Device Evaluation

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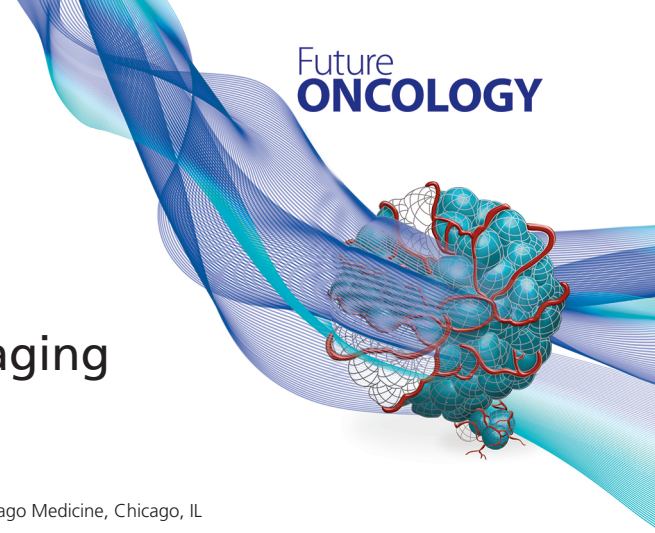

Use of augmented fluoroscopic imaging during diagnostic bronchoscopy

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The single pulmonary nodule evaluation is a complex problem. In particular, attempts to biopsy peripheral nodules with bronchoscopy have been hampered by difficulty navigating to the correct airway and then confirming the instruments' proximity to the nodule. Virtual systems in use do not provide real-time feedback of a live image of the nodule in question. Fluoroscopy has traditionally offered limited assistance as often the nodule is not visible and provides no information on airways/pathways to the nodule. We describe the use of LungVision augmented fluoroscopy to aid in real-time navigation assistance to peripheral lung nodules.

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Several modalities exist for sampling suspicious lung tissue for biopsy, ranging from highly invasive surgical techniques to less invasive bronchoscopy and transthoracic needle aspiration. One option for nonsurgical tissue diagnosis is computed tomography (CT)-guided transthoracic needle aspiration (TTNA), although there is an appreciable risk of pneumothorax, ranging from 9 to 54% [1], and other complications, including hemoptysis, hemothorax, infection and air embolism [2,3]. Bronchoscopy-based options, including bronchoscopy guided by standard fluoroscopy, electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopy navigation (VBN), as well as verification of lesion localization with radial endobronchial ultrasound (REBUS), appear to offer lower risk of complications, but a lower rate of successful sampling of the lesion when compared with TTNA. Data from the American College of Chest Physicians (ACCP) Quality Improvement Registry, Evaluation and Education initiative demonstrated that using any of the above techniques resulted in a diagnostic yield of <57% [4]. Such low yield can be attributed to the lack of real-time visualization during the biopsy portion of the bronchoscopy, potential for missing the biopsy target completely due to poor visualization, and inadequate biopsy sampling, among others.

A real-time enhanced imaging platform called LungVision (Body Vision Medical Ltd, Ramat Ha Sharon, Israel) recently gained clearance by the US FDA. LungVision is using a proprietary technology, utilizing artificial intelligence and machine-learning algorithms, to augment 2D fluoroscopic imaging with imperative information gained from preoperative CT. Frequently, a nodule is not visible on fluoroscopy, but the LungVision software is highlighting the lesion on the fluoroscope screen. Real-time fluoroscopic images obtained intraoperatively are thereby enhanced with guided pathways to the lesion and are provided to the bronchoscopist without interruption to the procedure flow. LungVision focuses on the major challenge in bronchoscopy, accurate localization and navigation to pulmonary lesions. With LungVision real-time navigation guidance, the bronchoscopist can take a biopsy accurately and efficiently.

Background: cancer screening & the relevance of incidental pulmonary nodules

Symptoms of lung cancer are often noticeable only in later stages of the disease [5], which in part explains the interest in developing risk-based screening profiles for earlier detection. While progress has been made regarding wider implementation of screening programs, there is still need to define optimal risk populations for screening and harmonize work-up and treatment paradigms for screen-detected nodules [6].

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Prognosis for incidentally discovered lung cancer is not necessarily poor, however. While many advanced disease cases are found incidentally, Quadrelli *et al.* examined a cohort of 593 retrospectively identified patients with non-small-cell lung cancer undergoing pulmonary resection with a curative intention [7]. They noted that while 53.9% were asymptomatic at the time of diagnosis, these patients were more likely to have earlier-stage disease and smaller cancers.

Regardless of mode of detection the relevant question becomes how best to differentiate suspicious nodules and/or lung mass in order to initiate appropriate interventions for the patient. After all, a majority of nodules found in high-risk patients will not be cancerous. Surgical resection is currently considered the gold standard for diagnosis and may result in a definitive diagnosis in 96–100% of cases [8]; however, the risk of discovering an inoperable lesion or making or confirming a benign diagnosis during a highly invasive procedure significantly undermines the applicability of this option in clinical practice. Yet, low diagnostic yield, incomplete specificity and risk of false negative outcomes associated with current nonsurgical biopsy options are confounding variables that raise important questions about how best to manage patients.

Nonsurgical biopsy modalities in individuals with asymptomatic nodules

The decision to obtain nonsurgical biopsy in individuals with suspicious nodules should consider several factors, including whether there is discordance in probability of malignancy and imaging studies, overall probability of malignancy, nodule size and change over time, nodule location, and patient preference for a definitive diagnosis prior to surgical resection [8]. In individuals with suspicious nodules, current guidelines from the ACCP recommend considering biopsy in the setting of solid nodules >8 mm, with the type of biopsy guided by nodule size, location and relation to the airway; risk of complications; and available expertise [8]. Whereas, nodules ≤8 mm in diameter, largely because they are infrequently malignant, are recommended to be followed with serial CT imaging as they are difficult to be characterized on imaging and due to the fact that they are challenging to approach with nonsurgical biopsy [8]. Surgical biopsy is often reserved for situations in which there is a high risk of malignancy, when functional image testing is positive, or when nonsurgical biopsy is suspicious for malignancy [8].

Options for nonsurgical tissue diagnosis include CT scan-guided TTNA and bronchoscopy guided by fluoroscopy, REBUS, ENB and VBN. Studies examining these modalities in individuals with pulmonary nodules are typically uncontrolled, single-armed, retrospective in nature and heterogeneous in study design. A few prospective trials exist for certain modalities, although they frequently contain low sample sizes. Thus, extrapolation to real-world settings and intrastudy comparisons become problematic. Meta analyses and systemic reviews have become a useful tool for assessing the options for nonsurgical biopsy. Nevertheless, there remains a paucity of data, particularly with respect to randomized, controlled, prospective, head-to-head comparison studies, upon which to form consensus opinion regarding application of the aforementioned techniques. Very often, operator preference and experience become deciding factors [8].

In formulating recommendations for assessing a nodule for likelihood of malignancy, the ACCP Evidence-Based Clinical Practice Guidelines suggest that "the type of biopsy should be selected based on nodule size, location, and relation to a patent airway; the risk of complications in the individual patient; and available expertise" [8].

The single pulmonary nodule

The small (i.e., <2 cm) peripheral lung nodule is a diagnostic dilemma, as accessing it via nonsurgical biopsy is challenging; yet, making a definitive diagnosis in this early stage may portend significantly better outcomes if the nodule is malignant. Current practice is to consider surgical excision when risk modeling indicates moderate to high suspicion of lung cancer, although potential for discovery of an inoperable tumor or a benign diagnosis must be accounted for, especially if other patient factors suggest a higher risk of complications associated with invasive surgery [9]. Intermediate- to low-risk tumors may be diagnosed by a number of mechanisms, although location and size of the nodule/mass are important factors in the effectiveness of the various nonsurgical biopsy modalities.

Chenna and Chen reviewed nine prospective studies investigating the role of VBN in diagnosing pulmonary nodules [10]. A diagnostic yield ranging from 62.5 to 80% was reported with VBN in nodules with an average size of 1.62–2.8 cm.

ENB uses a predetermined pathway on a virtual 3D image superimposed on simulated virtual bronchoscopic view, generated from preprocedure CT, using an electromagnetic sensor to track where the catheter is located in the lung. Several factors appear to influence the efficacy of ENB, such as lesion size (with smaller lesions negatively influencing diagnostic yield) and whether biopsy results are paired with rapid onsite evaluation (combined ENB + rapid onsite

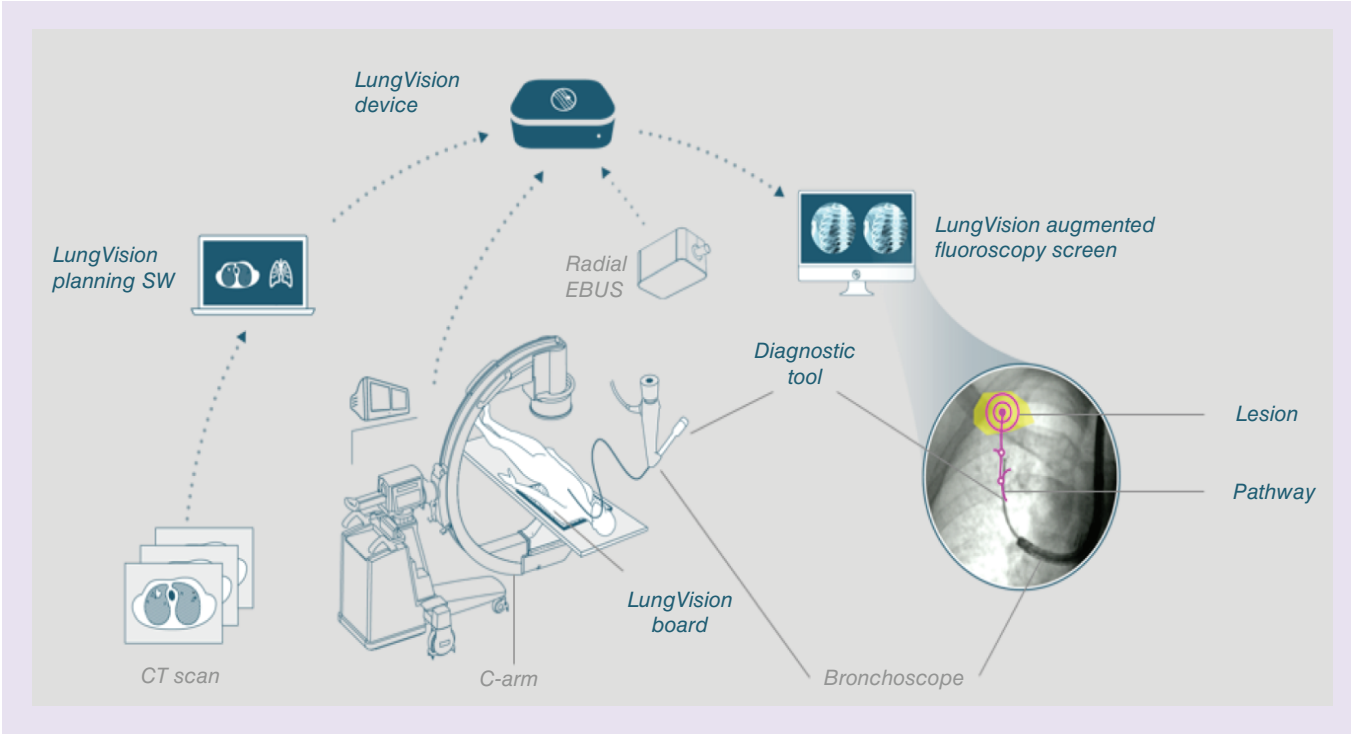

Figure 1. A graphic description of the LungVision system.
SW: Software.

evaluation demonstrated 85% diagnostic yield with a 5.8% pneumothorax rate in one study [11]). Overall, the reported diagnostic yield of ENB for diagnosing peripheral lung nodule is between 59 and 94% (average, 73.9%) in lesions with average sizes of 1.62–3.98 cm [10].

The aforementioned data should be noted with an important caveat. Ost *et al.* reviewing data from the ACCP Quality Improvement Registry, Evaluation and Education database, found lower than expected diagnostic yield for REBUS and ENB used as standalone procedures, as well as for combined REBUS-ENB procedures, compared with procedures in which neither was used [4]. Unadjusted diagnostic yields were 63.7, 57, 38.5 and 47.1% in procedures in which neither REBUS nor ENB was used, REBUS alone, ENB alone and REBUS + ENB, respectively.

Augmented real-time imaging-guided bronchoscopy

LungVision technology addresses the need for real-time visualization to help reach suspicious nodules in the deep periphery of the lungs. The system enhances in real time the intraoperative fluoroscopy with information sourced from preoperative CT scans. The system is designed to integrate previously underutilized imaging modalities, such as a standard C-Arm, CT imaging, REBUS together with standard biopsy tools. The system keeps the standard operation flow, but providing the benefits of real-time augmented imaging

Figure 1 presents a graphical scheme of the ecosystem created by LungVision to support Navigation Bronchoscopy procedure. Prior to procedure, the planning software is used by physician to identify the target and endoscopic pathway on preoperative CT. This enables physicians to identify and mark a suspicious lesion and plan a preferred pathway leading to the target lesion through the maze of bronchial airways. The planning step is performed by the bronchoscopist before entering the procedure room. During the procedure, LungVision system is visualizing and tracking the lesion and the pathways in real time, while compensating for respiratory motion during both navigation and biopsy. LungVision is able to integrate available imaging modalities and tools that are available in bronchoscopy and thereby allowing the bronchoscopist to drive the scope or catheter to the lesion, confirm localization and then obtain an adequate biopsy sample.

Figure 2 shows the examples of LungVision screens. The image on the left shows a screen shot from the planning application in which the bronchoscopist marks the lesion and selects the navigation pathway. The image on the right shows an image from the Navigation Bronchoscopy procedure presenting real-time information on the navigation pathway and lesion location and guide the bronchoscopist to the suspicious lesion.

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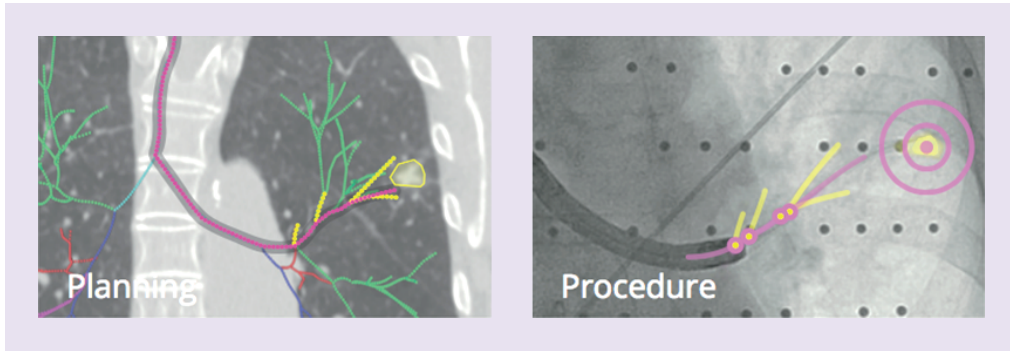

Figure 2. The LungVision screens during a bronchoscopy.

LungVision can be used as a 'stand-alone' technology for guidance and navigation or, if necessary, can be used in conjunction with other modalities (electromagnetic navigation, REBUS, etc.) and is potentially synergistic with these other modalities. For the bronchoscopist, the learning curve is slight, as its use builds on already familiar imaging modalities and tools.

In a subgroup of 85 patients from the LungVision Clinical Trial in eight US hospitals the localization of suspicious nodules accessed with the device was verified with REBUS, demonstrating localization success of 85% and diagnostic yield of 75% [12]. In another subgroup of 28 patients from the LungVision Clinical Trial, the LungVision localization of suspicious nodules was verified with cone-beam CT, demonstrating localization success of 96% and diagnostic yield of 92% [13].

Conclusion & implications for clinical practice

As the tracheobronchial tree divides in to increasingly narrow branches, the technical challenge of navigation becomes more relevant. Despite advancements in diagnostic instrumentation, approaching suspicious lesions in distal regions remains challenging.

Virtual and electromagnetic bronchoscopy techniques partially answer this conundrum, providing the bronchoscopist with limited navigation tools and a scripted, static route to a lesion identified on preoperative imaging. Their inherent limitations might be addressed by the availability of integrated real-time viewing ability and precise navigation tools that are available during the whole diagnostic procedure. This is the primary benefit of the LungVision system. Being able to see using fluoroscopy imaging, augmented with information sourced from preoperatively acquired CT imaging, allows the bronchoscopist to visualize the nodule (which is augmented and highlighted) and visualize the diagnostic instrument navigated to the nodule location. This innovative approach facilitates greater confidence that an adequate tissue sample at a relevant pathologic site has been obtained. The small but significant studies to date highlight this.

With all new technologies it is important to consider the learning curve involved with incorporation. The LungVision system incorporates into existing technology, and simply adds enhancement to the known fluoroscopic view. Learning the new modality is rather straightforward, and there was no change in yield noted from early to later cases at all centers.

As with any new technology, LungVision will need further validation in larger studies that enroll patients with various lung lesion types of variable sizes and geometry presenting in variety of locations within the lung. Proof of better outcomes than what is currently available should ultimately dictate the utility of LungVision. Early studies suggest feasibility and proof of concept that LungVision-guided transbronchial biopsy achieves accurate localization of suspicious lesions, and that it is potentially beneficial for diagnosing peripheral nodules.

Financial & competing interests disclosure

The author is a consultant for Body Vision (maker of LungVision) and has stock options holder for Body Vision. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Current limits to peripheral bronchoscopy

- Peripheral nodule biopsy with bronchoscopy continues to be limited by difficulty navigating to the correct airway and confirming the instruments' proximity to the nodule. Virtual systems in use do not provide real-time feedback of a live image of the nodule in question.
- Fluoroscopy has traditionally offered limited assistance as often the nodule is not visible and provides no information on airways/pathways to the nodule.

Currently available techniques for peripheral bronchoscopy

- Surgical biopsy (open versus video-assisted thorascopic surgery).
- Computed tomography (CT)-guided transthoracic needle aspiration.
- Bronchoscopy-based options:
  - Bronchoscopy guided by standard fluoroscopy, electromagnetic navigation bronchoscopy and virtual bronchoscopy navigation, as well as verification of lesion localization with radial endobronchial ultrasound (REBUS);
  - Data from the American College of Chest Physicians Quality Improvement Registry, Evaluation and Education (AQuIRE) initiative demonstrated that using any of the above techniques resulted in a diagnostic yield of <57%.
- Complications from transthoracic needle aspiration are higher than bronchoscopy approaches, but accuracy is lower in bronchoscopy.
- Surgical approach is most invasive.

Augmented reality fluoroscopy

- LungVision is approved by the US FDA.
- LungVision augments 2D fluoroscopic imaging with data gained from the preoperative CT.
- Nodules not seen on fluoroscopy are highlighted and enhanced on the fluoroscope screen.
- Guided pathways to the lesion are projected on the fluoroscopic screen in real time directing the endoscopist to the highlighted target.
- The system uses a standard C-Arm, the baseline CT imaging and standard biopsy tools.
- The system can also incorporate REBUS images on overlay of the fluoroscopy.
- The software accounts for motion during breathing and adjusts accordingly intraoperatively.
- LungVision can be used as a 'stand-alone' technology for guidance and navigation or, if necessary, can be used in conjunction with other modalities (EMN, REBUS, etc.) and is potentially synergistic with these other modalities.

Data

- In a study of 85 patients the localization of suspicious nodules (confirmed with REBUS) accessed with LungVision only was 85%.
- In a study of 28 patients LungVision localization of suspicious nodules was verified with cone-beam CT, demonstrating localization success of 96%.

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