INTERVENTIONAL PULMONOLOGY (G CHENG, SECTION EDITOR)

Bronchoscopy: Past, Present, and Future

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Abstract



Purpose of Review To review the history of the bronchoscope and how pulmonologists have implemented it in clinical practice. Bronchoscopy has changed more in the last 20 years than in the previous century. The role of the pulmonologist has changed with the evolution of technology.

Recent Findings Over the last 20 years, endobronchial ultrasound and electromagnetic navigation have been employed in the diagnosis and staging of lung cancer. Most recently, robotic technology has been incorporated in bronchoscopy to provide enhanced stability, flexibility, and reach.

Summary Bronchoscopy has emerged as a minimally invasive technique to diagnoses, stage, and potentially treat lung cancer.

Keywords Bronchoscopy \cdot Rigid bronchoscopy \cdot Flexible bronchoscopy \cdot Interventional pulmonology \cdot Lung biopsy \cdot Electromagnetic navigational bronchoscopy \cdot EBUS \cdot Robotic bronchoscopy \cdot Lung cancer \cdot Cryobiopsy \cdot Lung cancer staging

Introduction

Bronchoscopy is the defining technology around which interventional pulmonologists have developed their specialty and based their careers. The technology has been available for more over 120 years, yet we have seen more change in the last 20 years than in the previous century. The bronchoscope provides minimally invasive visualization of airway anatomy and recognition of lung pathology previously only possible by surgical exploration, pathological examination, or in cadaveric studies. Although bronchoscopy has emerged as a minimally invasive technique for achieving diagnosis and staging with small tissue specimens, there has been parallel development in the amount of information that can be gleaned from tissue biopsies. Today, needle biopsy specimens are routinely used to evaluate cytomorphology, immunohistochemical markers, mutational analysis, and advanced genetic panels. This increasing battery of tests can quickly exhaust a biopsy specimen, leaving pathologists and oncologists wanting more. As

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¹ Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA 19111, USA we enter the age of immune therapy, bronchoscopists will often be asked to re-biopsy patients to evaluate acquired mutations that render tumors resistant to initial therapy. In the past, bronchoscopists have attempt to meet this challenge by using minimally invasive techniques to collect larger and larger samples. [1]

Within the last few years, technological developments in bronchoscopy have given rise to treatments with curative intent. This is a new age for bronchoscopy and an exciting time for the interventional pulmonologist. In the history of bronchoscopy, there have been five independent evolutionary leaps: rigid bronchoscopy, flexible bronchoscopy, endobronchial ultrasound, navigational bronchoscopy, and most recently robotic bronchoscopy. The first four of these technologies remain in routine clinical use. The fifth, robotic bronchoscopy, is a new addition of promise but has yet to develop supporting data. This chapter gives an overview of each of these technologies and their use in clinical practice.

Rigid Bronchoscopy

Rigid bronchoscopy is rooted in otolaryngology where physician surgeons developed instruments to better examine the larynx and central airways. It was once thought an impossible feat to examine the tracheobronchial tree in a living patient. In his book published in 1907, Chevalier Jackson reports Jan Mikulicz as having the first successful cases of tracheoscopy in 1896 but Gustav Killian is most lauded for developing bronchoscopy 1 year later. Jackson states in his book published in 1907, "Killian, in 1897, removed a foreign body from the bronchus and demonstrated the feasibility of upper bronchoscopy. Later he developed lower bronchoscopy. These were the greatest steps in endoscopy." Killian would go on to become an avid educator of bronchoscopists throughout Europe. In 1905, Chevalier Jackson in turn augmented the Killian tube with new lighting technology, an auxiliary canal, and a drainage canal. This device would still be recognizable as the rigid bronchoscope many use today. Jackson is credited with formalizing the discipline of interventional pulmonology in the USA and, throughout a long and illustrious career, would go on to use his rigid bronchoscope to remove 2374 foreign objects from patients' airways. Regarding his approach to foreign bodies, he reported, "The first 24 hours is the period during which expulsion is the most likely to occur, if at all. By the end of that time it is so buried in the swollen mucosa that it is seldom expelled until after sloughing has occurred." Jackson's reported mortality rate due to retained aspirated bodies was at least 27% with numerous cases of death in children attributed to unexplained pneumonia. He reported the mortality rate for bronchoscopy with foreign body removal was 3.–9.6%, thus favoring intervention. [2]

As pulmonologists gained experience with rigid bronchoscopy throughout the twentieth century, their role in therapeutic treatment increased. The integration of laser therapy to the rigid bronchoscope for debridement of central airway tumors is generally attributed to Jean Françoise Dumon, although meaningful contributions were also made by Unger, Toty, Vourc'h, and others [3, 4]. In 1987, Dumon introduced silicone airway stents. These were placed in areas of stenosis for relief of malignant and benign central airway obstruction. [5] Dumon attracted myriad visitors to his practice in Marseilles to train in rigid bronchoscopy with laser debulking and stent placement. These techniques are still widely practiced today. A survey of 26 European countries in 2017 found that every country had at least one center performing stent placement, the majority of which are performed by pulmonologists under general anesthesia. Dumon silicone stents remained among the most popular of those employed. [6] Stent technology has continued to evolve to incorporate memory metals such as nickel titanium alloy, or nitinol as the stent structure. These metallic devices have better wall-lumen ratios than the thicker wall silicone stents. Nitinol self-expanding stents can be placed by flexible or rigid bronchoscopy.

Ko Pen Wang was among the first to describe diagnosis of primary lung carcinoma in paratracheal nodal metastases by needle biopsy under rigid bronchoscopy. [7] The initial transtracheal needle aspiration technique used an esophageal varices needle passed through a rigid bronchoscope. The needle was then directed to the tracheal wall and advanced into the lesion. In a small case series, Wang et al. reported an ability to achieve diagnostic results in those with paratracheal masses or large nodal metastasis. In 1972, Anderson and Fontana reviewed 450 cases of trans-bronchoscopic forceps biopsy by rigid bronchoscopy. The technique is described by advancing the rigid scope into a mainstem bronchus and then extending a set of long rigid forceps into the lung parenchyma. They reported a pneumothorax rate of 14% and mediastinal emphysema or significant bleeding at about 1%. Of 450 cases, tissue was obtained in 84% patients.

Flexible Bronchoscopy

While therapeutic palliative procedures have remained relatively unchanged over the last half century, diagnostic procedures have continued to leap forward. This is largely attributable to the development of the flexible bronchoscope by Shigeto Ikeda in Japan in 1966. [8] This device allowed bronchoscopists to explore distal airways for presence of tumor, foreign bodies, and signs of infection. Ikeda's original specifications of the bronchoscope as described did not include a working channel for passing instruments although one was added to the first Olympus and Machida models released commercially. Early flexible bronchoscopes used glass light fibers to illuminate airways and transmit images. Ikeda described it as an instrument "so fragile and complicated in mechanism that the most gentle handling of the fiberscope is necessary and under no circumstances should there be forceful manipulation or careless handling such as bending the instrument out of curiosity." [9] Despite the device's fragility, Ikeda and colleagues proved its value in diagnosing early-stage lung cancer in segmental airways under direct visualization. As light and camera technology improved, flexible bronchoscopes became more robust due to video technology. This technology allowed smaller diameter bronchoscopes and larger working channels to be developed. In the years following, a variety of sizes including thin (4 mm) and ultrathin (3 mm) scopes were employed to reach peripheral lung lesions [10, 11]. Needles were adapted to fit through the working channel of the flexible bronchoscope and before long pulmonologists played an emerging role in diagnosing and staging lung cancer. The open tube biopsies performed by Anderson and Fontana using a rigid scope described earlier may have provided larger specimens, but due to the ease of use, improved patient acceptance, and low complication rates, transbronchial biopsy by flexible bronchoscope soon became standard practice. [12]

Since the introduction of transbronchial biopsies, there has been little consensus on their utility in the diagnosis of diffuse lung disease. Many critics report the small biopsy size and crush artifact as a major limitation in making a diagnosis. Within the last 10 years, cryobiopsies have gained favor mainly because proponents of this technique report a larger sample size without crush artifact and higher diagnostic yield. [13] Cryobiopsies are performed using a flexible cryoprobe, a thin metal–tipped probe (1.9 mm or 2.4 mm), which uses carbon dioxide or nitrous oxide to rapidly cool the tip of the probe to -89 °C. The probe can be passed through a flexible bronchoscope or passed along side to keep the working channel free to control bleeding. A meta-analysis of the cryobiopsy technique reported the diagnostic yield ranged from 51 to 98%. The estimate of pneumothorax was 12% and moderate to severe bleeding was 39%. [14]

Due to the risk of bleeding at biopsy site when a specimen is taken through a flexible scope, many interventional pulmonologists employ the use of occlusion balloons such as Fogarty balloons or endobronchial blockers to control biopsy site bleeding. Some pulmonologists have returned to the rigid bronchoscopy rather than an endotracheal tube to protect against the spillage of blood into the contralateral airways [15, 16]. Since we moved away from Anderson and Fontana's transbronchial biopsy technique through a rigid scope described above, we may have returned to it almost 50 years later.

Endobronchial Ultrasound

As lung cancer treatments continue to evolve, the therapeutic decisions rely on adequate staging. Current staging relies on three main components: tumor size, lymph node involvement, and presence of metastatic disease. This staging practice requires tissue sampled from mediastinal and hilar nodes often in addition to the primary lung lesion. Mediastinoscopy and excisional biopsies were the standard practice for initial lymph node staging. Radial Endobronchial ultrasound (R-EBUS), first described in 1992, employed a small rotating ultrasound probe attached to the end of a long filament and encased in an oil-filled plastic sheath. First-generation R-EBUS could be

Fig. 1 Rigid bronchoscope

passed through a 2.8-mm working channel and employed a 20-Mhz transducer with an inflatable balloon to provide a liquid interface between the ultrasound probe and the airway wall. Lymph node stations could be inspected for enlargement and marked for biopsy. Almost all lymph node stations could be imaged by this technique and standard transbronchial needle aspirate (TBNA) could be performed with less risk of complication than previously (Figs. 1, 2, 3, 4, and 5) [17, 18].

Linear Array Endobronchial Ultrasound

Linear array endobronchial ultrasound (linear EBUS) was introduced in 2002 and allowed transbronchial needle aspiration to be performed under continuous real-time visualization for the first time. [19] The 6.9-mm linear ultrasound probe was incorporated into the tip of a 6.2-mm bronchoscope. The scope included a working channel that oriented the needle pathway in plane with ultrasound probe. The probe was covered by silicone balloon which could be inflated with saline to provide a liquid interface.

Imaging with linear EBUS is performed by turning the bronchoscope-ultrasound tip to face the area of interest. Lymph node staging is performed by scanning the airway walls at each lymph node station, beginning contralateral to the suspected site of malignancy and moving toward the lesion of interest. By scanning the nodal stations with ultrasound, lymph nodes can be assessed for abnormality. Once a target is located, the needle sheath is advanced from the working channel and the needle is inserted through the airway wall. Penetration of the needle through the wall is visible on ultrasound and the needle pathway can be tracked as it travels through the lymph node. The linear EBUS has a Doppler function which allows the bronchoscopist to detect blood







- B. Outer diameter 5.4mm; Working channel 2.0mm
- Outer diameter 5.8mm; Working channel 2.8mm

Fig. 2 Flexible bronchoscope

vessels prior to biopsy. Linear EBUS is a major leap forward in the diagnosis and staging of lung cancer.

As EBUS-TBNA did not require a surgical incision, could be performed with or without general anesthesia, and allowed for evaluation of hilar lymph nodes not accessible by mediastinoscopy, it quickly became the standard modality for lymph node staging, replacing mediastinoscopy. [20] One drawback of the linear EBUS was because the ultrasound probe was positioned at the front of the scope, the white light video image had to be proximal to the ultrasound and oriented at 35 degrees forward oblique. This off-center view made scope driving difficult, and if airway inspection was to be performed, it typically required use of a traditional bronchoscope prior to lymph node staging. Later generation linear EBUS bronchoscopes now improve upon this design with better separation of the ultrasound probe and the video camera allowing for a 10 degree forward oblique viewing angle and a more natural image orientation [21].



camera at 10 degree viewing angle (left) Olympus EBUS with camera and lights in front of and lateral to biopsy port with camera at 30 degree viewing angle (right)





skin with paper clip)



Navigational Bronchoscopy

Advancements in data processing throughout the 1990s gave rise to software-enhanced CT scans that generate threedimensional renderings of the bronchial trees to aid in planning the treatment of central airway tumors and in navigation to peripheral nodules for biopsy [22, 23]. By generating virtual airway path, bronchoscopists can better orient themselves with the airway anatomy prior to starting a case. They can refer to the airway plan if they became disoriented during the bronchoscopy. This technology is limited by the ability



Fig. 5 Robotic bronchoscopy. Top right image used with permission from Auris Health

of the bronchoscopist to orientate the scope. A map, no matter how detailed, is inadequate without a compass to provide direction.

Electromagnetic navigation (EMN) provided that compass. When paired with a detailed virtual airway map, EMN provides turn by turn real-time directions to a virtual target within the lung parenchyma. If the virtual pathway and target are adequately matched with the anatomy of the patient, lesions can be approached with specificity even when the airways are too small to accommodate a video bronchoscope. EMN generates an electromagnetic (EM) field around the thorax. An electronic board is positioned under or above the supine patient. An active locatable guide (LG) is passed through the bronchoscope and into the airways. As the locatable guide moves through the magnetic field, it generates a signal which is interpreted as the location of the probe within the field. Once the position of key landmarks within the airways are registered, information from a pre-procedure CT scan is overlaid to generate a detailed airway map. With the CT scan providing a map and the electromagnetic sensors providing location and orientation, a locatable guide can be inserted through a directable plastic catheter or incorporated directly to biopsy instruments. The goal is then to use the EMN navigation to reach small targets in the periphery of the lung. Once the lesion is reached, blind biopsies are performed, typically under fluoroscopy. EMN bronchoscopy offers a significant advantage to the bronchoscopist. The combination of orientation and direction means that biopsies can be performed with enhanced accuracy. Navigating with a detailed airway map helps to avoid critical structures in the chest such as major vessels or cardiac structures.

While these technologies help bronchoscopists localize and biopsy small peripheral nodules with improved safety compared with traditional transthoracic needle biopsy, diagnostic yield yet remains sub-optimal [24, 25]. There were three main disadvantages of the EMN system. First, a pre-procedure CT scan does not perfectly match the airway orientation of the patient at the time of the procedure due to changes in patient orientation. This error, known as CT-body divergence, can lead to significant difference between the actual lesion and the virtual target. Second, because the navigation field is generated by electromagnets, it may be distorted by the presence of metal or electronics that generate their own EM fields. For this reason, procedure rooms need to be stripped of metal components. Metallic and electronic items must be kept away from the patent otherwise significant distortion of the navigation field develops. Radial ultrasound and fluoroscopy are commonly employed to provide external validation that a target site has been reached prior to biopsy.

The third disadvantage of EMN bronchoscopy is that once the target has been reached, the scope must be maintained in position while held by the bronchoscopist. Any small movements of the scope articulation or insertion depth can lead to changes in biopsy location. This can lead to variability in each needle pass while performing biopsies and can decrease reproducibility of sampling when performing multiple passes to attain adequate tissue specimens.

In evaluating the utility of EMN, many have struggled to adequately define accuracy and diagnostic yield. Studies have reported yields between 50 and 80% [26, 27]. The main limitation in defining diagnostic yield has been in interpreting negative biopsy results. Because of inherent sources of error in the EMN described above, a biopsy that does not show malignancy but also does not provide enough information to conclude a non-malignant diagnosis must be considered nondiagnostic. There are many benign causes of pulmonary nodules including inflammatory process and infectious or post infectious scaring; arriving at a non-malignant diagnosis with a small biopsy sample is often impossible. Without knowing the prevalence of cancer in a study population, we are unable to discern between a true-negative result and a false-negative one. To combat this, non-diagnostic nodules are followed with serial CT scans to ensure that they remain stable. The most comprehensive study to date by Folch et al. are following nondiagnostic nodules for a period of 2 years to confirm stability. While this clinical trial is still on-going, interim results at 1 year report a diagnostic yield of 73% with sensitivity of 69%, specificity of 100%, positive predictive value of 100%, and a negative predictive value of 56%. [28•]

One method employed to improve navigation accuracy and diagnostic yield is to incorporate a second technology to provide external validation of catheter position. X-ray fluoroscopy is a standard modality to provide reference during bronchoscopy but visualizing a nodule on standard fluoroscopy is challenging. CT fluoroscopy has been previously described to aid mediastinal TBNA for lymph node staging as early as 2001 but until recently had not been incorporated with bronchoscopic peripheral lung biopsies. [29] Advancements in hybrid procedure suites incorporating cone-beam CT (CBCT) have been safely employed with peripheral bronchoscopy with acceptable radiation dose to the patient and with a navigation accuracy of 91% [30, 31]. CBCT with augmented live fluoroscopy and EMN has recently been employed with significant improvement, reporting a diagnostic yield of 83.7%. In these cases, a CBCT scan is performed immediately after intubation. The nodule is then located on the CT then highlighted and overlaid on live fluoroscopy using proprietary software. The bronchoscope is then introduced into the airway and the catheter with locatable guided is advanced to the lesion under EMN guidance. Additional scans with CBCT can be acquired to confirm catheter position or biopsy needle position. [32]

The use of complementary technologies such as CBCT provides additional assistance in navigating to a lesion and confirming needle placement inside the area of interest. These technologies will likely reduce the rate of nondiagnostic biopsies but are associated with a high cost. Few hospitals are willing or able to devote resources to toward diagnostic procedures with low reimbursement. However, for many, the natural extension of bronchoscopy is accessing nodules with a therapeutic intent. Early studies in therapeutic lung nodule ablation using bronchoscopic image–guided microwave ablation catheters with CBCT are promising. [33••]

Robotic Bronchoscopy

Robotic technology has been incorporated into many aspects of medicine. In 2018, the Auris Monarch was the first robotic bronchoscopy platform introduced in the USA followed by the Intuitive Ion in 2019. Both platforms combine advanced robotic technology to control a small flexible bronchoscope. Early studies suggest that robotic technology incorporated into navigational bronchoscopy provides improved flexibility, reach, and stability. [34] In the case of the Monarch, the bronchoscope has two parts, a 4.4-mm robotic camera and an independent controlled robotic outer sheath. The sheath and camera can be advanced and flexed together in a paired mode or telescoped to flex in a complementary manner. By balancing the scope tension between the inner and outer robotic limbs, the tip of the inner scope can be advanced to the peripheral lesion under improved stability and specificity. The Monarch scope uses traditional EMN sensors. It also records scope insertion depth and incorporates pattern recognition software to map airways while driving. With the Ion platform, Intuitive has introduced a new shape sense technology that does not rely on EMN technology. The Ion robotic system records the shape of the catheter with a high degree of specificity and overlays the catheter shape on the CT scan to provide navigation. The main difference between the two systems is the scope size and presence of working channel. While the Monarch is a 4.4-mm scope with incorporated 2.1-mm working channel, the Ion is a 3.5-mm scope with a removable 2.0mm camera. The Ion working 2.0-mm channel is occupied by the camera during driving. The camera is removed prior to introducing biopsy instruments. It is too early to determine if either the Monarch or Ion technologies have specific advantages over the other. It will most likely depend on operator technique and predilection as to which device is preferred. Both devices have been used safely in small clinical trials [35••, 36].

Both robotic platforms offer unparalleled stability during driving and maintain their position in the airway after the bronchoscopist has left the robot controls. Instruments can be passed into and out of the devices during biopsies with improved control, stability, and reproducibility. These robotic systems thus offer advantages over previous-generation electromagnetic navigation. There is a significant capital expense involved in this robotic technology; however, the improvements in workflow, case duration, reach, flexibility, and control have led to continued interest and early adoption. Large prospective studies are on-going.

The integration of robotic technology into bronchoscopy has been seen as a disruptive force in the field of interventional pulmonology. Proponents of the technology highlight the stability and control a robotic platform offers while detractors site the high capital cost and unproven diagnostic yield against modest procedure reimbursement. Whether for or against robotic technology, most agree that we are in an exciting time of innovation in the field of interventional pulmonology.

Summary

The bronchoscope originated as a device to evaluate central airways provides therapeutic relief of airway obstruction. It has evolved to become an advanced diagnostic platform and is poised to offer curative intent of early-stage lung cancer. Palliation of airway obstruction will remain a corner stone of interventional pulmonology; however, the future of bronchoscopy seems to lie with accessing the lung periphery. Further evolution is sure to bring increasingly accurate minimally invasive techniques for diagnosis, staging, and treatment of lung malignancy.

Compliance with Ethical Standards

Conflict of Interest Christopher Manley reports personal fees as a consultant for Boston Scientific and Auris Health

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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