Endobronchial Ultrasound (EBUS)

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EBUS-FNA and Biopsy

• Although mediastinoscopy is the gold standard for preop staging of NSCLC; Minimally invasive techniques such as EBUS have become increasingly accepted as tests of first choice for lymph node staging

• The technique provides tissue for diagnosis, staging and ancillary testing
Objectives

• Indications
• Technique
• Comparing staging techniques
• The advantages and limitations and potentials for diagnostic pitfalls
• Reviewing cases
Clinical approach to patients with lung mass

• Imaging studies to develop clinical staging
  – CT Scan
  – PET scan
  – Brain MRI

• Tissue diagnosis and confirmation
• 56 year old female with 6 cm RUL mass confined to lung
• CT scan shows large (1.8 cm) station 7 lymph nodes and peribronchial lymph nodes
• No evidence of brain met; no evidence of extrathoracic metastasis
• Clinical staging: T3N2 (IIIB)
  – If confirmed to be N0: IIB
  – If confirmed to be N1: IIIA
  – If confirmed to be N2: IIIB
CT Scan

- Although CT remains the first technique for evaluating mediastinal LNs, its predictive value is predominantly based on a dimensional criteria (short axis diameter >1.0 cm)
- Neither sensitive nor specific for detecting metastatic disease, since some benign nodes may be larger and small nodes may be malignant (Sensitivity: 51%; Specificity: 86%)
- Some studies claim that approximately 40% of all LNs that are considered malignant by CT criteria are not involved by tumor
PET

• PET provides greater accuracy than CT for mediastinal staging with an excellent negative predictive value, but granulomatous infections and other inflammatory diseases might result in positive PET findings (false positive rates of 10-15%; Sensitivity: 74%; Specificity: 85%)

• Positive PET findings should be verified by cytohistologic LN sampling before excluding surgical resection
Nodal Staging in lung cancer

• In patients with suspected or established diagnosis of non-small cell lung cancer (NSCLC), nodal staging is the single most significant factor in determining surgical resectability and prognosis.
Proper staging

- Data shows that patients who underwent proper staging had a significantly lower risk of death
  - Decreasing futile operations performed with curative intention
  - Allowing overstaged patients to receive curative therapy
  - Allowing use of neoadjuvant therapy
N1: Met within ipsilateral perbronchial (lung)
N2: Met in Ipsilateral mediastinal or subcarinal
N3: Met in contralateral or level 1 (supraclavicular)
• **N1**: Resectable
• **N2**: Some may be surgical candidates, often requiring neoadjuvant therapy
• **N3**: Is usually considered contraindication for surgery
Staging Methods

- **Imaging studies**
  - CT scan, PET scan

- **Minimally invasive techniques for mediastinal sampling**
  - Transbronchial Needle Aspiration (TBNA)
  - Transthoracic (percutaneous) image-guided FNA and Biopsy
  - Endoscopic Ultrasound guided FNA (EUS)
  - EBUS guided FNA

- **Mediastinoscopy**
Transbronchial Needle Aspiration (TBNA)

• To obtain cytology specimens, 20-22 gauge needles are usually used, while 19 gauge needles are needed to obtain a core of tissue for histology.

• Conventional TBNA is a *blind* procedure guided by static CT scans and is often restricted to the large subcarinal (station 7) and right para-tracheal (4R) nodes and some 4L.

• The procedure is highly operator dependent, and the needle trajectory often changed during the procedure becoming parallel to the bronchial wall resulting in abundant respiratory epithelium sampling.

• Sensitivity varies between 20-89%.
Historic perspective

• The first description of sampling mediastinal LNs through the trachea using a rigid bronchoscope was by Dr. Eduardo Schieppati, who presented his technique in the Argentine Congress of Bronchoesophagology (1949)

• Schieppati’s technique was to introduce a 1 mm steel needle through a rigid bronchoscope and perform trans-bronchial aspiration of the carina to aid in the diagnosis of patients thought to have either esophageal or bronchogenic carcinoma (at the time, carinal lymph node involvement was accepted as a contraindication for surgery...)

• His technique, however, gained little acceptance
In 1978, Dr. KP Wang published the first paper on TBNA

Bronchoscopic Needle Aspiration Biopsy of Paratracheal Tumors

KO PEN WANG, PETER TERRY, and BERNARD MARSH
• “...we have developed a transtracheal needle aspiration technique using an esophageal varices needle. This permits access to paratracheal nodes and tumor masses through a rigid bronchoscope”

• “...the routine posteroanterior roentgenogram taken from a distance of 6 feet was used to determine needle placement. The distance from the right main stem bronchus origin to the midpoint of the lesion was measured on the roentgenogram. This distance was then used in placement of the needle”

“The discomfort associated with rigid bronchoscopy may be minimized if a similar device can be developed for use with the fiberoptic bronchoscope”
In 1983, Dr. Wang reported the use of TBNA for lung cancer staging.

Transbronchial Needle Aspiration for Diagnosis of Lung Cancer*

Ko Pen Wang, M.D., F.C.C.P.; Bernard R. Marsh, M.D.;
Warren R. Summer, M.D., F.C.C.P.; Peter B. Terry, M.D.;
Yener S. Erozan, M.D.; and R. Robinson Baker, M.D.

Thirty-two consecutive patients with mediastinal lesions suggestive of bronchogenic carcinoma underwent transbronchial needle aspiration. Eighteen of 20 patients (90 percent) with proved bronchogenic carcinoma had malignant cytology specimens or tissue fragments. Of 12 patients with normal cytology specimens, six were subsequently proved to have nonneoplastic disease. Transbronchial needle aspiration appears to offer a sensitive and specific alternative to more invasive surgical techniques used in the diagnosis of malignancies with mediastinal involvement.
Endobronchial Ultrasound guided Transbronchial Needle Aspiration (EBUS-TBNA)

- EBUS-TBNA is a novel minimally invasive technique to sample peribronchial lesions using real time guidance.
- The most important use of this technique is in the nodal staging of patients with lung cancer or suspected diagnosis of lung cancer.
EBUS-TBNA

- Provides real time image of the mediastinal structures adjacent to the airway
- The integration of ultrasound technology enables imaging of LNs, lesions and vessels located beyond the tracheobronchial mucosa
- Real-time control allows not only sampling lesions <1.0 cm, but also allows targeting of lesions in difficult locations
- Mediastinal and hilar nodal staging is the main indication, but intrapulmonary tumors located adjacent to the main bronchi can also be targeted
- Doppler mode, allows identification of the blood vessels
EBUS Clinical application

• Staging of lung cancer
• Acquiring tissue for diagnosis
  – In some cases, the only diagnostic sample
  – neoplastic condition and non-neoplastic conditions
  – Primary thoracic and extrathoracic origin
• Allow sampling for molecular studies
  – It may provide a higher yield of tumor than conventional CT-guided FNA/Bx
EBUS probes

Radial probe

Linear or Convex probe
EBUS-TBNA

- Can be performed in endoscopy unit or operating room, by pulmonologist or thoracic surgeon
- Conscious sedation or general anesthesia
- Nodal sampling is performed beginning at the contralateral hilum, then ipsilateral mediastinum and moving towards the N1 nodes
Number and size of lymph nodes sampled by EBUS

- Staging requires sampling of at least the three following stations: 4R, 4L and 7 regardless of size
- Any lymph node measuring 0.5 cm or larger
EBUS Technical details

- At every LN station, 3-5 passes
- The specimen is air flushed on a slide after each pass
- Size of the needle: 21G or 22G
- Procedure time: 12-20 minutes per site aspirated
Tissue preparation

• Smears air dried and alcohol fixed
• RPMI (rinsed in transport media) for cell block and flow cytometry.
• Cell block
  • We use a 50/50 mixture of ethanol (hardening agent) and 10% formalin (fixative).
Diagnostic yield for EBUS

• Sensitivity: 89%, Specificity: 95%
• Diagnostic yield varies depending on the
  – Size
  – Type of lesion
  – Difficulty accessing target
  – Skills and experience of the operator
  – Availability of on site pathologist
Trans-Esophageal Ultrasound-Guided FNA (EUS)

• Initially designed for diagnosis of pancreatic tumors and staging of GI malignancies in 1990s, EUS-FNA has proven to be an accurate diagnostic method for the diagnosis and staging of lung cancer
• It has limited access as only lymph nodes in posterior and inferior mediastinum (stations 2L, 4L, 7, 8, and 9) are accessible
• The procedure is usually performed in an ambulatory setting, under local anesthesia and conscious sedation
• Complications are rare including infection and hemorrhage
• Accuracy is greatly enhanced by rapid on site evaluation (ROSE)
Cont.

- It is usually performed by gastroenterologists who are not typically managing lung cancer patients and cannot eliminate the need for bronchoscopy.
Mediastinoscopy

- Is considered the gold standard for staging mediastinal LNs in lung cancer
- Sensitivity 81-87% and excellent specificity (100%)
- The complication rate is approximately 2.5% and includes hemorrhage, pneumothorax, mediastinitis, esophageal perforation, and trauma to the azygus and recurrent laryngeal nerves
- Requires general anesthesia and the use of an operating room and related costs
- Access to the posterior and inferior (posterior carina and hilar stations) mediastinum is limited and requires either extended cervical mediastinoscopy or a thoracoscopy

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Role of On-Site Immediate Assessment

• or ROSE (Rapid On-Site Evaluation)
  – Provides immediate feedback on adequacy of the specimen
  – Facilitates appropriate triage of the tissue
    • Optimal preparation; smears, cell block
    • Flow, culture, molecular studies
  – Provides important information on FNA technique
Role of ROSE, Cont.

- Important in reducing the rate of non-diagnostic samples
  - <5% Non-diagnostic rate at MDACC
- Reduced procedure time and improved yield
- The negative predictive value reported in institutions without on-site interpretation appears inferior to those with such facilities
  - A meta-analysis showed that with on-site cytologic interpretation, sensitivity is 88%, whereas without it, sensitivity is 80% (MicamesCG et al. Endoscopic ultrasound–guided fine-needle aspiration for non–small cell lung cancer staging: a systematic review and metaanalysis. Chest. 2007;131:539-548)
EBUS, station 7, FNA

Received 72 direct smears and 1 cell block prepared from 6 needle passes. Passes #1-5 non-diagnostic. Pass #6 has some lymphocytes and two slides with few cells of carcinoma.
Adequacy criteria for EBUS

• It is not well established
• There is significant variability from center to center and pathologist to pathologist
• Nayak et al. consider adequate as any smear with at least 100 lymphocytes and less than 2 groups of bronchial cells in each of at least 5 lpf (100x) (Diagn Cytopathol. 2012 Feb;40(2): 128-37)
• Alsharif et al. reports 40 lymphocytes/hpf in the more cellular areas of the smear and/or the presence of clusters of pigmented macrophages as indicator of adequacy (Am J Clin Pathol. 2008 Sep;130(3):434-43)
• Evidence of lymph node sampling
  – lymphocytes,
  – germinal center
  – Pigmented histiocytes
  – granuloma
  – tumor
Sampling error in EBUS

- False negative 15-20%

• MDACC pathology database was searched for EBUS-TBNAs performed on mediastinal lymph nodes during a 1 yr period (11/06-10-07)
• Cytologic diagnoses were correlated with resection results
• 927 LNs from 356 patients
• M/F: 186/170
• 27-86 yr old (mean: 63)
• 1-6 sites per patient
• The most common site aspirated was station 7, followed by 4R and 11R
• 879 cases (95%) were “sufficient for diagnosis”
Diagnostic Categories

- Benign: 640 (69%)
- Malignant: 226 (24%)
- Suspicious for malignancy: 4 (0.4%)
- Atypical: 9 (1%)
Follow-Up Resections

- 89 cases (9.6%) had subsequent surgical resection;

  Primary lung carcinoma: 80
  Metastatic extra-thoracic carcinoma: 5
  Granulomatous inflammation: 4

77 cases (87%) showed concordance between cytology and resection material
Non-diagnostic & Discrepant

11 cases (12%)

• 4 Non-diagnostic 1 Granuloma: 1; 3 Negative
• 5 Negative 5 NSCLC
• 2 Positive Negative (received neoadjuvant)
False negative

Re-review of cytology slides failed to show any missed diagnoses in the 5 false negative cases

- In 2 cases only 1 out of 2-3 nodes had been initially aspirated because the others did not meet the size criteria for sampling
- In 2 cases, metastatic foci were microscopic, and could have easily been missed during sampling
- 1 case had 2/2 peribronchial nodes were positive on resection, likely not accessible by EBUS
Diagnostic Pitfalls

• **False positive** Bronchial contamination especially in the setting of marked reactive atypia and dysplastic or therapy changes can lead to misdiagnoses
  – Precaution with samples of scant cellularity

• **False negative**
  – Well differentiated/ low grade tumors

• **Incorrect tumor classification**
Reactive respiratory epithelium
• 62 year old female with a history of breast cancer presents with mediastinal lymphadenopathy and bone mets
• A biopsy of the rib was done at outside hospital and was reviewed at MDACC and interpreted as metastatic carcinoma of lung primary (TTF-1 positive)
• EBUS was performed to evaluate mediastinal lymph nodes
EBUS-FNA of stations 4R and supraclavicular lymph nodes were both positive for tumor
Congo Red
Metastatic medullary thyroid carcinoma

• Patient underwent total thyroidectomy and neck dissection
• 76 year old female h/o smoking found to have abnormal CT for lung cancer screening
SYN
• PET: LUL suprahilar hypermetabolic 2 cm nodule and adjacent hypermetabolic LN
• CT Scan: showed a possible satellite nodule in LUL and enlarged left hilar and mediastinal LNs
• Clinical staging: T3 N2
• 08/18: EBUS was performed; LNs (11, 4R, 4L, 7): negative; FNA of the mass: Ki67 15%; Rare groups of NEC, favor carcinoid tumor
• 10/18: Patient underwent a left VATs left upper trisegmentectomy with node dissection
- Small cell carcinoma with satellite nodule
- Lung margin and vascular margin: positive
- LVI and STAS
- Station 5, 7, and peribronchial LNs: Positive
- Pathologic staging: pT3N2
What went wrong?

1. Limited sample
   - Scant tissue and tumor, precluding optimal evaluation of morphology
What went wrong?

1. Limited sample
   - Scant tissue and tumor, precluding optimal evaluation of morphology
2. Ki67 did not work!
Ki67 index

- Ki67 index is not part of the grading criteria for lung NET unlike GEP-NET
- Ki67 is used in the context of separating low/intermediate grade from high grade NEC
- Low/intermediate grade: <20% vs. high grade NEC: >50%
- Particularly helpful in small biopsy with crush artifact or FNA material
CytoLyt fixation significantly inhibits MIB1 immunoreactivity whereas alternative Ki-67 clone 30-9 is not susceptible to the inhibition: Critical diagnostic implications

Darren J. Buonocore MD, Fumiko Konno MD, Achim A. Jungbluth MD, PhD

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MIB-1 clone Ki67

- CytoLyt fixative, methanol based fixative
- Mean labeling index was significantly lower in samples fixed in cytolyt vs. formalin
- Not all the samples are affected to the same extent
- A different clone, 30-9, was not susceptible to fixative
Follow up

- Post-op concurrent chemo/XRT was recommended, Patient decided to receive additional therapy close to home, no f/u available since 01/19
Take home message

• Limited samples should be interpreted with caution
• Ki67 MIB-1 clone can be comprised by type of fixative
Summary

• EBUS-TBNA is a novel minimally invasive technique to sample peribronchial lesions using real time guidance.
• EBUS to stage the mediastinum have become increasingly accepted and are the tests of first choice
• As pathologist play a crucial role in the success of technique, it is important to be familiar with the procedure, indications, limitations and diagnostic pitfalls.
• ROSE has important role in diagnostic yield and also provides feedback on the FNA technique which is important in early phase of developing skill
Thank you