Video Article

Sequential Radial probe Endobronchial Ultrasound and Electromagnetic Navigation Bronchoscopy for the Diagnosis of Peripheral Pulmonary Lesions

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Abstract

Bronchoscopic diagnosis of peripheral pulmonary lesions remains a challenge for lung physicians. Advancements in ultrasound and electromagnetic guidance have improved the ability for clinicians to localize peripheral lesions despite the lack of direct visualization. Radial probe endobronchial ultrasound (pEBUS) and guide sheath aids the physician in confirming sampling tool placement. Electromagnetic navigation bronchoscopy (ENB) aids in peripheral lesion localization with a combination of electromagnetic tracking of navigation instruments and a steerable guidance probe. In patients who are not suitable candidates for surgical resection or percutaneous biopsy of peripheral lung lesions, endobronchial ultrasound and electromagnetic navigation bronchoscopy are useful tools in diagnosis. The localization rates of combined pEBUS and ENB have been reported above 90% and the diagnostic yield is as high as 88%. We describe a technique for bronchoscopy using radial probe endobronchial ultrasound to localize and sample peripheral lung lesions with electromagnetic navigation bronchoscopy used as a navigation tool if necessary.

Introduction

Lung cancer is the greatest cause of cancer related death worldwide and early diagnosis has been shown to improve survival. Computed tomography(CT) screening has been shown to reduce lung-cancer mortality but in the discovery of peripheral lung nodules, there is a risk that patients with benign nodules are treated with unnecessary surgeries[1]. In patients where surgical resection of a nodule is high risk, alternative therapies are such as stereotactic body radiotherapy(SBRT)[2] are considered. However, biopsy of nodules is usually preferred prior to therapy[3]. Diagnostic biopsy of peripheral lung nodules remains a challenge for pulmonary physicians. Non-surgical biopsy options include transthoracic needle aspiration (TTNA), conventional bronchoscopy, or bronchoscopy with advanced imaging techniques such as radial probe endobronchial ultrasound (pEBUS) and electromagnetic navigation (ENB). TTNA has a high diagnostic sensitivity for lung cancer but when a lung nodule is separated from the pleural surface, there is an elevated risk of pneumothorax[4]. Conventional bronchoscopy has limited diagnostic yield for nodules < 2 cm[5]. Advanced bronchoscopic biopsy techniques have a higher diagnostic yield[6] but are limited to specialized centres with interventional pulmonology.

Radial probe endobronchial ultrasound has an established record of success in confirming the location of peripheral pulmonary nodules. The radial probe, with a diameter of 1.7 mm, and guide sheath fit within the working channel of a bronchoscope. The probe emits a 20 MHz ultrasound pulse laterally and with rotation, is able to capture a 360° view around the ultrasound probe. This allows the bronchoscopist to interrogate peripheral airways and differentiate normal lung tissue from a nodule. The guide sheath[7] allows the probe to be removed but the location preserved for lesion sampling.

Electromagnetic navigation bronchoscopy consists of three elements: A multi-planar reconstruction of Computed Tomography data, generation of an electromagnetic field around the patient, and a steerable electromagnetic navigation probe. Virtual bronchoscopy software is able to reconstruct a CT scan into multiple planar views and automatically perform airway segmentation to create a virtual airway for navigation. Electromagnetic tracking (EM) involves the generation of a low power electromagnetic field in a region of interest. Electromagnetic probes placed within this field detect EM field strength and are able to localize to the region of space specific to that field strength. The EM field is able to pass through objects, allowing probes to be localized within a patient. EM systems are able to identify the position of guidance probes within the thorax and, when combined with a steerable probe, can help the bronchoscopist navigate to peripheral lesions that are not visible under white light bronchoscopy.

Combined electromagnetic navigation bronchoscopy with radial probe endobronchial ultrasound has shown a diagnostic yield as high as 88%[8]. In the same study, pEBUS alone (69%) had a higher yield than ENB alone (59%) and the combination was higher than either alone. ENB is used to help localize the sampling instruments at the peripheral lung lesion and pEBUS is used to confirm guide sheath placement. Alternatively, the pEBUS probe can often be navigated to the peripheral lung lesion with careful CT pre-procedure planning with virtual bronchoscopy and still have a high diagnostic yield (80%)[9]. ENB can be used alone for the evaluation of nodules with a good sensitivity for malignancy[10,11]. One factor against the routine use of ENB for all peripheral lung lesions is the cost of the disposable ENB guidance catheter. Although ENB can be used prior to pEBUS, lesions can often be found using pEBUS alone and the cost of the disposable ENB probe can be spared. We have found that

the pEBUS probe alone can localize peripheral lung lesions in up to 75% of cases and the addition of ENB after initial pEBUS attempts increases localization rates to over 90%[6]. Lung tissue can then be sampled through the extended working channel.

We aim to demonstrate bronchoscopy using radial probe EBUS and, if needed, electromagnetic navigation bronchoscopy to localize and biopsy peripheral lung lesions.

Table 1: Patient Selection
Inclusion Criteria
Age over 16 years
Lung nodule(s) identified on Computed Tomography
Clinical decision to obtain a tissue biopsy of lung lesion
CT-guided biopsy not the preferred technique
Exclusion Criteria
Lack of informed consent for procedure
Suggestion of an endobronchial lesion or centrally located lesion (peripheral ultrasound not necessary)
Implanted electronic medical device
Uncontrolled coagulopathy
Medical contraindication to bronchoscopy

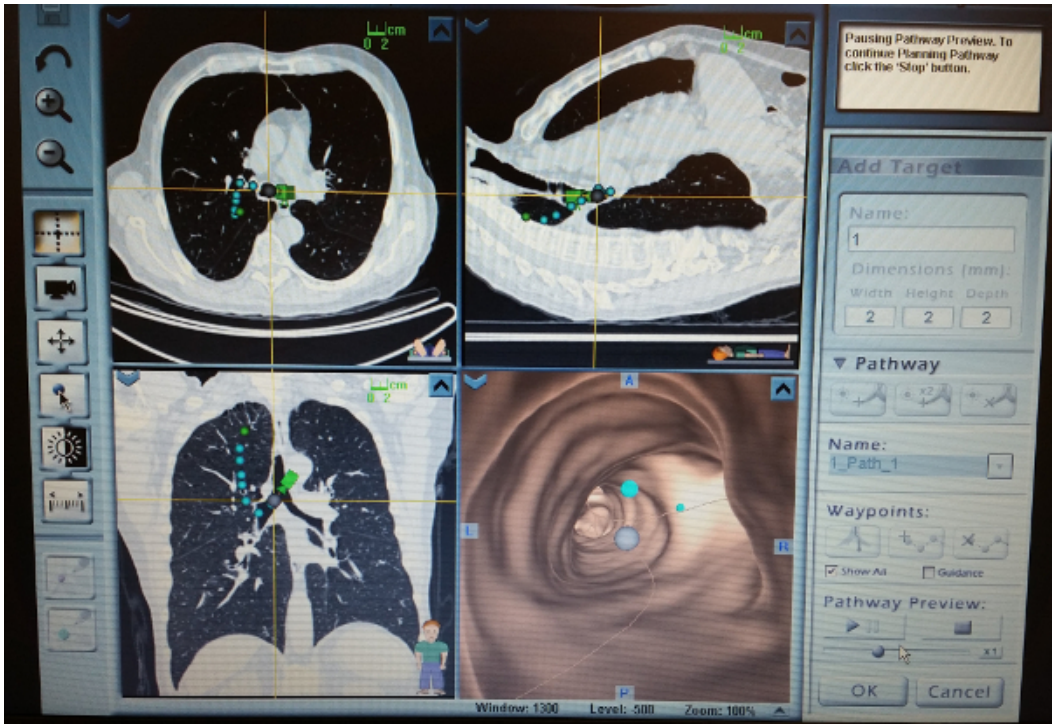
Table 2: Diagnostic Yield According to lesion characteristics			
	Study cohort	pEBUS alone	pEBUS + ENB
Total	60	45	15
Lesion localized	56/60	45/60	15-Nov
Overall Yield: +result/total (%)	30/60 (50)	26/45 (58)	4/15 (27)
Adjusted Yield (%)(n.s. vs. pEBUS ENB)		26/60 (43)	
Tsuboi Classification:+result/total (%)			
1 (air bronchus within lesion)	14/25 (56)	13/22 (59)	1/3 (33)
2 (air bronchus through lesion)	7/14 (50)	7/12 (58)	0/2 (0)
3 (air bronchus adjacent to lesion)	7/14 (50)	4/8 (50)	3/6 (50)
No air bronchus visible	2/7 (29)	2/3 (67)	0/4 (0)
Air Bronchus Sign – Tsuboi 1 & 2 (%)	21/39 (54)	20/34 (59)	1/5 (20)
EBUS image: +result/total (%)			
Within lesion	21/33 (64)*	20/31 (65)	1/2 (50)
Adjacent to lesion	9/23 (39)	6/14 (43)	3/9 (33)
No lesion visualized	0/4 (0)	N/A	0/4 (0)

Protocol

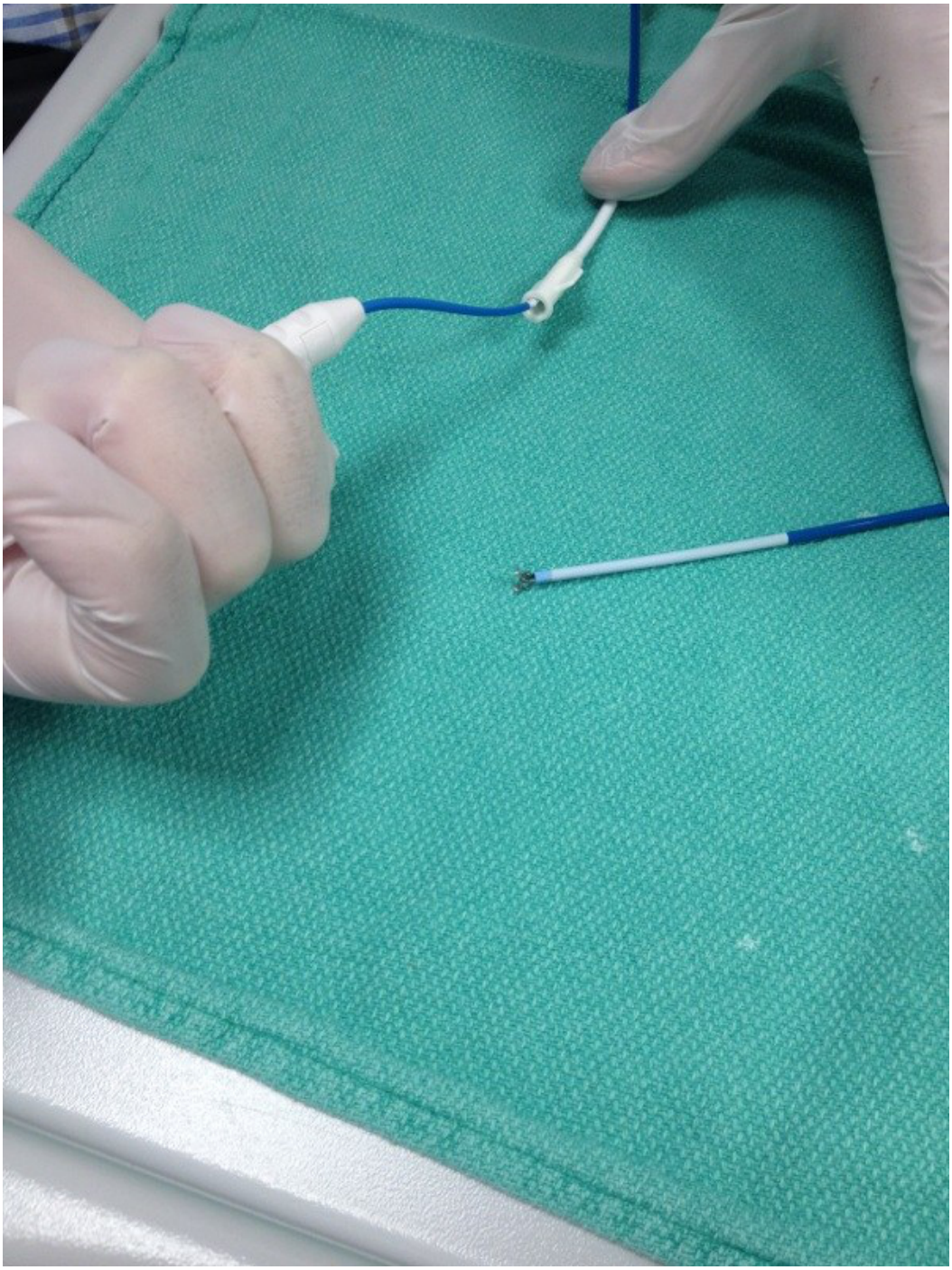
1. Pre-procedural Planning

1. Load the patient chest CT onto the ENB planning computer in digital imaging and communications in medicine (DICOM) format for virtual bronchoscopy procedure planning.
2. Identify the lung lesion and using virtual bronchoscopy, plan the most direct route through airways to the lesion of interest.
    1. Using the computer mouse, scroll through the axial, sagittal and coronal windows of the CT images to identify the lung lesion. Left-Click the crosshairs button in the left side of the screen then left-click the target lesion and select a name for the lesion in the upper right corner text box.
    2. Using the mouse or other human interface device, steer the virtual bronchoscopy to the lesion from the trachea. The mouse scroll wheel will advance the virtual bronchoscopy image and the left-click will adjust the center of the image.

3. Starting from the trachea, attempt a virtual bronchoscopy to the lesion by following the airway segments in the most appropriate trajectory. If the lesion is not reached, then attempt different bifurcations of peripheral airways in an attempt to reach the lesion. Use the axial, sagittal and coronal views of the multi-planar CT for pathway correction.
Note: Alternatively, the ENB planning program will generate an automated pathway to the lung lesion to be followed. The virtual bronchoscopy map may be used in an attempt to navigate to the lung lesion with the pEBUS probe alone.



3. Once an ideal pathway is found to the lesion, save the planning file and export it to the ENB procedure system.
Note: Multiple pathways can be planned in the event that there are multiple airways leading to the lesion.
4. Use the ENB extended working channel as a guide sheath for the pEBUS probe and ENB probe. Measure and mark the biopsy tools to the length of the sheath prior to the procedure. Mark the biopsy forceps when it is extended through the sheath and able to open.

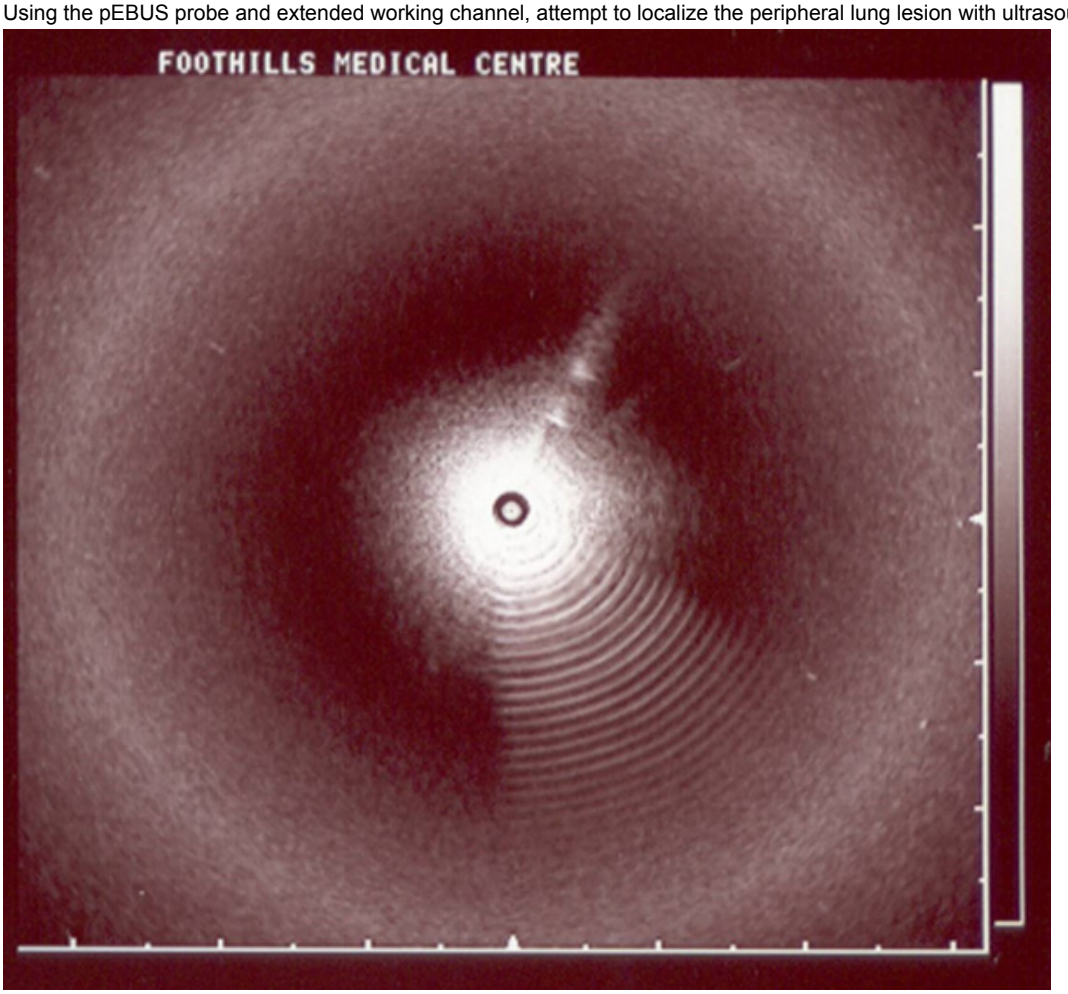


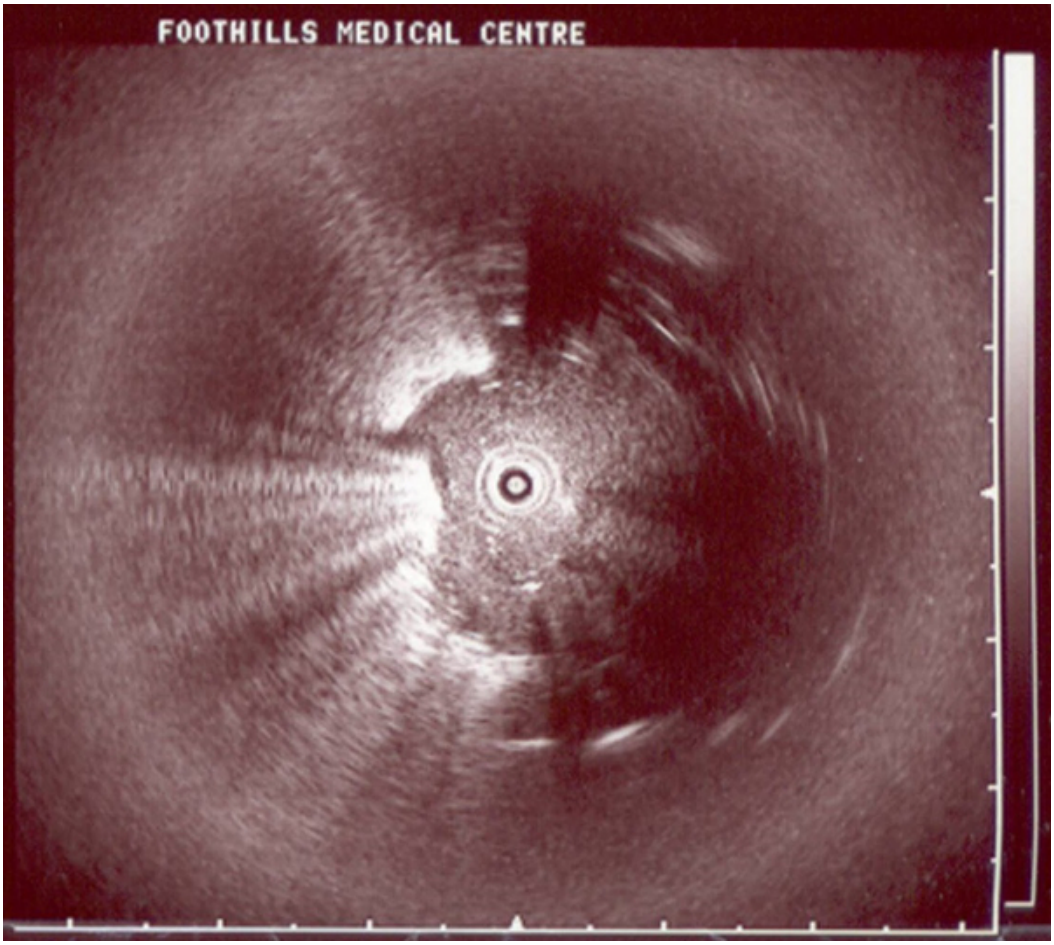
Mark the brush and needle when the hub is flush with the end of the guide sheath.

2. Bronchoscopy

1. On the day of the procedure, ensure that the patient remains a good candidate for bronchoscopy with transbronchial biopsy[12] under moderate sedation or general anesthesia. For moderate sedation, the patient should require no airway intervention, have adequate spontaneous breathing, maintain blood pressure and respond to verbal or tactile stimulation.[13]
2. Place a peripheral intravenous line and provide supplemental oxygen via nasal prongs or face mask.
3. Place the patient on a fluoroscopy bed with the electromagnetic field generator and monitor according to standard bronchoscopy guidelines[12] with pulse oximetry, cardiac telemetry and blood pressure monitoring.
4. Administer topical lidocaine to the nasopharynx and oropharynx. Achieve moderate sedation with intravenous medication. Give a combination of benzodiazepine and opiode in small aliquots (i.e. midazolam 1-2 mg IV, fentanyl 10-25 µg IV) and titrated to patient sedation. If general anesthesia is used, then defer to the anesthesiologist for sedation protocol.

5. After moderate intravenous sedation is administered, insert the bronchoscope through the nose or mouth into the trachea. Carry out standard visual inspection of the airways.
6. Using the pEBUS probe and extended working channel, attempt to localize the peripheral lung lesion with ultrasound image confirmation.





1. Steer the bronchoscope into airway most suspected of containing the lung lesion.
2. Advance the EBUS probe through the bronchoscope working channel until it is in the area of interest.
3. On the EBUS module on the bronchoscopy cart, press the Ultrasound button to turn on EBUS. If the lesion is not visible in an airway, interrogate other airway subsegments with the EBUS probe by retracting the probe and inserting it into different airways. To prevent damage to the probe when moving from airway to airway, turn the Ultrasound off between airway segments.
4. If the lesion is identified with pEBUS, remove the probe (guide sheath kept in place) and sample the lesion using the pre-measured biopsy tools (see step 3). Obtain multiple passes from the same region by keeping the guide sheath in place while samples are taken.

7. If the lesion is not localized using pEBUS alone, then apply the ENB system. Place the three ENB registration markers on the patient torso, preferably one superiorly at the sternal notch or sternal angle and the others laterally at the level of the false ribs to measure maximal chest expansion with respiration.
   Note: This can also be performed prior to the bronchoscopy and pEBUS procedure.
   1. Turn the ENB system on and insert the USB key into the computer.
   2. Select ‘Procedure’ on the main screen and enter the patient name, identification, and operator name, then click ‘next’.
   3. Verify that the three ENB registration markers are visible on the ENB screen as yellow dots within the square. If not, then move the markers so that they are spread out in the square but are still within the square. Click ‘next’ to start ENB probe registration.

8. Once the ENB probe is connected to the guidance system and placed through the working channel of the bronchoscope with the guide sheath, register the CT map to the position of the ENB probe within the patient.
   1. Carry out registration by performing a repeat airway inspection, being careful to place the tip of the ENB probe into each visible airway segment. On the ENB system screen, the bronchoscope image will be projected with a yellow border. Once the system automatically registers the map, the border will turn green and a virtual bronchoscope image will appear next to the bronchoscope image.
      Note: The ENB system matches the airway tree generated via airway inspection to the airway tree made from the CT airway segmentation.
   2. Once the electromagnetic probe is registered with the CT planning file, commence nodule localization as described below. With the mouse, left-click the target name on the computer screen to select it as the ENB target.
      Note: The ENB guidance system generates the airway route from the trachea to the peripheral lesion, though typically the first four generations of airways can be navigated using white-light bronchoscopy alone.

9. Once the electromagnetic probe and guide sheath are beyond the visibility of the bronchoscope, navigate the more peripheral airways using the guidance system and virtual bronchoscopy map.
   Note: Virtual bronchoscopy is able to project an image of the airway subsegments that are not visible with regular bronchoscopy, and will improve the spatial orientation beyond the bronchoscope tip.

1. Use the instructions provided by the guidance system to choose the optimal airway to place or steer the ENB probe.
2. Use the information provided by the guidance system (such as current probe position in relation to the nodule and the distance from the probe tip to the nodule) to navigate to the nodule.

10. When the ENB system localizes within 1 cm of the nodule centre, verify the position with the radial EBUS probe.
    1. Keep the guide sheath in place while the ENB probe is removed and replaced with the EBUS probe. Advance the EBUS probe to its pre-marked distance then turn the Ultrasound on.
       Note: If localized, a nodule can be readily identified with the EBUS though ground glass opacities are more difficult to characterize(see step 2.6)[14].
    2. If the lesion is confirmed on EBUS, then remove the EBUS probe and commence biopsy. Otherwise, reinsert the ENB probe and redirect the sheath to an alternative location.
    3. If the lesion cannot be confirmed on EBUS despite multiple attemps to adjust position with the steerable ENB probe, keep the guide sheath in place and perform a directed BAL(Step 3.4).

3. Biopsy Procedure

1. Remove the probe while the guide sheath is kept in place.
2. Pass the pre-measured biopsy forceps[7,12], transbronchial needle, bronchial brush through the guide sheath to sample the lesion.
    1. For biopsy forceps, insert the closed forceps into the sheath at the pre-measured depth.
        1. Open the forceps, then retract the open forceps onto the sheath to ensure that they are open and outside the sheath.
        2. Advance forceps about 1 cm until meeting resistance then close the forceps and pull them out of the sheath.
        3. Open the forceps into a saline container to remove the sample, then repeat the step.
        4. Once complete, transfer the biopsy samples from a saline container to formalin fixative with a syringe.

    2. For a transbronchial needle, pass the needle to the pre-measured depth within the guide sheath.
        1. Extend the needle then apply light suction on the syringe, confirming that there is resistance to suction.
        2. Slowly move the needle several millimeters back and forth for several movements.
        3. Discontinue syringe suction by letting go of the syringe plunger then retract the needle and remove the apparatus from the sheath.
        4. To expel the sample, extend the needle onto a slide or liquid fixative and push 20cc of air from the syringe through the needle.

    3. For a bronchial brush, insert the brush to the pre-measured depth within the guide sheath.
        1. Extend the brush then slowly move the brush back and forth several millimeters for several passes.
        2. Retract the brush then remove from the sheath.
        3. To obtain the brush sample, either rub the brush onto a slide or cut the brush tip into liquid fixative for processing.
           Note: If rapid on-site examination is not available, we recommend a minimum of four passes with the forceps and needle.

3. If there is suspicion of sheath movement during the sample procedure, reinsert the EBUS probe(see step 2.10.1) into the guide sheath to verify nodule visualization.
4. Perform a directed bronchoalveolar lavage (BAL) through the guide sheath using a 20 mL syringe with normal saline after the biopsies are obtained. Attached the syringe to the guide sheath, inject 20 mL of normal saline and then apply suction to the syringe in an attempt to retrieve the saline.
   Note: If the directed BAL yields insufficient sample, then perform a conventional BAL[12] with 120 mL of normal saline through the working channel of the bronchoscope after the guide sheath is removed.

4. Post-biopsy care

1. Use transthoracic ultrasound with a 12 MHz probe to rule out a pneumothorax immediately after the procedure[15].
2. Carry out chest radiography one hour after the procedure if there is ongoing suspicion of a pneumothorax[16].
3. Monitor the patient in a recovery area with nursing support for a minimum of two hours to ensure adequate alertness and return of the gag reflex prior to discharge.

Representative Results

With the combined approach of pEBUS and ENB if needed, localisation rates of peripheral lung lesions is as high as 100%[6] with diagnostic yield as high as 88%[8]. There is a gap between localization rates and diagnostic yield that may be affected by sampling tools[17]. Pneumothorax rates range between 0-10%[8,17-20]. Probe position relative to the nodule on pEBUS imaging[21] and the presence of an air bronchus sign on computed tomography increase diagnostic yield[18]. If the pEBUS probe is localized adjacent to the lesion, then there is a reduced diagnostic yield compared to the probe localizing within the lesion[17] [Table 2]. The risk of pulmonary hemorrhage is minimal and not significantly increased over conventional bronchoscopy.

Figure 1: Virtual Bronchoscopy screenshot. Axial (top left), sagittal (top right), coronal (bottom left) views of computed tomography with virtual bronchoscopic image of right mainstem bronchus (bottom right). The pathway with waypoints (blue dots) and target lesion (out of plane, green dot) are visible.

Figure 2: Measurement of biopsy forceps for guide sheath. The forceps are opened beyond the guide sheath and that length is marked on the shaft of the forceps probe.

Figure 3. Radial probe EBUS image of a) normal lung parenchyma and b) pulmonary nodule. Image courtesy of Dr. Alain Tremblay.

Table 1: Patient selection criteria for sequential radial probe endobronchial ultrasound and electromagnetic navigation bronchoscopy

Table 2: Representative results of technique[17]. EBUS – endobronchial ultrasound; ENB – electromagnetic navigation bronchoscopy; n.s. – not statistically significant.

Discussion

The majority of peripheral pulmonary lesions can be localized with the sequential use of pEBUS and ENB if needed. The ENB system helps lesion localization even without the steerable probe. The virtual bronchoscopy system helps pre-procedural planning of airway navigation with the pEBUS probe and guide sheath. If the lesion is not identified with pEBUS alone, then the steerable EM probe increases the localization rate up to 18% over pEBUS alone[17].

There is a learning curve identified in the use of pEBUS and ENB[22]. Both modalities are considered interventional bronchoscopic techniques[23] and although there is no minimum number of procedures identified for competency in ENB, diagnostic success is likely to improve with experience. It is recommended that clinicians perform at least 40-50 supervised EBUS procedures prior to competency[24].

A critical step within the protocol is the pre-bronchoscopy planning of navigation to the pulmonary lesion with virtual bronchoscopy. This will improve the ability to navigate to the lesion and confirm its position with EBUS[9]. Measurement and marking of the biopsy tools (forceps, needle, brush) in relation to the guide sheath length must be precise. If the biopsy forceps are measured too short, then the forceps will be opened inside the guide sheath and will not sample the lesion. If the tools are measured too long, then they may either sample tissue distal to the lesion or increase the risk of pneumothorax.

There are alternative methods when using pEBUS and ENB in lesion biopsy. ENB may be used prior to pEBUS for localization[8]. This order of technique may be considered when on pre-procedure virtual bronchoscopy it is noted that use of ENB is likely required. However this order of lesion sampling would increase the overall cost of the procedure since the disposable ENB probe is used for every case. Factors predicting the use of ENB include lack of air bronchus sign and nodule diameter. General anesthesia may limit patient movement during navigation and biopsy is associated with higher diagnostic yield[6]. Rapid on-site examination (ROSE), if available, may also improve diagnostic yield[22,25,26]. There is evidence that ROSE increases diagnostic yield both in conventional bronchoscopy as well as transbronchial needle aspiration of mediastinal lymph nodes[27,28]. The gap between localization rates and diagnosis rates is being approached with the investigation of newer sampling modalities. New sampling tools such as cryobiopsy[29] and optical frequency domain imaging[30] warrant further study.

For lesions that are non-diagnostic, clinical judgement must be used to determine the next course of action. Surgical biopsy, percutaneous CT-guided biopsy, repeat bronchoscopy and observation are all possible options that require careful consideration of patient factors and clinical suspicion.

Disclosures

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