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A study on Transesophageal Endoscopic Ultrasonographic detection of Mediastinal Lymph node involvement in non-small cell lung cancer

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Abstract: *Lung cancer is one of the commomest cancer by prevalence and incidence. Treatment of Lung cancer depends on staging. Staging of Lung cancer includes mediastinal nodes.Mediastinal nodes can be detected by imaging like x-ray , CT scan, MRI and also by Endoscopic Ultrasound.We did a study to see whether mediastinal nodes could be picked up by Endoscopic USG as much as it could be picked up by CT scan.*
Aim: *To compare the detection rate of mediastinal lymph node involvement in non-small cell lung cancer by x-ray chest, Computed tomographic (CT) scan of chest with transesophageal endoscopic ultrasonography.*

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I. Introduction:

Lung cancer ranks among the most commonly occurring malignancies and currently is the leading cause of cancer related deaths worldwide.[1] In the United States, lung cancer incidence is 70 per 100,000 and approximately 157,200 died of this disease in 2003.[2] Claiming 187,000 lives annually, lung cancer currently accounts for one-third of all cancer related deaths in the European Union.[3] This disease is rapidly emerging as a major cause of mortality in Asia as well. For instance, in Japan, lung cancer is responsible for approximately 55,000 cancer related deaths per year.[4] In China, the mortality rate from lung cancer in males now approximates 33 per 100,000 and deaths rates are expected to substantially increase over next several decades.[5]

Cancer of the lung has been one of the foremost oncological problems among Indians over the past several decades, in fact, ever since tobacco was first introduced to the subcontinent by the Spanish, and smoking and tobacco chewing, along with betel nut, became a popular habit with the locals. This habit of tobacco in any form steadily caught on, irrespective of social, economic or educational status and attributes to the rising trend in incidence of lung cancer in India from 32,000 in 1989, to 41,000 new lung cancer cases every year.[6] Madras Metropolitan Tumor Registry registers around 1800 lung cancers in 1983-94.[7]

At the department of Medical oncology, Coimbatore Medical College, around 2500 new cancer patients are registered annually. Of this patient load roughly 20% are constituted by lung cancer.

Accurate staging of the lung cancer is essential because the stage of the disease is an important factor that influences the treatment planning, prediction of the outcome and to avoid unnecessary morbidity and cost associated with over treatment.

The Primary aim of intra-thoracic staging in non-small cell cancer (NSCLC) is the evaluation of mediastinal lymph node involvement. Accurate assessment of mediastinal lymph node status affects a patient's prognosis and treatment plan, as the presence of mediastinal lymph node involvement indicates the presence of stage III A or III B lung cancer. This suggests either inoperability and / or the need for the treatment by chemotherapy and / or radiotherapy. Since mediastinal lymph node involvement is found in 30 to 44% of patients with newly diagnosed lung cancer, testing is required to rule out such disease.

Despite technical advances, in non–small cell lung cancer (NSCLC), accurate staging remains a challenge. CT scan remains inadequate in picking lymph node involvement in certain mediastinal lymph node stations like subaortic, subcarinal and upper and lower paraesophageal lymph nodes.[8-9] Endoscopic ultrasound is proved useful in diagnosing lymph node involvement in these mediastinal locations.[10] More over transesophageal ultrasonography can detect lymph node enlargement more than 3 mm, and can be histologically confirmed by fine needle aspiration, where as CT scan can detect lymph node enlargement which are more than 10mm only.[11]

In our institute so far the standard staging procedure for NSCLC is x-ray chest and CT scan of the chest. Among the newer modalities MRI though available in our institute studies shows that it does not score over CT scan and certainly not cost effective. Other newer modalities like PET and nuclear scan are not

available in our institute. Therefore, we sought to determine the clinical impact of transesophageal endoscopic ultrasonography (EUS) in staging NSCLC and its comparison with existing staging procedures namely x-ray chest and CT scan chest.

Importance of mediastinal lymph node staging

Non–small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers. NSCLC. Direct spread to contiguous structures such as pleura, chest wall, diaphragm and mediastinal structures like, heart, great vessels, nerves, esophagus and vertebral column. Lymphatic spread occurs to hilar, mediastinal and supraclavicular. Hematogenous spread occurs to distal organs like liver, adrenals, bone and brain.

Among the three modes of spread lymphatic spread is very important as it determines the treatment plan especially the surgery. Surgery is the best treatment modality for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision. In stage I and stage II disease, when the tumor has not extended beyond the bronchopulmonary lymph nodes, complete (R0) resections are almost always feasible.[12,13] Ipsilateral N2 mediastinal lymph node involvement, despite being potentially resectable, typically portends limited survival after resection alone. Because of this, pathologic staging of the mediastinum is critical for determining treatment and prognosis for individuals with locally advanced lung cancer.[14,15] Patients in whom N2 disease is identified preoperatively have a much poorer prognosis than individuals with occult N2 disease discovered only at the time of thoracotomy (less than 10% vs. 30% 5-year survival rates, respectively).[15] Stage IIIB disease by virtue of incontrovertible evidence of contralateral (N3) lymph node typically is inoperable.

Chemotherapy when used in sequence or concurrently along with radiation therapy prolongs median survival and increases the fraction of patients with stage III disease who are long-term survivors. The International Adjuvant Lung Trial (IALT) and Cancer and Leukemia Group B (CALGB) studies suggest that adjuvant platinum-based chemotherapy used after surgical resection may improve survival of patients undergoing resection of stage I, II, or IIIA NSCLC.[16-19] Induction chemotherapy followed by radiotherapy prolongs the median survival time in patients with unresectable stage III disease compared with patients receiving radiotherapy alone.[20]

So it is imperative to stage the N stage of the disease very accurately to plan the treatment perfectly for the particular stage of the disease, so that the outcome of the patient can be increased, with less morbidity and cost effective manner.

Mediastinal nodes

Naruke and associates in 1978 suggested the use of an anatomic map with the lymph node stations numbered so that the various lymph node stations involved by tumor could be uniformly recorded in patients with lung cancer. [23] This mapping scheme is used by most Japanese surgeons and has been used with minor modifications by the Sloan-Kettering Memorial group and others in North America. The American Joint Committee for cancer staging and End results reporting published a similar map in its 1983 fascicle. The following descriptions are by Tisi and colleagues (1983) in American Thoracic Society.[24]

Station 1. Highest mediastinal
Nodes lying above a horizontal line at the upper rim of the left innominate vein.
Station 2. Upper paratracheal
Nodes lying above a horizontal line drawn tangential to the upper margin of aortic arch and below the brachiocephalic vein .
Station 3. Pre tracheal and retrotracheal
Nodes lying over and under the trachea.
Station 4. Lower paratracheal
Right – Nodes lying on the right of the midline between tangential line drawn on the upper margin of arch of aorta and line extending across the right main bronchus at the upper margin of upper lobe bronchus. **Left** – Nodes lying on the left of the midline below the tangential line drawn at the upper margin of arch of aorta to the line extending across the left main bronchus at the upper margin of left upper lobe bronchus.
Station 5. Sub-aortic (aortopulmonary window)
Nodes lying lateral to ligamentum arteriosum or the aorta or left pulmonary artery.
Station 6. Para-aortic (ascending aortic or phrenic)
Nodes anterior and lateral to the ascending aorta and the aortic arch or innominate artery.
Station 7. Sub-carinal
Nodes lying caudal to carina but not associated with lower lobe bronchi.
Station 8. Para-esophageal
Nodes lying adjacent to the wall of the esophagus on both sides of the midline.
Station 9. Pulmonary ligament nodes

Nodes lying within the pulmonary ligament including those in the posterior wall and lower part of inferior pulmonary vein.

Bronchopulmonary nodes

Station 10. Hilar nodes

Proximal lobar nodes distal to the mediastinal pleural reflection and nodes adjacent to the bronchus intermedius on the right.

Station 11. Interlobar nodes

Nodes lying between the lobar bronchi.

Station 12. Lobar nodes

Nodes adjacent to the distal lobar bronchi.

Station 13. Segmental nodes

Nodes adjacent to the segmental bronchi.

Station 14. Sub-segmental nodes

Nodes around sub-segmental bronchi.

Mediastinal lymph node staging

Mediastinal lymph node staging is a challenging job. Various modalities are available which vary from non-invasive, semi-invasive to invasive technique. Each one unique in its advantages and disadvantages. Traditionally, computed tomography (CT) and mediastinoscopy are used. Modern staging modalities include magnetic resonance imaging (MRI), positron emission tomography (PET), and endoscopic ultrasound with fine-needle aspiration (EUS-FNA).

Computer tomography scan

Traditionally, assessment of mediastinal lymph nodes in NSCLC patients is performed with thoracic CT.[25] Based on anatomic imaging, lymph nodes with a short axis of more than 1 cm are considered to have malignant involvement.[26] However, the main problem is the fact that CT only depicts the shape and size of mediastinal lymph nodes, rather than actual tumor involvement. Due to signal averaging and inadequate contrast within the mediastinum only lymph nodes of more than 1 cm in size are reliably detected.[27] this inherently results in moderate operating characteristics.

Magnetic resonance imaging

The role of MRI in the mediastinal staging of NSCLC is not as well studied as CT. MRI experiences the same disadvantages of the size-related definition of lymph node positivity as CT.[34,35]The use of contrast-enhanced MRI may improve staging results slightly. MRI might assess hilar and aortopulmonary window nodes more accurately than CT, because of a better distinction between lymph nodes and blood vessels. In case of allergy to CT contrast agent, MRI may be useful. With few exceptions, MRI offers no advantages in the mediastinal staging of NSCLC when compared with CT, against higher costs for MRI.

Positron emission tomography

Positron emission tomography (PET) using ^{18}F-fluordeoxyglucose as a tracer showed metabolic tumor properties instead of size criteria, positivity of mediastinal lymph nodes might approach the actual presence of tumor more closely than CT or MRI.[28] PET is significantly more accurate than CT in identifying mediastinal lymph node metastasis.[29-31] However false-positive PET results are caused by inflammation (tuberculosis, histoplasmosis, sarcoidosis), whereas false-negative results may be caused by carcinoid, bronchoalveolar cell carcinoma, and small lesions (less than 5-7 mm).[32] With the high negative predictive value, a negative mediastinum on PET leads directly to thoracotomy, without further preoperative mediastinal staging. The lower positive predictive value makes cytologic or histologic confirmation necessary in case of a positive mediastinum on PET. The detection of unexpected distant metastasis in about 15% of the cases is another important advantage of PET.[29]

Nuclear scan

The usefulness of some myocardial perfusion imaging tracers such as ^{201} Tl and ^{99m}Tc-sestamibi has also been reported in mediastinal lymph node detection using SPECT acquisition; in particular, recent data have demonstrated a higher specificity and accuracy for ^{99m}Tc-sestamibi SPECT than for CT, but a lower sensitivity.[33] More recently, another cationic lipophilic complex, ^{99m}Tc-tetrofosmin, largely used for myocardial perfusion scintigraphy, has also been used as a tumor-seeking agent.

Mediastinoscopy

Cervical mediastinoscopy (CM) can assess lymph node levels 2 left and right, 4 left and right, and 7. It is often considered as gold standard for the mediastinal staging of NSCLC. Debate is ongoing about how 'gold' this standard is. Cervical mediastinoscopy can be extended (ECM) to reach lymph node levels 5 and 6. The complication rate of CM is approximately 2.5%, including paresis of the left laryngeal recurrent nerve, hemorrhage, pneumothorax, pneumonia, injury to the azygos vein, perforation of the esophagus, and mediastinitis.[36]

Anterior mediastinotomy (Chamberlain procedure)

Anterior mediastinotomy (AM) is suitable for lesions in the anterior and superior mediastinum or hili, when CM is contraindicated, or in case of a left upper lobe tumor. The complication rate of AM is 6.7–9%, with 1% mortality.[37]

Video-assisted thoracoscopy

Video-assisted thoracoscopy (VATS) can image an entire hemithorax plus almost every mediastinal lymph node level, with minimal incision and morbidity, but generally only one-sided. There are (relative) contraindications, like previous mediastinoscopy, previous local surgery or irradiation, aortic aneurysm, superior vena cava obstruction, and inability to withstand single-lung anesthesia. The complication rate of VATS may be as high as 14%, with hemothorax, air embolism, or lacerations to the lungs or blood vessels. Emergency thoracotomy is required in 1-3%, and the mortality rate is approximately 4.5%.[38]

Percutaneous transthoracic needle biopsy

Percutaneous transthoracic needle biopsy (PTNB) can be used for the mediastinal staging of NSCLC. Meta-analyses on this subject are not available. [39] CT guidance is preferred; because the lesions tend to be small and adjacent to major blood vessels. PTNB usually permits puncture of mediastinal lymph nodes larger than 1.5 cm Overall sensitivity, specificity, and accuracy were 0.88, 1.00, and 0.89, respectively. Post biopsy pneumothorax occurred in 22% of the procedures. Post biopsy pneumothorax was reported in 34%, and 14% required a chest tube. Other complications, such as hemothorax, hemoptysis, air embolism, or empyema are rare. Implantation of tumor cells at the puncture site is rare, reported to be approximately 1 in 4000 procedures. Contraindications for PTNB are COPD, poor lung function, diffuse pulmonary disease, clotting disorders, pulmonary hypertension, contralateral pneumonectomy, and arteriovenous malformation.

Transbronchial fine-needle aspiration

Transbronchial fine-needle aspiration (TBNA) for the mediastinal staging of NSCLC has been described in literature, although it was applied in patients with established mediastinal lymph node (N2) enlargement on CT.[40] Only lymph nodes next to the large airways can be reached, mainly on levels 4 right, 4 left, and 7. CT guidance increases the sensitivity of TBNA, as may endobronchial ultrasonography. Both cytologic and histologic specimens can be obtained.H:\dissertation\downloads\5.htm - r7-5#r7-5 The complication rate is 2-5%, including hemorrhage and pneumothorax.

Endoscopic ultrasonography (EUS)

For approximately two decades, endoscopic ultrasonography (EUS) has been used for the diagnosis and staging of gastrointestinal malignancies. EUS provides accurate images of the entire posterior mediastinum, including lymph nodes in the subcarinal, aortopulmonary, and paraesophageal regions. Compared with CT, the detection rate of malignant lymph nodes is higher with EUS, with less false-positive results. EUS can assess mediastinal lymph nodes at most levels, particularly at levels 4 left, 5, 7, 8, and 9, as well as metastasis in the left adrenal gland. Levels 1, 2, 3, and 4 right are not always assessable, because of interference by air in the larger airways.[41-43] Properties of lymph nodes indicating possible malignancy are a hypoechoic core, sharp edges, round shape, and a long axis diameter exceeding 10 mm. Histoplasmosis, sarcoidosis, and anthracosilicosis may cause false-positive EUS images.

Diagnostic accuracy of EUS improves substantially with fine-needle aspiration (FNA). The development of echoendoscopes capable of imaging parallel to the long axis of the scope made EUS-guided FNA possible. In two studies with decision-analysis models, EUS-FNA was shown to be less expensive compared with mediastinoscopy for the assessment of the entire mediastinum.

Endoscopy

The word endoscopy is derived from the Greek by combining the prefix endo-, meaning within, and the verb skopein, meaning to view or observe. The result is apt term for the procedure of peering into the recesses of the living body. The original concept of using a tube to peer into the hidden cavities of the living human body is

well conceived but is associated with lot of difficulties like, the design of the tube which is simple, straight, rigid, hollow probe. Second was lack of materials suited to the construction of a proper endoscope. In the early 19th century, a variety of metals was available, but machines to fashion metals of high tensile strength were relatively crude. Later after the advent of vulcanization in the year 1893 rubber was rendered strong and elastic and scientist started using rubber for a scope. Third and the most serious impediment, was lack of adaptable light. Before the invention of incandescent bulb, the only convenient source of artificial light was a burning candle, the wick of oil or gas lamp, or an exposed, glowing, platinum wire. None of these were adequate.

The earliest recorded attempt at endoscopy was by Philip Bozzini of Mainz and Frankfurt who, in 1806 devised a tin tube illuminated by a wax candle fitted with a mirror. With this instrument which he called Einer Lichtleiter (a light conductor), he tried to peer into the urinary tract.[44] In 1826, Pierre Salomon-Seagalas introduced a "urethra-cystic speculum," the first endoscope of any practical use in diagnosis.

In 1868 Adolf Kussmaul, a German physician who is more often remembered for diabetic acidotic breathing, is credited with fashioning and employing what might be hailed as the first gastroscope. Kussmaul's instrument was a straight, rigid, metal tube, passed over a previous inserted flexible obturator. The light source was a Desmoreaux lamp that burned a mixture of alcohol and turpentine, illumination being concentrated by a reflector and lens.

The first clinician to seriously consider the special requirements of a workable gastroscope was Johann von Mikulick-Radecki, a polish surgeon who understood that the longitudinal axis of the esophagus is not the same as that of the stomach. Therefore in 1881, he reported his design of a tube, 65 cm long and 14 mm in diameter, with a slight angle in its distal fourth.

Rudolf Schindler born in Berlin, Germany embarked on his career of life long dedication to the advancement of gastroscopy. This one man, almost single-handedly, provided an impetus for the method and sparked the promotion of gastroscopy throughout Europe and, later in the Americas. He combined with Georg Wolf, a skilled Berlin instrument maker and developed the famous Wolf-Schindler semi flexible gastroscope in 1932.

Fiberoptic endoscopy

The era of fiberoptic gastgrointestinal endoscopy might be said to have dawned on a wintry day in Ann Arbor, Michigan, when Basil Hirschowitz picked up the January 1954 issue of Nature, in which he had come across two articles on the optical properties of fine glass fibers.[44] This fired his imagination of how an endoscopic image might be transmitted by a coherent bundle of fully flexible glass fibers from the alimentary tract of a patient to the eye of an examiner. John Tyndall, a British physicist, in 1870 first demonstrated that light would follow the curved path of a stream of water pouring from a tank. The idea of using flexible glass fibers to propagate light was proposed in patient applications by J.L. Baird of England in 1927 and by C. W. Hansell of the United States in 1930.

The important part is construction of a coherent bundle intended to convey an image, wherein many thousands of hair-thin fibers must be in precisely the same array at both ends of the bundle. Any appreciable leakage of light from one fiber to another defeats the purpose of a coherent bundle. This principal impediment to the development of a fiberscope was overcome by Lawrence Curtiss, then an undergraduate physics student at the University of Michigan. Curtiss devised a process whereby an individual fiber of optical glass could be clad in a layer of glass of lower refractive index that served as an insulating coat and this is revered as the single most important innovation in the advent of fiberoptic endoscopy.[45]

The new era of video endoscopy

Fiberoptics dominated the field for barely a quarter century. The burgeoning technology of video endoscopy has now largely superseded use of the coherent, image transmitting, fiberoptic bundle for most gastroenterologic applications. Black and white televised images of bronchoscopy were reported in 1957. Rider and Hirschowitz collaborated in a demonstration of televised images of gastrointestinal endoscopy at the 1963 meeting of the American Society of Gastro Enterology (ASGE). Television cameras were devised that could be attached to the eye piece of standard fiberoptic gastrointestinal endoscopes, but the cameras were unwieldy and heavy (about 7 lbs) and had to be suspended from the ceiling. With the advent of charge-coupled device the much needed means of incorporating within the endoscope itself an electronic device capable of registering and transmitting a vivid image. The first video endoscope was introduced by Welch Allyn Inc. of Skaneateles, New York.

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is an established imaging technique that combines fiberoptic endoscopy and high-frequency ultrasonography in the evaluation of the gastrointestinal tract and surrounding structures with the use of high-frequency transducers The Olympus GF-UM3/EU-M3 and GF-UM20/EU-M20

models are the commonly employed units. These incorporate a radial scanning system (rotating piezoelectric transducer) with a fiberoptic endoscope and an accompanying display unit. This system produces a B-mode 360-degree real-time ultrasound image, allowing circumferential visualization of the intestinal wall. The above devices have the advantage of being able to image with either 7.5 or a 12 MHz transducer, offering a choice of imaging depth. With high frequency transducers, the depth of sound penetration is decreased but the resolution is better. But with low frequency transducer the penetration is increased but the resolution is low. The curved-array echoendoscope provides images parallel to the long axis of the endoscope allowing continuous visualization

Instruments

Three different types of instruments are available for transesophageal endoscopic ulsonography: echoendoscopes, echoprobes and catheter probes.

Echoendoscopes

An echoendoscope is an endoscopic instrument with an ultrasound device incorporated in its distal tip. In general, the optical component of an echoendoscope provides a view field that is oriented lateral or oblique to the long axis of the insertion tube; fields of view are relatively small compared with those provided by standard diagnostic/therapeutic endoscopes. Currently available echoendoscopes may be classified into two types; radial sector and linear array. The radial sector includes instruments in which the scanning plane oriented perpendicular to the axis. The sector of radial scanning instruments can be switched from a full 360 degree image to 180 degrees or 90 degrees. The linear array comprises instruments with a scanning plane parallel to the axis.

Echoprobes

Echoprobes do not have optical components and are passed over a guidewire that has been placed endoscopically or fluroscopically. Elimination of the optical elements reduces the diameter of the probe, thereby making this type of instrument especially suitable for imaging malignant tumors that markedly narrow the esophageal lumen.

Catheter echoprobes

Catheter echoprobes are small diameter US devices that can be introduced through the accessory channel of a large-caliber endoscope .

Technique

The technique for endosonography of the esophagus is similar to that for esophagogastroscopy and includes topical oropharyngeal anesthesia and conscious sedation. Patients may experience discomfort during passage of the rigid distal end of the echoendoscope. Scanning should be performed in 1 cm contiguous sections, working from the distal to the proximal.

The involved lymph nodes will appear as a structure with hypoechoic core, sharp edges, round shape, and a long axis diameter exceeding 10 mm. Its location is noted as lymph node station described earlier.

Complications of gastrointestinal endoscopy

1. Aspiration of gastric content leading to aspiration pneumonia.
2. The application of topical anesthetic to the oropharynx results in loss of gag reflex leading aspiration.
3. Systemic absorption of topical anesthetic leading to central cyanosis and oxygen refractory hypoxemia.
4. Tetracaine preparation have been associated with cardiac arrhythmias, seizures, altered mental status, and death.
5. Intravenous sedatives may give rise to Rrespiratory depression producing severe hypoxemia, cardiac arrhythmia
6. Esophageal perforation is the major complication occurring in approximately 0.10% of cases performed.

We undertook a study on the detection rate of superior mediastinal lymphadenopathy by transesophageal ultrasound in cases of non-small cell lung cancer as a corollary to compare the detection rate of x-ray chest, CT scan of chest with transesophageal ultrasound with regard to mediastinal lymph node

I. Conditions for Patient Eligibility

1. Patients with histological proof of non-small cell lung cancer.
2. Patients with a Zubrod/ECOG performance status of 0-1
3. No distant metastatic disease.

4. Patients with adequate bone marrow function defined as an absolute peripheral granulocyte count (AGC) of ≥2000 cells/mm^3, platelet count of ≥100,000 cells/mm^3, adequate hepatic function with bilirubin ≤1.5 mg% and serum creatinine ≤1.5 mg%.
5. No symptomatic coronary artery disease (angina) or myocardial infarction within the last 6 months.
6. Informed consent form signed prior to study entry.

II. Ineligibility Criteria

1) Poor performance status.
2) Uncooperative patient.
3) Infections like tuberculosis, HIV
4) Other co morbid cardiac condition.

TNM staging

Tx	Positive malignant cell. No lesion
T1 -	**CT scan** Mass lesion less than 3 cm surrounded by normal lung tissue all around **FOB**
T2 -	**CT scan** Mass lesion more than 3 cm Mass lesion of any size involving the visceral pleura Atelectasis involving the segment or lobe **FOB** Tumor involves the main bronchus but stays two cm away from carina
T3	**CT scan** Mass lesion of any size involving the parietal pleura, chest wall, diaphragmatic pleura or mediastinal pleura Atlectasis of the ipsilateral whole lung **FOB** Involvement of main bronchus within two cm of carina.
T4	**CT scan** Mediastinal structure invasion Pleural or pericardial effusion Satellite nodule in the same lobe of lung Satellite nodule in the pleural **FOB** Involvement of carina and/or trachea
N0	No nodal involvement
N1	Ipsilateral bronchopulmonary or hilar lymph node involvement
N2	Ipsilateral mediastinal or subcarinal lymphnode involvement
N3	Contralateral mediastinal, hilar or supraclavicular lymphnode Involvement
M0	No distant metastasis
M1	Presence of metastasis

Revised staging system (AJCC / UICC)

Stage 0	Carcinoma in situ		
Stage I A	T1	N0	M0
Stage I B	T2	N0	M0
Stage II A	T1	N1	M0
Stage II B	T2 T3	N1 N0	M0 M0
Stage III A	T1 T2 T3	N2 N2 N1, N2	M0 M0 M0
Stage III B	T1, T2, T3 T4	N3 N0, N1, N2, N3, N4	M0 M0
Stage IV	Any T	Any N	M1

Diagnostic evaluation

This study design has been submitted to ethical committee and ethical committee clearance was obtained. Cases of carcinoma lung attending the Department of Medical Oncology, Madras Medical College, Chennai between October 2005 to March 2008 are included. Informed consent obtained for all the patients.

Patient presenting with the complaints or respiratory symptoms of more than 4 weeks which was not controlled with course of higher antibiotics or a trial ATT are selected. Detailed history and complete and through physical examination is done. X-ray chest is taken first. If there is a central lesion then the patient is investigated with sputum cytology for malignant cells or FOB for biopsy or bronchial washing or brushing. If there is peripheral lesion then CT guided biopsy is done to establish the histopathological diagnosis.

Staging evaluation

After establishing diagnosis then staging work up is done by CT scan of chest plain and contrast including liver and adrenals. Skeletal survey by x-rays to look for bone metastasis is done if the patient is present with bone pain or elevation of alkaline phosphatase or serum calcium. CT scan or MRI of the brain is done if the patient had headache, vomiting, blurring of vision, focal fits or focal neurological deficit. Then if the patient general condition is fit to under go endoscopy first a regular transthoracic echocardiogram is taken and then planned for transesophageal ultrasonogram. The eligible patients were taken to Department of Cardiology, where transesophageal echo cardiogram is done with Olympus echoendoprobe which is a curved array endoscope. It transmits ultrasound signal parallel to esophagus but can be manipulated to cover all around. The same transesophageal echo probe is used for ultrasonographic evaluation of mediastinum.

Upper endoscopy preparation

The patients should refrain from eating solid food 6 to 7 hours beforehand and drinking liquids 4 hours prior to the procedure. Retention of gastric contents increases the risk of aspiration and limits adequate visualization.

Sedation and analgesia

The aim of sedation and analgesia is to optimize patient comfort based on individual sedation needs and facilitate safe completion of the endoscopic procedure.

Topical anesthetics

The application of topical anesthetic xylocaine preparations to the oropharynx in the form of gargles is sued prior to passing the endoscope. The aim of the topical anesthetics is to improve the patient tolerance and to abolish the gag reflex and aspiration.

An informed consent is obtained to subject the patient for transesophageal ultrasonogram. Then the patient is subjected to transesophageal ultrasonogram using the transesophageal echocardiographic probe which is a linear array ultrasound probe which will view parallel with an angle 100 degree.

Mediastinal lymph node stations from station nine is evaluated below upward to upper most tracheal lymph node. The involved lymph node will be seen as well circumscribed hypoechoic mass.

These lymph nodes detection by endoscopic ultrasonogram is compared with detection by x-ray chest and contrast CT scan of the chest. The findings are noted in a fixed Proforma and the results are analyzed for statistical value. If more than one station of lymph nodes are involved the station of highest echelon in the normal course of lymphatics is taken.

II. Materials And Methods

During the study period December 2005 to March 25, 2008 , 112 cases had been enrolled in this study. Among the 112 cases 87 cases are males and 25 cases or females. Youngest patient is a 22 year old male and oldest is a 67 year old male. Majority of cases fall into 51 – 60 years age category numbering 51 (45%). Second commonest group is constituted by 41 – 50 age group, 35 cases (31%).

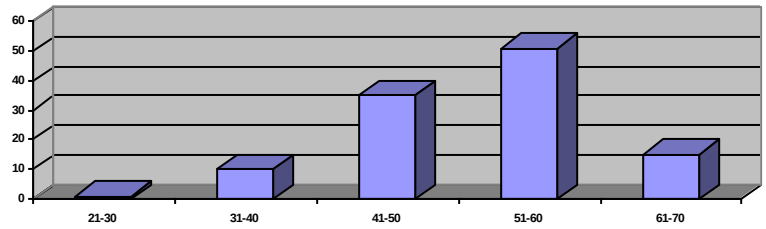
Table showing number of cases based on sex.

Total	**112**
Male	87
Female	25

Table showing distribution cases according to age group

Age group	**Number**	**Percentage**
21 – 30	1	0.08
31 – 40	10	8
41 – 50	35	31
51 – 60	51	45
61 – 70	15	13

Agewise distribution of NSCLC



Histological types

When analyzed based histological subtype adenocarcinoma constituted 53 cases closely followed by squamous cell carcinoma 50 cases. There are 2 large cell carcinomas and in 7 cases subtype was not possible.

	Male	Female	Total
Adenocarcinoma	36	17	53
Squamous cell carcinoma	44	6	50
Large cell carcinoma	2	0	2
Subtype not known	5	2	7

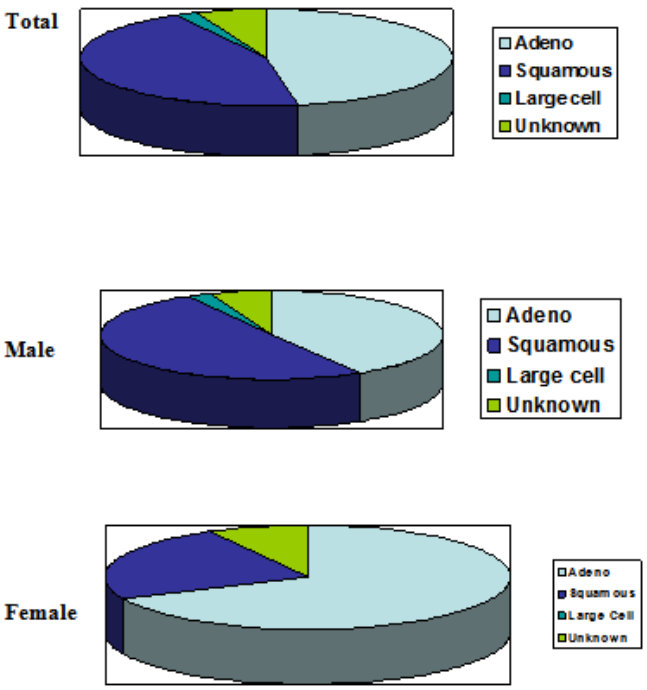


Diagram depicting the histological subtype distribution

Documentation

Histopathological documentation of malignancy was established by CT guided biopsy of lung paranchymal mass lesion in 76 cases, fibro optic bronchoscopic biopsy in 11 cases and bronchial wash in 17 cases. In one case documentation was done from pleural fluid cytology.

Diagnosis by

	Adeno		**Squamous**		**Large cell**		**Unknown**	
	♂	♀	♂	♀	♂	♀	♂	♀
CT guided biopsy	28	11	31	4	2			
FOB - Biopsy	2	5	4					
Bronchial wash	5	1	9	2			5	2
Pleural effusion	1							

When analyzed on stage no cases presented with stage IA, IIA or IIIA. 7 cases fall in to stage IB. Stage II B due to $T_3N_0M_0$ 10 cases, due to $T_2N_1M_0$ 11 cases. Stage III A due $T_3N_1M_0$ were 18, due to $T_2N_2M_0$ were 11 and due to $T_3N_2M_0$ were 26. stage III B due to $T_4N_0M_0$ were 8 cases, due to $T_4N_1M_0$ 8 cases and due to $T_4N_2M_0$ were 14 cases. In total the number of N 1 cases were 37 all of them were due to involvement of ipsilateral hilar lymphnode picked by CT scan and x-ray chest could pick only18 cases (35%).

Stage wise distribution in all the histologcial subtype

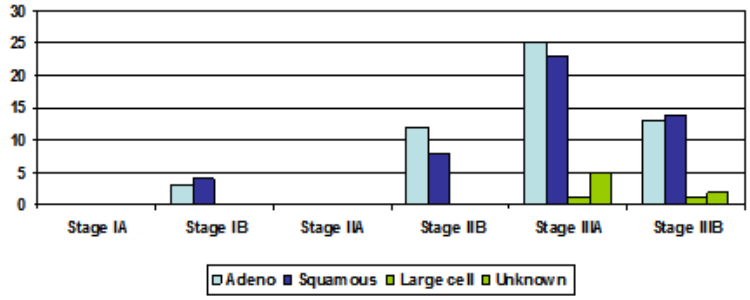


Table showing Stage wise distribution

Stage		**Adeno**		**Squamous**		**Large cell**		**Unknown**	
TNM	**Group**	♂	♀	♂	♀	♂	♀	♂	♀
$T_1 N_0 M_0$	I A								
$T_2 N_0 M_0$	I B	3		4					
$T_3 N_0 M_0$	II B	3	3	4					
$T_4 N_0 M_0$	III B	3		4		1			
$T_1 N_1 M_0$	II A								
$T_2 N_1 M_0$	II B	4	3	4					
$T_3 N_1 M_0$	III A	5	3	6	1	1		1	1
$T_4 N_1 M_0$	III B	3	1	4					
$T_1 N_2 M_0$	III A								
$T_2 N_2 M_0$	III A	2	2	6				1	
$T_3 N_2 M_0$	III A	9	4	8	3			1	1
$T_4 N_2 M_0$	III B	4	2	4	2	1		1	

In our study the upper lobe non-small cell lung cancer is 45 (21 on the right side and 24 on the left side. Right middle lobe tumors are 12 where as left lingular lobe tumors constitute 2. Most number of cases occurred in lower lobes right side 27 and left side 26 adding up to 53.

Table showing Lobe wise involvement

	Right	**Left**	
Upper lobe	21	24	45
Middle lobe	12		
Lingular lobe	2		
Lower lobe	27	26	53

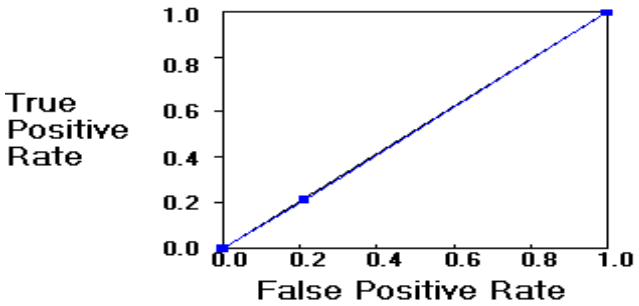
Mediastinal lymph node evaluation

X-ray chest

X-ray chest was very useful in assessing the primary as in almost all cases it picked up the primary lesion. But using it for lymph node staging especially mediastinal lymph nodes very limited. Apart from identifying hilar lymph node the usefulness in assessing the superior mediastinal lymph node, it showed 13 cases with superior mediastinal widening out of 51 cases of N2 disease detected by both CT chest and EUS together constitution only 25%. All the cases had primary in the upper lobes or middle lobe. But all the 13 cases were picked by CT scan. Receiver operating curve is of no value as it fall almost on the midline.

Sensitivity	25%
Specificity	100%
Positive predictive value	100%
Negative predictive value	61%
Percentage of false negative	64%
Percentage of false positive	0%

Receiver Operating Curve for x-ray chest

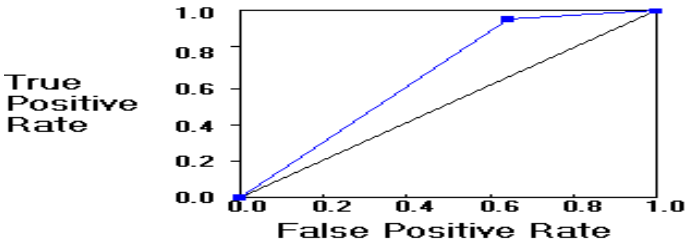


CT scan chest

In this study there were 51 cases of N2 disease. 37 cases have been picked by CT scan. In the remaining 14 patients the N2 disease diagnosed by transesophageal ultrasonogram. CT scan picked 2 cases of upper para-tracheal lymph node involvement (station 2), 11 cases of lower para-tracheal lymph node involvement (station 4), 5 cases of subcarinal lymph node(station 7), 14 cases of paraesophageal lymph node (station 8) and 5 cases lymph node at the level of pulmonary ligament (station 9). Receiver operating curve showing a reasonably good specificity despite moderate sensitivity and positive predictive value.

Detection rate	73%
Sensitivity	41%
Specificity	78%
Positive predictive value	41%
Negative predictive value	57%
Percentage of false positivity	78%
Percentage of false negativity	21%

Receiver Operating Curve for CT scan

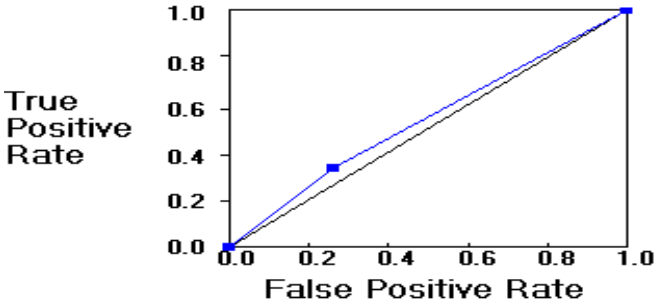


Transesophageal endoscopic ultrasonography

Transesophageal endoscopic ultrasonogram picked mediastinal nodes altogether in 24 cases (47%). It identified 3 cases of lower para-tracheal (station 4) lymph node, 3 cases of sub-aortic lymph node (station 7), 5 cases of sub-carinal lymph node (station 7), 8 cases of para-esophageal lymph node (station 8) and 5 cases of station 9 lymph nodes. Transesophageal ultrasonogram had picked all 3 cases of sub-aortic or aorto-pulmonary window lymph node (station 5) where the CT scan had completely failed to pick any. In posterior mediastinal lymph node (station 8 & 9) 11 cases the transesophageal ultrasonogram had picked which was missed by CT scan. Receiver operating curve showing only moderate results, mainly because of low sensitivity.

Sensitivity	42%
Specificity	58%
Positive predictive value	21%
Negative predictive value	78%
Percentage of false negativity	58%
Percentage of false positivity	42%.

Receiver Operating Curve for EUS



If we consider only the posterior mediastinal lymph nodes are analyzed (station 7, 8 and 9) the sensitivity became 54%, specificity 89%, positive predictive value 39%, negative predictive value 94%, percentage of false negativity 46% and percentage of false positivity is 11%.

Mediastinal Lymph node involvement

Lymph node station	CT scan		TEU		Both CT + TEU	
	Right	Left	Right	Left	Right	Left
1						
2	1	1				
3						
4	6	5	1	2	1	2
5			3			
6						
7	5		5			
8	6	8	3	5	1	1
9	3	2	2	3		

Histological subtypes giving rise to mediastinal lymph nodes

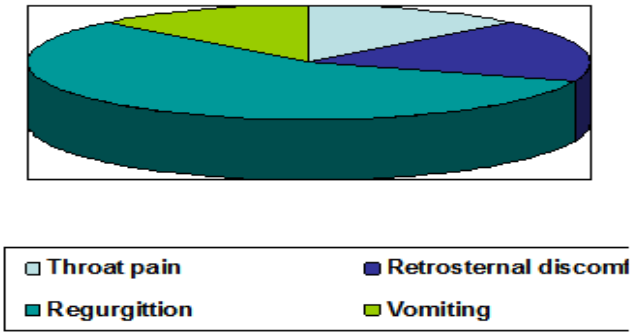
In this study out of 51 cases with mediastinal lymph node spread 23 cases are of adenocarcinoma and squamous cell carcinoma each. One large cell carcinoma and in 4 cases subtype is not known. CT scan picked 18 cases of mediastinal lymph node in squamous cell subtype and 15 cases of adenocarcionoma. Out of 24 cases picked by transesophageal endoscopic ultrasonogram, 15 cases of squamous cell carcinoma, 8 cases are adenocarcionma and in 1 case subtype is not known.

Complications with TEU

The procedure had been well tolerated, in no patient the procedure had abandoned due to poor cooperation by the patient. No major complication like hemetemesis, perforation, cardiac rhythm disturbance, shock or aspiration leading to pneumonitis had been noted. Only minor complications like throat pain, retrosternal discomfort, regurgitation and vomiting has been encountered and all had been managed effectively symptomatically.

Throat pain - 58
Retrosternal discomfort - 14
Regurgitation - 23
Vomiting - 17

Pictorial representation of complications



III. Discussion

Cancer lung is the number one killer malignancy world over. Accurate staging very essential as it has very important therapeutic implication. A report from the Society of Cardiothoracic Surgeons of Great Britain and Ireland (1985) revealed that approximately one in five thoracotomies performed for lung cancer were "open and close." Certainly, thoracotomy for unresectable non–small cell lung cancer (NSCLC) is not only costly but would be expected to impact negatively on the patient's quality of life. Detection of NSCLC metastases to various mediastinal lymph node stations is the challenge of regional staging. Multiple lymph node station involvement predicts a poor prognosis.[46] Patients with N1 or N2 disease may benefit from surgery, while patients with N3 disease do not. The prevalence of N2 disease ranges from 24.9 to 62%.[47,48] It is important to identify patients with N2 disease, as they may benefit from neoadjuvant therapy.[20,21] Various modalities are available for evaluation of mediastinal lymph nodes namely, CT scan of thorax, transbronchial needle aspiration, endobronchial ultrasound, MRI, PET, mediastinoscopy, mediastinotomy and of course endoscopic ultrasonogram (EUS).

The current American Thoracic Society guidelines for the staging of non-small cell lung cancer suggest that CT should be considered the standard investigation for the evaluation of mediastinal involvement of lung cancer. But due to signal averaging and inadequate contrast within the mediastinum only lymph nodes of more than 1 cm in size are reliably detected.[49] Based on anatomic imaging, lymph nodes with a short axis of more than 1 cm are considered to have malignant involvement, although it is known that some benign nodes may be larger, and that normal-sized nodes may contain malignancy.[50-52] Based on CT findings, approximately 23% of NSCLC patients are overstaged, and 19% are understaged.

It was hoped that alternative imaging techniques such as PET might give better results. Recent studies on PET reported a high sensitivity of 67% to 100%and with a specificity of 70 – 100%.[53] Unfortunately, nonspecific inflammatory reactions in lymph nodes may also accumulate FDG . The false positive results with PET have been reported with tuberculosis, sarcoidosis, histoplasmosis, and other fungal infections. Several studies, comparing PET and CT demonstrate PET to be significantly superior to thoracic CT because it is able to demonstrate an increased tumor metabolism even in normal-sized nodes. Although it may usefully define distant metastases, a known drawback of PET is that the FDG uptake can only be localized to the hilar or mediastinal areas differentiating left-sided form right sided activity. In routine usage at present, it has inherent limitations in defining the precise individual location of the involved groups of lymph nodes as defined in the ATS classification, which may have therapeutic implication in some of the patients. A more detailed anatomic classification of mediastinal lymph nodes may become possible by combining emission and transmission-corrected PET scan or PET – CT fusion. PET still remains costly affair and relatively limited availability in our part of country.

Endobronchial ultrasound is a fairly new technique performed by pulmonologists. The depth of imaging is 1.75 cm; hence, mediastinal lymph nodes are not readily visualized.

MRI is not reliable for detecting mediastinal involvement. It is useful, however, in detecting pericardial involvement. The sensitivity and specificity of MRI in detecting metastases to mediastinal lymph nodes ranges from 52 to 65% and from 48 to 79%, respectively.[35] It is limited by motion artifact.

Mediastinoscopy and mediastinotomy are performed by surgeons if suspicious or enlarged nodes are seen on radiographic imaging or CT. Some surgeons perform mediastinoscopy routinely in the absence of radiographic abnormalities. But it is a invasive procedure associated with morbidities like pneumothorax and left recurrent laryngeal nerve injury, avulsion of the pulmonary artery branch, bleeding from blood vessels within the mediastinum, esophageal tear, cautery burn of the bronchus, wound infections, bleeding from a lymph node biopsy site, air leak, as well as risks of general anesthesia.

Endoscopic ultrasonogram

In this context endoscopic ultrasonogram (EUS) is an accurate, relatively noninvasive, highly sensitive imaging technique in the detection of mediastinal lymph node involvement It was explained that higher resolution of EUS may be the reason that this technique was statistically significantly superior to CT. EUS precluded unnecessary surgery in 12% or one of every eight patients with NSCLC without mediastinal lymphadenopathy on CT based on the presence of a stage IIIa and stage IIIb (malignant contralateral mediastinal lymph node) disease. EUS-FNA may be more useful in staging hilar and lower lobe NSCLC compared with upper lobe NSCLC. Anterior, hilar, and paratracheal lymph nodes are not reliably imaged with EUS because of air interference from the air-filled trachea. Lymph nodes that are readily imaged are located in the aortopulmonary window (station 5), subcarina (station 7), paraesophageal region (station 8), inferior pulmonary ligament (station 9)

IV. Conclusion

The standard staging procedure so for in our institute is x-ray chest, and contrast CT scan of the chest for evaluation of mediastinal lymph node in NSCLC. As various studies indicated that the sensitivity of CT scan chest is low especially in subaortic (station 5), subcarinal (station 7) upper and lower paraesophageal (station 8 and 9), it has been planned to take up a study for evaluation of mediastinal lymphnode in NSCLC with available resources. Out of many options available to evaluate mediastinal lymph nodes the modalities like PET, nuclear scan and mediastinoscopy are not available in our institute. Though MRI is available here, it has been well known that MRI does not score over CT scan both in results as well as cost benefit. Since transesophageal endoscopic echocardiogram is available in the Department of Cardiology, and the since the same probe can be used to evaluate the mediastinal structures, and the it is a relative safe procedure with proven credential it has been decided the evaluate the mediastinal lymph nodes in NSCLC with this available modality. It is effectiveness in picking up mediastinal lymph nodes, is primarily evaluated and is compared with the results of x-ray chest and CT scan chest.

X-ray chest

X-ray chest in this study picked mediastinal lymph node involvement in only 13 cases of total 51 cases that make up a pick up rate of 25% only. More over all the 13 cases are picked up by CT scan also, so it does not score over CT scan. Statistically x-ray chest is found to have 25 % sensitive and 100 % specific. It has positive predictive value of 100% and negative predictive value of 61%. All most cases are in the upper or middle lobes. So it is an extremely unreliable test for mediastinal lymph node staging purpose. Literature search for the role of x-ray chest in mediastinal lymph node evaluation is proved futile. No recent studies compared this modality with any of the newer modality.

CT scan chest

CT scan in total picked 37 cases constituting 73% pick up. It picked upper paratracheal lymph node (station 2) in 2 cases one each side. It is very useful in station 6 that is lower paratracheal where it picked 11 cases (6 on the right and 5 on the left). It does not pick up any nodes in subaortic region. Interestingly it picked subcarinal (station 7) in all 5 cases, where it is believed to be better evaluated with EUS. Pick up at upper paraesophageal site is 14 (6 on the right and 8 on the left) and at lower paraesophageal site (station 9) is 5 (3 on the right and 2 on the left).

CT scan sensitivity is moderate only at 41%, that means if CT scan has identified mediastinal disease the chances of it being false positive is high. So the disease may be over staged and curative treatment may be denied on that basis. It has a relatively high specificity of 78%, that is if the CT scan did not pick mediastinal lymph node involvement, there are still 22% of chances of N2 disease being there, which will result in under staging of this result. So the patient may be subjected to unnecessary surgery. Positive predictive value of 42%, negative predictive value of 57% , percentage of false positivity 78% and percentage of negative predictive value 21%. Looking into literature thoracic CT has varying but limited sensitivity (43 to 81%) and specificity (59 to 85%). Some series reported even low specificity of 44%. In this the sensitivity when compared to TEU still very low to the extent of 27% and specificity of 78%. Based on CT findings, approximately 23% of NSCLC patients are overstaged, and 19% are understaged.

Two meta-analyses discussed this topic, enclosing 5420 nonoverlapping patients Dales et al included 42 studies (3194 patients) from 1980 to 1988, resulted in the following operating characteristics: sensitivity 0.83 (95% CI, 0.78–0.87), specificity 0.82 (95% CI, 0.78–0.85), and accuracy 0.80 (95% CI, 0.78–0.84).[55]H:\dissertation\downloads\5.htm - r10-5#r10-5 Dwamena et al included 29 studies (2226 patients) from 1990 to 1998. Sensitivity was 0.60 (95% CI, 0.58–0.62), specificity 0.77 (95% CI, 0.75–0.79), and accuracy 0.75 (95% CI, 0.74–0.76).[56]H:\dissertation\downloads\5.htm - r11-5#r11-5 Combining the 2 meta-analyses, the overall accuracy of CT in mediastinal staging of NSCLC seems to be only 0.75 to 0.80, with 20–40% false-negative and 18-23% false-positive results. Apart from these 2 meta-analyses, 3 prospective and 2 retrospective studies with surgical lymph node verification recently showed quite varying operating characteristics, with sensitivities of 0.33–0.75, specificities of 0.66–0.90, and accuracies of 0.64–0.79.[57]

EUS

In this study EUS is able to pick up mediastinal lymph node in 24 persons of total 51 persons with mediastinal lymph nodes combined together by CT and EUS accounting to 47%. EUS is capable identifying 11 cases of lymph node in paraesophageal (station 8) and at the level pulmonary ligament (station 9) which are missed by CT scan, and 3 cases of subaortic (station 5). Interestingly CT scan could not pick up even in single case at this site EUS is not found to be superior in subcarinal lymph node detection as 5 cases the subcarinal lymph nodes were picked by both CT and EUS. This is in contrast to the references, Julia K. LeBlanc et al

reported an EUS accuracy of 69 – 72% in diagnosing subcainal lymph nodes. EUS was found useful in subaortic lymph node (Station 5) were it picked 3 nodes which were completely missed by CT scan.
This study when compared to CT thorax the EUS is also found to have only moderate sensitivity 42%, reasonable specificity 74%, positive predictive value 33% and negative predictive value 78%.

In this study the sensitivity of CT scan and EUS are not much different (41% and 42% respectively). The specificity is also almost same 78% for CT scan and 74% for EUS. This shows the neither test is superior to the other, and neither of them can replace the other as standard staging procedure of mediastinal lymph node evaluation in NSCLC.

The values have definitely improved if consider the posterior mediastinal lymph nodes alone namely station 7, station 8 and station 9, which read as sensitivity 54%, specificity 89%, positive predictive value 39% and negative predictive value 94%. Annete Fischer Ravens et al have reported a sensitivity of 94%, specificity 74%, positive predictive value 75% and negative predictive value 92%.[58] Julia k LeBlanck reported a sensitivity of 42% and Jouke T. Annema et al have demonstrated a sensitivity of 49%, both of which are close to this study 54%.[59] The results of seven studies involving flexible bronchoscopy guided FNAB of mediastinal lymph nodes in 257 patients with NSCLS demonstrated a sensitivity of 25% - 81% and specificity of 92% - 100%.[42]
All these reports clearly demonstrate the EUS is having a highly variable sensitivity though have a relatively high specificity. So EUS evaluation of mediastinal lymph node involvement cannot replace CT thorax as staging procedure in NSCLC. However it can be used as an additional investigation especially in case of lower lobe NSCLC, which will be helpful in identifying the posterior mediastinal lymph nodes which may upstage disease to Stage III A, prompting the use of neo-adjuvant chemo or to Stage III B where the principle itself will change to palliative avoiding unnecessary surgery. Unfortunately, lymph nodes that are far away from the esophagus, such as lobar (station 12) and interlobar (station 11), cannot be readily seen by EUS.[61] This is one limitation of EUS. Likewise, lymph nodes anterior and lateral to the trachea (station 3, station 6) cannot be imaged reliably with EUS due to air interference.[61] EUS is complementary to mediastinoscopy, as aortopulmonary window (station 5) and subcarinal (station 7) lymph nodes are stations readily accessed with EUS.[62]

Safety

EUS done on 112 patients is not associated with any major complication. Considering the fact it is done in 66 of patients above 50 years of age it is a reasonably safe procedure even in elderly provided good performance status. Barawi et al prospectively studied the incidence of complications associated with EUS-FNA. In 842 mediastinal EUS, 2 hemorrhages, and 1 inexplicable transient hypotension were reported.H:\dissertation\downloads\5.htm - r86-5#r86-5 EUS is contraindicated in patients with a Zenker's diverticulum or bleeding tendency. [60]

Histological subtype

Looking into the histological subtype CT scan picked 18 cases of N2 disease in squamous cell carcinoma, 15 cases of adenocarcinoma, 3 cases of unknown subtype and 1 case of large cell carcinoma. Where as EUS has detected 15 cases of squamous cell carcinoma, 8 cases of adenocarcinoma and 1 case of subtype unknown. So in both the conditions the pick up of squamous cell carcinoma is high compared to adenocarcinoma. So neither investigation is superior to each other in identifying any particular subtype. No study could be found on search that analyze the individual histological subtype, and its influence on various methods of mediastinal lymph node evaluation.

On the flip side this study has been done on side viewing endoscopic ultrasound probe which has a maximum viewing angle of 180 degrees and requiring meticulous evaluation by rotating the scope externally. Most of the studies reported done on circular end viewing probe which can view all 360 degrees helping easy and accurate viewing. This EUS not accompanied by fine needle aspiration cytology from the identified node which will increase the diagnostic accuracy of the mediastinal lymph node especially if they are less than 1 cm and do show characteristic echo pattern of a involved lymph node. The cases are not followed with surgery which could have improved the value of the study and improved the diagnostic accuracy of EUS.

- Endoscopic ultrasonography (EUS) is relative safe, semi-invasive procedure that can be performed with minimal risk even in elderly individual provided good performance status prevails.
- EUS is able to pick up mediastinal lymph node involvement even if it is missed by CT scan which will upstage the disease to stage IIIA or IIIB and alter the therapeutic implication.
- EUS pick up is substantial in posterior mediastinal lymph nodes namely subcarinal (station 7), upper paraesophageal (station 8) and lower paraesophageal (station 9) and middle mediastinal lymph node, sub-aortic (station 5).
- EUS cannot replace CT scan as standard staging procedure for mediastinum as it pickup rate is below that of CT scan and shows decreased sensitivity in superior and middle mediastinum.

- Sensitivity and specificity of EUS not significantly superior to CT scan so it cannot replace the CT scan thorax as standard staging procedure but certainly has a role as complimentary investigation to the CT scan of the thorax, especially in the lower lobe lung cancers.

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