Cytology Workshop #6

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Disclosure information

“The speakers have no relationship that represents a possible conflict of interest with respect to the content of this presentation.”
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Cytology Workshop #6:
Optimizing Your EBUS Cytology Sample:
Doing More with Less

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Background
Fine needle aspiration biopsy of lung masses for diagnosis is routine clinical practice throughout the United States and other countries. Useful diagnostic information and, in many cases, staging information can be gained using minimally invasive methods. Pathology laboratories that process material from medium- to large-sized hospitals with standard imaging facilities (CT, MRI) and/or with active pulmonary services will commonly receive image-guided fine needle aspiration samples. Most of these samples will be relatively straightforward in their classification; however, recent advances in the understanding of lung cancer biology have altered somewhat the diagnostic approach to lung cancer, as well as the types of ancillary studies performed. This workshop will provide current cytohistologic guidelines in lung cancer classification, particularly with respect to adenocarcinoma. In addition, strategies to optimize an EBUS or other limited cytology sample will be discussed, as well as troubleshooting tips to maximize specimen yield in this era of molecular (targeted) diagnostics. Please note that sputum samples, bronchoalveolar lavage, pleural fluid collection, bronchial washing and bronchial brushing are all appropriate, minimally invasive methods for investigating lung pathology with variable cellular yields and diagnostic rates, each with their own artifacts and diagnostic challenges. These methods will not be discussed in today’s workshop.

Sampling modality
Lung lesions can be sampled by fine needles using a transthoracic or transbronchial approach. The transthoracic approach utilizes image-guidance (CT) to insure
proper placement of the needle and to monitor the patient for complications of the procedure (small pneumothorax is the most frequent complication). The interventional radiologist will often use a co-axial system that allows repeated passes without significant needle repositioning. Sensitivity of transthoracic fine needle aspiration ranges from approximately 75 to 95%, with specificity ranging from approximately 95 to 100%. False negative results are generally due to sampling error. A common source of false positive results is reactive atypia. The transbronchial approach utilizes a needle that extends through a channel in the bronchoscope and can be maneuvered and manipulated by the bronchoscopist to obtain a sample. More recently, this technique has been combined with endoscopic (transesophageal) or endobronchial ultrasound (EBUS) and even with electromagnetic navigational biopsy (ENB) systems to allow increased access to more deeply situated or peripheral masses. Each approach offers differing technical challenges for the FNA operator as well as variable specimen yield. It is important to understand the tissue path of the sampling needle to recognize normal cellular contaminants of the sample, and to distinguish these from lesional tissue.

**Adequacy**

There are no published or recommended absolute criteria for specimen adequacy of lung fine needle aspirations. In general, the degree of cellularity considered adequate for fine needle aspirations of other solid organs is a good approximation; however, adequacy is realistically best appraised within the clinical and radiologic context of each individual case. Multidisciplinary input will be paramount in determining what represents an adequate sample, as well as how to best triage specimen. If a pathologist or cytotechnologist is present at the time of the biopsy, immediate adequacy assessment can be performed; as with biopsy sampling of other organs, this often decreases the non-diagnostic biopsy rate and allows for the most efficient and appropriate specimen triage. If sample yield is persistently low and the radiologist or pulmonologist is comfortable in the given patient setting, a core needle biopsy may also be performed, further increasing the amount of diagnostic tissue. Confirming the presence of lesional tissue by FNA prior to performing core needle biopsy may also be helpful in cases requiring immunohistochemistry for definitive diagnosis and/or prognostic/predictive molecular studies. In the bronchoscopic setting, transbronchial forceps biopsy may not be adequate to sample more deeply located lesions, leading to increased importance of the transbronchial FNA, which is now more frequently accomplished with endobronchial ultrasound guidance (EBUS).

**Benign entities**

Although not the focus of this workshop, the cytologic diagnosis of benign entities will be briefly presented in this handout (but not discussed during the workshop).

Fine needle aspiration samples of benign lung lesions may range from paucicellular to hypercellular. The hallmark of benignancy in lung fine needle aspiration is the presence of cilia. Even in the setting of a truly benign aspirate sample, it may be difficult to make a specific diagnosis of a benign entity. However, lung FNA can be useful in the differential diagnosis of malignancy versus infection.

It is difficult to make a specific diagnosis of an inflammatory condition, unless a particular micro-organism can be identified. If there is suspicion of infection, a portion of the sample should be submitted for
appropriate cultures. In addition, cell block material or direct smears can also be histochemically or immunohistochemically stained to highlight some organisms. If no specific organism is identified, a descriptive diagnosis with a differential may be useful for clinicians. It may be helpful to include a statement indicating that results should be correlated to clinical and radiologic findings, and to the area sampled. While the presence of mixed inflammation suggests a benign infectious or inflammatory process, malignancy often cannot be entirely excluded. Necrosis, likewise, is not a specific finding and can be seen in both infectious/inflammatory processes as well as in the setting of malignancy (particularly squamous cell carcinoma).

Benign neoplasms include hamartoma, solitary fibrous tumor, and sclerosing hemangioma. Pulmonary hamartomas are usually straightforward given the typical abundance of cartilaginous or fibromyxoid material (similar cytologic appearance as pleomorphic adenoma in the salivary gland). Solitary fibrous tumor is composed of cytologically bland spindle cells in a variably fibrotic background, and CD34 immunoreactivity is considered almost definitonal. In the absence of convincing CD34 immunoreactivity or the characteristic pleural location, it is probably best to descriptively report cases and suggest obtaining additional material if possible. Fine needle aspiration of sclerosing hemangioma may be quite cellular and consists of a uniform population of bland cells. Stromal cells may be present, imparting a biphasic appearance.

Interstitial disease is essentially undiagnosable by fine needle aspiration. A discussion with the clinician or pulmonologist may result in the selection of a more appropriate biopsy approach to diagnosis.

Pulmonary sarcoidosis is a diagnosis of exclusion. Fine needle aspiration samples can be very helpful in confirming a granulomatous pattern and in obtaining material for culture to exclude microorganisms. Granulomas are often abundant in sarcoidosis, and inflammatory cells may be less prominent in the aspiration sample than in classic granulomatous infections.

Neoplasms
Small cell (“oat cell”) carcinoma is characterized by a typically hypercellular sample with a relatively uniform population of small round to ovoid nuclei that may or may not show neuroendocrine features. Nucleoli are usually not prominent. Small clusters of cells may be present and often show nuclear molding; single cells are usually abundant in the background, often stripped of their cytoplasm. Streaking of nuclear material can be a helpful feature and is caused by the fragility of the cells. Confirmatory immunohistochemistry may be helpful in making this diagnosis. As small cell carcinoma is typically treated with neoadjuvant chemotherapy, there is limited use to date for specific molecular studies (e.g., mutation analysis) outside the setting of routine diagnostic immunohistochemistry.

Non-small cell carcinoma includes adenocarcinoma, usually characterized by highly pleomorphic nuclei, prominent nucleoli and abundant mitotic figures, and squamous cell carcinoma, typically characterized by dense cytoplasm, features of keratinization, and necrotic debris. Non-keratinizing squamous cell carcinoma can be difficult to distinguish from adenocarcinoma. Overlapping cytologic features or features of both adenocarcinoma and squamous cell carcinoma in the same
FNA sample may be seen; it is now considered most helpful to report this finding and indicate approximate percentages of each subtype.

The diagnosis of bronchioloalveolar carcinoma (BAC) was never possible to definitively establish by cytology, and the use of the term is now discouraged, even in histologic resection specimens. Tumors that feature flat sheets of cells, a clean background, orderly arrangement of cells with uniform nuclei, fine granular chromatin and nuclear grooves or inclusions may now be classified as having a lepidic pattern (non-mucinous) or as being mucinous adenocarcinoma. Definitive classification of this subset of tumors may not be possible until surgical resection, when the presence and amount of invasion can be completely evaluated. If possible on cell block or cytologic material, patterns such as papillary, acinar, solid or micropapillary should be described.

While the clinical and managerial relevance of distinguishing small cell carcinoma (primarily treated with chemotherapy) from non-small cell carcinoma (primarily treated surgically) remains important in lung FNA, subclassification of non-small cell carcinomas (usually into squamous or adenocarcinoma) has become increasingly important with new chemotherapeutic regimens and targeted therapies. While these new agents have shown efficacy in advanced lung carcinomas (usually adenocarcinoma), the risk of fatal hemoptysis is increased in the setting of squamous cell carcinoma, particularly with centrally located, cavitated or necrotic tumors. Ancillary studies may provide some assistance in tumor typing and molecular studies are increasingly essential to lung cancer therapy (see below). An attempt to subclassify the tumor should be made; however, uncertainty in typing should be communicated in the pathology report.

Pulmonary carcinoid tumors are often endobronchial. Fine needle aspiration samples from carcinoid tumors are typically cellular and feature a uniform and monotonous population of rounded cells with moderate to high N/C ratios, plasmacytoid features, stippled chromatin, and scant granular cytoplasm. Confirmatory immunohistochemical stains may be helpful. Features such as significant nuclear pleomorphism, mitotic activity, necrosis, or prominent nucleoli may indicate an atypical carcinoid tumor. Molecular studies are not indicated in carcinoid tumors.

Pulmonary blastoma and sarcomatoid carcinoma are rare biphasic tumors composed of neoplastic epithelial and spindle cells. Cytologic features of both entities overlap; the clinical and radiologic features may provide assistance in distinguishing the two entities. In general, these tumors are not as frequently submitted to molecular testing.

Mesothelioma rarely presents as a parenchymal mass targeted for fine needle aspiration. Distinguishing features suggesting mesothelial differentiation include flat sheets with scalloped borders, usually central round nuclei surrounded by variably dense cytoplasm, “windows” or spaces between cells, and ruffled cytoplasmic “skirts”. Obtaining material for cell block is extremely helpful for diagnosis; a panel approach to immunohistochemistry is suggested.

Recognizing pulmonary metastases is important in lung FNA. The most common primary tumors that metastasize to the lungs are breast, renal, bone sarcomas, prostate, colorectal, head and neck tumors, thyroid,
melanoma and germ cell neoplasia, but metastases from virtually every site are seen. Clinical history or radiologic findings can be very helpful, but may not be immediately available. Immunohistochemistry may be of great utility in suggesting a possible primary if cell block material is obtained.

Occasionally, large mediastinal masses may mimic a pulmonary lesion. Thymoma, germ cell neoplasia, lymphoma, neurogenic tumors and paraganglioma may all present as “lung masses” undergoing fine needle aspiration. Recognition of these tumors and appropriate ancillary studies will result in accurate diagnosis.

**Diagnostic classification**

Malignant samples with mixed features may be confusing or difficult to classify, but are not entirely unusual. A comment regarding the presence of more than one tumor subtype, especially if approximate percentages can be given, may be very helpful to clinicians. In most instances, tumors with any component of small cell carcinoma will be treated with chemotherapy, so the identification of any features of small cell carcinoma in a mixed tumor is clinically relevant.

As discussed above, the distinction between small cell and non-small cell carcinoma is clinically important. Most of the time, this determination is not problematic, but rare cases will show overlapping features. Cell block material will be useful for immunohistochemical studies, but should be used sparingly to conserve tissue for molecular studies. Cases that are not readily resolved by cytologic or immunophenotypic features should include a comment in the report about the unusual findings. Molecular studies can then be performed, which may provide additional insight into tumor subtype and/or clinical prognosis.

Small cell carcinoma can usually be distinguished from carcinoid tumor by the more ovoid nuclei, less abundant cytoplasm, nuclear molding, and more prominent nuclear streaking. Cases with overlapping features may show distinctive immunophenotypes. Problematic or uncertain cases require comment; additional tissue may be helpful in these cases.

Well-differentiated adenocarcinoma (including papillary adenocarcinoma) may be difficult to distinguish from reactive processes. In general, low-grade malignancy will present with a more cellular smear than a reactive process. Sheets of disordered cells with enlarged nuclei will dominate in malignant entities; cilia favor a reactive process. Focal nuclear membrane irregularities and minimal nuclear pleomorphism are likely to occur in both processes. If possible, obtaining additional material such as needle cores may be helpful in paucicellular samples. Problematic cases without distinguishing features are best considered “atypical” or “suspicious” with a request for additional tissue.

With adequate clinical history, the question of primary pulmonary malignancy versus metastatic disease is usually not difficult to answer. Comparison to prior material, if available, may be very helpful. Characteristic cytologic findings (e.g., dirty necrosis in metastatic colorectal carcinoma) may also provide clues to tumor origin. Immunohistochemistry is also helpful, when cell block or needle core material is available. Distinguishing primary pulmonary squamous cell carcinoma from metastatic squamous cell carcinoma (e.g., from head and neck sites) is essentially impossible on cytologic grounds alone.

In some cases of poorly differentiated carcinoma, tumor subtyping may be
difficult. Clear and concise comments elaborating on the presence of any distinguishing features may be of some aid to clinicians. Immunohistochemistry (to confirm carcinoma and exclude other poorly differentiated tumors) may also be of use, but should be relatively limited so that material can be reserved for important molecular tests.

As with cytologic samples from other sites, clinical and radiologic correlation with cytology findings can be quite useful. In addition, open discussion and clear communication with involved clinicians, radiologists and surgeons will facilitate diagnostic and therapeutic decisions.

**Utility of ancillary studies**

Classification of lung tumors can be aided by special studies, particularly immunohistochemistry. Mucin stains can be valuable in confirming intracytoplasmic mucin and supporting glandular differentiation. Most (85%) pulmonary adenocarcinomas will react positively with antibodies to cytokeratin 7 (CK7) and approximately 75% will react with thyroid transcription factor (TTF1). Virtually all pulmonary squamous cell carcinomas will react with antibodies to cytokeratin 5/6 and/or p63, and will not react with either CK7 or TTF1. Small cell carcinoma is usually pan-keratin positive and reacts with neuron-specific enolase or CD57. Small cell carcinoma may show faint or focal synaptophysin or chromogranin staining, but is usually less intense and diffuse than staining seen in carcinoid tumors.

Cytokeratin 20 (CK20) staining is very helpful for confirmation when metastatic colorectal carcinoma is suspected; in conjunction with CK7, it may also provide information about other sites of metastasis. Organ-“specific” markers such as BRST2 (GCDFP-15), Heppar1, RCC, and CDX2 may be helpful in suggesting the primary site of metastatic disease. A panel including two or more antibodies that stain adenocarcinoma and mesothelioma, respectively, is recommended for this differential diagnosis.

### Small cell versus non-small cell carcinoma

<table>
<thead>
<tr>
<th>Small cell</th>
<th>Non-small cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform cells</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td>Scant cytoplasm</td>
<td>More cytoplasm</td>
</tr>
<tr>
<td>IHC helpful</td>
<td>Prominent nucleoli</td>
</tr>
</tbody>
</table>

### Adenocarcinoma versus squamous cell carcinoma

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Squamous cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wispy cytoplasm</td>
<td>Dense cytoplasm</td>
</tr>
<tr>
<td>Macronucleoli</td>
<td>Dark nuclei</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>More uniform</td>
</tr>
<tr>
<td>Glands</td>
<td>Keratin/bridges</td>
</tr>
<tr>
<td>CK7 and TTF1</td>
<td>CK5/6 and p63</td>
</tr>
</tbody>
</table>

### Carcinoid versus small cell carcinoma

<table>
<thead>
<tr>
<th>Carcinoid</th>
<th>Small cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round cells</td>
<td>Ovoid cells</td>
</tr>
<tr>
<td>Intact</td>
<td>Crush artifact</td>
</tr>
<tr>
<td>More cytoplasm</td>
<td>Scant cytoplasm</td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td>Nuclear molding</td>
</tr>
<tr>
<td>Single cells</td>
<td>Groups/single cells</td>
</tr>
<tr>
<td>Loose clusters</td>
<td>Tight clusters</td>
</tr>
</tbody>
</table>

### Primary versus metastatic adenocarcinoma

<table>
<thead>
<tr>
<th>Primary</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant mass</td>
<td>Multiple masses</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Clinical history</td>
</tr>
<tr>
<td>No history</td>
<td>Specific features</td>
</tr>
<tr>
<td>CK7 and TTF1</td>
<td>TTF1 negative</td>
</tr>
</tbody>
</table>
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Optimizing your EBUS cytology sample: Doing more with less
Kristin Jensen, MD; Rana Hoda, MD; Chuong Hoang, MD
Stanford University and Palo Alto Veterans Affairs Health Care System, and Weill Cornell Medical College

Conflict of interest
- All speakers have no conflicts to disclose

Outline and Goals
- Brief background
- Review of technology
- Basics for supporting EBUS FNA
- Strategies for sample optimization
- Troubleshooting
- Electromagnetic navigation

How it All Started ...
- January 4, 2011 ASC listserv post (Dr. Hoda)
  - Pressure from oncologists for lung core biopsies
    - J Clin Oncol 2010;28(36):5311-5320
      - “Fine-needle aspiration does not provide optimal specimens to enable histologic diagnosis based on architectural patterns”
    - J Clin Oncol 2011;29(24):3331-3332
      - “Can we use cytologic diagnosis?” “YES”!

In the Past ...
- Critical: small cell versus non-small cell
- Much less important: adeno versus SCC
- Staging
- Surgical options
- Chemotherapy (options)
- Radiation options

Now ...
- Small cell still critical (but not common)
- Increasingly important: adeno versus SCC
- Non-invasive pathologic staging
- Surgical options
- Chemotherapy options **
- Radiation options
Lung cancer survival

- American Cancer Society estimates (2011):
  - Over 220,000 new lung cancers will be diagnosed
  - Male to female ratio equalizing (115K:106K)
  - Greater than 155,000 deaths from lung cancer
  - 85% non-small cell carcinoma
  - Decrease in death rates (men, 1991; women, 2003) and increase in one-year relative survival, but overall 5-year survival still very poor (16-17%)

Lung cancer subtypes

- Small cell carcinoma
- Adenocarcinoma
- Squamous cell carcinoma
- Non-small cell carcinoma, not otherwise specified
- Non-small cell carcinoma, with squamous cell and adenocarcinoma patterns
- Poorly differentiated NSCLC


Subtype diagnosis

- Cytomorphology
- Immunohistochemistry
- Molecular diagnostics
- Commercial tests
### Adenocarcinoma

- Nonmucinous: TTF1 (100%), EGFR in never smokers (10-30%), KRAS in smokers (10%), variation by pattern
- Mucinous: TTF1 (0-33%), no EGFR mutation, KRAS mutation (80-100%)
- EGFR mutations higher in Asians, never smokers, nonmucinous
- KRAS mutations higher in non-Asians, smokers, mucinous tumors

Travis WD et al. J Thorac Oncol; 2011:244-285. (Table 5)

### Predictive testing

- Many drugs (erlotinib, bevacivimab, crizotinib, etc.)
- Many reasons (fatal hemorrhage, better/worse response)
- Many tests (EGFR, KRAS, BRAF, ALK, others)
- Many methods (FISH, PCR, etc.)
- Many submissions (PET, thick sections, fresh, etc.)
- Same need: as much tissue as possible!

### Technology

- Transthoracic FNA
- Transbronchial needle aspiration
  - Wang
  - EBUS
- Electromagnetic navigation biopsy

### Basics for supporting EBUS

- Communication and multidisciplinary approach (pulmonary, radiology, thoracic surgery, pathology, oncology, radiation therapy)
- Pulmonary nodule clinics and tumor boards
- Rapid on-site evaluation by cytology or clear sample submission guidelines
- Flexible approach to cytology/histology and IHC

### Optimizing Sample

- Establish diagnosis -> request needle cores
- Establish diagnosis and concentrate sample
- Establish diagnosis, concentrate sample and request needle cores/additional sample
- Tailor histology and immunohistochemistry to cytology/adequacy impression (minimize)
- Work with molecular lab to establish best specimen (cell block, unstained thin/thick sections)
Troubleshooting

- Consider the setting (staging versus diagnosis)
- Consider your preliminary diagnosis and/or clinical/radiologic features (adeno vs. SCC)
- Observe the procedure; ask questions
- Report findings such as necrosis (consider portion of sample for micro, SCC?)
- Be patient and collegial
- Alert cyto/histo/molecular lab, oncologists

References


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Electromagnetic Navigation Bronchoscopy for the Diagnosis of Peripheral Lung Lesions

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219,000 new cases & >159,000 died of Lung cancer in the US in 2010
American Cancer Society, 2009
whistler’s mother

Lung Cancer
• ~70% are diagnosed late → low cure rate (<15% 5-year-survival)
• Non-small cell lung cancer (>80%)
  • 5-yr-survival is low with ipsilateral mediastinal LN metastasis
  • 88% 10-yr-survival if diagnosed at stage I
• 65-70% Stage III or IV
• Only 15% will survive 5y

Solitary Pulmonary Nodule
• >150,000 patients
• Intraparenchymal lesion <3cm not associated with atelectasis or adenopathy
  • Benign >> malignant
• Size correlates with the risk of malignancy
  • <2.0 cm = 18%
  • >2.0 cm = >50%
Types of Lung Lesions

- Central lung lesions
  - EBUS, brush or wash → high yield
- Peripheral lung lesions

Approaches to Peripheral Lung Lesions

- Bronchoscopy
  - 65% fail to reach periphery
  - Diagnostic yield <2cm = 14%
- CT-guided FNA
  - Diagnostic yield 64-97%
  - Complication risk ~30%
  - Not all lesions accessible
- CT-guided Bx:
  - High complication risk

Electromagnetic Navigation Bronchoscopy (ENB)

- Minimally-invasive GPS-like navigation system (superDimension Inc. Minneapolis)
- FDA-approved in 2004
- Guides bronchoscopic bx tools to the periphery of the tracheobronchial tree

Basic Elements of ENB

- Electromagnetic field surrounding thorax
- Steerable electromagnetic sensor
- Extended working channel
- Computer software shows real time visual guide with location of the sensor

ENB Process

CT Scan: \(\rightarrow\) PLANNING: \(\rightarrow\) PROEDURE:
- Prepare for procedure
- Learn pt’s anatomy
- Navigate, sample
- Plan for Rx

Initial Planning Phase

- CT data is used to create 3D reconstruction of the bronchial tree
- Target lesion is marked
**Initial Planning Phase**

- Reference points (5-7) are marked during virtual bronchoscopy.

**Procedure**

**Peripheral Lung Navigation**

**Target Acquisition**

**Tissue Sampling**

- EWC is locked into place
- Locatable sensor removed
- Bronchoscopic tools are advanced to the lesion
- Fluoroscopy (optional)

**Specimen Triage**

- Similar to EBUS procedure
- Immediate correlation with Frozen section
Clinical Prospective Study

- No on-site cytopathologist
- 56 peripheral nodules, 31 LN, majority <2cm
- Success in obtaining definitive diagnosis
  - Peripheral lung lesions = 74%
  - Lymph nodes = 100%
- Minimally invasive & safe method for <2.5cm peripheral lung lesions difficult to reach with bronchoscopy

Schroeder J Thorac Cardiovasc Surg 2010;140:1137

ENB Limitations

- Target nodule size <8-10mm
- 10% of lesions are still difficult to reach
- Secretions & blood cannot be aspirated
- Learning period
- Contraindicated in patients with pacemakers & defibrillators
  - Risk of electromagnetic field interfering with devices

ENB at VAPAHCS & NYPH

- 51 patients, (M=42; F=9; age range: 49 to 88, mean: 66)
- 4 year & 2 month-period (07/’07 – 09/’11)
- Rapid on site cytopathologic evaluation
- FNA (all), bronchial brush (33) & TBBX (25)
- Peripheral nodule mean size 2.5 cm
- Primary, 38 and Suspected metastasis, 13
- Diagnostic tissue obtained in 46/59 (78%)
  - 73% for <2cm, 88% for >4cm

Granulomatous Process

References