Video Article

Substernal Thyroid Biopsy Using Endobronchial Ultrasound-guided Transbronchial Needle Aspiration

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Abstract

Substernal thyroid goiter (STG) represents about 5.8% of all mediastinal lesions[1]. There is a wide variation in the published incidence rates due to the lack of a standardized definition for STG. Biopsy is often required to differentiate benign from malignant lesions. Unlike cervical thyroid, the overlying sternum precludes ultrasound-guided percutaneous fine needle aspiration of STG. Consequently, surgical mediastinoscopy is performed in the majority of cases, causing significant procedure related morbidity and cost to healthcare. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) is a frequently used procedure for diagnosis and staging of non-small cell lung cancer (NSCLC). Minimally invasive needle biopsy for lesions adjacent to the airways can be performed under real-time ultrasound guidance using EBUS. Its safety and efficacy is well established with over 90% sensitivity and specificity. The ability to perform EBUS as an outpatient procedure with same-day discharges offers distinct morbidity and financial advantages over surgery. As physicians performing EBUS gained procedural expertise, they have attempted to diversify its role in the diagnosis of non-lymph node thoracic pathologies. We propose here a role for EBUS-TBNA in the diagnosis of substernal thyroid lesions, along with a step-by-step protocol for the procedure.

Video Link

The video component of this article can be found at http://www.jove.com/video/51867/

Introduction

Substernal thyroid goiter (STG) is a slow growing tumor, eventually causing symptoms in 70-80% of cases. As per literature review, between 2.5-22.6% of STG can have malignant transformation[2]. Compression of the trachea, esophagus, recurrent laryngeal nerve, and superior vena cava often causes symptoms like dyspnea, stridor, cough, dysphagia, dysphonia, vocal cord paralysis, Horner's syndrome, superior vena cava syndrome, and cerebral edema. Occasional cases of overt hyperthyroidism have also been reported. A retrospective study by Shin *et al.* reported a positive correlation between thyroid size and presence of shortness of breath, globus sensation, and symptoms of hyperthyroidism[3]. This study, however, did not find a correlation between goiter size and presence of dysphagia, local discomfort, changes in voice, hemoptysis, or symptoms of hypothyroidism. Both substernal and cervical goiters carry similar malignancy risk. However, the retrosternal location makes diagnostic biopsy and treatment of STG very challenging. Most cases eventually require surgical removal using mediastinoscopy or sternotomy.

Endobronchial ultrasound (EBUS) was first described in 1992 by Hurter and Hanrath[4]. Over the years, EBUS-TBNA has become the procedure of choice for diagnosis and staging of non-small cell lung cancer. The reported sensitivity, specificity, and positive predictive value of EBUS-TBNA for mediastinal and hilar lymphadenopathy is 94%, 100%, and 100% respectively, with a low complication rate making it very safe, effective and superior to conventional TBNA[5]. However, both conventional and EBUS-guided TBNA were found to have statistically similar results for subcarinal lymph nodes[6].

Two types of EBUS probes have been developed so far – the radial probe (RP-EBUS) and the curvilinear probe (CP-EBUS). RP-EBUS was the first one to become commercially available in 1999. It has a thin ultrasound probe inside a water-inflatable balloon tip. The probe rotates 360° at an angle perpendicular to the axis of insertion. The inflated balloon provides a circular contact for the probe, enabling it to obtain 360° view around the airways. It is used for evaluation of the central airways, assessment of airway invasion and obtaining biopsy of peripherally located lesions[7,8]. After the lesion is localized, radial probe must be taken out of the guide sheath in the bronchoscope's working channel to make way for the biopsy tool. Hence, a real-time ultrasound guided biopsy cannot be performed. Three different radial probes are currently available - 20-MHz and 30-MHz miniature probes, and the 20-MHz ultra-miniature probe. The miniature probes can be inserted through the 2.8 mm working channel of a bronchoscope and reach sub-segmental airways; the higher frequency probe provides better image resolution[9]. With an outer diameter of 1.4 mm, the ultra-miniature probe fits into the 2 mm working channel of the smaller bronchoscope and reaches more peripheral lesions.

CP-EBUS was introduced in 2005. It is a 7.5 MHz convex probe inside a saline-inflatable balloon at the tip of the bronchoscope (**Figure 1**). The outer diameter of the bronchoscope tube is 6.3 mm, and of the tip is 6.9 mm. The inner diameter of the working channel is 2.2 mm. The scope looks at a 35° forward oblique angle, with an angle of view of 80° (**Figure 2**). The convex probe itself generates a 50° image, and scans parallel to the insertion axis. Ultrasound images can be obtained by either placing the probe directly over the bronchial wall using forward flexion, or by additionally inflating the balloon with saline. Water is a better conductor than air of ultrasound waves, and improves image quality. Vascular structures can be differentiated from tissues using the color Doppler mode scan. Biopsy is performed using a dedicated 22 or 21 G TBNA needle with an echogenic-dimpled tip (**Figure 3**), which comes out at an angle of 20° to the long axis of the bronchoscope. The needle has a maximum extruding stroke of 40 mm, with a safety mechanism that stops it at 20 mm to prevent excessive protrusion. The internal wire of the needle minimizes sample contamination while the needle passes through the bronchial wall. It is also used to clean up the needle after it has passed through the bronchial wall and into the targeted lesion. The optimal number of aspiration “passes” is reported to be 3-7 for a satisfactory sample, but the highest yield is from the first pass[10,11]. The images are processed in a dedicated ultrasound processor. Both ultrasound and white-light bronchoscopy images are simultaneously visible on the monitor, allowing for easy navigation to the site of the suspected lesion. CP-EBUS has the ability to perform real-time TBNA with direct ultrasound guidance under moderate sedation or general anesthesia. The procedure can be performed in an outpatient setting, eliminating surgery-related morbidity and need for inpatient admission.

The use of EBUS-TBNA for diagnosis of substernal thyroid is new, and has been reported in only a few case reports[12-18]. Based on the review of the current literature, this paper seeks to elaborate on the procedural requirements and propose EBUS-TBNA as a modality for biopsy of substernal thyroid gland. Please note that the above equipment description is more specific to Olympus Inc. There are other commercially available products as well, and minor variations do exist.

Protocol

The protocol outlined below follows the guidelines of the institution (Roswell Park Cancer Institute, State University of New York at Buffalo, NY).

1. Initial Preparation

1. Perform Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) under moderate sedation, monitored anesthesia care (MAC), or deep sedation and general anesthesia.
   NOTE: Patient surveys show favorable satisfaction scores with moderate sedation[19], but recent data shows higher diagnostic yield using general anesthesia[20].
2. Optionally, perform the procedure without an airway device under moderate sedation. Use a laryngeal mask airway (LMA; size 4) for procedures involving deep sedation or general anesthesia.
   NOTE: Use LMA for lesions that are higher in the trachea. Because of the high tracheal location of substernal thyroid gland, endotracheal intubation should not be used in these cases
3. During the procedure, use the lowest effective dose of 1% or 2% lidocaine (cumulative maximum dose of ≤7 mg/kg; maximum serum level ≤5 mg/L) for topical airway anesthesia through the bronchoscope’s working channel [21].

2. Pre-procedure Surveillance Bronchoscopy

1. Introduce a conventional flexible bronchoscope into the airway through the oral cavity, or the LMA. Perform a sequential inspection of each sub-segment of both the left and right tracheobronchial tree for obvious endobronchial abnormalities and ensure adequate airway patency. Clean the airway of any secretion or mucus by suctioning. Remove bronchoscope from the airway when done.

3. Localizing the Lesion of Interest

1. Introduce Convex Probe-Endobronchial Ultrasound (CP-EBUS) bronchoscope with a 35° forward oblique angle view. Observe the anterior airway wall and a small portion of the adjacent lumen while advancing the bronchoscope centrally in the airway. When passing through the vocal cords, ensure that only the anterior angle of the glottic opening is visible. When in trachea, visualize the entire lumen with 35° backward flexion as needed.
2. Observe the display-screen while using the white-light bronchoscopy. Advance the bronchoscope to the estimated level of the lesion. Always, ensure that the lumen is not fully visible when advancing the bronchoscope. Full view of the lumen indicates that the tip of the CP-EBUS probe is in backward flexion, and poses the risk of traumatic scraping against the posterior airway wall.
3. After reaching the desired site of interest, inflate the balloon using about 2 ml of normal saline. Flex the tip of the CP-EBUS forward to bring it in contact with the airway.
4. Turn on the ultrasound view using the dedicated ultrasound processor. Use the two-screen display (or split-screen display) to see both the endoscopic view of the lumen, and the corresponding ultrasound image together on the screen.
5. Ensure that the EBUS bronchoscope is in flexion position. Move the CP-EBUS both clockwise and counterclockwise in small angles at the same level to identify the substernal thyroid gland. Identify the lesion. Adjust the CP-EBUS probe by moving it up-and-down so that the largest diameter of the lesion is seen.
6. Using the Doppler mode, identify the adjacent vascular structures to determine lesion’s accurate station[22], and avoid accidental puncture of the blood vessels.
7. At the level of the lesion, flex the tip of the EBUS bronchoscope forward so its ultrasound probe comes in contact with the airway to obtain an ultrasound view of the lesion. When needed, flex the tip backward for full endoscopic view. Repeat the manoeuver and identify a point of entry for the TBNA needle between two tracheal rings.

4. Obtaining Endobronchial Ultrasound-guided Transbronchial Needle Biopsy

1. With the CP-EBUS tip in neutral (non-flexed) position, introduce the dedicated the 22 or 21 G TBNA needles into the working channel of the EBUS bronchoscope. Fasten the needle assembly onto the working channel using the locking mechanism.
2. Loosen the sheath adjuster knob and advance the sheath so that the tip can be barely visualized on the endoscopic image. Fasten the sheath adjuster knob now.
3. Flex the CP-EBUS probe forward to bring it in contact with the airway wall. On the ultrasound image, reconfirm that the longest diameter of the lesion is aligned with the projected path of the needle. Ensure that the needle exits the working channel at an angle of 20°.
4. Loosen the needle adjuster knob, and puncture through the airway wall into the lesion under real-time ultrasound guidance. With the EBUS needle inside the lesion, shake the internal stylet to clean out the needle tip.
5. Remove the internal stylet and attach the 20 ml vacuum-generating syringe to apply negative pressure.
6. Move the needle back-and-forth ("passes") inside the lesion, with – 20 ml negative pressure applied by a special vacuum-generating syringe. A total of 3-7 passes is suggested based on the current literature[10,11].
7. After making sufficient number of passes, negative pressure knob is turned off, and needle is retrieved out of the working channel.
8. Push out the histological core using the internal sheath. Obtain both histological core as well as cytological aspirate by this method. Alternatively, use an air-filled 6 or 12 ml syringe to expel the content of the needle onto the slide or in the specimen cup.
9. Determine the adequateness of the specimen using on-site cytology services.

5. Post-procedure Surveillance Bronchoscopy

1. Remove the CP-EBUS bronchoscope out after biopsy. Reintroduce a conventional bronchoscope and perform a surveillance bronchoscopy to confirm absence of significant bleeding at the TBNA site. After hemostasis is ensured, remove the bronchoscope out and conclude the procedure.

Representative Results

Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) biopsy of substernal thyroid has been reported in eight case reports as per literature review[12-18]. The first case of substernal thyroid biopsy using Endobronchial Ultrasound was reported by Rosario *et al.* in 2006[12], wherein a CT chest done for metastatic work-up of prostate adenocarcinoma showed mediastinal lymphadenopathies. EBUS-TBNA of the lesion revealed a previously undiagnosed papillary thyroid carcinoma metastasis. In 2010, Harris and Chalhoub[16] biopsied a symptomatic substernal thyroid, found to be colloid thyroid adenoma (**Figures 4** and **5**). Six more cases of substernal thyroid biopsy using EBUS-TBNA were reported across the world. None of the cases reported any biopsy-related procedural complications, suggesting that the procedure could be performed safely. Most of these lesions were found to be papillary thyroid carcinoma on pathological analysis. **Table 2** lists all the cases reported thus far. We acknowledge that more cases may have been done, and not reported in medical literature.

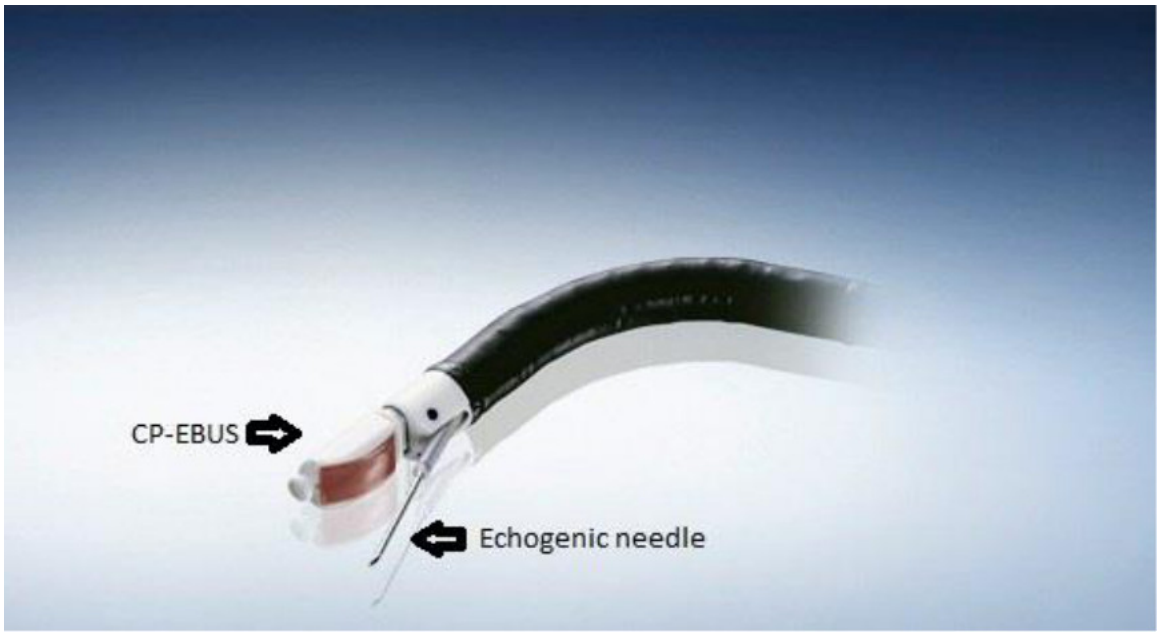

Figure 1: Convex-probe EBUS Bronchoscope.

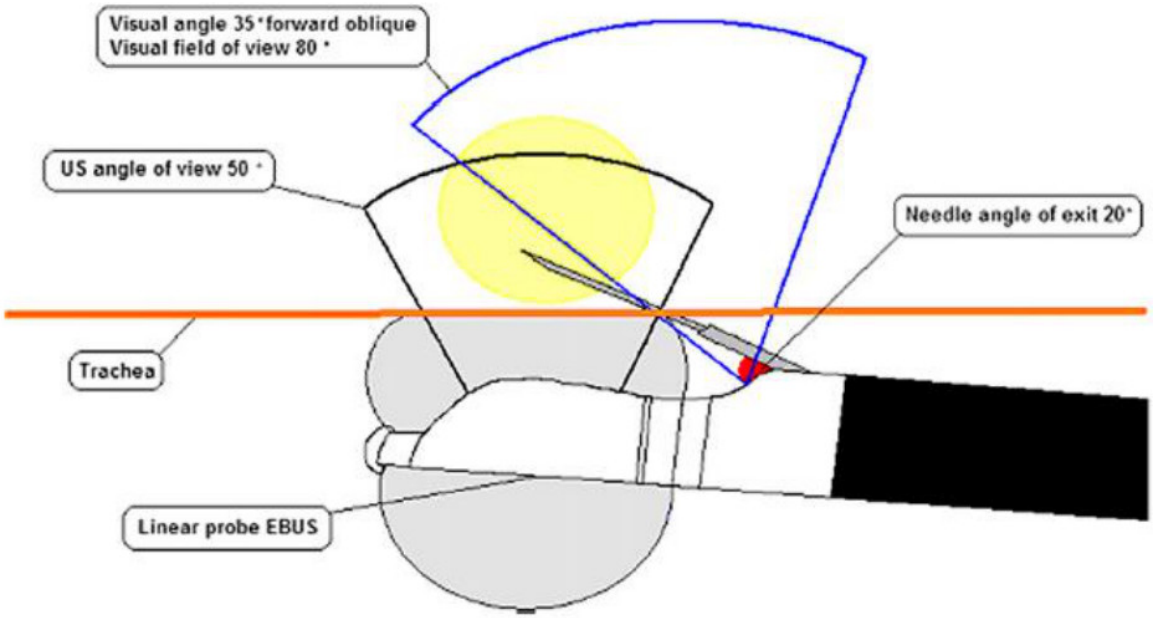

Figure 2: Schematic diagram of convex-probe endobronchial ultrasound (EBUS) system. Reprinted with permission from the American Thoracic Society[47].

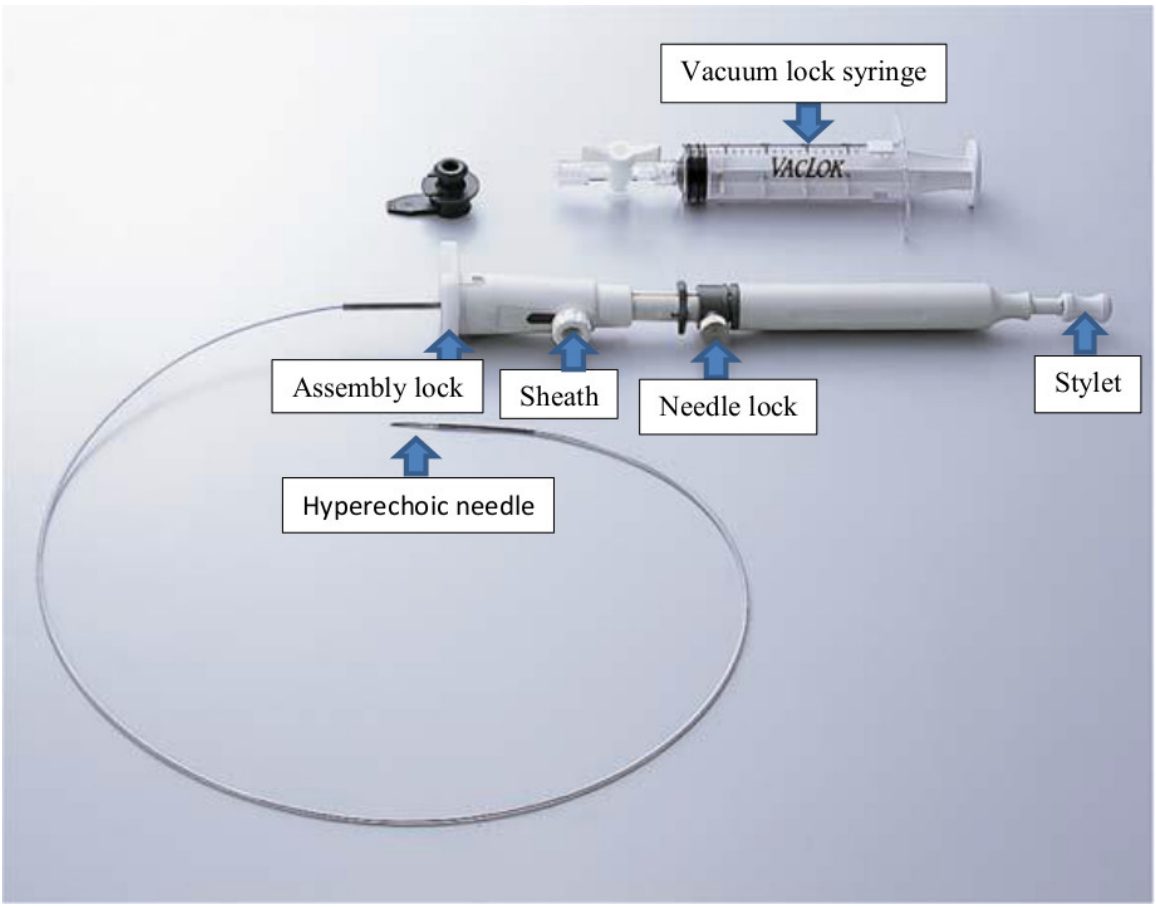

Figure 3: Needle assembly for Endobronchial Ultrasound-guided Transbronchial Needle Biopsy.

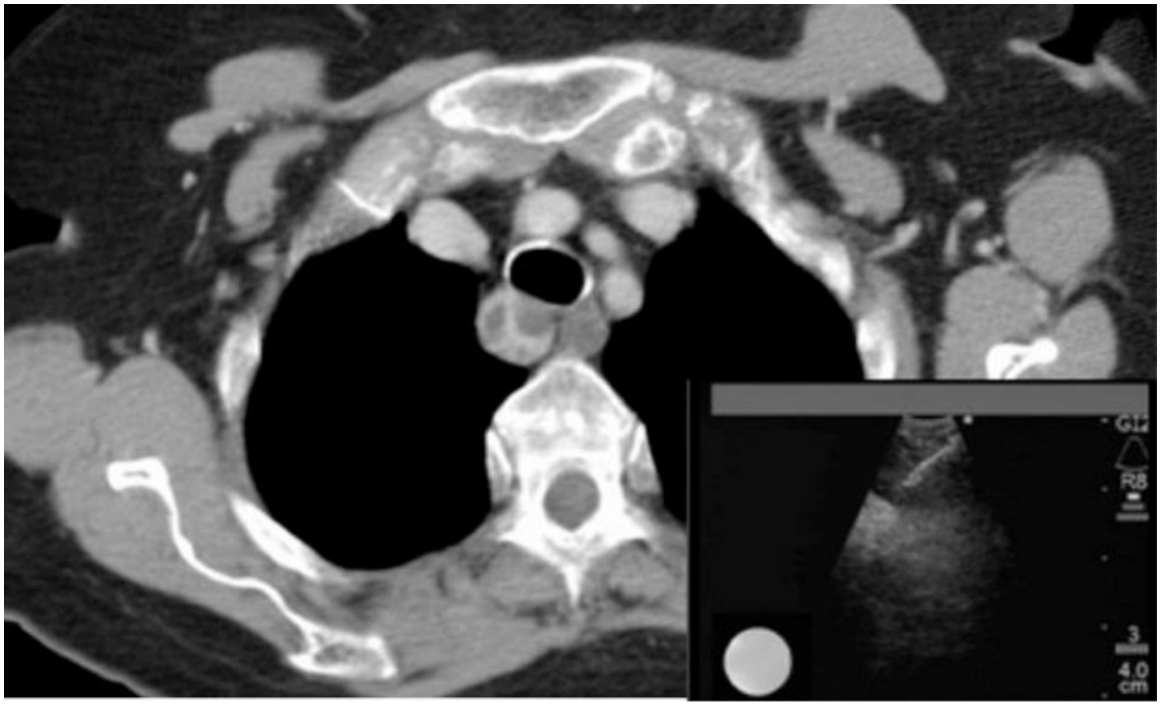

Figure 4: CT image and endobronchial ultrasonography with transbronchial needle aspiration. Reproduced with permission from the American College of Chest Physicians[16].

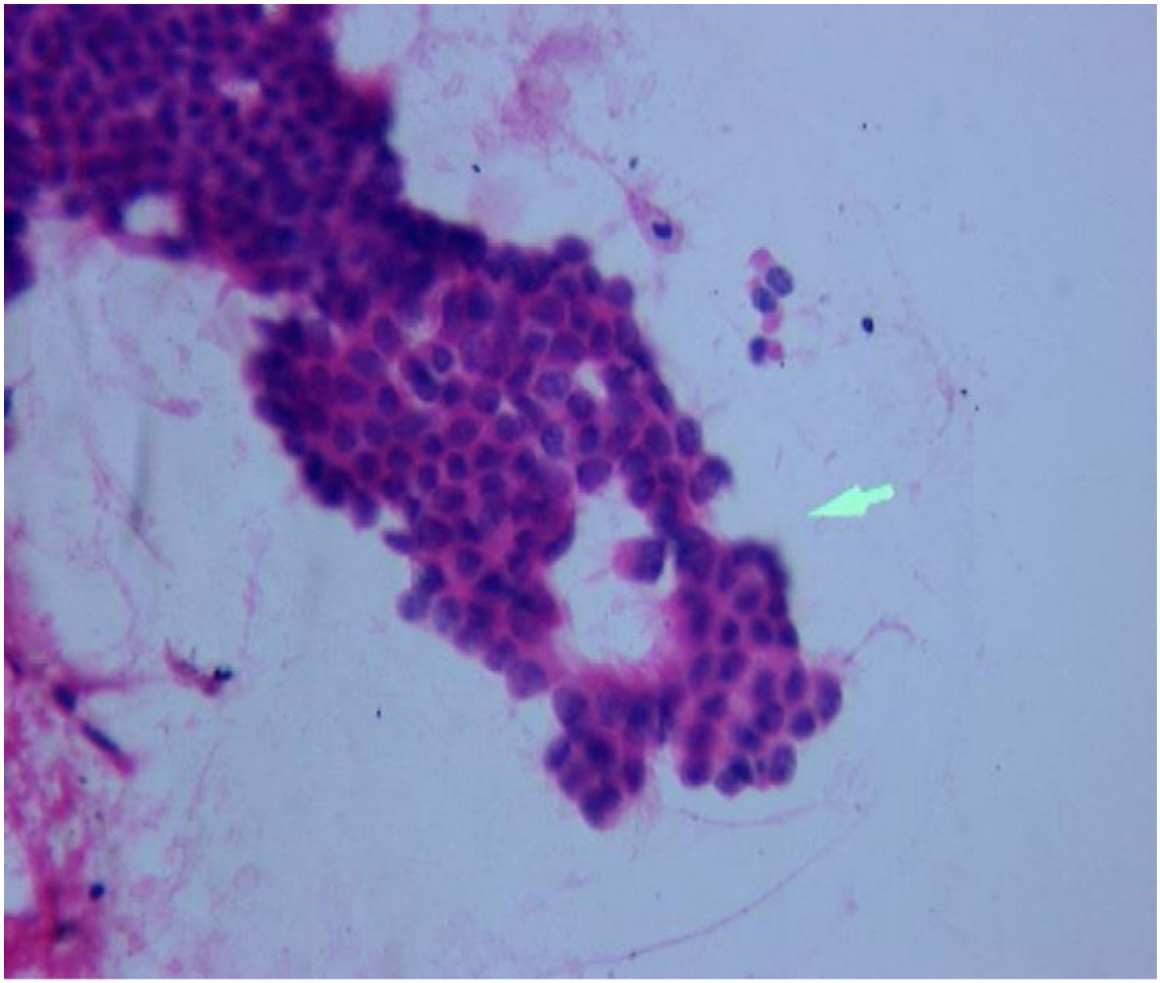

Figure 5: Benign follicular thyroid tissue (hematoxylin-eosin stain, magnification 10X) biopsied using EBUS-TBNA. Reproduced with permission from the American College of Chest Physicians[16].

Year	Author	Country	Final Diagnosis
2006	Rosario *et al.*[12]	Portugal	Papillary thyroid cancer
2009	Jeebun *et al.*[13]	United Kingdom	Benign multinodular goiter
2009	Chow *et al.*[14]	Japan	Papillary thyroid cancer
2009	Diaz *et al.*[15]	United States	Papillary thyroid cancer
2010	Chalhoub *et al.*[16]	United States	Colloid thyroid adenoma
2012	Chalhoub et al.[17]	United States	Colloid thyroid adenoma
2013	Roh *et al.*[18]	South Korea	Benign ectopic thyroid
2013	Florczak *et al.*	Poland	Papillary thyroid cancer

Table 1: The eight reported cases of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration biopsy of substernal thyroid lesions, arranged by the year of publication, the authors, the country of reporting, and the final pathological diagnosis.

Discussion

Substernal goiter was first described in 1749 by Haller[23]. The reported incidence of substernal or mediastinal goiter varies between 0.2% and 45% of all goiters, depending on the definition used[24]. More than ten definitions of substernal goiter have been proposed. By the simple clinical definition, a part of the substernal thyroid remains permanently retrosternal on physical exam without neck in hyperextension, as opposed to with neck in hyperextension as per Torre's definition[25]. Katlic's definition suggests that at least 50% of the gland by volume be retrosternal[26]. A broader definition where any thyromegaly with ≥2-3 cm (or 2-3 fingerbreadth) extension through the thoracic inlet below the clavicles is considered retrosternal has also been proposed[27]. Interestingly, intra-operative and postoperative complications rates did not differ when patients

were selected based on the various definitions, suggesting that many definitions were clinically irrelevant. A study by Rios *et al.*[24] leaned in favor of clinical definition (ease of use) and Kaltic's definition (predicting sternotomy for extirpation of goiter).

The malignant potential of substernal goiter is similar to that of cervical goiter[2,28-31]. There are no separate guidelines for work-up and management of substernal goiter[32-34]. Work-up for substernal thyroid nodule follows the same protocol as for the cervical thyroid nodules. The major challenge in diagnosis and treatment of substernal thyroid comes from its location, making it inaccessible for percutaneous needle biopsy due to the overlying bone. Without a formal diagnosis, both symptomatic and asymptomatic substernal thyroid go for surgery due to concerns for malignancy. Some patients are poor surgical candidates, and are managed conservatively without a formal diagnosis. A minimally invasive technique such as EBUS-TBNA can obtain real-time ultrasound-guided biopsy of mediastinal thyroid lesions, and has potential of preventing unnecessary surgeries, including for patients who would otherwise be high-risk surgical candidates.

There are no prospective studies describing the role of EBUS in TBNA of thyroid nodules. This review is based on the eight published cases (**Table 1**) describing the successful use of EBUS-TBNA for biopsy of substernal thyroid gland. Caution must be exercised since some thyroid nodules may be close to the vocal cords (risk of inadvertent injury) and the oral cavity (risk of infection). Also, thyroid tissue is devoid of the lymphoid component, and may be relatively vascular. As with every procedure, initial preparation is crucial to successfully obtaining good samples with EBUS-TBNA. Appropriate airway selection and level of anesthesia ensures more maneuverability and time during the procedure. Propofol and remifentanil infusions are commonly used for deep sedation and general anesthesia. Benzodiazepine (*e.g.*, midazolam) and opiates (*e.g.*, fentanyl) can be used intravenously for procedures performed under moderate sedation. Paralytics are only rarely needed. A detailed review of the anesthesia technique is beyond the scope of this article. Additional reading is highly recommended[21,35-37].

Laryngeal mask airway is preferred for lesions at or above lymph node station two. Pre-procedure surveillance white light bronchoscopy should be performed to rule out intraluminal lesions and obstruction. While performing EBUS, one must be mindful of the oblique angle of view of the EBUS bronchoscope, and keep the tip in "neutral" position when advancing. It is also important to keep the tip in "neutral" position while inserting the needle to avoid damage to the bronchoscope. At the end of the procedure, a repeat surveillance white light bronchoscopy should be performed to ensure hemostasis and airway patency by removing retained clots or tissue fragments. Onsite cytology availability to ensure sample adequacy is desired, but not mandatory.

Generally, the EBUS scope is easy to assemble to start the procedure. All bronchoscopy parts should be connected to software as recommended by the company's guidelines. It is extremely rare to encounter a software malfunction that requires system repair. Rebooting the EBUS system usually solves most problems related to software malfunction. If rebooting the system doesn't solve the problem, changing the EBUS scope is the next appropriate step. If the problem persists, the software system should be replaced if institutionally available.

During the EBUS procedure, the balloon of the EBUS scope should be inflated as needed to optimize the ultrasound image of the targeted lesion and to ensure bronchoscopic contact with the airway. Practice variation exists in that some proceduralists may not use the balloon when performing the biopsy. The inflation of the balloon is usually clearly visualized by the bronchoscopic view of the EBUS scope. If the EBUS image remains unclear, the balloon of the EBUS scope should be evaluated. In general, three technical balloon problems should be evaluated. First is the presence of air-bubbles when the balloon is inflated. This condition is usually solved by insuring the removal of the all air bubbles by inflating the balloon with more saline and allowing the air bubbles to wash out from the balloon tip. Second is the balloon leakage as a result of balloon tip dislodgement, which is easily fixed in place. Third is balloon leakage secondary to rupture, which requires balloon exchange. In some cases, the location of the targeted lesion precludes the bronchoscopic contact with the airway at this level despite balloon inflation and scope manipulation and thus, sampling these lesions with EBUS would not be possible.

Post-acquisition processing of the EBUS-TBNA sample varies depending on whether a rapid on-site evaluation (ROSE) cytopathology service is available. The aspirate is first carefully expelled on a slide using air-filled syringe, followed by replacing the stylet in the needle. The remaining cells are washed out into commercial methanol-water solution by injecting saline through the EBUS needle. The sampling is deemed adequate only when several tissue particles are available for cell-block, failing which more "passes" may be needed. Some of the tissue fragments from the first slide are smeared on two different slides. Using commercial Romanowsky stain, the air-dried slide is stained for on-site analysis. In our center, where ROSE is not available, the specimen is directly discharged into the Roswell Park Memorial Institute (RPMI) solution and sent to the lab for further processing. A detailed review of the sample processing is beyond the scope of this paper. We advise interested readers to refer to relevant reviews for more information[48-50].

EBUS-TBNA has some limitations as well. It is not possible to maintain sterility of the EBUS needle, and procedure-related infection after substernal thyroid biopsy has been reported[38]. Adequacy of samples compared to mediastinoscopy is another concern. This is somewhat offset by the availability of onsite cytology in many places. Although American College of Chest Physicians (ACCP) recommends 50 supervised interventional procedures for credentialing, questions have also been raised as to what is considered optimal level of competency to perform EBUS-TBNA independently[39-41]. Also, the competence to perform EUS-EBUS combined procedures is limited to a few tertiary care centers. With these limitations in mind, patients should be carefully selected on a case-to-case basis depending on the comfort level and experience of the proceduralist.

As physicians gain expertise in performing Endobronchial Ultrasound (EBUS), increasing number of non-lymph node specific applications are being attempted. Usefulness of EBUS for diagnosis of metastatic extrathoracic malignancies[42,43], assessment of preoperative tracheobronchial invasion[44], assessment of airway remodeling in asthma[45], and diagnosis of non-lymph node intrapulmonary and mediastinal lesions has been reported, to name a few. Recently, Yang *et al.* reported a sensitivity of 93.4%, specificity of 100%, and accuracy of 95.1% in their study examining the role of EBUS in diagnosis of non-lymph node thoracic lesions[46]. Given its proven safety and efficacy profile, we propose EBUS-TBNA as a suitable alternative to surgical biopsies of substernal thyroid gland in high-risk patients with substernal thyroid abnormality requiring a tissue diagnosis.

Disclosures

The authors have nothing to disclose.

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