CHEST

The Evolutional History of Electromagnetic Navigation Bronchoscopy

State of the Art

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Electromagnetic navigation bronchoscopy (ENB) has come a long way from the early roots of electromagnetic theory. Current ENB devices have the potential to change the way lung cancer is detected and treated. This paper provides an overview of the history, current state, and future of ENB.

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KEY WORDS: biopsy; electromagnetic navigation bronchoscopy; localization; lung cancer; SPiN thoracic navigation system; superDimension navigation system

> "The best way to predict the future is to create it."
>
> —Abraham Lincoln

Cancers of the lung and bronchus account for more than one-quarter of all cancer-related deaths.[1] Although reductions in smoking have led to a general decline in lung cancer incidence rates,[1] one United States study has reported evidence of increased lung adenocarcinoma rates among women between 2008 and 2012 compared with between 1998 and 2002, particularly among low socioeconomic groups.[2]

Increased adoption of lung cancer screening in indicated risk groups may contribute to lower mortality[3]; however, a high proportion of false-positive nodules on low-dose CT scans necessitates a carefully implemented follow-up plan made on the basis of the patient's probability of malignancy and risk profile.[4] Furthermore, although molecular testing is recommended for late-stage non-small cell lung cancer,[5] adherence to guidelines is generally not good.[6] This may be partially because of the challenge of obtaining adequate tissue for broad molecular profiling, particularly in community centers.[7] A high proportion of patients with poor lung function are also at risk for complications following surgical or percutaneous biopsy. These factors contribute to an increased need for minimally invasive devices and procedures able to obtain diagnostic tissue and facilitate a quick path to treatment.

Electromagnetic navigation bronchoscopy (ENB) displays images of the tracheobronchial tree to aid the physician in guiding specialized endoscopic tools to lung targets.[8] ENB has been used to aid in the biopsy of peripheral lung lesions and lymph nodes and in placing fiducial markers or

ABBREVIATIONS: EBUS = endobronchial ultrasound; ENB = electromagnetic navigation bronchoscopy; ENB-SD = electromagnetic navigation bronchoscopy-superDimension navigation system; ENB-VM = Veran Medical Technologies' electromagnetic navigation system; TTNA = transthoracic needle aspiration

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pleural dye in preparation for stereotactic body radiation therapy or surgical resection, respectively.[9,10] This review article describes the conception and historical development of ENB as well as the current state of the technology and clinical evidence of its use.

The History of Intraprocedural Image Navigation

Before there was electromagnetic navigation, the field of image-guided surgery was mostly developed using mechanical and optical systems that would track surgical instruments and display them on previously acquired images. With mechanical systems, position was judged on the basis of the joint position of an articulated, surgical arm or a coordinate-based frame.[11-15] With optical systems, reflectors were attached to surgical instruments and their positions were triangulated by optical cameras located in the room (passive tracking) or light-emitting diodes that were attached to the patient and instruments and then detected by a camera (active tracking).[16] This work was mostly done in the neurosurgical realm where the skull was fixed and motion concerns with respiration or heart beats were not at issue.

Although optical and mechanical tracking systems are still used today in certain clinical situations, there were two limitations that have made them not as useful with flexible-type instruments such as a bronchoscope. The first limitation was that with the tools had to be rigid. Both systems used knowledge of the proximal part of the instrument to determine where the instrument tip was located. With the mechanical tracking system, it was the angulation of the joint that located the proximal end; with the optical system, it was where the reflectors were located on the surgical instrument. The second limitation was that optical systems required a direct line of sight to the instrumentation, which obviously limited internal instrumentation where the external cameras could not "see" them.

The initial electromagnetic tracking systems were applied in neurosurgery and sinus surgery; however, the electromagnetic sensor size was not well suited for endoscope tips.[17,18] It was not until miniature sensors were developed that applications that relied on flexible instruments such as catheters and endoscopes could be applied.

Historical Roots in Electromagnetic Theory

Electromagnetic tracking devices are used in a variety of applications in medicine, such as neurosurgery, urology, endonasal procedures, and cardiac procedures.[19] The basic concept consists of a field generator that generates a spatially changing (varying in magnitude and direction multiple times per second) electromagnetic field, and a sensory probe containing coiled wire(s) or other magnetometers. When the sensory probe is introduced into the magnetic field, it induces a voltage whose strength and polarity reflect the probe's position and orientation within the electromagnetic field.[19-21]

Although it is impossible to briefly describe the centuries of scientific discoveries leading up to this technology, the ability to generate and detect electromagnetic fields is largely made on the basis of the collective works of Ampère, Biot and Savart, and Faraday. To track the position of the sensor probe, one must first understand the geometry of the electromagnetic field. This was made possible by André-Marie Ampère (1820), who described the electromagnetic effect as the force that one current exerts upon another. Biot and Savart further defined this effect in 1824 by mathematically modeling the magnetic field generated by an electric current.[22] Also, once the reference field is known, one must be able to detect it via the sensor probe through magnetic induction. It was Michael Faraday in 1831 who proved empirically that a changing magnetic field induces an electric current inside a coil that can be detected.[22] In 1832, Joseph Henry further developed the practical application of Faraday's work.[22]

The Origins of Electromagnetic Navigation in the Lung

The first electromagnetic navigation in the lung was developed by a Johns Hopkins radiology resident, Stephen Solomon, and colleagues. Solomon (Fig 1A) was developing an intrabody navigation system that used electromagnetic fields to track sensors attached to the tip of surgical instruments. This work was done with a small company called Biosense that was later purchased by Johnson & Johnson. The sensor detected the real-time location, orientation, and movement of the instrument and displayed it on a previously acquired CT, MRI, or fluoroscopic image. The method was first applied in hepatic shunt procedures[23,24] and cardiac catheters.[20]

Solomon adapted the technology for use in pulmonology and published the first conceptual study in swine in 1998, noting that real-time bronchoscopic positioning by ENB could complement CT-guided transbronchial needle aspiration (Fig 1B).[21] His work led to his being awarded the Young Investigator Award

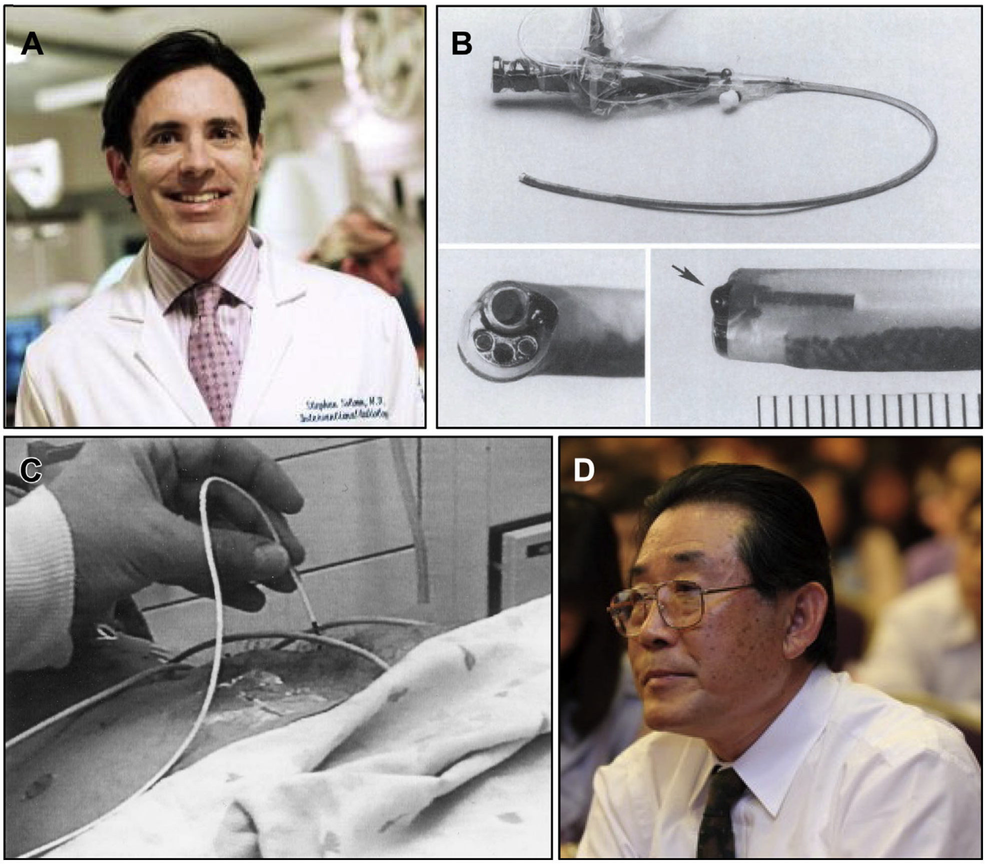

Figure 1 – *A, Stephen Solomon published the first study on electromagnetic navigation bronchoscopy in swine lung. B, Fiberoptic bronchoscope with attached position sensor, use by Solomon in 1998 (reprinted from Solomon et al,[21] 1998, with permission from Elsevier). C, Early registration method requiring the user to touch metallic markers on the patient's skin with the sensor (reprinted from Solomon et al,[25] 2000, with permission from Elsevier). D, Ko Pen Wang (reprinted from Panchabhai and Mehta,[121] 2015, with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Annals of the American Thoracic Society is an official journal of the American Thoracic Society.)*

and the Cecile Lehman Mayer Finalist award at the XIX World Congress on Diseases of the Chest and the 64th Annual International Scientific Assembly of the American College of Chest Physicians in 1998. Work with Dr Ko Pen Wang optimized the registration method, the process of aligning the patient's anatomy with the previously acquired images, using a technique of touching the wall of the trachea with the bronchoscope, which was found to be more accurate than the previous method that used metallic skin markers (Fig 1C, 1D).[25]

The first commercial ENB system was developed in Herzliya, Israel, by Pinchas Gilboa.[26] Gilboa had designed electromagnetic navigation systems for Israeli defense systems and established superDimension in 1995 as a toy company using an enhanced version of the navigation technology for computer-active games.[26] Gilboa joined with David Tolkowsky (son of Dan Tolkowsky, commander of the Israeli Air Force from 1953 to 1958) in 1996 (Fig 2); in 1998, they shifted the focus of the technology to image-guided interventional cardiology.[26]

In 2001, Gilboa and Tolkowsky moved the technology into interventional pulmonology, adding steerable catheter, three-dimensional image processing, and image-to-body algorithmic registration to their system.[26]

Preclinical Studies

The first preclinical study of the superDimension ENB (ENB-SD) system was conducted at the Sheba Medical Center Hospital in Ramat Gan, Israel, on October 31, 2002, by Yehuda Schwarz (Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel) et al (Fig 3). Ten artificial lesions were created in four animals. The procedure was a technical success with all anatomical landmarks identified and all targets successfully reached, and no animal complications. The average procedure time was 2 min for the mapping component and 5 min for the navigation component. The paper was published in 2003,[27] paving the way for clinical studies.

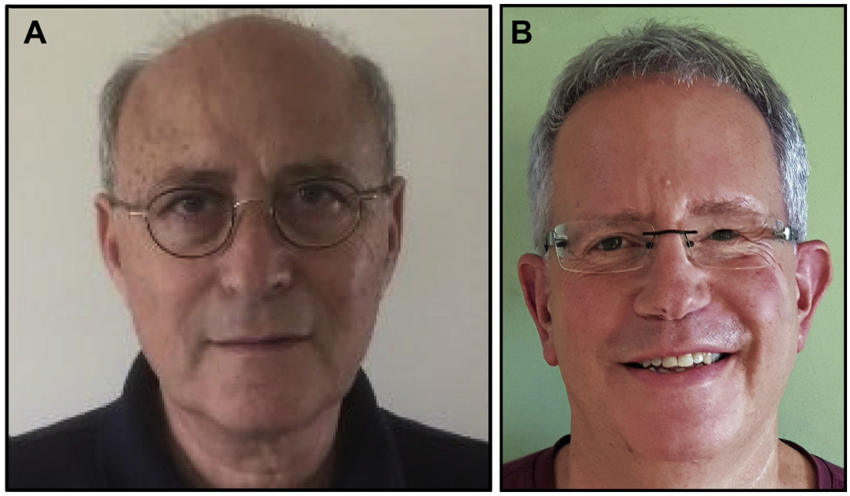

Figure 2 – *A, Pinchas Gilboa and (B) David Tolkowsky.*

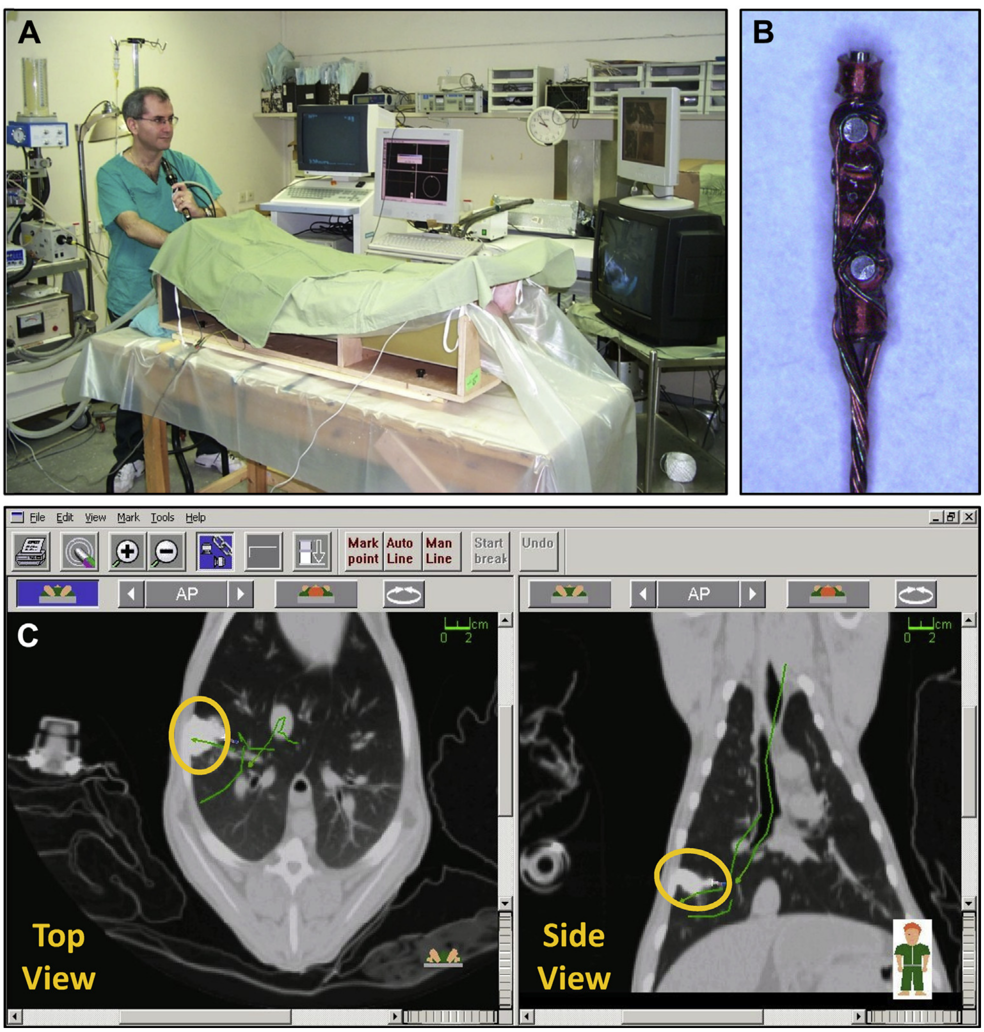

Figure 3 – *First preclinical study of the electromagnetic navigation bronchoscopy-superDimension navigation system at the Tel-Aviv Sourasky Medical Center October 2002. A, Dr Yehuda Schwarz and the animal model. B, Early sensor probe. C, Software view. (Images property of Medtronic, all rights reserved.)*

First Human Studies

The first use in man of an electromagnetic bronchoscope was performed with the Solomon group. Next, a clinical team including Atul Mehta, Ko Pen Wang, Praveen Mathur, Peter White, and Charlie Wiener were assembled to design a multicenter trial. The lack of funding limited further study with this sensor. The first human study with the ENB-SD system was performed in Israel in June 2003. A few weeks later, the first clinical study was initiated in Thoraxklinic, Heidelberg, Germany (July 28-29, 2003), under the guidance of Drs Yehuda Schwarz and Heinrich Becker (Fig 4). Thirteen subjects were included. Positive biopsy diagnoses were obtained in 9/13 cases, and there were no complications. The average navigation accuracy was 5.7 mm.[28] A second study of 30 subjects was subsequently conducted, with conclusive biopsies in 20/29 cases and only one pneumothorax.[29]

During the same timeframe, a second electromagnetic navigations system, the Aurora electromagnetic tracking device (Northern Digital, Waterloo, ON, Canada), was described by Dr Hubert Hautmann at the Medizinische Klinik in 2005 (Fig 5). Dr Hautmann and colleagues[30] conducted a study in 16 patients and reported that the system was able to identify all lesions, supporting the ability of ENB to improve the yield of bronchoscopic procedures.

The first large-scale prospective clinical study using the ENB-SD system was published from the Cleveland Clinic, Cleveland, OH, in 2006.[31] This was a prospective study of 60 subjects with peripheral lung lesions (n = 54) or lymph nodes (n= 31). More than one-half (57%) of the lesions were < 2 cm in diameter. ENB was conducted in 58 subjects with a diagnostic yield of 74% for lung lesions and 100% for lymph nodes. Pneumothorax occurred in two subjects (3.5%). The first generation of the ENB-SD system was cleared for use in both Europe (2002) and the United States (2004).

A third system, developed by Veran Medical Technologies, originated with the SPiN Interventional Radiology device in May 2006. This was followed by

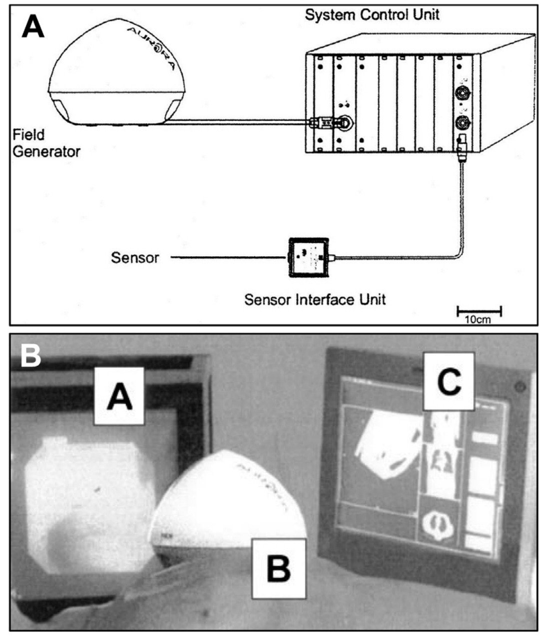

Figure 5 – *First clinical study of the Aurora flexible electromagnetic tracking system by Hubert Hautmann at the Medizinische Klinik, Munich. A, Device schematic. B, Procedural setup. (Reprinted from Hautmann et al,[30] 2005, with permission from Elsevier.)*

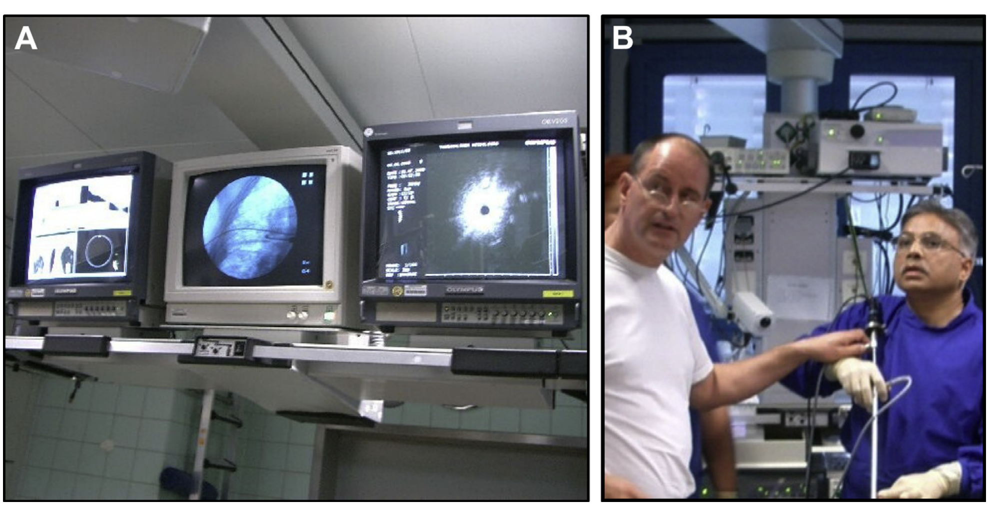

Figure 4 – *First clinical study of the electromagnetic navigation bronchoscopy-superDimension navigation system at the Thoraxklinic in Heidelberg, Germany, July 2003, with Drs Heinrich Becker and Atul Mehta.*

both percutaneous and bronchoscopic (Fig 6) electromagnetic tracking systems (ENB-Veran Medical [VM]) that use real-time procedure scans to account for respiratory gating.[32] A 2016 pilot study of the ENB-VM system for transthoracic needle aspiration (TTNA) guidance was published in 2016 and demonstrated that ENB-guided TTNA was feasible, with no bleeding events and a 21% pneumothorax rate (8% requiring chest tube). The diagnostic yield was 33% for navigational bronchoscopy alone, 83% for ENB-guided TTNA alone, and 87% when the two technologies were combined.[33] A second study by Flenaugh and Mohammed[34] enrolled 44 patients and reported a diagnostic yield of 37/41 (90.2%) using the bronchoscopic ENB-VM system.

ENB Technology Takes Off

Following publication of the initial clinical studies in 2006, clinical research into the safety and efficacy of ENB increased at a rapid rate. To date, there have been 63 clinical research studies published on the ENB-SD system[28,29,31,35-93] and eight clinical studies published on ENB-VM systems.[33,94-100]

Diagnostic yield of ENB to aid in the sampling of suspicious lung lesions had been examined in $>$ 30 clinical studies and ranges from 33% to 97% (Fig 7),[28,29,31,33,35-39,41,43-62,64,66,94,95] with most studies reporting diagnostic yields between 67% and 84% (quartile 1-quartile 3). Diagnostic yield of navigated bronchoscopy is similar between the two commercially available systems (Fig 7). One large retrospective registry observed lower diagnostic yield rates than typically reported, but this study used a different definition of diagnostic yield than most studies and did not include follow-up of true-negative diagnoses over time.[58]

Adverse events following ENB procedures are uncommon. Pneumothorax is the most frequently reported complication, with pooled rates typically around 3%[101] and much lower than the 20% rate reported for transthoracic needle biopsy[102] and ENB-guided TTNA.[33] These results were corroborated by the recently reported Clinical Evaluation of superDimension Navigation System for Electromagnetic Navigation Bronchoscopy study, the largest prospective, multicenter ENB study conducted to date. In 1,000 patients, the ENB-related pneumothorax rates were 4.9% overall and 3.2% for pneumothorax requiring chest tube or hospitalization.[89,92] The safety of ENB has also been demonstrated in high-risk patients with severe COPD.[93]

An increasing body of literature has also been published on the use of the ENB-SD system (Fig 8) to aid in fiducial marker placement to guide stereotactic body radiation therapy,[76-86,103-106] pleural dye marking in

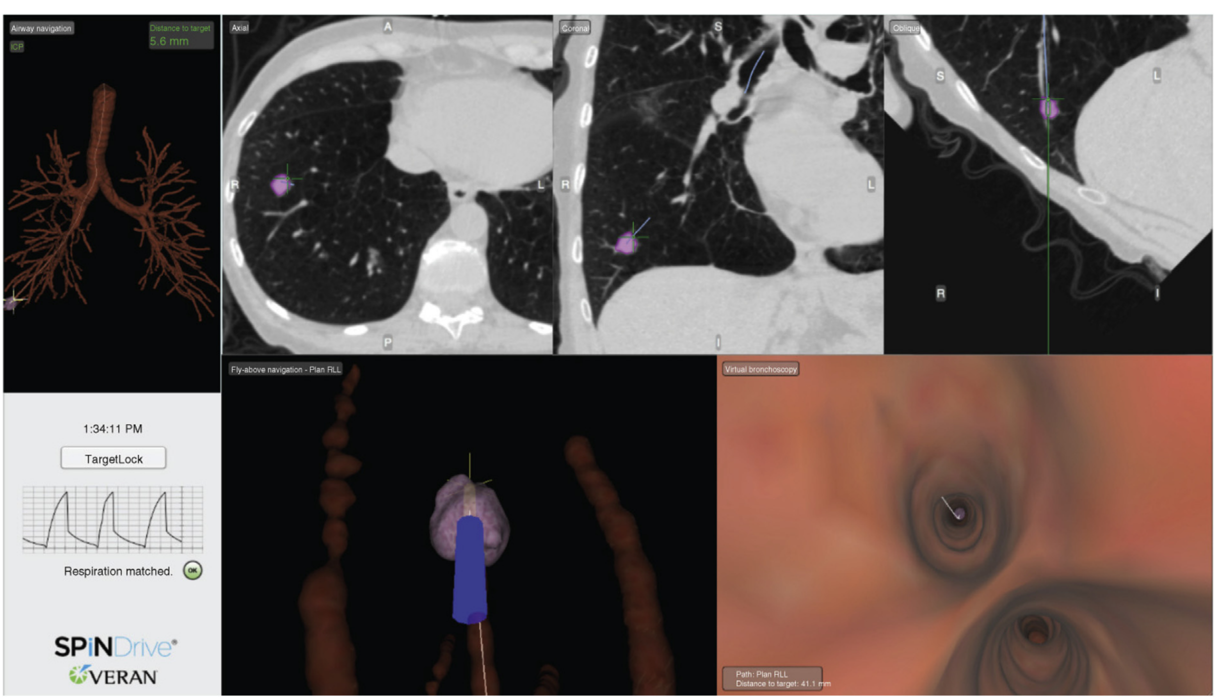

Figure 6 – *Image of a peripheral pulmonary nodule on the ENB-VM system (Reprinted from Raval and Amir,[95] 2016, with permission from Future Science Group.)*

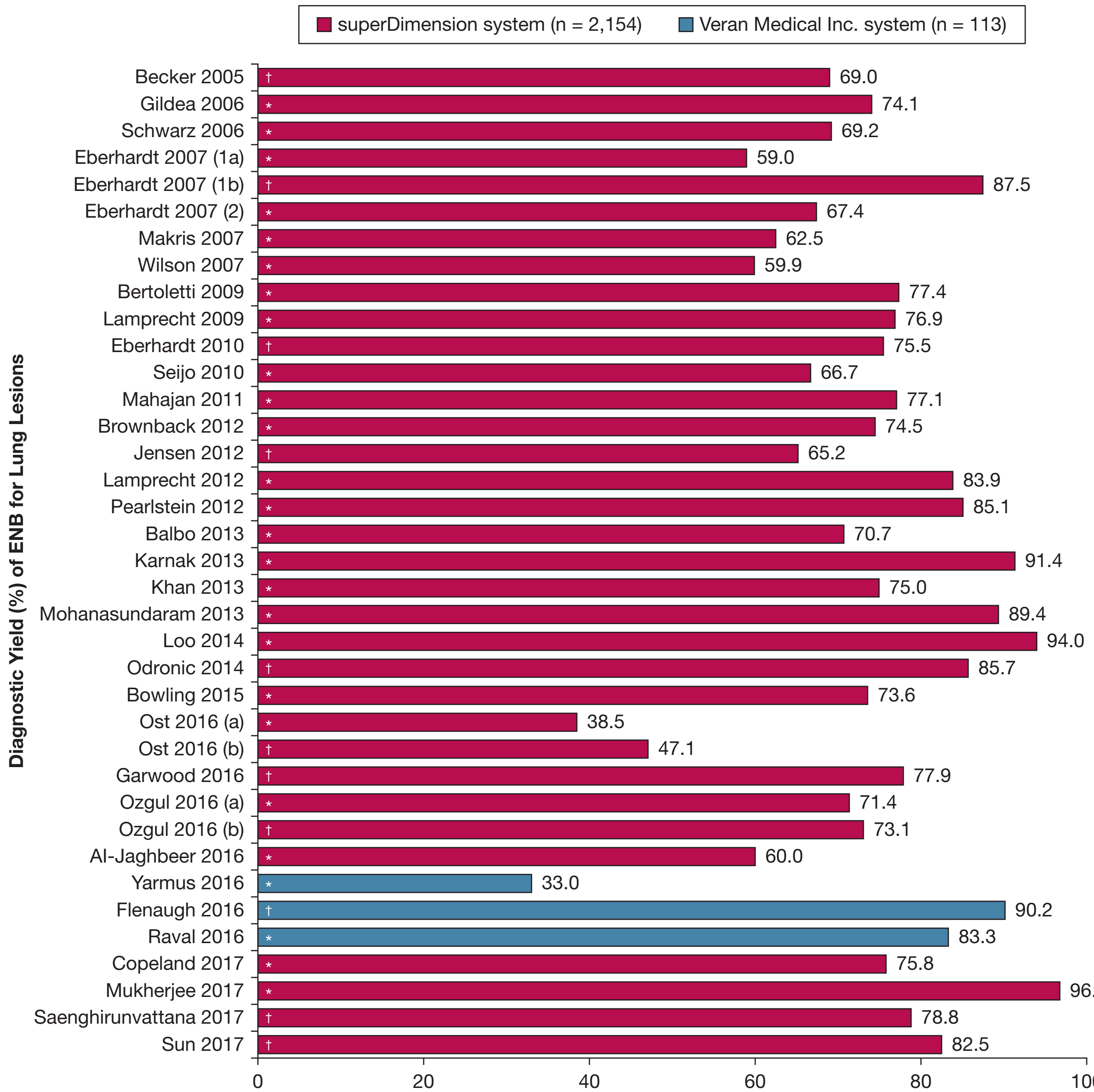

Figure 7 – *Diagnostic yield for ENB-aided biopsy of lung lesions. Diagnostic yield is defined as the percentage of peripheral lung lesions with a definitive diagnosis (true positives plus true negatives, made on the basis of guideline-recommended follow-up) as reported in the original paper, with the exception of Ost, 2016, which defined diagnostic yield as a specific malignant or benign diagnosis (excluding inflammatory tissue or lymphocytes) made on the basis of the ENB procedure without follow-up (true negatives were not included). *ENB without radial EBUS. †ENB plus radial EBUS to confirm lesion location. EBUS = endobronchial ultrasound; ENB = electromagnetic navigation bronchoscopy.*

preparation for surgical resection,[67-75,107,108] tissue collection for molecular profiling,[87,90] and mediastinal lymph node sampling.[42] Because ENB can be done in the operating room at the time of resection, it can allow greater flexibility and efficiency. One study compared ENB-SD–guided dye localization to CT-guided wire localization before minimally invasive video-assisted or robot-assisted thoracic surgery. Although localization time was similar between methods, the time from localization to surgery was significantly shorter for ENB-guided localization because of shorter down time (189 mi vs 26 min).[109] The ENB-VM system has also been investigated for navigated percutaneous thermal ablation[98] and ENB-guided TTNA.[33,97] The learning curve of ENB has also shown to be acceptable. In a study of the ENB-VM system, diagnostic yield was 80% in the first 25 patients enrolled compared with 87% in the last 23 subjects enrolled.[95] Very similar results were reported using the ENB-SD system, with diagnostic yields of 80% vs 87.5% in the first 30 and last 30 subjects,

Figure 8 – *Planning screen of the electromagnetic navigation bronchoscopy-superDimension navigation system. (Images property of Medtronic, all rights reserved).*

respectively.[51] In this way, ENB provides a user-friendly, integrated approach to aid in the diagnosis of suspicious lung lesions and prepare for treatment in the same minimally invasive setting. Some studies have suggested that the ability of ENB to diagnose smaller, more peripheral lesions may aid physicians in diagnosing lung cancer at earlier stages of disease, when it is more amenable to treatment.[46,88] Lung cancer diagnosis at earlier stages of disease has also been associated with significantly lower treatment costs.[110]

In recent years, increased user experience, knowledge into the factors contributing to improved diagnostic yield, and product advancements have provided better performance of the technology in a variety of clinical settings. Lesion size,[37,38,47,55,58] lesion location,[36,44,53,58] use of rapid on-site pathology evaluation,[36,48,52] presence of a bronchus sign on CT scan,[36,62] concurrent use of radial endobronchial ultrasound (EBUS) to confirm lesion location,[43,45] use of catheter aspiration,[45,58] and user experience and volume[47] have all shown to be predictors of better ENB outcomes.

Although improved user experience has resulted in ENB diagnostic yields in the high 80%[55,60] and mid-90%[48,52,56] range in some single-center studies, the diagnostic yield of ENB is generally lower than that of transthoracic needle biopsy (range, 75% to 97%; pooled rate, 92% across 48 studies).[102] Although complication rates are higher with transthoracic biopsy,[111] the lower diagnostic yield has limited the adoption of ENB by some centers. For this reason, technology improvements in both of the two major ENB systems have been introduced to improve yield and performance.[8,10,112] The ENB-VM system includes sensory tracking tips built into biopsy instruments to allow real-time tracking of biopsy tools. It has also introduced upgrades to its thoracic navigation system to track moving targets during respiration. In addition, the ENB-VM system includes the ability to switch to navigated TTNA in the same procedure as navigated bronchoscopy, as well as simultaneous navigation with radial EBUS. The ENB-SD system has introduced seven upgrades to the operating system or software since 2004, including a fiducial marker guidance system.[113] The ENB-SD system also has a transbronchial access tool to reach lesions outside the bronchial airways.[65,114] The newest version of the ENB-SD system adds software algorithms to enhance the visibility of the target region with three-dimensional fluoroscopy and to compensate for CT-to-body divergence (Fig 9). Novel robotic technologies, such as the Monarch (Auris Health) and ION (Intuitive Surgical)[115] robotic endoscopy platforms, use a flexible robotic endoscopy system to reach peripheral lung lesions and are in the early stages of clinical evaluation.

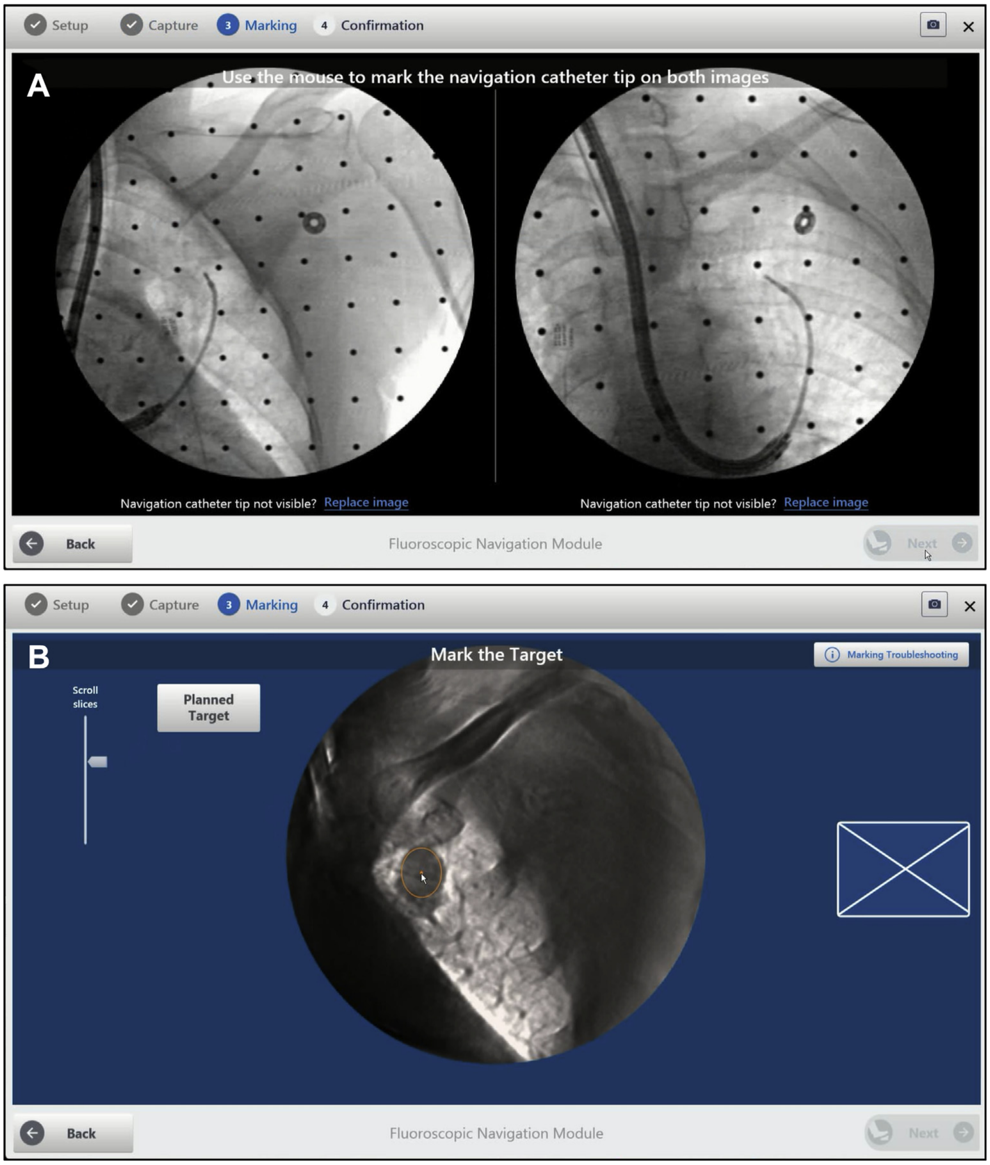

Figure 9 – *Most recent version of the ENB-SD system. A, Without CT-to-body divergence correction with ENB-SD fluoroscopic navigation. B, Six-millimeter error corrected with ENB-SD local registration and confirmed by cone beam CT scans. Images courtesy of Krish Bhadra, MD, all rights reserved. ENB-SD = electromagnetic navigation bronchoscopy-superDimension navigation system.*

Guidelines

ENB has been recommended in the guidelines of the American College of Chest Physicians as follows, with a 1C recommendation grade.[116]

> 3.4.2.1. In patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available (Grade 1C).
>
> Remark: The procedure can be performed with or without fluoroscopic guidance and it has been found complementary to radial probe ultrasound.
>
> Remark: If electromagnetic navigation is not available, TTNA is recommended.

ENB has been mentioned, along with endobronchial ultrasound and TTNA, in the most recent version of the National Comprehensive Cancer Network guidelines for non-small cell lung cancer. The guidelines recommend the least invasive method with the highest diagnostic yield possible and note that patients with nodules in the outer one-third of the lung would benefit most from ENB, radial EBUS, or TTNA as a first diagnostic study.[5]

ENB was also recently added to the interventional pulmonology fellowship accreditation standards.[117]

The Future

Since the initial inception of the technology in the mid-1990s, research into the ideal patient, lesion, user, and technological factors influencing ENB performance have come far. Going forward, continued unmet needs include continuous guidance, real-time confirmation and visualization of lesion location, advanced tools and imaging to locate and access challenging lesions, and seamless integration of concurrent imaging such as CT fluoroscopy and cone-beam CT scans.[10] Technological advancements to enable bronchoscopic ENB-guided ablation are also being explored. Improved technology will allow a more accurate, efficient, and streamlined procedure with a shorter time to proficiency. ENB will be an invaluable adjunct to transparenchymal lung biopsy, robotic bronchoscopy, and use of cone-beam CT scans.[65,109,118]

In addition, a better understanding is needed of the patient and lesion characteristics most ideally suited to ENB-aided biopsy. Despite the publication of > 60 clinical studies on ENB use, most studies to date have been single-center, retrospective, and included generally < 100 patients. The prospective, multicenter Clinical Evaluation of superDimension Navigation System for Electromagnetic Navigation Bronchoscopy study, which will enroll up to 1,500 patients at 37 sites in the United States and Europe, will help to answer many of these questions.[89] The study has currently published preliminary 1-month safety data on the first 1,000 subjects enrolled[92] and will publish 1-year diagnostic yield data in 2018. Planned multivariate and subgroup analyses on the predictors of diagnostic yield, as well as ENB use for fiducial marker placement, pleural dye marking, and tissue capture for molecular profiling, will help define the ideal ENB patient. The cost of the technology could be prohibitive in certain parts of the world; however, increasing expertise will improve both diagnostic yield and cost effectiveness. Initial studies in Asia have been promising,[75,119] with an acceptable learning curve.[66]

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