Technical description of endoscopic ultrasonography with fine-needle aspiration for the staging of lung cancer

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\textbf{Summary} \textbf{Background:} Endoscopic ultrasonography (EUS) is a novel method for staging of the mediastinum in lung cancer patients. The recent development of linear scanners enables safe and accurate fine-needle aspiration (FNA) of mediastinal and upper abdominal structures under real-time ultrasound guidance. However, various methods and equipment for mediastinal EUS–FNA are being used throughout the world, and a detailed description of the procedures is lacking. A thorough description of linear EUS–FNA is needed.

\textbf{Methods:} A step-by-step description of the linear EUS–FNA procedure as performed in our hospital will be provided. Ultrasonographic landmarks will be shown on images. The procedure will be related to published literature, with a systematic literature search.

\textbf{Results:} EUS–FNA is an outpatient procedure under conscious sedation. The typical linear EUS–FNA procedure starts with examination of the retroperitoneal area. After this, systematic scanning of the mediastinum is performed at intervals of 1–2 cm. Abnormalities are noted, and FNA of the abnormalities can be performed. Specimens are assessed for cellularity on-site. The entire procedure takes 45–60 min.

\textbf{Conclusions:} EUS–FNA is minimally invasive, accurate, and fast. Anatomical areas can be reached that are inaccessible for cervical mediastinoscopy. EUS–FNA is useful for the staging of lung cancer or the assessment and diagnosis of abnormalities in the posterior mediastinum.

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\begin{itemize}
\item \textbf{KEYWORDS} \textsuperscript{\textcopyright} \textsuperscript{\textcopyright} \textsuperscript{\textcopyright} \textsuperscript{\textcopyright} \textsuperscript{\textcopyright} Lung neoplasms; Neoplasm staging; Endoscopy; Ultrasonography; Fine-needle aspiration; Mediastinum; Retroperitoneal space
\end{itemize}
Introduction

Endoscopic ultrasonography (EUS) is a novel method for the investigation of the surroundings of the esophagus and stomach. It is an evolving technique for the staging of the mediastinum in lung cancer patients. EUS can be combined with fine-needle aspiration (FNA) to obtain cytological specimens under direct ultrasound vision. EUS was first performed with radial scanning endoscopes, scanning 360° transaxially from the esophagus to view the mediastinum. The development of linear scanners enabled safe and accurate FNA because needle insertion into a lymph node was real-time visible. EUS–FNA has shown to be highly accurate in the diagnosis and staging of masses and lymph nodes related to the gastrointestinal tract.1,2 Mediastinal lymph node imaging in lung cancer with EUS was first described in 1988, while EUS–FNA of mediastinal lymph nodes was first reported in 1993.3,4 Operating characteristics of EUS–FNA for mediastinal lung cancer staging seem promising and highly accurate.5–7 However, various methods and equipment were used for mediastinal EUS–FNA, while only few investigators described their EUS–FNA procedure in detail. A more systematic description of the procedure may be useful for standardization, research, and teaching purposes. We will systematically describe the EUS–FNA procedure as performed in our hospital and relate it with literature. We will provide images of the major ultrasonographic landmarks for the mediastinum.

Methods

A step-by-step description of the EUS–FNA procedure as performed in our hospital will be provided. Ultrasonographic landmarks will be shown on images. The procedure will be related to published literature. We searched literature with PubMed for original, peer-reviewed, full-length original articles and meta-analyses in English. We used the following search terms: [lung AND cancer AND staging] and [endoscop*], [ultraso*], [biopsy], or [punct*]. Further exploration of literature was guided by the reference lists in the articles found with these searches.

Results

Equipment

The EUS–FNA procedure for staging of lung cancer will be described step-by-step, from high retroperitoneal area to the upper mediastinum. The locations of mediastinal lymph nodes are described according to the mediastinal lymph node map of Naruke, revised by Mountain and Dresler.8 A linear ultrasound endoscope (FG-34UX, Pentax GmbH, Hamburg, Germany) and a scanner unit (EUB-525, Hitachi Ultrasound BV, Reeuwijk, The Netherlands) are used. The endoscope has a 60° forward oblique viewing video camera, a 120° scanning ultrasound transducer with a 105° field of view, and a 2.0 mm working channel. The tip can be deflected 60° to the left and 60° to the right, 65° upwards, and 65° downwards. A water-filled balloon may be put around the tip to decrease ultrasound disturbance by air. However, in our experience omission of the balloon does not result in much more scattering, and pressing the tip of the endoscope against the mucosal surface gives adequate images. Therefore, the balloon is not used anymore. Scanning frequency is switchable between 5 and 7.5 MHz, and Doppler flow imaging can be used to detect blood vessels. FNA is performed with a hollow 22 gauge needle with a stylet (Echotip®; Wilson-Cook Medical Inc., Winston-Salem, USA), but other needles can be used as well.

Linear scanning endoscopes produce images with vertical orientation (Fig. 1). On the screen the esophagus is the rotation axis, positioned at the top of the image, while the bottom of the image reflects the area most peripheral of the esophagus. The right side of the ultrasound image is cranial and the left side caudal, although this can be adjusted.

On ultrasound images, hypoechoic structures are darker than the surrounding tissue, and hyper-echoic structures are lighter than their surroundings. Fluids such as pleural effusion and blood are extremely hypoechoic (black). The ultrasonographic appearance of lymph nodes may give a

![Figure 1 Orientation of the EUS image.](image-url)
suggestion of malignancy. Lymph nodes are suspicious for malignancy when they have a hypoechoic structure, sharp edges, and a round shape (Fig. 2A).9–11 Benign lymph nodes are hyperechoic (representing fat) sometimes with central calcification (indicating old granulomatous disease), with unclear edges and a long, narrow, draped, or triangular shape (Fig. 2B).10 The adrenal gland is adjacent to the kidney, and it normally has an iso- or hypoechoic appearance, with a triangular, elliptical, or “seagull” shape, not exceeding 3 cm in length (Fig. 3A).12,13 A suspicious adrenal gland is larger than 3 cm and will lose its particular shape, becoming round and more hypoechoic (Fig. 3B).

**Endoscopic ultrasound imaging**

Before the procedure, all equipment is installed. When a balloon is used, it should be checked whether the balloon is water-filled and free of air. For the largest overview, the scanner unit is tuned to 5 MHz and at a minimum of image zoom. For detailed images, the scanner unit should be switched to 7.5 MHz to enhance resolution.

The procedure is typically performed in an outpatient setting after at least 5 h of fasting. Five ml of lidocaine-HCl 20 mg/ml oral gel is administered orally for local pharyngeal anesthesia. Midazolam 2–5 mg is administered intravenously for conscious sedation, except for those patients who are prone to suffer ventilatory depression. The patient is monitored continuously on oxygen saturation and pulse. The patient is placed in left lateral decubitus position. After deflecting the tip of the endoscope 70–80° vertically by turning the larger button counterclockwise, the endoscope is introduced in the oropharynx by placing the ultrasound tip on the back of the tongue. Tension on the larger button is then released, and the endoscope is inserted into the esophagus while the patient is swallowing. The endoscope is advanced into the stomach. The lower esophageal sphincter is located approximately 45–55 cm from the incisors. Inside the stomach, the balloon may be filled...
with water. With a counterclockwise turn of the larger button, the ultrasound tip will be pressed against the gastric wall. With axial rotating movements the abdominal aorta can be looked for, projecting as a hypoechoic band. Using the aorta as a guide, the celiac trunk and the superior mesenteric artery will be imaged by slightly advancing or retracting the endoscope (Fig. 4). Enlarged lymph nodes may be observed cranial to the celiac trunk. Subsequently, the left kidney is imaged with a clockwise movement of the endoscope (Fig. 3). By gently retracting the endoscope, the left adrenal gland is exposed at the kidney’s top, and can be assessed for size, shape, and structure (Fig. 3). If abnormal, FNA is performed. Parts of the liver, spleen, and pancreas are observed by EUS–FNA as well. Spleen and liver have characteristic ultrasound appearances (Fig. 5). We only assess the ultrasonographically visible parts of the liver for lesions since EUS is inadequate for assessment of the entire liver for metastases. The right adrenal gland may be observed only if the endoscope is put through the pylorus. We only perform this procedure on indication. Right adrenal enlargement is often assessed with transabdominal ultrasonography.

After assessment of the left adrenal gland, the endoscope is retracted until its ultrasound device lies in the distal esophagus, which can be observed via the luminal video camera and the ultrasonographic view of the beating heart. When used and inflated, it may be necessary to deflate the balloon before retracting the endoscope into the esophagus. Behind the heart, possible lymph nodes at Naruke level 9 are looked for by rotating the endoscope 180° up to the aorta, both clockwise and counterclockwise. The diaphragm will be observed as a hyperechoic band below the heart.

The endoscope is retracted in steps of 1–2 cm, and after each step a 360° view is performed, until the pulmonary arteries come into view. Lymph nodes adjacent to the esophageal wall above Naruke level 9, adjacent to the atria of the heart, are classified as Naruke level 8. Naruke level 7 (subcarinal) lymph nodes are typically located on top of the left cardiac atrium, close to the right pulmonary artery (Fig. 2). Especially the posterior part of Naruke level 7, which is difficult to assess with mediastinoscopy, can easily be viewed and punctured for aspiration cytology. Parts of the heart (such as the aortic and pulmonary roots, and the aortic and mitral valves) can be viewed in detail.

With a 360° movement both hila can be imaged. Scattering occurs due to air in the trachea or main bronchi. With slight counterclockwise movement, the left pulmonary artery can be followed towards the left hilum. After a 2–3 cm retraction, the left tracheobronchial angle (Naruke level 4-left) and

Figure 4 Image of the celiac trunk (C) on EUS, above the superior mesenteric artery (M) and anterior to the abdominal aorta (AO), which is used for orientation when approaching retroperitoneal lymph nodes.
the aortopulmonary window (Naruke level 5) come into view (Fig. 6). Naruke level 4-left is located immediately adjacent to the esophagus, while Naruke level 5 projects more peripherally under the aorta. Para-aortic lymph nodes (Naruke level 6) can sometimes be seen in this view, located on the outer side of the aortic arch (Fig. 6). This makes FNA of Naruke level 6 from the esophagus often difficult or even impossible. Rotating the endoscope 180° clockwise and counterclockwise, the rest of the mediastinum is assessed, including the right tracheobronchial angle (Naruke level 4-right). To view around the air-filled trachea, it will be necessary to bend the endoscope’s tip with both the larger and smaller buttons in 2 dimensions. Nonetheless, right-sided abnormalities are difficult to image due to scatter from the air-filled trachea. After this, the endoscope is rotated back to the aortopulmonary window. With the aortic arch in view, the endoscope is retracted until the area above the aortic arch can be imaged. In this area, the upper paratracheal lymph nodes (Naruke level 2-left) are located. After a 180° rotation, the right paratracheal lymph nodes (Naruke level 2-right) can occasionally be viewed.

At these upper lymph node levels, the patient is likely to feel uncomfortable because of regurgitation or coughing reflex. This makes imaging followed by FNA of the paratracheal lymph nodes difficult. Imaging of the upper mediastinal and pretracheal lymph nodes (Naruke levels 1 and 3) from the esophagus is not possible under conscious sedation; cervical mediastinoscopy is more appropriate for these lymph node levels.

After assessment of lymph node levels, a decision should be made to perform FNA on particular lymph nodes (see below). Apart from enlarged or otherwise abnormal lymph nodes, direct ingrowth of tumor into mediastinal structures such as the aorta or the pulmonary artery can sometimes be seen, and discrimination between T3 and T4 status is possible.

After all observations and fine-needle aspirations have been performed, the balloon is deflated completely, and the endoscope is removed. The patient is transferred to the recovery room to recover from sedation, and is discharged after approximately 1 h. The patient may eat and drink approximately 2 h after administration of the pharyngeal anesthesia. Mean duration of the procedure (including FNA) is approximately 45–60 min.

Fine-needle aspiration

A lymph node or tumor is selected for FNA on the basis of its malignant appearance and the feasibility of FNA in relation to surrounding vital structures. It may be important to puncture normal lymph nodes around abnormal structures to assess the stage of disease or even the resectability of a very proximal located tumor. It is recommended to puncture at least abnormalities on each level that may alter clinical tumor stage.

For FNA, the needle with stylet is introduced into the working channel of the endoscope. For the last few centimeters of the introduction, tension is released from the endoscope buttons to prevent laceration of the inner lining of the working channel. Tension on the buttons can be re-adjusted after the needle has been introduced completely. After the optimal puncture site has been identified, the distance from the needle exit to the lymph node center is measured on screen, and the needle stopper on the needle shaft is set to this distance. The needle is then introduced into the mediastinum. After slight retraction of the stylet, the lymph node is punctured (Fig. 6). The stylet is now completely removed, and suction is applied with a 10-cc syringe. After 15–20 up-and-down movements of the needle inside the lymph node observed real-time on the monitor, the syringe is closed and the needle is retracted and removed from the endoscope. The specimen is put on a glass slide, stained with a modified Giemsa method, and evaluated on its cellularity by an attending cytotechnician. If the yield is inadequate, additional punctures can be performed. In case of too many erythrocytes in the specimen, the next puncture may be performed without suction.
Discussion

EUS is performed with radial or linear scanning ultrasound endoscopes. Radial scanning endoscopes produce transaxial CT-like images, which can be interpreted more easily. The more recently developed linear scanning endoscopes produce sagittal images, making anatomical interpretation somewhat more difficult. However, linear FNA is safer and more accurate than radial FNA because the needle is visible during the entire procedure. As described, a balloon is placed around the ultrasound tip, but the EUS–FNA procedure may also be performed without a balloon. The tip is then pushed against the esophageal or gastric wall. In our experience, this does not influence the sensitivity of the procedure.

Various needle types and sizes are in use, but no significant differences in accuracy have been reported in a study with four brands of needles. Suction can be applied with a syringe of 10, 20, or 30 ml. Cellularity and quality of the FNA specimen seems to be better with a 10 ml syringe than with one of 20 or 30 ml. On the other hand, without suction less blood will be aspirated, and this seems favorable when an earlier puncture contained too many erythrocytes.

Key question is which lymph nodes have to be aspirated, and which not. Using ultrasound appearance properties as outlined above, some investigators have reached accuracies of 0.72–0.96, with a large range in sensitivities and specificities. It is clear that large lymph nodes may be benign and contain inflammatory cells, while small lymph nodes may be affected by micrometastasis. It is therefore necessary to perform FNA on each observed lymph node that may alter clinical tumor stage, starting with the lymph node most distant to the primary lung abnormality. A new needle should be used for every lymph node station. Debate is ongoing about whether an on-site cytopathologist is necessary for adequate FNA specimen assessment. A trained cytotecnician is present at our EUS–FNA procedures, to indicate whether cellularity of the specimen is adequate. In our opinion, this prevents unnecessary additional punctions or too early termination with inconclusive results. Full cytological assessment is performed by a cytopathologist afterwards.

Not all mediastinal lymph nodes can be imaged with EUS, due to air in the larger airways. Lymph nodes at Naruke levels 1, 2-right, 3, and 4-right are generally difficult to assess. However, in our experience apparently enlarged lymph nodes on these levels may be visible and may be punctured as well. Smaller lymph nodes on these levels may better be assessed with cervical mediastinoscopy. The left adrenal gland can usually be evaluated adequately. However, the right adrenal gland can only be imaged with EUS by crossing the pylorus. This is unpleasant for the patient and the right adrenal gland is also much more difficult to evaluate due to its location.

With more than 150 EUS–FNA procedures performed, we did not encounter EUS–FNA-related morbidity or mortality. In a prospective study on EUS–FNA associated side-effects including 842 mediastinal EUS–FNA procedures, 4 minor complications (infection, hemorrhage, inexplicable transient hypotension) were reported. Contraindications for EUS–FNA include increased bleeding tendency and Zenker’s diverticulum. FNA should not be performed on cystic lesions, because of risk of infection. It seems wise to administer prophylactic antibiotics in patients with implants or generally increased infection risks.

In conclusion, we described the EUS–FNA procedure for the mediastinal and retroperitoneal staging of lung cancer, with landmarks for adequate orientation. With EUS–FNA, anatomical areas can be reached that are inaccessible for cervical mediastinoscopy. This makes EUS–FNA very convenient for the staging of lung cancer or the assessment and diagnosis of any abnormality in the posterior mediastinum. It offers great opportunities for endoscopists such as pulmonary physicians.

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References