子宮頸癌篩檢結果異常與子宮頸癌前驅病變之處理

Management for Abnormal Cervical Cancer Screening Tests and Cancer Precursors

馬偕紀念醫院

陳子健

Outline

- **概述 2019 ASCCP guidelines for abnormal cervical screening and cancer precursors**
- Colposcopy 簡述
- Treatments for histologic HSIL
- CIN2 with pregnancy consideration
- Management for histologic CIN1
- AGC
- Treatment for histologic AIS
- 治療後之追蹤
- Unsatisfactory colposcopy / Pap 沒看到 T-zone或 endocervical cell / Pap 14 / 孕婦 / 全子宮切除後

OPEN

2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors

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Key Words: cervical cytology, HPV testing, management of abnormal cervical cancer screening tests, guidelines

(*J Low Genit Tract Dis* 2020;24: 102–131)

- Based on a patient's risk of CIN3+ determined by a combination of current results and past history

6:45

ASCCP

Screening | Management | Publications | Definition

Age

Under 25 YEARS | 25 to 29 YEARS | 30 to 65 YEARS | Over 65 YEARS

Clinical Situation

- Routine screening (within past 5 years)
- Rarely screened (>5 years ago)
- Evaluation of a colposcopic biopsy
- Management of results during post colposcopy surveillance (within past 7 years)
- Follow-up after treatment

Special Situation

- Unsatisfactory cytology
- Post hysterectomy
- Symptomatic
- Immunosuppressed

Help me decide | Next →

6:55

ASCCP

Screening | Management | Publications | Definition

Clinical Situation — Testing — Recommendation

Current testing

HPV

None | Negative | Positive (untyped) | Positive (genotyped)

HPV DNA

HPV 16 | HPV 18 | HPV Other

Cytology

S | LSIL | ASC-H | AGC | HSIL

Does the patient have previous results

6:50

ASCCP

Screening | Management | Publications | Definition

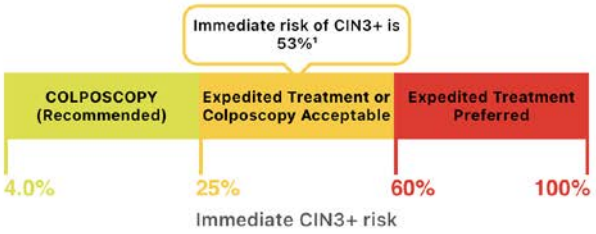
Clinical Situation — Testing — Recommendation

Recommendation

Colposcopy/Treatment[1]

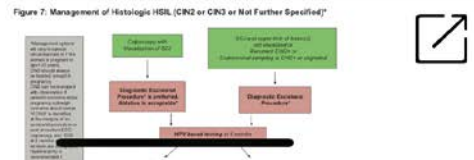
After treatment, HPV-based testing at 6 months is preferred at follow-up visit[2]

Risk



Immediate risk of CIN3+ is **53%[1]**

Figure



Immediate CIN3+ risk

- **考慮expedited treatment** (可不必先做 biopsy而直接治療) (risk >= **60%**)
  - HPV16(+) HSIL cytology (其 immediate cancer risk 8.1%)
- **可 colposcopy 或 expedited treatment** (risk 25~59%之間)
  - HPV(+) HSIL cytology (49% risk)
  - HPV(-) HSIL cytology (25% risk). HPV(+) ASC-H (26% risk). HPV (+) AGC (26% risk)
- **需 colposcopy** (risk 4-24%)
  - HPV(+) ASCUS/LSIL (但若preceding HPV(-), 則risk 只2%)
  - 連續兩年 HPV(+) NILM
- **可追蹤** (risk < **4%**)
  - HPV(+) NILM → 2.1%. HPV(-) LSIL → 1.1%

然而其實不太週全.....

- **Immediate CIN3+ risk**
  - HPV18 (+) but Pap NILM → 3 %
  - Pap ASC-H but HPV (-) → 3.4 %

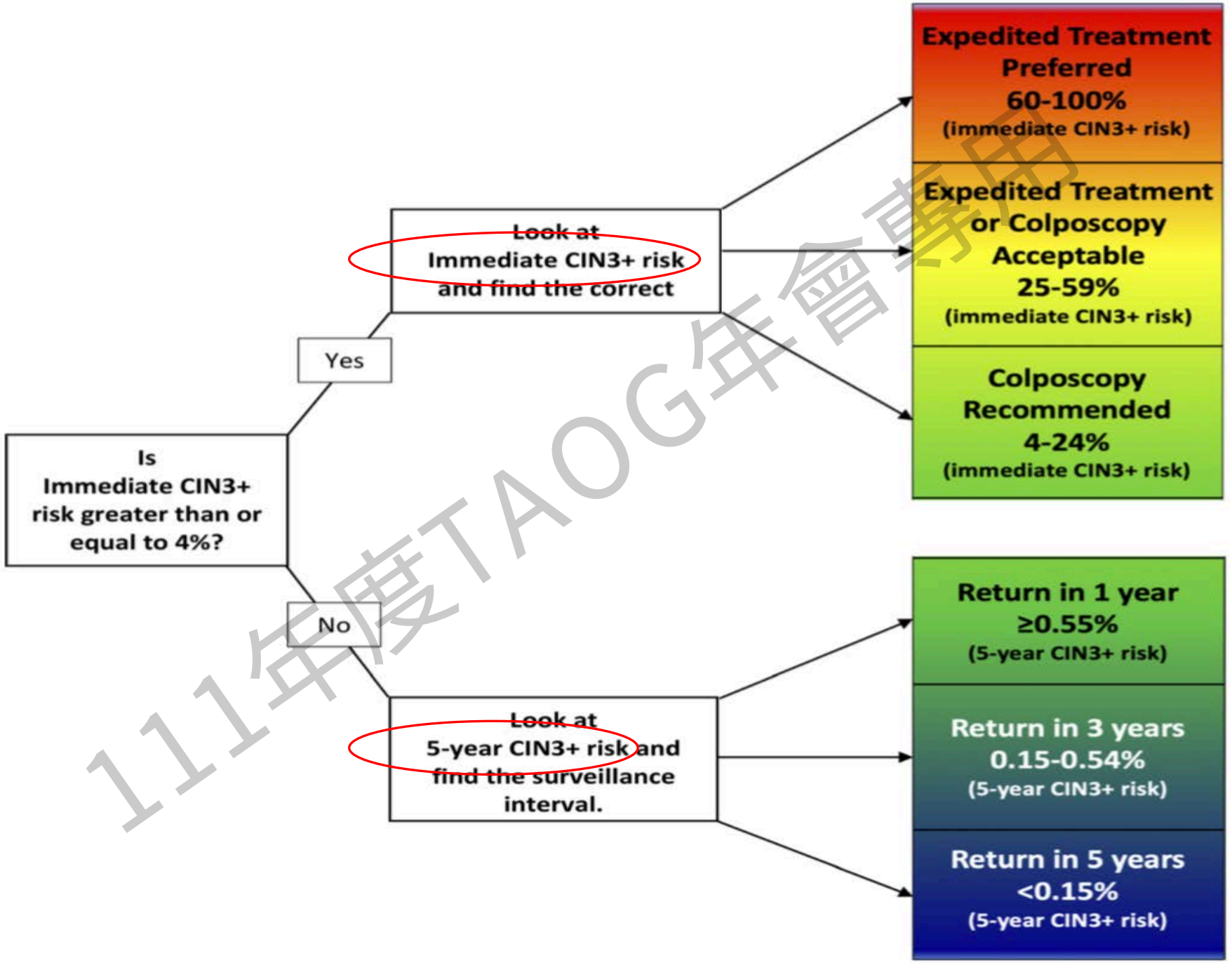
皆 < 4% → 尚未符合 ASCCP 2019 的 colposcopy 門檻

- 可是, 其 **immediate cancer risk**
  - HPV18 (+) but Pap NILM → 0.2 %
  - Pap ASC-H but HPV (-) → 0.69 %

→ 因此仍應 colposcopy

5-year CIN3+ risk

- < 0.15% → return in 5 years
- 0.15% to 0.54% → return in 3 years
- >= 0.55% → return in 1 year



HPV-Based Surveillance

- FDA-approved HPV ***primary*** testing **(+/- reflex cytology)**
  - cobas® HPV (Roche, Indianapolis, IN) (approved 2014)
  - Onclarity HPV (Becton Dickinson, Franklin Lakes, NJ) (approved 2018)

或

- ***Cotesting*** with cytology + HPV
  - *其他廠牌*的 HPV testing 只能用於 cotesting

Surveillance with Pap Alone

- HPV-based surveillance **每年**一次時
  → Pap alone 需**每半年**一次

- HPV-based surveillance **每三年**一次時
  → Pap alone 需**每年**一次

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Colposcopic Biopsy

- Colposcopy with targeted biopsy ***remains the primary method*** of detecting pre-cancers requiring treatment.
- To ensure that CIN 2+ is not missed, the ASCCP Colposcopy Standards ***emphasize the need for biopsies even when*** the colposcopic ***impression is normal*** but any degree of acetowhitening, metaplasia, or other abnormality is present.
- Evidence-based practice recommends that biopsies be taken of all discrete acetowhite areas, ***usually 2 to 4 biopsies*** at each colposcopic examination.

Colposcopy

- Normal saline 滋潤 cervix, 以**綠光或藍光**模式觀察有否 abnormal vessel
- 3-5% **acetic acid** for 30” to 60” (acetowhite change 若褪色, 可再重擦 acetic acid)
- **Vaginal fornix** 之觀察
- 最後考慮用 **Lugol solution**
- 先切 posterior lip

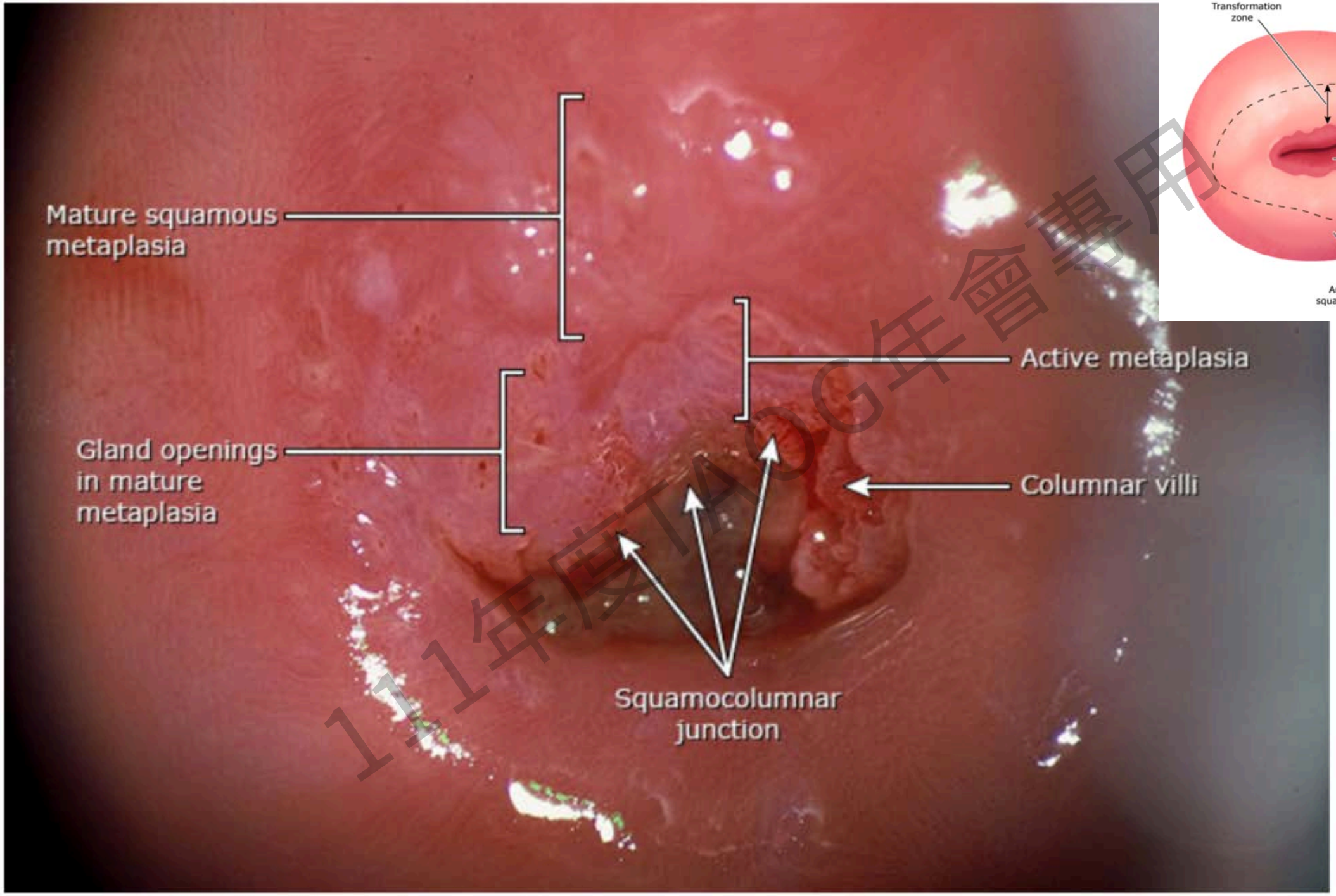
- **Unsatisfactory colposcopy**

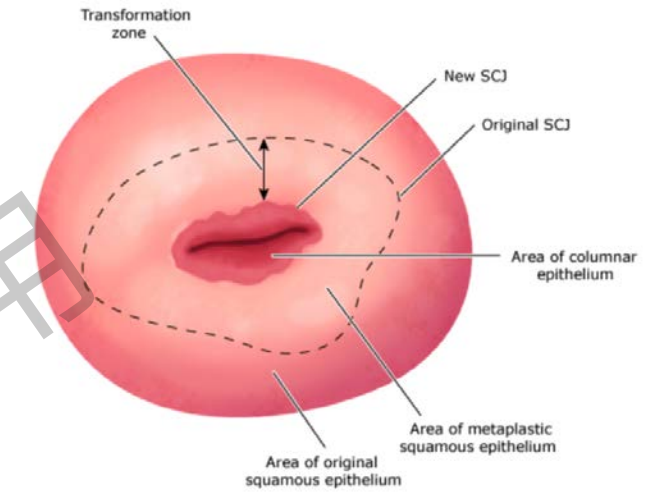
  # the *entire new SCJ* is not visualized (360 degree), OR

  # *the proximal and distal limits of a lesion* are not seen

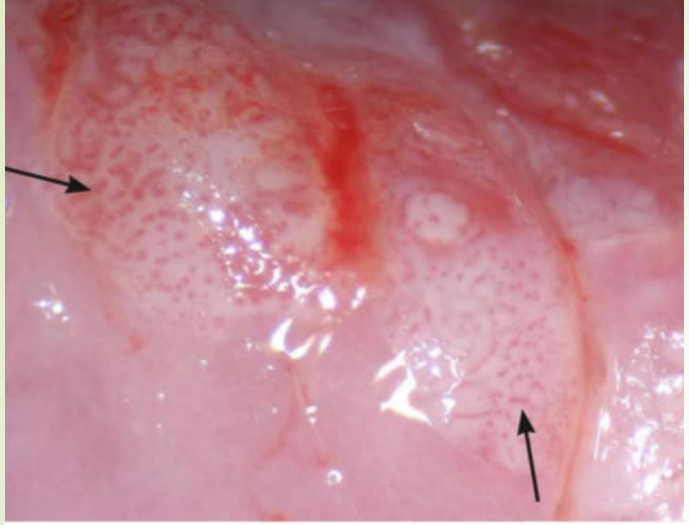
Colposcopy with ECC (EndoCervical Curettage)

- ECC is preferred for ***non-pregnant*** patients when
  - ***unsatisfactory*** colposcopy
  - cytology >= ASC-H, but ***no lesion is identified***
  - ***also acceptable*** when a lesion is seen

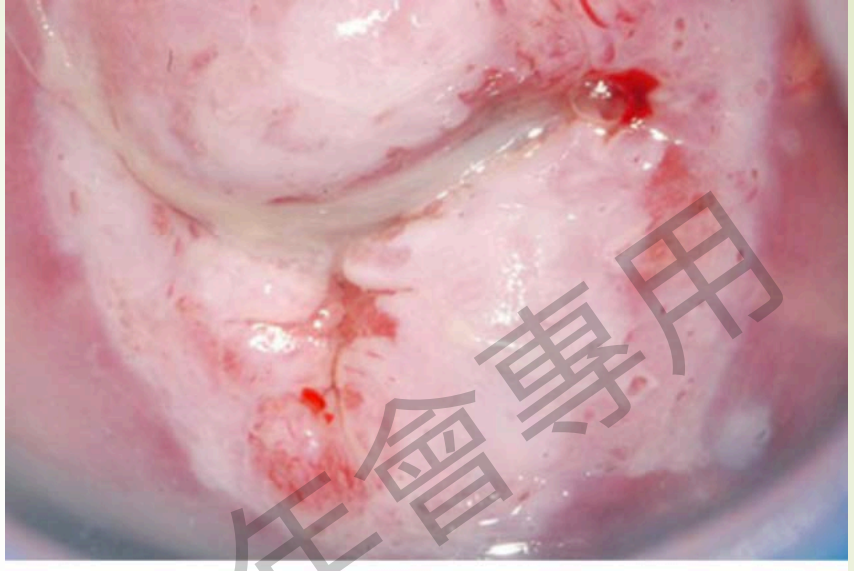




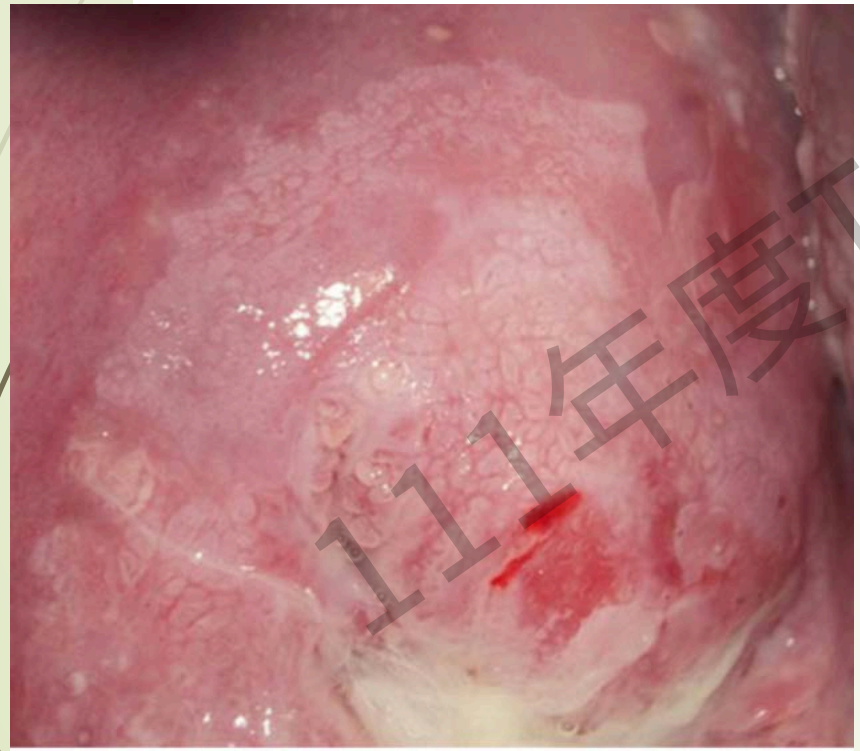
UpToDate



Punctation *(arrows)*.



Dense acetowhite change.



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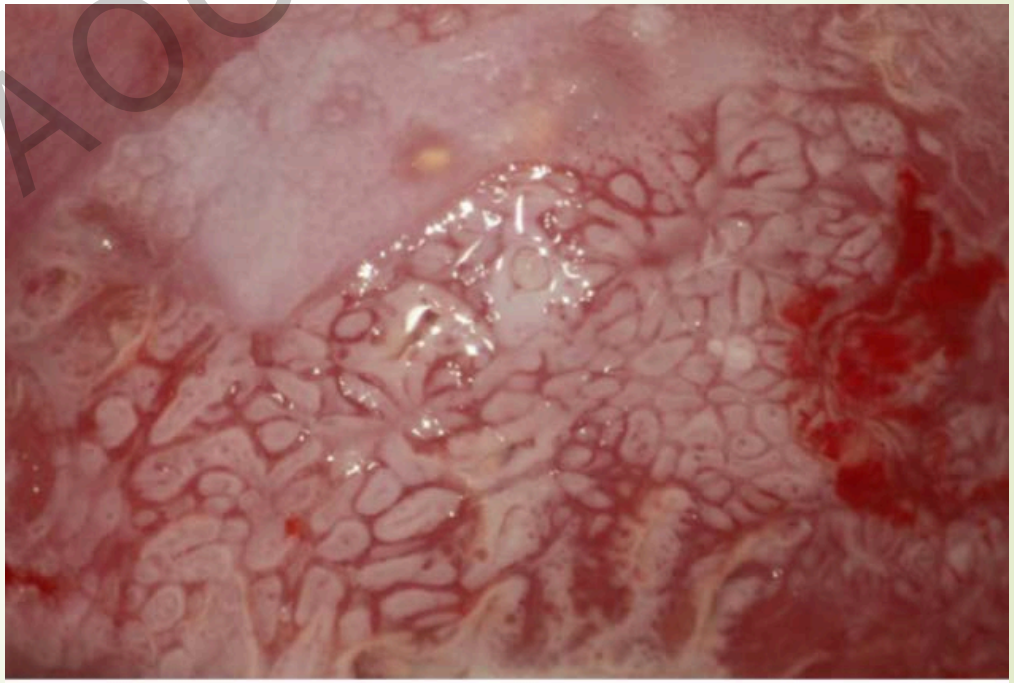

Mosaicism.

Am Fam Physician 2020;102:39-48.

Suspicious Gross Lesion

- Patients with symptoms such as abnormal uterine or vaginal ***bleeding*** or a visibly ***abnormal-appearing*** cervix require appropriate diagnostic testing as this may be a sign of cancer.

- 看起來怪怪的, *但抹片沒大礙 → 切片 !*
  - 對於子宮頸癌病變作抹片, 有一半的機會只顯示正常或發炎

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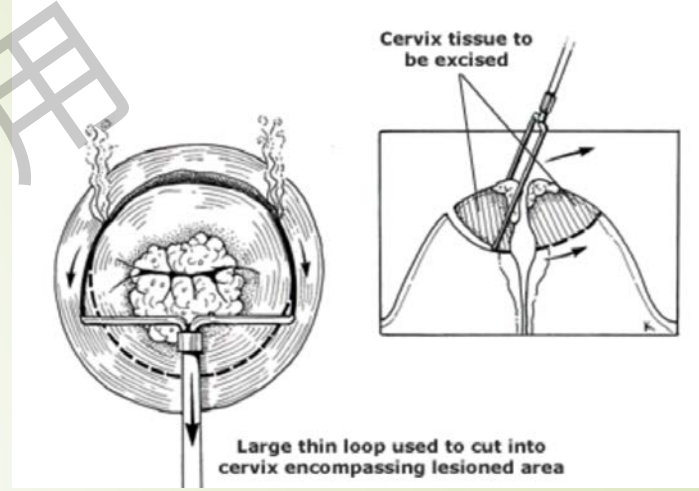
Histologic CIN2, CIN3 → Favor Excisional

- ***Excisional therapy*** includes loop electrosurgical excision procedure (LEEP or LLETZ), cold knife conization, laser cone biopsy
- ***CIN recurrence at 12 months***:
  - 26.6% (after LEEP) vs. 31% (after cryotherapy) in a meta-analysis of randomized trials
- Excisional therapy → ***providing a histologic specimen***
  - may reveal a higher grade lesion
  - provides information on margin status

Gynecol Minim Invasive Ther 2018;7:145–51. J Low Genit Tract Dis 2020;24:102-131.

LEEP (Loop Electrosurgical Excision Procedure)



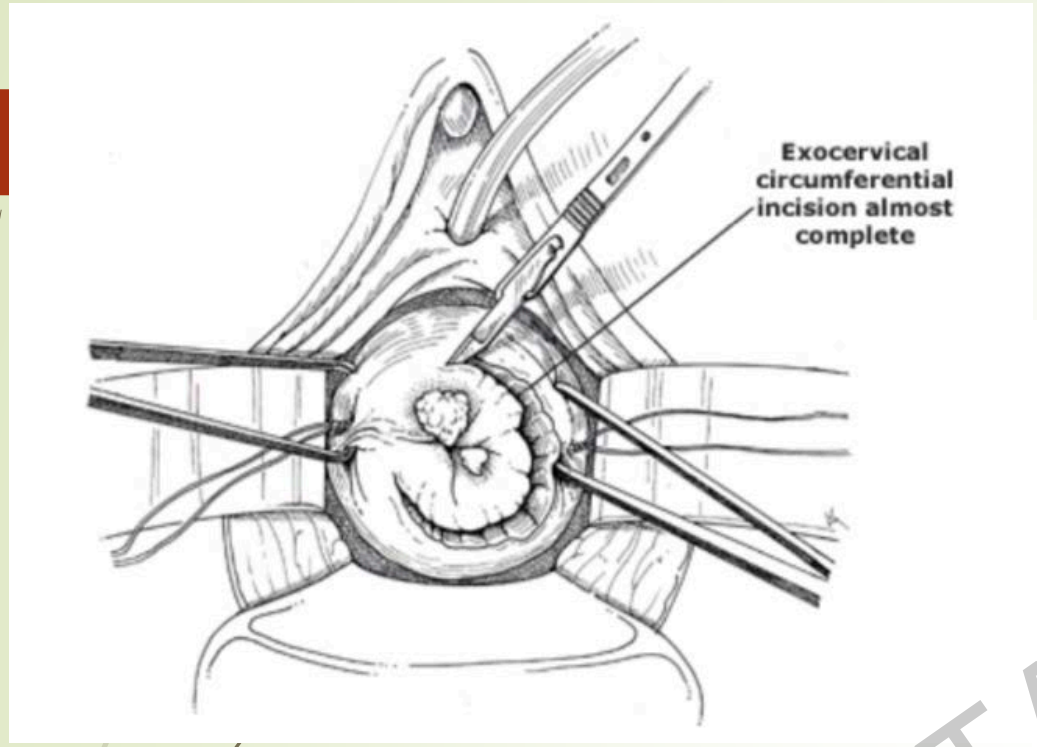
- iv general anesthesia, or local anesthesia
- 考慮 Lugol solution to demarcate the outer limits
- **30 to 40 watts, blend 1**
- 先按 cutting 鍵使 **loop 預熱**, 再讓loop 接觸目標組織
  - loop 行進太快 → 會卡住組織 → 切得比預期的淺
  - loop 行進太慢 → specimen 的 **thermal damage** 會過大, 影響判讀
- 有時需進行 **additional passes** 以確保完全切除
- post LEEP **ECC**
- 電燒止血, 或塗 ferric subsulfate paste

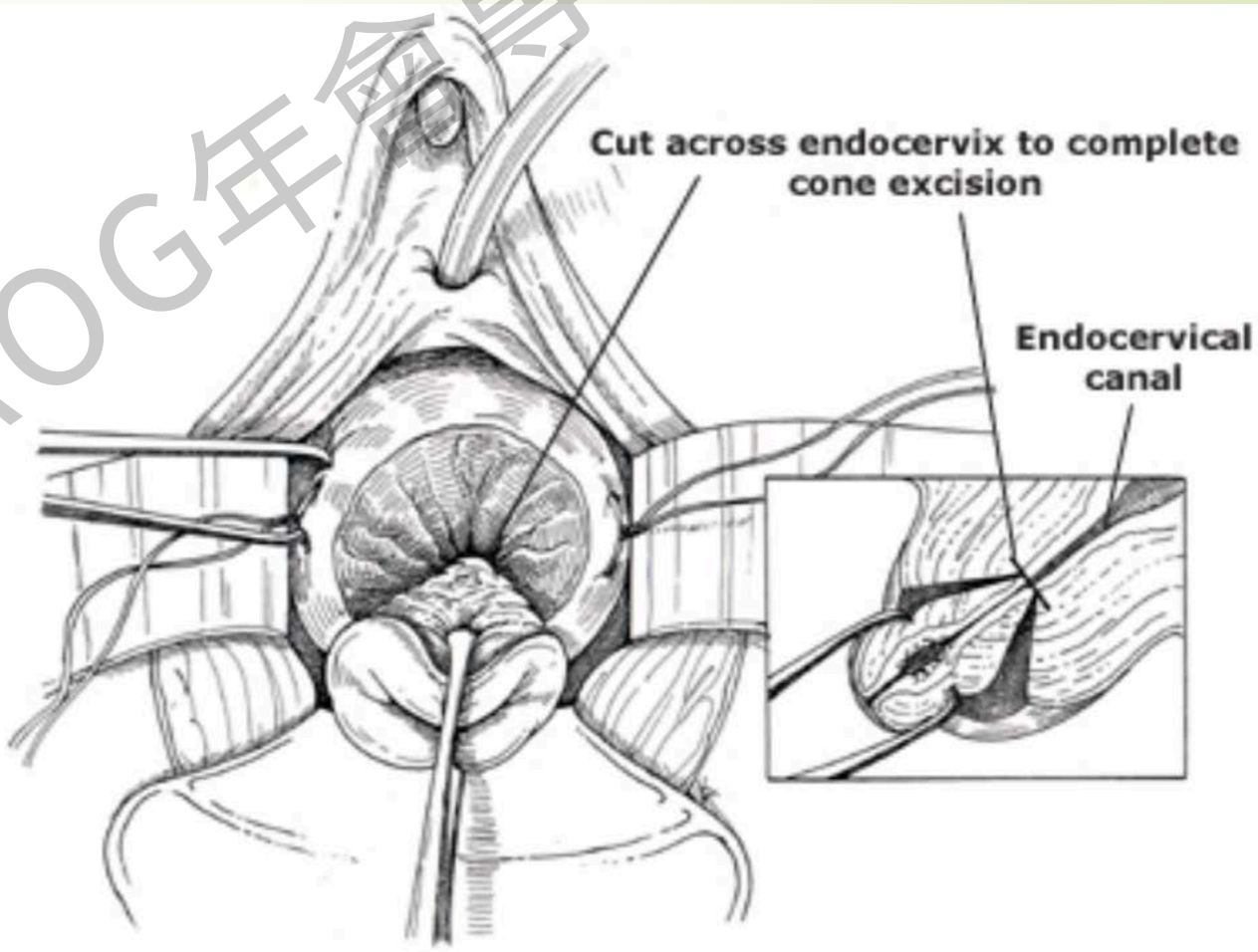
UpToDate

CKC (Cold-Knife Conization)

- general or regional anesthesia
- 考慮 Lugol solution 來定界
- 20 to 30 mL of ***vasopressin*** (0.5 U/mL) or 1:200,000 epinephrine solution injected circumferentially (注射在預定切線的外側, 深入 cervical stroma)
- 長刀柄, 11號刀片 circumferential incision just lateral to the outer limit of the transformation zone
- 考慮藉 uterine sound 來導引切割之路線
- ***慎勿誤切入*** peritoneal cavity 或膀胱 (考慮膀胱引流)!
- post-CKC ***ECC***
- ***Hemostasis***: suture (e.g., Sturmdorf suture), 或 Surgicel packing tie

UpToDate





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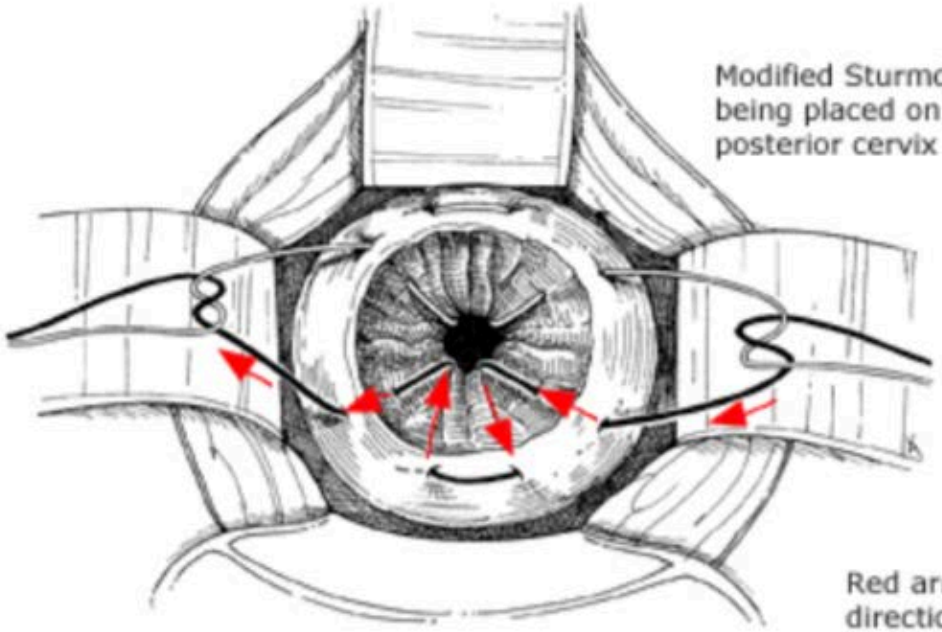

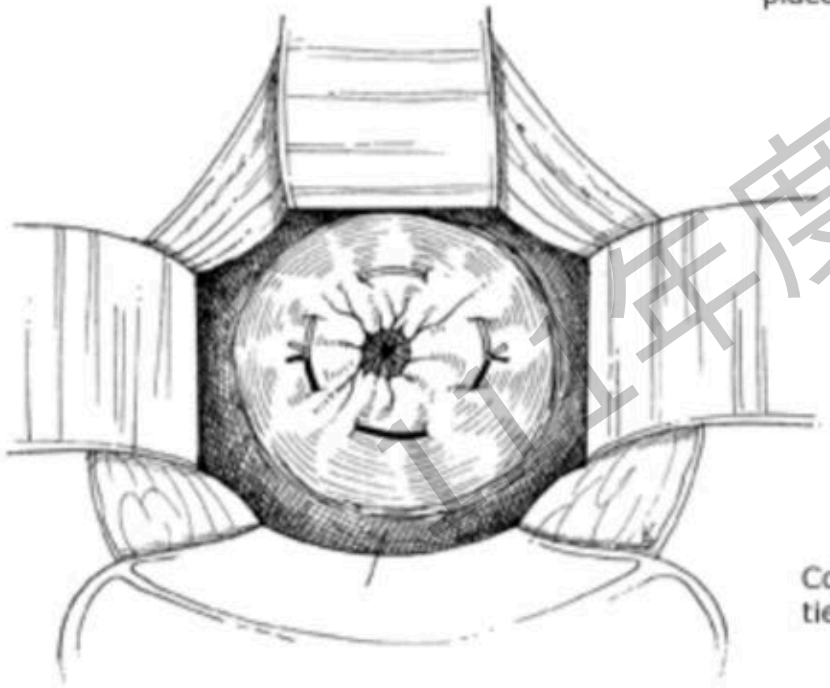

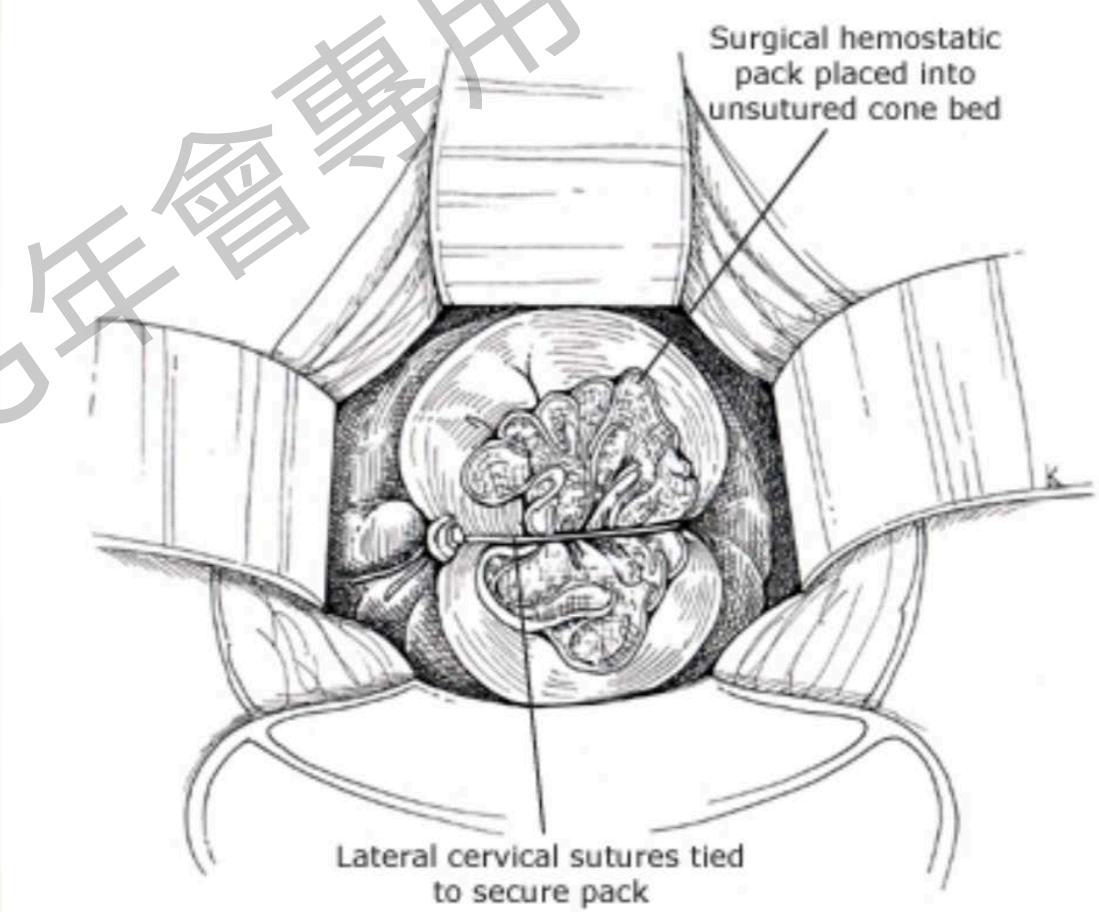

UpToDate

Ablation Treatment for CIN2 CIN3

- ***Ablation treatment*** includes cryotherapy, laser ablation, and thermoablation.
- ***Unacceptable when***:
  - ***Unsatisfactory*** colposcopy
  - ***ECC pathology*** > CIN1 or ungraded
  - ***Recurrent CIN 2+***
  - ***Cancer*** is suspected
  - (for cryotherapy) the lesion ***extends beyond the cryotip*** being used

WHO Guidelines: Use of Cryotherapy for Cervical Intraepithelial Neoplasia. Geneva: World Health Organization; 2011. **J Low Genit Tract Dis 2020;24:102-131.**

Laser Ablation

- May be appropriate for:
  - Large cervical lesion with satisfactory colposcopy
  - Lesion extends to the vagina

Laser ablation

- Colposcopic guidance
- ***Protective*** measures
  - Eyewear / Coated or brushed speculum
  - Drape the patient's perineum and thighs with wet towels.
  - Avoid flammable paper drapes
- ***Ablation depth*** → 5 mm on the ectocervix, 8-9 mm around the endocervix
- ***Power density*** of 600 to 1200 watts/cm^2 (6-12 watts/mm^2)
  - e.g., 20 watts, spot size of 1.5 mm → power density of 889 watts/cm^2 (8.89 watts/mm^2)
- ***Ultrapulse mode*** to decrease thermal damage to the surrounding cervical stroma

UpToDate

Topical Imiquimod for the Treatment of High-Grade Squamous Intraepithelial Lesions of the Cervix

A Randomized Controlled Trial

- 250 mg of 5% imiquimod cream weekly for 12 weeks → then LEEP
- Regression to <= CIN1
  - Imiquimod group → in 61%
  - Control group → in 23%

P=0.001

Obstet Gynecol 2021;137;1043-1053.

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Histologic CIN2

- 50% regressed, 32% persisted, and 18% progressed to CIN 3+
- Regression rates were higher (60%) in women younger than 30 y/o

Histologic CIN2 with Pregnancy Consideration

- Observation for histologic CIN2
  - < 25y/o, or concern about future pregnancy outweighs
  - ***必須 satisfactory colposcopy, ECC < CIN2***
  - ***先 Colposcopy*** + HPV-based testing (若<25y/o 則 cytology) q6m 兩到四次 → ***再*** q1y HPV-based testing (若<25y/o 則 cytology) 三年 → ***然後*** q3y
  - 追蹤期若出現 histologic CIN3, 或 超過兩年 Pap >= ASC-H → ***excision***

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Persistent CIN1

- LEEP for 2-year persistent CIN1:
  - <= histologic CIN1 in 87%
  - histologic CIN2+ in 13%

- For patients >= 25 y/o with persistent (>= 2 years) histologic LSIL (CIN 1):
  - ***observation is preferred***
  - treatment is acceptable

Cx Bx <= CIN1, but previous Pap HSIL/ASC-H

- Observation
  - ***Only if*** satisfactory colposcopy, ECC < CIN2
  - 先看兩年 (一年一次 HPV-based testing, 或半年一次 Pap, (若原 Pap HSIL) ***+ colposcopy***)
  - 之後每3年 HPV-based testing, 至少 ***25年***
  - (若任一年PAP HSIL or 連兩年 ASC-H → ***excision***)
- Or ***Diagnostic excision*** (若原 Pap HSIL)
- Or review (cytology, histology, colposcopy)
  - No cervical lesion → check ***vagina, vulva***

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AGC (Atypical Glandular Cell)

- Cytologic AGC
  - histologic AIS in 3% to 4%
  - histologic CIN 2+ in 9%
    - HPV (+) → immediate histologic CIN3+ in 26%.
    - HPV (-) → immediate histologic CIN3+ in 1.1%
  - invasive cancer in 2% to 3%

- Cancers of the endometrium, fallopian tube, ovary, and ***other sites*** are also found, especially in older women who test HPV negative.

AGC (Atypical Glandular Cell)

- Colposcopy + cx bx + ECC
- Endometrial sampling
  - >=35 y/o, 或
  - <35y/o 但有 risk for endometrial neoplasia (如 abnormal uterine bleeding, chronic anovulation, obesity 等)

- 若 Pap AGC NOS, 但查無 histologic CIN2+
  - 則 Cotest q1y x 2, 然後 q3y

AGC favor Neoplasia, Pap AIS

- HPV-positive AGC favor neoplasia or Pap AIS
  - immediate CIN 3+ risk of 55%

- 若查無 >= histologic CIN2+, 則應進行 ***diagnostic excisional procedure*** (需有 intact specimen with interpretable margins)

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AIS (Adenocarcinoma in Situ) (1)

- 常位於 ***endocervical canal***, 以至於可能沒有顯著的 colposcopic changes

- 常為 ***multifocal***, 以至於即使 negative margins on an excisional procedure specimen 亦無法確保有完全切除病灶
  - 即使 negative surgical margins, 仍有<10% 的復發率
    - → 故建議 ***total hysterectomy***

- 在切除子宮之前, 仍應先有 ***diagnostic excisional procedure***, 以盡量排除 invasive adenocarcinoma 之虞

AIS (Adenocarcinoma in Situ) (2)

- 關於 diagnostic excision, cold knife conization 或 LEEP 皆可, 但要做到有 ***intact specimen*** with interpretable margins (specimen length 至少10mm)
- Diagnostic excisional procedure specimen 若有 ***positive surgical margin***, 則宜再 re-excision 到 negative surgical margin 為止 (即使將 hysterectomy)

- ***Fertility sparing 條件***
  - negative surgical margins
  - cotesting + ***ECC*** q6m 至少 3 年 → q1y 至少兩年 → q3y

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輕症之追蹤

- HPV(-) ASCUS
  - **三年度** (每3年 HPV-based, 或每年 Pap)
- HPV(+) NILM, HPV(-)LSIL, Histologic CIN1 (previous Pap ASCUS/CIN)
  - **先一年度 x 1** (1年後 HPV-based, 或每半年 Pap)
  - **之後三年度** (每3年 HPV-based, 或每年 Pap)

- <= Histologic CIN1 (previous Pap HSIL/ASC-H/AGC-NOS)
  - **先一年度 x 2** (每年 HPV-based, 或每半年 Pap) (加 colposcopy if previous Pap HSIL)
  - **之後三年度**至少25年 (每3年 HPV-based, 或每年 Pap)

中重症之追蹤(1)

- Histologic HSIL
  - 先*半年度* (半年後 HPV-based) → 再*一年度*連續正常3年 (每年 HPV-based, 或每半年 Pap)→ 再*三年度*至少25年 (每3年 HPV-based, 或每年 Pap)
  - Histologic HSIL with margin (+) or ECC (+) → 也可 repeat excision, 也可半年後 ECC + colposcopy

- Untreated CIN2
  - 先*半年度* 兩年內連續正常2次 (每半年 **colposcopy** + HPV-based (or Pap if < 25y/o) →再*一年度* 連續正常3年 (每年 HPV-based, 或每半年 Pap) →再*三年度* 至少25年 (每3年 HPV-based, 或每年 Pap)

中重症之追蹤 (2)

- AIS 子宮頸仍保留者
  - 先***半年度***連續正常3年 (每半年 **ECC** + HPV-based) →再***一年度***連續正常2年(每年 **ECC** + HPV-based) →再***三年度***至少25年 (每3年 **ECC** + HPV-based)

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Unsatisfactory Cervical Cytology

- Repeat after 2-4 months
- 2 consecutive unsatisfactory screening tests → perform colposcopy

Pap 沒看到 T-zone或 endocervical cell 時

- 若 < 30y/o → 之後 routine screening 即可
- 若 >= 30y/o
  - prefer HPV testing
  - 亦可只 routine screening

PAP 第14號

- 抹片上有 benign endometrial cells, endometrial stromal cells, 或 histiocytes
- ***已停經者*** → 要檢查 endometrium
- 尚未停經, 又無異常出血者 → 免處理

孕婦

- *不宜* ECC, endometrial biopsy; 但*可* colposcopy-directed biopsy
- 除非疑似 cancer, 否則*不宜* diagnostic excisional procedure
- Histologic HSIL 不宜於孕期治療 → colposcopy and testing (diagnostic cytology/HPV depending on age) is preferred ***every 12 to 24*** weeks
- AIS → 轉介 gynecologic oncologist
- ***生產完4週之後***才作 colposcopy

the Immunosuppressed

- 開始有 sexual activity 一年, 即進行 cervical screening
  - 每年一次 x 3, 然後每三年一次直到終生
- HPV(+) 或 Pap 異常 → 則 colposcopy

全子宮切除之後

- 若25年內並無 HSIL, AIS → 免 vaginal screening

- 若曾有HSIL, AIS
  - 先*一年度*連續正常3年 (每年 HPV-based, 或每半年 Pap)→再*三年度*至少25年 (每3年 HPV-based, 或每年 Pap)

Take Home Message

- **Risk-based** management, **HPV–based** surveillance
- **Colposcopy** for higher Pap → >= 2-4 切, +/- ECC
  - **HPV 16/18 (+),** Pap NILM→ colposcopy
  - **Suspicious gross** cervical lesion but Pap NLIM → biopsy !
  - **AGC** → + ECC, +/- endometrial biopsy
- **HSIL:** prefer excision. **AIS:** excision. **Persistent CIN1:** prefer observation.
- **CIN2** might be observed in some circumstances
- **Pregnancy** → No ECC/Em Bx/LEEP/conization (unless r/o cancer)
- 追蹤: **HPV-based** 或更密集之**Pap** (+/- **colposcopy**) (+ **ECC** for cx[+] AIS)
  - 輕症: 一年度 x 1~2, 再三年度
  - 中重症: 半年度 x 1~6, 再一年度 x 2~3, 再三年度 **(>= 25 年 .....)**