Changing Practice Patterns: Implications for Histopathology and Cytopathology

Lester J. Layfield, M.D.
Professor and Head Anatomic Pathology
University of Utah School of Medicine

Presentation Bullet Points:
- Practice patterns are changing with emphasis on smaller specimens
- Use of cytology is increasing for initial diagnosis and intraoperative consultations
- Cytologic investigations can be preferable for certain sites including biliary tract, pancreas, lung, and liver
- Core biopsies may be the preferred technique for lesions in prostate and non-palpable breast lesions
- Histopathology and cytopathology are complimentary and not competing techniques

Over the past twenty years, the size of specimens submitted to pathology laboratories for initial diagnosis has decreased substantially in size. Despite this decrease in size, the amount of information from diagnostic biopsies required by clinicians has increased with an increasing number of prognostic features being mandated for inclusion in the pathology report. These changes have been coupled with a requirement for a shortened turn-around time to diagnosis as well as a desire to decrease patient discomfort and mortality from the diagnostic process. Pathologists have responded to these demands in a number of ways including the increased use of special techniques such as immunohistochemistry and molecular diagnostics. In the past, the majority of biopsies sent for diagnostic work excisional or incisional biopsies allowing evaluation of both architectural and cellular features. Present practice patterns have changed substantially.

Currently, a majority of biopsies are small tissue specimens other core biopsies, endoscopically directed group biopsies, or cytologic specimens obtained by either fine-needle aspiration or brushing and washing techniques. This dominance of small tissue samples has led to considerable changes in pathology practice patterns. While occasionally viewed as competing techniques, cytopathology and histopathology are complimentary for routine diagnostic purposes for these diagnoses. These two approaches frequently supplement each other to improve overall diagnostic accuracy. Hence, an increasing utilization of cytopathology has accompanied the decrease in biopsy size. Initially, cytology was restricted to specimens exfoliated into body fluids or from epithelial surfaces. Hence cervical cytology, sputum samples and analysis of pleural, peritoneal and cerebral spinal fluid samples dominated the specimens sent to the cytology laboratory. However, the increasing demand for rapid diagnosis has led to the utilization of FNA and brushing and washing techniques which can provide information in a shorter time frame.

The interactions between cytopathology and histopathology continue to develop, and the best technique has not invariably been established for a number of body sites. The areas where utilization of cytology remains controversial for diagnostic inclusion, salivary gland lesions, mesenchymal tumors, ovarian masses, renal masses and lymphomas. Our understanding of the complimentary nature of cytopathology and histopathology techniques continues to evolve. Cytology, in the form of touch preparations, is being increasingly utilized as an adjunct to or even replacement for frozen section evaluation in the intraoperative period. Touch preparations have gained widespread acceptance for aiding frozen section evaluation in the diagnosis of lesions of the central nervous system and may become the preferential technique for the evaluation of sentinel lymph nodes.

The speakers taking part in the Papanicoloau Society of Cytopathology Scientific Session for 2007 will address the advances made in the evaluation of small tissue specimens and the interactions between cytopathology and histopathology. The speakers will stress areas where cytopathology can substantially improve pathology diagnostic accuracy, decreasing turn-around time or increasing patient acceptance of the biopsy procedures. Areas of controversy will also be addressed, including the relative advantages and disadvantages of fine-needle aspiration versus core biopsy in the diagnosis of breast lesions.
Cytopathology and Histopathology are Complimentary Technologies for Tissue Diagnosis

Biopsy size has constantly decreased over the past 20 years

Initially, cytology was restricted to specimens exfoliated into body fluids or from epithelial surfaces

- Cervical cytology
- Sputum samples
- Pleural and peritoneal fluids
- CSF

Increasing utilization of cytology has accompanied the decrease in biopsy size
Primary Tissue Diagnostic Techniques

<table>
<thead>
<tr>
<th>SITE</th>
<th>1970</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Intraoperative evaluation</td>
<td>Frozen Section</td>
<td>Frozen section and touch preparation</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lobectomy</td>
<td>Fine Needle Aspiration</td>
</tr>
<tr>
<td>Lung Nodule</td>
<td>Open biopsy</td>
<td>Fine Needle Aspiration</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>Open biopsy</td>
<td>Fine Needle Aspiration</td>
</tr>
<tr>
<td>Liver mass or nodule</td>
<td>Open biopsy or large core biopsy</td>
<td>Fine Needle Aspiration</td>
</tr>
<tr>
<td>Bile duct lesion</td>
<td>Open Biopsy</td>
<td>Brushings</td>
</tr>
<tr>
<td>Pancreatic Mass or stricture?</td>
<td>Incisional or core biopsy</td>
<td>Fine Needle Aspiration and or Brushing</td>
</tr>
<tr>
<td>Prostate</td>
<td>Core Biopsy</td>
<td>Core Biopsy</td>
</tr>
</tbody>
</table>

Intra-operative cytologic evaluation of neural lesions by touch preps has become standard.

Cytology and Histopathology are not competitors in our diagnostic evaluations but are complimentary techniques.

Areas where cytology is still controversial for diagnosis:
- Salivary Gland Lesions
- Soft Tissue and Bone Lesions
- Diagnosis of Primary Liver Neoplasms
- Ovarian Masses
- Renal Masses
- Breast (non-palpable)
- Lymphoma

Cytology (Touch Preps) are being increasingly utilized as an adjunct to frozen section for intra-operative diagnoses.

Touch Preps have been used for evaluation of sentinel lymph nodes.
INTRAOPERATIVE CYTOLOGY:
PAST, PRESENT, AND FUTURE

Steven G. Silverberg, M.D., FRCPath
Department of Pathology
University of Maryland, Baltimore

Presentation Bullet Points

• Intraoperative consultations are requested for a variety of reasons in addition to diagnosis.
• Cytology is increasingly utilized for microscopic assessment of intraoperative specimens.
• Advantages of intraoperative cytologic assessment include: accuracy, speed, more complete sampling and preservation of specimen for later study.
• Intraoperative cytology is highly useful in evaluation of breast, parathyroid, CNS and sentinel lymph node specimens.

Please see Dr. Silverberg’s PowerPoint presentation for his handout information.
INTRAOPERATIVE CYTOLOGY:
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The psychic atmosphere at a frozen-section-at-operation scene is not conducive to accurate scientific reasoning. One, there is the position in which the pathologist himself is placed. To any other consultation, the consultant is asked as to an appointment between peers and his convenience is considered. To one of these occasions, the pathologist is summoned arbitrarily through subordinates: his sensations are those of being summoned. A general attitude prevails about the hospital that any surgical operation is an emergency and is entitled to ride rough-shod over every other consideration in the institution. Though considered less so than the clinician, the pathologist is nevertheless somewhat human. To be uncannily summoned in disregard of previous appointments and other important duties, will, in spite of his own conscientious efforts to be obliging and cooperative, prove distracting to his diagnostic reasoning.


INDICATIONS FOR INTRAOPERATIVE CONSULTATIONS

I. Immediate therapeutic decision
   A. Diagnosis
   B. Adequacy of excision
   C. Extent of spread

II. Adequacy of diagnostic material

III. Unexpected finding

IV. Special procedures

V. Demonstration of specimen

VI. Psychological
GEORGE WASHINGTON UNIVERSITY
OPERATIVE CONSULTATIONS
INDICATIONS

- Diagnosis 50%
- Adequacy of excision (margins) 6%
- Extent of spread 6%
- Adequacy of specimen 6%
- Special procedures 30%
- Specimen demonstration 2%

GEORGE WASHINGTON UNIVERSITY
OPERATIVE CONSULTATIONS
PROCEDURES PERFORMED

- Gross only 10%
- Gross and cytology 54%
- Gross and frozen section 10%
- Gross, frozen and cytology 26%

INTRA-OPERATIVE CYTOLOGY

- Imprint (touch prep).
- Smear: 1) scrape and streak.
  2) scrape and spread.
- Squash prep.
- Mincing.
- Mash and move.
INTRAOPERATIVE CYTOLOGY: PAST, PRESENT, AND FUTURE

- Past: Breast
- Present: Parathyroids
- Future: Lymph nodes (inc. sentinel)

WET FIXATION:
- Immediate immersion
- 95% ethyl alcohol.
- H&E, Papanicoloau

DRY FIXATION:
- Allow to air dry.
- 100% methanol.
- Diff-Quick stain.

ADVANTAGES
- Accurate
- Fast
- More complete Sampling (Large, multiple or necrotic samples)
- Preserves tissue for permanent sections
- Prevents contamination of cryostat
- Prepares pathologist to interpret FNA’s
### Table 1: Outcomes by Body Site

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>RECIPIES</th>
<th>ACCURACY</th>
<th>DISTINGUISH</th>
<th>FALSE (-)</th>
<th>FALSE (+)</th>
<th>DIFFERENT</th>
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<tbody>
<tr>
<td>ENDOC</td>
<td>973</td>
<td>93.6%</td>
<td>0.9%</td>
<td>1.1%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>EL</td>
<td>31</td>
<td>91.6%</td>
<td>8.2%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>OMENTUM</td>
<td>52</td>
<td>86.8%</td>
<td>13.0%</td>
<td>2.2%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>LYMPH NODES</td>
<td>53</td>
<td>84.8%</td>
<td>8.3%</td>
<td>3.5%</td>
<td>1.1%</td>
<td>2.7%</td>
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<tr>
<td>LUNG/TUMOR</td>
<td>33</td>
<td>81.6%</td>
<td>7.6%</td>
<td>1.3%</td>
<td>1.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td>LIP</td>
<td>39</td>
<td>83.0%</td>
<td>6.0%</td>
<td>3.0%</td>
<td>0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>LUNG LYMPH</td>
<td>85</td>
<td>83.3%</td>
<td>6.7%</td>
<td>0%</td>
<td>0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>LYMPH NODES</td>
<td>52</td>
<td>98.6%</td>
<td>0%</td>
<td>5.4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>THYROID/THYROID</td>
<td>86</td>
<td>79.9%</td>
<td>13.1%</td>
<td>8.3%</td>
<td>0%</td>
<td>5.6%</td>
</tr>
<tr>
<td>STOM</td>
<td>25</td>
<td>92.0%</td>
<td>7.5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>GI</td>
<td>23</td>
<td>96.2%</td>
<td>3.8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>SPEECH</td>
<td>4</td>
<td>90.7%</td>
<td>8.3%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>OTHER</td>
<td>4</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>TOTAL</td>
<td>1000</td>
<td>92.4%</td>
<td>6.1%</td>
<td>2.5%</td>
<td>5.2%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

* Lymph node resectional report.
* Lymph nodes metastatic disease.

### Parathyroid Exploration

**Surgical identification of 4 glands *in situ***

**Pathologic confirmation of 4 glands microscopically**

### Distinguish

**Parathyroid**

**Thyroid**

**Thymus**

**Lymph node**

**Fat**

### Touch Prep Process

Averages 45 seconds
Intraoperative Cytologic Evaluation of Lipid in the Diagnosis of Parathyroid Adenoma

Hironobu Sasano, M.D., Glenn W. Geelhoed, M.D., and Steven G. Silverberg, M.D.
TABLE 1. Probability of Finding a 1-mm Peripheral Lesion (D_s) Located Greater Than 1/2 the Node Radius from the Node Center, on Center and Quarter Sections of Lymph Nodes of Various Diameters (D_n) (Fig. 6)

<table>
<thead>
<tr>
<th>D_s (mm)</th>
<th>D_n (mm)</th>
<th>Success on center section</th>
<th>Success on each quarter section</th>
<th>Total success on two quarters &amp; center sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>56.8%</td>
<td>35.8%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>39.5%</td>
<td>30.3%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>30.2%</td>
<td>25.8%</td>
<td>81.9%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>24.5%</td>
<td>21.9%</td>
<td>68.4%</td>
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<tr>
<td>7</td>
<td>1</td>
<td>20.6%</td>
<td>18.9%</td>
<td>58.4%</td>
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<tr>
<td>8</td>
<td>1</td>
<td>17.7%</td>
<td>16.6%</td>
<td>50.9%</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>15.6%</td>
<td>14.7%</td>
<td>45.1%</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>13.9%</td>
<td>13.7%</td>
<td>40.4%</td>
</tr>
</tbody>
</table>
SENTINEL LYMPH NODES IN BREAST CANCER: INTRAOPERATIVE PATHOLOGIC EVALUATION
(Cserni, The Breast J 12:S152, 12/2006)

<table>
<thead>
<tr>
<th></th>
<th>Frozen Section</th>
<th>&quot;Imprint Cytology&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>79-98%</td>
<td>78-99%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>55-91%</td>
<td>46-96%</td>
</tr>
<tr>
<td>False negative rate</td>
<td>9-45%</td>
<td>5-70%</td>
</tr>
</tbody>
</table>

NOTE: False negative rates vary directly with extent of permanent section examination and proportion of micrometastases

BREAST CANCER SENTINEL LYMPH NODE EVALUATION: EUROPEAN PATHOLOGY LABORATORY PRACTICE
• 123 different protocols reported by 204 labs
• IOC done in 61%, 69% of these are FS
• European/German guidelines presented in Cancer 103:451-461, 2005

PUBLISHED GUIDELINES FOR INTRAOPERATIVE SENTINEL NODE ASSESSMENT

<table>
<thead>
<tr>
<th>Group</th>
<th>Reference</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US/CAP</td>
<td>Arch Pathol Lab Med 12:1026, 2000</td>
<td>IOC &gt; FS</td>
</tr>
<tr>
<td>US/Consensus</td>
<td>Hum Pathol 33:579, 2002</td>
<td>IOC = FS</td>
</tr>
<tr>
<td>UK</td>
<td><a href="http://www.cancer">www.cancer</a> Screening nhs uk</td>
<td>FS not recommended</td>
</tr>
<tr>
<td>Germany</td>
<td>Cancer 103:451, 2005</td>
<td>Gross + IOC or FS</td>
</tr>
<tr>
<td>Austria</td>
<td><a href="http://www.pathology.at/sentinel.ht">www.pathology.at/sentinel.ht</a></td>
<td>FS (2-3 from mid-portion)</td>
</tr>
<tr>
<td>Australia</td>
<td><a href="http://www.cancer.org.au">www.cancer.org.au</a></td>
<td>IOC = FS</td>
</tr>
<tr>
<td>EWGBSP</td>
<td>monograph only</td>
<td>IOC = FS</td>
</tr>
</tbody>
</table>

SENTINEL NODES IN BREAST CANCER: COMPARISON OF SMEAR TECHNIQUES
(Zhang et al, USCAP 2005)
• 462 smears → 65 positive, 383 negative, 14 inconclusive
• 65 positive → 53 macromets, 7 micromets, 5? on permanent sections
• 383 negative smears → 24 (6.3%) positive on H&E permanents
  — 7 macro, 15 micro, 2 isolated tumor cells
  — 11 additional cases (2.9%) positive on CK-IHC only (all ITCs)
• 14 inconclusive → 5 (36%) positive on H&E permanents
• False negative rate 14.5% in ILC, 4.4% in IDC (p=0.02)
• Among 43 positive cases with 4 techniques available for review:
  — 2 FN touch prep Diff-Quick,
  — 4 FN touch prep H&E,
  — 6 FN scrape smear DQ,
  — 14 FN scrape smear H&E
PERSONAL RECOMMENDATIONS FOR INTRAOPERATIVE SENTINEL NODE ASSESSMENT

• No study if further immediate surgery not contemplated
• If needed, gross examination of multiple planes followed by smears of any gross lesion
• If no gross lesion, smears and imprints of each cut surface
• High false negative rate to be understood by the surgeon
• Ref: Treseler, The Breast J 12:S143, 12/2006

VALUE OF INTRAOPERATIVE CYTOLOGY

Rapid
Preserves tissue
Large specimens
Multiple specimens
Necrotic tissues
Infected tissues
Preparation for FNA

SITUATIONS IN WHICH FROZEN SECTION IS MANDATORY

MARGINS
STROMAL INVASION
DEPTH OF INVASION
GROSS/CYTOLoGIC DISCREPANCY
INADEQUATE SMEAR
SPECIFIC REQUEST

250 THE BRITISH JOURNAL OF SURGERY

A NEW METHOD FOR THE RAPID MICROSCOPICAL DIAGNOSIS OF TUMOURS:
WITH AN ACCOUNT OF 200 CASES SO EXAMINED.

By LEONARD S. DUDGEON, C.M.G., C.B.E.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF LONDON.

AND C. VINCENT PATRICK,
RESIDENT ASSISTANT SURGEON, ST. THOMAS’S HOSPITAL, LONDON.

Fig. 187—Fig. 185. Spheroidal-tubular carcinoma of breast. Note large size of cells, masses of cells, and the large number of isolated cells. (x 165.)
Conclusions

1. A wet-film method for the examination of new growths and inflammatory tissues is introduced.
2. The technique is very simple and requires no elaborate apparatus.
3. The time required for the preparation of the microscopical specimen of a tissue removed at operation is from eight to ten minutes.
4. The method is unsuitable for post-mortem specimens.
5. Two hundred cases have been so examined and 191 correct diagnoses returned.
6. Special experience of this method should be acquired before it is employed in practice.
Presentation Outline

- Diagnosis of Lymphoma using WHO Classification
- Grades of Lymphoma
- Prognostic Index
- Transformation
- FISH
- Immunophenotyping
- Reactive and Infectious Lymphadenitis

"An Approach to the Diagnosis of Lymphoma by Fine Needle Aspiration: What the Clinician Needs to Know"

By Ruth L. Katz, M.D.
Professor of Pathology

Lymphomas

Classifications

Burkitt's-like lymphoma (BLL) defines a lymphoma which formerly fell between the morphological categories of Burkitt's lymphoma and diffuse large B-cell lymphoma. In order to call a lymphoma Burkitt's-like, it must exhibit some of the features of Burkitt's lymphoma, such as t(2;8) and t(8;22) as BL, or t(14;18) seen in a small subset of diffuse-large cell lymphoma. In order to diagnose a case as Burkitt-like, the presence of one of these translocations must be documented by either cytogenetics or FISH analysis.

FISH

FISH, or fluorescence-in-situ-hybridization, is a powerful technique for the detection of specific DNA sequences in tissue samples. It is particularly useful for the detection of chromosomal translocations that are characteristic of certain types of lymphoma. FISH can be performed on a single cytospin preparation prepared in a similar manner as for immunocytochemical analysis, or it can be performed on tissue sections or paraffin-embedded tissue.

Controls

Controls are isotype controls using IgG1- or IgG2-PerCP/IgG1-PE/IgG1-FITC, while monocytes are excluded from the gate using CD45-PerCP/Cy5.5/PE/Lambda-PE/Kappa-FITC, CD45-PerCP/CD11 C-PE/CD-22-FITC. Target cell preparations are incubated for 15 minutes in the dark before washing with PBS.

Labeling

The minimal requirement is to label at least 50,000 cells per tube to ensure adequate signal-to-background ratio. If fewer cells are available, a higher antibody concentration may be required. The minimal number of cells per tube is determined by the needs of the specific experiment and the requirements of the flow cytometer.

Interpretation

Interpretation of the patterns generated by the flow data is critical to accurate interpretation of a malignant versus a reactive population. For an excellent discussion of the interpretation of FISH data, see the book "Flow Cytometry in Lymphoma Diagnosis: A Comprehensive Guide" by Ruth L. Katz, M.D.

Cytology

Cytology is a valuable tool in the diagnosis of lymphoma. Cytology is particularly useful in the evaluation of aspirates that are inadequate for the evaluation of morphology and immunophenotyping. Cytology can be used to identify characteristic features of lymphoma, such as Reed-Sternberg cells in Hodgkin's lymphoma or Reed-Sternberg-like cells in non-Hodgkin's lymphomas.

Proliferation Indices

Proliferation indices can be determined by flow cytometry, immunocytochemistry using Ki-67 % labeling index. DNA image analysis can also determine the proliferative index, which has shown a strong correlation with the histological grade of lymphoma. It is important to be aware of the potential for false-negative results with Ki-67 immunostaining, especially in cases of low-grade lymphoma.

Presence of Transformation

The presence of transformation is important in the diagnosis of lymphoma, as it can affect the prognosis and treatment of the disease. The presence of a transformed lymphoma cell is usually determined by immunophenotyping, cytogenetics, or FISH analysis.

Diagnosis

A definitive diagnosis of lymphoma is made by the examination of the cytological and immunophenotypic characteristics of the tumor cells. The diagnosis is typically made by a pathologist who is experienced in the examination of cytological preparations and immunophenotyping.

International Collaboration

The WHO classification for lymphoma combined with sophisticated phenotyping by flow cytometry and molecular studies makes it possible to provide accurate diagnoses of lymphomas. This technique is particularly useful in cases of lymphoma that are difficult to classify by morphology alone.

Conclusion

The accurate diagnosis of lymphoma is critical to the treatment and prognosis of the disease. Flow cytometry, immunophenotyping, and molecular studies are important tools in the diagnosis of lymphoma. Cytology can be a valuable tool in the evaluation of aspirates that are inadequate for the evaluation of morphology and immunophenotyping. The presence of transformation is important in the diagnosis of lymphoma, as it can affect the prognosis and treatment of the disease.
An increase in the numbers of parzellinpositive cells may indicate a more aggressive clinical course than the typical small lymphocytic lymphomas, with a predominance of large cells in grade 3. Immunohistochemistry is important in distinguishing the B-cell lymphomas compared to small cells. While both mantle cell lymphoma and small lymphocytic lymphoma are CD5 positive, and CD20 negative, only the latter is positive for CD10. Follicular lymphomas show CD21 expression. Mantle cell lymphoma may be confused with the centroleukemic cells of marginal zone lymphoma, however, the latter show a far more heterogeneous population of cells including scattered myeloid cells. Remnant cells, high grade B-cell lymphomas, and follicular lymphomas may be distinguished by lack of CD10.

**Mature Zone Lymphoma**

Mature zone lymphoma is rare, low grade. It will transform to two major clinical presentations, extramedullary and nodal. Extramedullary mature zone lymphomas also known as non-Hodgkin lymphoma (NHL) and the majority of these cases have been detected in the bone marrow. In addition, there is a heterogeneous population of shared forms (mature zone lymphoma and B-cell lymphoma) which can occur in lymphocytic and B-cell lymphomas.

**Immunohistochemistry**

Mature lymphoma shows a variety of morphologic images ranging from the classic large lymphoid to a monotonous population of small lymphocytes. Mature Zone Lymphoma occasionally shows a monotonous population of small lymphocytes admixed with a clone of lymphocytes with prominent nucleoli and occasional plasma cells. The lymphoid cells may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. The lymphoid cells may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes may be monotonous in all instances or there may be an admixture of lymphocytes and small lymphoid cells. Small lymphocytes
Practical FNA in Lymphoma Diagnosis: What the Clinician wants to Know and How to Get There!

Ruth L. Katz, M.D.
Chief Research Cytopathology, Professor of Pathology, University of Texas M.D. Anderson Cancer Center Houston, Texas

What does the treating clinician need to know from the FNA in order to treat?
Valuable not Redundant procedure!

Indications for Fine Needle Aspiration of Lymphoproliferative Disorders at University of Texas M. D. Anderson Cancer Center
- Diagnosis
  - To firmly establish relapse and cell type
  - For primary diagnosis of selected cases
- To rule out transformation of low grade lymphoma
- To diagnose second primaries, i.e., LCL in patients with previous Hodgkin’s disease, new non-lymphoid primaries
- To obtain tissue for immunophenotyping or FISH
- To clarify stage of disease
- To rule out divergent histologies
- To obtain fresh material for research purposes such as DNA microarrays

What the treating physician needs to know and what the Diagnosis should contain
- Diagnosis of lymphoma, WHO Classification
- Grade of Lymphoma
- Immunophenotype
- Proliferation index
- ? Transformation

How to get sufficient cells!
- Aspiration without suction (French technique) using 25 gauge needle
- Suction introduces blood!
- Move needle in rapid iterations up and down 250 times (takes about 90 seconds)
- Look for creamy white tissue arising in hub of needle (Radiologists use same method)
- Place tiny drop to make smears (gently), air dried (Diff Quik) and Alcohol fixed Pap smears

Tricks of the Trade
- Flush most of specimen by reattaching syringe with air to needle and flush into RPMI 1640
- Carry on aspirating and rinsing needle until a minimum of 10 million cells obtained by Coulter Count, hematocytometer or visual inspection...usually 2-3 passes sufficient
- Examine smears and triage for ancillary studies based on morphology
Establishing a standardized approach to the work up of lymphocyte-rich FNA is Key to Success!

- Complementary Papanicolaou and Romanowsky stains
- Classify by WHO classification
- Immunophenotyping by Cytospin or FCM or both
- FISH on selected cases

MYTH

In order to make a diagnosis of lymphoma, the whole lymph node should be excised and examined histologically

Lymphoma With “Architecture”

- Follicular center cell
- Mantle cell (follic/diffuse/mz)
- Marginal zone

Cell Counterparts of Follicular, Mantle Zone and Marginal Zone Patterns

Follicular Lymphoma
Diffuse large Cell Lymphoma

Methods:

Cell Count (10 million)

Flow Cytometry

Immunocytochemistry

Labeling Index (Ki-67)

Kappa & Lambda

B-cell markers

T-cell markers

CD-19/CD10

CD-19/CD5

CD5/CD20

Cytospins

Ficoll-Hypaque density gradient

FISH

Pre-Ficoll Hypaque Pleural Fluid, SLL, Plasmacytoid

Post-Ficoll Hypaque Pleural Fluid, SLL, Plasmacytoid
**Immunophenotyping General Statements FCM vs. Cytospins**

- High degree of concordance irrespective of method
- Tailored panel vs. larger battery
- Spurious or inconclusive results by both methods if necrotic, or large lymphoma cells with fragile cytoplasm
- Need to interpret results in conjunction with the morphology on smears and the pattern on the flow histogram

**Problems with Immunophenotyping Flow Cytometry**

- Gating on wrong populations by FCM (miss a small malignant subpopulation, example;)
- Reporting markers on a predominant reactive small lymphocytic subpopulation without noting tight clonal distribution or “trailing” seen in a benign process
- Sampling problems, excessive peripheral blood contamination

**Problems in Flow Cytometry Related to Improper Gating**

- All lymphoid cells regardless of size gated
- Net result - looks polyclonal

**FCM With Correct Gating**

- Gated on larger lymphoid cells
- Monotypic Lambda “tight”
**MONOMORPHOUS POPULATION OF DISASSOCIATED CELLS + LYMPHOGLANDULAR BODIES**

**NON HODGKIN LYMPHOMA**

**IDENTIFY SMALL CELL TYPE**

- SMALL LYMPHOCYTIC/PLASMACYTOID
- MANTLE CELL, FOLLICULAR LYMPHOMA GRADE1, MARGINAL ZONE, LP HODGKIN’S LYMPHOMA

**MEDIUM SIZED CELLS**

- LYMPHOCYTIC
- MANTLE CELL LYMPHOMA, BLASTOID VARIANT
- BURKITT'S LYMPHOMA

**LARGE CELLS**

- LARGE CELL LYMPHOMA
- IMMUNOBLASTIC LYMPHOMA
- ANAPLASTIC LARGE CELL LYMPHOMA (Ki-1)

---

**WHO CLASSIFICATION B-Cell Neoplasms**

- Precursor B-cell neoplasm: precursor B-lymphoblastic leukemia, lymphoma
- Peripheral B-cell neoplasm
  - B-cell chronic lymphocytic leukemia, prolymphocytic leukemia, small lymphocytic lymphoma
- Lymphoplasmacytoid lymphoma, immunocytoma
- Mantle cell lymphoma
- Follicle center lymphoma, Grades 1, 2, 3
- Marginal zone B-cell lymphoma
- Extranodal (MALT-type with or without monocytoid B cells)
  - Hairy cell leukemia
  - Plasmacytoma, plasma cell myeloma
- Diffuse large B-cell lymphoma
- Burkitt's lymphoma

---

**Lymphomas Composed of Small Cells**

![Image of lymphoma cells]

**Differential diagnosis of Small Cell Lymphomas**

- SLL/CLL, B or T cell
- Lymphoplasmacytic lymphoma
- Mantle Cell lymphoma
- Marginal zone lymphoma/MALT/Splenic lymphoma with villous lymphocytes
- Follicular lymphoma
- Lymphocyte rich Hodgkin Lymphoma
- Progressive transformation of Germinal Centers

---

**Low Grade B-Cell Lymphoma**

<table>
<thead>
<tr>
<th>Small Cells</th>
<th>Large Cells</th>
<th>Phenotype</th>
<th>FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-CLL/SLL</td>
<td>Round</td>
<td>Prolymphocyte</td>
<td>CD5+, CD23+, cap 12, p53, LSI13, LAMPI, ATM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraimmunoblast</td>
<td>slg+(k, lambda), CD10, Co-express CD5/CD19</td>
</tr>
<tr>
<td>Mantle Cell</td>
<td>Cleaved,</td>
<td>None</td>
<td>slg+(k, lambda)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>notched (+ round/oval)</td>
<td></td>
<td>CD5+ CD10+/ CD23- CD5/CD19</td>
</tr>
</tbody>
</table>

---

**Small Lymphocytic Lymphoma**

![Image of small lymphocytic lymphoma]
Small Lymphocytic Lymphoma transformed to Large Cell Lymphoma (Richter's Syndrome)

56 YO woman with history of SLL, and recent posterior chest wall mass

CD23
Lambda
Kappa
p53
Ki-67

Results of FISH Panel for SLL derived from 42 FNAs

SLL PANEL

<table>
<thead>
<tr>
<th>GRADE</th>
<th>NO:OF CASES</th>
<th>12</th>
<th>13q14</th>
<th>LAMP1</th>
<th>P53</th>
<th>ATM 11q22-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLL LOW</td>
<td>20</td>
<td>3/20 (15%)</td>
<td>8/20 (40%)</td>
<td>1/20 (5%)</td>
<td>3/20 (15%)</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td>SLL HIGH *</td>
<td>22</td>
<td>2/22 (9%)</td>
<td>14/22 (63.6%)</td>
<td>5/22 (22.7%)</td>
<td>11/22 (50%)</td>
<td>8/22 (36.3%)</td>
</tr>
</tbody>
</table>

*SLL High grade, Accelerated phase, Richter’s syndrome

P53 deletion associated with poor survival
Mantle Cell Lymphoma: Cytomorphologic Features

- Monotonous population of small, atypical lymphoid cells
- Slightly irregular eccentrically placed nuclei, condensed chromatin, absent or small nucleoli, scant pale cytoplasm
- Prolymphocytes, paraimmunoblasts, and large noncleaved cells are absent

Morphologic Variants of MCL

- Blastic (blastoid, anaplastic, pleomorphic, Centrocytoid-centroblastic) – important to diagnose
- Lymphoblastic-like cells with very dispersed chromatin, usually inconspicuous nucleoli and a high mitotic rare
- Large cell-like with more prominent nucleoli
- Predominance of small round lymphocytes
Interphase FISH positive for bcl-1 (t 11;14) performed on Cytospin of Mantle Cell Lymphoma showing Multiple Fusion signals ( preferred to Cyclin D1 immunostain)

Marginal Zone vs Mantle Cell

- Features favoring Mantle cell include:
  - Monomorphic cellular population
  - Prominent nuclear irregularities
  - Scattered pink histiocytes
  - Frequent mitoses

- Features favoring Marginal Zone include:
  - Polymorphous cell population
  - Frequent plasma cells
  - Centrocyte-like cells with clear cytoplasm

- Overlapping morphologic features, immunophenotyping is essential

FNA Diagnosis: Nodal Marginal Zone Lymphoma

Seventy three year old lady with decreased appetite, fatigue, 30 lb weight loss, night sweats, CT scan showed massive splenomegaly and abdominal lymphadenopathy.

- Previous excisional biopsy of lymph node in inguinal region was non-diagnostic. Outside FNA suggested low grade B cell lymphoma.

- At MDACC, a periportal lymph node FNA was performed.

Well spaced monotonous small to intermediate lymphoid cells. FCM showed monoclonal kappa, CD19, CD22, CD11c, CD23 dim, negative CD5 and negative CD10, c/w MZL

Marginal Zone Lymphoma
Spleen, (weight 2390 grams)
Effacement of architecture, and replacement by monotonous population of both medium and large cells

Ki-67, 25% to 50 %
Bcl-2 positive cells
Spleen with Marginal Zone Lymphoma, and focal large cell transformation, increased Ki-67 labeling index
Follow up: Patient developed a large right pleural effusion, hypotension, and renal failure. Pleural Fluid, Large B cell lymphoma transformed from MZL.

Differential Diagnosis of a Polymorphous Mixed Cell Population

- Reactive Hyperplasia
- Lymphoma
  - MZL / MALT
  - Follicular lymphoma, grade 2
  - Peripheral T-Cell lymphoma
  - Immunocytoma, (transformed SLL plasmacytoid)

Follicular Lymphoma, grade 2, admixture of large centroblasts and smaller centrocytic cells

Follicular Lymphoma versus reactive hyperplasia?

Reactive Lymphoid Hyperplasia, spectrum of lymphoid cells

Mitosis and Apoptosis

Reactive Hyperplasia: Germinal center cells, and apoptosis with tingible body macrophages X40
Here we rely on cytospin immunophenotyping to resolve the problem... advantage of morphology together with phenotyping and Ki-67.

Reactive Hyperplasia:
- Polymorphous infiltrate: small round, small cleaved, small and large non-cleaved
- Plasmacytoid lymphocytes, immunoblasts, tingible body macrophages
- Florid immunoblastic reaction may confuse with large cell lymphoma
- Apoptosis
- Frequently high Ki-67
- Polyclonal, lacks CD10

Follicular Lymphoma, Approach to Diagnosis by FNA

Follicular Lymphoma:
- Follicular Lymphoma most prevalent subtype of NHL in the Western Hemisphere, is very frequently aspirated in retroperitoneum
- A B cell neoplasm compared of a mixture of cleaved follicular center cells (centrocytes) and large non-cleaved follicular center cells (centroblasts).
- FL may have a pure follicular pattern or it may have a partial follicular and diffuse pattern on histology
- WHO classification grades FL from 1-3 to reflect the reality of a cytologic continuum
- Grade 3 lymphomas are associated with poorer survival compared to grade 1 and 2, if treated with regimens not containing anthracyclines
Grading Definition

Grade 1 0-5 centroblasts per hpf*
Grade 2 6-15 centroblasts per hpf*
Grade 3 >15 centroblasts per hpf*

3a Centrocytes present
3b Solid sheets of centroblasts

Follicular Lymphoma: Grading on histology according to WHO classification

<table>
<thead>
<tr>
<th>Groups</th>
<th>Centroblast cell count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (n =31)</td>
<td>9.7 (5.1 - 15.7)</td>
</tr>
<tr>
<td>Grade 2 (n = 46)</td>
<td>24.7 (15.9 - 35.5) *</td>
</tr>
<tr>
<td>Grade 3 (n = 10)</td>
<td>48.3 (37.5 - 60.8) * #</td>
</tr>
</tbody>
</table>

* = p < 0.05 vs. grade 1 group
# = p < 0.05 vs grade 2 group
+Grading is based on centroblasts within follicles, easier to perform on Pap smears

FL grade 1
Centroblast count within follicles, 10%

FL grade 2
Centroblast count within follicles 25%

FL grade 3a
Centroblast count within follicles >50%, note residual centrocytes

FL grade 3b
>90% centroblasts within follicles and forming sheets
The Distribution of Ki67 (%) by Grade of Follicular Lymphoma. A Clinical Outcome Study of 57 Patients (40/57 relapsed FL)

<table>
<thead>
<tr>
<th>Follicular Lymphoma</th>
<th>N</th>
<th>Ki67 (%) Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>7</td>
<td>10 (2-26)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10</td>
<td>15 (8-25)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>21</td>
<td>40 (5-90)</td>
</tr>
<tr>
<td>Transformed</td>
<td>14</td>
<td>50 (25-90)</td>
</tr>
</tbody>
</table>

SD (P-value < 0.0001) between combined grades 1 and 2, and grade 3 and grade 3 transformed.

Cut-off between LG (1 and 2) and HG (3 inc TL) is 25%.

Between FL1 and FL2 by Ki67.

It is possible to determine the grade of FL on an FNA by determining the percentage of centroblasts within the follicular structures. This should be done after clonality has been established by FCM or immunocytochemistry.
When do we request a biopsy?

- Insufficient numbers of cells to do immunophenotyping
- New cases of lymphoma where tissue has never been obtained, is easy to obtain and diagnosis by FNA is unclear
- Composite lymphoma (MZL lymphoma) or when architecture is important for treatment such as mantle zone lymphoma
- For classifying Hodgkin Lymphoma
- For unusual benign lymphadenopathies, such as Castleman’s disease when excision may be curative
- When diagnosis is not straightforward or does not fit clinical history or presentation
- For some suspected low grade T cell lymphomas where gene rearrangement studies are equivocal

Using Multiparameter Testing on FNA, Will Enable The Treating Physician To Have:

- Reasonable approach to first evaluation of lymphadenopathy
- Can be used confirm recurrent disease in patients with lymphoma
- May be used as definitive diagnosis particularly when contraindication to biopsy such as palliative therapy in a compromised patient
- Access to sites such as the retroperitoneum and mediastinum without resorting to open biopsy

Conclusions

- Collection technique and on-site documentation of adequacy (quantity and quality) optimizes FNA Dx outcome
- Case by case allocation of cytologic material for ancillary studies remains critical for successful cytologic evaluation
- Above all, understand the limitations of the technique, and be an advocate for the patient rather than for a particular technique of diagnosis!!
### Relative Frequency of Intracranial Tumors

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>&lt;2</th>
<th>3-14</th>
<th>15-65</th>
<th>&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>Fistula astrocytoma</td>
<td>Anaplastic astrocytoma</td>
<td>Meningioma</td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Acoustic neuroma</td>
<td>Glioblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td>Epidermoid cyst</td>
<td>Astrocytoma</td>
<td>Anaplastic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td>Chordoma</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lymphoma</td>
<td>Inflammatory lesions</td>
<td>Inflammatory lesions</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Anaplastic astrocytoma</td>
<td>Ependymoma</td>
<td>Ependymoma</td>
<td></td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>Metastatic carcinoma</td>
<td>Gliosarcoma</td>
<td>Gliosarcoma</td>
<td></td>
</tr>
</tbody>
</table>

### Distribution of Intracranial Lesions: Supratentorial

- Meningiomas
- Schwanomas
- Metastatic neoplasms
- Gliomatous lesions

### Distribution of Intracranial Lesions: Infratentorial

- Meningiomas
- Schwanomas
- Metastatic neoplasms
- Gliomatous lesions

#### Basic Principles

- Relationship of Neoplastic Cells to Blood Vessels
- Blood Vessel Type
- Type of Background (follicular vs. diffuse)

#### Intraoperative CNS Cytology by Pattern

**Recognition**

Matthew A. Zarka, M.D.
Mayo Clinic Arizona
Scottsdale, Arizona

**Presentation Bullet Points**

- Definition of Practical Pattern Based Approach to Intraoperative CNS Cytology
- Method of CNS Squash Preparation
- Advantages and Limitations of Cytologic Smear Preparation
- The Importance of Clinical History
- Practical Architectural Pattern Approach to CNS Smear Cytology:
  - Basic Principles

**A. Definition of Practical Pattern Based Approach to Intraoperative CNS Cytology**

A consistent approach to rapid CNS smear diagnosis is to categorize lesions that exhibit a one or more cytocytic architectural patterns first at low to intermediate magnification (40x, 100x, 200x), and then confirm ones impression of a lesion at high magnification (400x-600x). I term this the practical pattern recognition approach to cytocytic smear diagnosis. These patterns do not necessarily rely on the presence of a specific cell type, for instance, astrocytes in a case of an astrocytoma. For example, a cytocytic pattern may include a specific type of architectural structure that the tumor cells and associated stromal cells or blood vessels exhibit, such as a papillary structure. Another pattern may encompass the interrelationship that clusters of neoplastic cells have with surrounding blood vessels, stromal tissue, extracellular matrix, or inflammatory cells. This approach first emphasizes grouping pathologic processes with an element or elements that they have in common with one another, and then subdividing these processes into their respective diagnostic categories based upon their unique cellular characteristics. This diagnostic approach is intuitive to many experienced cytopathologists, however, it is all too easy to rush to high power magnification when examining a case, carrying the risk of “missing the forest for the tree”.

**B. Method of CNS Squash Preparation**

Preparation of a squash preparation is simple. I prefer to prepare a smear by taking a small piece of tissue with a scalpel blade (less than 0.5 mm in diameter), placing the material on a slide, and subsequently exposing the specimen to a small slide, holding the second slide at right angles to the first, and applying uniform pressure during preparing. This approach is similar to preparing a routine Papanicolaou smear. If a reticent core biopsy is submitted, I will often remove a small piece of tissue from opposite sides of the core biopsy specimen and place both fragments of the same slide and subsequently smear both pieces, in order to better evaluate the representative material that is present within that specific core specimen. The smear is immediately fixed in alcohol and stained with hematoxylin and eosin. Additional slides can be air dried and stained with a Wright stain. The most common artifacts include crush and air drying with loss of cytocytic detail. It is important not to smear too large a specimen, which may yield a slide too thick for optimal cytocytic detail. Recognition of the fine fibrillary processes that often are associated with glial tumors is dependent on a thin specimen.

**C. Advantages and Limitations of Cytologic Smear Preparation**

**Cytologic Smears: Advantages**

- Speed
- Ease of preparation
- Simplicity
- Cytologic preservation
- Small sample size

**Cytologic Smears: Limitations**

- Relies on an intact neoplasm
- Histologic architecture not apparent
- Relies on an accurate localization by the surgeon

**D. The Importance of Clinical History**

When examining an intraoperative CNS case, it is essential to know the age of the patient and the location of the lesion in question before the specimen arrives in the frozen section suite. Useful clinical information includes the type and duration of clinical symptoms. For example, a history of seizures is more in keeping with a slower growing lesion such as a low grade astrocytoma, as compared to a rapidly growing lesion such as a glioblastoma.
Randomized Clusters With or Without Vascular Affinity
- Example: Metastatic Colonic Adenocarcinoma

2. Blood vessel type
- Thin walled blood vessels
  - Oligodendroglioma; Grade 2 and Grade 3 Astrocytomas
  - Metastatic Carcinoma
  - Lymphoma
  - Gliosis
- Vessels with endothelial cell proliferation
  - Glioblastoma
  - Metastatic Carcinoma
  - Lymphoma

Thin Walled Vessels

Vessels with Endothelial Cell Proliferation

3. The importance of presence or absence of fibrillary matrix.
- Normal brain matrix is characterized by a felt-like background.
- Astrocytomas usually demonstrate the presence of fine, well-defined glial processes in the background (Fibrillary background)
- Better seen without the microscope condenser
- Oligodendrogliomas may have more of a pool table felt background
- Gliomas may show a fibrillary background
- Metastatic carcinoma: fibrillary background generally absent; often a felt pattern
  - Watch for gliosis
- Lymphoma: fibrillary background generally absent; often a felt pattern
  - Watch for gliosis

Felt Pattern
- Example: Normal White Matter

Fibrillary Pattern
- Example: Astrocytoma

Summary: Pattern Based Approach to CNS Intraoperative Smeared Preparations
I. Evaluate the Slide at Low-Intermediate Magnification (40-200x)
- What Is The Relationship of Neoplastic Cells to Blood Vessels?
- What Type of Blood Vessels Are There?
- What Type of Background: Fibrillary Versus Felt-Like?
II. Evaluate the Slide at High Magnification (400-600x)
- Look for cytologic features to confirm your low magnification impression
Intraoperative CNS Cytology by Pattern Recognition
Matthew A. Zarka M.D.
Mayo Clinic Arizona
Scottsdale, Arizona

Case 1

This is a 68 year old male with a history of a right nephrectomy for renal cell carcinoma 10 years ago, and seed implantation for prostate cancer 5 years ago. One month prior to admission, he began to have symptoms of confusion, slight unsteadiness with his posture, and headaches. CT scan shows a large peripheral enhancing mass in the right posterior temporal and parietal lobe, 5 cm in diameter, with adjacent vasogenic edema and mass effect.

Relative frequency of intracranial tumors by age (yrs)

<table>
<thead>
<tr>
<th>&lt;3</th>
<th>3-15</th>
<th>15-65</th>
<th>&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>Pilocytic astrocytoma</td>
<td>Glioblastoma</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Medulloblastoma</td>
<td>Anaplastic astrocytoma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Ependymoma</td>
<td>Astrocytoma</td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td>Choroid plexus tumor</td>
<td>Astrocytoma</td>
<td>Meningioma</td>
<td>Meningioma</td>
</tr>
<tr>
<td>Germinoma</td>
<td>Choroid plexus tumors</td>
<td>Pituitary tumors</td>
<td>Acoustic schwannoma</td>
</tr>
</tbody>
</table>

Distribution of intracranial lesions

- **Intraparenchymal - supratentorial**
  - Astrocytoma
  - Anaplastic astrocytoma
  - Glioblastoma
  - Oligodendroglioma
  - Ependymoma
  - Metastatic neoplasms
  - Lymphoma
  - Inflammatory lesions
  - Vascular disorders
- **Intraparenchymal - infratentorial**
  - Cerebellar astrocytoma
  - Medulloblastoma
  - Ependymoma
  - Hemangioblastoma
  - Metastatic neoplasms
  - Lymphoma
  - Inflammatory lesions
  - Vascular disorders
DDX: Small Blue Cell Tumor

- Glioblastoma/Anaplastic Astrocytoma: small cell variant
- Neuroblastoma
- Metastatic small cell carcinoma
- Pineoblastoma
- Pituitary adenoma
- Oligodendroglioma
- Lymphoma
- Central neurocytoma

Tumor distribution in relation to blood vessels

- **Gliomas**: especially astrocytomas, usually demonstrate aggregation of tumor cells close to blood vessels
- **Lymphoma**: can infiltrate blood vessel walls but are often dispersed away from blood vessels also
- **Metastatic carcinoma**: clusters of malignant cells are distributed close to and away from blood vessels; variable with tumor type

Blood vessel type

- Thin walled blood vessels
  - Oligodendroglioma; Grade 2 and Grade 3 Astrocytomas
  - Metastatic Carcinoma
  - Lymphoma
  - Gliosis
- Vessels with endothelial cell proliferation
  - Glioblastoma
  - Metastatic Carcinoma
  - Lymphoma

CNS: The importance of presence or absence of fibrillary matrix

- Astrocytomas: usually demonstrate the presence of fine, well defined glial processes in the background
  - Better seen without the microscope condenser
  - Oligodendrogliomas may have more of a pool table felt background
  - Gliosis may show a fibrillary background
- Metastatic carcinoma: fibrillary background generally absent
  - Watch for gliosis
- Lymphoma: fibrillary background generally absent
  - Watch for gliosis
Case 2

This is a 68 year old male with a history of mycosis fungoides who states over the last two and three weeks he and his wife have noticed significant memory loss.

An MRI at time of admission demonstrates diffuse enhancement in the subependymal tissue of the body of lateral ventricles and in the splenium along the temporal horn. There is also a small amount of enhancement in the Virchow-Robin spaces of the left occipital and parietal lobes. The radiographic findings are consistent with CNS lymphoma.
Pattern Based Approach to Diagnosis

- Relationship of Neoplastic Cells to Blood Vessels
- Blood Vessel Type
- Type of Background

Glioblastoma, Small Cell Variant
Summary: Pattern Based Approach To CNS Intraoperative Smear Preparations

- Evaluate The Slide At Low-Intermediate Power
  - What Is The Relationship of Neoplastic Cells to Blood Vessels?
  - What Type of Blood Vessels Are There?
  - What Type of Background: Fibrillary Versus Felt-Like?
- Evaluate The Slide At High Power
Accuracy and Usefulness of FNA vs Core Needle Biopsy in Breast Diagnosis

Brett Marie Lyon, MD
Professor of Pathology
University of California at San Francisco
USCAP ASC – companion meeting
March 24, 2007

Presentation Bullet Points

• Accuracy of both FNA and CORE are variable and dependent on proficiency of operators, number of specimens collected, type of lesion, method of guidance and for core needle, size of needle.

• Under defined conditions the accuracy of FNA and CORE is high and similar for both methods.

• FNA and CNB should be used in the context of the Triple test (clinical and/or imaging findings).

• FNA was relatively successful in the 1980s with limited numbers of better trained operators. Lower accuracy in the 1990s as more operators without training joined in.

• FNA is faster, less costly and better tolerated by patients than CNB and similar procedures.

In recent years automated core needle biopsy, and various cannulated assisted devices of increasing core diameter, with mounting numbers of tissue pieces collected from each lesion, have replaced Fine Needle Aspiration Biopsy (FNA) as the first line diagnostic method in many settings.

This review will explore some of the consequences of this trend and also examine the accuracy and usefulness of both FNA and Core Needle Biopsy (CNB) in various settings and conditions.

PAIN

It is generally agreed that one of the advantages of FNA over CNB and other diagnostic breast procedures is its minimal morbidity, primarily in terms of pain level. As the core needle diameters have increased in size and the number of tissue cores collected for each lesion has mounted, in attempting to increase the accuracy of the test, the patient’s discomfort associated with the test appears to have increased. I have chosen to illustrate this by two examples from the last 2 months of 2008. The first one is a case from the Dec 11 issue of Stereotactic and Radiosurgical Surgery. The headline reads: “Targeting Needleless Breast Biopsies”.

Following are selected pertinent quotes from the text: “Think mammograms are unpleasant? Breast biopsies are much worse...3.6 million breast biopsies per year...80 percent bitches. Isn’t there a better way?” The writer had attended a radiology meeting and learned about a new ultrasound technique that would potentially make biopsies of the breast unnecessary. The second example is from a study, conducted at Harvard Medical School and presented at the same radiology meeting by Lang et al describing the benefits of hypnosis in coping with breast biopsy in 216 women. The authors concluded that, with hypnosis, there was “significant decrease in pain, anxiety during the procedure”.

COST

Although billing and reimbursement rates vary widely, generally FNA is less costly than CNB and other biopsy systems. The cost of using micro-cannulated, large bore (7-11 gauge) devices is similar to the cost of an open, surgical biopsy.

SPEED

Using FNA, a preliminary diagnosis can often be rendered at the time of the procedure or shortly thereafter. Giard and Hermance10, on the other hand, a CNB needs to be processed and a diagnosis takes longer, often days longer.

FNA ACCURACY IN PALPABLE BREAST MASSES

Giard and Hermance10, found in a meta-analysis that the accuracy of FNA varies widely, with sensitivity ranging from 65-99 percent and specificity from 52-100 percent. They concluded that FNA is an operator-dependent test and suggested that local test characteristics should be established before relying on the test. Most observers agree that training and experience in the interpretation of the specimen is important for accuracy and at least one study has shown that, in addition to knowledge of histology of breast lesions, it is important to have training in the interpretation of cytologic material from breast lesions, Cohen et al.11.

Like FNAB the accuracy of CNB in diagnosing breast cancer also varies in the literature. ACCURACY OF CNB IN BREAST DIAGNOSIS

Under defined conditions the accuracy of FNAB and CNB is high and similar for both methods.

• FNAB or any other biopsy modality of the breast, with a false negative rate of about 5 percent, should be used in the context of the “Triple Test” which includes clinical presentation and any imaging findings. When all indicators are consistent with a benign process, the lesion may be safely observed clinically. If the indicators are not concordant, further investigation is indicated, Lau S. et al.

ACCURACY OF CNB IN BREAST DIAGNOSIS

Like FNAB the accuracy of CNB in diagnosing breast cancer also varies in the literature. Dillon M. et al10, based on a meta-analysis, reports false negative ranges as follows:

FNAB: 95 percent diagnostic samples, from palpable lumps, after initial biopsy practice followed by performing between 100-150 FNABs in training. Not all training FNABs however, need to be from breast lesions. In our experience, operators require this amount of training in order to be exposed to sufficiently challenging cases to develop their skills to an acceptable level.

FNA or any other biopsy modality of the breast, with a false negative rate of about 5 percent, should be used in the context of the “Triple Test” which includes clinical presentation and any imaging findings. When all indicators are consistent with a benign process, the lesion may be safely observed clinically. If the indicators are not concordant, further investigation is indicated, Lau S. et al.

Stereotactic CNB: 0.2-8.9 percent

Ultrasound guided CNB: 0-12 percent

SPEED

Using FNAB, a preliminary diagnosis can often be rendered at the time of the procedure or shortly thereafter, Giard and Hermance10. On the other hand, a CNB needs to be processed and a diagnosis takes longer, often days longer.

FNA ACCURACY IN PALPABLE BREAST MASSES

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COMPARISON OF ACCURACY OF FNAB AND CNB OF NON-PALPABLE LESIONS WITH IMAGE GUIDANCE.

The best known prospective study collecting data, from 18 institutions on 462 women who underwent FNAB with image guidance was undertaken by the Radiologic Diagnostic Oncology Group V and published by Pisano et al.20 The findings varied significantly from one institution to another but overall the results show low sensitivity for breast cancer. FNAB, in this study, worked better for masses than for microcalcifications and also better with ultrasound guidance than with stereotactic guidance.

No training or experience in FNAB sampling was required for individual radiologists participating in the study. Although there was a requirement that at least 50 FNABs had been collected at each participating institution.

A second study by Symmans F et al examined 455 breast lesions using stereotactically guided FNAB in a single private practice setting. Two hundred fifty-two of the same patients also underwent stereotactic CNB. In each case at least 5 FNABs were collected and when CNB was utilized at least 5 cores were taken. In a subset of cases, additional sampling, using FNAB and/or CNB, was conducted based on evaluation of the material collected, by microscopy or presence of microcalcifications. All pathologists participating in the study had training in FNAB sampling technique. In cases of cancer found on FNAB, a core biopsy was added in order to assess invasion.

### Table: Sensitivity, Specificity, and Reports

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB</td>
<td>90%</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>CNB</td>
<td>90%</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>FNAB</td>
<td>95%</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>CNB</td>
<td>95%</td>
<td>95%</td>
<td>5%</td>
</tr>
</tbody>
</table>

In summary the literature sets forth wide variability of results of both FNAB and CNB. Factors influencing the accuracy of both include: proficiency of operators, number of specimens collected, type of lesion (mass, microcalcifications, etc.), and method of guidance (palpation, ultrasound, and stereotactic).

Clearly, FNAB works less well in settings where operators are not trained adequately in how to collect the specimen. Studies reporting high rates of accuracy were conducted with operators well versed in FNAB sampling and usually with immediate evaluation of the specimen at bedside. For CNB, poor results have been found when using relatively thin (18 gauge) needles and a collecting limited numbers of cores. Thus, there has been a strong trend in recent years to increase the size of the needles usually to between 14-15 gauge and to recommend increasing the numbers of cores collected to between 5-15 depending on type of lesion and mode of guidance. Some authors have advocated still larger bore instruments and higher numbers of cores. It is not clear from the literature how specific training in the use of CNB may influence the diagnostic rates of individual or groups of operators. Perhaps improved training in CNB could reduce the need for large numbers of specimens from big needles.

Although increased numbers of core samples currently collected with larger needles has improved the accuracy of CNBs, the increased accuracy has come at a price, both financial and in the form of increased morbidity.

In a world where information is becoming increasingly available to patients, insurers and buyers of insurance, it is likely that at least three factors will be important for future success. These factors are cost, quality and patient satisfaction. FNAB, when practiced by well-trained operators, compared well in all three categories to CNB and similar methods. Thomas Friedman’s book “THE WORLD IS FLAT” provides an interesting perspective on the impact of information technology in many fields, including medicine. I expect that individual institutions will, in the not too distant future, be asked to report accuracy data for procedures such as breast biopsy, as part of quality assurance and improvement. These data may not only be used to direct what method is the best choice in a particular setting. In settings with the required expertise, FNAB sampling, with triage to CNB when indicated in a small subset of cases, optimizes patient satisfaction and cost, and delivers accuracy comparable to CNB.

Accuracy of FNAB with triage to CNB, mostly CNB, in 6% of cases:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB</td>
<td>97.5%</td>
<td>100%</td>
</tr>
<tr>
<td>CNB</td>
<td>97%</td>
<td>100%</td>
</tr>
</tbody>
</table>

In the Symmans 2 out of the 3 cancers missed by FNAB were also missed by CNB.

### Table: Accuracy of FNAB and CNB

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB</td>
<td>98.3%</td>
<td>100%</td>
</tr>
<tr>
<td>CNB</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

ACCURACY OF FNAB WITH TRIAGE TO CNB IN A SMALL SUBSET (6%) OF CASES.

A recent study at UCSF (manuscript in preparation) comparing consecutive ultrasound guided FNAB with subsequent histologic follow-up of any lesion over a year period was analyzed. A total of 1435 FNABs with ultrasound guidance of almost exclusively non-palpable lesions were done during this period. Three hundred (21%) of these cases had histologic follow-up at one institution. One hundred sixty five cancers were found among these 300 cases. There were no known cancers among the lesions without histologic follow-up however, matching of all 1356 with a population-based cancer registry is planned in order to get true complete follow-up. Ninety four percent of all 1356 cases were diagnosed by FNAB alone. An average of 2 FNAB samples were collected from each lesion. All radiologists collecting samples were trained in the procedure and cytopathologists attended and performed immediate interpretations of the samples. Sixty two (5%) of all 1356 cases were converted to CNB at the time of initial FNAB sampling based either on insufficient sample or immediate interpretation of the FNAB sample discordant with the imaging findings. Fourteen (23%) percent of these 62 cases were cancers. An additional 18 cases (1%) had FNAB samples determined to be insufficient at FNAB sign-out, and as a result had subsequent histology for diagnostic purposes. Nine (50%) of these 18 cases were cancers. Three cancers (1.7% of all 1356 cancer found) were not triaged to CNB at the time of sampling or FNAB sign-out and were false negatives by FNAB report. All 3 were grade 1 cancers, 1 cm in size or smaller. These were no delays in treatment. All three cases had discordant imaging findings and were triaged to excisional biopsy, soon after FNAB sign-out.

Accuracy of FNAB with triage to CNB in 6% of cases:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>CNB</td>
<td>100%</td>
<td>95%</td>
</tr>
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In the Symmans study 2 out of the 3 cancers missed by FNAB were also missed by CNB.

### Table: Accuracy of FNAB and CNB

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<tr>
<th>Procedure</th>
<th>Sensitivity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>FNAB</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>CNB</td>
<td>99.5%</td>
<td>91%</td>
</tr>
</tbody>
</table>

References

4. Ballo M and Sniege N. Factors influencing the accuracy of both tests include: proficiency of operators, number of specimens collected, type of lesion (mass, micro-calcifications, etc.) and method of guidance (palpation, ultrasound, and stereotactic).
Accuracy and Usefulness of FNA vs. Core Needle Biopsy in Breast Diagnosis

Britt-Marie Ljung, MD
Professor of Pathology
University of California at San Francisco
USCAP PSC – companion meeting
March 24, 2007

Why Bother?

Newsweek article

“Think mammograms are unpleasant? Breast biopsies are much worse.”
“…tense wait for results…four days during which she agonized over the prospect of…small children…left without a mother.”
“…1.4 million breast biopsies per year … 80 percent benign.”
“Isn’t there a better way?”

Targeting Needles Breast Biopsies

Cost

Surgical bx and Assorted devices

CNB

FNAB
SPEED

- FNAB – typically preliminary dx at time of procedure- final 24-48 h
- CNB – typically 2 days+

Hidden Reality – Missed Cancers

Low index palpatory findings
Threshold for any biopsy or imaging study
Young women < 35 and post menopausal with negative imaging

FNAB Accuracy Palpable Breast

- Sensitivity 65% - 98%
- Specificity 34% - 100%

Giard R and Herman SJ
Cancer Apr 15, 1992
Vol 69, No 8, p. 2104

FNAB Accuracy – Impact of Training in Sampling Technique

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Training</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>Without Training</td>
<td>75%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Definition of training in sampling technique:
> 100 cases during up to one year supervised by experienced teacher with proven track record.

Ljung et al
Cancer (Cancer Cytopathology) 2001; 93: 23-268

The problem with FNAB

CME for OBGYN doctors
FNAB is useful and quick….safe and simple
10 ml syringe, 21 guage needle
Mass stabilized…needle inserted…vacuum is maintained on the syringe while moving the needle for a few passes through the lesion. Release suction…withdraw..push onto slide..smear
Send to experienced cytopathologist
In experienced hands false pos <1% and false negative rate 5%
FNAB as part of Triple Test in palpable lesions

- Reported False neg rate FNAB alone 7%
- When applying Triple Test False negative rate 0%

Lau S et al
The Breast Journal
Vol 10 No 6 2004
p. 487-491

Accuracy Core Biopsies

Guided by:

- False Negative
  - Palpation 0 – 13%
  - Ultrasound 0 - 12%
  - Stereotactic 0.2 – 8.9%

Dillon M et al
Annals of Surgery
Vol 242 N 5 2005

Image Guided Core Needle Biopsy Accuracy

Strategy: Increase number of cores/weight of tissue

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity with 5 14 guage cores</th>
<th>Recommended no of cores 14 guage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Lesions</td>
<td>98%</td>
<td>5-6</td>
</tr>
<tr>
<td>Ca++</td>
<td>91%</td>
<td>15</td>
</tr>
<tr>
<td>Anc. Dist</td>
<td>86%</td>
<td>15</td>
</tr>
<tr>
<td>US-guided</td>
<td>98%</td>
<td>5-12 cores</td>
</tr>
</tbody>
</table>

Operator dependent

Brenner RJ et al
AJR Am J Roentgenol
166:341-346 1996

Number of Cores Needed – Mass Lesions

- Germany 3
- Sweden 3
- Spain 3

Sauer G, et al
British Journal Cancer
2005; 92:231-5

Leifland K, et al
Acta Radiol.
2004; 45(2):142-7

Comparison FNAB vs. Core bx

Palpable, without guidance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNB (3+)</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>FNAB (3)</td>
<td>97.5%</td>
<td>100%</td>
</tr>
<tr>
<td>CNB</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>FNAB</td>
<td>99%</td>
<td>99.5%</td>
</tr>
</tbody>
</table>

Ballo M, Sniege N.
Cancer, Aug 15, 1996
Vol. 78 No 4 p 773

Antley C, et al
The Breast Journal
Vol 4 No 1 1998 p 3-7

Comparison FNAB vs Core Needle Bx

Non-Palpable with US-guidance

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB (2)</td>
<td>76-100%</td>
<td>46-99%</td>
</tr>
<tr>
<td>FNAB</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>CNB</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Pisano, et al
Radiology June 2001
Vol 219 No 3 p. 785

Symmans, F et al
Cancer Mar 1 1999
Vol 85, No 5 p. 1119
UCSF US Guided FNAB Breast
(Consecutive cases for 7.5 years)

- Total 1356 cases
- 300 cases with histologic follow-up of any kind at UCSF
- 173 cancers (13%) of Total 1356
  - 6% Triaged to histology, mostly CNB
  - 94% Dx by FNAB alone

Algorithm at UCSF- US-guided bx of Non-palpable lesions

- Average 2 FNAB samples with Quick Stain
- If material deemed adequate, and preliminary diagnosis is c/w imaging finding = Done.
- If material insufficient or preliminary diagnosis inconsistent with imaging or atypical and do not expect to be able to reach definitive diagnosis = Convert to histology, usually core biopsy
- 6% converted to primarily Core Needle Biopsy

UCSF US Guided FNAB Breast

- Reasons for histologic exams:
  - Insufficient FNAB
  - Discrepancy cytology/ imaging
  - Atypical cytology findings
  - Patient or physician request

UCSF US-guided
N = 1356

- 6% triaged to histology
- 98.3% sensitivity
- 100% specificity
- No treatment delay

UCSF US-guided
N = 1356

- 3 (1.8%) of 173 cancers reported benign by FNAB
- All 3 grade I ca ≤ 1.1cm
- No treatment delay, all discordant cyto-imaging

UCSF US-Guided FNAB

<table>
<thead>
<tr>
<th>Cytologic Diagnosis (N)</th>
<th>Rapid Review Vs Final Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (66)</td>
<td>93%</td>
</tr>
<tr>
<td>Malignant (126)</td>
<td>98%</td>
</tr>
</tbody>
</table>
UCSF US-guided
N = 1356

- 80 (6%) of total cases triaged to histology, mostly CNB
- 23 cancers (29% of 80) converted

Factors for success

- Accuracy
- Cost
- Patient satisfaction
- Speed

Conclusions

- FNAB is operator dependent
- Fairly successful in 1980s, limited number of better trained operators. Lowered accuracy in 1990s as more operators without training joined in.
- FNAB and CNB should be used in the context of the Triple test (clinical and/or imaging findings)
- Under defined conditions the accuracy of FNAB and CNB are high and similar.
- FNAB is faster, less costly and better tolerated by patients than CNB and similar procedures.