

The Diagnosis of Mediastinal Lesions by EBUS-FNA and EUS-FNA



3rd KAMC CYTOPATHOLOGY
SYMPOSIUM

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OUTLINE

1. Diagnostic Modalities for Mediastinal/Lung Lesions:

1. CT Transthoracic FNA
2. Transbronchial FNA (Wang needle)
3. EBUS/EUS FNA
4. Mediastinoscopy & Thoracoscopy

□ Cytology Perspective:

1. Team Approach
2. Adequacy
3. On-Site evaluation
4. Cytomorphology: Granulomas; Carcinomas; Lymphomas
5. Selected cases: DD; challenges; & pitfalls.

1. Selected EBUS/EUS FNA Cases (1-6)

2. Use of Core Needle biopsy:

3. Conclusions:

Mediastinal Mass



Non-neoplastic

Neoplastic

RLH

Granulomatous

Other

Lymphoma

Primary

Metastases

Sarcoidosis

Infectious

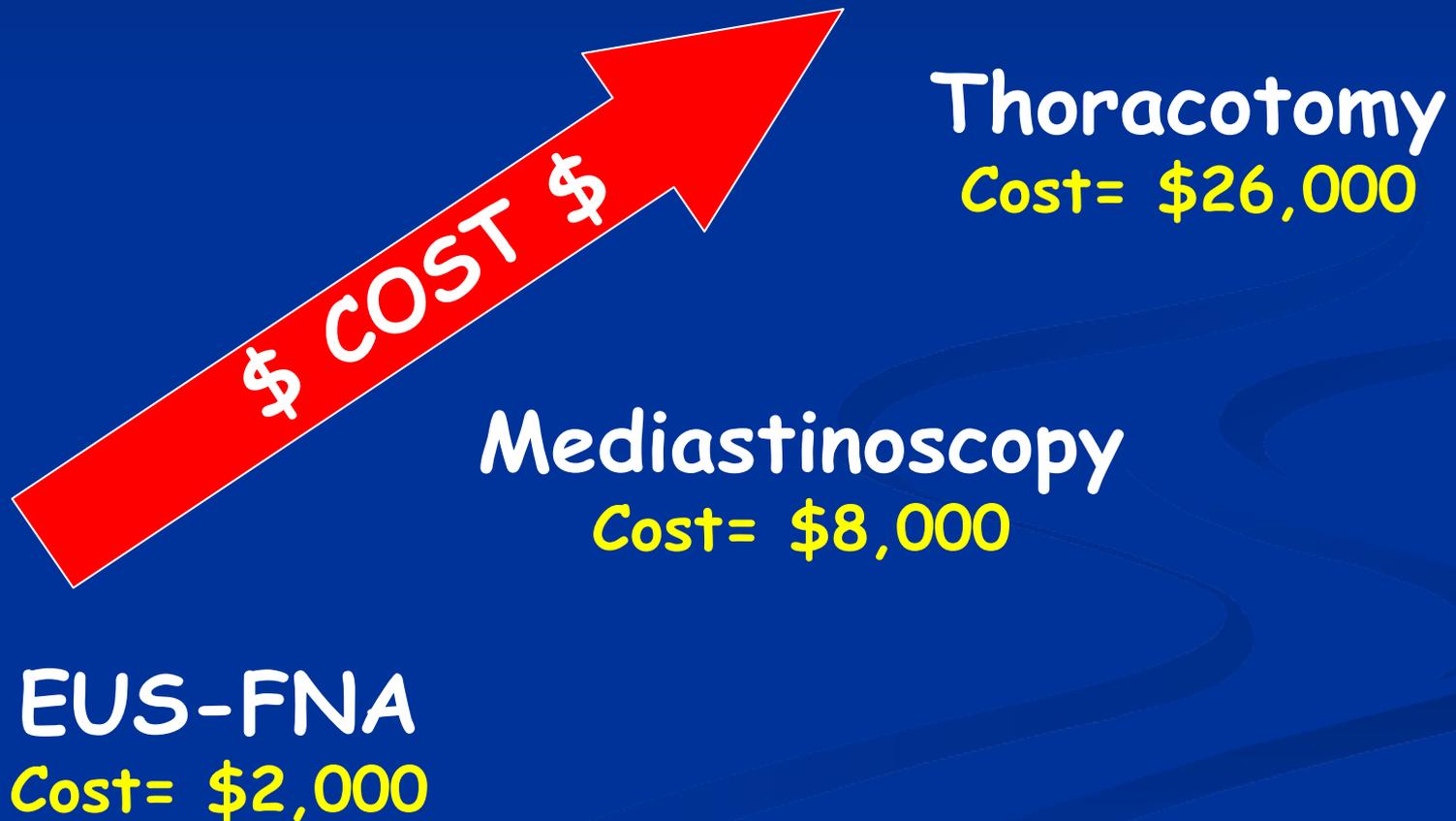
NHL

HL

Lung Ca

Other

Diagnostic Modalities for Mediastinal/Lung Lesions



Imaging & Diagnosis of Mediastinal/Lung Lesions

■ Imaging Modalities

- Chest Xray
- CT Scan
- PET CT Scan

■ Diagnostic Modalities

- Transthoracic CT-Guided FNA
- Transbronchial FNA (Wang Bx)
- Mediastinoscopy
- **EBUS & EUS guided FNA**

CLINICAL Sx



IMAGE



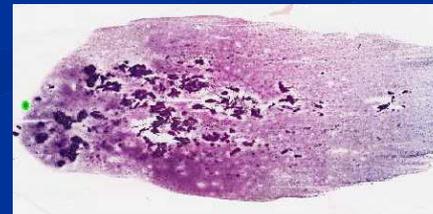
DIAGNOSE



STAGE



TREAT



Diagnostic Modalities for Mediastinal/Lung Lesions

CT-Guided Transthoracic FNA

- Detects LNs > 1cm
- Sen and Spec: 70-75%
- Limitation:
 - No real-time visualization
 - Risk of PNX (10-60%)

Transbronchial FNA (Wang needle)

- Useful for enlarged subcarinal and paratracheal LNs
- Sens. about **25-81%**
- Limitation:
 - No real-time visualization
 - Cannot access aortopulmonary window and inferior mediastinal LNs

Mediastinoscopy & Thoracoscopy

- Gold-standard for preoperative staging of mediastinal lesions
- **Invasive/ Costly**
- Slower recovery postoperatively, requires general anesthesia
- Diagnostic yield **83-89%**
- Limitation:
 - Surgical complication rate 1-3%
 - Inability to access certain LNs
 - Hard to repeat due to post-procedural fibrosis

Cost=
\$8,000

EBUS/EUS FNA

- 1st available in 2004-2005
- Minimally invasive way to sample the lung/mediastinum
- Indications:
 - Staging
 - Diagnosis of lung or mediastinal tumors

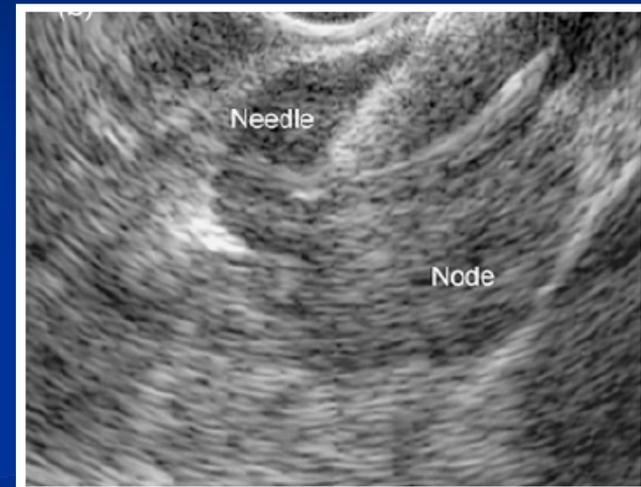
EBUS/EUS FNA

■ Advantages:

- Minimally invasive
- Broad sampling capability
- Image guidance
- Tissue confirmation of +PET/CT findings & evaluation of LNs <1 cm
- On-site evaluation → triage

■ Disadvantages:

- Inability to access all LNs
- Not universally available
- Time requirement
- Non-diagnostic specimens

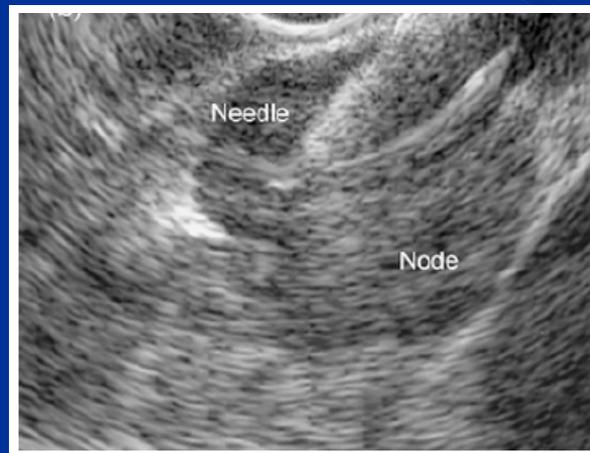


**Remember
Special
Situations!**



EBUS/EUS FNA

- **Important in Special Situations**
 - Restaging
 - Small LNs < 1 cm
 - Poor Operative Candidates
 - Non-surgical diseases



EBUS FNA vs. EUS FNA

■ EBUS FNA

- US-Guided thru bronchus
- Anterior mediastinal sampling
- Limitation: Inability to access posterior & inferior mediastinal lymph nodes
- Sensitivity and specificity generally > 85%

■ EUS FNA

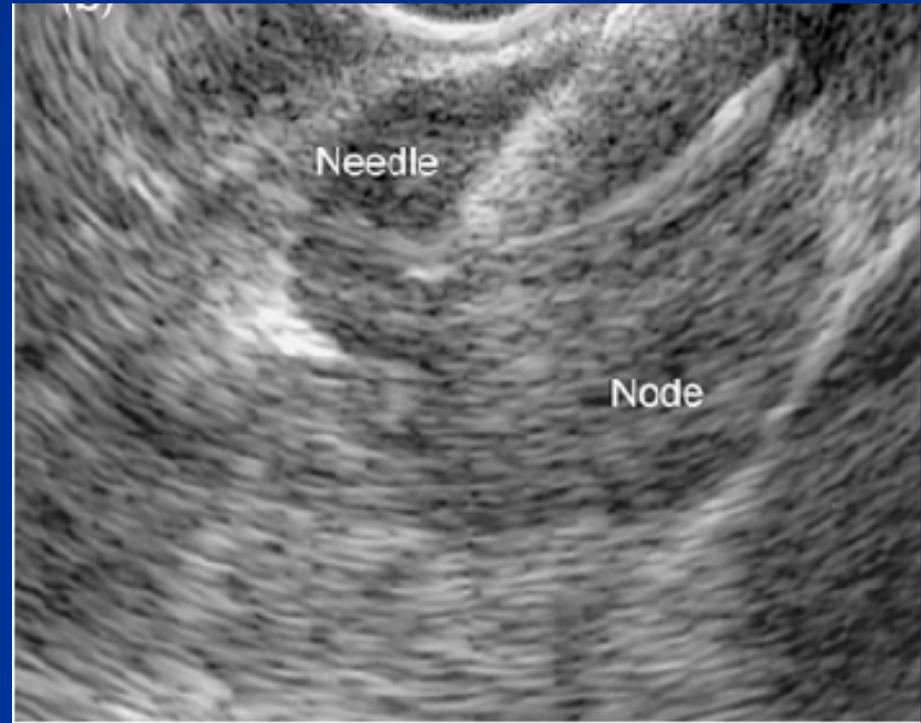
- US-Guided thru esophagus
- Staging of GI cancers
- Posterior mediastinal sampling
- Can sample central lung masses and upper retroperitoneum
- Limitation: Inability to access anterior mediastinum
- Sensitivity 82-100%

Surgical Perspective

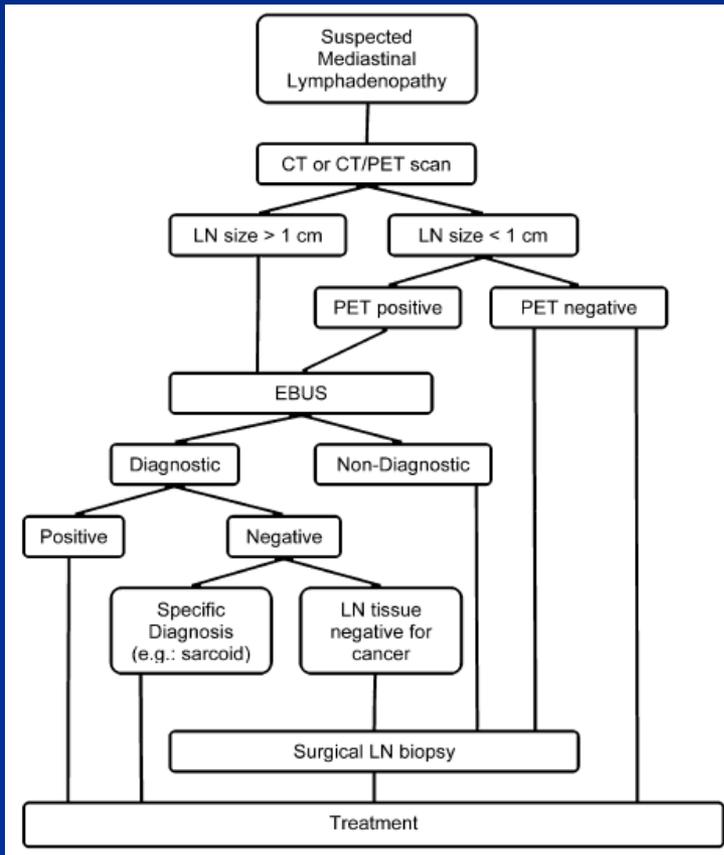


EBUS/EUS FNA

- **Sonographic features of lymph nodes worrisome for malignancy:**
 - Diameter >5-10 mm on the short axis
 - Round, sharp, & distinct margins
 - Hypoechoic texture

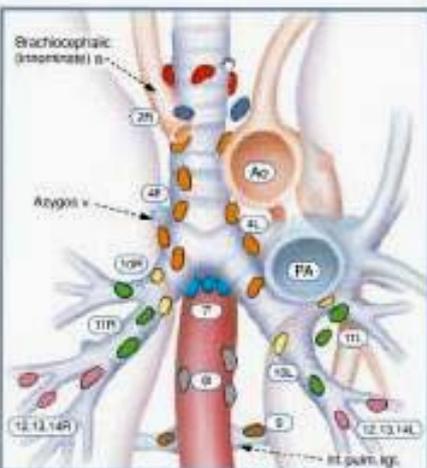


The Surgical Approach



Of the patients with a
+PET scan suspicious
for clinical stage III
Lung Cancer

↓
EBUS-FNA
downstaged 40%
patients



Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N₁, a single digit, ipsilateral
N₂, a single digit, contralateral or supracardiac

Aortic Nodes

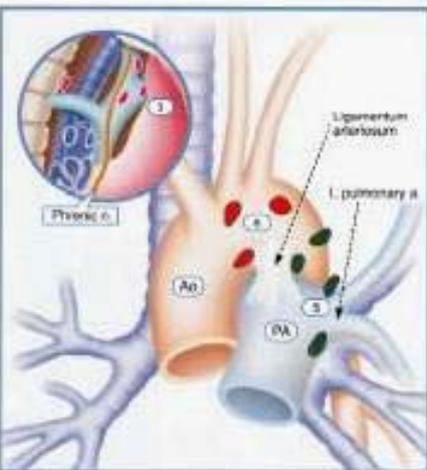
- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N₁ Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental



(Mountain, Dresler modification from Nanda MS (1993) Med)

© 1997 American Association for Thoracic Surgery

■ EBUS FNA

- Access to L4, L7, Hilar (L10-12)
- Cannot access L5, L6, L8, L9

■ EUS FNA

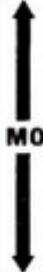
- Access to L5, L6, L7, L8, L9

■ Mediastinoscopy

- Access to L2, L4, L7

TNM STAGING OF LUNG CANCER

Supraclavicular	Scalene (ipsi-/contralateral)		Mediastinal		Subcarinal	Hilar		Peribronchial (ipsilateral)	LYMPH NODE (N)	
	(contralateral)	(ipsilateral)	(contralateral)	(ipsilateral)		(contralateral)	(ipsilateral)			
+	/	/	+		/	+			N3	Stage IV M1 (any T, any N)
-	-	-		+ & / +		-			N2	Stage III B
-	-	-	-	-	-		+ & / +		N1	Stage III A
-	-	-	-	-	-	-	-	-	N0	Stage II A Stage II B
-	-	-	-	-	-	-	-	-	N0	Stage I A Stage I B Stage II B
Stage 0										
										T1
										T2
										T3
										T4
										PRIMARY TUMOR (T)

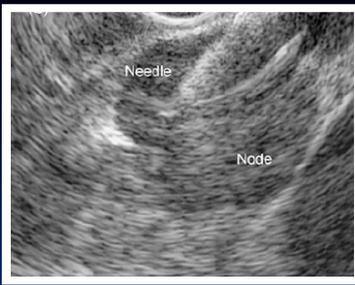


M0

- **Accurate staging is crucial because:**
 - Guides prognosis & treatment planning
 - Prerequisite for clinical trials
- **Treatment of lung cancer depends on:**
 - Histologic subtype (SCLC vs NSCLC)
 - Presence of mediastinal LN involvement
 - Presence of distant metastases

Cytology Perspective

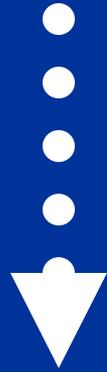
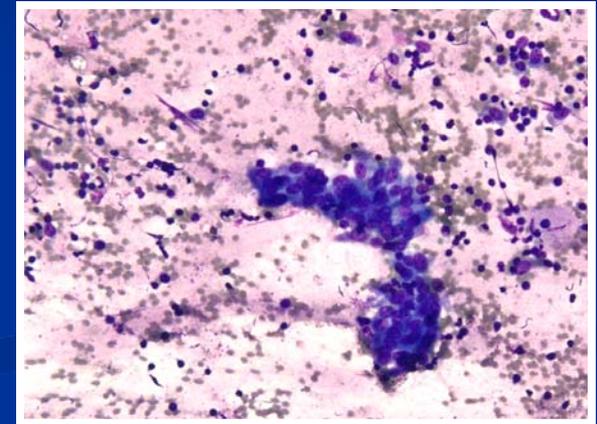




**EBUS/EUS
FNA**



**On-Site Evalu.by
Cytopathology**



? Mediastinoscopy

EBUS/EUS FNA

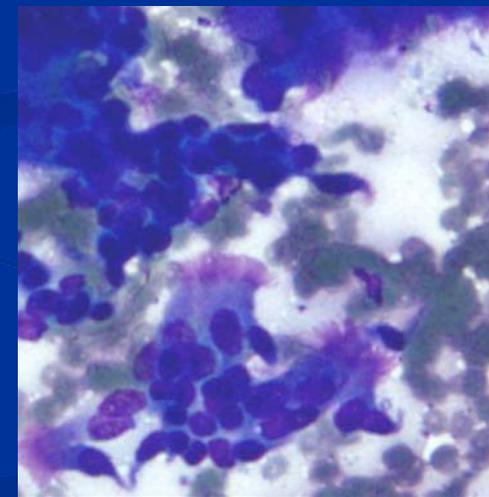
■ Team Approach

- Performer of the biopsy
 - Surgeon (Operating Room)
 - Pulmonary/Critical Care Physician (Bronchoscopy)
- Cytopathology Team
 - Cytotechnologist
 - Cytopathologist
- Support Staff



Role of Rapid On-site Evaluation

- Immediate feedback
- Adequacy assessment
- Quality of material
- Triage: *Cell block; Flow, Culture*



FNAB Adequacy

The Approach: Quantity and Quality

- Quantitative Guidelines
- Qualitative Guidelines
- Combined approach (optimal/the goal)
 - Quantitative and Qualitative Criteria
 - **Evaluation of all aspects:** background material, cellularity, cell preservation, and architecture

FNAB Adequacy

The Approach: Quantity and Quality

- Depends on the type of specimens

EBUS-guided FNA

-Normal: Cellular

- BEC, Lymphocytes
- Mucus present

-Abnormal: Cell types present

- Qualitative features

Are the correct type of cells present?

Are there tumor cells present?

Transthoracic CT-guided FNA

-Normal: Hypocellular

- Few BECs, macrophages
- No mucus present

-Abnormal: ↑ in cellularity

- Quantitative features

Inflammation

Neoplasia

Pitfalls of EBUS FNA

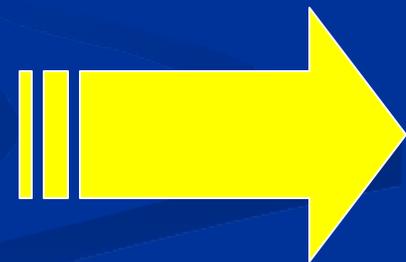
- **Reactive/metaplastic changes in bronchial epithelium**
- **Germinal center cells, large lymphocytes, and macrophages**
- **Granulomatous inflammation**
 - Differential diagnosis includes a variety of entities: infectious (ex. TB), inflammatory, sarcoidosis, malignancy
 - The diagnosis of sarcoidosis requires clinical and radiologic correlation
- **Lymphoid cells with crush artifact vs. SCLC vs. other tumors with neuroendocrine differentiation**
- **Single, dyscohesive malignant cells**
- **Lymphoma**
 - Consider the possibility of abnormal lymphoid cells or lymphoma because triage with flow cytometry is helpful

Selected Cases



EBUS FNA Adequacy Issues

- # Passes
- Sufficient # of lymphocytes
- Anthracotic Macrophages
- Non-diagnostic cases

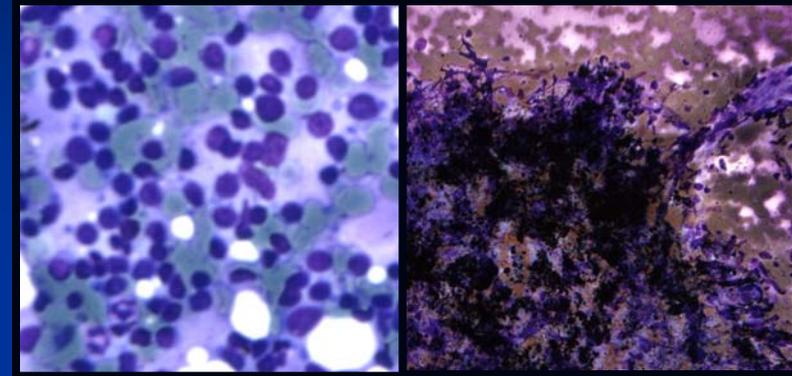


EBUS FNA Adequacy

- Usually 3-5 passes

- Adequate if:

- Malignant lesion is identified
- Sufficient nodal tissue is obtained
 - Numerous lymphocytes and/or
 - Anthracotic pigment-laden macrophages



Adequacy Criteria

1 smear with many small lymphocytes and/or FCC

35 % Unsat
(55/155 cases)

Surgical &/or Histologic F/U in all cases
EUS-FNA

Lymphocytes comprise >30% of cellularity

18 % Unsat
(35/194 cases)

Histologic F/U in small %
TBNA

> 40 lymphocytes/hpf in the most cellular areas and/or APLM

15.7 % Unsat
(26/229 cases)

Histologic F/U only in 28% cases (54/193 diagnostic samples)
EBUS-FNA

EBUS Diagnostic Yield

- Variable depending on:
 - Site & Size
 - Malignant vs. Non-malignant
 - Prevalence of cancer
 - # of passes
 - On-site evaluation by cytologist
 - Experience of the performer
 - Adequacy criteria
 - Surgical confirmation

Surgical Perspective of Inadequate EBUS/EUS FNA

- Clinical Question:
 - How do you deal with inadequate/LTO EBUS/EUS FNAs from a management perspective?

Differential Dx/Pitfalls

- Granulomatous Inflammation
 - Necrotizing- infection (TB), other
 - Non-necrotizing- sarcoidosis, other
 - Granulomas associated with malignancy
 - *Lymphoma, Seminoma, Metastatic Carcinoma*
- Lymphohistiocytic aggregates in Reactive lymphadenopathy.
- Non-small cell carcinoma
 - Lung origin
 - Non-pulmonary origin- bland metastatic neoplasms

Granulomatous Diseases & Diagnosis

■ Transbronchial Bx

- Non-diagnostic in 30% (1/3) patients
- Risks

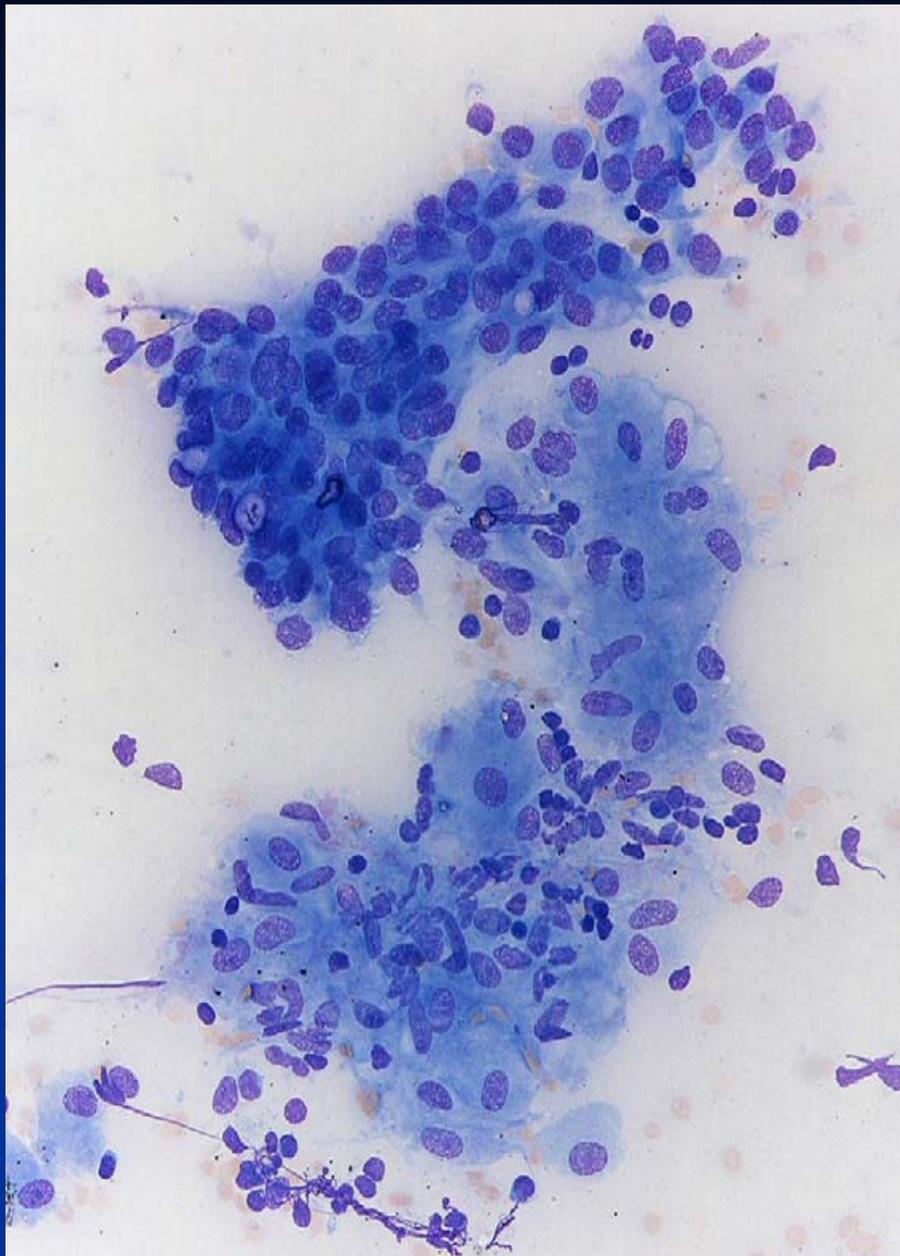
■ EBUS/EUS FNA

- Dx Yield of 60-82%
- Sen 89-100%
- Characteristic US appearance
- Minimal/No Risks

Tissue diagnosis or culture is needed for diagnosis and treatment

Granulomatous Inflammation & Risk of Metastasis

- Co involvement of sarcoidal reaction and metastatic NSCLC is possible, but uncommon
- Sarcoidal reactions in LNs of patients with NSCLC
 - Occurred in 4.3% patients (8 of 187 patients)
 - None coexisted with metastatic carcinoma
 - None had a prior history of sarcoidosis or other granulomatous disease
- Rare reports of metastatic carcinoma coexisting with sarcoidal reaction
 - Highest rate was 18% (4 of 22 with micromets)



Rare reports of
metastatic carcinoma
coexisting with
sarcoidal reaction

Highest rate was
18% (4 of 22 with
micromets)

Sarcoidal reactions in regional lymph nodes of patients with non-small cell lung cancer: Incidence and implications for minimally invasive staging with endobronchial ultrasound

Daniel P. Steinfort_, and Louis B. Irving; Lung Cancer

Results

EBUS-TBNA revealed non-necrotizing granulomas in one patient, and in 45 patients it revealed metastatic primary lung malignancy. Surgical lymph node sampling was performed in 187 patients undergoing treatment for, or staging of, NSCLC. **Sarcoidal reactions were seen in regional lymph nodes of eight (4.3%) of patients, with all lymph nodes free of metastatic NSCLC (pathologic Stage I) ($p = 0.02$).** Four of these patients were pre-operatively assessed as Stage III (cN2/3). None had a prior history of sarcoidosis or other granulomatous diseases. All eight patients remain alive and recurrence-free.

Conclusions: Sarcoidal reactions are seen in 4.3% of all patients with NSCLC. Metastatic involvement by NSCLC is not seen in lymph nodes exhibiting sarcoidal granulomatous reactions. **Non-necrotizing granulomas revealed by EBUS-TBNA of lymph nodes during staging of NSCLC should serve to indicate the absence of lymph node metastases.**

Granulomatous Diseases & EBUS/EUS FNA

- Clinical Question:
 - Do you do surgery in cases with non-necrotizing granulomas?
 - What other workup do you do to prove the diagnosis of sarcoidosis?

D.D./Pitfalls

- Dyscohesive lesions/neoplasms to be aware of:
 - Signet ring adenocarcinoma
 - Squamous cell carcinoma, keratinizing type
 - Small cell carcinoma
 - Lymphoma
 - Seminoma
 - Melanoma
 - Mesenchymal lesions- spindle cell lesions

Difficult Cases in EBUS/EUS FNA

- Consider the possibilities of primaries outside of the lung
 - Cell block material for IHC can help
- Beware of single atypical cells
 - Single dyskeratotic squamous cells
 - Signet-ring type adenocarcinoma

Pitfalls of NSCLC in EBUS/EUS FNAs

Germinal Center Cells

Granulomatous Inflammation

Dyskeratotic Cells

Reactive Bronchial Cells

Single Cells

Management of Difficult Cases in EBUS/EUS FNA

- **Clinical Question:**
 - When on-site evaluation is atypical/suspicious, how do you manage these patients?
 - Do you go on to mediastinoscopy or wait for the final diagnosis?

D.D. & Pitfalls

- Reserve cell hyperplasia
- Benign lymphoid cells
- Small cell carcinoma
- Non-small cell carcinoma
 - With neuroendocrine features/LCNEC
 - Basaloid carcinoma
- Lymphoma

Neuroendocrine Tumors in EBUS/EUS FNA

- Distinguishing NSCLC vs. SCLC is not always easy
 - **NSCLC mimics of SCLC:** LCNEC, Basaloid Ca
- Many entities can mimic SCLC
 - Lymphomas, Benign lymphoid cells → crush artifact, dyscohesive small cells with scant cytoplasm
 - Other tumors: LCNEC, BSqCC

Large Cell Neuroendocrine Carcinoma

- Uncommon, about 1-3% lung tumors
- Poorly recognized & underdiagnosed
 - About 50% diagnosed as poorly differentiated NSCLC, intermediate-type SCLC, atypical carcinoid
- High grade NE tumor, like SCLC
- Grouped with LCC (NSCLC), but has a poorer prognosis
- Optimal treatment is questionable
 - Treat like SCLC (chemo) or NSCLC (surgery)?
 - Resection with adjuvant SCLC-based chemo may be optimal, shown to significantly improve survival

Neuroendocrine Carcinomas in EBUS/EUS FNA

- Clinical Question:
 - Does the distinction of metastatic SCLC versus LCNEC matter from a treatment perspective?

D.D. & Pitfalls

- Benign lymphoid cells
- Lymphoma
- Small cell carcinoma
- Basaloid carcinoma

Lymphomas in EBUS/EUS FNA

- Low sensitivity
 - Lowest sensitivity in one study of 187 cases (12%)
- Triage for ancillary studies is crucial
 - Flow cytometry
 - FISH
 - IHC
- Obtaining material for ancillary studies

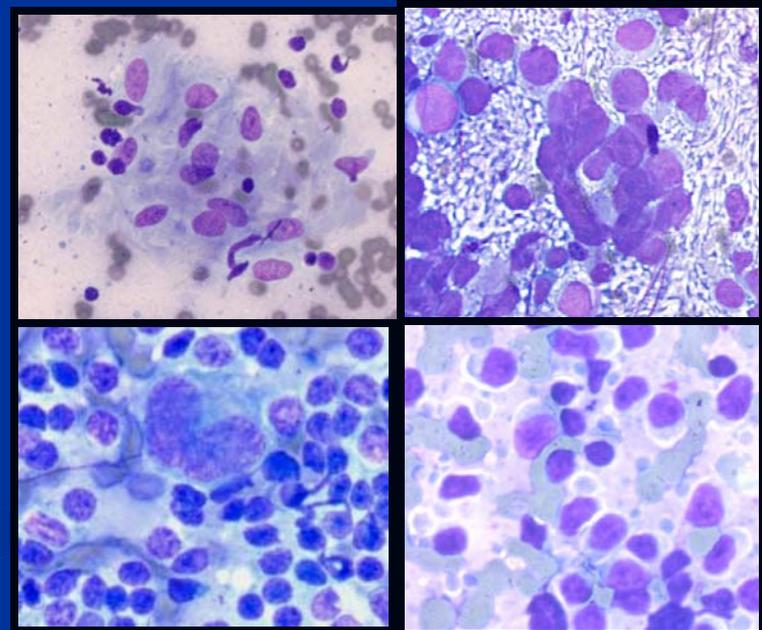
Lymphomas in EBUS/EUS FNA

- What do you do to get adequate material for ancillary studies?
- Can a core biopsy be performed in EBUS or EUS guided FNA?

Use of Core Biopsy in EBUS/EUS FNA



- Helpful for further characterization of certain neoplasms and for the acquisition of sufficient material in some cases
- May have a role in the following entities:
 - Granulomas/Sarcoidosis
 - Thymomas
 - Germ cell tumors
 - Neurogenic tumors
 - Soft tissue neoplasms
 - Benign tumors
 - Mediastinal Cysts
 - Lymphoma



Use of Core Biopsy in EBUS/EUS FNA

- Use of core biopsy is possible with real-time USG
 - Allows visualization and avoidance of vessels to avoid bleeding
- High sensitivity for EBUS/EUS FNA usually refers to NSCLC Staging
 - Dx value in other settings less clear
 - Ex: Lymphoma and Non-neoplastic entities
- Larger Biopsy (miniforceps biopsy) increased Dx yield for HL, NHL, and Sarcoidosis
 - Increase in yield from 10-30% to >80%
 - Better evaluation of architecture
 - More material for ancillary studies
 - May be only way to get sufficient diagnostic tissue in patient's with poor baseline health and/or with mediastinal fibrosis from prior treatments where mediastinoscopy may not be possible

Spindle cell lesions in the mediastinum

- **Difficult:** better to be called spindle cell lesion or tumor
- **Differential Diagnosis:**
 - Thymomas- spindle cell type
 - Neurogenic tumors
 - Metastasis: spindle cell melanoma, sarcomatoid carcinoma
 - Soft tissue neoplasms: schwannoma; inflammatory pseudotumor...
 - Benign Mimics: granuloma,

Conclusions

- EBUS/EUS FNA have changed the way that thoracic/mediastinal lesions are approached
 - May be used together to evaluate entire mediastinum with success
 - Team approach- cytology, surgeon/physician, tools
- The cytological diagnosis in these cases can be difficult and one must be aware of pitfalls
- Rapid on-site evaluation (ROSE) can improve & optimize the FNA performance
 - Decrease unsatisfactory cases
 - Optimize sensitivity and specificity