. The combination of medical and procedural expertise has made interventional pulmonologists an integral part of comprehensive care teams for patients with oncologic, airway, and pleural needs. This review surveys key areas in which interventional pulmonologists have impacted the care of thoracic disease through bronchoscopic intervention.

INTRODUCTION

Over the last several decades, interventional pulmonology (IP) has evolved as a subspecialty of pulmonary medicine. Fellowship training programs for IP are available following standard American Board of Internal Medicine pulmonary medicine certification. The IP fellowship was recently included in the National Resident Matching Program, and an internal advanced IP certification process is used by some hospitals (1). The field has developed out of necessity given the rapid expansion of diagnostic and therapeutic technologies that have supplanted older techniques. IP physicians are often pivotal members of interdisciplinary teams that include surgical, radiological, oncological, transplant, and general pulmonary doctors, where they provide both procedural and medical insight. While IP is frequently tasked with diagnosing, staging, and treating patients with thoracic malignancies, the scope of practice extends to a wide array of noncancerous diseases including interstitial lung disease, chronic obstructive pulmonary disease, pleural and complex airway disease, and persistent bronchopleural fistulas, with further innovations currently under investigation. In this article, we review the current state of the art in IP and outline its major applications. Pleural disease, the care of which can be optimized through subspecialist care, is beyond the scope of this review and the reader is referred to other manuscripts detailing the management of pleural disease (2–6).

DIAGNOSTIC BRONCHOSCOPY

Bronchoscopy is a fundamental tool for the management of pulmonary disease, allowing airway inspection and facilitating diagnostic and therapeutic interventions. A prominent advancement in the field of bronchoscopy, endobronchial ultrasound (EBUS) extends the endoscopic view beyond the airway lumen, furthering the depth of inspection and interventions to mediastinal structures using real-time ultrasound guidance. More recently, peripheral bronchoscopic platforms have used image-guided localization, such as electromagnetic navigational bronchoscopy and shape-sensing robotic-assisted bronchoscopy, to intervene in regions beyond the reach of conventional flexible bronchoscopes. With its excellent safety profile and ability to provide sufficient tissue with small biopsies for in-depth studies including genetic analysis, bronchoscopy often supplants surgical techniques as the first-line procedure in the diagnosis of thoracic disease (7).

DIAGNOSTIC BRONCHOSCOPY AND MEDIASTINAL DISEASE

For many years, surgical mediastinoscopy was considered the gold standard for the biopsy of mediastinal masses and paratracheal lymph nodes. However, mediastinoscopy has limited access to hilar structures and is technically complex in patients who have undergone prior mediastinoscopy or radiation due to scarring. Larger central tracheobronchial airways are adjacent to the mediastinal and hilar structures and accessible to bronchoscopy up to the secondary lobar bronchi. EBUS has simplified mediastinal and hilar biopsies through incorporating a linear ultrasound probe (7.5 MHz), which allows visualization of the peri-bronchial structures and real-time guidance for needle aspiration of tissue while avoiding vascular structures (**Figure 1**).

Linear EBUS has consistently proven to be a powerful tool with a diagnostic yield of over 90% for malignancy. Its use is supported by several prospective trials that demonstrate excellent agreement between EBUS and surgical mediastinoscopy with high negative predictive values (91%) of nodal involvement in the preoperative setting (8–12). The imaging modalities CT (computed tomography) and PET (positron emission tomography), though critical in clinical staging, often lack the sensitivity and specificity to distinguish between benign and malignant lymphadenopathy (13, 14). Given its superior safety profile, cost effectiveness, and option to perform on an outpatient basis, EBUS has become an integral part of thoracic oncological evaluation. EBUS

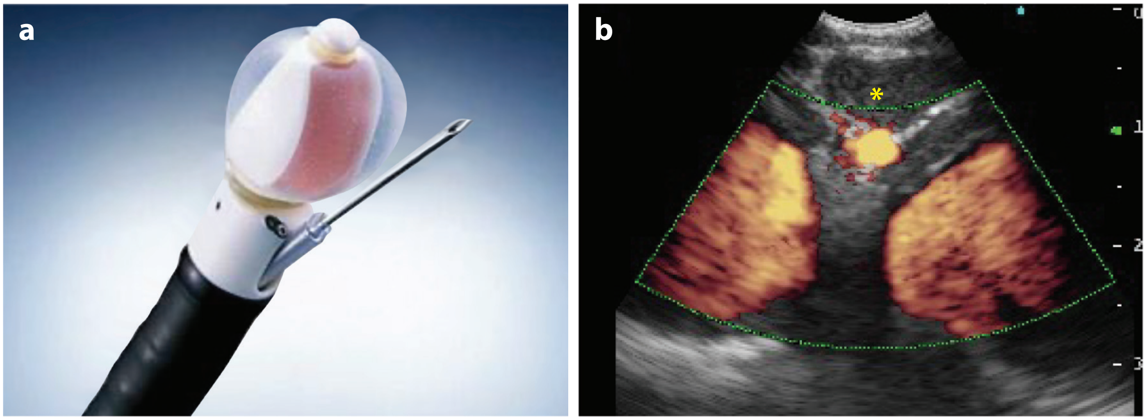


Figure 1

Endobronchial ultrasound. (*a*) Endobronchial ultrasound probe with a sterile water-filled balloon that allows airway apposition for image acquisition (image with permission from Olympus). (*b*) Image of a left paratracheal lymph node (asterisk) bordered by the aorta (*right*) and pulmonary artery (*left*) as seen in Doppler mode.

is also invaluable for providing adequate tissue for molecular analysis and immune profiling to assess candidacy for targeted therapy with specific molecular and checkpoint inhibitors (15).

EBUS is commonly performed for the evaluation of lymphoma. Though surgical specimens provide architectural information that is key for lymphoma classification, EBUS can provide sufficient material for diagnosis and classification of lymphomas and is routinely used as an initial diagnostic approach given the relative technical simplicity and patient tolerance (16). For benign disease such as sarcoidosis, EBUS is also favored as a first-line diagnostic tool given the high diagnostic yield [87%; 95% confidence interval (CI) 94–91%] and safety profile (17).

DIAGNOSTIC BRONCHOSCOPY AND PERIPHERAL LESIONS

The rising frequency of lung nodule detection on CT scans and the increasing implementation of lung cancer screening programs, which has unequivocally demonstrated the ability to reduce lung cancer–related mortality, have heightened the demand for safe and efficient tools to assess lung nodules (18, 19). Defined as lesions smaller than 3 cm in diameter, nodules are frequently located in the periphery of the lung and beyond the reach of traditional bronchoscopic biopsies. While most lung nodules are benign, clinical and radiographic features cannot distinguish early and potentially curable malignant from benign nodules; tissue confirmation is often required. Though CT-guided transthoracic needle aspiration has a diagnostic yield of >90% for peripheral lung nodules, it lacks the ability to concomitantly stage the mediastinum and carries a higher risk of iatrogenic complications, including pneumothorax and bleeding, compared to bronchoscopy (20, 21). Furthermore, studies demonstrating a 2.5-times increased risk of ipsilateral pleural recurrence among patients with early-stage disease who have undergone CT-guided transthoracic needle aspiration raise concern for pleural seeding from non-bronchoscopic biopsies (22). However, bronchoscopic biopsies are often technically limited by small airway caliber, where visual feedback is lost, and difficulty directing the sampling instruments to the lesion. Features such as target size, centrality, and the presence of adjacent airways ("bronchus sign") to the target lesion are established predictors of bronchoscopic biopsy success (23, 24). Technical factors such as intraprocedural deviation of the location of a pulmonary nodule compared to a previously obtained CT scan (CT to body divergence) and sheath stability during sampling challenge the diagnostic yield of bronchoscopic biopsies (25, 26).

Reaching the Peripheral Nodule with Bronchoscopic Guidance

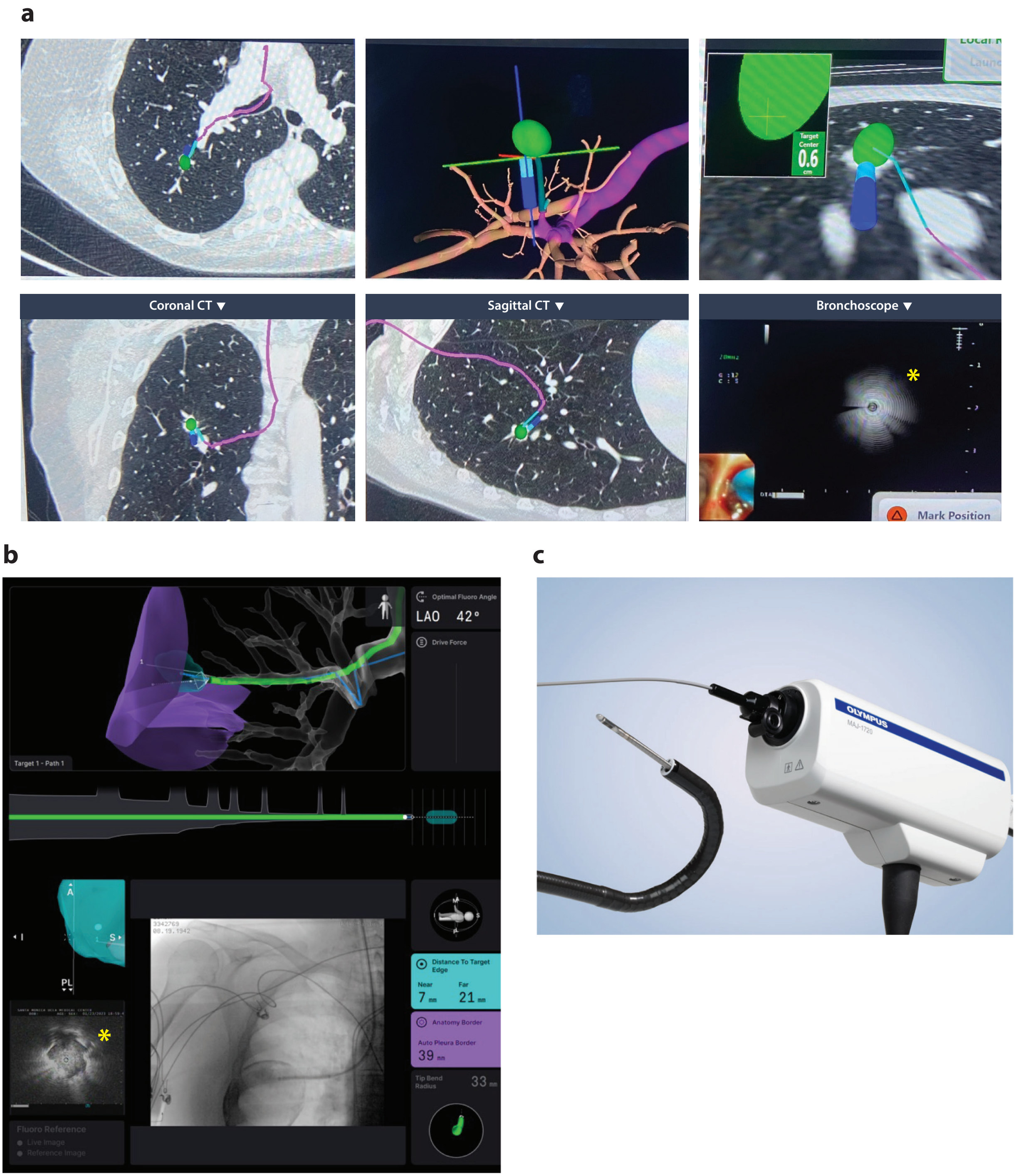
Recently, new technologies have become available to overcome peripheral bronchoscopy's limitations, including electromagnetic bronchoscopy and robot-assisted bronchoscopy. Electromagnetic navigation (EMN) is a guided bronchoscopic technology by which peripheral airways are accessed using a smaller, maneuverable guide sheath that is passed through the working channel of a conventional bronchoscope (27). The patient's tracheobronchial tree is outlined in advance on a preprocedure planning CT and a pathway to the target lesion is designated using special software (**Figure 2*a***). This pathway is then correlated to a 3D electromagnetic field generated around the patient. A 2-mm maneuverable and locatable guided sheath is steered to the target lesion by deflecting the magnetic field and signaling the progress of the sheath along the designated pathway. NAVIGATE, the largest national multicenter trial evaluating EMN, reported results of 1,215 prospectively performed procedures from 29 centers across the United States. This study showed a sensitivity, specificity, positive predictive value, and negative predictive value for malignancy of 69%, 100%, 100%, and 56%, respectively, with a subsequent decline in diagnostic yield to 73% at 1-year and 68% at 2-year follow-up (23, 28).

Robotic-assisted bronchoscopy has emerged as a promising modality for peripheral bronchoscopy, utilizing highly articulating catheters and spatial recognition software. Cadaveric studies have suggested improved nodule localization and puncture relative to other peripheral bronchoscopic modalities, including EMN, in cadavers with nodules <2 cm in diameter (80% versus 45% for EMN; $p = 0.02$), making robotic bronchoscopy an area of great interest (**Figure 2*b***) (25, 29, 30). The three commercially available robotic systems (Monarch, Ion, and Galaxy) utilize different approaches for peripheral bronchoscopic guidance including electromagnetic navigation, shape-sensing stabilization, and integration of real-time imaging modalities such as digital tomosynthesis (31–35). The performance characteristics of these modalities have improved the ability to successfully access and sample peripheral lung nodules, especially when using adjunct imaging modalities. However, further research is needed to better understand the optimal utilization of these platforms (36).

Real-Time Image Guidance of Peripheral Bronchoscopy

Perhaps the most significant limitation of peripheral bronchoscopy is the loss of real-time visual feedback to guide the proceduralist during tissue acquisition. To compensate for this, several tools provide real-time visual feedback during peripheral bronchoscopic biopsies. Radial EBUS is a thin-caliber, flexible probe capable of extending through the bronchoscope's working channel and provides a 360° ultrasound view at the distal tip of the probe (**Figure 2**). This allows for real-time localization of a nodule immediately prior to biopsy. Radial EBUS is a safe, inexpensive, and effective technique and is frequently used with other advanced navigational platforms (37, 38).

Conventional 2D fluoroscopy is also an inexpensive and readily available portable imaging modality frequently used for lung nodule biopsies. However, the low-fidelity images limit its utility for navigating to target lesions, which are often too small to be seen with fluoroscopy alone. Augmented fluoroscopy improves on conventional fluoroscopy by overlaying data from the patient's CT scan to reconstruct the tracheobronchial anatomy on which the target is designated during the procedure. In a prospective study of five centers in which 57 nodules were biopsied, the localization success rate was 93% and the overall diagnostic yield of augmented fluoroscopy-guided biopsies was 75.4% (39). Digital tomosynthesis also leverages conventional C-arm fluoroscopy by reregistering the target's location based on intraoperative fluoroscopic images and is used for electromagnetic navigation platforms. Digital tomosynthesis provides real-time compensation for intraprocedural deviations from the planning CT, allowing redirection of the locatable guide based



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Guided peripheral bronchoscopy using various representative platforms. Panels *a* and *b* show the proceduralist's perspective when performing electromagnetic navigational bronchoscopy with (*a*) an Illumisite system and (*b*) an Ion robotic platform with the navigated pathway highlighted by a purple and green line, respectively. Both are using a radial endobronchial ultrasound probe for tissue confirmation (asterisk). (*c*) A 2-mm radial endobronchial ultrasound probe through the working channel of a bronchoscope (image with permission from Olympus).

on real-time imaging. Aboudara et al. retrospectively reviewed their initial experience comparing standard EMN with and without digital tomosynthesis (67 versus 101 nodules, respectively) and reported an increase in diagnostic yield with the use of digital tomosynthesis (79% versus 54%; $p = 0.0019$) (40).

Cone beam CT is a powerful real-time imaging modality where high-definition images are created with volumetric data acquisition in a single gantry rotation. It allows intraprocedural CT imaging to be performed during the bronchoscopy, without the need to transport the patient. Two recent single-center studies evaluating the efficacy of cone beam CT reported diagnostic yields of 74.8–89.9%, with improvement in diagnostic yield relative to stand-alone electromagnetic navigation (41, 42).

While these innovative modalities have demonstrated the feasibility of improving diagnostic yields for peripheral bronchoscopic biopsies with great safety profiles, the suboptimal performance illustrates that there are obstacles yet to be overcome to further improve the diagnostic yield. Comparative data are limited to a recent retrospective single-center study comparing robotic-assisted bronchoscopic-guided biopsy (143 nodules) to EMN in conjunction with digital tomosynthesis (197 nodules). This study showed no difference in diagnostic yield (robotic-assisted bronchoscopy 77% and EMN with digital tomosynthesis 80%), suggesting that robotic-assisted bronchoscopy with adjunct real-time imaging modalities may further the effectiveness of guided peripheral bronchoscopy (43).

Peripheral Nodule Resection and Ablation

Beyond diagnostics, peripheral bronchoscopy has also proven helpful in facilitating minimally invasive robotic resection of nodules. Using any of the peripheral bronchoscopic navigational approaches, a small aliquot of dye, typically methylene blue or indocyanine green, is injected into the target lesion. By "tattooing" the nodule, the surgeon gains a visual cue for resection in place of palpation alone, which can minimize the extent of resection. Fiducial markers can also be placed using peripheral bronchoscopy at the time of the initial biopsy and help to pinpoint the tumor's location for greater accuracy of surgical resection and therapeutic stereotactic radiation.

With the increasing accuracy and stability of the current navigational platforms, research into bronchoscopic methods to therapeutically ablate malignant pulmonary lesions is now underway. A preliminary study in nonsurgical patients that evaluated bronchoscopy-guided radiofrequency ablation with a flexible electrode demonstrated safety in a cohort of 20 patients with 23 lesions (44). Tumor shrinkage was seen in 11 tumors while 8 tumors remained stable. Similarly, a single-arm pilot study in which navigational bronchoscopy-guided microwave ablation was performed in 13 patients (19 ablation sessions for 14 tumors) showed an overall safe profile (2 nonlife threatening pneumothoraxes), with complete response in 11/14 tumors (45). While these modalities are promising, the variability of ablation zones must be overcome in order for these technologies to be widely adopted.

INTERSTITIAL LUNG DISEASE—CRYOBIOPSY

Interstitial lung diseases (ILDs) include a wide range of diseases that are often challenging to diagnose without a confirmatory biopsy. Large biopsies containing histological architecture are required to distinguish the various ILDs, which differ in treatment approaches (46, 47). Conventional transbronchial lung biopsies can provide smaller samples that are often insufficient and marred by crush artifact. While surgical biopsies provide sufficient tissue, they carry higher risk, with 30-day mortality rates of 2%, or even higher when done in a nonelective fashion (48). Transbronchial cryobiopsy has emerged as a middle-ground procedure that can provide larger tissue samples devoid of crush artifact using a safer endoscopic approach. Cryobiopsies are done with a probe that rapidly freezes to −89°C and adheres to the adjacent lung parenchyma. Though the diagnostic yield of cryobiopsy is higher than that of conventional transbronchial biopsies, especially for nonspecific interstitial pneumonia, rates of adverse events are also higher, including a 56% risk of moderate to severe bleeding and a pneumothorax rate of 8% (49). Given safety concerns, its use is frequently limited to high-volume centers with local expertise. Oberg et al. have recently described the use of cryobiopsy to increase the diagnostic yield of lung nodule biopsies when performed with robotic-assisted bronchoscopy, demonstrating additional potential utility for bronchoscopic cryobiopsy (50). For the diagnosis of ILDs, integrating genomic gene signatures has shown promise to improve the yield of conventional transbronchial biopsies (51).

BRONCHOSCOPY FOR DIAGNOSIS AND MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION

Bronchoscopy plays a central role in the diagnosis and therapeutic management of central airway obstruction. Central airway obstruction can lead to significant shortness of breath, functional limitation, post-obstructive pneumonias, and death by asphyxiation. Therapeutic bronchoscopy can recanalize airways by ablating and debriding obstructing tumors, dilating airway strictures, stenting extrinsically compressed or weakened airways, and removing foreign bodies.

The prevalence of malignant central airway obstruction is estimated at 13% of lung cancer patients at the time of diagnosis, with an additional 20–30% of patients developing airway obstruction during the course of their disease. Malignant airway obstruction contributes to mortality in 40% of patients (52, 53). Cancers commonly involving the airway include lung and breast cancer, though a wide variety of tumors including lymphoma and esophageal and thyroid cancer can also involve the airway. Radiation and systemic therapies can control the underlying disease, but the lag to treatment effect may leave patients symptomatic for a prolonged period of time. By taking advantage of a variety of techniques such as lasers and stents, therapeutic bronchoscopy can provide immediate symptom improvement, manage post-obstructive pneumonia and hemoptysis, and palliate symptoms either as a bridge to therapy or definitively when therapeutic options are exhausted. Therapeutic bronchoscopy has been shown to result in discontinuation of mechanical ventilation in a significant percentage of critically ill patients with respiratory failure due to malignant central airway obstruction (54, 55). Therapeutic bronchoscopy may also help delineate tumor from distal atelectasis, helping to more effectively stage patients and provide the most appropriate therapy (56). In a retrospective study, 45 of 75 patients with malignant central airway obstruction gained spirometric improvement after bronchoscopy, subsequently allowing parenchyma-sparing surgery (57). The technical success rate of restoring airway patency declines with time, warranting early consultation with a physician skilled in therapeutic bronchoscopy (58). Unfortunately, chest CTs may miss up to 30% of malignant central airway obstructions, warranting a high level of clinical suspicion for this disease in patients with dyspnea in the appropriate setting (59).

While many of the nuances to treating central airway obstruction have evolved with time, the principles of airway recanalization still rely heavily on mechanical debridement, ablation, and stent placement for structural support (**Figure 3**) (60, 61). Rigid bronchoscopy is a commonly used modality for therapeutic bronchoscopy. The sizeable diameter of the rigid bronchoscope

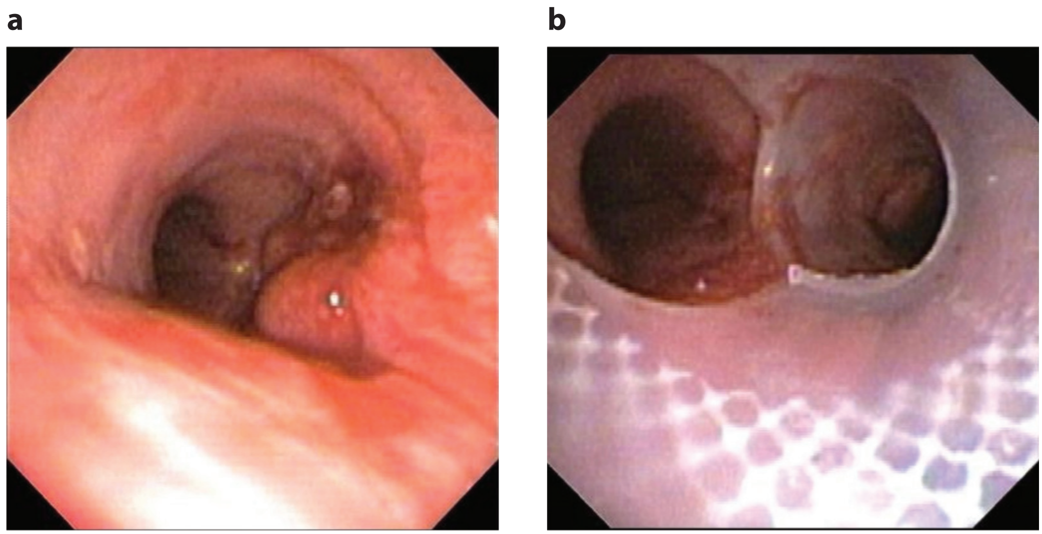


Figure 3

Therapeutic bronchoscopy. A tumor obstructing the right mainstem bronchus (*a*) before and (*b*) after recanalization with placement of a modified silicone stent.

provides a conduit for larger tools and suction catheters, thus improving the speed and efficiency of removing endobronchial lesions or foreign objects. Additionally, the rigid bronchoscope serves as an endotracheal tube, allowing patient ventilation while minimizing soilage of lung from secretions or blood. The barrel of the rigid scope can also debulk endobronchial tumors using an "apple coring" technique. Other mechanical debulking devices such as the microdebrider, a rigid catheter that suctions tumor through rotating teeth, can provide immediate relief from centrally located tumors.

Endoscopic ablative tools are classified by their thermal profile and the need for tissue contact. "Hot" thermal contact electrocautery-based catheters such as knives, forceps, blunt probes, and snares incise tumors or strictures while providing excellent hemostasis. Non-contact modalities such as lasers [e.g., Nd:YAG (neodymium-dope yttrium aluminum garnet)] precisely vaporize tumors, while argon plasma coagulation and photodynamic therapy are used to treat larger surface areas of mucosa (62). "Cold" therapies leverage the apoptotic and adhesive effects of rapid cellular freezing on tissue. Cryosurgery utilizes a small probe that requires direct contact to treat small areas, while cryospray induces cell death over larger areas. The choice of modalities depends on operator preference and local expertise.

The degree and mechanism of central airway obstruction determines the therapeutic approach. Endobronchial tumors are amenable to local ablation while tumors that compress the airways extrinsically require structural support through stenting. Stents differ in their material and mode of deployment (63). Silicone stents require rigid bronchoscopic deployment, have strong radial force, and vary in shape with tubular and Y forms. Silicone stents are modifiable, inexpensive, and easily removed using rigid bronchoscopy. Custom 3D printing technology has enhanced the applicability of silicone stents for the management of aberrant airway anatomy. Metallic stents are often easier to deploy than silicone stents and do not require rigid bronchoscopy. However, these stents are more expensive than their silicone counterparts and removal can be complicated due to epithelialization and stent fracturing. The choice of stents is typically dictated by the clinical context and local expertise.

Therapeutic bronchoscopy has also been used to treat tracheoesophageal and bronchopleural fistulas when definitive surgical correction is not feasible. Stents and other occlusive devices can seal airway defects, restoring function and preventing lung soilage (64–66).

Benign tracheal and bronchial stenoses from rheumatic disease, prior tuberculosis, prolonged intubation, tracheotomy, and idiopathic airway stenosis often require serial therapeutic bronchoscopy with balloon or rigid bronchoscopic dilation combined with focal incisions in the webbing to maximize the diameter. Flexible bronchoscopy is considered the gold standard for diagnosing dynamic airway narrowing (e.g., tracheobronchomalacia). For patients who may be candidates for surgical management of tracheobronchomalacia, a brief trial of airway stenting may be performed to assess for symptom improvement (67, 68). In severe cases of recalcitrant benign airway disease where surgery is not an option, stenting may be considered for definitive management.

ENDOBRONCHIAL VALVES IN THE TREATMENT OF EMPHYSEMA

Emphysema is a progressive disease for which pharmacological treatments may be inadequate to control symptoms and lung transplant may be considered. The randomized controlled National Emphysema Treatment Trial demonstrated the utility of lobar resection for symptomatic improvement and even survival in patients with upper lobe–predominant disease and reduced baseline exercise capacity (69). However, given surgical concerns for this vulnerable population, alternative approaches such as bronchoscopic lung volume reduction (BLVR) have been developed. In BLVR, one-way valves are placed bronchoscopically to achieve lobar atelectasis in a diseased lobe of the lung, reducing hyperinflation and restoring respiratory mechanics. LIBERATE and EMPROVE were two international randomized controlled trials comparing BLVR to standard of care (**Figure 4**) (70, 71). Patients randomized to BLVR had improved physiology with improved spirometry and 6-min walk tests. Due to the high post-procedure pneumothorax rates of 25–30%, post-procedure in-hospital observation is required. One study showed a sustained benefit for patients who underwent placement of endobronchial valves at 3-year follow-up (72). BLVR has also been shown to benefit patients with homogeneous disease with where air trapping is profound (residual volumes >200%) (73). As experience grows with BLVR, additional insights regarding the cardiovascular benefits of reducing hyperinflation are being realized as well, with improvements in cardiac preload and contractility and improved cardiac output (74). Endobronchial valves are also approved for compassionate use in the management of persistent broncho-pleural fistulas, which can often occur postoperatively or result from underlying chronic obstructive pulmonary disease, cancer, or infection (75).

SUMMARY

The complexities of patients with thoracic disease and the frequent need for procedural interventions highlight the value of comprehensive interdisciplinary management. The foundation of internal medicine and pulmonary medicine training, coupled with robust procedural skills, allows IP physicians to balance the procedural and medical aspects of caring for this increasingly vulnerable patient population.

Endoscopic advances have extended the reach of bronchoscopy both beyond the airway lumen to the mediastinum and in the periphery, enhancing confidence in biopsies where conventional bronchoscopy performs poorly. IP has also been instrumental in the multifaceted care of patients with symptomatic complex thoracic disease. Advances in ablative modalities hold great promise as future complementary therapies for cancer patients. Beyond cancer care, IP is also equipped to treat patients with benign pulmonary diseases, including ILDs, emphysema, and airway

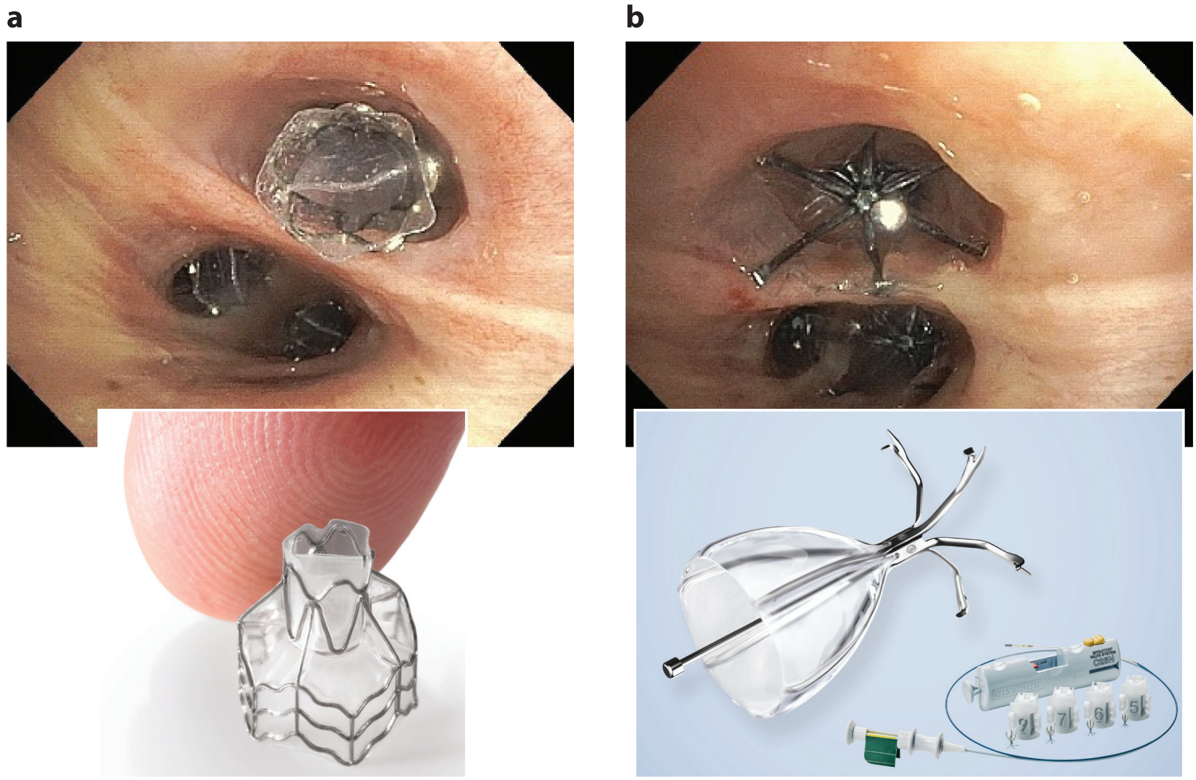


Figure 4

Endobronchial valves for lung volume reduction. (*a*) Zephyr valve (image with permission from Pulmonx Corp.) and (*b*) Spiration Valve System (image with permission from Olympus).

stenosis. The span of pathologies and the range of tools that IP can offer make interventional pulmonologists a valuable resource for the patient with complex thoracic disease.

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