Therapeutic Modalities of Cervical Preinvasive Lesions
(Cryotherapy, LLETZ, Cold Conization)

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Treatment of SIL

Cytology

Colposcopy

Histology

HPV Test
<table>
<thead>
<tr>
<th></th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to CIN 3</th>
<th>Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>%60</td>
<td>%40</td>
<td>%10</td>
<td>%1</td>
</tr>
<tr>
<td>CIN 2</td>
<td>%40</td>
<td>%40</td>
<td>%20</td>
<td>%5</td>
</tr>
<tr>
<td>CIN 3</td>
<td>%33</td>
<td></td>
<td></td>
<td>&gt;%12</td>
</tr>
</tbody>
</table>

Östör AG, Int J Gynecol Pathol, 1993
Treatment of CIN

- High grade disease (CIN 2+)
  - AIS
- Low grade disease
  - Persistent
- Insufficient colposcopy or ECC CIN2+
- Previous cytology ASC-H or HGSIL, no lesion on colposcopy >30 years
The Goal of Treatment Modalities for CIN

✓ is to prevent progression of high grade disease to cervical cancer

  This goal is achieved with completely excision or ablation of TZ

✓ to avoid overtreatment of lesions that are likely to regress

✓ Treatment modalities must have low morbidity and cost-effectivity
Treatment Modalities for CIN

• Ablative or destructive modalities

• Excisional modalities
How can we decide about the choice of treatment modalities?

- Colposcopic findings (Sufficient or unsufficient, Grade of disease, EC involvement, Diameter of lesion)
- Type of TZ
- Patient’s age and further desire for fertility
- Experience of the physician
Indications for Ablative Treatment

1. Colposcopy must be sufficient and lesion must be completely visible on ectocervix

2. ECC (-)

3. No suspicion of invasive cancer and glandular disease on colposcopy and cytology

4. Consistency between cytology, colposcopy and histology
Cryotherapy

- A freeze-thaw-freeze technique is commonly used
- 5 mm ice-ball beyond the probe is obtained
- **Should be used in low grade and small preinvasive lesion on the ectocervix**
- Cure rate decreases with increasing grade of the disease and diameter of the lesion

Cure rate is for CIN1 and CIN2 over 90%, but for CIN3 is 84%
Excisional treatments

LEEP (LLETZ)
Cold knife conization (CKC)
HF Needle Conization
Laser conization
Hysterectomy
Definition

LEEP
• Loop Electrosurgical Excision Procedure

LLETZ
• Large Loop Excision of the Transformation Zone
Indications for Excisional Treatment

• Lack of correlation between cytologic- colposcopic and histologic findings

  Previous Cytology ASC-H or HGSIL, no lesion or CIN 1 on colposcopic examination >30 years

• Unsatisfactory colposcopy (TZ is not fully seen)

• Glandular lesion

• Suspicion of invasive cancer

• Endocervical canal involvement (ECC CIN2+)

• Recurrence after ablative treatment
Excisional Treatment of CIN

- The goal of excisional treatments is to remove the entire TZ under direct colposcopic vision.

- The size and shape of the cone biopsy should be tailored according to the type of TZ.
Advantages vs disadvantages of Excisional Treatments

• Provide a specimen for pathological reassessment to define the grade of the disease as well as therapeutic benefit

• Excision can be incomplete in cases of
  ✓ Pregnancy
  ✓ Type 3 TZ
  ✓ Large Lesion on ectocervix(multiple pass)

• Too large volum excision is associated with immediate and late complications
The Type of TZ should be taken into consideration to achieve negative surgical limits.
Type 1 TZ and Excision

- TZ is completely located on ectocervix
- The cutting depth from the external orifice must be 8 (6-10) mm and 6 mm may be sufficient for periphery of the TZ, because crypt involvement does not usually exceed 5 mm
Type 1 Excision
Multiple Excision Technique (Large lesion on the ectocervix)
Type 2 TZ and Excision

• The TZ extends into the EC but the upper border (SCJ) is visible on colposcopy
• TZ extends 7-10mm into EC, a second resection of the adjacent canal with a small square loop is performed to achieve clear endocervical margins (top-hat, cowboy-hat)
Type 3 TZ and Excision

- The TZ extends into the EC and the upper border (SCJ) is not visible on colposcopy.
- The shape of removed sample resembles an Indian pagoda with loop or a cylindrical shape with HF needle (NETZ).
- Type 3 excision is associated with an increased risk of incomplete excision and subsequent pregnancy-related morbidity.
NETZ (HF Needle Excision of the TZ)

- is usually used in the excision of type 3 TZ
- provides more commonly clear margins than LEEP
- takes somewhat longer time
- is more difficult to learn
After Excisional Treatment

- Cone margins status, glandular crypt involvement and removed cone volume predict the success and morbidity of the excisional treatment.
LEEP Conization
Equipment for LEEP Conization

- The cutting wire loop
- High-frequency electrosurgical unit
LEEP Conization-Equipment

- Non-conductive speculum with a smoke suction attached
- Ball electrode
- Solutions
  - Local anesthetic with a vasoconstrictive agent
  - Monsel’s solution
  - Lugol’s solution
Choose appropriate loop for type of TZ excision
For coagulation
- 3 mm top 30 W
- 5 mm top 50 W

For cutting
- 1.5x0.5 cm 30 W
- 1x1 cm 35 W
- 2x0.8 cm 40 W
- 2x1.2 cm 50 W

Proper wattage should be used to reduce the degree of thermal injury. THE LARGER THE LOOP THE HIGHER WATTAGE IS NEEDED.

After resection of the TZ, residual EC disease needs to be excluded by ECC or brush.
Advantages of LEEP

✓ Simple procedure with an easy learning curve
✓ Can be used in all cases of CIN, microinvasive and glandular disease (CKC is commonly preferred)
✓ Cost-effective
✓ Usually does not require general anesthesia (out-patient)
✓ Less complication rate than CKC
✓ Diagnosis and treatment of the lesion in sametime (see-and-treat protocol) can be performed with LEEP
See and Treat Protocol

- Popular
- Can protect loss of patients for a second clinic attendance.
- But, the risk of over-treatment does exist in young women with CIN
Problems associated with LEEP

1. Burn-necrosis (Thermal injury) at the surgical margins
2. Unable to remove the tissue in one-piece.

Difficulty in differentiating the surgical borders.
The degree of thermal damage is significantly less with pure-cut mode compared to blend mode.
Cold knife conization
Cold knife conization

If there is suspicion of invasive CC and AIS on colposcopic biopsy, CKC is preferred to LEEP

✓ Involved margins in AIS are higher in LEEP than CKC
✓ CKC provides a specimen devoid of marginal artifacts and permits accurate histological assessment of EC and margins
CKC Techniques for Lesions

- The volume of removed specimens with CKC is bigger than LEEP
The removed specimen is marked at 12 o’clock
Haemostasis

- Stumdorf sutures are not advisable because of burying the residual disease
- Cauterization and Monsel’s solution is adequate for haemostasis of dome
POSTOPERATIVE INSTRUCTIONS

• The patient is informed for complications and black or brown vaginal discharge for the next 2 to 4 weeks

• is advised to avoid of intercourse for the next 4 to 6 weeks

• is seen six weeks later to be sure that the cervix is healing and the endocervical canal is open
The three excisional methods (cold knife, laser, LEEP) have similar outcomes over 90%.

A Cochrane Systematic Review (2013) Summary

- Examined evidence from 29 randomized controlled trials
- Reported that there was no obviously superior surgical technique in terms of treatment failures and operative morbidity
- More research is needed
**Comparison of LLETZ/LEEP and CKC in positive margin**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>LLETZ/LEEP Events</th>
<th>Total</th>
<th>CKC Events</th>
<th>Total</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, random, 95% CI</th>
<th>Year</th>
<th>Risk ratio M–H, random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td><strong>Randomized controlled trial</strong></td>
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<tr>
<td>Duggan et al²²</td>
<td>16</td>
<td>89</td>
<td>20</td>
<td>85</td>
<td>11.6</td>
<td>0.76 (0.43, 1.37)</td>
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<td><strong>Subtotal (95% CI)</strong></td>
<td>16</td>
<td>89</td>
<td></td>
<td>85</td>
<td>11.6</td>
<td>0.76 (0.43, 1.37)</td>
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<tr>
<td><strong>Total events</strong></td>
<td>16</td>
<td>89</td>
<td></td>
<td>85</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: not applicable</td>
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<td>Test for overall effect: Z=0.50 (P=0.37)</td>
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<td><strong>Nonrandomized controlled trial</strong></td>
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<tr>
<td>Bornstein et al²⁰</td>
<td>18</td>
<td>52</td>
<td>5</td>
<td>22</td>
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<td>1.52 (0.65, 3.59)</td>
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<td>Huang and Hwang²⁷</td>
<td>7</td>
<td>73</td>
<td>4</td>
<td>43</td>
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<td>1.03 (0.32, 3.32)</td>
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<tr>
<td>Bozanovic et al²⁰</td>
<td>10</td>
<td>72</td>
<td>8</td>
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<td>Chen et al²²</td>
<td>109</td>
<td>453</td>
<td>32</td>
<td>660</td>
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<td>4.96 (3.41, 7.22)</td>
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<td>Miroshnichenko et al²⁰</td>
<td>36</td>
<td>96</td>
<td>10</td>
<td>61</td>
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<td>Panna and Luanratanakom²⁰</td>
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<td>Shin et al²³</td>
<td>26</td>
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<td>Grimm et al²⁵</td>
<td>96</td>
<td>412</td>
<td>81</td>
<td>392</td>
<td>13.1</td>
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<td><strong>Subtotal (95% CI)</strong></td>
<td>1,506</td>
<td>1,511</td>
<td>88.4</td>
<td>1,511</td>
<td>88.4</td>
<td>1.58 (0.88, 2.83)</td>
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<td><strong>Total events</strong></td>
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<td>180</td>
<td></td>
<td>327</td>
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<tr>
<td>Heterogeneity: $I^2=0.59; \chi^2=63.23, df=7 (P&lt;0.00001); I^2=89%$</td>
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<tr>
<td>Test for overall effect: Z=1.53 (P=0.12)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

1 randomize 8 non-RCTs, CKC ‘da marjin pozitifliği %13, LEEP %22
2 randomize 5 non-RCTs, CKC ‘da LEEP’e göre daha düşük rekürrens, LEEP (RR=1.75)
Follow-up

- There is increased risk after treatment for at least 10 years; routine follow-up for 10 years should be continued (ASCCP Guideline)
Factors associated with an increased risk of recurrence

- Positive margins
- Large lesion involving 2/3 of the surface of the cervix
- Grade of disease (CIN 3)
- Persistent HPV DNA positivity (especially HPV 16 Positivity)
- Endocervical glandular involvement
- Human immunodeficiency status (HIV)
- Advanced age
# Recurrence of Cervical Intraepithelial Neoplasia After Cone Biopsy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Negative Margins</th>
<th>Positive Margins</th>
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<tr>
<td>Larsson et al.</td>
<td>683</td>
<td>56</td>
<td>246</td>
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<tr>
<td>Bjerre et al.</td>
<td>1226</td>
<td>64</td>
<td>429</td>
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<tr>
<td>Kolstad et al.</td>
<td>1121</td>
<td>27</td>
<td>291</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>3030</strong></td>
<td><strong>147(4.9%)</strong></td>
<td><strong>966(31.9%)</strong></td>
</tr>
</tbody>
</table>
(+) Surgical margin

Observation

Reconization

Hysterectomy
Management of margin positive cases after excisional procedure

- **CIN 1 at the margins;**
  Observation is preferred because of high rate of spontaneous regression

- **CIN 2-3 at the margins;**
- **Re-excision**; preferable (if excision is not feasible or other problems hysterectomy acceptable)
- **Reassessment at 4-6 months with cytology and ECC**
  presence of recurrence; further surgery
  absence of recurrence; follow up (ASCCP Guideline)
Complications of Excisional Treatments

Early

- Bleeding
- Risks of anesthesia
- Infection (0.2%-6.8%)

Late

- Bleeding
- Cervical stenosis
- Cervical incompetence
- Subsequent pregnancy-related morbidity
  - PROM
  - Preterm labor
## Complication of Electrosurgical Excision

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of Patients</th>
<th>Operative Hemorrhage</th>
<th>Postoperative Hemorrhage</th>
<th>Cervical Stenosis</th>
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<tr>
<td>Prendiville et al.</td>
<td>111</td>
<td>2</td>
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<td>Whiteley et al.</td>
<td>80</td>
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<td>3</td>
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<td>Mor-Yosef et al.</td>
<td>50</td>
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<td>Bigrigg et al.</td>
<td>1000</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Gunasekera et al.</td>
<td>98</td>
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<td>Howe et al.</td>
<td>100</td>
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<td>1</td>
<td>0</td>
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<td>Minucci et al.</td>
<td>130</td>
<td>0</td>
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<td>2</td>
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<td>Wright et al.</td>
<td>432</td>
<td>0</td>
<td>8</td>
<td>2</td>
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<td>Luesley et al.</td>
<td>616</td>
<td>0</td>
<td>24</td>
<td>7</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>2617</strong></td>
<td><strong>3(0.001%)</strong></td>
<td><strong>48(1.8%)</strong></td>
<td><strong>11/6178(1.0%)</strong></td>
</tr>
</tbody>
</table>
Meta-analysis of cold-knife conization versus loop electrosurgical excision procedure for cervical intraepithelial neoplasia

Comparison of LLETZ/LEEP and CKC in cervical stenosis

3 randomize 2 non-RCTs, CKC ve LEEP’ de fark yok

Jiang Y-M, OncoTargets and Therapy, 2016
Effects of excisional treatments on obstetric outcomes

- The elevated risk for preterm delivery seems likely that the amount of removed cervical tissue.
- If measurements of the cone are not wider than 1.8 cm and deeper than 1.5 cm, conization has no impact on further pregnancy outcome.
- CKC and excision of type 3 TZ is associated with the highest risk of subsequent premature delivery (RR: 5.33)
Effects of excisional treatments on obstetric outcomes

- < 15 mm: No unfavorable effect
  - Frencezy A, 1995
  - Haffenden DK, 1993
  - Tan L, 2004

- < 18 mm
  - 25% Preterm birth
  - 18% PROM

- > 18 mm
  - Sadler L. Et al., Am J Med Ass, 2004
Hysterectomy

- Rarely indicated in primary management of CIN
- Co-existing with uterine pathology (fibroids vs)
- Involved margins after excisional treatment in patient whose family is completed
- AIS (no fertility desire)

- Incidence of VAIN following hysterectomy for CIN3: 7.8%
- Patient should be screened by vaginal vault smears on the annual basis
Preinvasive lesion in pregnancy

- Treatment should be postponed until 2 months after delivery
- Invasive disease must be excluded by colposcopy.
- Loop biopsy is more appropriate than punch biopsy to obtain sufficient stroma
- Cone biopsy during pregnancy should be performed only when there is a strong suspicion of invasive cancer
SUMMARY

• Excisional treatments are diagnostic and therapeutic procedure

• The technique and the configuration of the cone should be designed depending on the type of TZ

• TZ should be excised entirely

• The most significant perioperative complication of cone biopsy is bleeding, which is generally managed with local measures
SUMMARY

• The excisional treatment of CIN do not compromise future fertility, but is associated with an increased risk of preterm labour according to type of excision.

• The excisional treatment of AIS can be performed if fertility is desired. But close follow-up is mandatory.