PREINVASIVE DISEASE OF THE LOWER GENITAL TRACT

DR AI LING TAN
GYNAECOLOGICAL ONCOLOGIST
ASCOT CLINIC,ADHB

"Cervical cancer is caused by the human Papillomavirus, with 99.7% of cervical cancers containing Papillomavirus DNA[1,2]"

HPV 200 types

HR 16,18

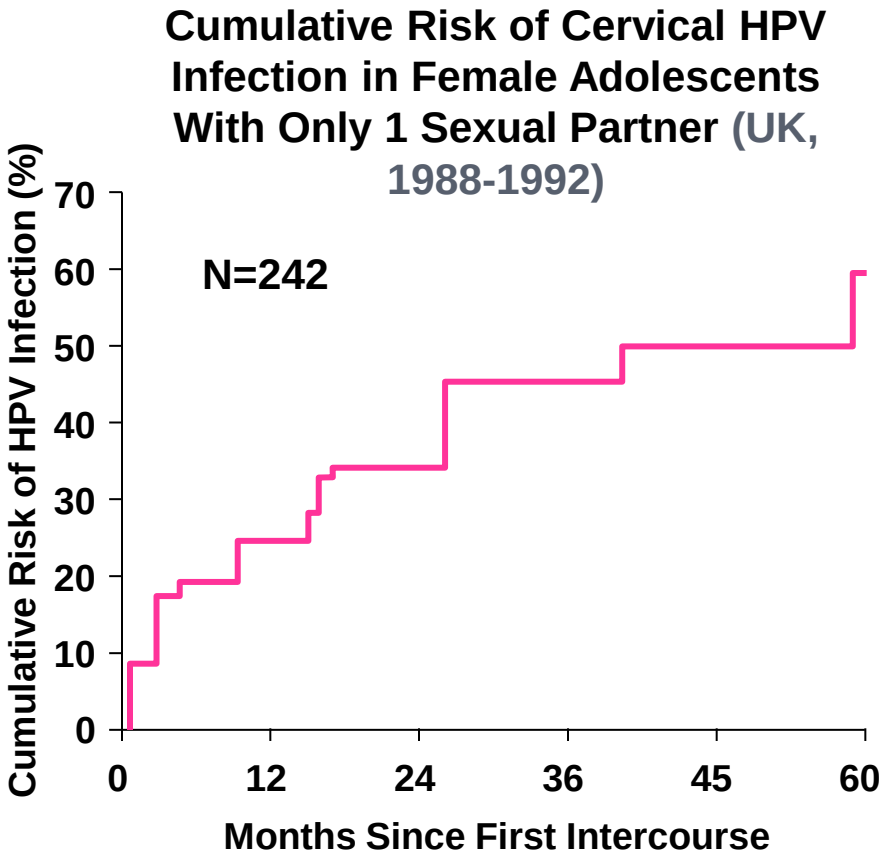
LR 6,11

IARC[1]

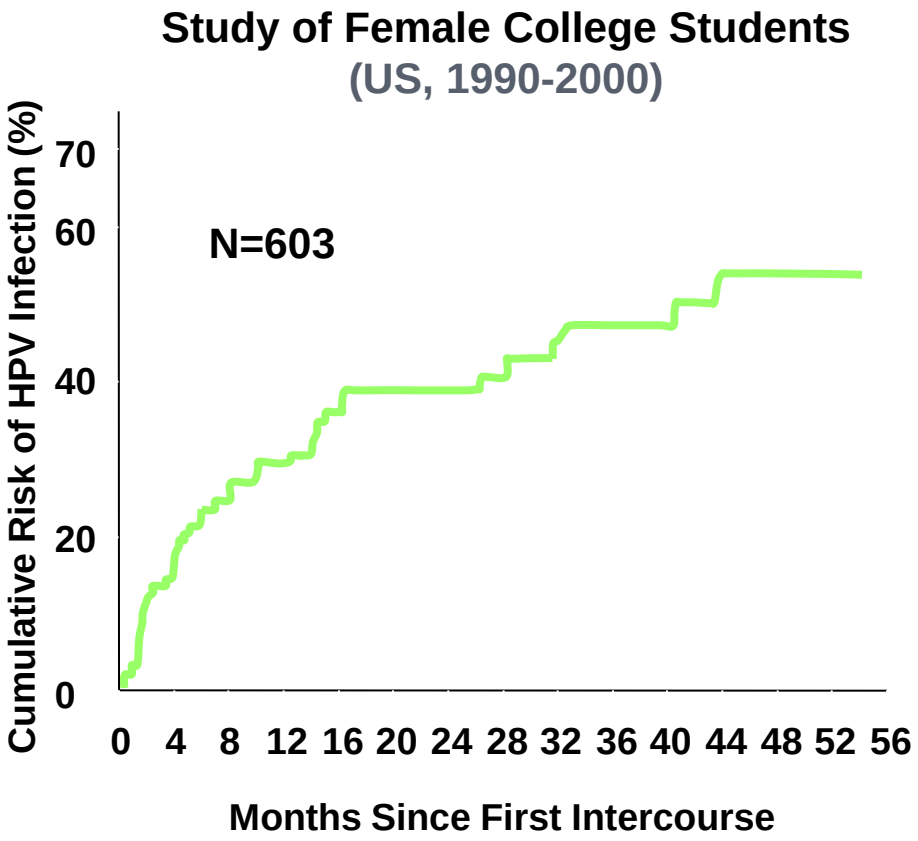
Association between HPV DNA and risk of S.C. Cancer Cervix

	RR/OR
HPV 16	**435**
HPV 18	**248**
HBV / Liver cancer	*50*
Smoking / Lung cancer	*10*

Risk of Acquiring HPV After First Intercourse

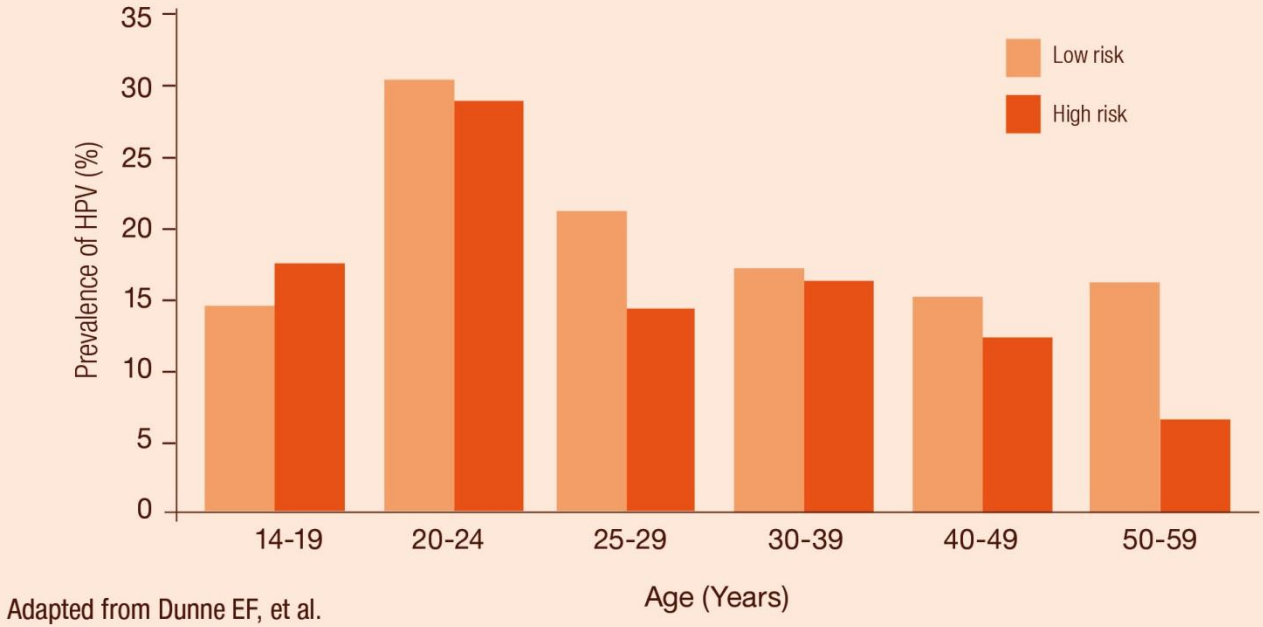


Adapted from Collins, et al.



Adapted from Winer, et al.

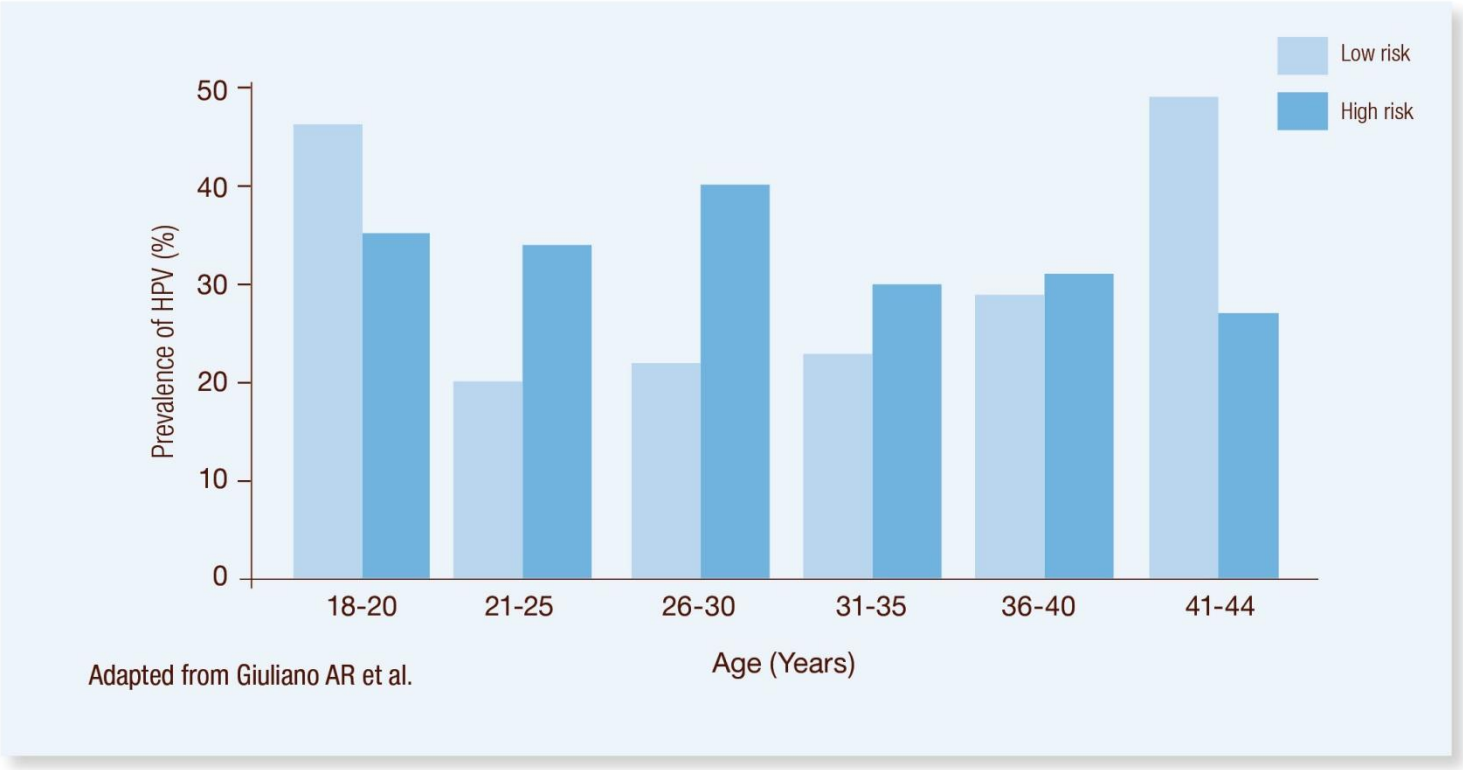
Prevalence of HPV infection by age - Females



Prevalence of HPV in US females (n=1921) as assessed by self collected vaginal swab specimens

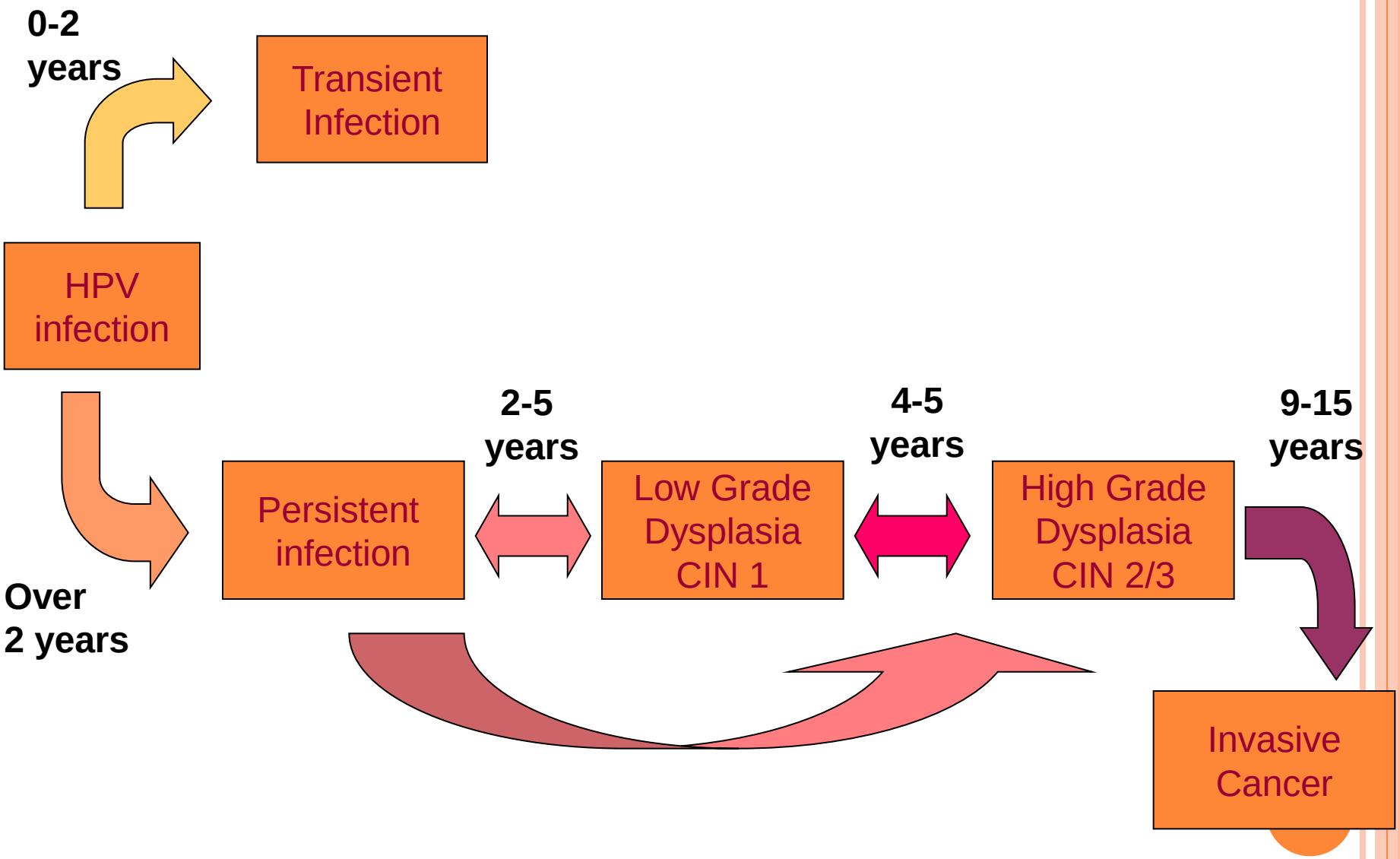
Reference: Dunne EF, et al. Prevalence of HPV Infection Among Females in the United States. JAMA. 2007;297:813–819

Prevalence of HPV infection by age - Males



Males aged 18–44 years in Tucson, Arizona (N = 290).

Reference: Giuliano AR et al. Age-Specific Prevelance,Incidence and Duration of Human Papillomavirus Infections in a Cohort of 290 US Men. J Infect Dis. 2008;198:827–835.


0-2 years
Transient Infection
HPV infection
Over 2 years
Persistent infection
2-5 years
Low Grade Dysplasia CIN 1
4-5 years
High Grade Dysplasia CIN 2/3
9-15 years
Invasive Cancer

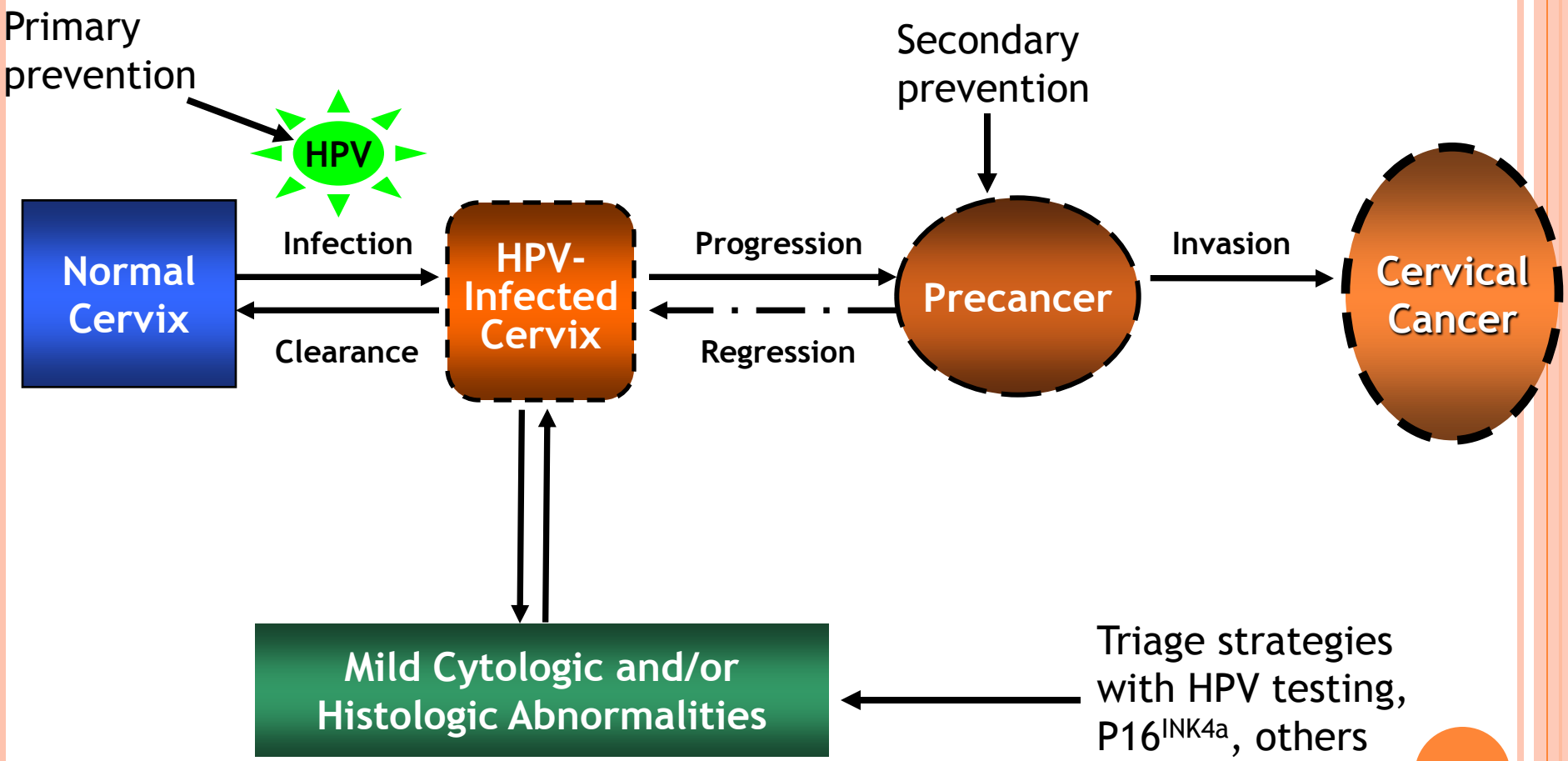
Carcinogenic mechanism :HPV Persistence

- Persistent infection: Detection of same HPV type two or more times over 2 years
- Persistence of hr HPV is crucial for the development of cervical precancer and cancer.
- Co factors
  - High parity
  - Immune suppression(transplants,meds,HIV)
  - Smoking
  - genetics

Carcinogenic mechanism :HPV Persistence

- **HPV 16** is the most carcinogenic: 12% risk of inducing CIN 3 or invasive disease after 3 years of persistent infection
- Most common subtype in cervical, vulvar and oropharyngeal cancers
- **HPV 18** is 2nd most common subtype in cervical and glandular lesions

Natural History of Cervical Carcinogenesis



HPV=human papillomavirus.

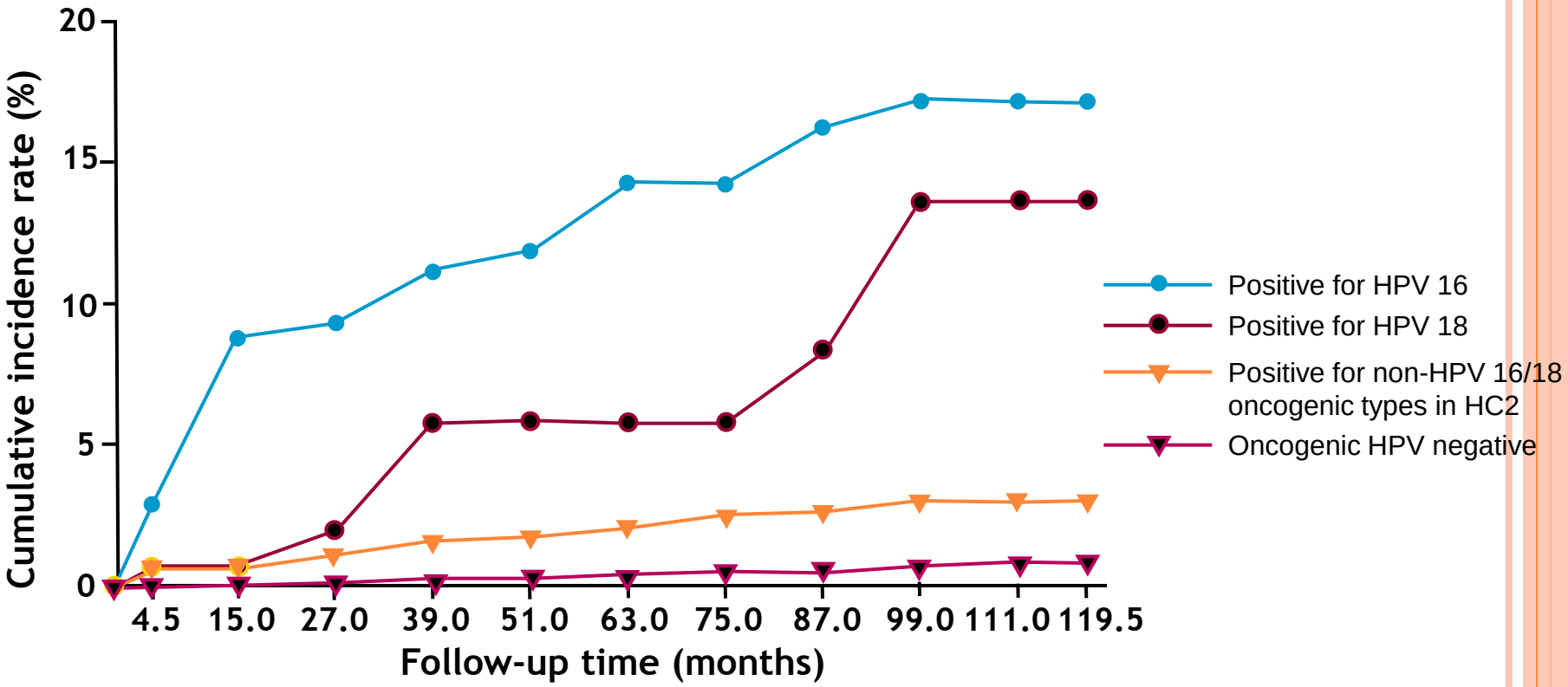
Schiffman M, Kjaer SK. J Natl Cancer Inst Monogr. 2003;(31):14-19.

Estimated Annual Incidence of HPV Cervical Infection/ Dysplasia

- Virtually all cases of cervical cancer come from high-grade dysplasia

Cervical Infection	Worldwide(millions)
Dysplasia	
• HPV infection without detectable cytological abnormalities	300
• Low grade dyplasia	30
• High grade dyplasia	10

Cumulative Incidence of CIN 3+ in 20,512 Women: 10-year Follow-up



HC2=Hybrid Capture 2 HPV Test.

Khan M. et al. J Natl Cancer Inst. 2005;97:1072-1079.

HPV AND CANCER PREVENTION

- **Primary Prevention**

Vaccination

- **Secondary Prevention**

Cytology

HPV testing

- **Treatment of preinvasive disease**

HPV AND CANCER PREVENTION

- **Primary Prevention**

1. **Prophylactic Vaccination**
2. **Condom use** Consistent use reduced HPV infection by 70%
3. **Male circumcision** decreases HPV infection in men and reduces womens exposure to Hr HPV. Also decrease risk of HIV, herpes(males) BV, trichomoniasis (females)
4. **Potential for microbicides** carrageenan (inexpensive safe gelling agent) tested for HIV but x1000 more effective in HPV

Quadrivalent HPV Vaccine

- **Prophylactic vaccination is highly effective against[1-5]**
  - cervical intraepithelial neoplasia (CIN)
  - vulvar intraepithelial neoplasia (VIN)
  - vaginal intraepithelial neoplasia (VaIN)
  - adenocarcinoma in situ (AIS)
  - genital warts (GW)
- **The quadrivalent HPV Vaccine prevents re-infection and disease related to the same vaccine HPV type[6]**

1. N Engl J Med 2007;356(19):1928-43; 2. N Engl J Med 2007;356(19):1915-27; 3. Lancet 2007;369:1693-702. 4. Lancet 2007;369:1861-8; 5. Lancet 2009;373:1921-2; 6. Human Vaccines 2009; 5:696-704.

GARDASIL® - Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine

- VLPs manufactured in *S. cerevisiae*
- Aluminum Adjuvant 225 μg per dose
- 0.5 mL injection volume given in a 0, 2, 6 (month) dosing regimen

Type	Women	Men
16/18	70% of Cervical Cancer 60% of CIN 2/3 25% of CIN 1	70% of HPV-related Cancer Prevention of infection
6/11	10 to 15% of CIN 1 90% of Genital Warts	Prevention of infection 90% of Genital Warts

Impact on Screening

- 75% reduction of cervical cancer in 25 years
  - HPV 16 – 50-60%
  - HPV 18 – 20-30%
- Decrease in CIN 3
- ASCUS/LSIL continue with less CIN 3
- Decrease in cost-effectiveness of cervical cytology and colposcopy

CA: A Cancer Journal for Clinicians. 53(1):27-43, 2003.

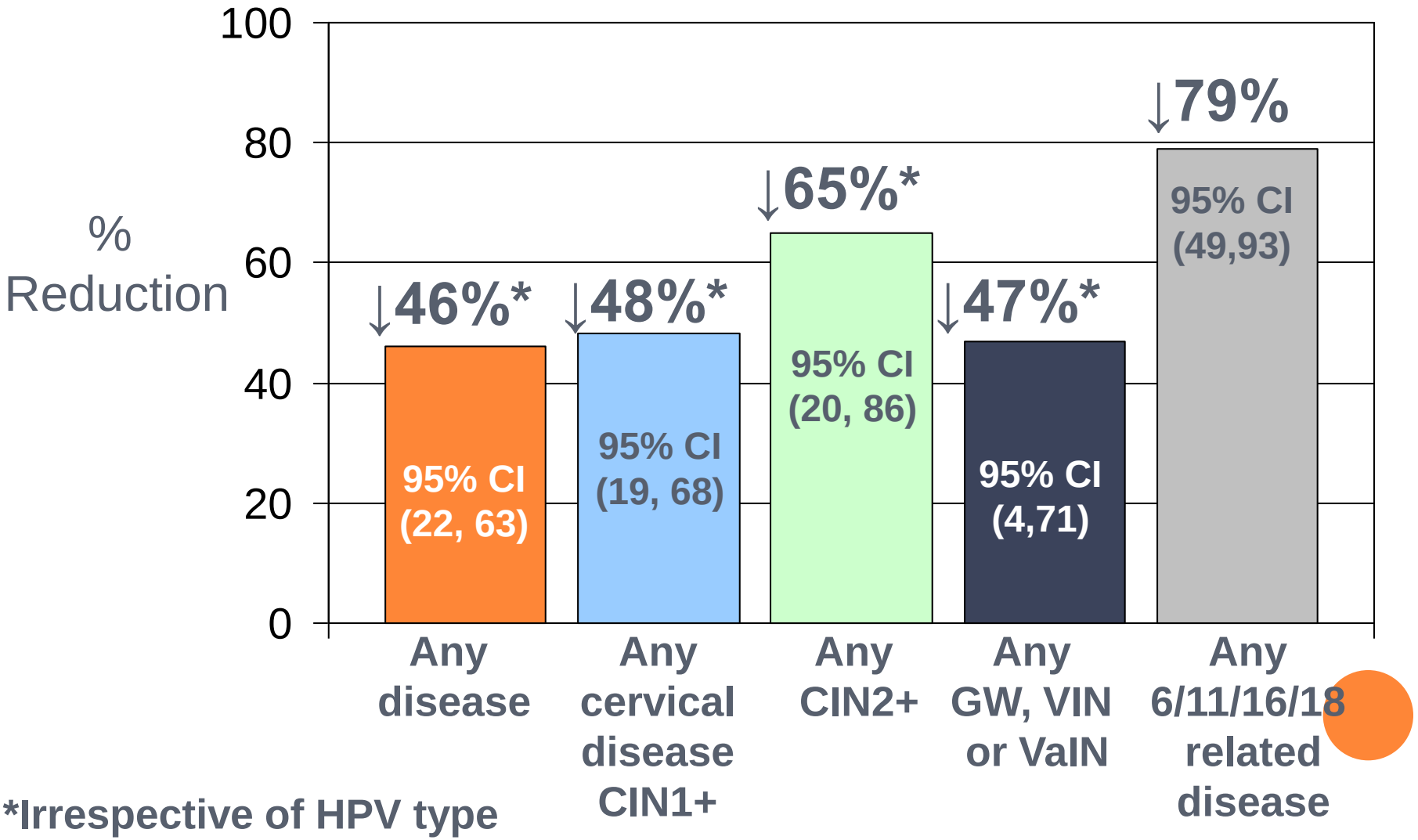
Clinical Results with HPV Vaccines

Large phase 3 trials demonstrated that the quadrivalent vaccine is

- **99% effective** in preventing HPV 16/18 associated CIN2/3 and adenocarcinoma in situ
- **100% effective** in preventing HPV16/18 associated vulvar and vaginal intraepithelial dysplasia

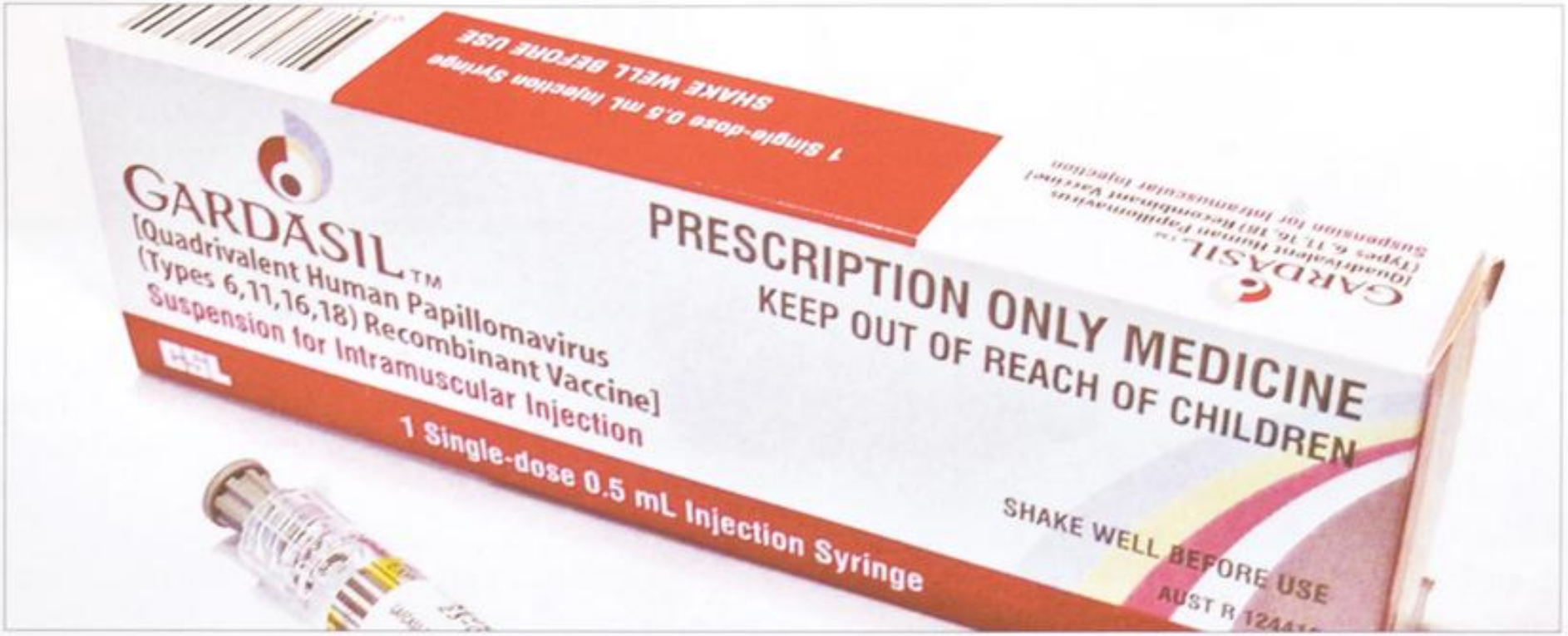
New data also suggest that the vaccine prevents most cases of CIN and anogenital lesions **in women who have been previously been infected with at least one of the HPV types targeted** by this vaccine

Impact of qHPV Vaccine on the incidence of new HPV disease – after treatment for cervical disease



*Irrespective of HPV type

Gardasil protects for 10 years

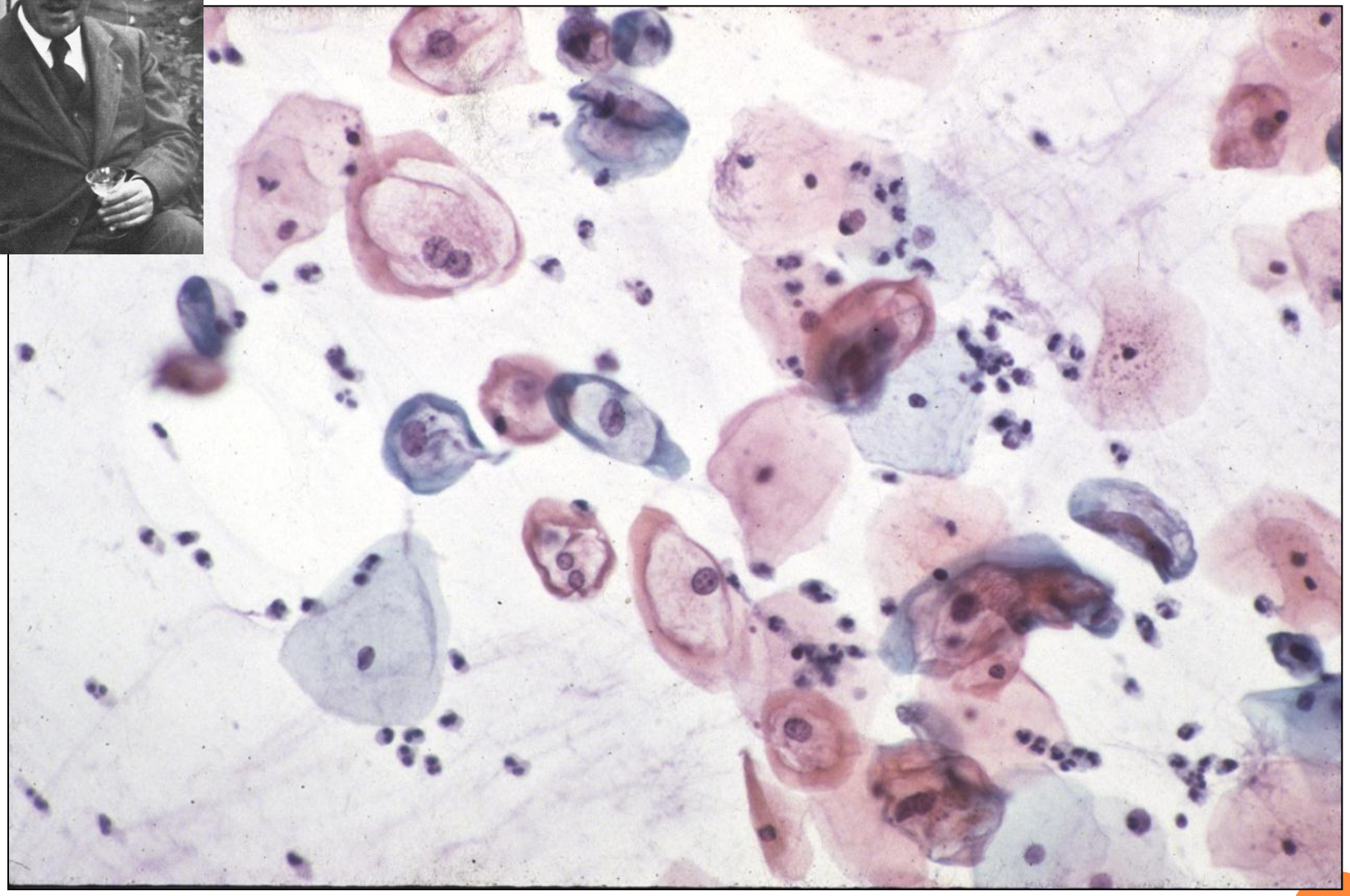


Smallpox Vaccination Act 1840.

Free vaccination. Not compulsory.

Take Home Messages

- Prophylactic HPV vaccines demonstrate high-level protection from HPV 6/11/16/18 infection and related preinvasive and invasive cervical, vaginal and vulvar lesions
- Pap screening to detect and treat lesions in women infected prior to vaccination or infected with HPV types not covered by the vaccine will continue
  - Fewer women will require cervical biopsies and treatments

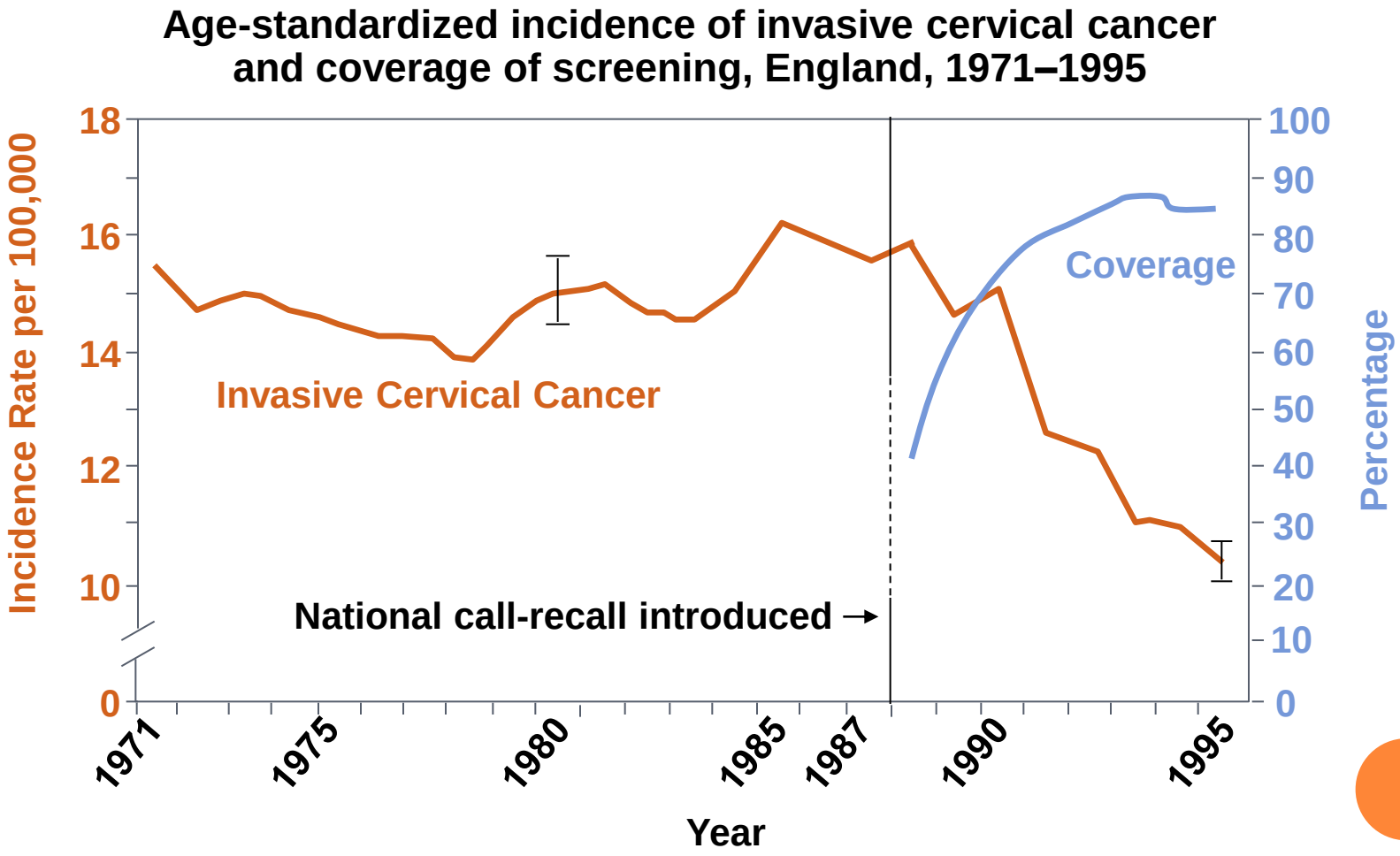


Cytopathology (1)

“Pap” Test

- Historical perspective
- Most widely used screening test
- Impact on cervical cancer

Improvements in Screening Coverage Can Further Reduce the Incidence of Cervical Cancer[1]



1. Adapted from Quinn M, Babb P, Jones J, Allen E. *BMJ.* 1999;318:904–908.

Cytopathology (2)

Concerns

- False negatives

  Sensitivity 58%*(lab dependent-78%)
  Specificity 68%*

- ‘Unsatisfactory’ rates
- Sampling: Screening errors 2:1

Meta-analysis. Fahy, Am J Epidemiol 1995; 141: 680-9.

HPV DNA TESTING

- Amenable to automation
- **Hybrid Capture (**Digene) nucleic acid hybridization assay with signal amplification →detects 13 Hr HPV but does not type
- **PCR** techniques allow typing (Cervista,Roche)
- **CCCaST** confirms HPV testing more sensitive (95% vs 55%)but less specific than cytology(94% vs 97%) in detecting high grade CIN

TRIAGE OF hrHPV +VE WOMEN
AGE OF STARTING hr HPV TESTING

- Cytology is best triage of hrHPV+ve women needing immediate colposcopy. Using HPV alone will --→increase in colposcopies and overtreatment
- Use of P16

- Start at 30 years as highest prevalence is 20-25 yrs and decreases by 35 yrs .Detecting clinically relevant lesions

HPV Testing

HrHPV testing is currently recommended in the Guidelines in three clinical situations:

Situation	Who usually initiates the HPV test
1. Women **30 years and older** with ASC-US or low-grade changes, to help assess risk of progression	Laboratories (the HrHPV result is reported at the same time as the ASCUS/LSIL result) Smear takers are required to ensure that all women over 30 years are informed about HPV testing.
2. Women (all ages) treated for a high-grade lesion to help assess whether the lesion has been completely resolved. *Includes 'historical testing' for women on annual smears for previous high-grade lesions and with negative smears since, to assess whether they can return to routine 3 yearly screening - refer page 3.*	The smear taker, after discussing with the woman.
3. Where colposcopy has shown discordant results from cytology, to help interpret these results.	Colposcopists

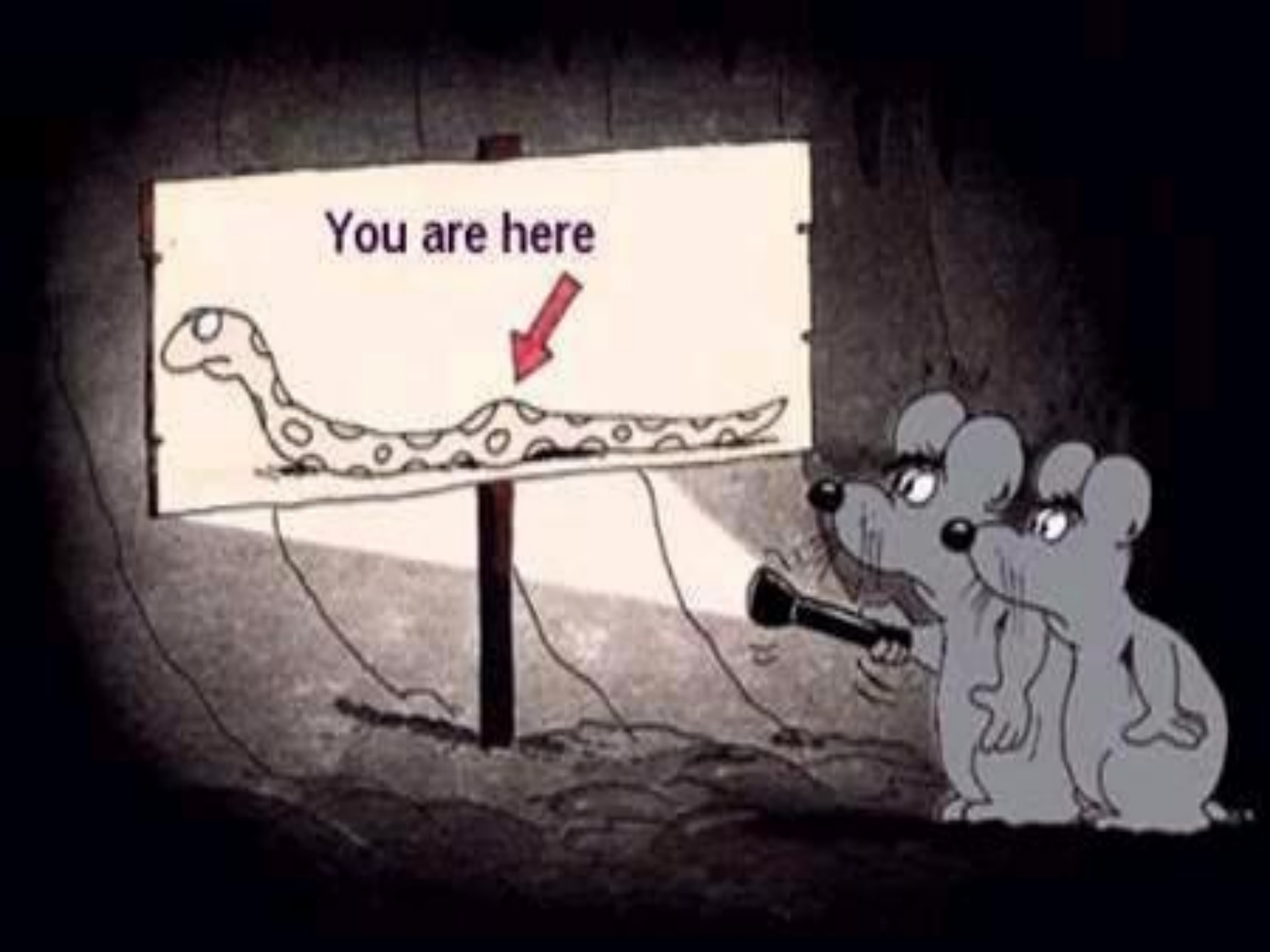
Who should not be offered HrHPV testing as part of the NCSP?
Women under 30 years (unless they have had a previous high-grade (HSIL/ASC-H) lesion).
Note that where HrHPV testing is requested outside the Guidelines, women may be asked to pay for it.

HPV DNA TESTING(>30 YRS)

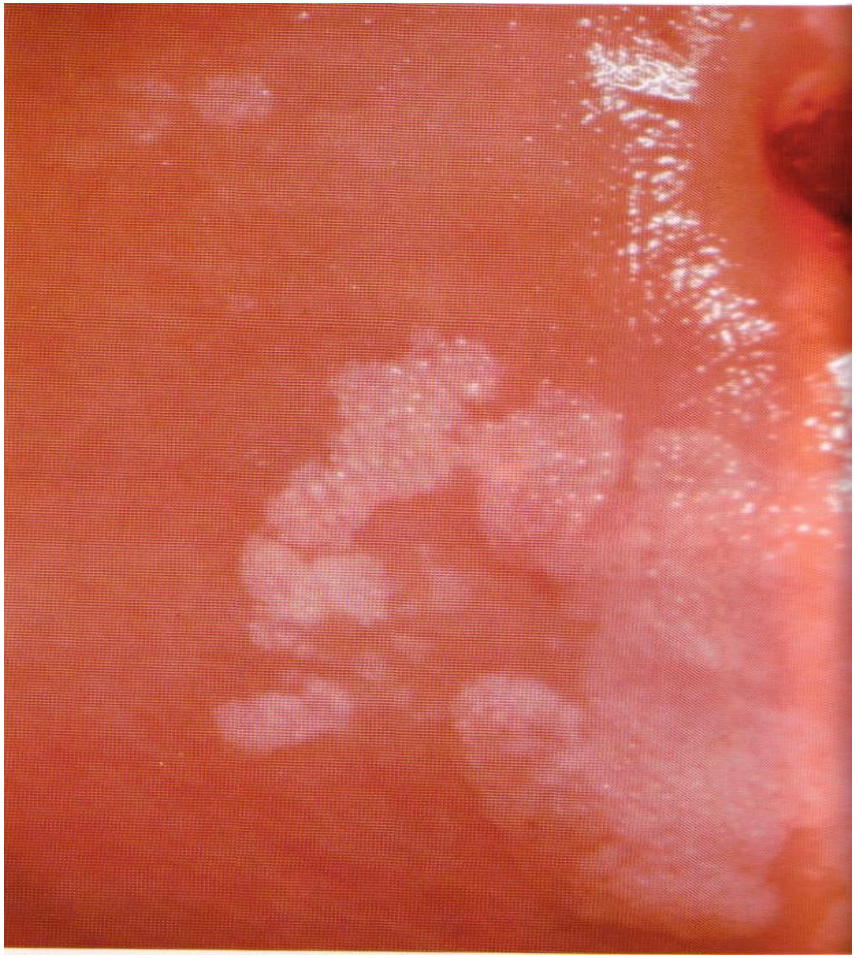
- Hr HPV test is 30% more sensitive than cytology in detecting CIN2 and 22 % more sensitive than cytology in detecting CIN3.Specificity is 4-6% lower than cytology
- Combined test CYTO and hr HPV no added value to single hrHPV test in detecting CIN 2 or CIN3
- hrHPV –ve is better protection than cyto –ve

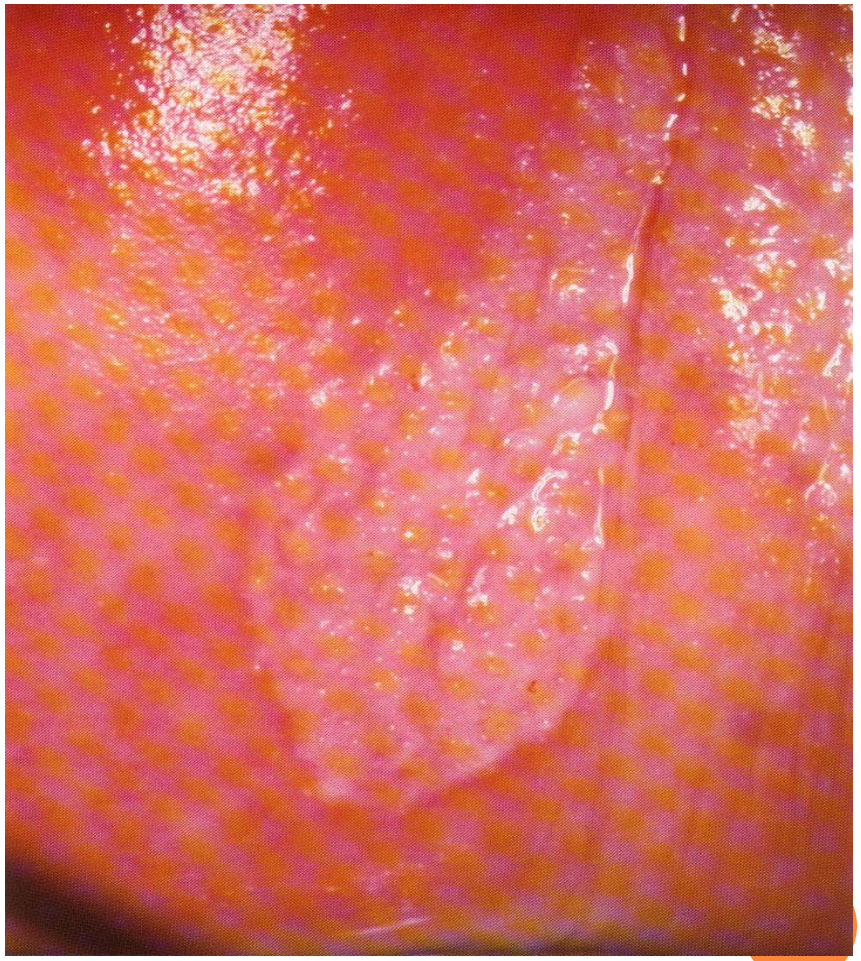
50% lower CIN 3 detection rate in hrHPV-ve 1st round vs CYTO-ve 1st round.(2nd round testing)

NO CANCERS in hrHPV –ve 1st round vs 8 in cytol -ve

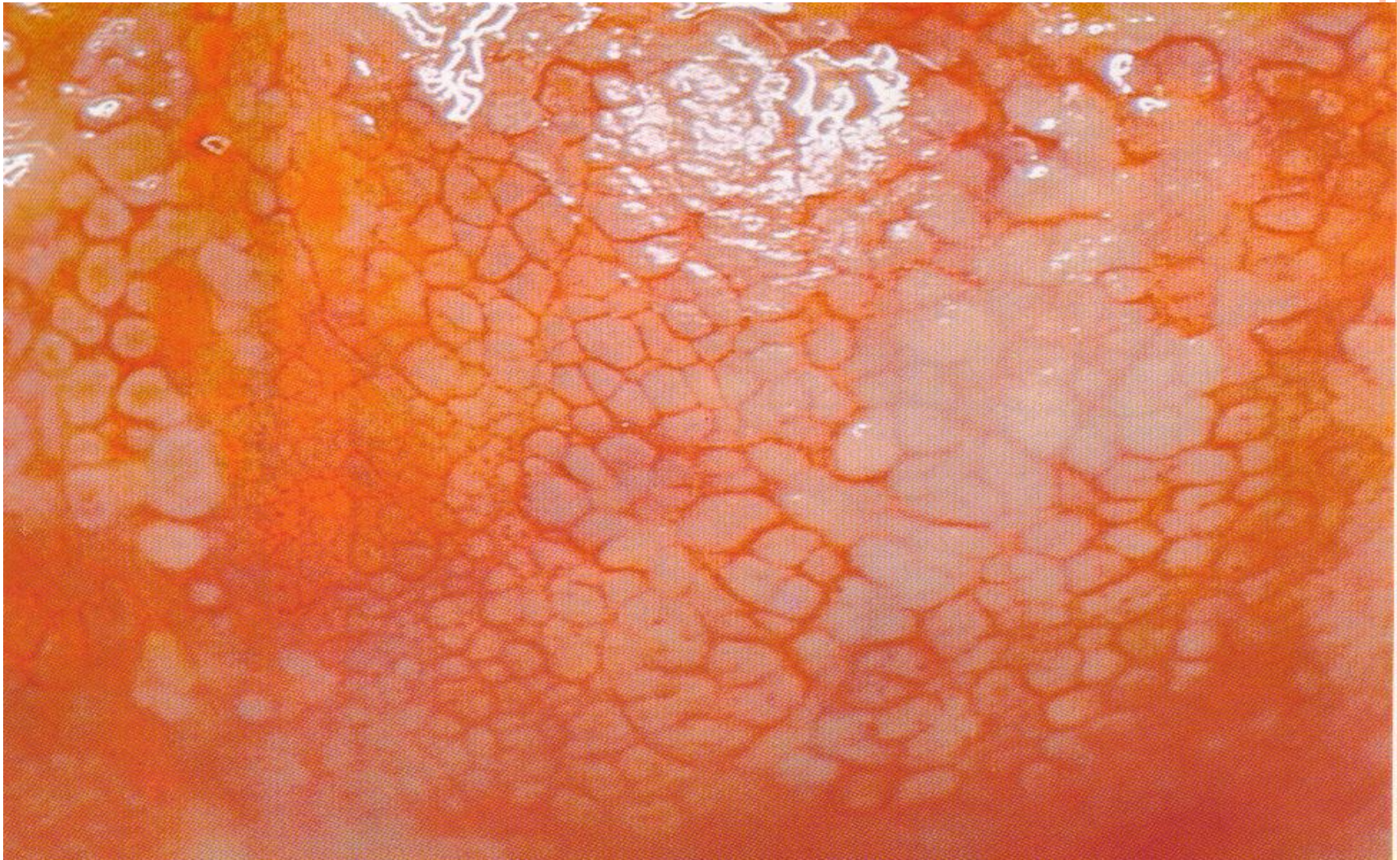

You are here

Low grade dysplasia granular, ill defined

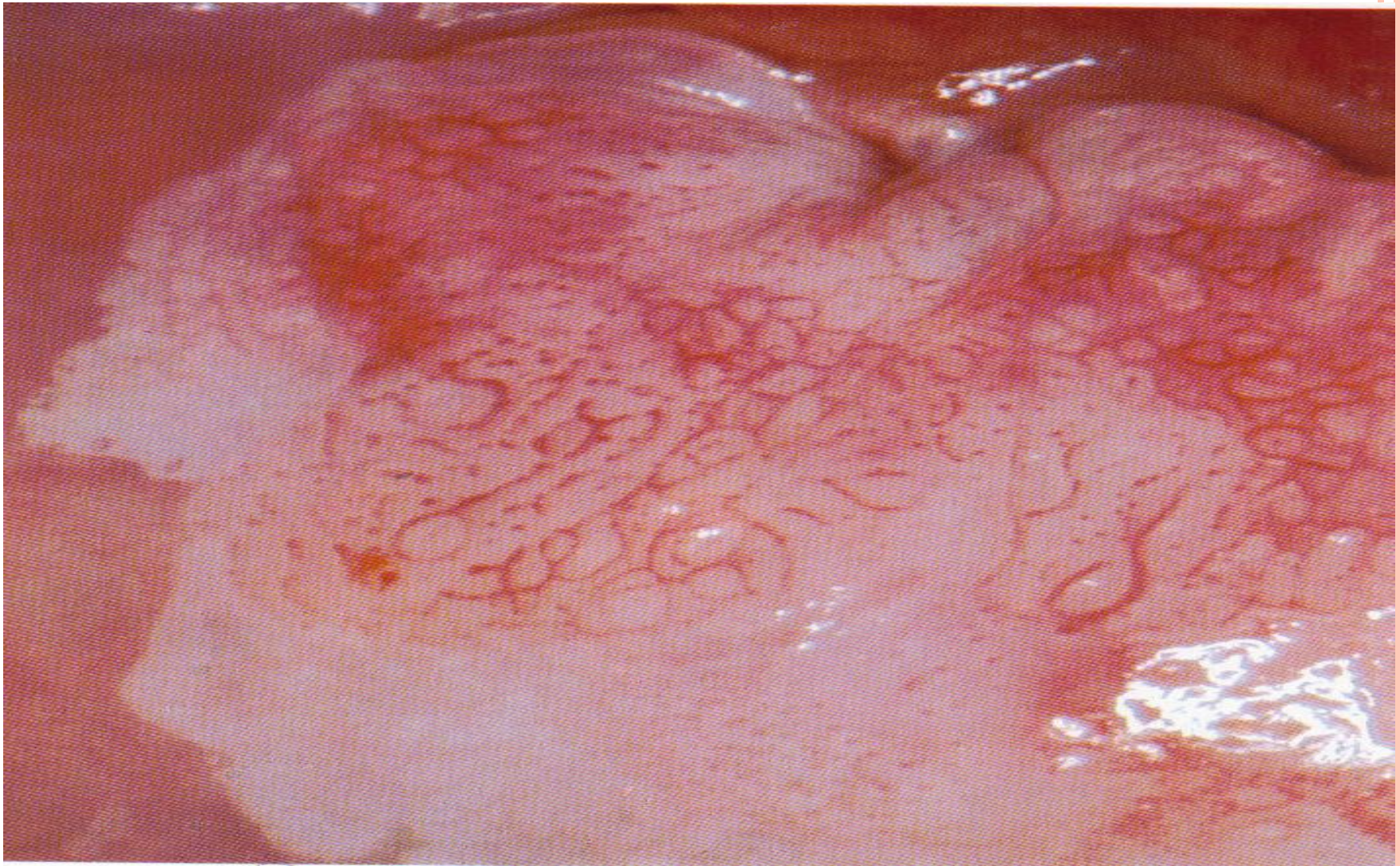




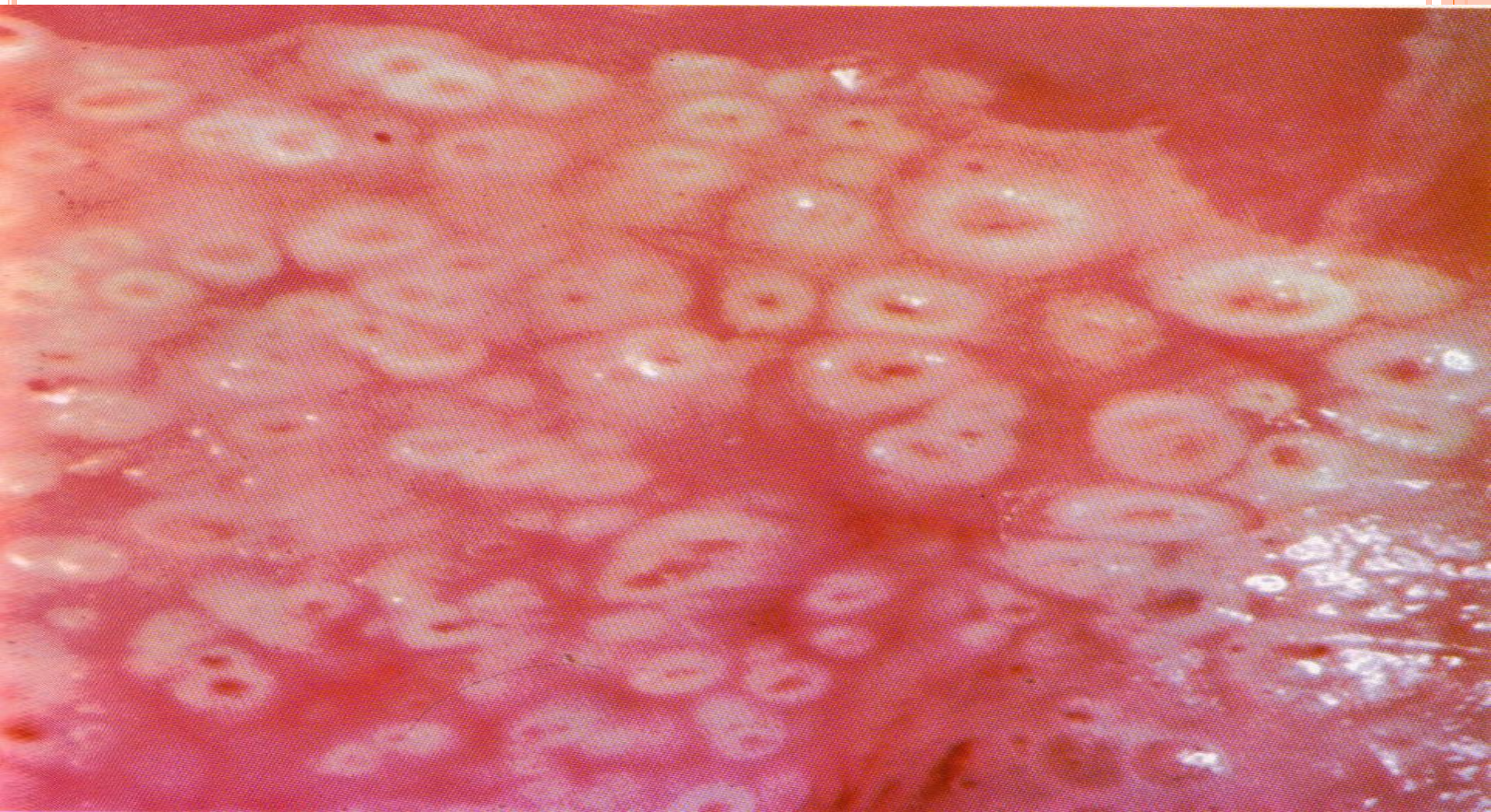
High Grade Dysplasia mosaicism



High Grade Dysplasia punctation

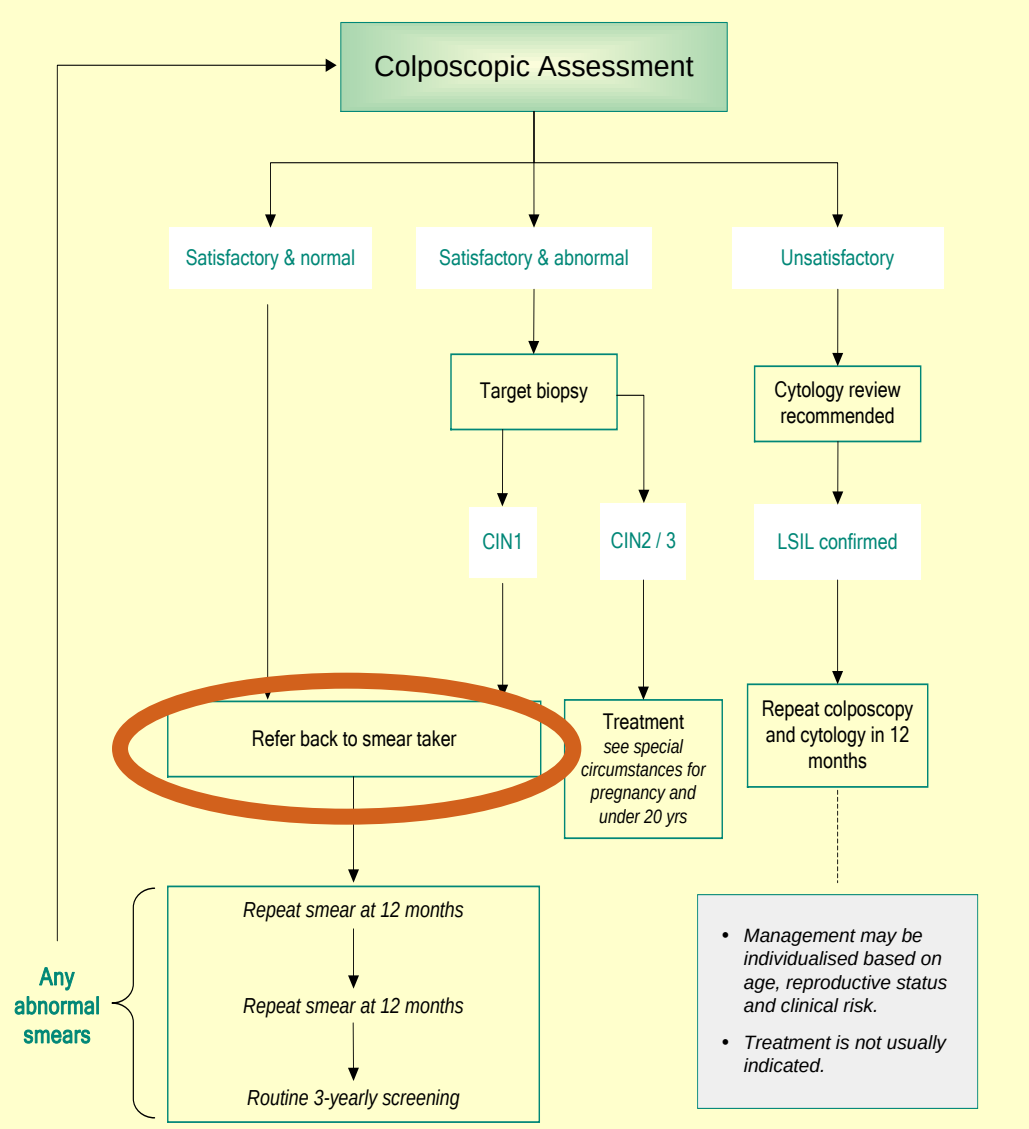


High Grade Dysplasia
gland cuffing



PUNCH BIOPSY OF CERVIX

LSIL Follow up



RISK OF CIN 2-3

2 year cumulative risk CIN2-3

- **ALTS ASCUS smear =15%**

  ASCUS+ HR HPV =27%

No difference in subsequent risk of CIN2-3 between women with no disease and CIN1 at initial colposcopy

- **NCSP registrar data ASCUS smear = 16%**

GLANDULAR LESIONS

- 15-20% of all invasive cancers
- Smears are less effective in preventing this
- Hr HPV is associated with 90% of ACIS and adenocarcinoma of the cervix
- Not uncommon to have both squamous and glandular lesions co existing

Treatment of cervical intraepithelial neoplasia

Modalities

- Ablation -- cryotherapy, CO2 laser

- Excision –LEEP/LLETZ(+LLETZ cone), cold knife cone biopsy,

  laser cone biopsy,

  hysterectomy

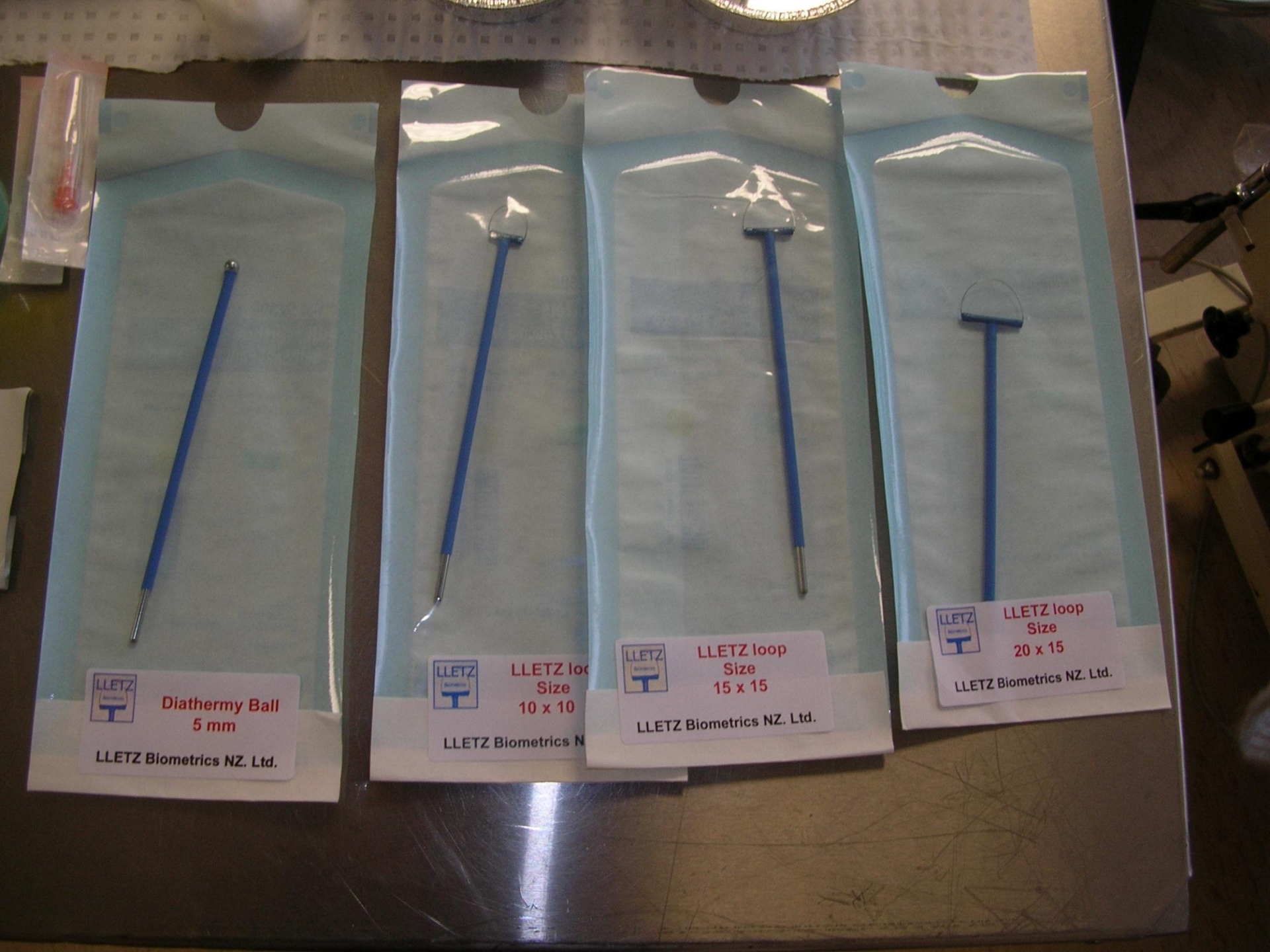
Cochrane database –no superior method (28 RCT)

Ablative methods

- High primary cure rates with minimum morbidity (80% cryo, 95% laser ablation)
- When cancer occurred after ablative therapy, occurred within 12 months in 66% of cases and within 2 years in 90% --triage error at initial assessment
- Experienced clinician

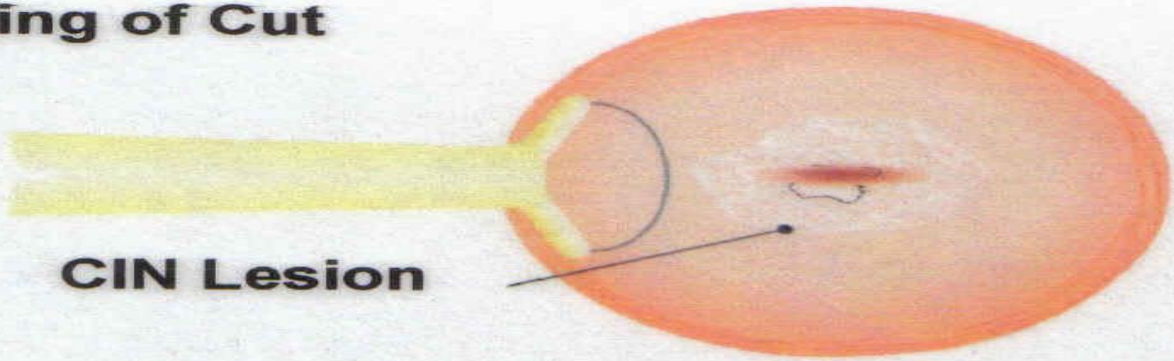
LEEP/LLETZ

- Most commonly used treatment modality in NZ
- Allows for excision of TZ , with no greater morbidity
- When performed by inexperienced operator, histological assessment can be difficult

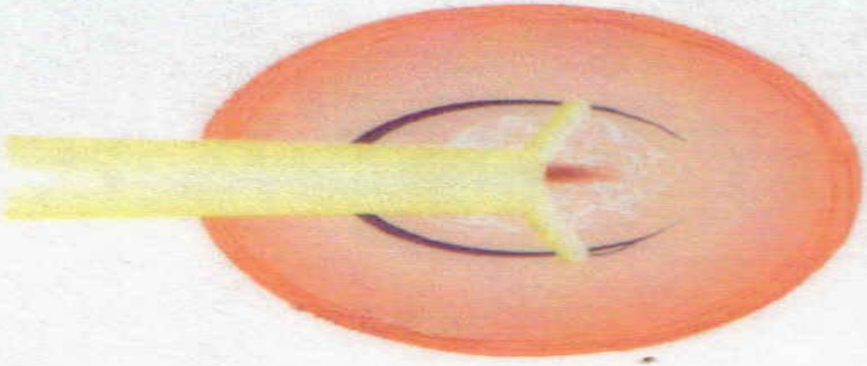

Diathermy Ball
5 mm
LLETZ Biometrics NZ. Ltd.
LLETZ loop
Size
10 x 10
LLETZ loop
Size
15 x 15
LLETZ Biometrics NZ. Ltd.
LLETZ loop
Size
20 x 15
LLETZ Biometrics NZ. Ltd.

LLETZ PROCEDURE

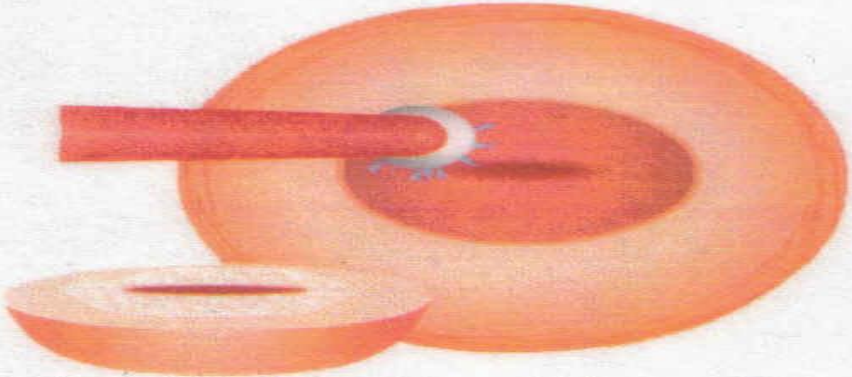
Beginning of Cut



End of Cut

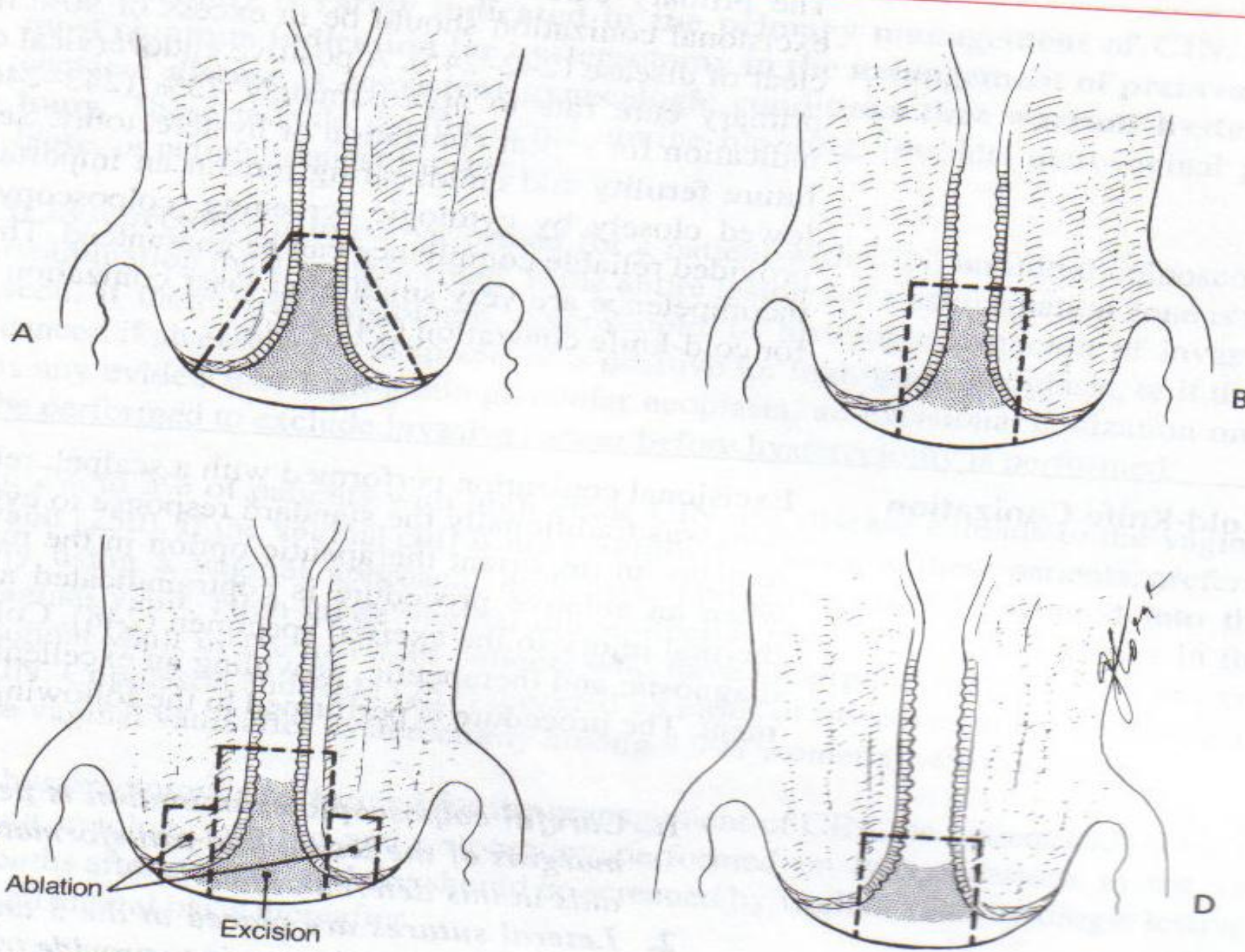


Diathermy



COLD KNIFE CONE BIOPSY

- Tailor treatment to the individual woman
- Size of lesion
- Extent of lesion
- Severity of lesion


A
B
C
Ablation
Excision
D

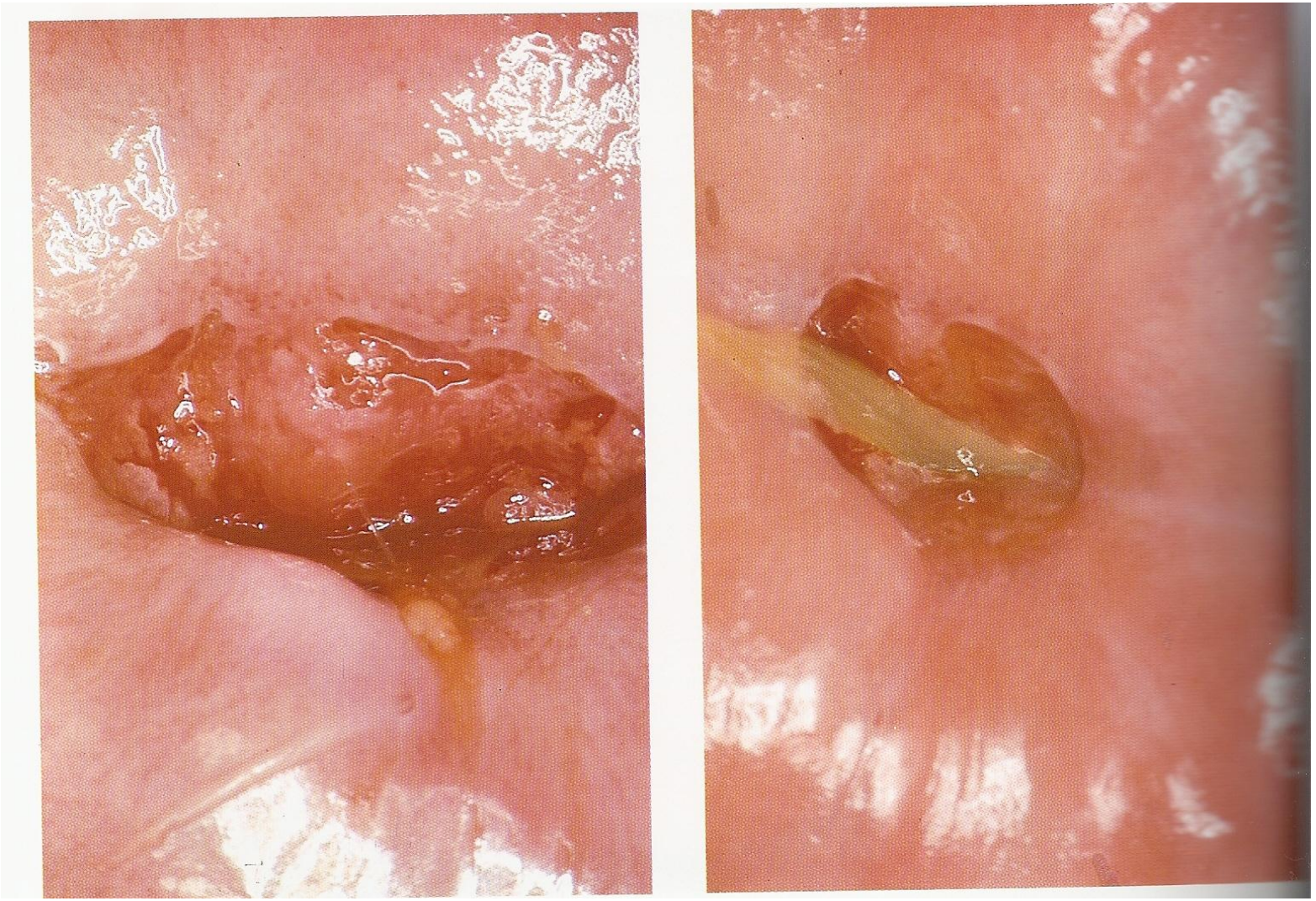
HYSTERECTOMY

- Rarely indicated for primary treatment for CIN. Used if there is **coexistent gynae pathology** warranting hysterectomy

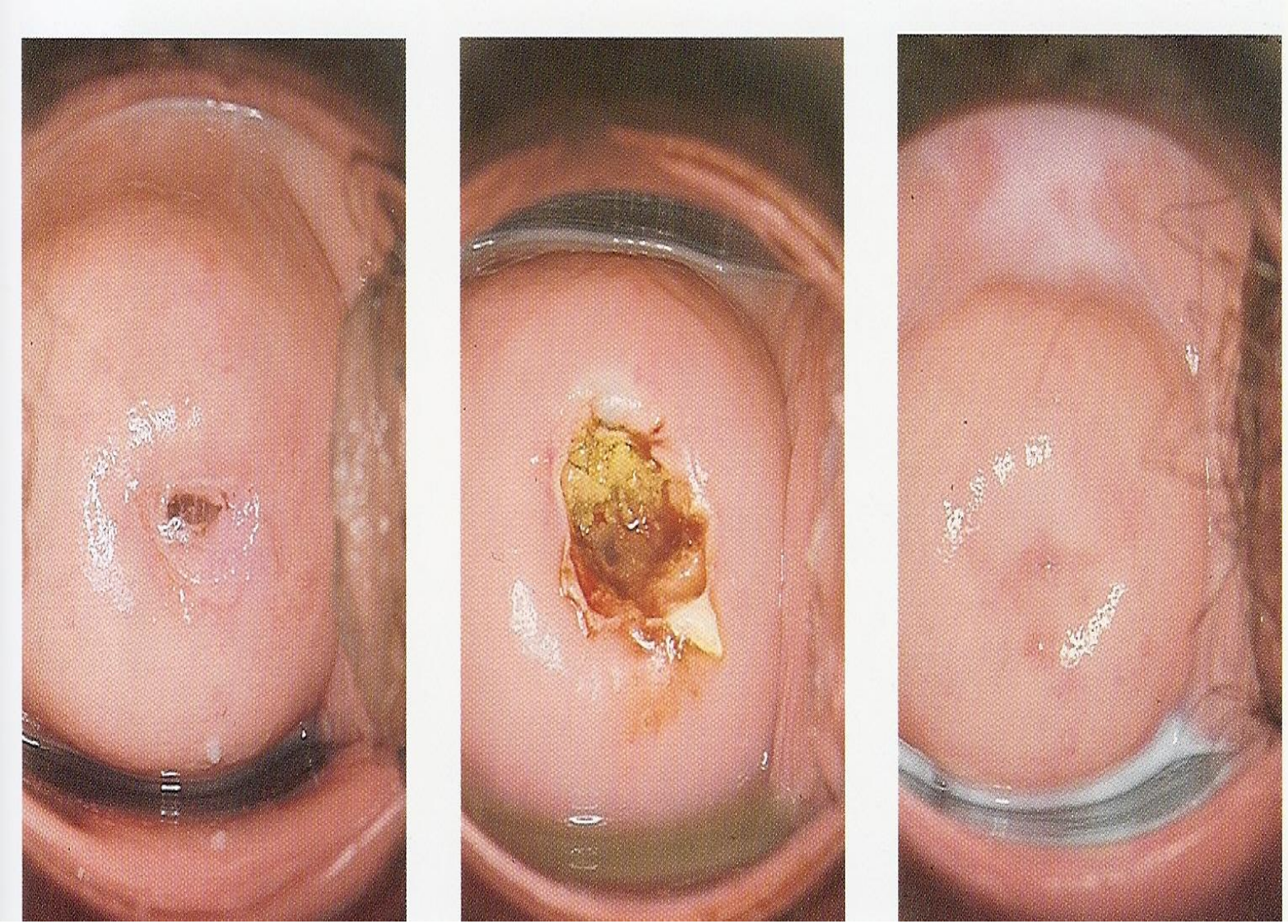
- Need **colposcopic assessment** first, excisional conization might need to be performed to exclude invasion.

- 2-3% high grade CIN, **disease extends beyond vaginal vault →vaginal cuff** fashioned appropriately

Post Rx TZ



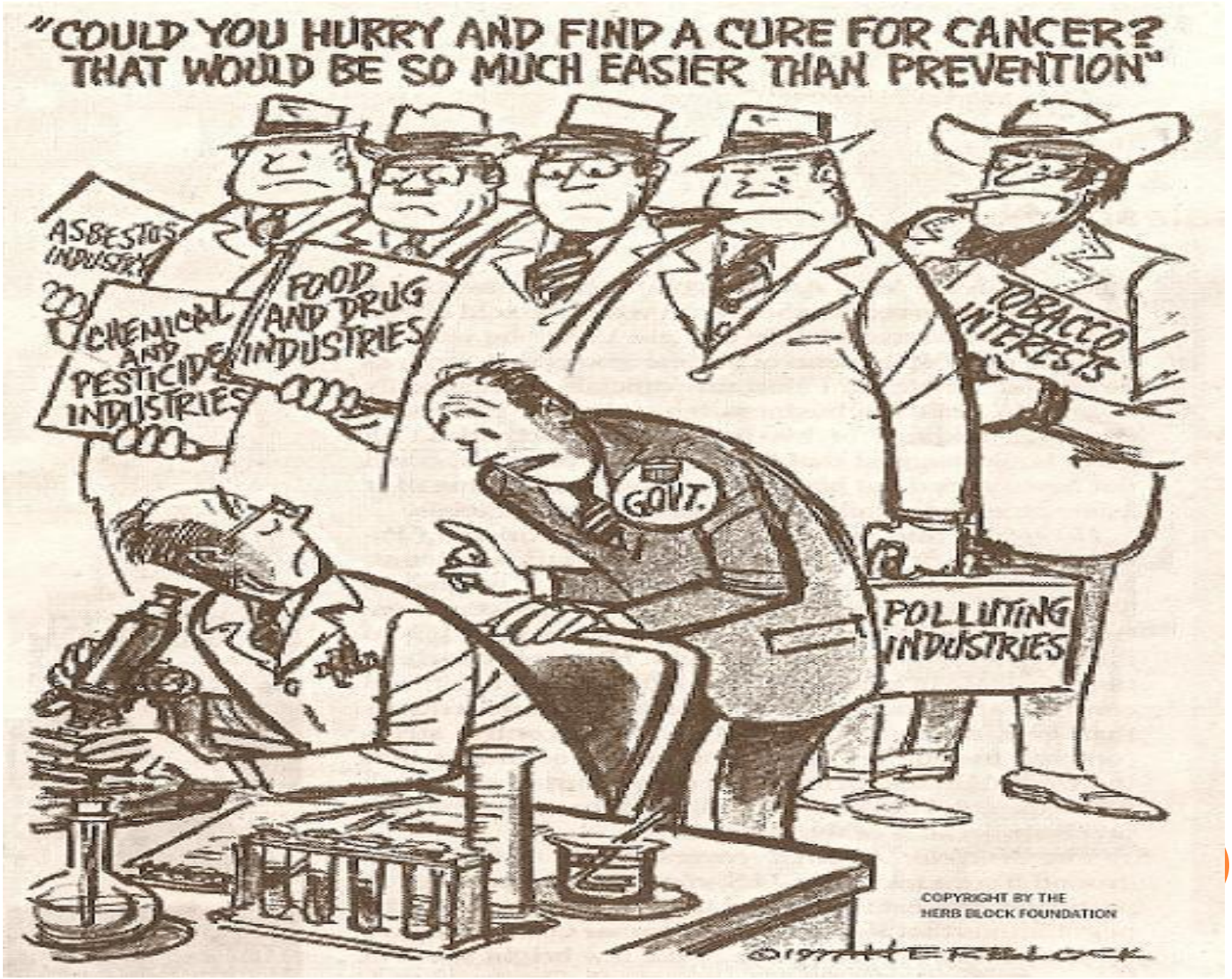
CERVICAL STENOSIS



Spontaneous HPV clearance- Evidence for not Rx <25

CIN 1	Regression rates
Adult women	70-80%
Adolescent/young women	90%

CIN2	progress
<25 yrs	8%
Older women	30-40%


"COULD YOU HURRY AND FIND A CURE FOR CANCER? THAT WOULD BE SO MUCH EASIER THAN PREVENTION"
ASBESTOS INDUSTRY
CHEMICAL AND PESTICIDE INDUSTRIES
FOOD AND DRUG INDUSTRIES
TOBACCO INTERESTS
GOVT.
POLLUTING INDUSTRIES
COPYRIGHT BY THE HERB BLOCK FOUNDATION
©1997 HERBLOCK

HPV and Cancer: A Broader Picture

Cancer	% Associated With Certain HPV Types
Cervical	>99%
Vaginal	~50%
Vulvar	~50%
Penile	~50%
Anal	~85%
Oropharyngeal	~20%
Larynx and aerodigestive tract	~10%

VIN
(Vulva Intraepithelial Neoplasia)

CLASSIFICATION OF VIN

- **VIN USUAL TYPE** high grade VIN only encompasses warty, basaloid and mixed **HPV related**

- **DIFFERENTIATED VIN**

  Non HPV related

- **VIN NOS**

HPV Prevalence: VIN warty/ basaloid

HPV 16 80% (CIN 3 50%)

Hillemans, Wang. Gynecol Oncol 2006; 100:276

IMPORTANCE OF VIN

- Symptoms that it causes
- The potential for progression to invasive cancers

SYMPTOMS

Absent in 20% of cases

MULTIPLE LOWER GENITAL TRACT NEOPLASIA (USUALLY CIN)

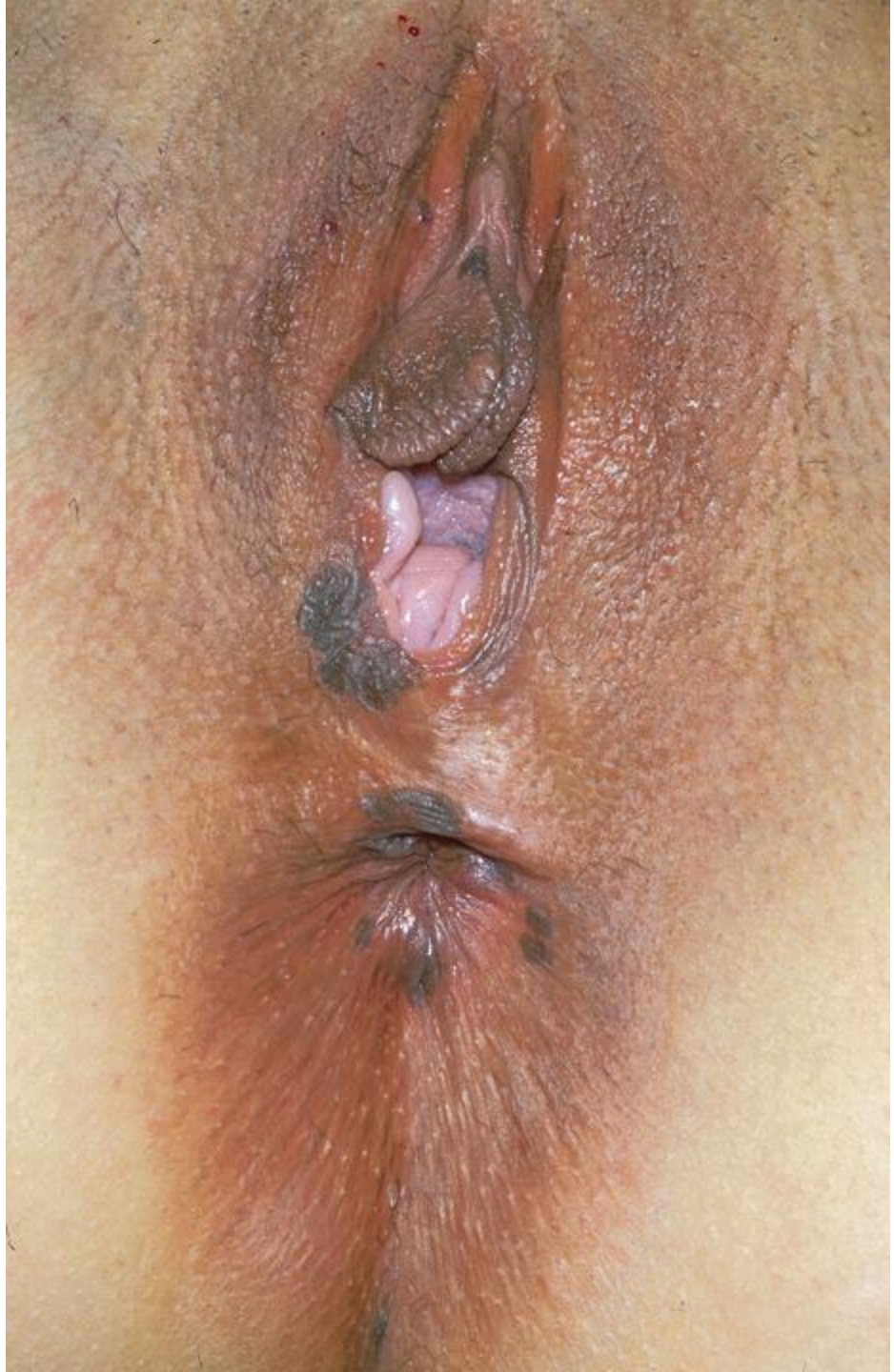
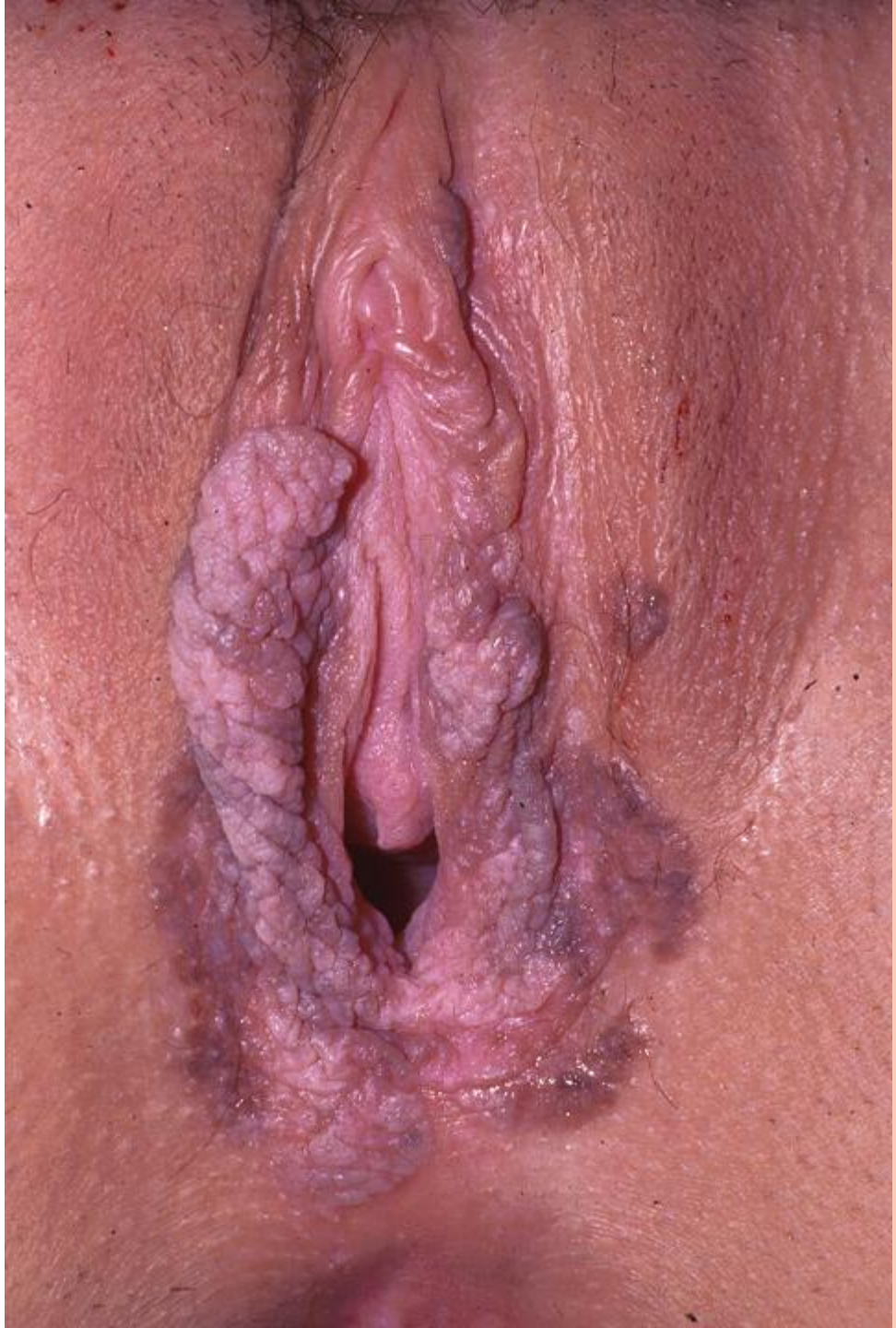
Occurs in 30-50% of cases of VIN

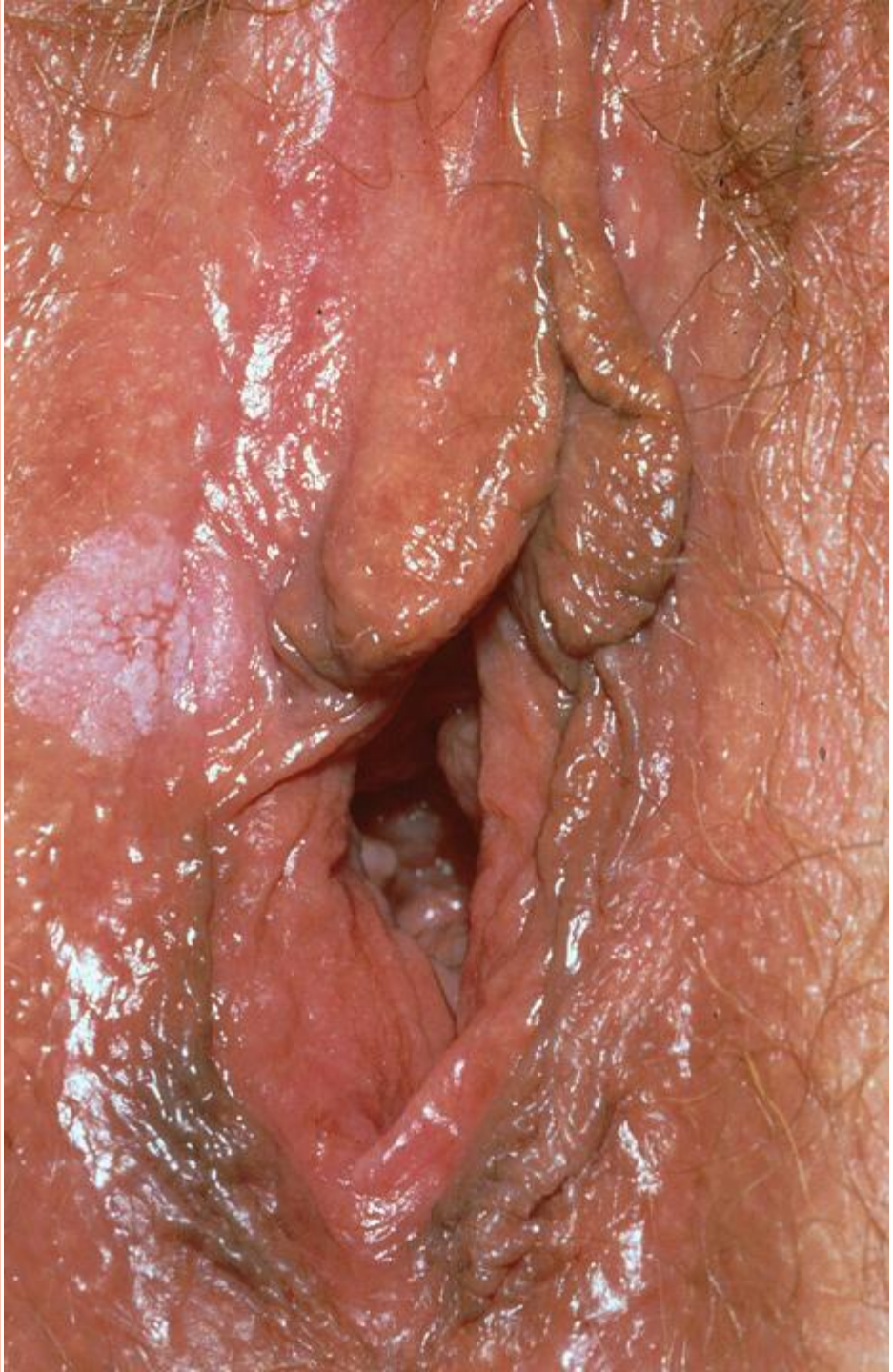
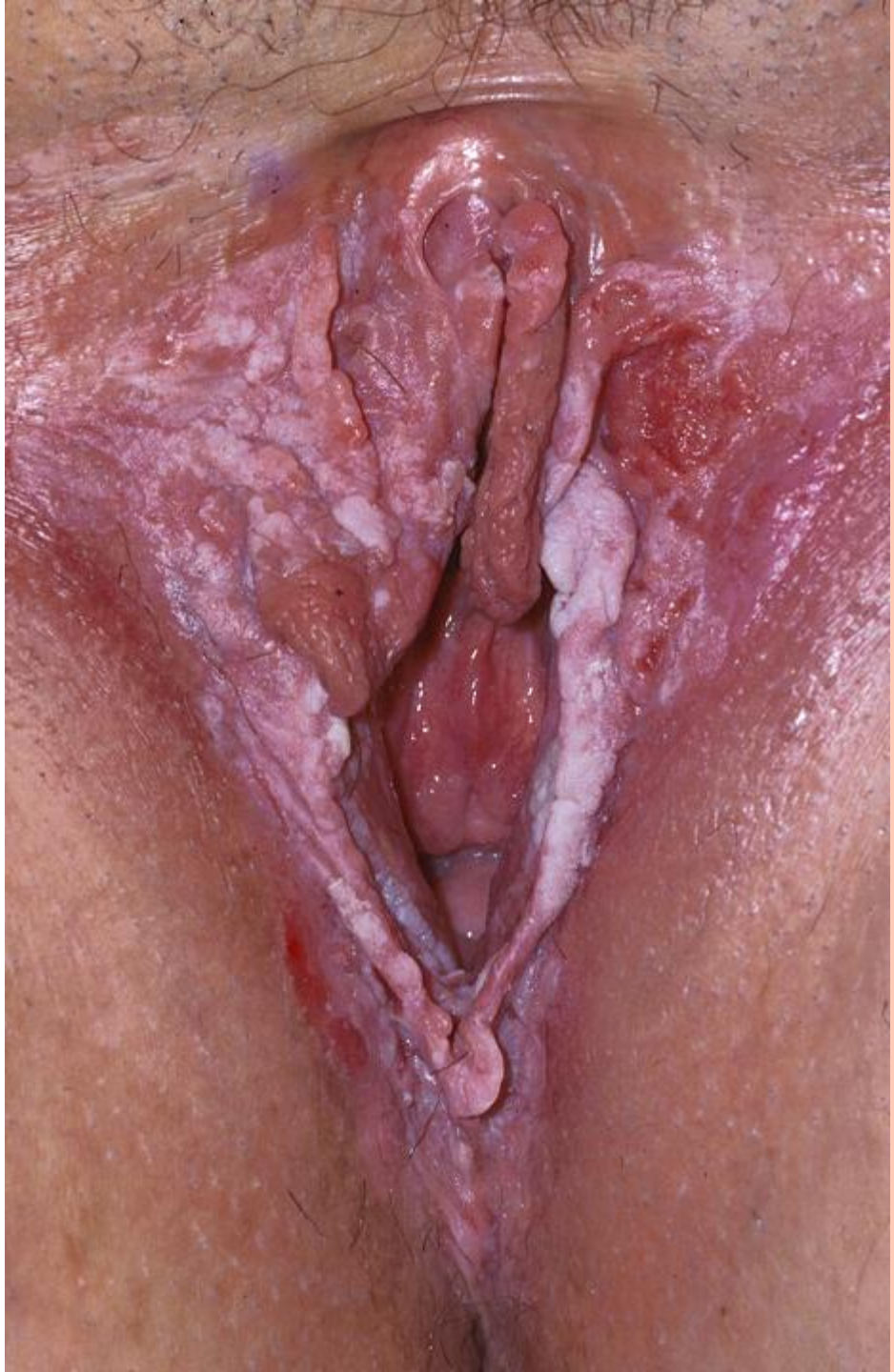
VIN

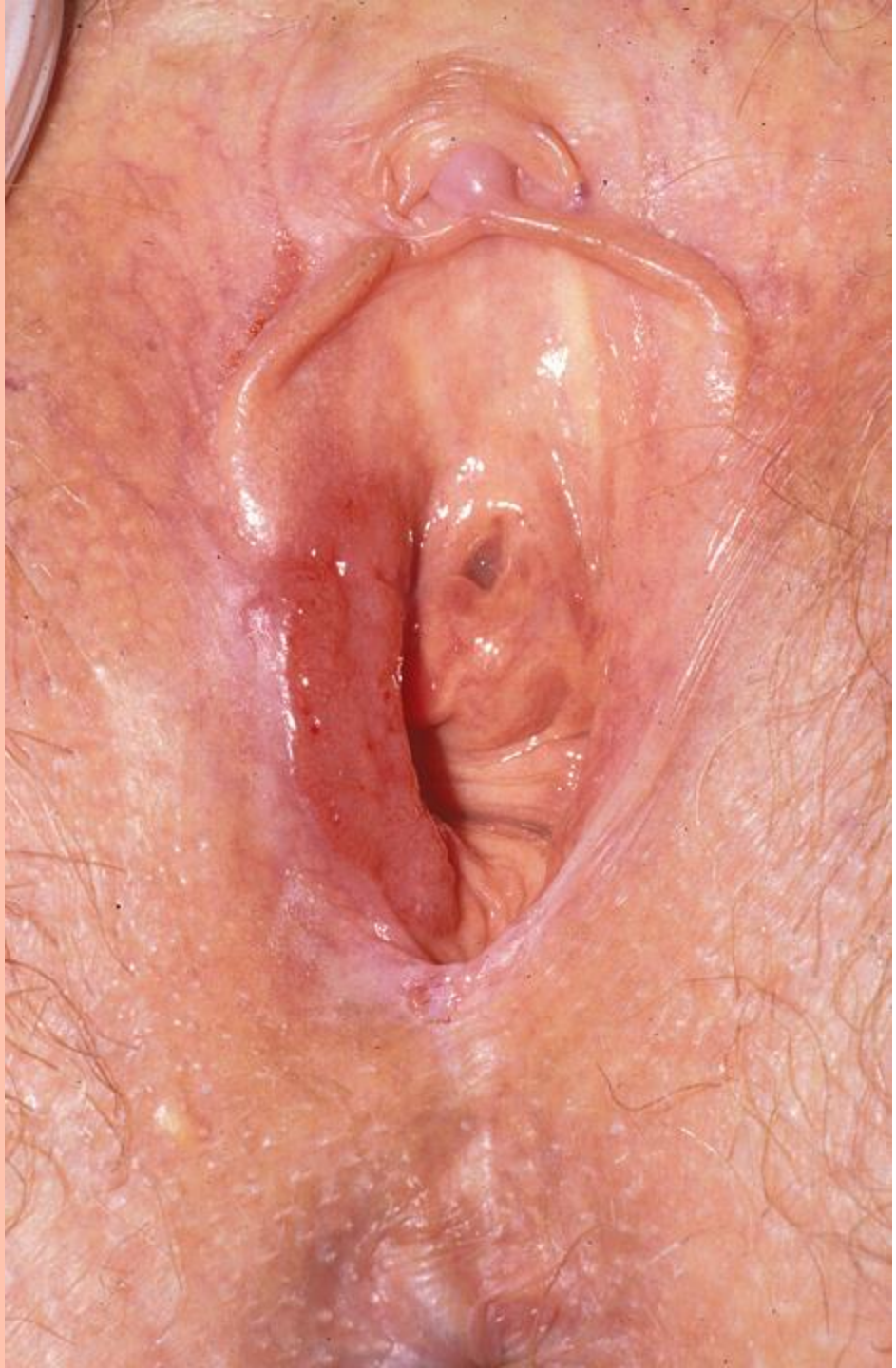
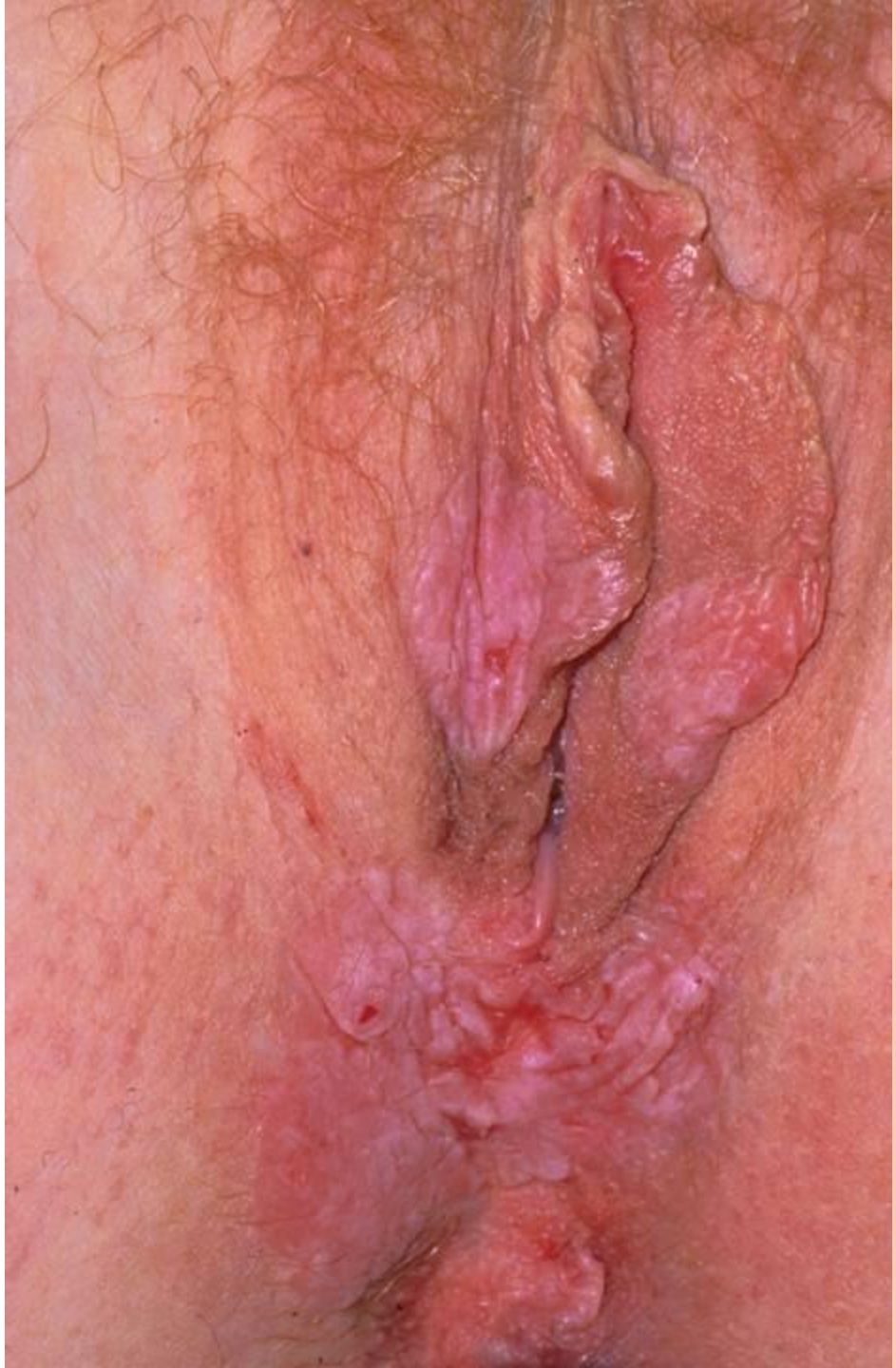
- Spontaneously regress
- Persist unchanged indefinitely
- Progress to invasive cancer

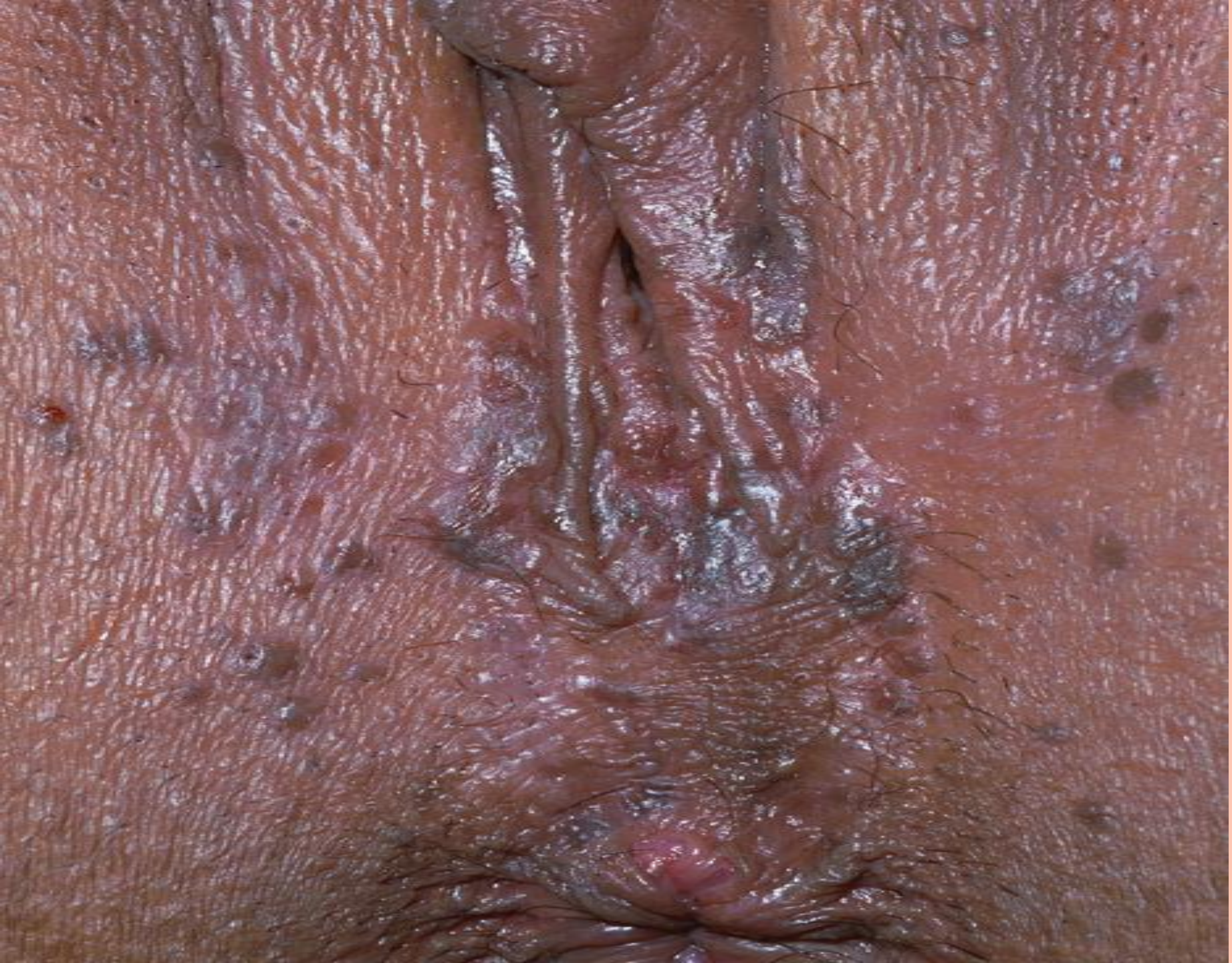
Heterogeneous clinical features VIN

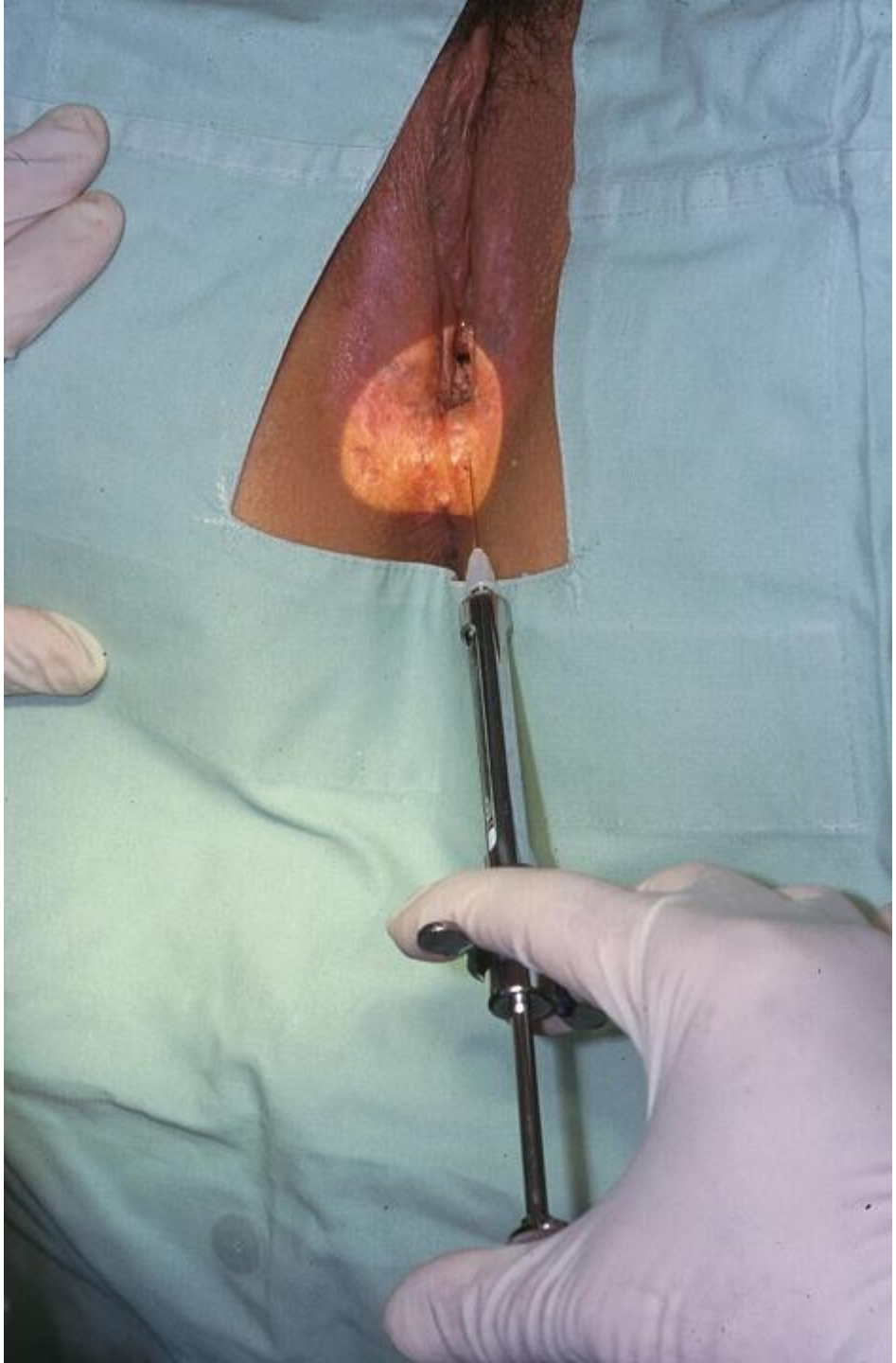
- Unifocal or multifocal
- Flat or Papular
- Red, White, Pigmented
- May involve perianal or urethral skin

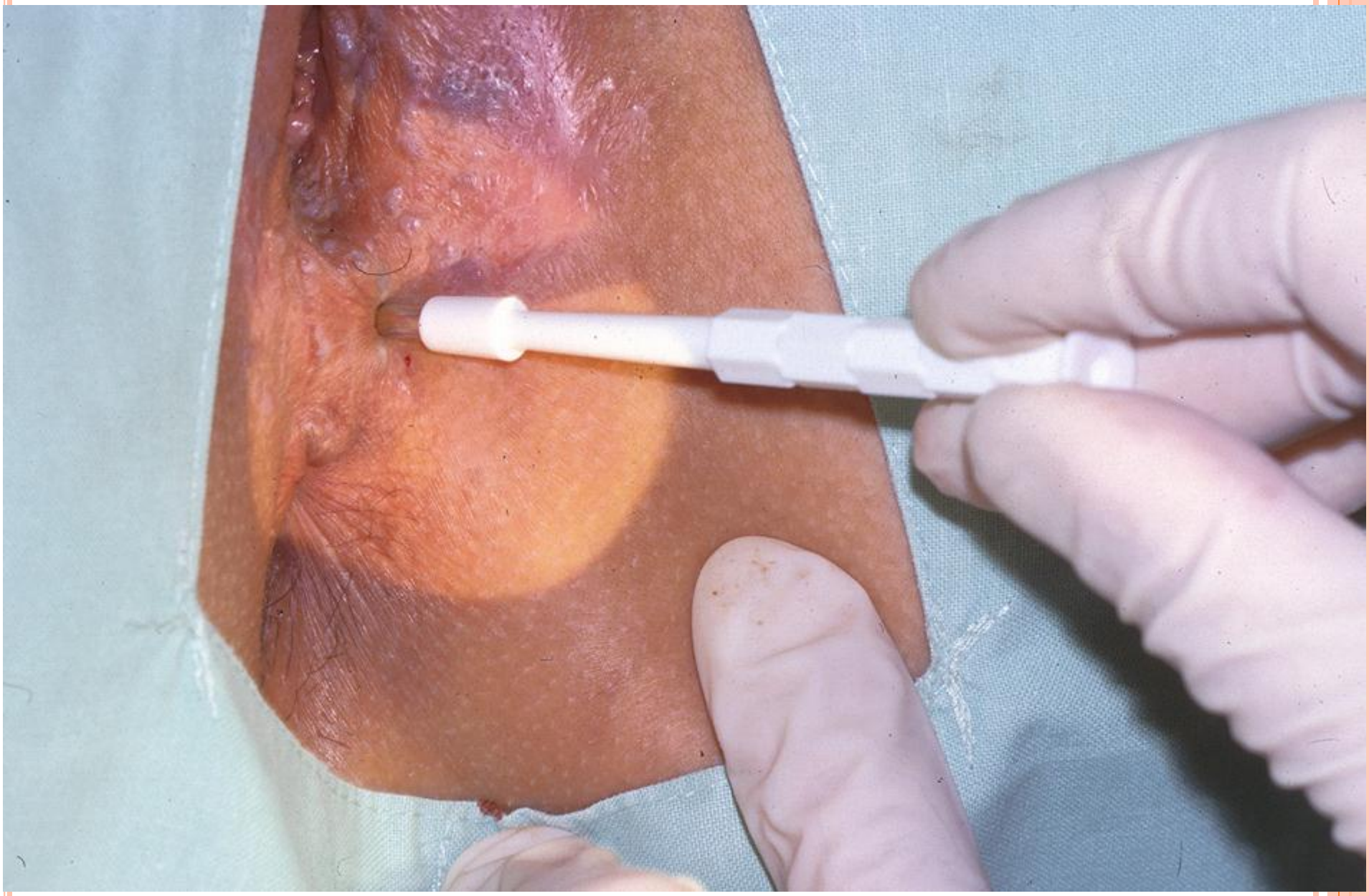



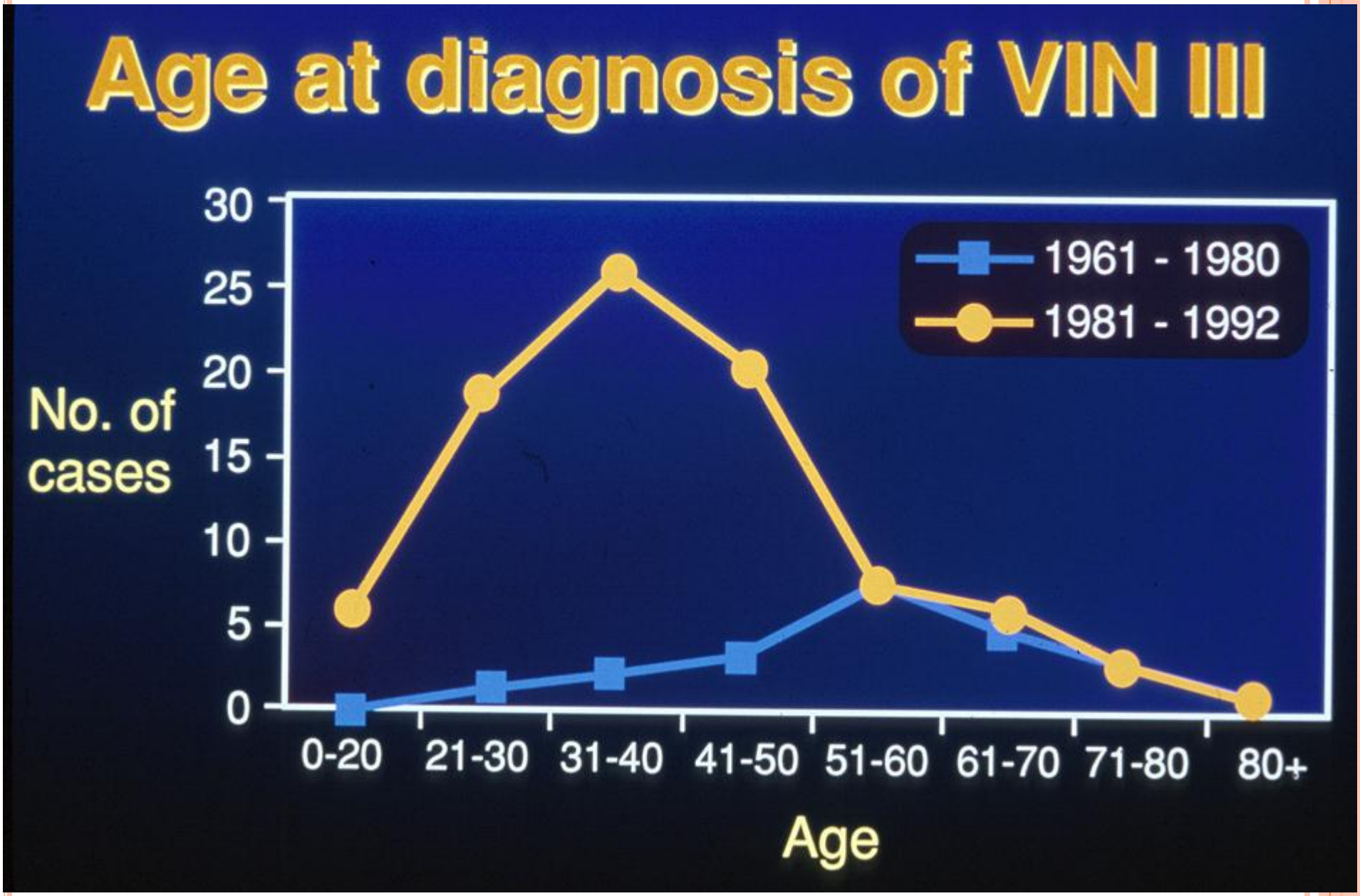






VIN 3. "Missed" (occult) Invasion on Vulvar Biopsy

	%
Chafe et al. Gynecol Oncol 1988; **31**: 154	18
Herod et al. Br J Obstet Gynaecol 1996; **103**: 453	16
Modesitt et al. Obstet Gynecol 1998; **92**: 962	23
Husseinzadeh et al. Gynecol Oncol 1999; **73**: 119	20


Age at diagnosis of VIN III
No. of cases
30
25
20
15
10
5
0
1961 - 1980
1981 - 1992
0-20
21-30
31-40
41-50
51-60
61-70
71-80
80+
Age

Invasive potential of VIN is both unclear and contentious

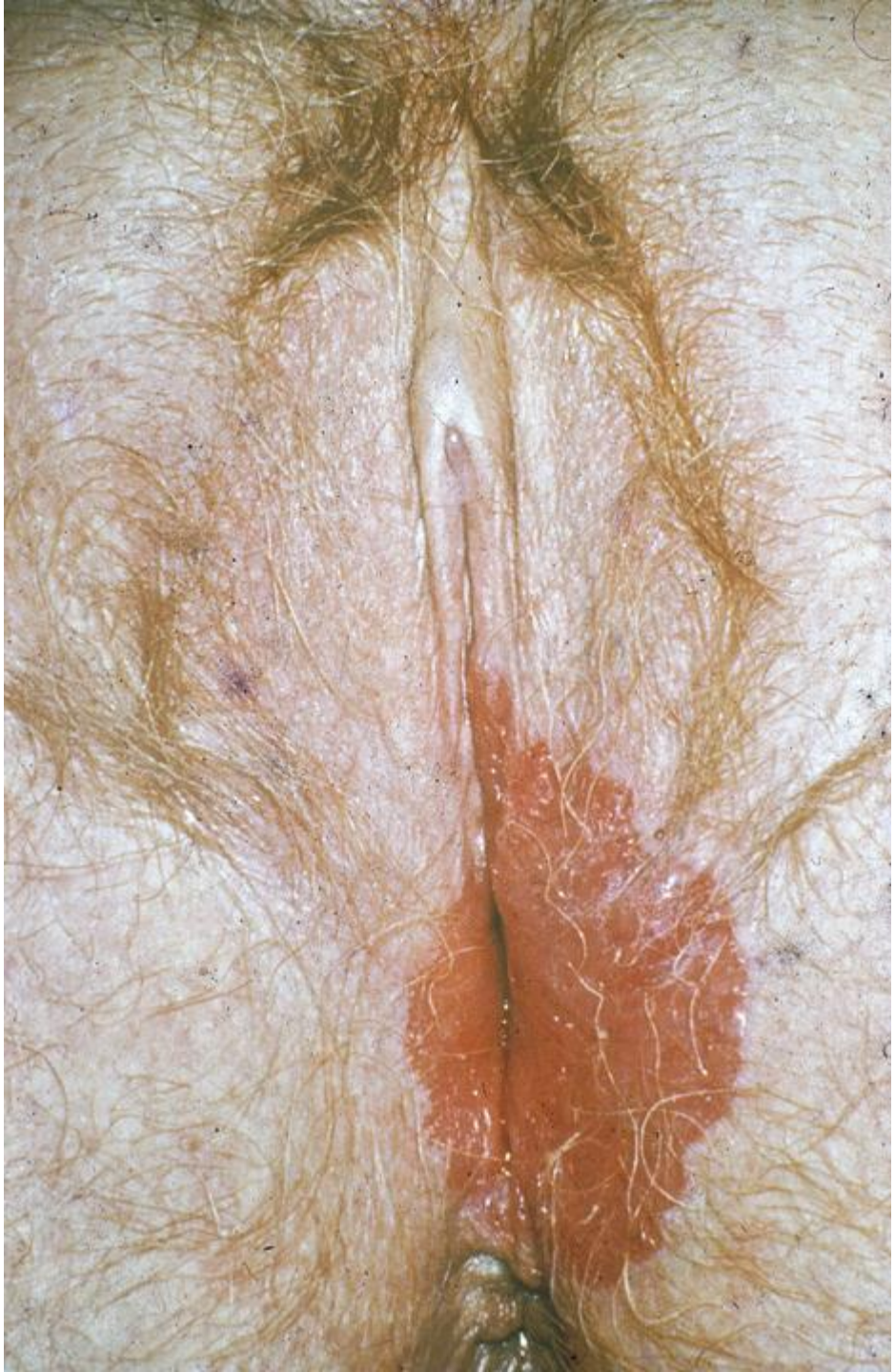
- LITERATURE FAILS TO CLEARLY ACKNOWLEDGE THE EFFECT OF TREATMENT ON THE NATURAL HISTORY OF THE DISEASE

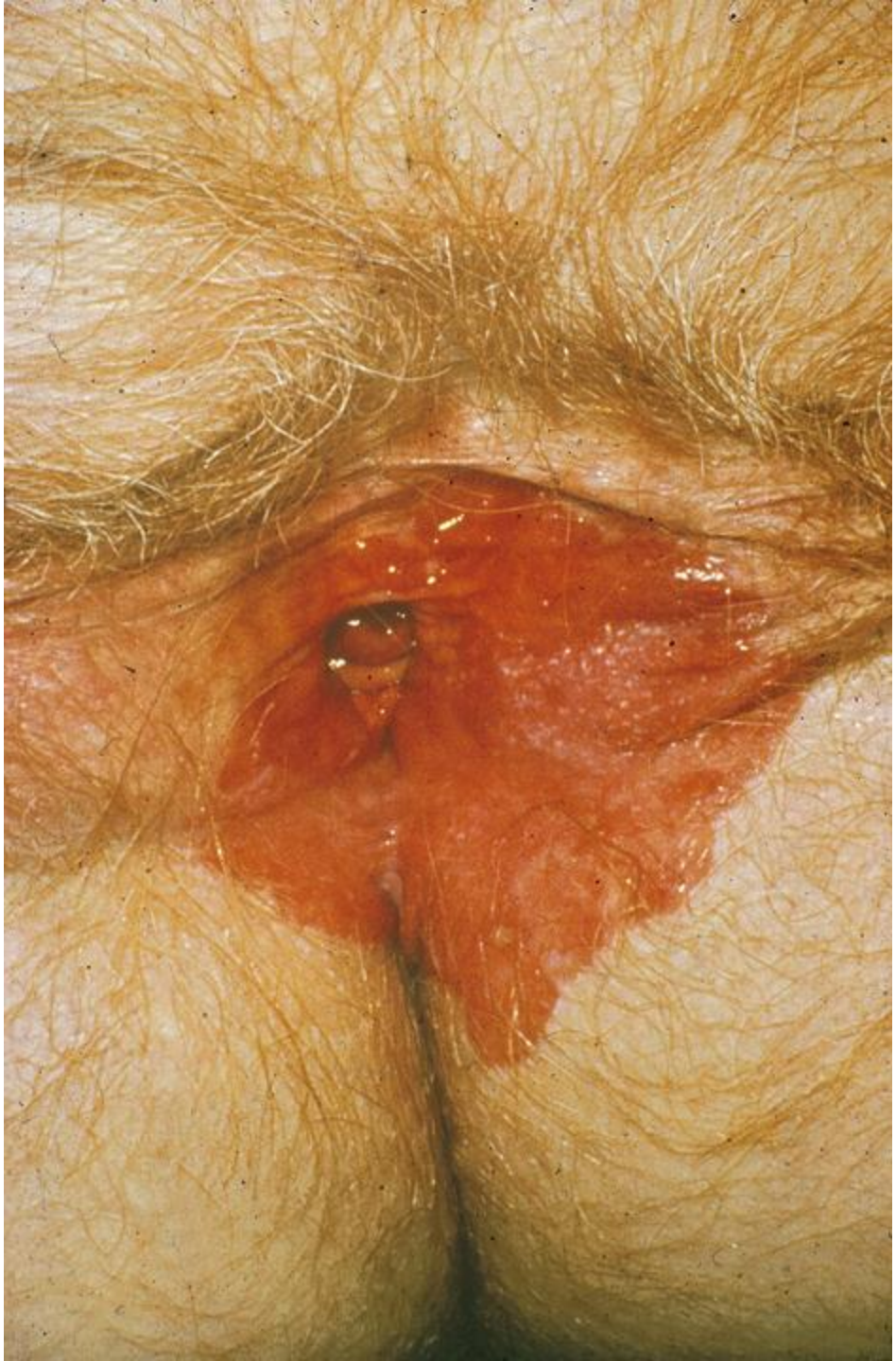
VIN 3

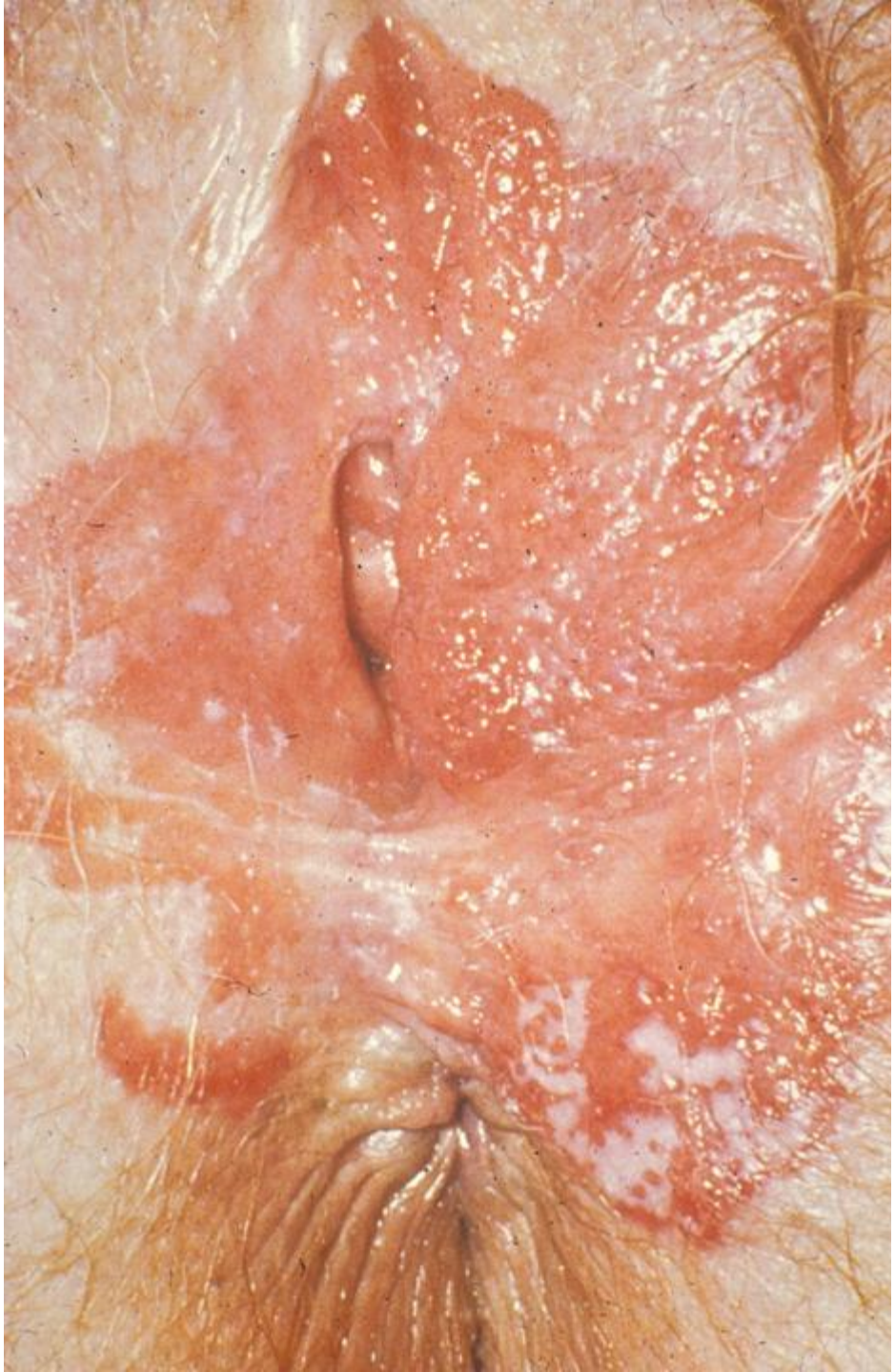
113

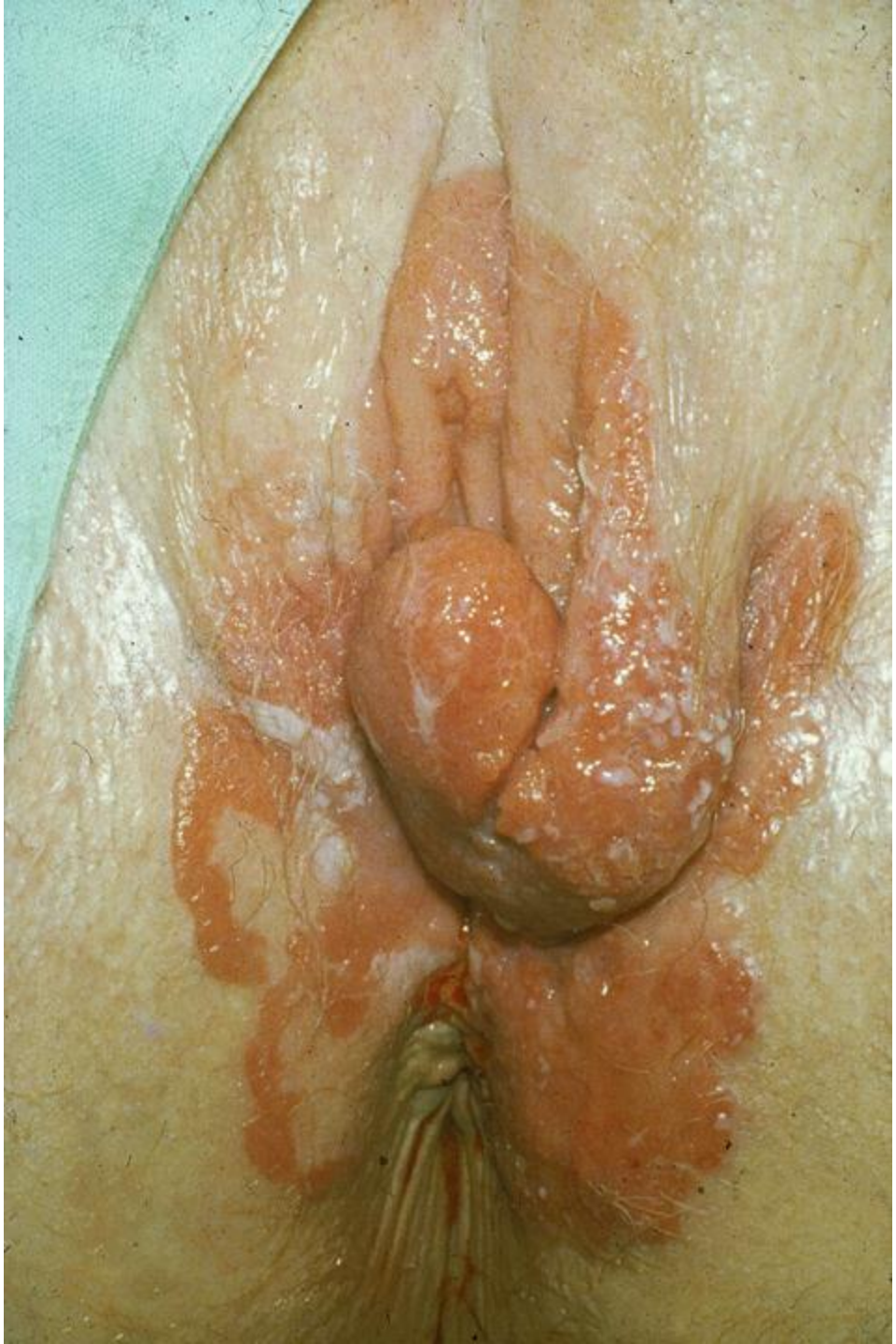
Treated 105	Invasive vulvar cancer	Untreated 8
4 (3.8%)		7 (87.5%) 1 spont. regression

Jones RW, Rowan DM
Obstet Gynecol 1994; 84:741

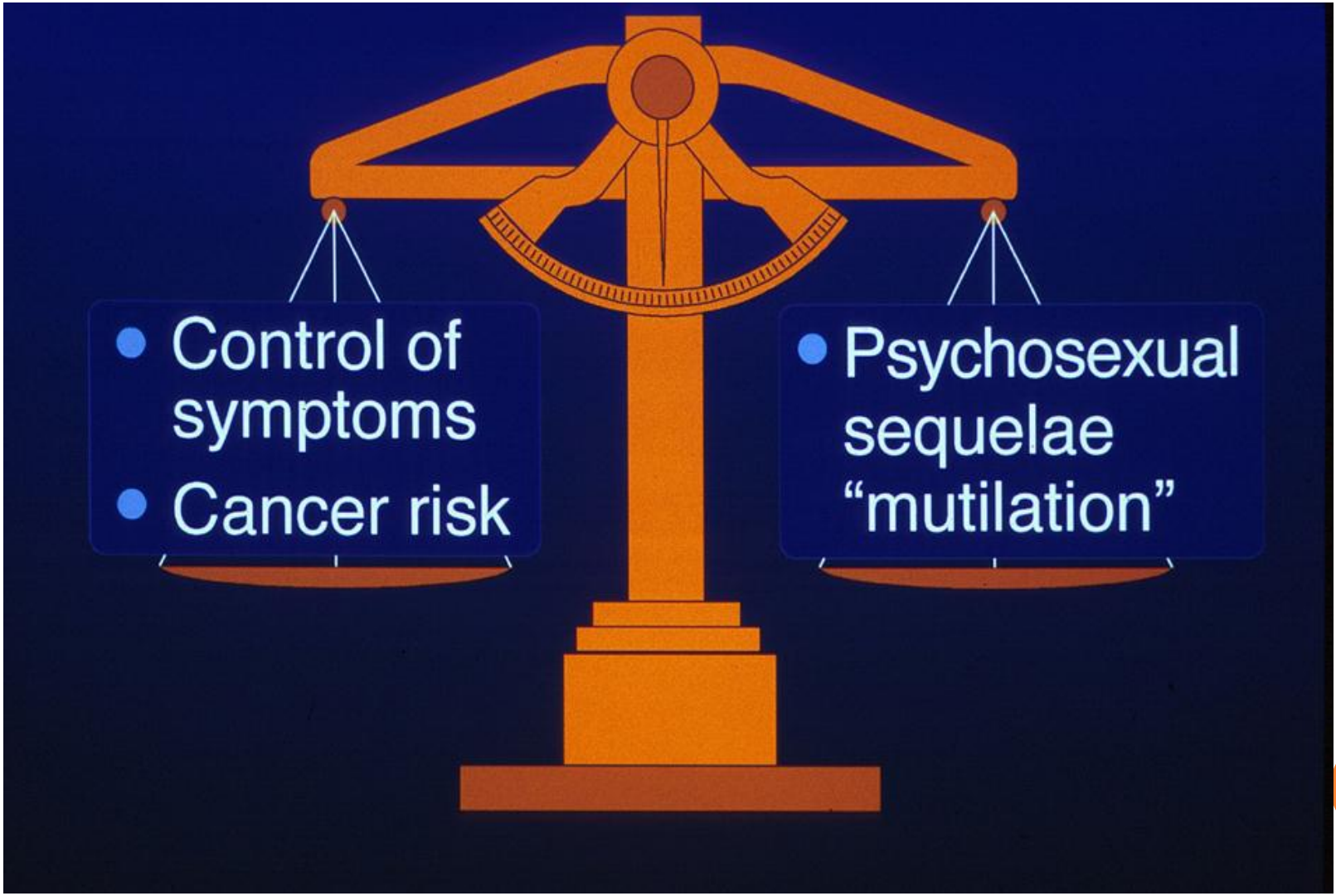








TREATMENT


Control of symptoms
Cancer risk
Psychosexual sequelae "mutilation"

VIN Management

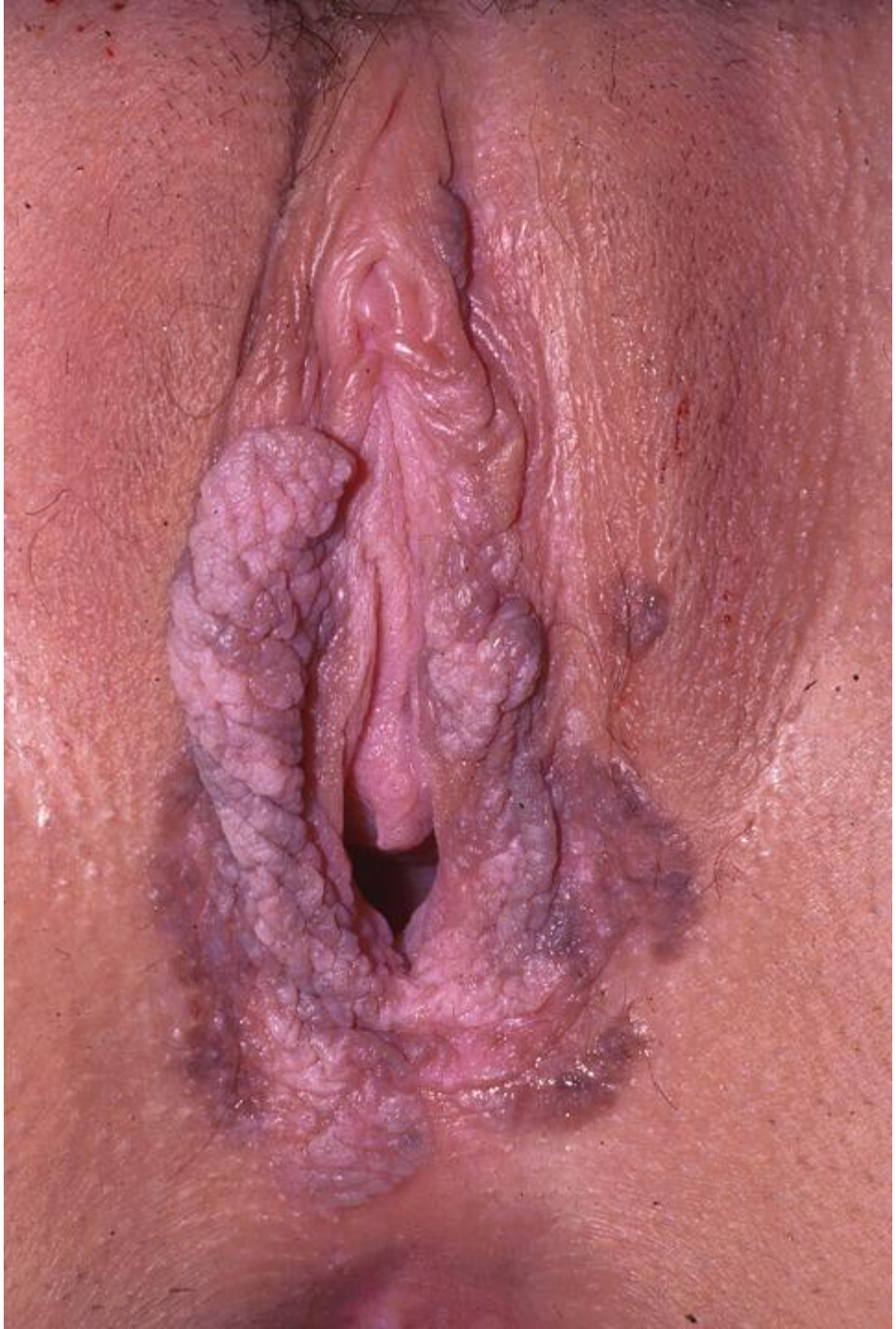
- Observation
- Surgery/Laser
- Medical
- Immunotherapy

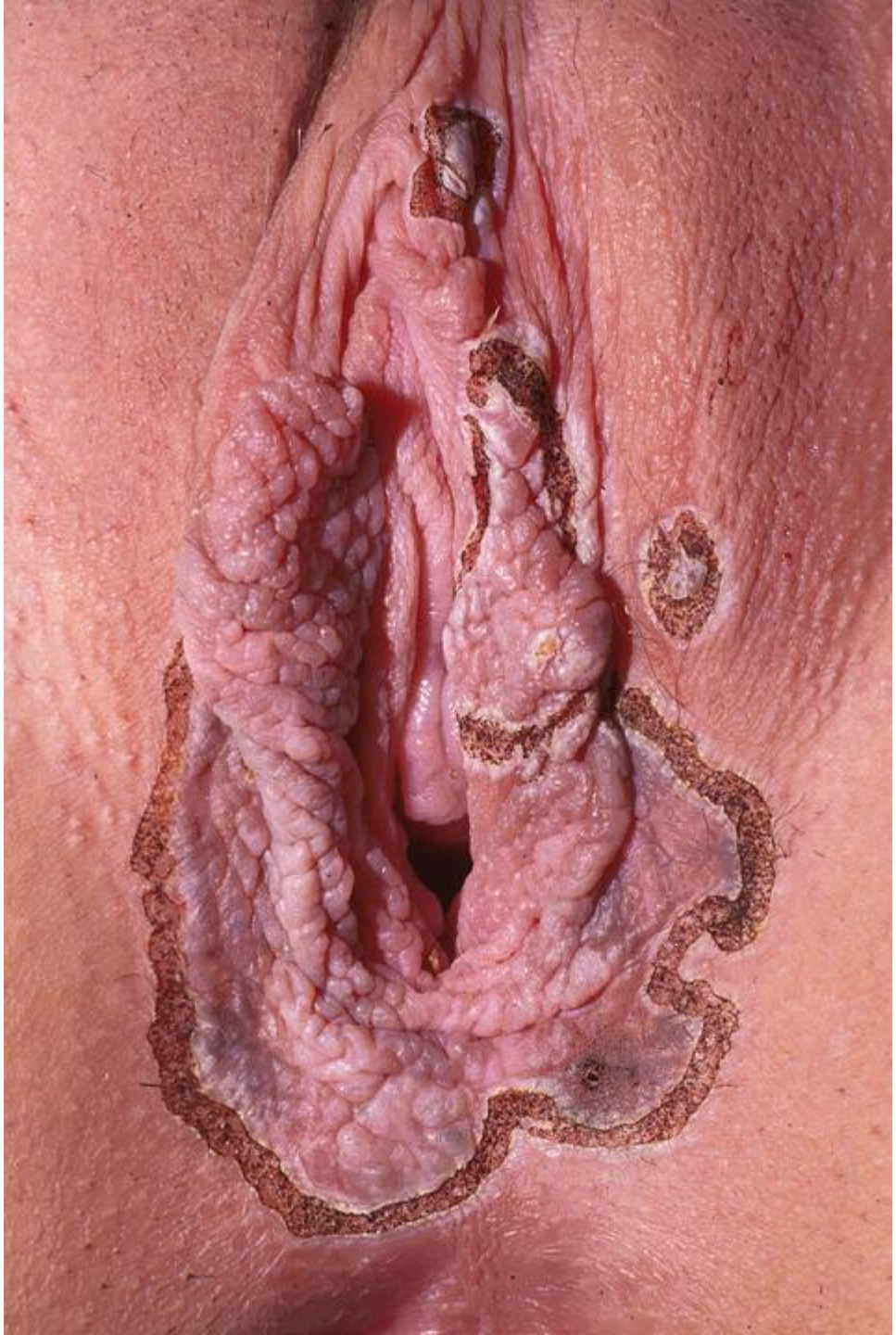
- EXCISIONAL THERAPY ALLOWS FOR HISTOLOGY
- SHOULD BE GOLD STANDARD

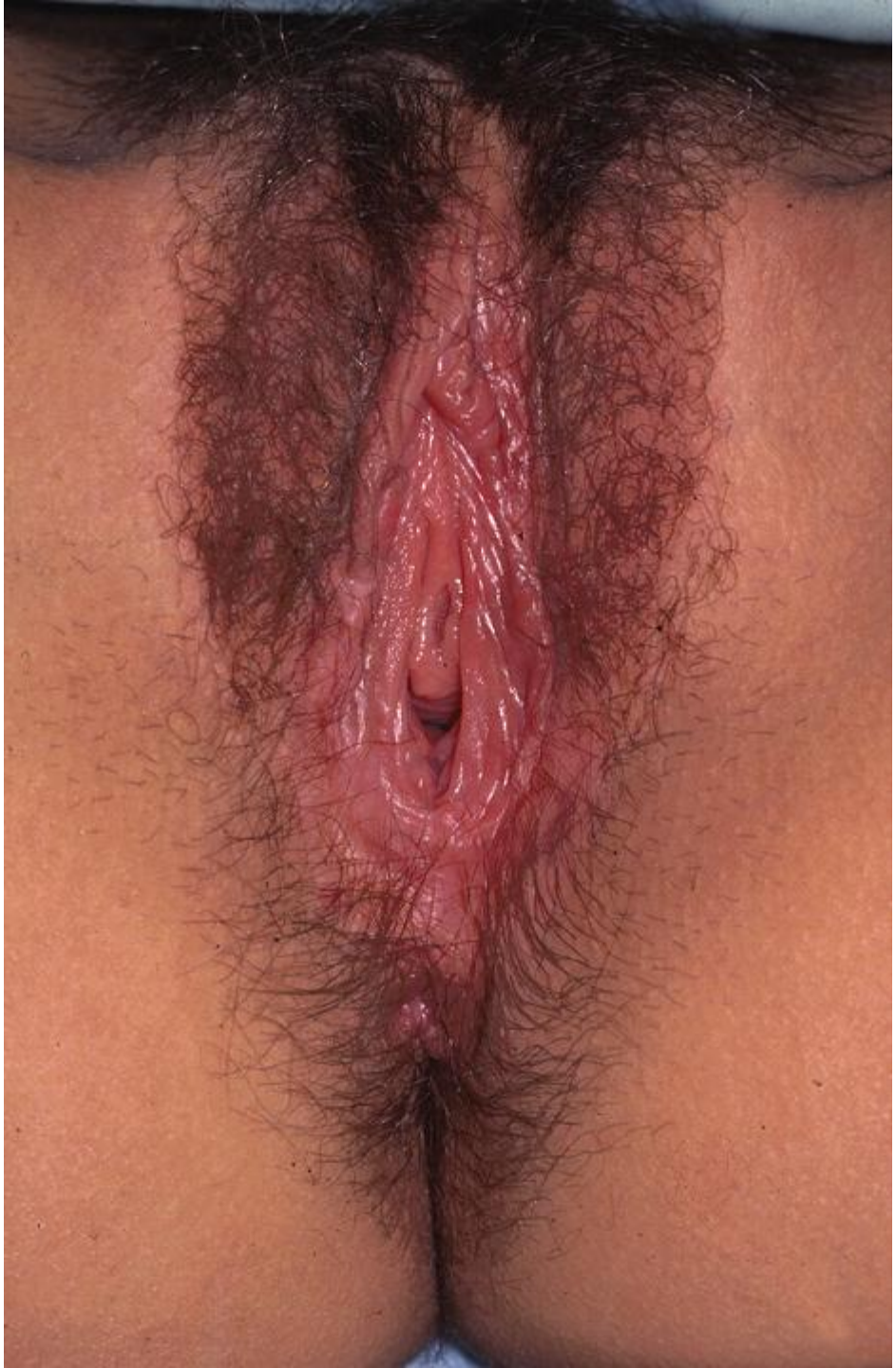
LASER AND VIN

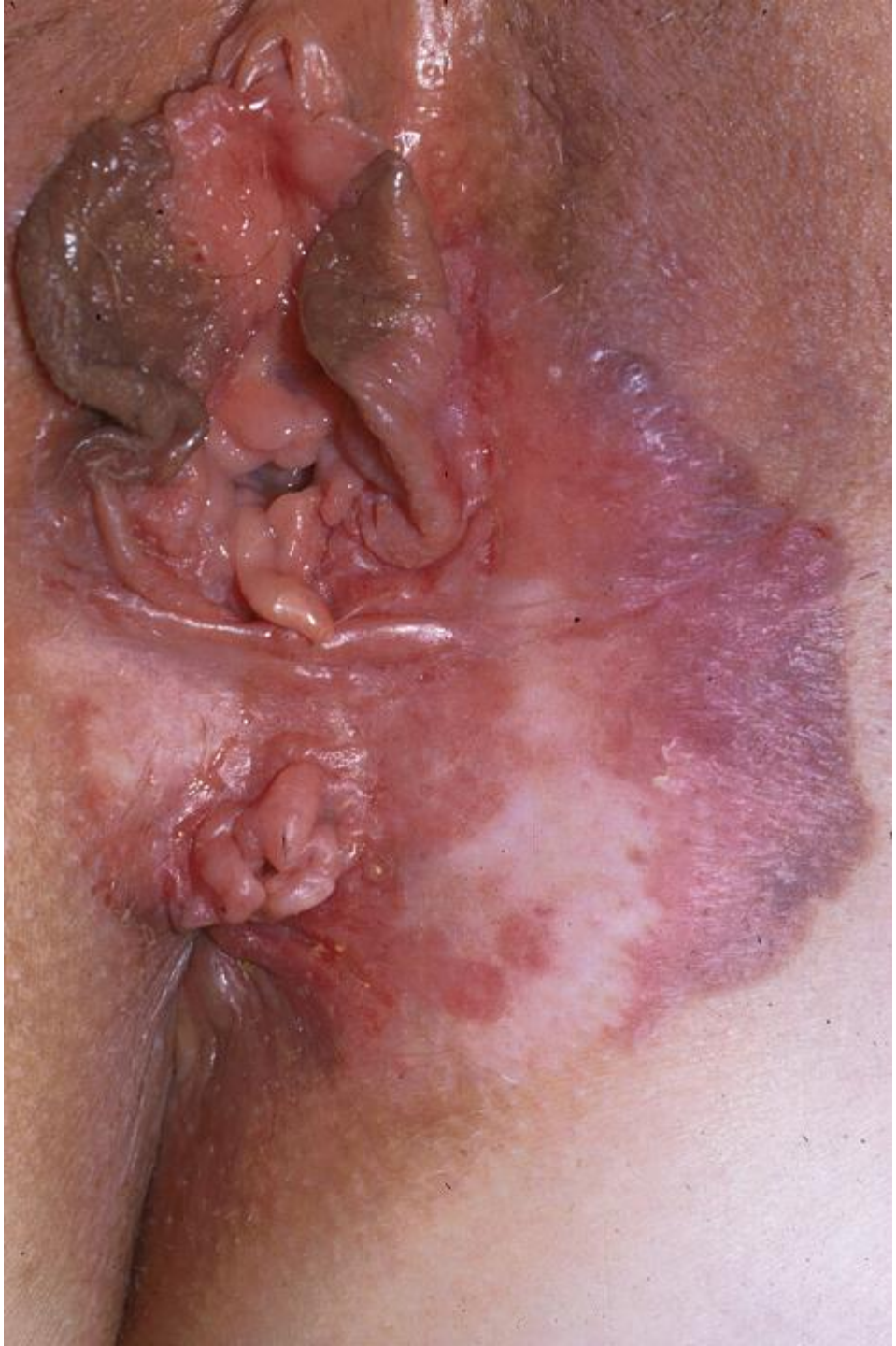
- Excellent results in young women with extensive multifocal disease

- Knowledge and skill of operator essential









Recurrences of VIN

- 30%+ of cases
- either - persistent disease
  (incomplete treatment)
  or - “new” disease
  (field effect”)

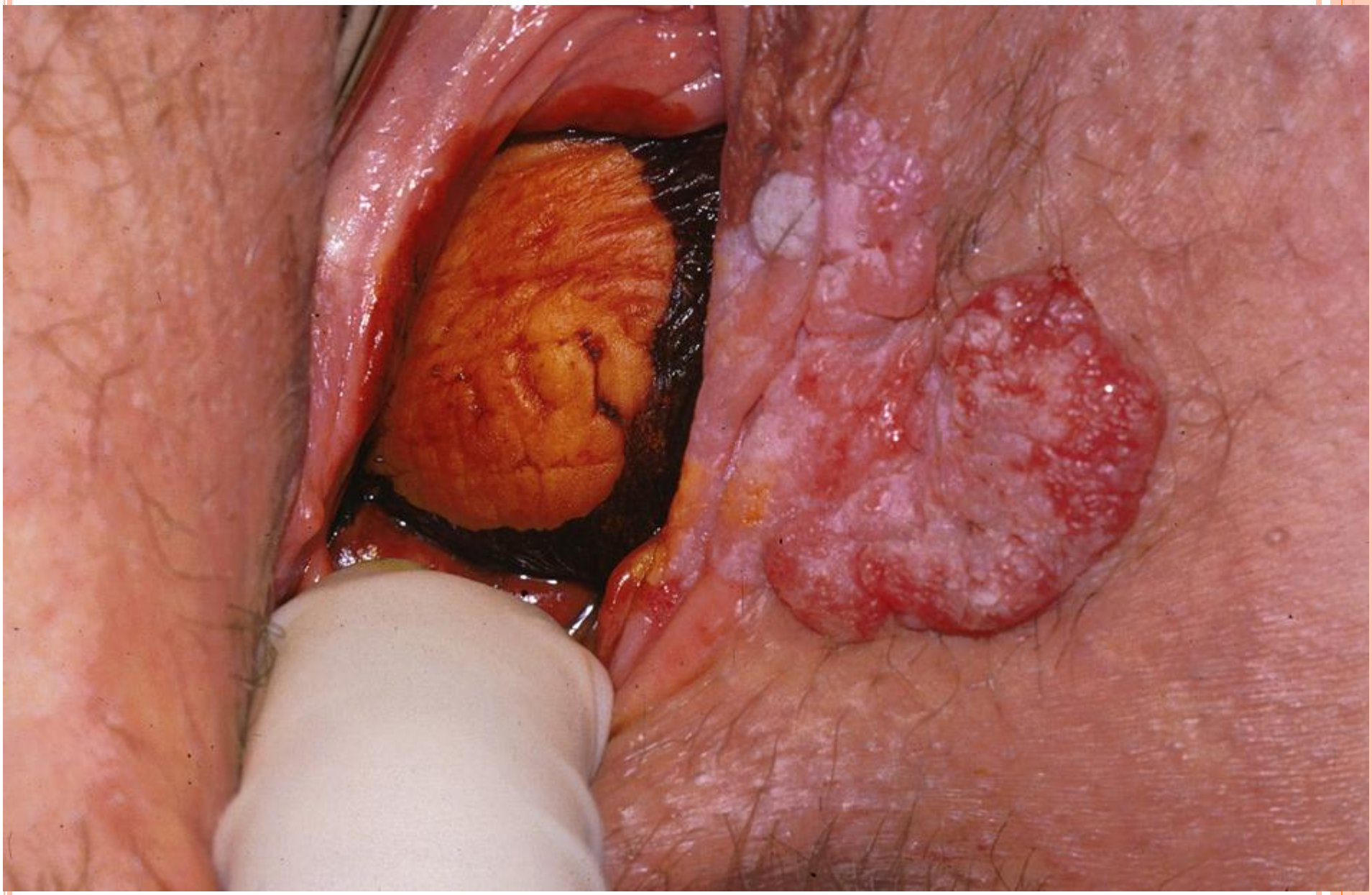
VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN)

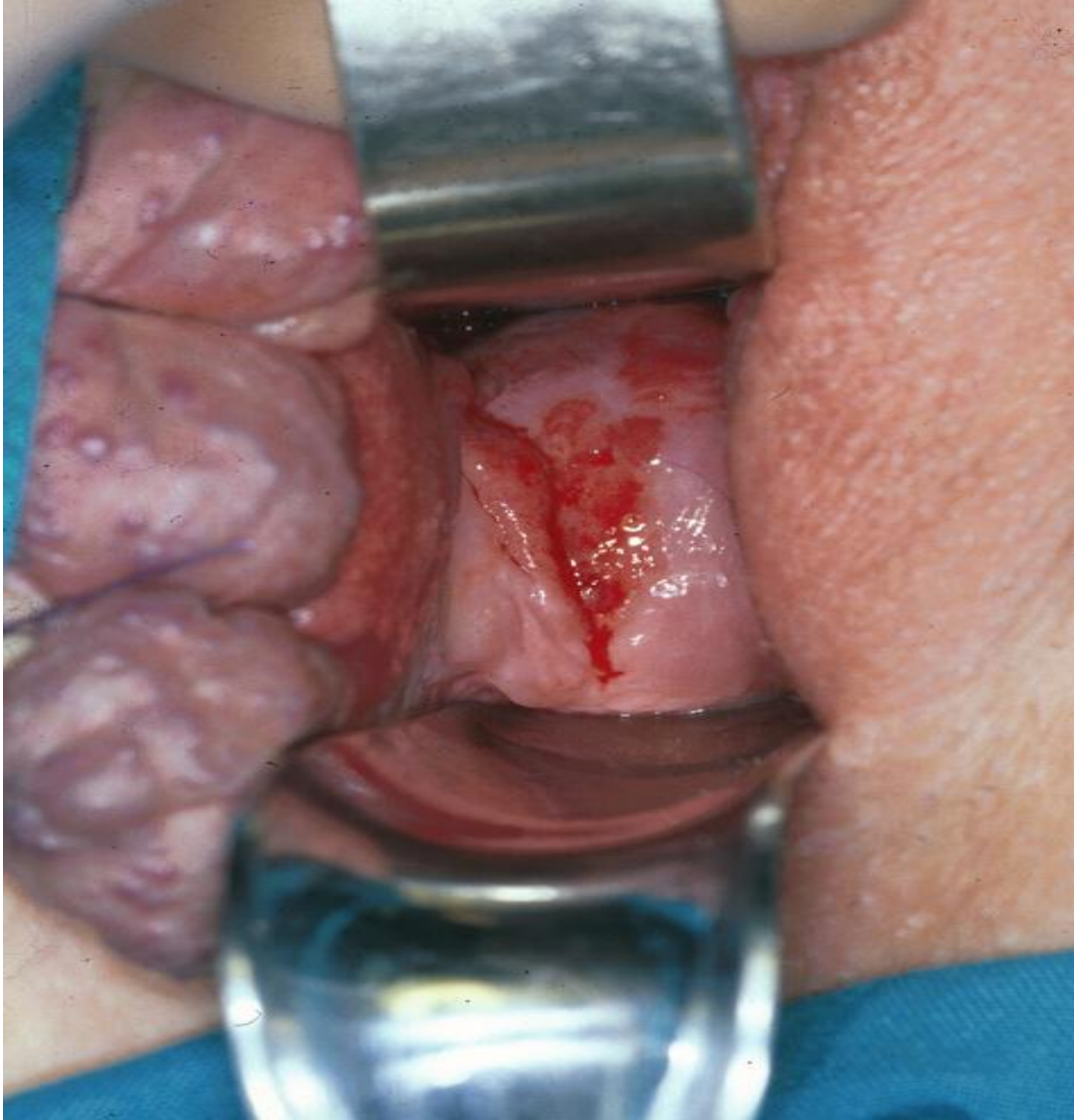
HIGH GRADE VAIN

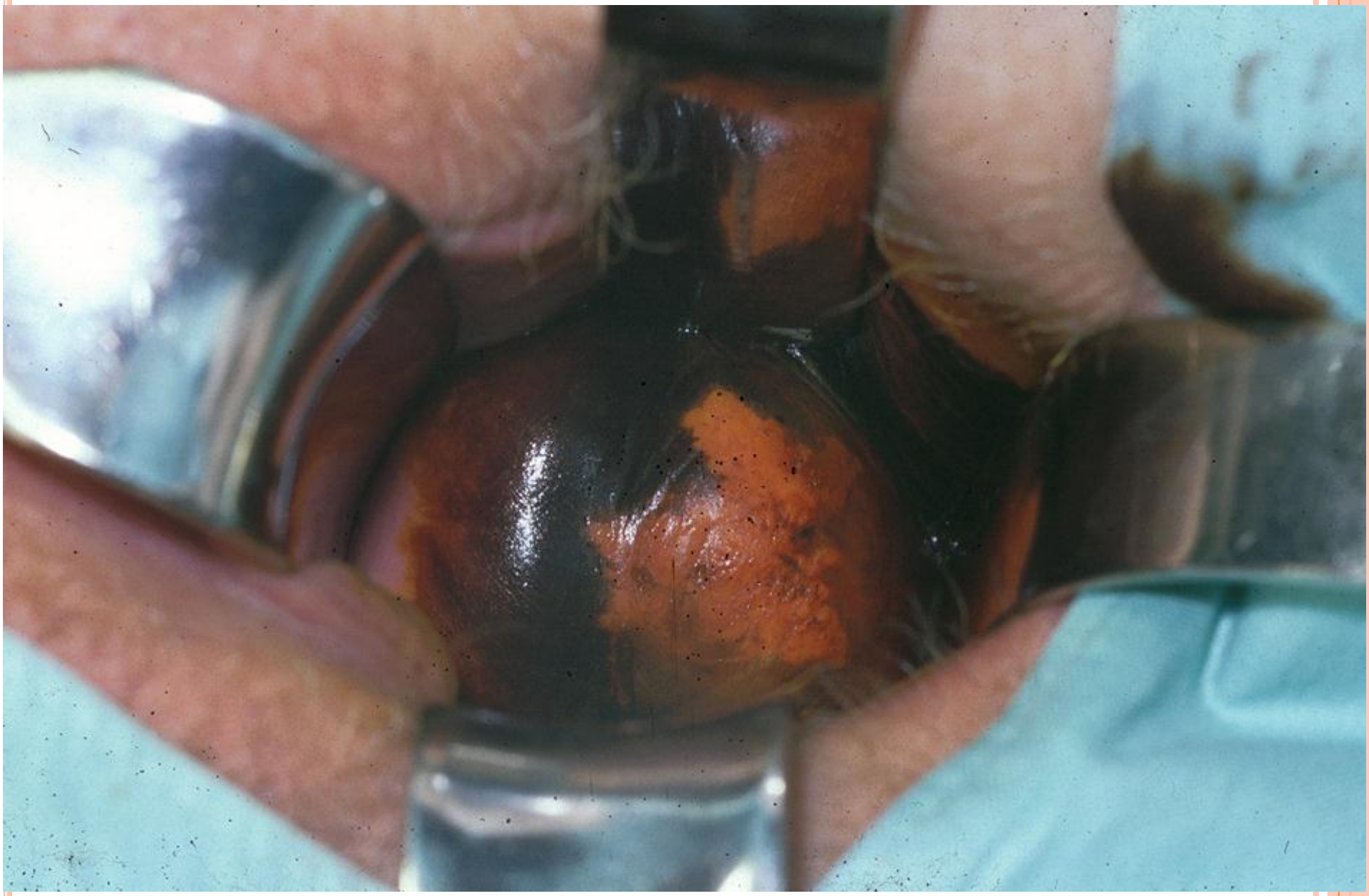
- Premalignant
- Incidence increasing, age of diagnosis decreased
- Rarity of vaginal cancer (1-2% of female genital tract cancers) suggest malignant potential is low
- In association with CIN3 (3%) or as primary lesion
- Involves upper 1/3 vagina in >70% of cases

DIAGNOSIS

- Colposcopy and biopsy
- **High Grade VAIN has colposcopic appearance similar to High Grade CIN**
- **Exam after aqeous Iodine**







TREATMENT

SURGICAL EXCISION

- **Lesion**
- **Vault**
- **Partial /total vaginectomy**

Access is difficult

Proximity to vital organs

30% can have occult cancers

TREATMENT

Radiotherapy

- Irradiate vagina using applicators
- Co morbidities/ difficult surgical access
- Morbidity

Bowel symptoms-proctitis

Bladder symptoms- cystitis

Vaginal stenosis

TREATMENT

Laser treatment

- Superficial treatment to 2-3mm to depth of lamina propia
- Delayed healing and scarring occurs with over enthusiastic treatment-→ problems in follow up and sexual function
- Young patients ,reliable follow up

TREATMENT :CHEMICAL

- **5-fluorouracil cream**
  - intravaginal 1/4 applicator
  - daily - > 2x per week
- **Overall cure rate**

  -Rome 45% (5/11)

  4 of those cured had previously received RT

  -Murta et al 63%(10/16)

Treatment:Immunological

- **5% imiquimod**
  - Studies usually small numbers, short follow-up, dubious end-points

  Buck and Guth (2003), Haidopoulos et al (2005)

Imiquimod effect is "non-permanent"

May also have a role in difficult cases


JUST...JUST STOP
Because the more you talk, the stupider you sound.
ICANHASCHEEZBURGER.COM