Brief Overview about Different Modalities of Pleural Biopsy For Undiagnosed Exudative Pleural Effusion

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Conflict of interest: None declared
Funding: No funding sources

Abstract

Background: In many cases of exudative pleural effusion, the results were not conclusive even after (repeated) thoracocentesis; that mostly need confirmatory pleural tissue biopsy. Pleural biopsy is indicated to define the etiology of pleural diseases; the biopsy obtaining techniques are variable starting from the older ones such as blind pleural biopsy reaching the newer techniques such as image guided pleural biopsy and thoracoscopy guided pleural biopsy.

Keywords: Exudative Undiagnosed pleural effusion, Pleural biopsy.

Tob Regul Sci. ™ 2023 ;9(1): 6234-6248
DOI : doi.org/10.18001/TRS.9.1.435

Introduction

Exudative pleural effusions result from local or systemic diseases that directly injure the pleural surface. Although a wide variety of processes can result in exudative pleural effusions, the two main etiologic categories are inflammatory and neoplastic disease.[1]

The pleural fluid cytology will be positive on the first specimen submitted in >50% of patients with pleural malignancy. Almost all adenocarcinomas will be diagnosed with cytology. Cytology may assist the diagnosis of several nonmalignant conditions e.g., esophageal rupture by detection of oral squamous cells or meat fragments (striated muscle) in pleural fluid.[2]

- **Indications for pleural biopsy.**[3]
    1. Malignancy: mesothelioma, metastasis of lung/extra respiratory tumors, lymphoma, leukemia (specific tumoral cells).
    2. Pleural TB (specific caseating granuloma, Ziehl-Neelsen positive acid-fast bacilli – Koch bacilli) or mycobacteriosis due to atypical mycobacteria.
    3. Systemic lupus erythematous (direct immunofluorescence staining positive – IgG, C3).

4. Sarcoidosis (non-necrotizing epithelioid granuloma).
5. Pleural plaques/pachipleuritis (hyaline fibrous tissue).
6. Asbestosis (ferruginous bodies and marked fibrosis at hematoxylin and eosin stain).

- **Contraindication of the pleural biopsy.**[4]

Lack of patient's agreement and uncooperative patients, intractable cough, uncorrectable bleeding disorders, anticoagulant treatment, respiratory failure, cutaneous lesions (Herpes Zoster, pyoderma), a dry tap (the absence of the pleural fluid determines the risk for pneumothorax) and Severe hepatic or renal failure.

Types of pleural biopsies:

- **1-Closed-Needle Pleural Biopsy (CPB)**

Copes and Abrams's needles were the most popular CPB needles after practical modification.[5]

Diagnostic yield: Needle biopsy of parietal pleural is more valuable in patients with suspected tuberculous effusion than in those with malignant effusion.[6] Using the Abrams needle, pleural biopsy yielded the diagnosis of tuberculosis and malignancy in 90.9% and 63.2% of cases.[7]

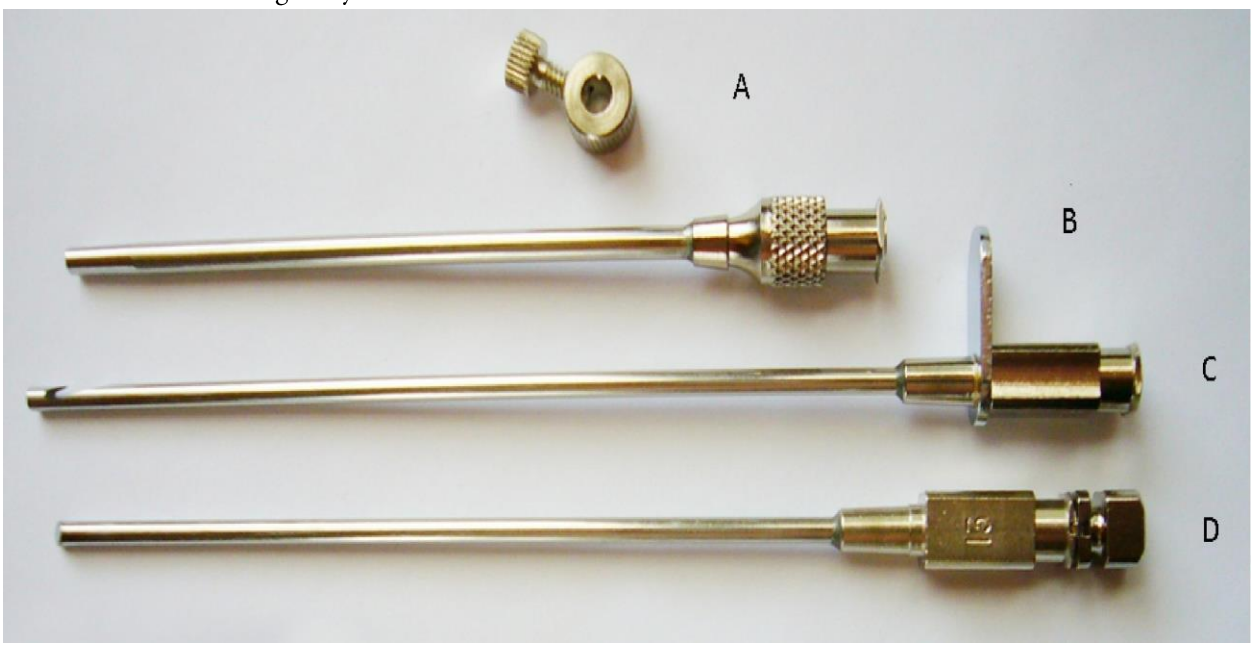

Figure (1): The Cope needle contains an outer needle 11G (B) with an adjustable needle stop (A). The inner 13G biopsy trocar (C) has a hook shape for pleural biopsy sample collection. The inner needle (D) has a fitted stylet.[8]

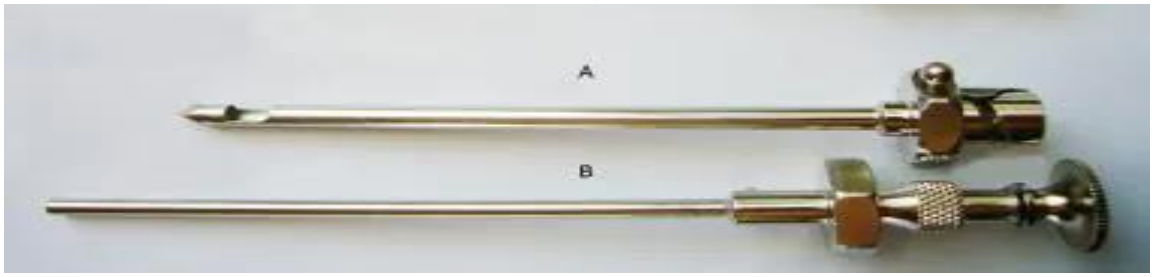

Figure (2): Abrams needle (A) outer cannula with trocar point and cutting window, which can be closed with a turning action of the inner tube (B) inner stylet.[8]

- ✓ **Procedure Cope needle pleural biopsy.**[9]

The patient is positioned, and the biopsy site is selected after careful physical examination and review of imaging. Under aseptic measures, lidocaine is injected locally to anesthetize the selected site. A small skin nick is made with a scalpel blade. The Cope needle with stylet is introduced through the skin incision at the upper surface of the rib to prevent neurovascular bundle damage. The needle is advanced until pleural fluid is obtained. The stylet is then removed, and the biopsy trocar introduced. A 50-mL syringe is attached with a biopsy needle, which provides a closed system through which pleural fluid may be withdrawn, confirming the location of the biopsy needle in the pleural space.

The biopsy needle is turned, with the right-angled projection facing downward. Both the outer cannula and the biopsy trocar are partially withdrawn until the parietal pleura is engaged. Gentle traction is applied to the biopsy trocar with one hand, and the outer cannula is advanced with a rotary motion. The biopsy needle is removed, during which the patient is instructed to make an "EEEEE" sound to minimize the risk of air entry. The biopsy specimen is collected with the attached syringe applying positive pressure.

- ➢ **The Abrams pleural biopsy needle** consists of 3 parts, with 2 concentric tubes and a stylet. The outer tube has a trocar point and a deep notch behind the trocar point that can be closed with inner tube rotary movement, allowing cutting of the pleural tissue. The general technique for pleural biopsy with the Abrams needle is like that described for the Cope needle.[10]

- ✓ **Complications and precautions**

Include chest pain, subcutaneous emphysema, pneumomediastinum, vasovagal reactions, and hemothorax. Chest radiography is recommended to exclude postprocedural complications, including hydropneumothorax. The incidence of pneumothorax with closed needle biopsy is approximately 8%-18%. Injury to adjacent organs during pleural biopsy, including liver, kidney, and spleen, is rare.[11] The coagulation profile should be corrected prior to any biopsy procedure to minimize the risk of bleeding, including chest wall hematoma and hemothorax. Percutaneous introduction of needles through areas of pyoderma, herpes zoster, or cutaneous infiltration with neoplasm is contraindicated. Finally, patients with uncontrollable cough should also be avoided.[12]

2-Image-Guided Pleural Biopsy

Ultrasonography is more sensitive in detecting loculated pleural effusions than CT scanning. It also has the advantage of providing a real-time approach to biopsy without radiation. CT guidance allows better visualization of the extent of focal pleural masses, in addition to a clearer delineation of parenchymal pathology. Contrast-enhanced CT scanning with "pleural phase" imaging can also highlight areas of pleural involvement and nodularity to aid in biopsy site selection.[13]

- ➢ **Procedure.**[14]

In plane ultrasound guiding method: the probe is placed above the lesion and the needle is inserted from the lateral end of the probe. This method has the advantage of showing the tip of the needle all the time of the insertion, but requires good probe - needle synchronization, so that the needle stays in the scanning plane. Probe - needle synchronization can be helped by a special needle attachment which can keep the needle in the scanning plane.

Out of plane ultrasound guiding method: the probe is also placed above the lesion, but the needle is inserted at the middle of the probe from out of scanning plane, in the direction of the lesion. This method does not require probe - needle synchronization but does only visualizes the tip of the needle when reaching the lesion. For both methods, color Doppler can be used to show the tip of the needle.

During the procedure the needle is seen as a whitish spot in the "black" anechoic image of the fluid. Aspiration biopsy will be performed by attaching a syringe to the needle holder or attaching an aspirator. 4-6 specimens are required for a satisfactory result of the examination.[15]

The needle has two parts: The outer guide has a sharp cutting edge in the front. The depth of the pleura is assessed as the point at which fluid is aspirated when the needle is advanced into the pleural space. The inner needle (18 G) with a cutting sheath that shaves off the tissue specimen; an 18 mm-long "specimen tray", which will collect the tissue, and a 5 mm-long "stylet" tip.[16]

After the biopsy and finishing of the procedure the availability of ultrasound at the time of the procedure allows for immediate checks on possible complications. The area should be scanned while the probe is still sterile. Any pneumothorax or bleeding is observed and should be treated as required. The patient is observed for 1-2 hours and then discharged.[17]

- **Advantages of ultrasound-guided pleural biopsies USPB**

Ultrasound guidance increases the yield of positive biopsies and decreases the risk of complication. TUS can identify even small pleural nodules and allow their targeted biopsy. USPB has increased the yield of diagnostic from 60% to 77% in malignant pleurisy, and over 87% for all pleural pathologies.[18] Ultrasonography-guided procedures are 50% shorter time (average duration, 17 minutes) and performed more often in patients with increased comorbidities, cost less, and avoid the need for ionizing radiation.[19]

Complications: Include pain, Vaso-vagal reactions, hematomas and hemothorax. Several studies have shown that the USPB technique may significantly increase the yield of diagnosis while decreasing the risk for complications (about 4%).[20]

3-Medical Thoracoscopy

Thoracoscopy is a minimally invasive procedure that allows visualization of the pleural space and intrathoracic structures. It enables the taking of pleural biopsies under direct vision, therapeutic drainage of effusions and pleurodesis in one sitting.[21]

Table (1): Absolute and relative contraindications to performing medical thoracoscopy:[22]

Absolute contraindications	**Relative contraindications**
• Circumferentially adherent pleurae • Uncorrectable coagulopathy • Intractable cough • Significant hypercapnia (PCO2 >60 mmHg) • Limited cardiopulmonary reserve to tolerate pneumothorax.	• Myocardial infarction or stroke within 6 weeks • Coagulopathy (platelet count <50,000, INR >2) • Obstructing central airway tumors • Hypoxemia (PO2 <50 mmHg on ambient air) • Lack of multidisciplinary collaboration with thoracic surgeons, anesthesiologists, and trained nursing staff • Inability to tolerate lateral decubitus positioning. • Morbid obesity

- **Equipment for Medical Thoracoscopy**

One or Two Ports of Entry for Medical Thoracoscopy?

Though several entries are needed for VATS, however single entry is preferred for diagnosis and treatment of pleural effusions (talc poudrage) in medical thoracoscopy.[23]

Two ports must be created when:

- The thoracoscope has no working channel available.
- Electrocautery must be used, whenever a hardly accessible area of the pleural cavity needs to be explored, and
- Very small telescopes are used (for pediatric patients or other selected cases).

The second point of entry is usually located one intercostal space superior or inferior to the main entry and close to it, to manipulate the instruments easily under visual control.[24]

- **Steps**

I. The one-entry technique is easy to perform under local anesthesia by local infiltration of 2% lidocaine, but some premedication (midazolam/ hydrocodone or others) should be routinely administered.

II. Thoracoscopy is usually carried out in the lateral decubitus position with the hemithorax to be studied facing upwards. Insertion of the cannula in the lateral thoracic region between the mid- and anterior axillary lines in the sixth or seventh intercostal space is preferred.

III. After introducing the trocar, the pleural effusion – if present – should be removed as completely as possible. This can be done without risk because, by using a suction tube which does not completely occlude the cannula; air rapidly enters the pleural space to provide pressure equilibration.

IV. After removing the effusion, the thoracoscope is introduced and the entire cavity inspected. In the case of a pleural effusion; biopsies are taken from several suspicious areas, including the anterior and posterior chest wall and the diaphragm. Biopsies are taken for histologic evaluation and if suspicious, for tuberculosis culture.

Following thoracoscopy, a chest tube should be introduced and connected to a suction system. Suction should be applied carefully; especially in cases of trapped lung, long-standing effusion, or pneumothorax; to avoid re-expansion pulmonary edema or creation of a fistula.[25]

- **Rigid thoracoscopy**

A rigid thoracoscopy set includes a telescope, light source, trocar, and forceps. The conventional stainless steel rigid telescope is 27–31 cm in length with a diameter of 7–12 mm, the larger ones (10–12 mm) often being favored by surgeons. Rigid telescopes have different angles of vision permitting straight-on (0°) or oblique (30° or 50°) viewing. Trocars are made from single-use disposable plastic or stainless steel with a variable diameter of 5–13 mm.[26]

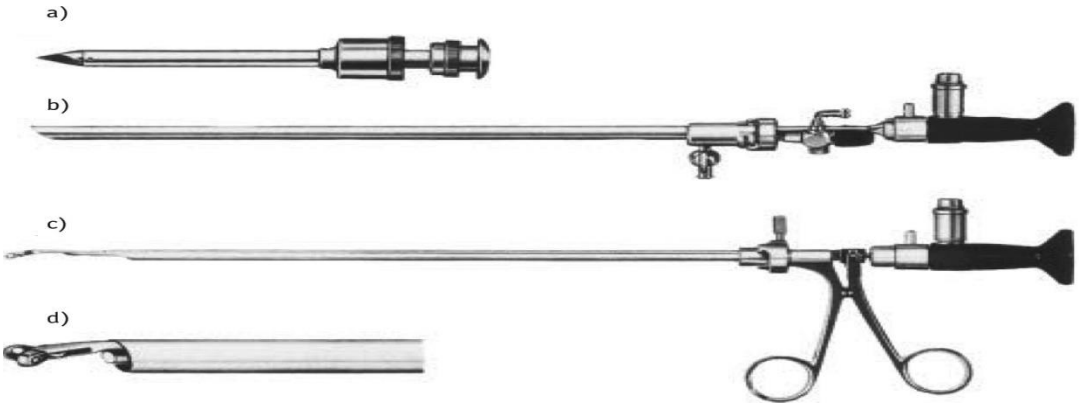

Figure (3): Thoracoscopy instruments (Storz Company): (a)trocar and cannula; (b) single-entry thoracoscope for adults (c) biopsy forceps with straight optics, which fit through the thoracoscope shaft; (d) forceps in the thoracoscope shaft ready for biopsy.[27]

- **Disadvantages**
  - The rigid thoracoscope must pass in a straight line and has limited maneuverability.
  - The operator inevitably must angle the scope by levering it against the underlying rib. The pressure and angling of the rigid instrument over the periosteum are believed to cause pain.[28]

➢ **Semi-rigid thoracoscopy**

Semi-rigid thoracoscopy (Olympus LTF 160 or 240) has a 22 cm proximal rigid shaft and 5 cm flexible distal tip with an outer diameter of 7 mm. The flexible tip allows two-way angulations (160° up and 130° down). The handle of the flexi-rigid thoracoscopy is like that of a flexible bronchoscope complete with a 2.8 mm working channel, lever, and suction port. The scope utilizes a custom-made plastic trocar of 8 mm diameter.[29]

- For visualization and illumination, the flexi-rigid thoracoscopy can be connected to the existing endoscopic processors (Olympus CV-160 and CLV-U40) and light sources (CV-240, EVIS-100 or 140, and EVIS EXERA-145 or 160). The image quality is significantly better with the flexi-rigid thoracoscopy.[30]

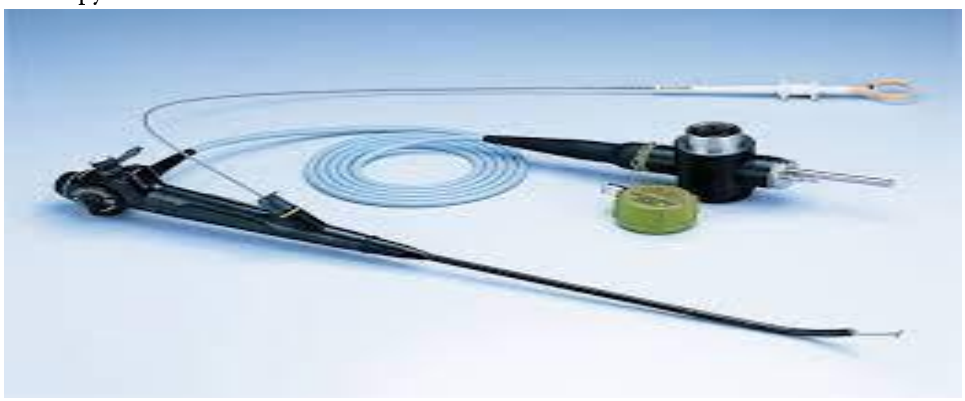

Figure (4): The semirigid thoracoscopy (Olympus Corporation).[31]

- Indication: The major clinical utility is thoracoscopic pleural biopsy and pleurodesis.[32]
- Contraindication: Lack of pleural space due to adhesions, uncontrolled cough, inadequate lung function parameters, uncorrectable bleeding tendency, and severe heart failure.[33]
- Disadvantages

- The disadvantage of the flexi-rigid scope is the small working channel which can limit adequate biopsies. The cusps diameter of the flexible biopsy forceps (FB-55CR-1) used with the flexi-rigid scope is 2.4 mm; considerably smaller than that of the optical rigid biopsy forceps (5 mm) used with rigid thoracoscopes.[34]

➢ **Mini thoracoscopy**

- It is an endoscopy using small instruments with a diameter from 2 mm up to 5 mm. The instruments comprise two metal 3.8 mm trocars with a pointed stylet, a 3.3 mm optic which is 25 cm in length and a 3 mm rotating biopsy forceps (available in different shapes). In addition, 3 mm scissors, needles and small rigid catheters for aspiration are available. All instruments are multi-use and autoclavable (121 °C per 15 min).[35]

Figure (5): Mini-thoracoscopy Richard Wolf GmbH Pforzheimer Strabe 32-75438 Knittlingen, Germany.[36]

- • **Indication** A small loculated effusion, evaluation for drainage of a loculated empyema, complete endoscopic examination of the pleural cavity and Pre-standard thoracoscopic evaluation in complex Cases.[37]

• **Contraindication**

- Absolute contraindications to the procedure are identical to those defined for standard thoracoscopy, particularly cardiac and respiratory insufficiency and coagulation disorders.
- Massive effusions should be avoided; especially those cases which require pleurodesis, as this necessitates a large caliber drain post-procedure.

• **Advantages**

The main advantage over the standard approach is the better tolerance of the patient to an instrument of 3.3 mm diameter compared to one of 7 mm. Sutures are not necessary, and the cosmetic result is excellent. The examination is easier to perform in patients with a small hemithorax or restricted intercostal space. The trocars can be moved more comfortably with less pain. It is also possible to examine small loculated effusions which are less accessible to the standard technique.[38]

- • **Disadvantages** Small size of biopsies, necessity of experience as in standard thoracoscopy and 20 % more time required.[39]

The main advantage of medical thoracoscopy compared with VATS is that the examination can be performed under local anesthesia or conscious sedation after adequate premedication, thus without the support of an anesthetist. Furthermore, medical thoracoscopy is also less expensive because it may be safely performed with non-disposable instruments and in an appropriate endoscopy room.[40]

➢ **4-Pleural Cryobiopsy**

Although use of an endoscopic cryoprobe was first described in 1966 by Kaplan and Kudish, cryo-technology as a diagnostic tool has only recently been getting attention in the world of bronchoscopy and medical thoracoscopy.[41]

The basic construction of a cryoprobe consists of an outer tube housing an inner cannula, which releases compressed CO2 or NO in the larger metallic tip of the probe. Following the Joule-Thomson concept, the resulting rapid expansion of the gas leads to rapid cooling at the hollow tip. The gas then egresses via the outer tube and is vented out, Via the working channel of the flexi-rigid thoracoscope, the cryoprobe can easily be guided to the target lesion.[42]

Once in opposition to the pleural lesion, it is typically activated for 3-6 s. The subsequent rapid cooling freezes the water in mucosal tissue to the probe tip creating a poly-crystalline solid that is then forcefully removed en bloc with the thoracoscope. This biopsy technique provides significantly larger (320 cu.mm vs 80 cu.mm) cryopreserved segments of tissue with stable architecture and adequacy for molecular testing.[43]

Biopsies obtained by cryoprobe compare favorably to biopsies obtained with the 5mm rigid optical cusp forceps. Additionally, the biopsy time may be shorter compared to flexible and rigid forceps biopsies, with a mean time of 4 minutes to obtain 3 pleural samples in one study. Several studies have reported a diagnostic yield with cryobiopsy in MT at least comparable to that of flexible forceps with a similar safety profile.[44]

Cryobiopsy diagnostic yield was comparable to flexible forceps (92.5% vs 91.3%) making it a viable tool that may reduce procedural time and number of biopsies needed in cases where flexible thoracoscopy approach is preferred to rigid.[45]

Cryobiopsy may also facilitate obtaining adequate specimens in thickened, fibrous pleura for the reasons mentioned above. This is especially true when mesothelioma is suspected. The pleura can often be thick and fibrous, and the diagnosis not only requires adequate sampling but deeper, full thickness biopsies to identify invasion. The cryoprobe has been shown to produce larger and deeper specimens than the flexible forceps.[46]

Electrocautery and Electrocoagulation

Another tool that has been developed to help circumvent the shortcomings of flexi-rigid thoracoscopy is the diathermic cutting knife. Sasada et al first described this technique in 2006. The insulated-tip (IT) diathermic knife (Olympus, Tokyo, Japan) was originally borrowed from gastric endoscopy and was designed to minimize the risk of intestinal wall perforation during biopsy. This approach involves a subpleural saline injection mixed with 0.5% lidocaine and 0.005% epinephrine at the site of interest resulting in an elevation of the pleural surface A puncture is then made with coagulation forceps and the IT knife is used to incise the pleura in a circular fashion with a combination of cutting and coagulating at a current of 30-40W. The isolated segments are then removed with forceps. They reported a diagnostic value of 85% for IT knife compared to 60% for forceps biopsy.[23]

Biopsy Guidance Techniques

The ability to improve the diagnostic yield while minimizing procedural time and risk of multiple and redundant biopsies. Autofluorescence is novel tool used to detect abnormal tissue not identified by traditional, white-light thoracoscopy.[23]

Inhaled aerosolized fluorescein was prior to induction and the pleura was inspected under a 300W xenon lamp in the violet-blue range.The use of IV autofluorescence in suspected pleural malignancy has also been shown to significantly improve visualization of pleural abnormalities and may help guide biopsy as well as provide accurate tumor staging.[47]

Infrared thoracoscopy is another technique used to differentiate normal, highly vascular tissue and abnormal, hypo vascular tissue in patients with spontaneous pneumothorax. Infrared guided lung resections were all demonstrated to have bullous disease by histopathology .[48]

Narrow band imaging (NBI) is another endoscopic visual aid that detects different wavelengths of color corresponding to peak oxyhemoglobin absorption. In practice, although NBI clearly demonstrates abnormal vasculature in pleural malignancy, it has not been shown to improve biopsy quality.[49]

Endomicroscopy is an exciting new application in various endoscopic procedures. Following IV administration of fluorescein, dye emissions allow for in vivo visualization of pleural cells (Cellvizio, Mauna Kea Technologies, Paris, France). The Alveoflex confocal laser endomicroscopy probe (pCLE) is used to provide biopsy guidance with microscopic accuracy.[50] The diagnostic yield of Alveoflex confocal laser endomicroscopy probe is 87% sensitivity and 99% specificity for malignant pleural effusion. [51]

Complications Of Medical Thoracoscopy[52]

Major complications include. Hemorrhage, Significant hypoventilation has been observed under sedation. The most serious complication of pneumothorax induction is air or gas embolism, which occurs very rarely (<0.1 percent), pulmonary re-expansion edema (rare) because immediate equilibration of pressures is provided, Empyema, Pneumonia. Tumor seeding along the procedure tract. Bronchopleural fistula causing postoperative pneumothorax or prolonged air leaks.

Minor complications include. Subcutaneous emphysema**,** Minor bleeding, Local wound infection, Hypotension during the procedure, Transient fever, Benign cardiac arrhythmias, low grade hypertension or hypoxemia, Delirium and Confusion due to sedation (midazolam).

The major concern of the procedure is pleural hemorrhage from underlying intercostal blood vessels. Immediate pressure using forceps and a small piece of gauze can be applied to control bleeding. If bleeding is significant, an additional incision should be considered to access the pleural cavity to perform tissue cauterization. If bleeding is not controlled with direct pressure and cauterization, ligation of the bleeding vessels with Endo clips should be considered. Ongoing bleeding may require thoracotomy.[53]

- **Video-Assisted Thoracic Surgery (VATS)**
  - It allows additional access to lung tissue and operative interventions, including lung biopsies, lobectomy, pericardial window placement, and empyema drainage. VATS is carried out by surgeons in an operating room under general anesthesia using single-lung ventilation with double-lumen endotracheal intubation.[54]

Figure (6): VATS three incisions are used, as shown, the thoracoscope most commonly is placed through the inferior incision, allowing other instruments to be placed through the two opposed incisions.[55]

- **Contraindications**[56]

Patients unable to tolerate lung isolation/dependence on bilateral ventilation.
Intraluminal airway mass (making double lumen tube placement difficult), Severe adhesions in the pleural cavity/pleural symphysis, Coagulopathy, Hemodynamic instability, Severe hypoxia, Severe COPD, Severe pulmonary hypertension.

- **Instruments**

- VATS is performed with rigid endoscopic equipment, high-resolution video camera, A light source (preferably high light output) and cable, Camera, Image processor, Monitors, Scissors, Hook, Trocar recording system.[57]

The standard VATS procedure involves using 3 to 4 incisions made in a triangular configuration for scope and instrument insertion. Alternatively, VATS with a single port has also been described.[58]

The patient is administered anesthesia in the supine position. A double-lumen endotracheal tube is the airway device of choice for most procedures. The position of the tube is confirmed with a fiberoptic bronchoscope via the lumen of the DLT. Care is taken to ensure adequate positioning of the cuff. The patient is positioned in the lateral decubitus position with the arm over the head. Arching of the table is done to allow adequate surgical exposure. The position of the DLT is then rechecked after final positioning for the procedure.[59]

Three incisions are made for the anterior approach. Together they form a triangular configuration with the utility incision at the apex of the triangle. The camera is inserted through this incision for the creation of other entry ports safely. A port is created to accommodate the camera in the auscultatory triangle. A third port is created in the mid-axillary line. This is created at the level of the utility port incision.[60]

After the creation of the 3 ports, assessment is done using the video thoracoscope. Further steps of the surgery are usually guided by the specific procedure to be performed. The pleural space is then inspected, and areas of interest are biopsied at multiple sites after a thorough inspection is completed. Biopsy samples can be collected with biopsy forceps or other endoscopic instruments. After completion of the biopsy, the camera is rotated between port sites to check for hemostasis. Depending on the surgery performed, 1 or 2 pleural drains, connected to an underwater seal drain are usually placed at the end of surgery.[61]

- **Postprocedural care**

Post-operative care depends on pain control, respiratory care, and chest tube management. Restrictive fluid therapy is also a crucial strategy for improving outcomes after surgery. Chest tubes are removed when air leaks have resolved, and drainage is at acceptable levels. Chest X- Ray is performed post-procedure and after removal of the chest tube to assess for pneumothorax.[62]

- **Limitations**

Several factors can limit this diagnostic intervention, including marked coagulopathy, an inability to obtain unilateral lung ventilation, or inability of the patient to tolerate the procedure because of hypoxemia. Adhesions represent a relative contraindication depending on their location and density.[63]

- **Complications**

The reported complications of VATS are like those seen with pleuroscopy, including mesothelioma tract metastasis.[64]

- **The advantages offered by VATS over conventional thoracotomy[65].**

Decreased surgery time, Easier control of bleeding, decreased postoperative pain including opioid usage, decreased chest tube duration, decreased length of hospital stay, Decreased inflammatory response and Cosmesis.

- **Thoracotomy with open biopsy**

Thoracotomy with direct biopsy of the pleura provides the best visualization of the pleura and the best biopsy specimens. The main indication for open pleural biopsy is progressive undiagnosed pleural disease that cannot be approached by or has failed to be diagnosed by thoracoscopy.[66]

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