DM SEMINAR
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STAGING PROCEDURES FOR LUNG CANCER

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SCOPE

- INTRODUCTION
- NON-INVASIVE PROCEDURES
- INVASIVE PROCEDURES
- PRIORITIZATION OF PROCEDURES
- PROBLEM SOLVING

INTRODUCTION

Steps in W/U of Suspected Lung Cancer

I **Risk factors + Clinical evaluation + CT**

- Presumptive diagnosis
- Presumptive cell type (SCLC vs NSCLC)
- Presumptive stage

II **Further radiologic imaging & invasive tests**

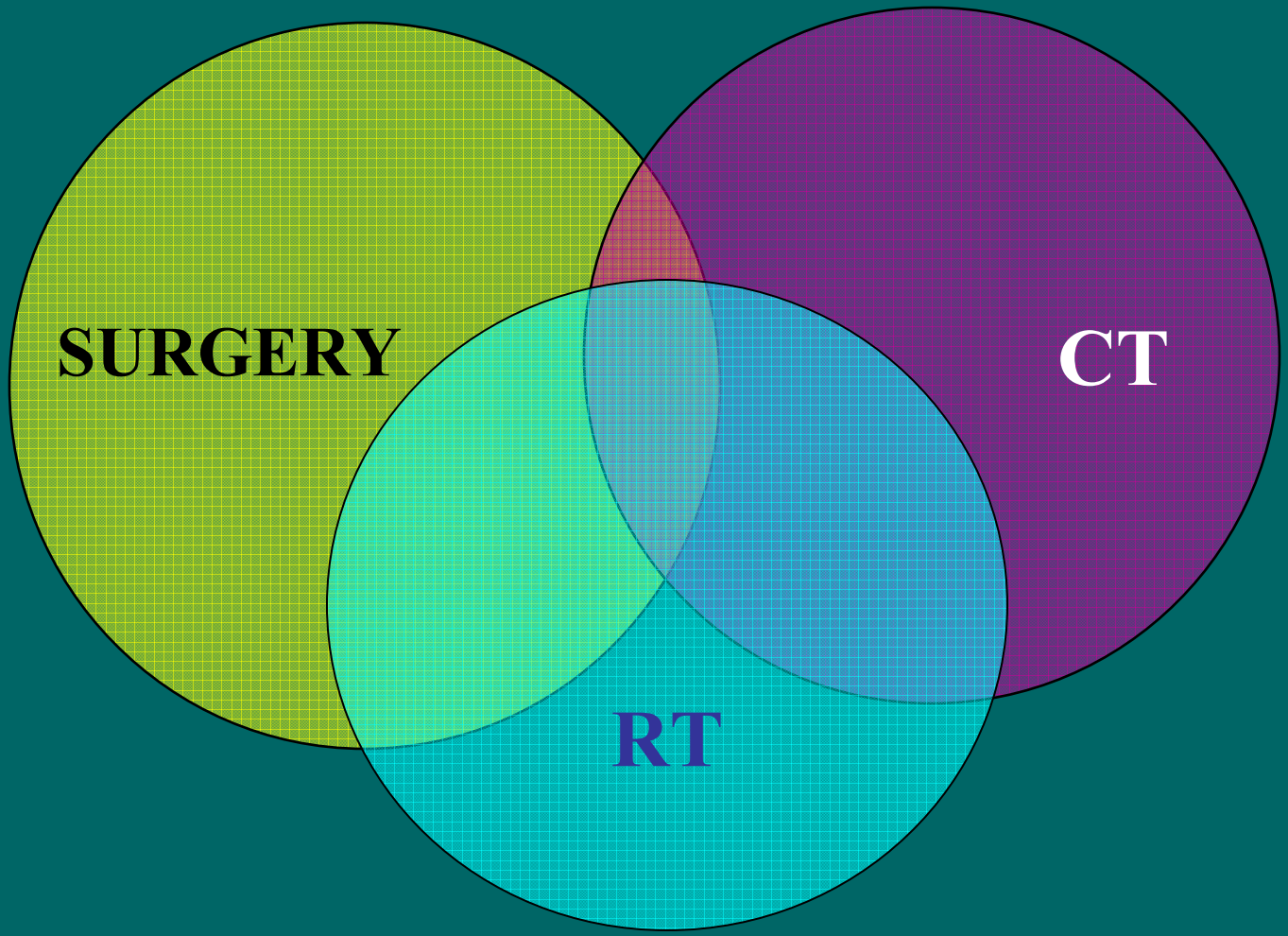
- Confirmation of diagnosis + Stage

III **Treatment**

- Surgery/RT/CT/Multimodality therapy

Detterbeck,Chest 2003; 123:167S–175

EARLY → ADVANCED



INTRODUCTION

- Staging is the process of assessment of presence & extent of local spread of tumor to adjacent structures (pleura, chest wall, pericardium & blood vessels) as well as metastasis to mediastinal LN & distant organs
- Accurate staging is important → implications for Rx & Survival:
  - Choosing most appropriate therapy
  - Prediction of survival

INTRODUCTION

- Tissue Dx of mediastinal lesions difficult by nonsurgical methods (well protected by bony covering of thorax & surrounding lungs)
- M.f cancer involving mediastinum is NSCLC (usually mets first to hilar & mediastinal LN)
- Use of traditional pre-op staging methods →
  - 10% of surgeries → explorative thoracotomy but NO Tumour Resection (advanced mediastinal disease not detected pre-op)
  - 25–35% of apparently curative resections unsuccessful due to early post-op recurrence

INTRODUCTION

- Surgery futile & unnecessary in up to 45% of operated pts of NSCLC because stage more advanced than expected pre-op
- Recent advances in technology in both imaging and endoscopic techniques → greater accuracy in staging lung cancer
- Confusion regarding indications and timing for each of these staging studies

PROBLEMS

- 59/M presented with 3 cm nodule in Lt lingular lobe on CT Chest → Bx poorly differentiated NSCLC. CT Abd → 2x4cm soft tissue mass adjacent to Lt adrenal suspicious for mets. Dx→Stage IV NSCLC
- 68/M ex-smoker presented with h/o lethargy → CT chest → Rt paratracheal & subcarinal LNE - no primary mass lesion apparent. Stage? (Primary?)
- 45/M presented with hemoptysis. CT → 4x3 cm mass in LUL with mediastinal LNE. FOB Growth LUL > 2 cm from carina – Sq CLC LUL. Dx→$T_2N_2M_0$ Stage IIIA NSCLC

NON-INVASIVE

CT

- CT used to stage pts with lung cancer since its introduction in the early seventies.
- CT (~ CXR) → imp info on localization, size & extent of tumor + locoregional/distal spread
- State-of-the-art spiral & multi-detector CT scanners → detailed 2D/3D images of tumor & its extent esp invasion of fissures, chest wall or mediastinum → decide resectability
- Despite improved image quality → many cases with unresolved issues after CT

CT For Lymph Node

- CT incl newer systems have poor specificity in determining LN involvement
- Common sign used by CT for predicting LN involvement is enlargement (not very reliable)
- Bx confirmation of neoplastic LN involvement necessary before pt is denied surgery
- Role of CT in LN staging is limited but imp → provides map of LN in hilum/mediastinum & guidance towards LN that req Bx
- CT + PET→ better LN staging of mediastinum → ↓ no of interventional staging procedures

CT For Metastasis

- Chest CT should always include visualization of upper abdomen (adrenals) in same setting
- Liver visualization is technically difficult because optimal contrast enhancement of liver is necessary in order to depict metastatic disease (difficult to obtain together with a good contrast enhanced chest CT
- CT relatviely insensitive to detect brain mets but used because more widely available

MRI

- Limited ability of CT to diff b/w fibrosis, active infl, tumor & edema → MRI (superior due to ↑ soft-tissue contrast resolution):
  - ? Diff Recurrence/Residual tumor from fibrosis
  - ? Diff Obstructive from Non-obstructive atelectasis
  - Assess chest wall invasion esp sup sulcus tumors
  - Assess mediastinal & vascular invasion
- MRI more sensitive & procedure of choice to detect brain mets

PET

- Relies on physiological rather than anatomical features of tumor cells/tissues
- Based on fact that malignant tumors have greater glucose utilization than normal tissue.
- Pt injected with 18F-fluoro-deoxy-D-glucose (radiolabeled glucose analog) → Cellular uptake ~ glucose → Phosphorylation → No further metabolism → Trapped within cells → Accumulation of isotope identified using a PET camera

PET

Common Indications

- Evaluation of nodules and masses
- Locoregional staging
- Extrathoracic staging

Molecular applications

- Early assessment of CT
- Assessment of molecular targeted therapy

Applications Under Evaluation

- Planning for RT
- Evaluation of response after RT & CT (induction)
- F/U & Dx of recurrence
- Prognostic information

PET

- Tumor evaluation and characterization:
  - More accurate than CT in evaluating nodules/masses (distinguishing b/w benign and malignant lesions)
  - Sensitivity & specificity = 85% & 88% resp in >1100 pts

    Toloza et al, Chest 2003; 123: 137S–146S
  - Useful in pre-op evaluation of pt with NSCLC being considered for radical surgery
  - Should be viewed in conjunction with CT (doesn't provide necessary anatomic detail of 1° tumor)

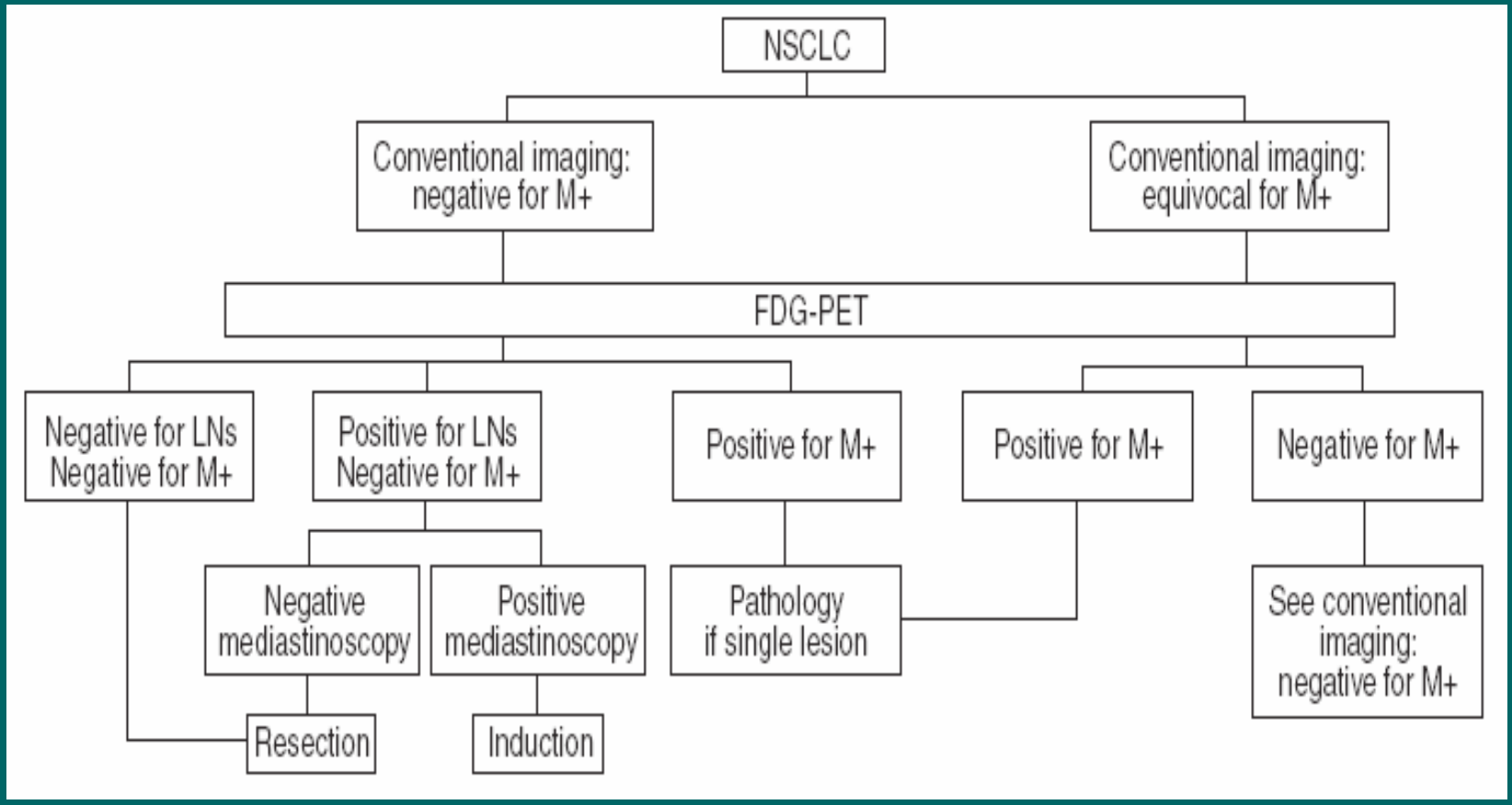
PET

- Staging (locoregional LN & extrathoracic):
  - Demonstrate neoplastic foci within N sized LN (False -ve in small malignant LN & False +ve in anthracosilicosis/infl with high metabolic activity)
  - Distinguish enlarged hyperplastic LN from neoplastic LN → Locoregional LN staging by PET (in conjuction with CT) >> CT alone → -ve predictive value ≥ mediastinoscopy
  - Improves extrathoracic staging by detection of lesions missed at conventional imaging or characterization of lesions that were equivocal

PET

- Molecular applications:
  - Newer tracers to identify receptors, transport proteins and intracellular enzymes that can be used for early response monitoring during CT/RT
    - 18F-fluoro-thymidine (assessment of SPN)
    - 18F-fluoro-misonidazole (quantification of regional hypoxia in neoplastic tissue)
    - Tc-Annexin V (Apoptosis imaging agent used for detection of recurrence of tumor cells)
  - Development of molecular-targetted therapy and gene therapy

PET



Vansteenkiste Eur Respir J 2002; 19: S35, 49S–60S

MISCELLANEOUS

- Whole Body Bone Scanning – Detect bony metastasis & prevent unnecessary thoracotomies in pts with apparently curable lung cancer
- 125 pts WBBS showed 73.5% PPV, 97.8% NPV and 91.2% accuracy higher than bone-specific clinical factors (53.8% PPV, 94.2% NPV & 81.6%). Adenoca most common cell type (39%)

Erturan et al, Chest 2005

MISCELLANEOUS

- Trans Esophageal Echocardiogarphy (TEE) – Helpful in determining aortic involvement in pts with lung cancer abutting the aorta
- 97 pts → results of TEE & CT compared with surgical/HPE results → TEE had a diagnostic accuracy of 91.8% while CT remained inconclusive in >85% *Schroder et al, Chest 2005*

INVASIVE

TBNA

- Technique for performing cytological, histological or microbiological sampling of lesions within airway wall, lung parenchyma & mediastinal structures adjacent to tracheobronchial tree
- Can access Rt &Lt paratracheal space (2R, 4L, 4R) & subcarinal space (level 7)

TBNA

- Selection of proper needle:
  - All diagnostic needles >13 mm long (except sampling submucosal lesions)
  - Specimen for HPE & cytology → 19G (or larger) & 22G (or larger) needle resp
  - Specimen from mediastinal/hilar & peripheral lesions → needle with stiff & soft catheter resp
  - All needles → Retractable design (to prevent damage to working channel of FOB)

TBNA

- Contamination of samples with br secretions to be avoided:
  - Introduce FOB into br tree without suction
  - Wash off tracheobr secretions covering target site
  - Perform TBNA before endobr examination & prior to obtaining any endobr specimens
  - Cease syringe suction (applied at prox end of TBNA catheter) before needle is withdrawn from tracheobr wall

TBNA

- Sample nodes with worst prognosis (N3>N2>N1) earlier in pts with multiple LN station involvement
- Two satisfactory specimens should be obtained from each target site
- Each disposable needle should be used in one patient only
- Rapid on-site evaluation of specimen improves the diagnostic yield

TBNA

- Small no of tumor cells alone insufficient for labeling specimen as +ve:
  - Large no of L in specimen → adequacy of LN sample while resp epi cells → possibility of contamination
  - True +ve → Large no of tumor cells in clumps or gland formation
  - True -ve → Large no of L but no tumor cells (However -ve result on TBNA does not R/O malignancy)

TBNA

- Diagnostic yield of TBNA → 15-83% with av sensitivity 76%, specificity 96% & +ve predictive value of 90-100%
- More likely to be successful when:
  - Histology needle is used
  - SCLC is present
  - Carina is abnormal
  - Radiological e/o mediastinal disease
  - Lesions/LN Rt sided, large or located in paratracheal/subcarinal region

TBNA

- Major complications rare.
- Minor complications:
  - Self-limited minor bleeding (0.045-0.12%)
  - PneumoTx/pneumomediastinum (1.8-2.9%)
  - Inadvertent puncture of adjacent structures
- Damage to FOB

TBNA

- Although Dx accuracy of FOB for central pul neoplasms is 80-97%, +ve yield of Dx info in peripheral neoplasms beyond range of FOB can be as low as 33% esp. if lesion < 2cm dia
- This is despite use of preprocedural CT, fluoroscopic guidance & use of variety of instruments because conventional TBNA is a **BLIND** procedure → exact site of peripheral intraluminal or extraluminal masses may not be evident

EBUS – TBNA

EUS – FNA

VAM

VATS

EBUS

- EBUS is a Dx technique that utilizes a catheter based miniaturized USG transducer for study of tracheobr wall and immediate surrounding structures
- USG waves → transmitted to anatomical structures → Reflected echoes transformed into electrical signals → Images created

EBUS

Equipment:

- USG probes – 2 types:
  1) Sectorial transducers of 7.5 MHz incorporated in tip of specially-designed 7-mm FOB
  2) Balloon-tipped miniaturized probes of 2.8–3.2 mm with 12 & 20-MHz transducers that can be inserted through the working channel of conventional FOB
- Driving unit to rotate miniaturized probes
- USG processor

EBUS

Technique:

- USG probe gently pressed to bronchial wall and passed along structures to be investigated
- For circular views, instrument rotated 360◦
- Target site → Balloon inflated with D water → Close circular contact achieved → Wall & surrounding structures visible

EBUS

Indications:

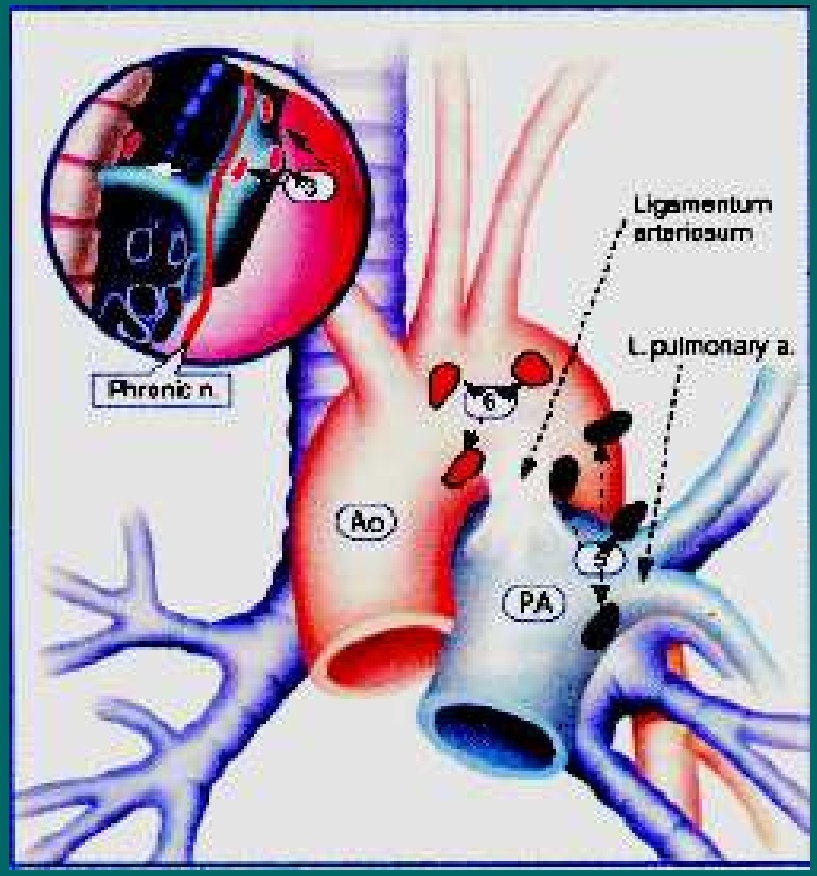
- Evaluate regional LN involvement
- Identify & localize mediastinal structures adjacent to airways before TBNA → minimize complications
- Stage depth of tumour invasion in bronchial wall

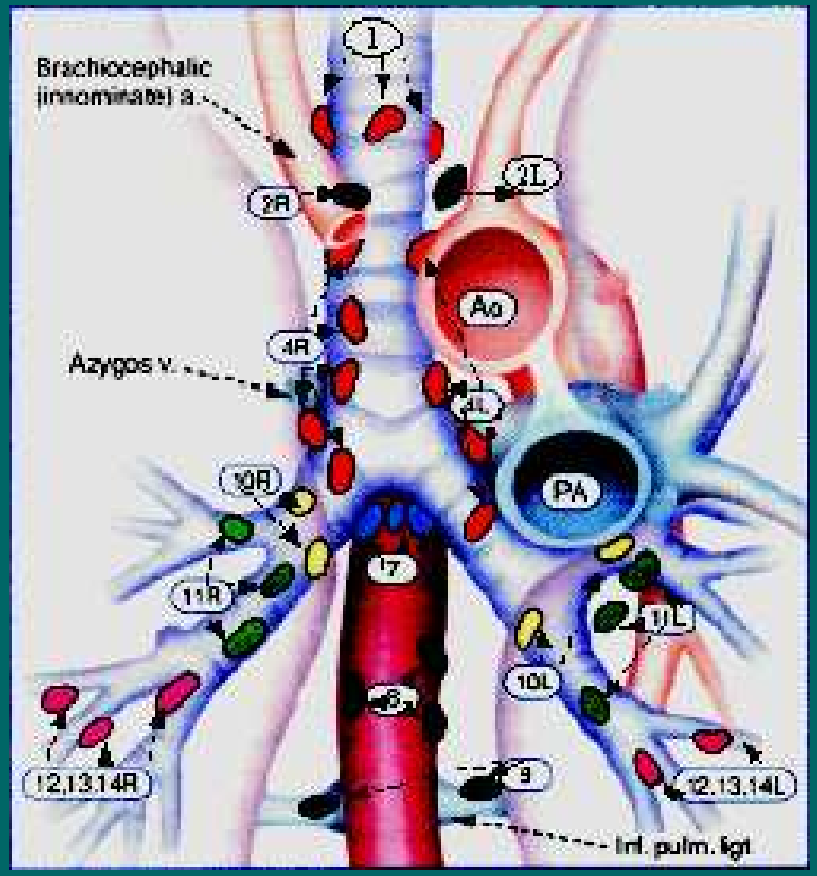
- Contraindications – same as for FOB/TBNA
- Complications – none specific for EBUS reported

EUS-FNA

- Procedure ≈ UGIE (special endoscope + real-time USG probe)
- OPD procedure (conscious sedation) & min complication rate
- Based on fact that esophagus lies post & to left of trachea and is in proximity of LN between these two structures
- LN level 5 (AP window), level 7 (subcarina), & inf mediastinal LN easily accessed

LN Stations





Mountain et al. Regional LN classification for lung cancer staging. Chest 1997; 111: 1718–1723

EUS-FNA

- After LN visualized → FNA → Cytology
- In addition to ability to visualize & sample enlarged LN, EUS can also detect malignancy in N sized LN
- Sensitivity reaches 90–98% in expert hands
- Inability to access Rt levels 2R, 4R & pretracheal space

EUS-FNA

- Pts with no LNE on CT→ ¼ LN mets after EUS-FNA → Change in Mx if EUS done routinely as initial invasive staging modality
- PET +ve pts should undergo EUS-FNA due to high false +ve rate of PET 9–39%
- Done ↓ Conscious sedation/OPD procedure
- Complication <0.5% (most minor) ~ 2-5% for VAM

Vilmann et al, Eur Respir J 2005

EUS-FNA

- 52 → EUS-FNA performed for Dx of mediastinal LNE of unknown etiology (34) & staging of NSCLC (18):
  - -ve results confirmed with VAM, VATS or lobectomy with mediastinal LN dissection
  - Sensitivity=93%, specificity=100%, PPV=100%, NPV=88% & Dx accuracy=95%
  - Mediastinal LNE of unknown etiology → no malignant disease was missed
  - EUS-FNA accurate for staging NSCLC & as an adjunct or alternative to VAM

Caddy et al, Eur Respir J 2005

EUS-FNA

- 76 pts → EUS-FNA used for staging NSCLC in absence of LNE on CT:
  - EUS-FNA performed on sites suspicious for mets
  - Surgical HPE after thoracotomy used as reference std for assessing accuracy
  - EUS detected malignant mediastinal LNE more frequently in pts with LL & hilar cancers ~ UL (senstivity = 100% vs 17%)
  - EUS changed Mx plan in 25%

LeBlanc et al, Am J Respir Crit Care Med 2005

TBNA vs EUS-FNA

- TBNA performed blindly → Sensitivity not as high as with EUS-FNA. (latter may be superior for Dx of mediastinal mets in NSCLC)
- TBNA can access precarinal & Rt paratracheal areas (not accessible by EUS-FNA)

EBUS-TBNA vs EUS-FNA

- Prototype EBUS probe → TBNA of paratracheal & hilar LN ↓ real-time imaging in 18/20 pts (conscious sedation)
  - N2/N3 disease in 11 cases & 1° Dx in 8 pts
  - EBUS-TBNA -ve 6 (confirmed by VAM & F/U)
  - EUS → Additional information in all cases
  - No procedural complications
  - EBUS-TBNA → Sensitivity=85%, specificity=100% & accuracy=89%
  - EBUS-TBNA>TBNA (sensitivity & accuracy)
  - Combination with EUS → staging of mediastinum in majority

Rintoul et al, Eur Respir J 2005

TTNA

- TTNA (TTNB) → percutaneous sampling of lesions involving chest wall, lung parenchyma & mediastinum for cytological or HPE
- Overall Dx sensitivity = 68–96%, specificity <100% & accuracy = 74–96% (lower in smaller lesions)
- PneumoTx ≈20–40% (50% req ICTD)
- Self-limiting h'ge & hemoptysis infrequent

ERS/ATS statement on interventional pulmonology Eur Respir J 2002

MEDIASTINOSCOPY

- Mediastinoscopy & LN Bx most reliable preop staging method for NSCLC esp. N2 disease
- Impractical & uneconomical to recommend VAM for all candidates before surgery
- Indicational criteria:
  - CT e/o mediastinal LNE
  - Elevated levels of serologic tumor markers
  - Diameters of primary cancers (> 2-3 cm)

Kimura et al, Ann Thorac Surg. 2003

MEDIASTINOSCOPY

- Retrospective review of 238 pts who had VAM for Dx of LNE (> 1 cm on CT) or staging of ca lung:
  - 192 → lung cancer (174 NSCLC)
  - 7→ malignancies other than lung cancer
  - 39 → sarcoidosis, reactive hyperplasia, TB (4)
  - Mediastinal LN inv seen in 107/174 (N2 = 79)
  - Postthoracotomy staging ~ 44/47 cases (93.6%).
  - Only 2 pts complications

Venissac N et al, Ann Thorac Surg. 2003

MEDIASTINOSCOPY

Comparison with PET in pts with NSCLC:

- 102 pts of bronchogenic Ca with suspected mediastinal LN disease on radiology
- Mediastinoscopy done within 6 wks of PET scan
- 87 → Malignancy in LN (82 bronchogenic Ca)
- 469 LN stations → Malignancy in 84 (PET → 79)
- Sensitivity, specificity, PPV, NPV & accuracy of PET≈ 94%, 79%, 49%, 98% & 82%
- Pts with +ve PET → HPE reqd for LN staging
- Pts with -ve PET → Omit mediastinoscopy

Graeter et al, Ann Thorac Surg 2003

MEDIASTINOSCOPY

Comparison with PET in pts with NSCLC:

- 1988 pts with known/suspected NSCLC → PET
- 202 pts without e/o distant mets → Cervical mediastinoscopy done (after PET)
- 65 pts (+ve results on PET) → 29 had +ve results on mediastinoscopy in corresponding LN station
- 137 pts (-ve results on PET) → 16 N2/N3 disease
- Sensitivity, specificity, PPV, NPV & accuracy of PET≈ 64%, 77%, 45%, 88% & 74%
- HPE in pts with false +ve PET incl granulomatous infl, sinus histiocytosis & silicosis
- Mediastinoscopy + LN Bx > PET for staging

Gonzalez-Stawinski et al, J Thorac Cardiovasc Surg. 2003

PRIORITIZATION

PRIORITIZATION

- CT should be performed in all pts with known/suspected lung cancer to help delineate characteristics of 1° tumor, assess best method for Bx & mediastinum
- Pts who are otherwise surgical candidates → PET (if available) should be performed
- If FOB performed to make initial Dx of lung cancer & CT/PET reveals LNE in an accessible area → TBNA should be performed prior to Bx of primary tumor

PRIORITIZATION

- If CT/PET reveals LNE in AP window or subcarina → EUS-FNA can be used for confirmation of mets to mediastinum
- EUS-FNA +TBNA can do minimally invasive mediastinal sampling in OPD setting and occ obviate need for mediastinoscopy and/or mediastinotomy ‘the gold standard’

PRIORITIZATION

- In pts with extensive mediastinal infiltration with tumor (esp. inability to see discrete lymph nodes) → main aim is confirmation of Dx since radiographic staging of mediastinal node involvement is adequate
  - TTNA/EUS-FNA procedures of choice (high sensitivity~ 90% & low morbidity–OPD procedure)
  - TBNA is alternative with appropriately located mediastinal involvement (lower sensitivity~75% & occ FP results)
  - Mediastinoscopy is least useful (higher morbidity)

Detterbeck et al, Invasive Staging: The Guidelines. Chest 2003; 123:167S–175

PRIORITIZATION

- In pts suspected of having NSCLC with no e/o distant mets but with enlarged, discrete mediastinal LN on CT:
  - Mediastinoscopy invasive procedure of choice → can stage most of commonly involved LN stations (low FP rate, low FN rate ~ 10% & low morbidity ~2%, OPD procedure)
  - TBNA, TTNA & EUS-FNA alternatives → less thorough mediastinal staging (difficulty in assessing many LN stations & higher FN rate)
  - Pts with LUL cancer → Ant mediastinotomy, extended cervical mediastinoscopy, EUS-FNA or thoracoscopy to evaluate APW LN (if other LN stations are found uninvolved)

Detterbeck et al, Invasive Staging: The Guidelines. Chest 2003; 123:167S–175

PRIORITIZATION

- In pts suspected of having NSCLC with no e/o distant mets & N mediastinal LN on CT:
  - Mediastinoscopy invasive procedure of choice to rule out mediastinal LN involvement → can stage most of commonly involved mediastinal LN stations (low FP rate, low FN rate ~ 10% & low morbidity ~2%, OPD procedure)
  - TBNA/TTNA & EUS-FNA not recommended (high FN rate)
  - Pts with LUL cancer → Ant mediastinotomy, extended cervical mediastinoscopy or thoracoscopy → to evaluate APW LN

Detterbeck et al, Invasive Staging: The Guidelines. Chest 2003; 123:167S–175

PRIORITIZATION

- Pts with +ve PET scan for mediastinum → confirm by sampling of PET +ve LN using mediastinoscopy (high sensitivity & low FN rate). Also applicable for pts with –ve PET scan for mediastinum in whom confirmation of absence of mediastinal involvement is deemed necessary

Detterbeck et al, Invasive Staging: The Guidelines. Chest 2003; 123:167S–175

PROBLEM SOLVING

PROBLEM SOLVING

59/M presented with 3 cm nodule in Lt lingular lobe on CT Chest → Bx poorly differentiated NSCLC. CT Abd → 2x4cm soft tissue mass adjacent to Lt adrenal suspicious for mets

? Stage IV

PROBLEM SOLVING

- PET study: Lt lingular mass →↑ metabolism c/w malignancy. No uptake in Lt adrenal region soft tissue mass Bx → benign columnar ciliated & mesothelial cells. No malignant cells
- FINAL Dx → STAGE I NSCLC

PROBLEM SOLVING

- 68/M ex-smoker presented with h/o lethargy → CT chest → Rt paratracheal & subcarinal LNE - no primary mass lesion apparent.
- ↓ conscious sedation → EBUS exam of mediastinal/hilar LN + FNA of Rt paratracheal LN. Same sitting → EUS exam of post & inf mediastinal LN. Small primary lesion seen paraesophageal area deep to subcarinal LN invading pleura → core Bx of lesion & LN → +ve for malignancy→ ChemoTx
- FINAL Dx → $T_3N_2M_0$ Stage IIIA NSCLC

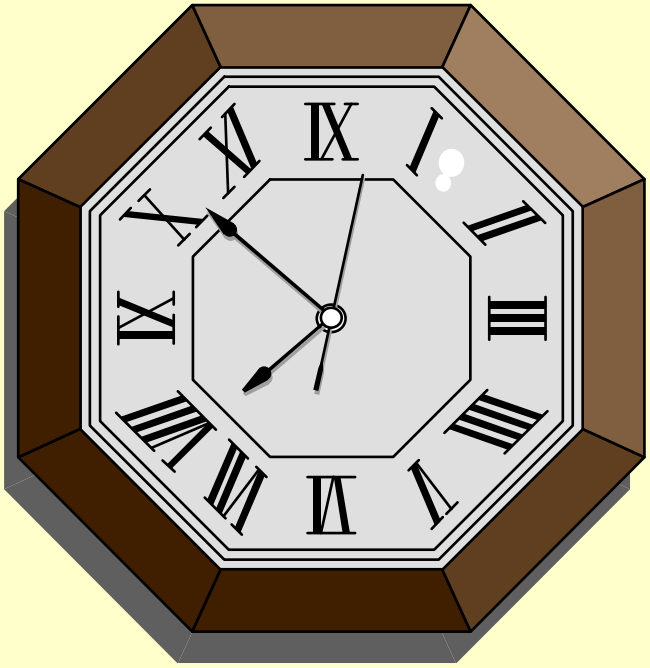
Rintoul et al, Chest 2004; 126:2020–202

PROBLEM SOLVING

- 45/M presented with hemoptysis. CT → 4x3 cm LUL mass + mediastinal LNE. FOB → Growth LUL >2 cm from carina – Sq CLC
- EBUS exam of mediastinal & hilar LN + FNA of pretracheal LN → -ve for malignancy. Same sitting EUS-FNA → posteroinf mediastinal & deep subcarinal LN →-ve for malignancy. Surgery + frozen section → no mediastinal mets (reactive infl in LN) → complete resection
- FINAL Dx → $T_2N_1M_0$ Stage IIB NSCLC

Rintoul et al, Chest 2004; 126:2020–202

TIME IS VERY IMPORTANT



CONCLUSION

- Most important Take-Home Message

  → Do not rely solely on imaging modalities while staging patients with lung cancer

  → Tissue confirmation is required so that patients with potentially curative cancer are not denied surgery & unresectable cancers are not subjected to unnecessary thoracotomies


LUNG CANCER