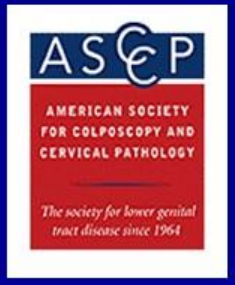
Cryotherapy

Meggan Zsemlye



Disclosures

I have no financial conflicts of interest to disclose.

Images: Modern Colposcopy, 2003, ASCCP
Darron Ferris, MD
Alan Waxman, MD

Objectives

- Discuss role of Cryotherapy among treatment options for CIN
- Discuss management principles for treating CIN with Cryotherapy
- Discuss mechanisms of cryonecrosis
- Contrast the risks and benefits of treating CIN with cryotherapy vs other modalities

Trends in treatment of CIN

- 1960s - Cold knife cone
- 1970s - Cryosurgery
- 1980s - Laser cone and ablation
- 1990s - LEEP / LLETZ
- 2000s – Observe where you can, treat if you must

CIN Treatment Options

- Observation
  - Active monitoring of the progress of low grade lesion with cytology or HPV DNA
  - Active monitoring of CIN 2,3
- Ablation
  - Destruction of the entire transformation zone
- Excision
  - Removal of the transformation zone
  - Provides tissue for histopathology evaluation

Ablation / Excision : general principles

- Treat the entire transformation zone
  - CIN almost always starts in the TZ
  - CIN 2,3 is invariably in contact with the squamo-columnar junction
  - Most advanced area of lesion usually most central
  - Normal mature squamous epithelium is resistant to the development of CIN
- Multifocal or “skip” CIN lesions very rare
  - Exception, glandular lesions

CIN: endocervical crypt involvement

- All grades of CIN may invade endocervical "glands"
  - Deep involvement more likely in higher grade
- Depth of crypt involvement in CIN 3
  - <3.0 mm in 95.9%
  - <4.0 mm in 98.2%
  - <5.0 mm in 99.1%
  - <6.0 mm in 100%
    - (Wright and Davies, 1983)
- Treat at least to 5 -7 mm depth throughout!

"…for destruction, ice is also great and would suffice." *Robert Frost*

CRYOTHERAPY

Cryotherapy for CIN

- Accpetable treatment for CIN as long as triage rules observed
- Office procedure
  - Inexpensive to set-up
- Easy to learn
- No anesthesia usually necessary

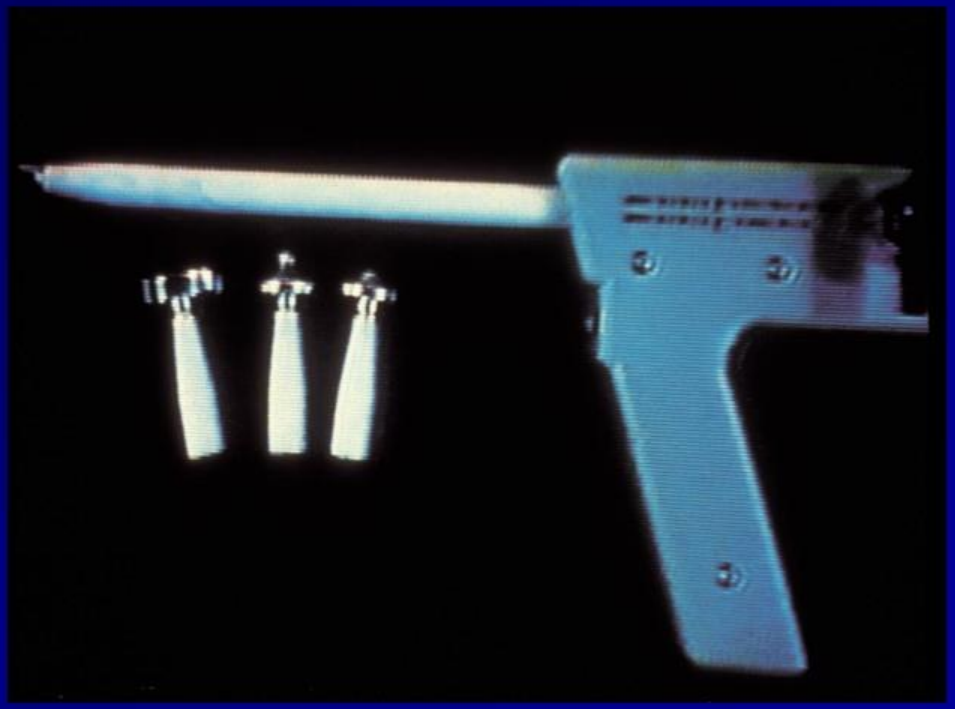
Cryotherapy for CIN: Colposcopic triage rules

- Entire SCJ must be visualized
- Entire extent of lesion must be seen
- CIN diagnosed by biopsy
- Disease in endocervical canal ruled out
- Colpo impression, cytology, histology must correlate
- Invasion ruled out
- Cryoprobe must cover lesion

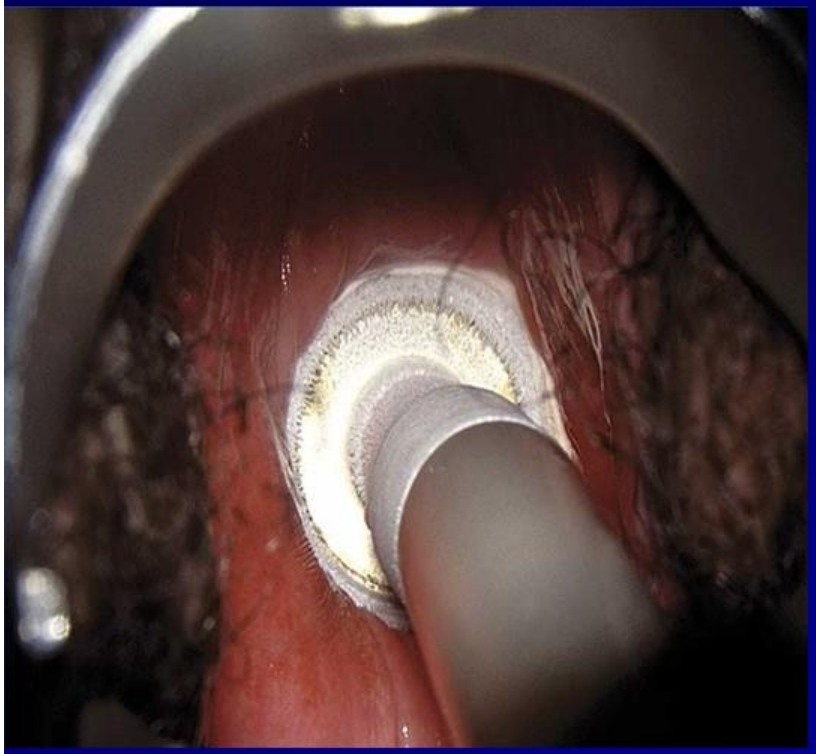
Contraindications to cryotherapy

- Invasive cancer
- Large (>2 quadrant) Lesion
  - WHO recommends excision if lesion involves >75% of cervix
- Cryoglobulinemia
- Pregnancy
- Acute cervicitis
- Menstruation

CRYOGUN WITH VARIOUS TIPS



Position of Cryoprobe on Cervix



Cryoprobe must cover the active transformation zone including the entire lesion.

If the probe extends into the endocervical canal, the risk of stenosis increases

Modern Colposcopy

Cryotherapy of the Cervix

Cervix immediately post cryotherapy

Photo: Darron Ferris, MD

Principles of cryotherapy

- Cellular injury depends on temperature and duration of freeze
  - Steady state after ~3 minutes
- Cell death occurs at -20^{0}C
  - $C0_2$ cryo: -60^{0}C N_20 cryo: -80^{0}C
- Temp at margin of iceball: 0^{0}C
  - Temp falls to -20^{0}C ~2mm from edge of probe
  - Iceball must exceed margin of lesion by $\geq$2mm
  - 7mm iceball needed to freeze to depth of 5mm

Freeze-thaw-freeze

- Need minimum of one minute freeze
- Need good contact throughout
- Freeze 5 mm beyond probe ensures 5 mm deep
- WHO recommendation:
  3 minute freeze → 5 minute thaw → repeat 3 minute freeze
  - Each cervix is different so timed freeze may not be enough

Principles of Cryonecrosis

- Cell death
  - Intra and extracellular ice crystal formation
  - Ruptures cell membrane
  - Dehydration
  - Release of lysosomal enzymes and cell destruction
  - Vascular stasis with eschemia and anoxia
- Immunologic response
  - Synergistic with cryodestruction

Cryonecrosis and Re-epithelialization

- Epithelial slough
  - 24-48 hrs
- Eschar formation
- Re-epithelialization and neovascularization
  - Complete in 6 weeks in 47%

Side effects of cryotherapy

- Menstrual like cramps
  - Mediated by prostaglandins
  - Severe 3% - 5%
- Vasomotor sx - 20%
  - Flushing, light headedness, rare vasovagal episode
- Profuse watery discharge - 3-4 wks
- Cervical stenosis - 1% - 4%

Complications of treatment of CIN

Mitchell et al Obstet Gynecol 92. 1998

	Cryo. N=139	Laser ablation N=121	LEEP N=130
Infection	1	1	1
Bleeding 1st 24 hrs	0	0	1
Bleeding after 24 hrs	0	3	6
Stenosis	2	1	1
Pain medication	0	0	1
Total	3 (2%)	5 (4%)	10 (8%)*

*=.09 re total complications by group

Persistence and Recurrence of CIN after Treatment

Mitchell et al Obstet Gynecol 92. 1998

- Persistence
- Diagnosis within 6 months of treatment
  - Cryotherapy: 5%
  - Laser ablation: 4%
  - LEEP excision: 3% (P=.72)

- Recurrence
- Disease free in first 6 months
- Mean f/u 16 months
  - Cryotherapy: 19%
  - Laser ablation: 13%
  - LEEP excision: 13% (P=.34)

CIN 2,3 After Cryotherapy

- British Columbia Study based on database of 37,142 women treated with LEEP, Cryotherapy, Laser
- Diagnosis of CIN 2,3 within first 6 years after cryotherapy
  - Generally lower in younger than older women
  - Lower with CIN 2 than CIN 3
    - 13.4% age 30-39 treated for CIN 2
    - 26.5% age 30-39 treated for CIN 3

- 2.6-3.2 X more likely after cryotherapy than LEEP with negative margins

Melnikow et al et al. JNCI. 2009;101:721-8

Cancer After Treatment of CIN

Retrospective study of 37,142 treated for CIN with Cryo, Laser, Cone, LEEP (*margins negative*)

British Columbia Cancer Agency cytology database

- Cancer (18 year follow-up)
  - 2.89 X more likely after cryotherapy than other treatments

Melnikow, et al J Natl Cancer Inst 2009;101:721-728

Does cryotherapy still have a role?

- Easy to learn
- Less expensive
- Fewer acute complications
- Common 3rd world choice-WHO supported
- Must apply triage criteria for safety of ablation vs. excision
- Consider lower cure rate


Thank you.
A. Waxman