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# Lung cancer screening: detected nodules, what next?

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## Practice points

- Low-dose computed tomography scan for lung cancer screening is recommended in high-risk patients, who are defined as: patients aged 55–80 years, who are current or former smokers (quit <15 years ago), with a >30 pack-year smoking history.
- Combining fluoroscopy with transbronchial biopsy has been shown to increase the diagnostic yield in focal lesions.
- A combination of peripheral endobronchial ultrasound and a guide sheath can be used to return to the position of a localized pulmonary nodule.
- Electromagnetic navigational technology uses low-frequency electromagnetic waves to guide the pathway from main airways to pulmonary nodule by using microsensor at the tip of the locatable guide.
- Computed tomography guided transthoracic needle biopsy is commonly used as the biopsy tool in the pulmonary nodule that is closer to the chest wall.
- Video-assisted thoracoscopic surgery is considered as the best option in patients at high risk for malignancy or an intermediate risk when nonsurgical biopsy is nondiagnostic.

Since the success of the NLST study, the incorporation of lung cancer screening programs into current academic programs has been growing. Center for Medicare and Medicaid Services have acknowledged the importance and potential impact of lung cancer screening by making it a reimbursable study. Based on Fleischner Society Guidelines, many nodules will require follow-up imaging. The remainder of those nodules will need tissue to appropriately make the diagnosis. The use of bronchoscopy with transbronchial biopsy has been a standard technique for many years, but as smaller nodules need to be assessed, more advanced tools, such as endobronchial ultrasound and electromagnetic navigation are now improving the yield on the diagnosis of these smaller peripheral nodules. As electromagnetic navigation and peripheral ultrasound are significant changes from practice only 10 years ago, further advancements in the technology, such as bronchoscopic robots and advanced optical imaging tools, that are becoming available, need to be assessed as to their possible incorporation into the evaluation of peripheral nodules. The ceiling to the diagnosis of these small lesions remains at 70–75%; techniques and tools need to be used to improve upon this to maximize the impact of lung cancer screening and minimize the risk to patients.

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## KEYWORDS

•electromagnetic navigation bronchoscopy  
•endobronchial ultrasound  
•lung cancer screening program • optical imaging tools

Lung cancer is the leading cause of cancer-related death in the USA and the world, with more than 1.6 million deaths reported annually [1–3]. The lack of nociceptors and the large area for potential growth in the chest, coupled with the significant reserves people have in terms of respiratory function, allow lung cancer to have significant growth prior to any detection. Due to this, more than 75% of all newly diagnosed patients with lung cancer have locally advanced or metastatic disease at the time of diagnosis, with a 5-year survival of less than 5% (despite the fact that the 5-year survival of stage Ia disease when it can be diagnosed is 70% with appropriate surgical resection). The overall 5-year survival for lung cancer in 1975 was 12%, with current 5-year survival reported at 15% [3]. Lung cancer is not only expensive in terms of life, but in addition, there is a loss of annual productivity in the USA alone – US\$36 billion USD per year – with the next being breast cancer at US\$17 billion USD [4].

It is a mistake made by many people, including those in healthcare, that it is active smokers who are the patients that we must focus on in terms of lung cancer risk. In contrast to that, current smokers only make up 35% of the cases of lung cancer. 50% of all newly diagnosed lung cancer cases are past smokers with nonsmokers making up the remaining 15% of cases. Therefore, identifying those at greatest risk is paramount to any type of meaningful intervention being implemented.

## Lung cancer screening

Screening is used in a population that is at risk for a disease, to identify the disease early and as a result, at a much more treatable stage. Screening has been used for many cancers: breast, cervical, prostate, among others as part of healthcare maintenance. Over the past several decades, several studies have been performed to attempt screening for lung cancer all of which, previous to the NLST, did not demonstrate positive results for lung cancer screening [5]. The NLST was a National Cancer Institute and ACRIN-sponsored controlled trial of 53,000 high-risk subjects randomized to either three annual chest radiographs or three annual low-dose chest computed tomography (LDCT) exams. High-risk patients were defined as patients aged 55–74 years, who were current or former smokers (quit within the past 15 years) and with a >30-pack-year smoking history.

NLST was designed to perform scans at baseline and for two consecutive years. Looking at only the LDCT group, 27.3% of the patients were found to have an abnormality (positive) at the time of the initial screen, with 27.9 and 16.8% positive on the second and third scans, respectively (abnormalities found in first 2 screens, were called negative on the third screen). Overall, 24.2% of screening LDCT scans were found to be positive.

Despite the clear benefit from LDCT, there is a concern that often is raised is the increased rate of finding an abnormality on LDCT scan. The rate of nodule detection varied from 3 to 30% in randomized controlled trials [6,7]. Across the studies, the rate of invasive procedures was low (1–4%) [6]. However, approximately 25% of invasive procedures were performed, which eventually demonstrated to be benign diseases. The number of false-positive screening studies was relatively high at 23.3%. Subsequent follow-up identified a false-negative rate of 0.8% [8].

In response to the high false positive rate, the American College of Radiology addressed the issue and proposed the use of a new interpretation system, lung CT Screening Reporting and Data System (Lung-RADS™; ACR Foundation, VA, USA), to replace the Fleischner criteria, which was used for the initial NLST (Tables 1 & 2). Lung-RADS is a quality assurance tool designed to standardize lung cancer screening CT-reporting using a system designed to mimic similar system such as Bi-RADS which is used for breast cancer screening. The Lung-RADS criteria were applied retrospectively to chest CTs in the NLST. It showed that the false-positive rate was reduced from 27 to 13% [9–11].

In response to the results of the NLST [5], which demonstrated a 20% lower risk of lung cancer death in smokers and past smokers screened with LDCT scans, and the recommendations of the United States Preventative Services Task Force for annual screening (grade B recommendation) [14], health plans and health systems throughout the USA are developing lung cancer screening programs. These programs will likely differ in screening eligibility criteria, radiologist training/expertise as well as out-of-pocket costs to consumers. Other health system and patient factors will also influence access to initial screens, quality of screening and compliance with follow-up exams. Combined, these differences from the original NLST design

**Table 1. Lung Reporting and Data System for lung cancer screening.**

Category	Category description	Category designation	Recommendation
Incomplete	–	0	Additional lung cancer screening CT images and/or comparison to prior chest CT examination is needed
Negative	No nodules or definitely benign nodules	1	Continue annual screening with LDCT in 12 months
Benign appearance and behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to lack of size or growth	2	Continue annual screening with LDCT in 12 months
Probably benign	Probably benign finding(s), short-term follow-up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	6-month LDCT
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A 4B 4X	3-month LDCT, PET-CT may be used when there is a $\geq 8$ mm solid component Chest CT with or without contrast, PET-CT and/or tissue sampling depending on the probability of malignancy and comorbidities, PET-CT may be used when there is a $\geq 8$ mm solid component
Other	Clinically significant or potentially clinically significant findings (nonlung cancer)	S	As appropriate to the specific finding
Prior lung cancer	Modifier for patients with a prior diagnosis of lung cancer who return to screening	C	–

CT: Computed tomography; LDCT: Low-dose chest computed tomography.  
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will undoubtedly affect the original estimates of risk reduction in lung cancer deaths due to low-dose CT lung screening. But most significantly, all forms of screening will increase the number of patients that present for assessment. The US Preventative Services Task Force estimates 7 million of the estimated 90 million smokers in the USA fulfill the current screening criteria. This gives an approximation that about 17 in every 100 smokers are screening candidates.

Despite improvements in screening (Lung-RADS), the number of patients that will need to be assessed in the future will continue to grow. To address these new findings in the high-risk patients, invasive procedures are necessary to determine the nature of these lung nodules. Advancements in the diagnosis of solitary pulmonary nodules have been made over the past decade, but new ceilings of diagnostic yield have been reached. The goal of this article is to introduce those tools and techniques currently used to reach peripheral lesions and then discuss current advanced optical techniques as they are applicable to the diagnosis of lung disease and finally, introduce some of the advancements that we hope to have in place in the next several years.

### Diagnostic approaches to the peripheral lung nodule

The lung is a complex structure. Beginning just distal to the vocal cords, the trachea branches initially to the mainstem bronchi on the right and left. The right then branches into three lobes and the left two lobes. Each lobe continues to divide into segments, subsegments and so on. The central eight generations typically are structured with cartilaginous rings to give architectural support to the airways. The middle, approximately, eight generations are the bronchioles, without cartilaginous support, ranging in size from 3 to just under 1 mm. These airways remain open due to the radial forces pulling it open from the surrounding lung parenchyma. As is suggested by this, the bronchioles in areas of lung injury or destruction, such as in a very emphysematous portion of the lung, have less tissue pulling them open and therefore the airways have a tendency to collapse, making them more difficult to maneuver through. Last, the terminals approximately eight generations are involved in gas exchange, from the respiratory bronchioles to the terminal alveoli. This said, lung cancer can happen at any level of the airway tree.

**Table 2. Fleischner Society recommendations for follow-up of small lung nodules detected incidentally on computed tomography scan in patients  $\geq 35$  years old.**

Nodule size (mm) <sup>†</sup>	Low-risk patient <sup>‡</sup>	High-risk patient <sup>§</sup>
$\leq 4$	No follow-up needed <sup>¶</sup>	Follow-up CT at 12 months; if unchanged, no further follow-up <sup>#</sup>
$>4-6$	Follow-up CT at 12 months; if unchanged, no further follow-up <sup>#</sup>	Initial follow-up CT at 6–12 months then at 18–24 months if no change <sup>#</sup>
$>6-8$	Initial follow-up CT at 6–12 months then at 18–24 months if no change	Initial follow-up CT at 3–6 months then at 9–12 and 24 months if no change
$>8$	Follow-up CT at around 3, 9 and 24 months, dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

Known risk factors: history of lung cancer in first-degree relative, exposure to asbestos radon or uranium.  
<sup>†</sup>Average of length and width.  
<sup>‡</sup>Low-risk: minimal or absent history of smoking and of other known risk factors.  
<sup>§</sup>High-risk: history of smoking or of other known risk factors.  
<sup>¶</sup>The risk of malignancy in this category ( $<1\%$ ) is substantially less than that in a baseline CT scan of an asymptomatic smoker.  
<sup>#</sup>Nonsolid (ground-glass) or partially solid nodules may require longer follow-up to exclude indolent adenocarcinoma.  
CT: Computed tomography.  
Reproduced with permission from The Radiological Society of North America (RSNA®) [13].

Bronchoscopy for the diagnosis of pulmonary disease has been used since the early 1970s. The original design of flexible bronchoscopy has been used for an inspection of airways and biopsy of the lung tissue. The tissue acquisition in the past included bronchoalveolar lavage, cytologic brushing and transbronchial biopsy (TBBx). These techniques have been frequently used in many institution around the world. However, the diagnostic yield is relatively low for several pulmonary diseases includes pulmonary nodule. Therefore, the modern technology and tissue biopsy tools have been introduced to the field of pulmonary medicine in an early 2000s. The next few sections will review approaches to lung a lung nodule.

Some institutions, due to a variety of reasons, instead of approaching nodules bronchoscopically, use transthoracic approaches, most commonly using CT, but others still approach the peripheral nodule with fluoroscopically guided transthoracic procedures. As these remain common practice, the techniques will also be addressed.

### Transbronchial biopsy

The technique of using TBBx uses a flexible forceps, which can be passed through the working channel of a bronchoscope and out into the lung parenchyma to take a biopsy. There are several types of jaws used including: cupped, alligator, with and without teeth. When open, most forceps are less than 5 mm, thus limiting the amount of tissue taken with each bite. The

number of biopsies taken can vary between four and 15 depending on the institutional practice. Most commonly, six TBBx will be acquired from a lesion. TBBx can be performed in a blind fashion (most commonly used in interstitial lung disease), using fluoroscopy guidance, peripheral endobronchial ultrasound (p-EBUS) guidance and with electromagnetic navigation (EMN). This section will focus on fluoroscopically guided procedures.

TBBx require positioning the bronchoscope into the airways that the bronchoscopist believes the lesion to be located in. Typically, the bronchoscope will only be able to extend to the fourth or fifth generation airway. This leaves up to 19 generations of airways that a moderately stiff 'flexible forceps' is pushed out into to get to the lesion in question. Bronchoscopists use a variety of techniques to manipulate the forceps but in the end, the native anatomy will guide it to its final point. As might be expected, studies on solitary pulmonary nodules have consistently shown that lesion size influences the diagnostic accuracy of bronchoscopy. The diagnostic accuracy is repetitively low in lesions measuring less than 20 mm, located particularly in the outer third of the lung. In addition to the size being larger than 2 cm, other findings that suggest a better diagnostic yield include: the nodule had a positive bronchus sign on CT and when the tissue was repeatedly sampled.

The diagnostic yield of TBBx is variable, ranging from 16 to 80% in the literature. Combining fluoroscopy with TBBx has been shown to

increase the diagnostic yield in focal lesions (Table 3) [15]. The use of fluoroscopy is also often suggested to reduce the risk of pneumothorax with TBBx, but somewhat surprisingly, TBBx with fluoroscopy has not been associated with a significantly lower incidence of pneumothorax than biopsy performed without fluoroscopy [16].

One advancement that is now being clinically used at some institutions is the use of cryobiopsy. Cryobiopsy is a technique where instead of forceps, a cryoprobe is placed through the bronchoscope and into the area of concern. The cryoprobe is then activated for 3–5 s, causing adherence to the tissue surrounding it and is bluntly removed. This technique has been used for the evaluation of interstitial lung disease and is now being reported by some investigators as case reports of its use for the diagnosis of lung nodules [17].

### Radial probe EBUS or peripheral EBUS

The incorporation of EBUS began in the 1990s. Most recently, the use of EBUS-guided transbronchial needle aspiration is the most visible and common use of EBUS with bronchoscopy. This technique is used for mediastinal and lymph node sampling, most particularly for lung cancer staging. The radial probe EBUS system was developed to demonstrate the imaging of lobar and small peripheral bronchi, identifying solid (tumor) from the surrounding lung parenchyma, giving a real time tool for the localization of lesions. The probe provides a complete 360° high-resolution image of parabrachial and paratracheal structures. At a standard frequency of 20 MHz, the resolution is less than 1 mm with a penetration depth of 4–5 cm. Radial probe EBUS has been used as a complementary imaging technique to guide a TBBx under fluoroscopic guidance. In normal air-filled alveolar tissue, the ultrasound image typically shows a 'snowstorm-like pattern'. The peripheral nodule that is located adjacent to the bronchus usually

appears well differentiated against the lung tissue by a bright border. Meanwhile, necrotic areas and vessels can be seen as circumferential dark areas (Figure 1; peripheral EBUS (p-EBUS) image of a lung nodule surrounded by normal lung).

The use of a guide sheath (GS) in combination with p-EBUS is a modification on the technique performed to obtain tissue from lung nodule. The p-EBUS probe is placed through a GS and both are introduced through working channel of flexible bronchoscopy. The combined tool is then placed out into the periphery, using the ultrasound to identify in real time the lesion that is targeted. Once the lesion location is established, the GS is left in place and p-EBUS can be replaced by biopsy tools, ensuring samples are biopsied from same location that was identified.

A systemic review and meta-analysis of p-EBUS for lung nodules includes 16 studies with 1420 patients. This review showed point sensitivity for diagnosis of lung cancer was 0.73. The positive likelihood ratio and negative likelihood ratio were 26.84 and 0.73, respectively. p-EBUS can be used to diagnose primary pulmonary nodule that is not visible by fluoroscopy. A study of using p-EBUS/GS without radiographic fluoroscopy in 123 lung nodules showed 61.8% of these nodules were diagnosed by p-EBUS/GS alone [18]. The only consistent predictor of high diagnostic yield is probe location in relation to the lesion. The concentric ultrasound image demonstrated a better diagnostic yield than eccentric location of ultrasound.

### Electromagnetic navigation

Conventional TBBx via flexible bronchoscopy has reached the limit of its diagnostic yield. With the relatively nonspecific 'guidance' through the airways to a lesion, the technique is limited. Although the addition of p-EBUS to traditional bronchoscopy has improved the yield, we have continued to be limited by the arbitrary path the catheter will often take during the procedure.

**Table 3. The diagnostic yields and complications of transbronchial biopsies with and without fluoroscopy guidance for nonendobronchial lung lesion (331 patients with fluoroscopy transbronchial biopsies vs 319 patients with nonfluoroscopy transbronchial biopsies).**

Procedures	Overall diagnostic yield (%)	Lung masses diagnostic yield (%)	Focal infiltrative lesions diagnostic yield (%)	Diffuse infiltrative lesion diagnostic yield (%)
TBBx with fluoroscopy	43.8	41.4	46.2	45.1
TBBx without fluoroscopy	32.9	29.5	29.4	40.0
p-value	0.003	0.036	0.008	0.289

TBBx: Transbronchial biopsy.



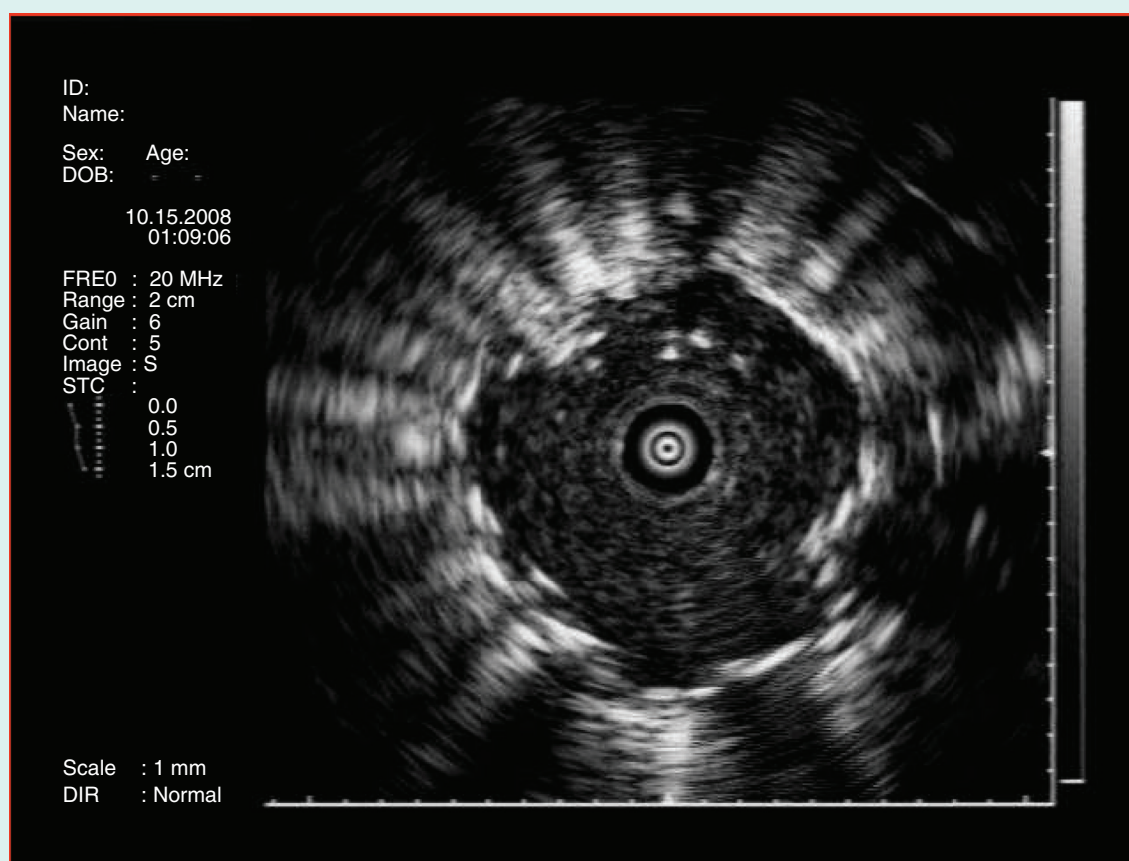


Figure 1. Peripheral endobronchial ultrasound image of a lung nodule surrounded by normal lung.

The next step in movement through the lung periphery has been EMN.

EMN techniques create systems that are in many ways global positioning satellite like for the chest. The patient lies on a board, which generates an electromagnetic field. A sensor system is then incorporated into the system placed through the bronchoscope (forceps, needle, sheath or probe), allowing the computer to 'know' where the device is in space. Most of these devices have a delivery system which allows 'steering' of the catheter through the airways. Just as in using a global positioning system, if you do not have an accurate map to link to this positional information, then it is useless by itself. The map is a CT scan of the chest, typically with smaller cuts and a greater overlap than standard CT scans of the chest. The CT scan is placed into a computer program, which helps create a 3D model of the lung, where the lesion of interest is identified and then a roadmap is drawn using the airways as the roads. The greatest limiting

factor to this technique is the fact that the roadmaps are generally not very good. Even with the best CT techniques, we usually only get six to eight generations of airways that are visible and as the nodule can be located at generation 16 of even 24, the guidance becomes a lot more by feel than driving right to the spot. This in conjunction to the alterations in magnetic fields created by the rooms, tables, instruments and patients themselves do limit this technology somewhat. The three major platforms for EMN available in the USA include: superDimension® (Medtronic, Dublin, Ireland), SPiNView® (Veran Medical Technologies, Inc., MO, USA) and Lung point virtual bronchoscopy (Bronchus Medical, Inc., CA, USA) (Figure 2; superDimension system).

The basic principle of the superDimension system is the use of low-frequency electromagnetic waves transmitted from a magnetic board placed below the patient's chest, which are intercepted by a microsensor. Currently the microsensor probe is located at the tip of the flexible

locatable guide (LG). The steerable LG can be rotated 360°. The newer Edge catheter has curved tips on the catheter in 45, 90 and 180°.

EMN bronchoscopy is performed in several steps. The first step is planning the procedure by uploading high-quality CT images into the planning software. The CT scanner should be a multislice, 4-detector at minimum. The software will reconstruct graphic in axial, coronal and sagittal views of the chest along with

a virtual bronchoscopic image. The procedure planning comprises into four phases:

- Marking the target lesion and creating pathway by using the most adjacent bronchus;
- Reviewing the pathway from proximal airway toward the targeted lesion;
- Registration phase is performed by matching preassigned anatomic landmarks on the

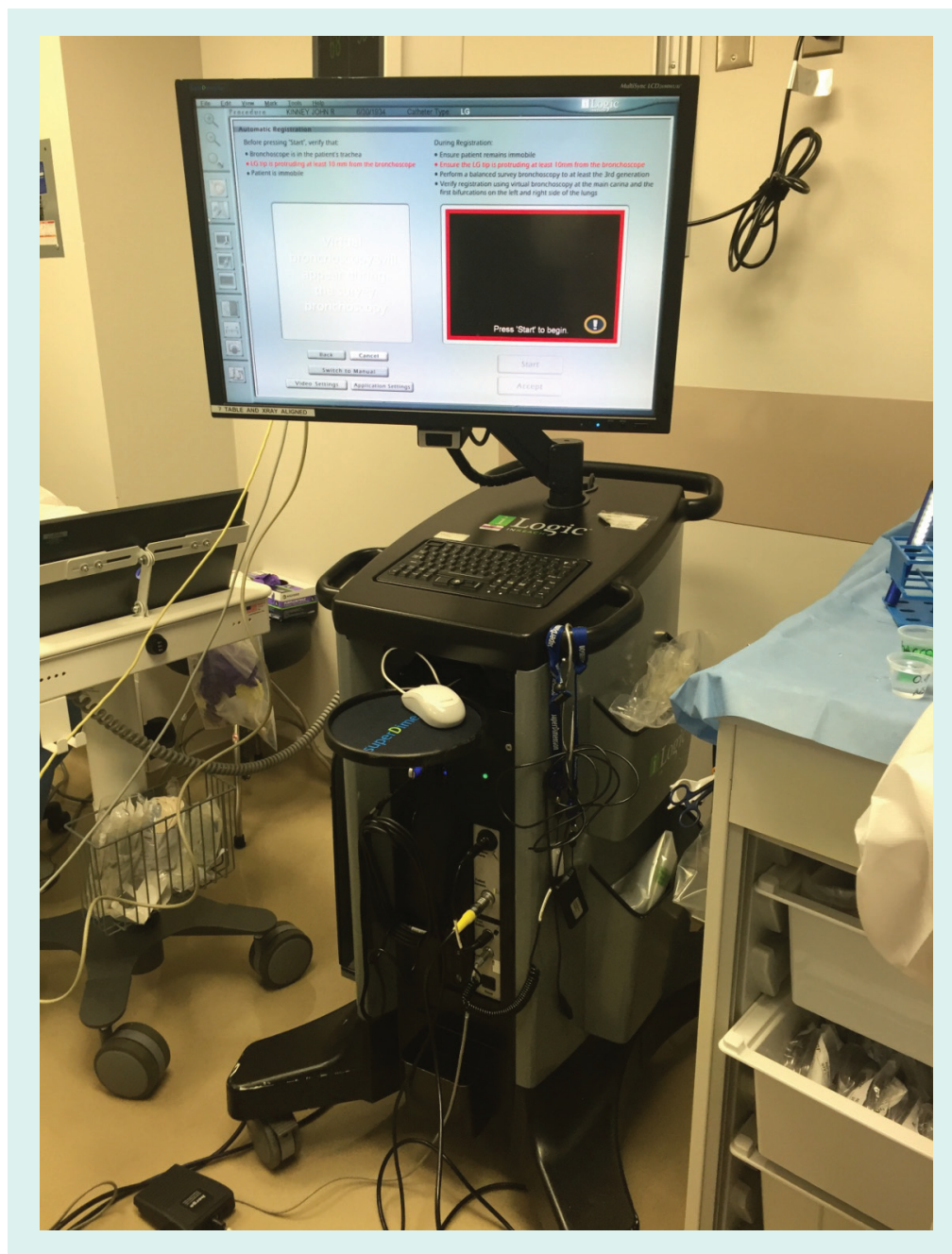


Figure 2. superDimension® system.

virtual bronchoscopy created from the patient's CT scan;

- Saving and exporting the plan to the actual procedural system.

Once the CT scan has been processed and uploaded to the superDimension navigation system, the device merges the CT images with the airway as a registration procedure is completed. This allows the bronchoscopist real-time virtual information to assist in guiding to the lesion through the multitude of sub and sub-subsegmental bronchi. The LG is placed through an extendable working channel (as was discussed in the p-EBUS section) and then placed through the bronchoscope. The position of the LG/Edge catheter is captured by the EMN system and displayed on the monitor superimposed on previously acquired CT images.

Following planning and registration, the bronchoscopy with the LG in place is advanced toward the segmental bronchus of targeted lesion. Once the LG reaches the desired location, the extended working channel is fixed at the proximal end of working channel. The LG is then removed and the bronchoscopic biopsy tools (e.g., forceps, needles and brushing) are inserted via the Extended Working Channel (EWC) to obtain the specimen. The position of the tip of the EWC may be confirmed by using the radial EBUS probe to determine the location of the lesion.

The SPiNView uses an always-on tipped track technology. The sensor tracking is built into the biopsy instruments allowing for real-time navigation of the biopsy tools. In addition, a phantom bronchoscopy catheter is available with steerability. The SPiNView has planning phase, navigation phase and biopsy phase which is similar to the superDimension system. An additional feature of the SPiNView system is that it incorporates a transthoracic needle system to biopsy lesions similar to CT-guided transthoracic needle biopsy (TTNB). The SPiNView offers what they call 4D respiration technology that monitors patient respiration during the procedure. Average motion of pulmonary lesions has showed to be approximately 17.6 mm. With this much respiratory motion, it may affect the diagnostic yield of EMN or any other lung biopsy procedures [19].

The use of ENB has improved the diagnostic yield for peripheral nodules. A pool data analysis of prospective and retrospective studies using

ENB for the diagnosis of peripheral nodules demonstrated an overall diagnostic yield of 71% and a pneumothorax rate of 4% [20]. Separately, the result of a large prospective study revealed the diagnostic yield of ENB for peripheral lesions to be 74% with a pneumothorax rate of 3.5% [21].

p-EBUS has been commonly used as a complementary imaging technique with ENB. The combination of radial probe EBUS with ENB can increase the diagnostic yield to 88%, compared with EBUS (69%) or ENB alone (59%) [22].

Another system, the LungPoint virtual bronchoscopy system, is designed to provide additional guidance for plotting an appropriate course through the bronchial tree. The CT data are uploaded to the navigation software platform. A 3D bronchial tree and roadmap is created. A region of interest is identified during planning phase. During the procedure phase, multiple different views are often available including views of the vascular tree, fluoroscopic views, as well as the ability to rotate a region of interest in any plane and direction. The lack of special catheters and probes provides a cost saving compared with other navigational systems. A combination of virtual bronchoscopic navigation (VBN) and p-EBUS/GS provides diagnostic sensitivities of 44.4% for lesions <20 mm and 91.7% for lesions ≥20 mm [23]. There was a randomized trial of using p-EBUS/GS with and without VNB for peripheral pulmonary nodule (PPN) ≤30 mm. The VBN group demonstrated higher diagnostic yield, shorter procedure time and shorter navigational time [24]. Recently, the application of p-EBUS and VBN has showed to improve the diagnostic outcome of bronchoscopy for peripheral nodules. The rate of EBUS detected lesion with VBN guided was significantly higher than the non-VBN group [25].

In summary, EMN is a useful diagnostic tool in guiding to a peripheral pulmonary nodule. However, this technology also has limitations based on the current imaging techniques, as well as intrinsic errors of electromagnetic systems as they interact with biologic spaces. EMN can be used along with p-EBUS as a complement technology which has shown to increase diagnostic yield. As with any advanced technology, the technology does not do the work for the bronchoscopist, it merely assists the bronchoscopist so in addition to additional equipment costs, training is important for optimal system use. The availability of equipment and availability of



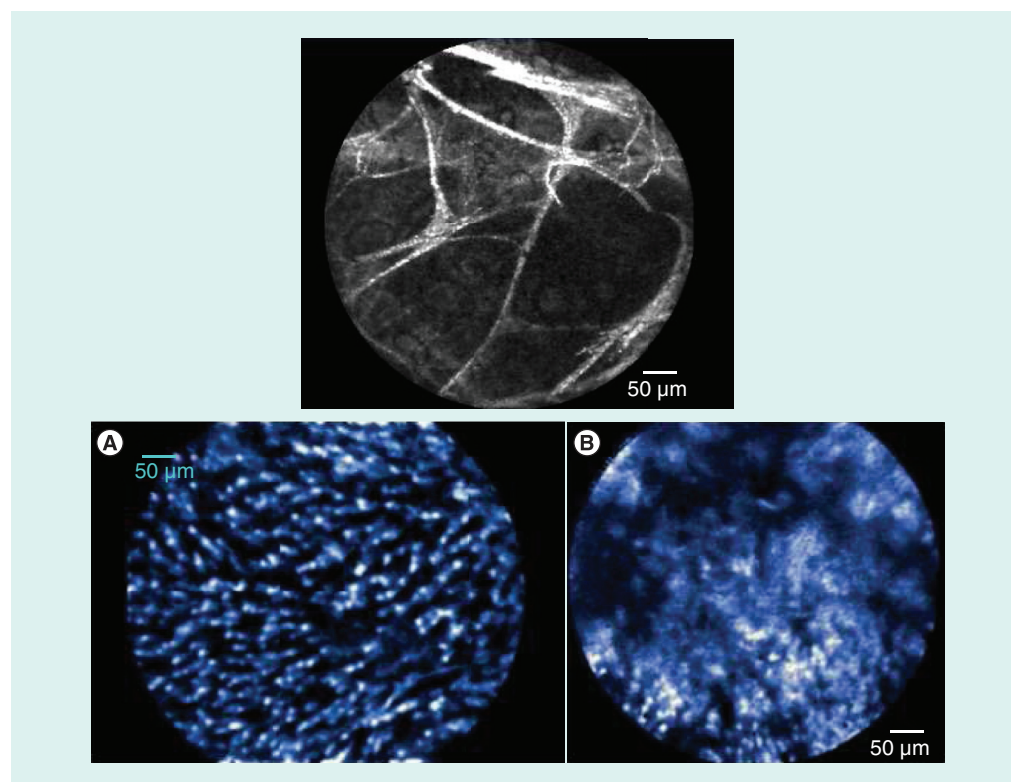
experienced personnel have limited the routine use of EMN in the general practice setting.

### CT-guided transthoracic needle biopsy

CT-TTNB is a technique most commonly offered by interventional radiologists at many institutions, but some interventional pulmonary programs in the country are offering this additional service. This technique uses the real-time localization of a nodule in the chest using CT-fluoroscopic imaging and then the placement of a needle through the chest wall, which is subsequently guided to the nodule by repeated imaging and positioning. The diagnostic yield of TTNB depends on several factors including the size of the nodule, the size of the needle, the number of passes and the presence on rapid onsite cytopathologic examination [26–28]. To date, there is no randomized controlled trial comparing TTNB with other approaches. Based on the American Collage of Chest Physician guidelines [29], overall sensitivity of TTNB for the diagnosis of lung cancer was more than 90%. The sensitivity ranges in the literature from 70 to 82% for nodules measuring <15 mm in diameter [30–32]. The distance

of the nodule from the pleura also affects the diagnostic yield. The diagnostic yield is less than 60% when the needle pass length is more than 40 mm [33]. The performance of TTNB can be made more complicated by the fact that the needle is coming through the chest in a fixed location and the nodule within the lung is moving in response to normal lung movement. As the lesion is closer and closer to the diaphragm, the difficulty of this procedure is increased due to this more dynamic motion.

In terms of complications, a population-based study demonstrated the risk of hemorrhage as 1%. Meanwhile, the risk of pneumothorax is 15% with the additional risk of chest tube insertion from pneumothorax at 6.6% [34]. The major risk factors for pneumothorax were age (60–69 years), active tobacco use and underlying emphysematous lung disease. Overall, TTNB is a useful diagnostic tool for the diagnosis of lung nodules in selected groups of patients. The case selection is important to minimize complications in high-risk patients. In addition, a non-diagnostic result from TTNB does not exclude the possibility of malignancy. Further investigations may be needed to pursue the definite



**Figure 3. Confocal microendoscopy.** (A) Image of normal lung unit and (B) patient with probe-based confocal laser endoscopy image.

diagnosis, especially in patients with high risk for malignancy.

### Video-assisted thoracoscopic surgery

Video-assisted thoracoscopic surgery (VATS) is a type of minimally invasive thoracic surgery which has become available as a diagnostic and therapeutic option for the management of pulmonary nodules. Surgery remains the gold standard for the management of early-stage lung cancer. Recovery times from traditional thoracotomies led to the development of VATS as a minimally invasive technique for thoracic resections. As most cases of lung cancer occur in patients with underlying lung disease, minimizing the limitations of chest wall motion due to pain in the postoperative phase has sped recovery times and decreased hospital stays [35,36].

VATS is best utilized for lung nodule located superficially to the pleural surface. For deeper lesion, localization techniques can be used to increase the diagnostic yield. ENB-guided bronchoscopy with fiducial placement or needle injection of methylene blue can be performed to decrease the time of localizing particularly small lesions for VATS [37]. Intraoperatively, the diagnosis is typically established by frozen section. If the nodule is found to be benign, only wedge resection is required. Conversely, if the nodule is found to be malignant, then lobectomy with complete lymph node dissection is recommended. In terms of complications, the mortality rate varies from 0 to 2% [38]. VATS is a safe procedure, but it must be remembered that it is a surgical procedure, which requires general anesthesia with single lung ventilation. The skill set of the surgeon, surgical team and anesthesia teams can have a significant impact on yields and impact.

### Future diagnostic applications

#### • Probe-based confocal laser endoscopy

Confocal laser endoscopy (CLE) is a newer optical technology that uses a 488 nm laser to create cellular excitation to stimulate fluorescent patterns that are then evaluated using both point-source illumination and pinhole light detection. Pinhole light detection produces fine optical sectioning with image resolution in cellular level by subtracting out-of-focus data beyond a thin focal plane. However, there is a reduction in light signal intensity that can be received by the photodetector. This issue is compensated by prolonging exposure time of the photodetector.

A focal plane can be located at different levels of the focused tissue, therefore this technique can obtain an optical cross-sectional image of the tissue in layer-by-layer, and has been referred to as an 'optical biopsy'. Under the CLE image **Figure 3A & B**. Due to the fact that the imaging is only of fluorophores, the use of this in lung pathology has been very limited.

Thiberville *et al.* analyzed the joint capability of fibered-confocal fluorescence microscopy images and scattering features for lung cancer diagnosis. The proposed method achieves a good recognition rate for a classification stage to assess the feasibility of lung cancer diagnosis [39,40]. Sorokina *et al.* described image characteristics of lung cancer by using *ex vivo* peripheral CLE on postlobectomy specimens. The examined areas were marked with brilliant green dye, and the surrounding tissues were stained by methylene blue dye. A total of 18 lobectomy specimens from 18 different patients were collected. Alveolar dystelectasis with thickening of alveolar walls, alveolar edema and a large amount of macrophages were pathologically identified. The stromal and parenchymal components of the studied subtypes of non-small-cell lung cancer differed from each other. The authors suggest that certain light microscopy features of lung carcinoma can be visualized with peripheral CLE [41].

Confocal laser microendoscopy is a novel diagnostic tool for the analysis of living cells during bronchoscopy. This technique may enable the rapid diagnosis of neoplasia during ongoing endoscopy in patients with suspected lung cancer in the future. At this time, the use of CLE remains experimental. Interpretation of the findings is limited by the fluorophore component of the tissue being evaluated, leading to more of a pattern recognition rather than an actual virtual histologic or optical biopsy.

### Robotics

Although currently not clinically available, there are several companies currently pursuing the development of a robotically driven bronchoscope. The goal is to integrate a device that has EMN in conjunction with an optically driven catheter. The device would need to be able to move into the small (less than 2 mm) airways with great accuracy and have a degree of freedom to perform different sampling procedures. Although this type of system will be expensive, the economic impact of lung cancer not being

diagnosed at early stages increases the overall cost of the management of lung cancer patients. Although this sounds like it is far in the future, the use of robotic systems should be in place in the USA by late 2017.

### Conclusion & future perspective

The NLST has the potential impact of saving 4000 lives per day. To achieve this goal, not only will institutions have to develop plans for lung cancer screening programs, but the appropriate algorithms as to how to address these findings will need to be developed in parallel. The flexible bronchoscope was invented in 1966 [42] with use in the USA beginning around 1970. From 1970 until approximately 2005 – a full 35 years – the diagnostic yield for peripheral nodules less than 30 mm was less than 20%. With the addition of EMN, better imaging technology and other techniques, the diagnostic yield is now approximately 70–75%. Despite these advancements in the past 10 years, we are now at a new ceiling. This ceiling is facing us as we begin on a course of increasing our discovery of smaller peripheral nodules. It will only be through the introduction and incorporation of newer tools (i.e., robotic bronchoscopy, optical

biopsy devices, among others), that we will be able to raise the ceiling. In the future, novel techniques for nodule localization and tissue acquisition will be emerged. The cytologic interpretation technique will be ultra-high sensitivity which could determine the type of cancer from only several cellular sample. These future technologies require intense researches in multidisciplinary fields which may occur in 5–10 years. Finding lung nodules earlier is an incredibly important step. Knowing how to approach them, and more importantly having a team capable of using the newest technologies with greater efficiency, will be a more difficult task – a goal which is difficult, but should not be insurmountable.

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