A Technique for Microscopic Assessment of “LEEP” Specimen Margin Status

Loop Electrosurgical Excisional Procedure (LEEP)

- Most common treatment for CIN
- Positive margins a clinical challenge
- Associated risks with loop excision of cervix and subsequent pregnancy performance

Large Loop Excision & Pregnancy

- Some studies show no impact on future pregnancy outcome
- Several studies show increased risk:
  - Preterm labor (PTL)
  - Preterm premature rupture of membranes (PPROM)
  - Low birth weight infants (LBW)

[Blomfield, P. et al] [Craw, J.] [Gentry, D. et al] [Ferenczy, A. et al] [Gluck, D. et al] [Larque, D. et al] [Paraskevaidis & et al] [Reiss, L. et al] [Sadler, L. et al] [Svenson, S. et al]
### Height of Loop Excision Specimen & Risk of PTL and PPROM

<table>
<thead>
<tr>
<th>Specimen Height</th>
<th>RR PTL</th>
<th>RR PPROM</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10 mm</td>
<td>1.8</td>
<td>--</td>
<td>.05</td>
</tr>
<tr>
<td>&gt; 12 mm</td>
<td>1.74</td>
<td>(0.35-3.1)</td>
<td>--</td>
</tr>
<tr>
<td>&gt; 17 mm</td>
<td>1.7</td>
<td>(1-2.7)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* 95% CI


### Disease Persistence After Loop Excision

- **Histopathologically Positive Margins**  
  - Persistence in 30-50% (if initial lesion was high grade)

- **Histopathologically Negative margins**  
  - Persistence in 6-20%.
  - Most persistent disease identified in first 6-10 months.

- 27-70% of patient with biopsy proven dysplasia will not complete follow up


### The Ideal Loop Specimen

- Remove all dysplastic tissue
- Negative endocervical margins
- Minimal thermal artifact
- Removes minimal amount of normal tissue to maximize cervical length

What could the colposcopist do to reduce the incidence of positive margins and persistent disease?

The Mohs Procedure

- Dermatologists have navigated through this issue of removing disease while preserving normal tissue
  - Treatment of choice for basal and squamous cell cancer of the skin
  - Removal of thin layer of tissue followed by immediate frozen section
  - Continue removing thin layers until margins clear
  - High cure rates and maximum preservation of normal tissue

Can intraoperative microscopic evaluation of specimens obtained by loop excision determine margin status?
Study Hypothesis

- At the time of electrosurgical loop excision the operating surgeon can accurately distinguish between a positive and negative endocervical margin by intraprocedural colposcopic and microscopic examination.

Study Methods

- On-going prospective, comparative, pilot study, started in 7/05 conducted in the Department of Obstetrics and Gynecology at Kaiser Permanente Los Angeles

- Specimens from all women undergoing loop excision were eligible for inclusion
  - Specimen excluded if canal not kept intact
  - Standard histopathological examination
  - Informed consent not necessary (Southern California Research Committee exemption)

Technical Overview

1. Identification of lesion
2. Local anesthesia
3. Loop excision under colposcopic guidance
4. Hemostasis with fulguration
5. Hemostasis with ferrous subsulfate (Monsel's)
Residual Disease in Canal

Negative Margin  Positive Margin

CIN

Residual Disease in Canal

Methods

- **Group A:**
  - Multiple surgeons
  - Use of colposcope to determine margin status
    - Positive, negative, indeterminate
  - Interim analysis:
    - Limitations for some holding specimen within colposcopic focus
    - Other difficulties evaluating specimens for some surgeons

- **Group B: Method Revisions**
  - 3 Surgeons
  - Availability of stable dissecting microscope.
Methods

- The primary outcome:
  - Correlation of the gynecologists’ and pathologists’ determination of endocervical margin status.

- Secondary outcomes:
  - Predict persistent/residual disease by:
    - Specimen (ECC or Apical Excision) positive for CIN at index procedure
    - + HPV on subsequent assay
    - ≥ LSIL at any subsequent Pap

Results

- 58 specimens included
  - 34 in Group A
  - 24 in Group B
- Most of the specimens were cut to allow visualization of the endocervical margin
- Colposcopists “indeterminate” included with positives
- Pathologist able to determine margin status in all cases; no severe thermal artifact.

Primary Outcome – Combined Group, N=58
Gynecologist-Pathologist Correlation

<table>
<thead>
<tr>
<th>Gynecologist</th>
<th>Pathologist</th>
<th># of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin+</td>
<td>Margin+</td>
<td>36</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>N=43</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>

- PPV: 44%, 95% C.I. (19%, 68%)
- NPV: 86%, 95% C.I. (75%, 81%)
### Primary Outcome – Group A, N=34

**Gynecologist-Pathologist Correlation**

<table>
<thead>
<tr>
<th>Gynecologist</th>
<th>Pathologist</th>
<th># of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin+</td>
<td>Margin+</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>N=20</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>

- PPV: 20%, 95% C.I. (-5%, 45%)
- NPV: 75%, 95% C.I. 58%, 92%)

### Primary Outcome – Group B, N=24

**Gynecologist-Pathologist Correlation**

<table>
<thead>
<tr>
<th>Gynecologist</th>
<th>Pathologist</th>
<th># of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin+</td>
<td>Margin+</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>N=23</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>0</td>
</tr>
</tbody>
</table>

- PPV: 83%, 95% C.I. (54%, 113%)
- NPV: 100%, 95% C.I. 100%, 100%)

### Secondary Outcome

**Prediction of Residual Disease**

<table>
<thead>
<tr>
<th>Gynecologist</th>
<th>Residual Disease</th>
<th># of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo Margin +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>7</td>
</tr>
</tbody>
</table>

- **(Combined N=35)**
  - PPV: 88% (65%, 110%)*
  - NPV: 98% (89%, 103%)*

- **(Group A N=24)**
  - PPV: 63% (29%, 96%)*
  - NPV: 71% (49%, 92%)*

- **(Group B N=11)**
  - PPV: 100% (100%, 100%)*
  - NPV: 89% (68%, 109%)*
**Secondary outcome - Group A + B**

<table>
<thead>
<tr>
<th>Colposcopist/Pathologist Margin Status</th>
<th>Residual Disease</th>
<th>Total</th>
<th>+</th>
<th>-</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>+/+</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
<td>(15%, 85%)</td>
<td>(17%, 50%)</td>
</tr>
<tr>
<td>+/+</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td>67%</td>
<td>79%</td>
</tr>
<tr>
<td>+/-</td>
<td>19</td>
<td>4</td>
<td>15</td>
<td></td>
<td>(13%, 120%)</td>
<td>(61%, 97%)</td>
</tr>
</tbody>
</table>

* 95% C.I.

**Discussion**

- Data demonstrates a correlation between the gynecologist’s colposcopic impression of margin status and the findings of the pathologist.
- Improved correlation in second half of study.
  - PPV increased from 20-83%, NPV 75-100%

**Discussion**

- Gynecologist training & equipment appears to have an influence on the quality of the colposcopic assessment
  - **Group A:**
    - Multiple attendings and residents
    - No formal training
    - Colposcope only
  - **Group B:**
    - 3 well trained surgeons
    - Availability of stable dissecting microscope
Discussion

- Some histopathologically false negatives were picked up colposcopically.

- Is histopathologic examination the gold standard?
  - High rates of persistence / recurrence despite negative margins
  - Positive margin frequently doesn’t = persistence

  Why might this be?
  - Thermal artifact
  - Shrinkage artifact
  - Processing issues

Discussion: Future Studies

- Larger sample size
- Multiple centers
- Long term clinical outcomes

Conclusion

- Technique shows promise

  If future studies confirm the validity of this technique one might expect:
  - Reduction in positive margins and decreased frequency of repeat evaluations and excisions with intraprocedural colposcopic exam
  - Minimize the amount of normal tissue removed
  - Possible reduction in rates of PTL and PPROM if associated with loop excision

Thank you

- Dr. Munro for his time, expertise, and guidance
- Vicky Chiu & Janice Yeo for their help with the statistics
- Thank you to all members of the Department of Obstetrics and Gynecology at Kaiser Sunset who participated in this study