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.
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• Intraoperative cytology is highly useful in evaluation of breast, parathyroid, CNS and sentinel lymph node specimens.
The psychic atmosphere at a frozen-section-at-operation seance is not conducive to accurate scientific reasoning. First, 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 subpoenaed. 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 unceremoniously called 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%
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross only</td>
<td>10%</td>
</tr>
<tr>
<td>Gross and cytology</td>
<td>54%</td>
</tr>
<tr>
<td>Gross and frozen section</td>
<td>10%</td>
</tr>
<tr>
<td>Gross, frozen and cytology</td>
<td>26%</td>
</tr>
</tbody>
</table>
INTRA-OPERATIVE CYTOLOGY

- imprint (touch prep).
- smear:  1) scrape and streak.
          2) scrape and spread.
- squash prep.
- mincing.
- mash and move.
WET FIXATION:
- immediate immersion
- 95% ethyl alcohol.
- H&E, Papanicoloau

DRY FIXATION:
- Allow to air dry.
- 100% methanol.
- Diff-Quick stain.
- **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**
INTRAOPERATIVE CYTOLOGY: PAST, PRESENT, AND FUTURE

- Past: Breast
- Present: Parathyroids
- Future: Lymph nodes (inc. sentinel)
### TABLE 1  OUTCOMES BY BODY SITE

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>NUMBER</th>
<th>ACCURACY</th>
<th>DEFERRALS</th>
<th>FALSE (−)</th>
<th>FALSE (+)</th>
<th>DIFFERENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREAST</td>
<td>371</td>
<td>94.6</td>
<td>4.3</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>95</td>
<td>91.6</td>
<td>4.2</td>
<td>4.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS/PNS</td>
<td>91</td>
<td>86.8</td>
<td>11.0</td>
<td>2.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LYMPH NODES*</td>
<td>91</td>
<td>80.2</td>
<td>11.0</td>
<td>5.5</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>LUNG/THORAX</td>
<td>81</td>
<td>86.4</td>
<td>7.4</td>
<td>1.2</td>
<td>1.2</td>
<td>3.7</td>
</tr>
<tr>
<td>ENT</td>
<td>50</td>
<td>92.0</td>
<td>4.0</td>
<td>2.0</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>GYN SYSTEM</td>
<td>45</td>
<td>91.1</td>
<td>6.7</td>
<td>0</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>SOFT TISSUE/BONE</td>
<td>43</td>
<td>93.0</td>
<td>4.7</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LYMPH NODES+</td>
<td>37</td>
<td>94.6</td>
<td>0</td>
<td>5.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>THYROID/PTH</td>
<td>36</td>
<td>75.0</td>
<td>11.1</td>
<td>8.3</td>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>SKIN</td>
<td>29</td>
<td>93.0</td>
<td>3.5</td>
<td>0</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>GU</td>
<td>21</td>
<td>95.2</td>
<td>4.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SPLEEN</td>
<td>6</td>
<td>66.7</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OTHER</td>
<td>4</td>
<td>100.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTALS</td>
<td>1000</td>
<td>90.4</td>
<td>6.1</td>
<td>2.3</td>
<td>0.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* LYMPH NODES LYMPHORETICULAR DISEASE.
* 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
## PARATHYROID EXPLORATION—TWO SERIES

<table>
<thead>
<tr>
<th>Tissue and Number</th>
<th>Cytologic Errors</th>
<th>Frozen Section Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid (111)</td>
<td>1 deferred</td>
<td>2 deferred</td>
</tr>
<tr>
<td>Thyroid (19)</td>
<td>1 parathyroid</td>
<td>1 parathyroid</td>
</tr>
<tr>
<td>Lymph node/thymus (17)</td>
<td>0</td>
<td>1 parathyroid</td>
</tr>
<tr>
<td>Adipose tissue (1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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 ($D_L$) 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>$D_n$ (mm)</th>
<th>$D_L$ (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>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>20.6%</td>
<td>18.9%</td>
<td>58.4%</td>
</tr>
<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**


<table>
<thead>
<tr>
<th></th>
<th>Frozen Section</th>
<th>“Imprint Cytology”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>79-98%</td>
<td>78-99%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>55-91%</td>
<td>46-96%</td>
</tr>
<tr>
<td><strong>False negative rate</strong></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/Consensus</td>
<td><em>Hum Pathol</em> 33:579, 2002</td>
<td>IOC = FS</td>
</tr>
<tr>
<td>UK</td>
<td><a href="www.cancerscreening.nhs.uk">www.cancerscreening.nhs.uk</a></td>
<td>FS not recommended</td>
</tr>
<tr>
<td>Germany</td>
<td><em>Cancer</em> 103:451, 2005</td>
<td>Gross + IOC or FS</td>
</tr>
<tr>
<td>Austria</td>
<td><a href="www.pathology.at/sentinel.htm">www.pathology.at/sentinel.htm</a></td>
<td>FS (2-3 from mid-portion)</td>
</tr>
<tr>
<td>Australia</td>
<td><a href="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,
  - 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
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/CYTLOGIC DISCREPANCY

INADEQUATE SMEAR

SPECIFIC REQUEST
It's a mammoth.

Early microscope
A NEW METHOD FOR THE RAPID MICROSCOPOICAL
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.—Case 115. Spheroidal-celled carcinoma of breast. Note large size of cells, plaques of cells, and the large number of isolated cells. (× 185.)
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.