Advances in Interventional Pulmonology

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KEYWORDS

• Interventional pulmonology • Therapeutic bronchoscopy • Malignant diseases of the lung
• Lung malignancy staging

KEY POINTS

- The rate of development of new techniques and their complexities require interventional pulmonology physicians to be constantly maintaining and updating their skill set.
- International agreed training pathways help ensure that the interventionalists of the present and future have the required knowledge of anatomy, manual dexterity, and clinical judgment to keep up with the continuing advances that are constantly expanding IP's diagnostic and therapeutic boundaries.
- Interventional pulmonology remains one of the most desirable subspecialities in pulmonology, and the technologic advances make the future an exciting one.

INTRODUCTION

Interventional pulmonology (IP)—the encompassing term for all nonsurgical procedures relating to the lung and mediastinum—has advanced significantly since the American Thoracic Society and European Respiratory Society published their Joint Statement on IP more than a decade ago.[1] Bronchoscopy can now diagnose malignancy and stage the disease at the same sitting, and by using techniques such as endobronchial ultrasound scan, the need for surgical exploration of the mediastinum has dramatically reduced. Now, as interventional pulmonologists, we can even sample metastatic disease from sites such as the left adrenal gland by using the endobronchial ultrasound scan via the esophagus.

Therapeutic bronchoscopy has been the mainstay of the interventional pulmonologist's workload, and the armamentarium available to the operator is ever increasing. The use of thermal destruction of tumors, laser, radiation treatment, and photodynamic therapy is increasing, as is the requirement for us to help our oncology colleagues with treatment planning by the placement of fiducial markers for radiotherapy. Significant advances are being made in the developments of tracheobronchial stents to overcome some of the side effects experienced by inserting such foreign bodies, and soon these will become biodegradable within the airways and will secrete chemotherapy agents to aid with the systemic management of malignant disease. As a therapeutic modality, bronchoscopy is also used for nonmalignant conditions and over the last decade has increasingly been used to treat airways disease such as asthma and emphysema.

Many of the techniques described in this article are now standard procedures for the interventionalist, but even though some are still in the trial phase, it is clear that IP is accelerating at an unprecedented rate.

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Advances in Interventional Pulmonology in Malignant Diseases of the Lung

Diagnostic imaging and early detection of lung cancer

Until screening for lung cancers becomes an established program internationally, many patients with lung cancer do not present until the disease is at an advanced stage. Any modality that enables high-resolution accurate imaging of the bronchial tree to enable early detection must therefore have its advantages. Flexible bronchoscopes are becoming ever more advanced; the high-resolution bronchoscopes available can now provide exceptional image quality and can even enable imaging of the endobronchial microvasculature. Combined with other techniques, this can improve the visualization of premalignant lesions.[2]

Autofluorescence bronchoscopy Autofluorescence bronchoscopy (AFB) is one method of identifying premalignant or malignant lesions not seen with standard white light bronchoscopy.[3] This technique uses the natural fluorescence of tissues when exposed to light of a certain wavelength, and the fluorescence is altered by infiltrating tumors.[4] AFB techniques use the different fluorescence exhibited by dysplasia, carcinoma in situ, and microinvasive carcinoma compared with healthy tissues, and the abnormal tissue appears as a different color compared with the normal tissue at bronchoscopy. The fluorescence phenomenon is based on the tissue concentration of substances called *fluorophores*, which absorb and emit fluorescence when irradiated by a light source.[5] This color change varies according to the system used, but when combined with white light bronchoscopy (WLB) is more sensitive in detecting abnormal mucosa than white light bronchoscopy alone.[6,7] Sun and colleagues[8] reported that the pooled relative sensitivity of WLB combined with AFB versus WLB alone was 2.04 for detecting intraepithelial lesions and 1.15 for invasive cancer, whereas the pooled relative specificity of WLB and AFB versus WLB was 0.65. Its current role lies in the monitoring of precancerous lesions already identified, and as yet it is not used solely as a screening tool, mainly because the benefit for detection of occult malignancies over and above low-dose computed tomography (CT) screening has not yet been shown.[9] It can, however, also provide an adjunct in surgical planning for the resection of lung cancers by providing surgeons with a regional identification of abnormal mucosal before surgery, thus potentially reducing incomplete resections and therefore recurrence rates.[10]

Narrow beam imaging Narrow beam imaging (NBI) allows examination of the submucosal microcapillary bed by using 2 narrow wavelengths of light to irradiate the tissue. The blue narrow band is absorbed by surface mucosal layer capillaries, and the green narrow band is absorbed by the hemoglobin in the deeper submucosal thick blood vessels.[11] The results are high-quality images of the endobronchial microvasculature architecture; this allows for differentiation between premalignant and malignant lesions, assessment of the degree of invasion, and identification of pathologic submucosal vessels. Recent work suggests that this technique is superior to AFB with increased pooled sensitivity and specificity for premalignant airway lesions at 80% and 84%, respectively[12]

High-magnification bronchovideoscopy High-magnification bronchovideoscopy (HMB) is a white light bronchoscopy system that provides up to 110 times the magnification of the bronchial mucosal vasculature; increased vessel density can be associated with premalignant or malignant change, and combining NBI and HMB enhances the detection of angiogenesis—an early sign in the development of premalignant lesions.[13]

Optical coherence tomography Optical coherence tomography (OCT) uses the properties of light waves in a similar manner to that of ultrasound, although does not require direct contact with the bronchial wall. It produces a much more detailed image and allows the first 2 to 3 mm of the bronchial wall to be visualized. This method has a role in both differentiating dysplasia from invasive carcinoma and quantifying the degree of airway remodeling.[14] In patients with superficial lesions suspected to be cancerous, OCT can detect whether there has been invasion deeper into the mucosa. Although this has not prevented the need for histologic sampling as yet, an advantage of OCT is that large areas can be imaged, to near histologic clarity, and biopsies can therefore be limited to appropriate areas.

In nonmalignant patients, such as those with asthma, it has been suggested that OCT may be able to establish the degree of smooth muscle hypertrophy in the airways, as it is superior to CT in developing a representative image of the airway wall.[15] This could help select suitable patients for bronchial thermoplasty and also to monitor treatment response.

Updates in the staging of lung malignancy

Endobronchial ultrasound scan Advanced diagnostic bronchoscopy has been revolutionized by the widespread and established introduction of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS TBNA). This technique enables a minimally invasive means of staging the

mediastinum with similar yields to mediastinoscopy but with lower complications and morbidity.[16]

In patients with non–small cell lung cancer whose treatment pathway is directed toward a radical intent, determining the disease status of the mediastinal lymph nodes is essential. Traditionally, the mediastinal nodal workup comprised noninvasive studies using CT and fused (18F) fluorodeoxy-D-glucose positron emission tomography (PET) with CT (FDG PET-CT), followed if needed by invasive diagnostic approaches with mediastinoscopy or thoracoscopy. The addition of PET to CT results in more accurate lymph node staging than CT alone with an overall sensitivity of 80% to 90% and specificity of 85% to 95%.[17] PET-CT alone is reliable if mediastinal lymph nodes that are less than 1 cm in the short axis are FDG negative. However, invasive sampling of the mediastinal lymph nodes is recommended when they are avid on PET-CT, the primary tumor is central, or any mediastinal node is larger than 1 cm in the short axis (irrespective of 18F-FDG uptake).[18] The 2014 European Society of Thoracic Surgeons algorithm for preoperative mediastinal staging updated the role of PET-CT in mediastinal staging such that surgery can be performed without mediastinal staging if all of the 3 criteria apply: no suspected lymph node on CT or PET, a tumor less than 3 cm, and tumor located in the outer third of the lung.[17] In the absence of this, accurate mediastinal staging is indicated.[19]

EBUS TBNA combines white light bronchoscopy with linear ultrasound scan to define mediastinal structures and parabronchial anatomy and enables a less invasive means of sampling mediastinal nodes than surgical mediastinoscopy. The advantage is that it can reach some of the lymph nodes that are inaccessible at mediastinoscopy and as standard will sample nodal stations 2, 3, 4, and 7; hilar station 10; and lobar station 11.[20,21] Furthermore, combining EBUS with transesophageal assessment of the mediastinum via endoscopic esophageal ultrasound scan with a dedicated esophageal ultrasound scope or by using the EBUS scope allows a more complete sampling range of nearly all the mediastinal and hilar nodes with a reported sensitivity of 93%.[22] This can reduce the need for surgical staging in up to two-thirds of patients[23] and can also enable sampling of adrenal metastases.[24] In a recent meta-analysis of 960 subjects, EBUS TBNA and mediastinoscopy were performed in the same patients. This study found that the diagnostic yields of the procedures are similar but that the rate of complications were lower with EBUS TBNA,[16] leading to a suggestion by some centers that mediastinoscopy may no longer be necessary.[25]

The use of linear EBUS also allows accurate visualization of the airway anatomy and can be used to assess degree of infiltration by tumors such as esophageal malignancies, which can help guide the esophagogastric surgeons plan operative management (Fig. 1).

Solitary pulmonary nodules

Radial probe endobronchial ultrasound scan A solitary pulmonary nodule (SPN) can be defined as single, well-circumscribed, radiographic opacity that measures up to 3 cm in diameter and is surrounded completely by aerated lung.[26] The frequency of SPNs varies across screening studies but can be greater than 50%.[27]

Although SPNs are a common finding, their management is often complex because of the numerous different etiologies. Current nodule guidance would support tissue sampling from SPNs, and these are often sampled by CT-guided transthoracic needle biopsy (TTNB). For peripheral lesions greater than 2 cm, TTNB has a high sensitivity (>90%)[11] but

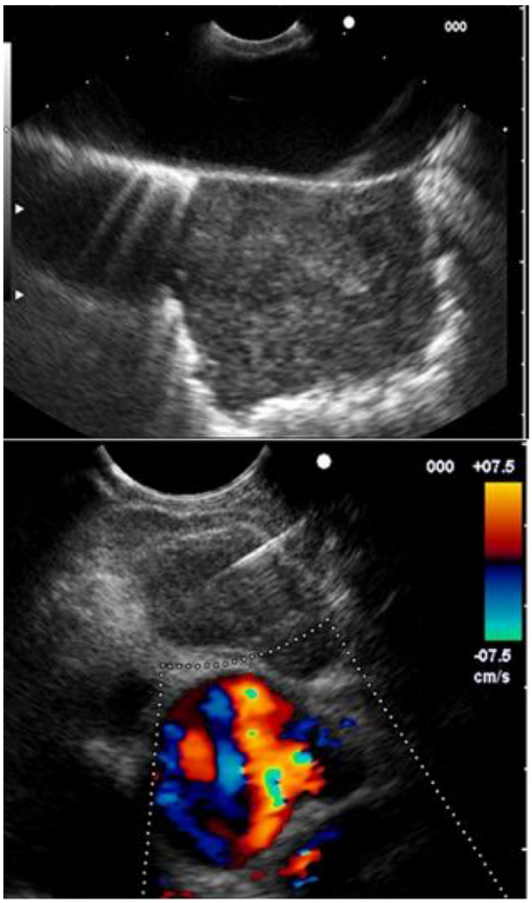

Fig. 1. Top image shows EBUS image of lymph node lying beneath a vessel. The lower image shows EBUS image of needle aspiration of lymph node. The vessel lying below the lymph node is demonstrated by use of color flow Doppler.

can be associated with complications, most frequently pneumothorax. This situation is more likely for central lesions in which much of the lung needs to be traversed to obtain tissue or if more than one pleural surface needs to be crossed. In some studies, the rates of pneumothorax can be greater than 30%.[11] The challenge, therefore, has been to find an alternative modality to TTNB, which can provide an equivalent yield but with lower morbidity.

Radial probe (RP)-EBUS incorporates a 20-MHz rotating probe that is passed through the normal working channel of a bronchoscope. This provides high-resolution 360° images of the airway and can identify peripheral lung nodules; the radial probe is advanced toward the lung nodule, which can then be identified using the ultrasound scan. With the use of a guide sheath as an extended working channel of the bronchoscope, the radial probe is withdrawn, leaving the guide sheath in the proximity of the target, and biopsy forceps, brushes, or needles are introduced into the working channel to obtain a histologic sample of the target lesion, with or without fluoroscopic guidance. Randomized, controlled trial data suggest a diagnostic yield of more than 70% using this technique.[28] RP-EBUS has also been used, with success, in the placement of fiducial markers to guide radiotherapy for solitary lung nodules and can enhance the delivery of these treatments[29] (Fig. 2).

Ultrathin bronchoscopes The limitation of RP-EBUS is that the radial probe needs to be removed before sampling can occur. A standard therapeutic flexible bronchoscope with a working channel up to 2.8 mm has an external diameter in the region of 6 mm. Peripheral lesions cannot be directly visualized with this bronchoscope, as it simply cannot be passed into the small airways to locate the lesion. Recently, development of an ultrathin bronchoscope with a 3-mm distal diameter and a 1.7-mm working channel has been found to provide a higher yield than even the standard thin bronchoscope (74% vs 59%, respectively). This ultrathin bronchoscope can reach as far as the fifth-generation airways and can be used in combination with fluoroscopic screening or RP-EBUS to reach lung nodules (Fig. 3).[30]

Electromagnetic navigation bronchoscopy Electromagnetic navigation bronchoscopy (ENB) is analogous to a global positioning system, but instead a satellite it uses an electromagnetic field to pinpoint the location of an 8-way maneuverable guide inside the patient. The components of ENB are the electromagnetic field, maneuverable guide, extended working channel, and computer software that generates a virtual bronchoscopic reconstruction of the patient's airways. This system allows the user to biopsy peripheral lesions with a diagnostic yield of 65% and a pooled sensitivity for malignancy of 71%[31] with low complications.[32] ENB has also been used to guide treatment via the placement of fiducial markers for radiotherapy,[33] guide brachytherapy,[34] and even to guide thermal ablation of peripheral tumors.[32] The main limiting factor remains the cost of the system, which can be prohibitive for many centers.

Virtual bronchoscopic navigation Virtual bronchoscopic navigation (VBN) is a method for displaying 3-dimensional images of the tracheal and bronchial lumens prepared from the CT data and reconstructed as if they have been observed at bronchoscopy. The VBN system then guides the

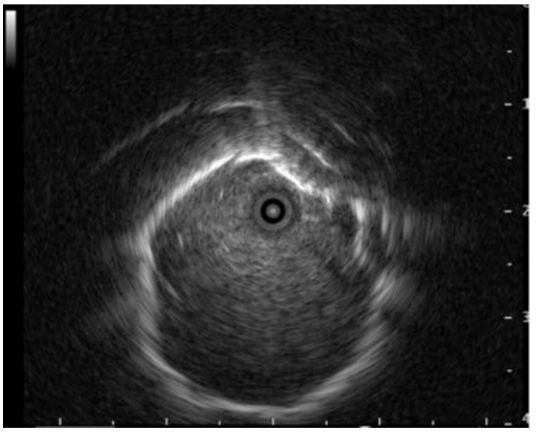

Fig. 2. RP-EBUS image of a peripheral solitary pulmonary nodule.

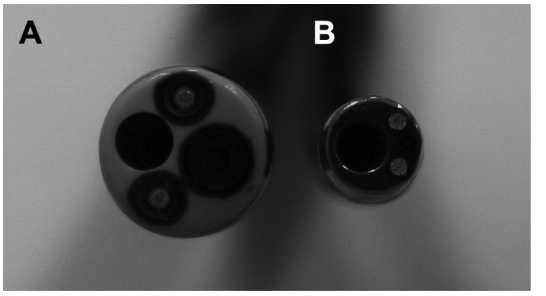

Fig. 3. (*A*) Standard bronchoscope with a distal end diameter of 5.9 mm and a working channel of 2.0 mm (BF-240; Olympus, Tokyo, Japan). (*B*) Thin bronchoscope with a distal end diameter of 3.5 mm and a working channel of 1.7 mm (XBF-3B40Y1; Olympus). (Reproduced with permission from the ©ERS 2008. European Respiratory Journal Aug 2008, 32 (2) 465–471; DOI: 10.1183/09031936.00169107.)

bronchoscopist to the target lesion.[35] VBN can be used in combination with other techniques such as fluoroscopy or RP-EBUS; recent data using VBN in combination with RP-EBUS increased the yield from peripheral lung lesions from 67% to more than 80% compared with RP-EBUS alone.[36,37]

Bronchoscopic transparenchymal nodule access Sometimes the most direct route to a lung lesion is through the airway wall into parenchyma, rather than following a bronchoscopic route. This is even more pertinent if there is no airway running directly into the lesion—known as the *bronchus sign* on CT.[38,39] Recently a new technique, bronchoscopic transparenchymal nodule access (Archimedes, Broncus Medical Inc, USA) that uses a reconstruction of the patient's CT scan into a 3-dimensional model has been trialed. This technique provides a point of entry through the airway wall and then via the lung parenchyma directly to the solitary pulmonary nodule rather than tracking to the lesion via the airways. Preliminary data suggest this is a safe and feasible means to gain tissue from a lung nodule.[40,41]

Therapeutics in interventional pulmonology

Central airway occlusion Therapeutic bronchoscopy has been shown to be effective in the relief of central airway occlusion (CAO) caused by malignancy and can improve quality of life.[42,43] The modalities available for CAO can be broadly divided into those that have an immediate effect (eg, mechanical debulking with rigid bronchoscope, thermal ablation with argon plasma coagulation, or laser destruction of a lesion) and those with a delayed effect (cryotherapy, brachytherapy, or photodynamic therapy). More recently, newer technologies have been explored such as microdebrider bronchoscopy—a technique well known to those in the otorhinolaryngology field but relatively new to the armamentarium of the interventional pulmonologist.[44] Microdebriders are made up of a hollow metal tube with a rotating blade coupled with suction. These are deployed through a rigid bronchoscope and provide an immediate means of debulking airway tumors—both benign and malignant.[44–46]

Photodynamic therapy (PDT) is well established in the treatment of lung cancer. The treatment requires administration of a light-sensitive drug that acts as a tissue photosensitizer, followed by illumination of the target tissue with visible light some 48 hours later transmitted through optical fibers via a bronchoscope. This method leads to the generation of reactive oxygen species, which results in the destruction of the tumor by a combination of direct cellular and secondary vascular effects.[47,48] Bronchoscopically delivered PDT has usually been limited to central tumors. In the treatment of peripheral tumors, the light has had to be delivered percutaneously under CT guidance directly into the lesion. This method carries similar complications to those of TTNB, such as pneumothorax or pulmonary hemorrhage, so if these lesions could be treated with PDT endobronchially, there would be a clear advantage in minimizing these risks. Locating the lesions would require the use of navigational bronchoscopic techniques, which are currently under development.

Percutaneous thermal ablation of lung tumors is an established therapy[49–51] with good success rates; a recent study of thermal ablation in stage IA non–small cell lung cancer found an overall survival rate of 86.3% at 1 year and 69.8% at 2 years with local progression-free rates of 68.9% and 59.8% at 1 and 2 years, respectively.[50] Percutaneous therapies, however, are associated with complications, most notably pneumothorax, so there is increasing interest in this technique delivered endobronchially, using either radio frequency ablation or microwave ablation.[52–55] This is a promising development, as the principle of delivering thermal ablation therapy could avoid some of the complications associated with percutaneous methods such as pain, pneumothorax, and pulmonary hemorrhage. More work is needed to finesse these techniques but the utilization of navigational bronchoscopic methods would be essential, with the use of a guidance sheath to allow placement of the thermal energy applicator at the target lesion.

Many of these techniques, if successful in restoring patency to the central airways may negate the need for endobronchial stent placement. However, if the central airways remain at risk of occlusion despite these procedures, or if the disease is extramural and therefore cannot be debulked, then an airway stent is often deployed. These provide radial force into the airway to maintain patency; however, they are still a foreign body and as such are associated with complications. These include sputum retention, granulation tissue formation and overgrowth, and even stent migration. To overcome this, new stents are in development that are biodegradable. The principle of biodegradable stents as an alternative is attractive, as they may overcome some of the complications associated with silicone or metallic stents, particularly if used in benign disease where a stent may be expected to be in situ for a long time. biodegradable stents have been developed for esophageal, intestinal, urethral, biliary duct, and vascular stenoses with good outcomes[56–58] and thus could prove a valuable option for CAO for both malignant and nonmalignant

conditions. Early work in this area has proven promising.[59] If this can be combined with delivery of chemotherapeutic agents, in the form of a drug-eluting stent, then the relief of CAO may also allow a direct anticancer effect to complement systemic anticancer therapies.[60]

Finally, the bronchoscopic delivery of chemotherapeutic agents directly into lesions has being explored,[61] and it is conceivable that with the navigational techniques available, this could be applied to peripheral tumors in patients who are deemed unsuitable for radical therapy. This could in theory enhance the tumoral response to the agent and could limit the systemic side effects of the chemotherapy.

Advances in Interventional Pulmonology in Airways Disease

Lung volume reduction techniques

Endobronchial valves Lung volume reduction techniques for emphysema have been evolving ever since the early work by Brantigan and colleagues[62,63] in the 1950s. These techniques have a recognized high mortality rate,[64] so the search has been for a lower risk, potentially reversible procedure that can provide the same benefit. Bronchoscopic lung volume reduction with 1-way valves has become an established procedure with reproducible and consistent outcomes for lung function, exercise capacity, and quality of life.[65–70] When placed in the airway, these valves prevent air from flowing into the most damaged lobe of the lung but allow air to exit the lobe thus creating atelectasis of the target lobe and subsequent lung volume reduction.

Endobronchial coils Endobronchial coils are nitinol devices delivered bronchoscopically into the airways and that induce lung volume reduction by contraction of lung parenchyma. Patients are most commonly treated bilaterally with approximately 11 coils per target lobe.[71] Three randomized controlled trials have been published[72–75] studying endobronchial coils. Those treated showed an improvement in 6-minute walk distance, forced expiratory volume in the first second, and symptoms measured by St. George's Respiratory Questionnaire (SGRQ) compared with the patients who received standard care with a meta-analysis in 2015 showing statistically increased lung function, quality of life, and exercise tolerance after coil insertion.[76]

Sclerosants Although endobronchial valves, and to an extent endobronchial coils, are reversible procedures to induce lung volume reduction, 2 techniques have been explored using sclerosing therapies to create the same effect. Both are irreversible; the first uses thermal energy from heated steam known as *bronchoscopic thermal vapor ablation* (BTVA) delivered into the airways and resulting in permanent fibrosis and atelectasis. The Step-up trial[77] randomly assigned patients to BTVA or standard therapy with improvements in lung function, quality of life, and exercise tolerance.

The second sclerosing therapy involves the delivery of polymerizing sealants into the bronchioles to block distal airspaces with severe emphysema. The only randomized trial exploring this (ASPIRE-2015) was terminated prematurely because of delivery problems with the sclerosant AeriSeal (Aeris Therapeutics, Woburn, MA) but seems to have shown an improvement in lung function and exercise tolerance as measured by 6-minute walk distance.[78]

Targeted lung denervation Targeted lung denervation (TLD) uses radiofrequency energy to ablate the parasympathetic pulmonary nerves surrounding the main bronchi. The effect is to decrease the release of acetylcholine in the airways, resulting in a permanent anticholinergic effect, a reduction in smooth muscle tone, and probable reduction in mucus production. Twenty-two patients were treated in the initial trial showing feasibility of the intervention.[79] There were improvements in lung function, exercise tolerance, and quality of life measure by SGRQ, and the effect seems to be proportional to the energy used. A randomized controlled trial is currently underway (ClinicalTrials.gov Identifier: NCT02058459).

Liquid nitrogen–metered cryospray Liquid Nitrogen Metered Cryospray is a method designed to bronchoscopically deliver liquid nitrogen spray into the central airways in a circumferential pattern. The principle is that this will destroy the mucus-producing goblet cells and reduce the airway inflammation. The system (RejuvenAir, CSA Medical, Lexington, MA) is currently being tested in a trial (ClinicalTrials.gov Identifier: NCT02483637) and the results are awaited with interest.

Interventional pulmonology in asthma

Bronchial thermoplasty For patients with persistent severe asthma, one option is to deliver thermal energy to the airways smooth muscle, not dissimilar to TLD, called *bronchial thermoplasty* (BT; ALAIR, Boston Scientific Marlborough, MA). The technique reduces excessive smooth muscle in the small airways and has been found effective in reducing asthma exacerbations, reducing steroid usage, and improving quality of life as judged by the asthma quality of life questionnaire.[80–82]

SUMMARY

Much has changed since the last review of IP published in this Clinics series. The rate of development of new techniques and their complexities require IP physicians to be constantly maintaining and updating their skill set. International agreed training pathways will help ensure that the interventionalists of the present and future have the required knowledge of anatomy, manual dexterity, and clinical judgment to keep up with the continuing advances that are constantly expanding IP's diagnostic and therapeutic boundaries. IP remains one of the most desirable subspecialities in pulmonology, and the technologic advances make the future an exciting one.

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