I tumori femminili: dal gene profiling alla terapia personalizzata

Casale M.to, 22-23 Novembre 2023

Trattamento delle CIN 3

M. Barbero, A. Villasco

S.C. Ginecologia e Ostetricia – ASL AT

NUOVI CASI STIMATI DI NEOPLASIE IN ITALIA NEL 2020

- 377.000 NUOVE NEOPLASIE

  - CORPO DELL'UTERO: 8335
  - OVAIO: 5179

- CERVICE: 2365

American Journal of Obstetrics and Gynecology

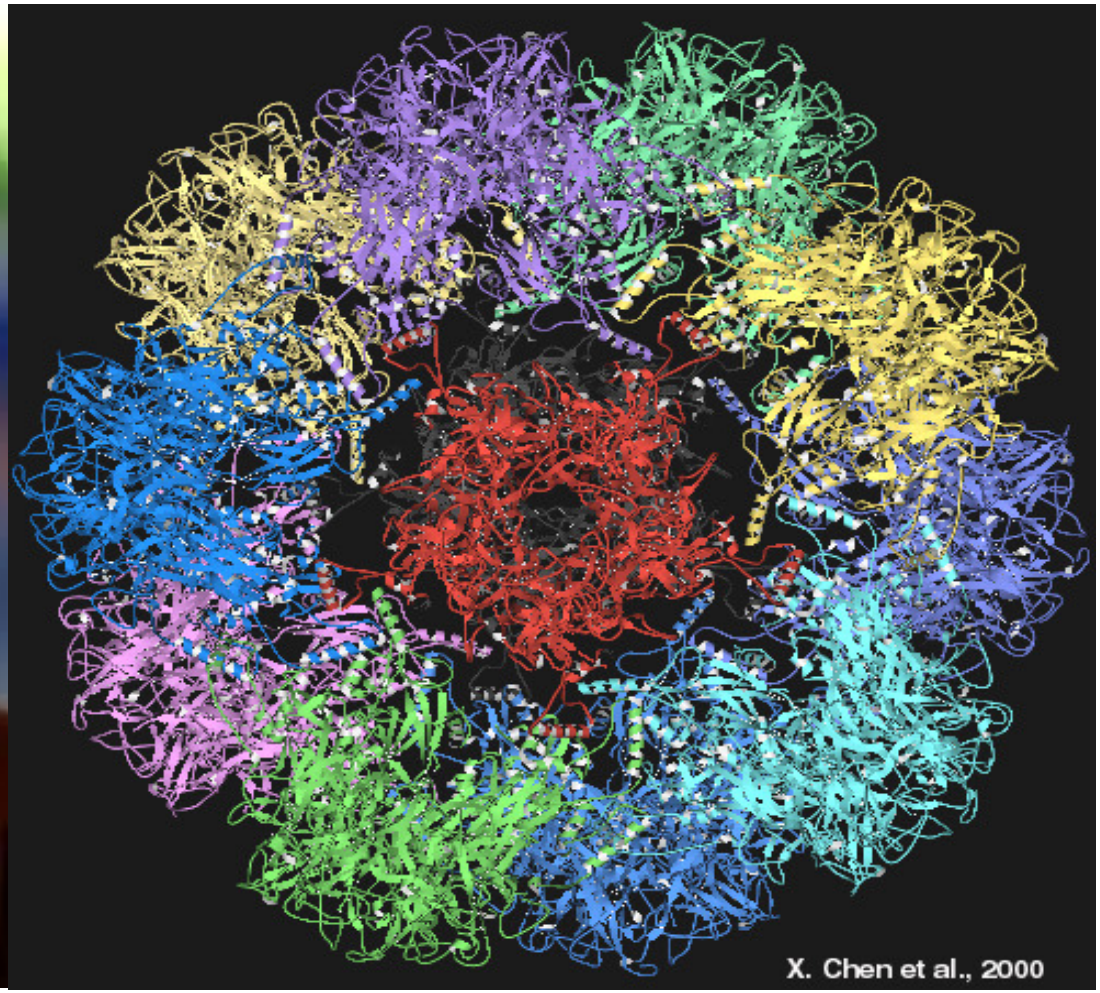
VOL. 42 AUGUST, 1941 NO. 2

Original Communications

THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS*

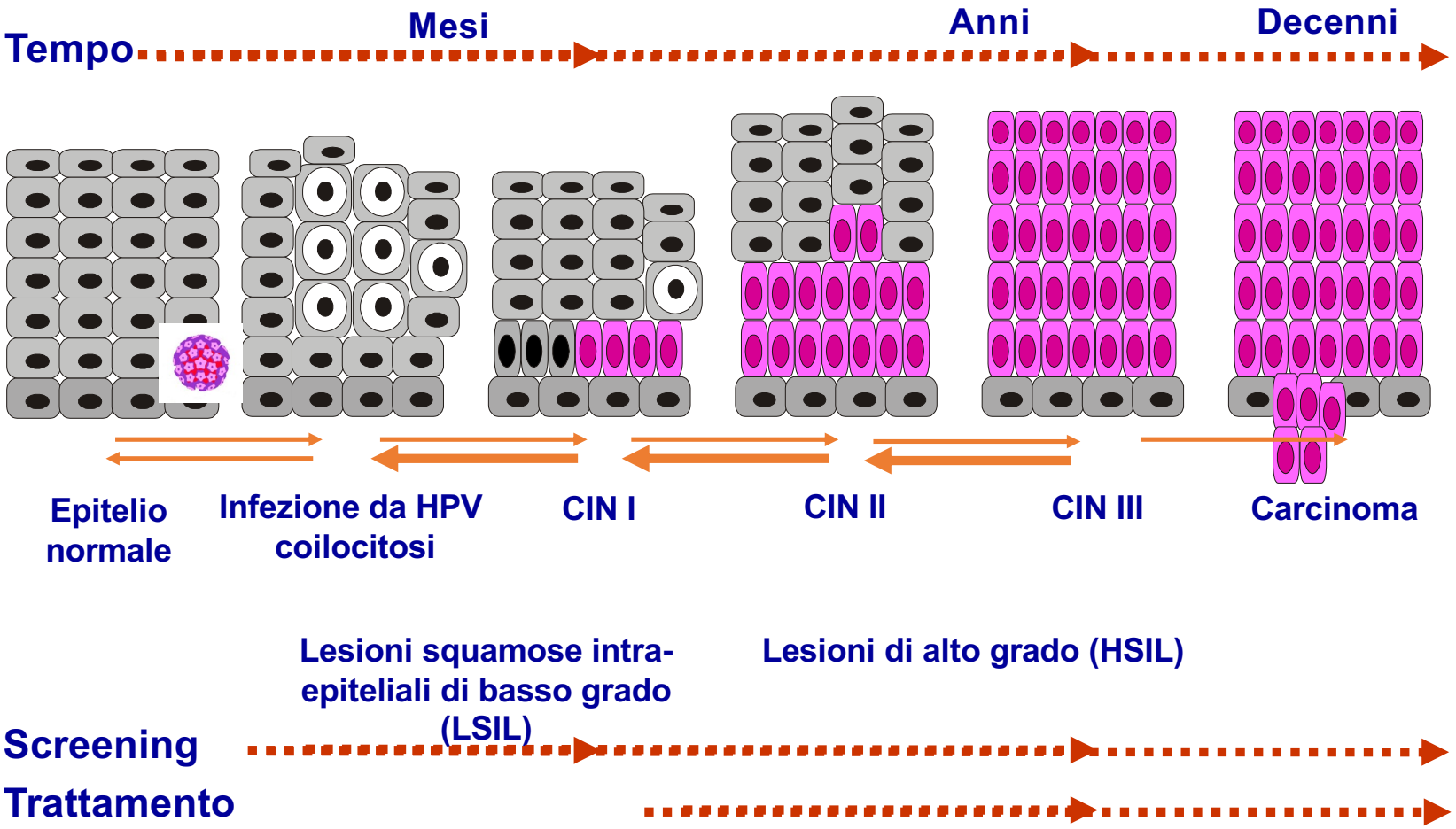
GEORGE N. PAPANICOLAOU, M.D., PH.D., AND HERBERT F. TRAUT, M.D.,
NEW YORK, N. Y.

(From the Departments of Anatomy and of Gynecology and Obstetrics of the Cornell University Medical College and the New York Hospital)

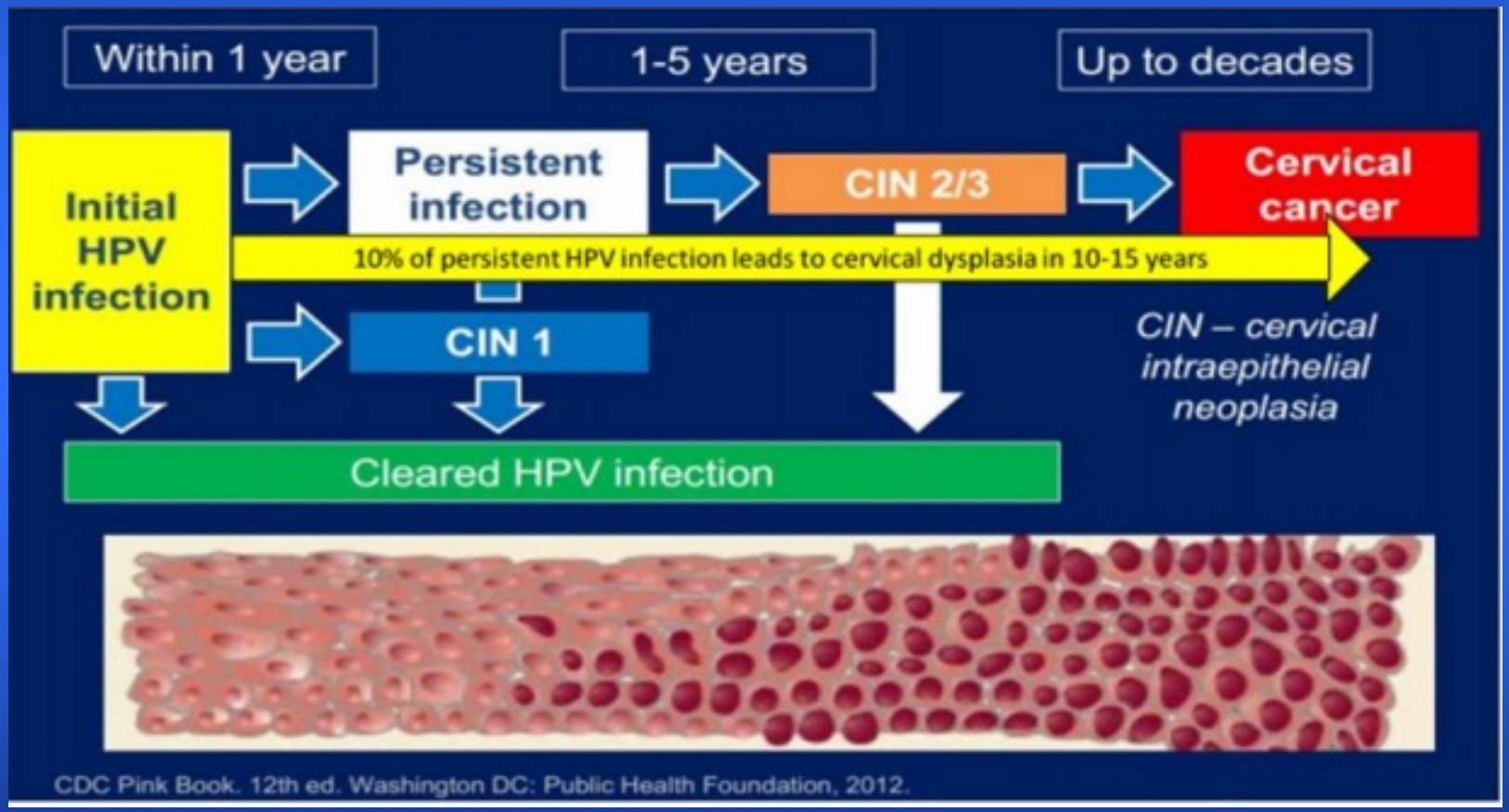


Harald zur Hausen

Progressione della malattia



NATURAL HISTORY OF HPV INFECTION



CDC Pink Book. 12th ed. Washington DC: Public Health Foundation, 2012.

RACCOMANDAZIONI SICPCV 2019

Gestione colposcopica delle lesioni del basso tratto genitale

CAPITOLO 2
Gestione delle lesioni istologiche

SICPCV

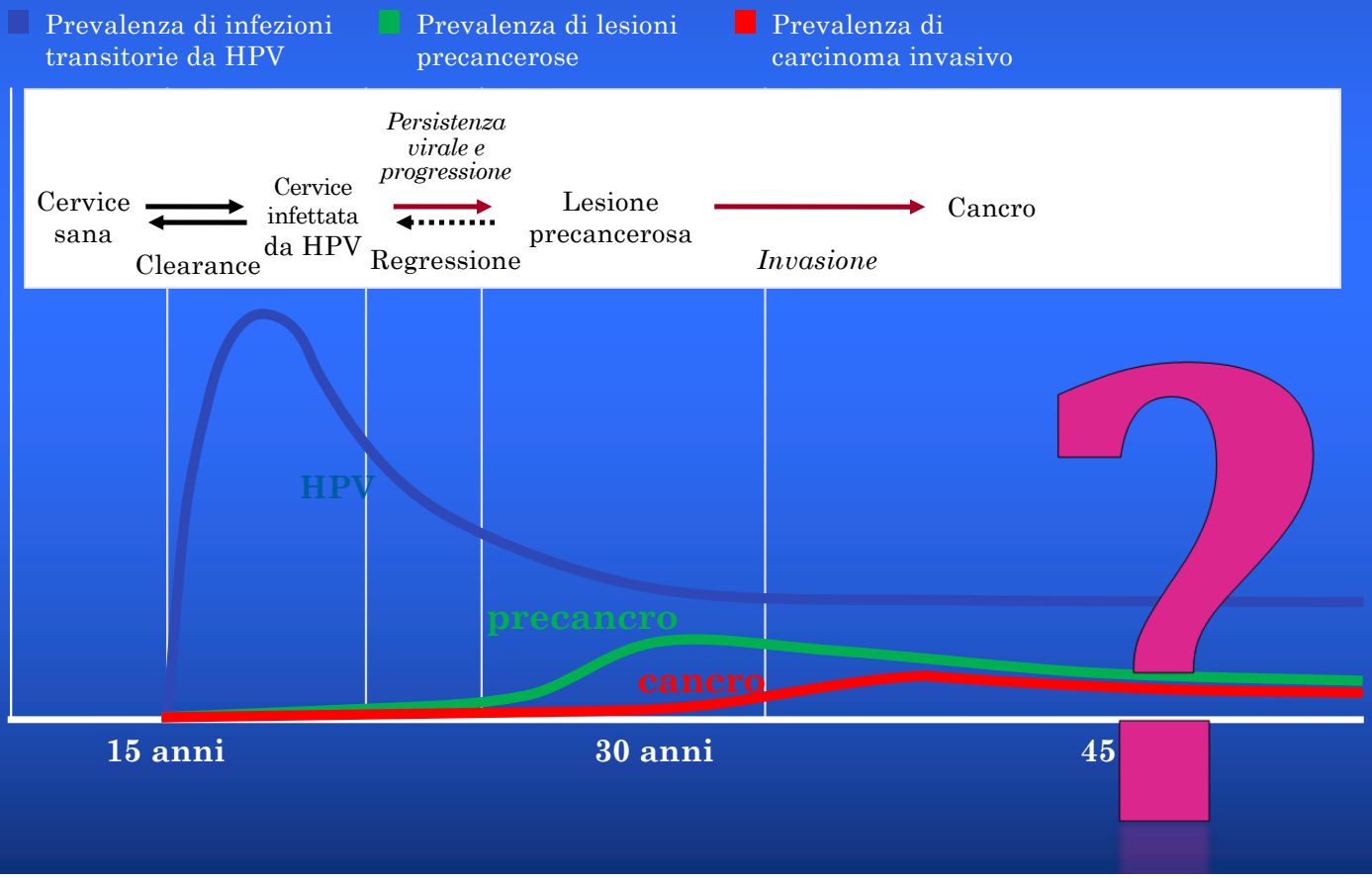
2. GESTIONE DELLA DONNA CON DIAGNOSI ISTOLOGICA DI HSIL (CIN2-3)

L'obiettivo primario della gestione della paziente con lesione istologica HSIL (CIN2-3) è l'eliminazione di lesioni potenzialmente evolutive e l'identificazione di lesioni invasive occulte presenti in circa il 6-12% dei casi, o francamente invasive (fino al 2% dei casi) (1-4), riducendone la mortalità.

Le pazienti con diagnosi istologica di HSIL (CIN2-3) all'esame bioptico devono essere sottoposte a trattamento. La sola osservazione della paziente non è considerata una opzione accettabile (5-6), se non in particolari casi (gravidanza in assenza di sospetto colposcopico di invasione, donne giovani < 25 anni - vedi capitoli dedicati).

RACCOMANDAZIONE	LIVELLO DI EVIDENZA	GRADO DELLA RACCOMANDAZIONE
Il trattamento della HSIL (CIN 2-3) è escissionale e rigorosamente sotto controllo colposcopico per riconoscere la presenza di un eventuale carcinoma invasivo occulto o microinvasivo	**2+**	**C**

STORIA NATURALE DEL CERVICOCARCINOMA



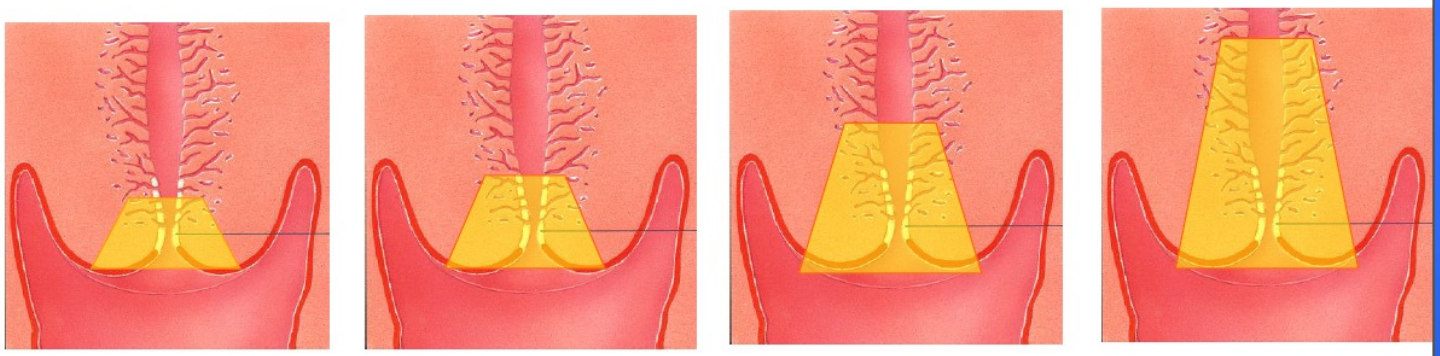
Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

BMJ

Maria Kyrgiou,[1,2] Antonios Athanasiou,[3] Maria Paraskevaidi,[1] Anita Mitra,[1,2] Ilkka Kalliala,[1] Pierre Martin-Hirsch,[4,5] Marc Arbyn,[6] Phillip Bennett,[1,2] Evangelos Paraskevaidis[3]

2016

<10/12mm	>10/12mm	>15/17mm	>20mm
1.54 [1.09, 2.18]	1.93 [1.62, 2.31]	2.77 [1.95, 3.93]	4.91 [2.06, 11.68]



The treatment effect increased with increasing Tx cone length/volume…

Treatment significantly increased the risk of PTB irrespective of the comparison group used … But the magnitude of effect was different..

Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis

2018

Karoliina Tainio,[1] Antonios Athanasiou,[2] Kari A O Tikkinen,[3] Riikka Aaltonen,[4] Jovita Cárdenas Hernándes,[5] Sivan Glazer-Livson,[1] Maija Jakobsson,[1] Kirsi Joronen,[4] Mari Kiviharju,[1] Karolina Louvanto,[1,6] Sanna Oksjoki,[4] Riikka Tähtinen,[7] Seppo Virtanen,[1] Pekka Nieminen,[1] Maria Kyrgiou,[8,9] Ilkka Kalliala[1,8]

- **RATIONAL**:
- Conservative management of CIN 1/LSIL and treatment of CIN 3 are widely accepted
- CIN 2 remains a somewhat equivocal diagnosis as some treatment guidelines advocate active surveillance for young women instead of immediate treatment[1]
  - Many studies have shown high rates of regression for CIN 2

[1]Massad, 2012 ASCCP guidelines; [2]Moscicki 2010; [3]Fuchs 2012

Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis

Karoliina Tainio,[1] Antonios Athanasiou,[2] Kari A O Tikkinen,[3] Riikka Aaltonen,[4] Jovita Cárdenas Hernándes,[5] Sivan Glazer-Livson,[1] Maija Jakobsson,[1] Kirsi Joronen,[4] Mari Kiviharju,[1] Karolina Louvanto,[1,6] Sanna Oksjoki,[4] Riikka Tähtinen,[7] Seppo Virtanen,[1] Pekka Nieminen,[1] Maria Kyrgiou,[8,9] Ilkka Kalliala[1,8]

Aim

- To estimate the rates of:
  - regression
  - persistence
  - progression
  - compliance with follow-up
- in women with CIN 2 managed with active surveillance.

Results

- **36 studies** with a total of **3160 women**
  - 7 RCTs with suitable data in the non-experimental arm
  - 16 prospective cohorts
  - 13 retrospective cohorts
- Mean follow-up 16 months (range 3-72 months)
- Largest study 924 women, smallest 12
  - 81% of studies with less than 100 patients
- 7/36 studies included only women under the age of 25
- 18/36 studies (50%) low risk of bias

Results

Main analysis

	6 months			12 months			24 months		
	Regression	**Persistence**	**Progression**	**Regression**	**Persistence**	**Progression**	**Regression**	**Persistence**	**Progression**
N of studies n/N [1]	7 139/328	5 96/278	5 42/278	13 300/628	9 110/414	13 131/834	11 819/1470	8 334/1257	9 282/1445
Summary % (95%CI; I^2) [2]	52 (36 to 68; 85)	34 (29 to 40; 0)	13 (8 to 20; 42)	46 (36 to 56; 81)	29 (17 to 43; 85)	14 (9 to 20; 75)	50 (43 to 57; 77)	32 (23 to 42; 82)	18 (11 to 27; 90)

Results

≤30-year-olds

	6 months			12 months			24 months		
	Regression	Persistence	Progression	Regression	Persistence	Progression	Regression	Persistence	Progression
N of studies n/N	3 63/205	3 74/205	3 37/205	6 182/349	5 63/254	6 47/349	4 638/1069	2 226/938	3 163/1033
Summary % (95%CI; I^2)	38 (21-57; 76)	36 (29-43; 0)	18 (12-23; 0)	51 (40-63; 71)	31 (15-49; 82)	9 (2-20; 84)	60 (57-63; 0)	23 (20-26; 97)	11 (5-19; 67)

- >30-year-olds at 24 months
  - Regression 44% (95% CI 36-52; I^2 61%); 7 studies, 181/401
  - Persistence 35% (95% CI 23-49; I^2 83%) ; 6 studies, 108/319
  - Progression 23% (95% CI 12-37; I^2 89%); 6 studies, 119/412

Conclusions

- Active surveillance of CIN 2 is justified in selected women, particularly if they are young, planning pregnancies, and the likelihood of compliance with surveillance is high
  - Multidisciplinary assessment advised when considering an active surveillance strategy
- In cases of persistent disease beyond 2 years, treatment is likely to be warranted

Conclusions

- There appears to be a marked difference in CIN 2 and CIN 3 natural histories
  - Classification as histological HSIL can lead to overtreatment
- Biomarkers with predictive potential?

2021

ORIGINAL RESEARCH ARTICLE: CERVIX AND HPV

The Natural History of Cervical Intraepithelial Neoplasia Grades 1, 2, and 3: A Systematic Review and Meta-analysis

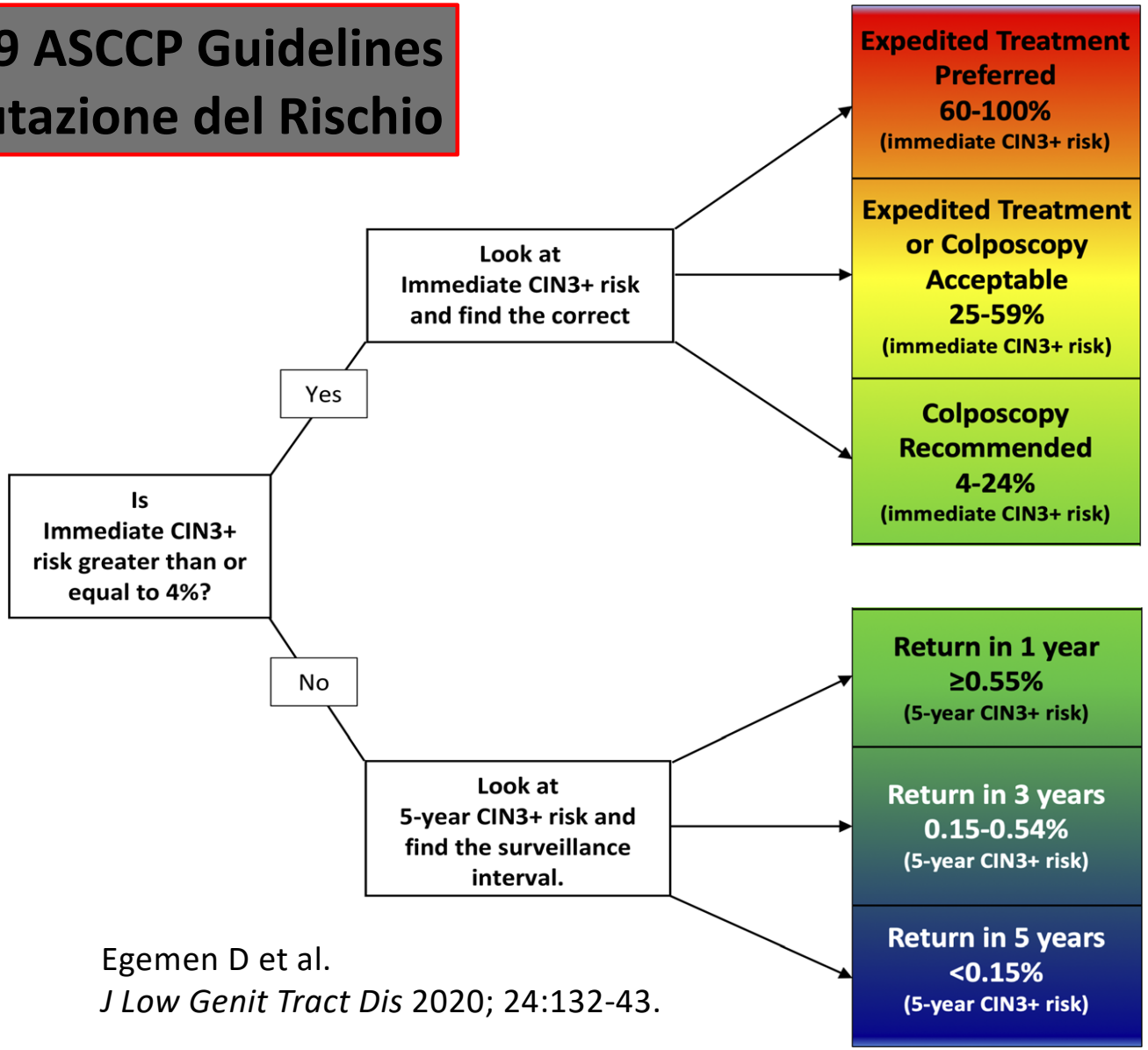
Diede L. Loopik, MD, PhD,[1] Heidi A. Bentley, MD,[2] Maria N. Eijgenraam, MsC,[1] Joanna IntHout, PhD,[3] Ruud L. M. Bekkers, MD, PhD,[4,5] and James R. Bentley, MB, ChB, FRCSC[6]

Aim

To obtain an updated overview of regression, persistence, and progression rates of conservatively managed cervical intraepithelial neoplasia grade 1 (CIN 1) /CIN 2/CIN 3 measures.

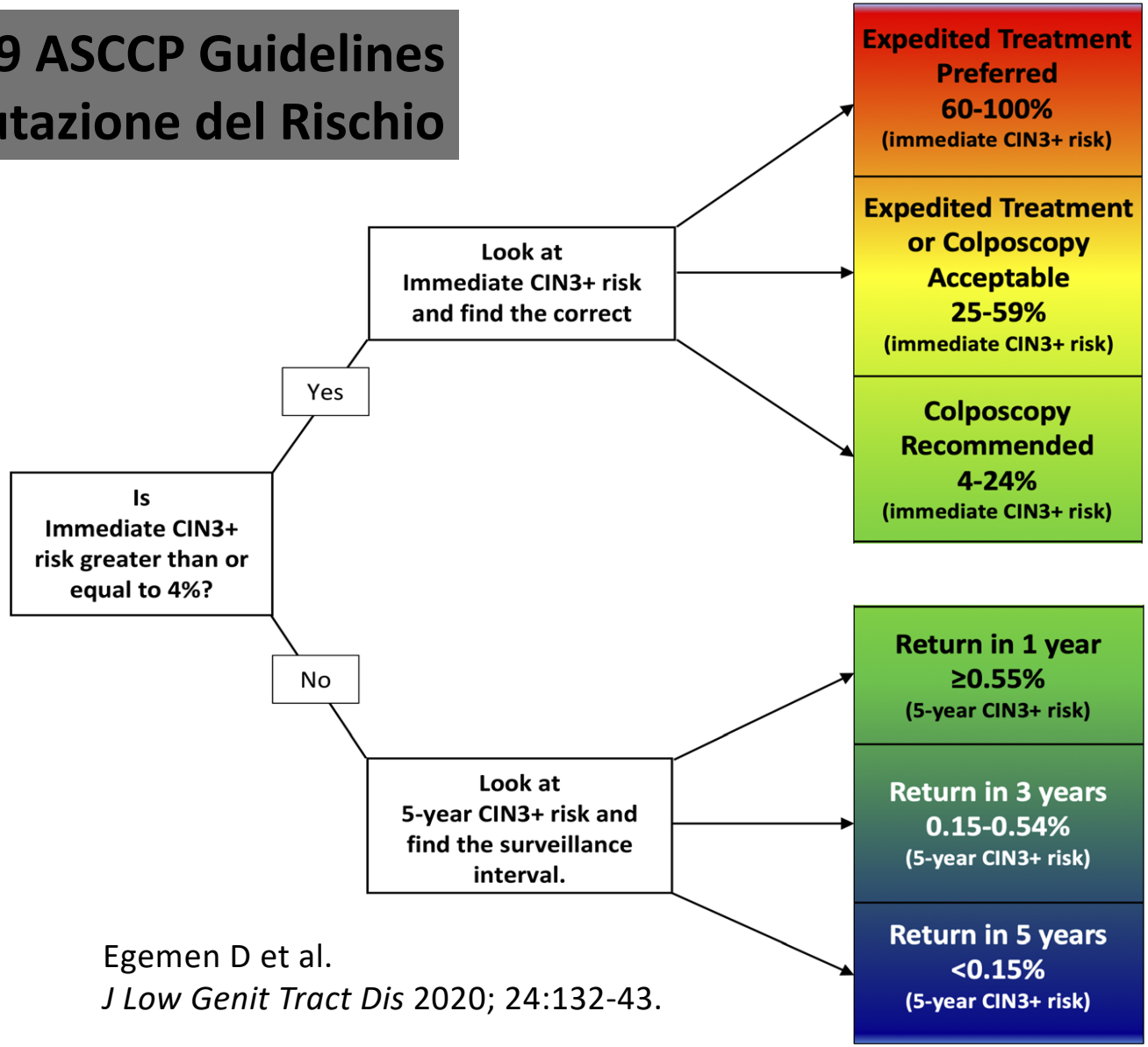
- **89 studies** were included:
  - 63 studies on CIN 1 (n = 6,080–8,767)
  - 42 on CIN 2 (n = 2,909–3,830)
  - 7 on CIN 3 (n = 245–351

2019 ASCCP Guidelines
Valutazione del Rischio



Egemen D et al.
J Low Genit Tract Dis 2020; 24:132-43.

2019 ASCCP Guidelines
Valutazione del Rischio



HSIL HPV 16+

ASC-H

LSIL o ASCUS HPV+
allo screening iniziale

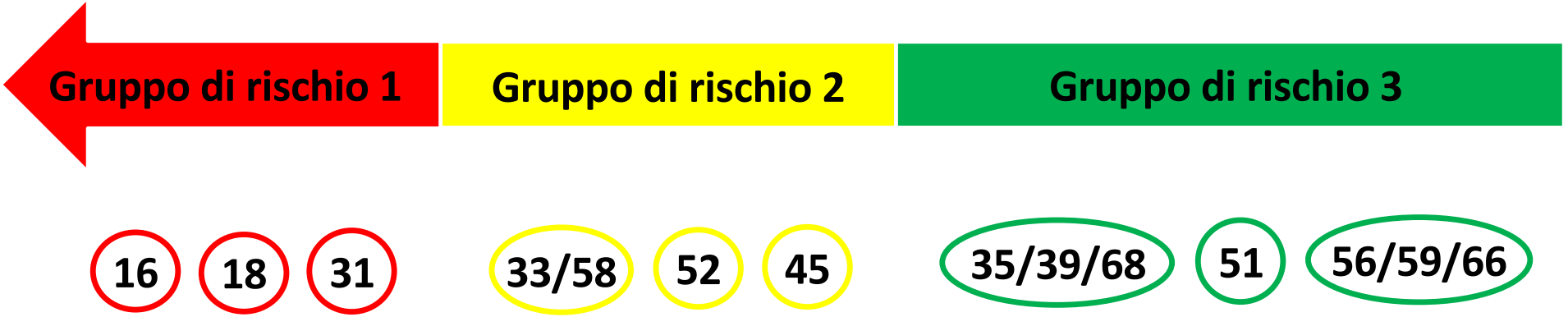
LSIL o ASCUS HPV+
(se istologia < CIN 2)

LSIL o ASCUS HPV+
(istologia < CIN 2 al secondo controllo negativo)

Screening primario con
HPV DNA test negativo

Egemen D et al.
J Low Genit Tract Dis 2020; 24:132-43.

Con la genotipizzazione estesa si identificano tre gruppi di rischio per lesioni ≥ CIN 3



Stesso rischio = Stesso trattamento

Egemen D et al. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis* 2020; 24(2):132-143.

TRATTAMENTI

- ABLAZIONE
- ESCISSIONE
- OSSERVAZIONE

Treatment

Overtreatment

TRATTAMENTO DELLA CIN

TRATTAMENTO DELLA DONNA AFFETTA DA CIN

TERAPIA DELLA CIN

- < 25 anni
- > 50 anni
- in gravidanza
- nella donna immunodepressa

Types of intervention

1) Laser Ablation
2) Laser Conisation
3) LLETZ
4) Knife Conisation
5) Cryotherapy

Conclusions

Implications for practice

The evidence from the 28 RCTs identified suggests that there is no overwhelming superior surgical technique for eradicating cervical intraepithelial neoplasia.

CRYOTHERAPY appears to be an effective treatment of LOW GRADE disease but not of high grade disease

Characteristics and Morbidity

1) Duration of treatment
2) Peri-operative severe pain
3) Peri-operative severe bleeding, primary and secondary haemorrhage
4) Depth and presence of thermal artifact
5) Adequate colposcopy at follow-up
6) Cervical stenosis at follow-up

Laser Ablation

Laser Ablation appears to cause more peri-operative severe pain and perhaps more primary and secondary haemorrhage compared to Loop Excision

Laser Conisation

Laser Conisation takes longer to perform, requires grater operative training, more expensive investment in equipment, produces more peri-operative pain, greater depth and severe thermal artefact than Loop Excision

TERAPIA ESCISSIONALE NEL TRATTAMENTO DELLA CIN

ESAME ISTOLOGICO SU TUTTA LA LESIONE

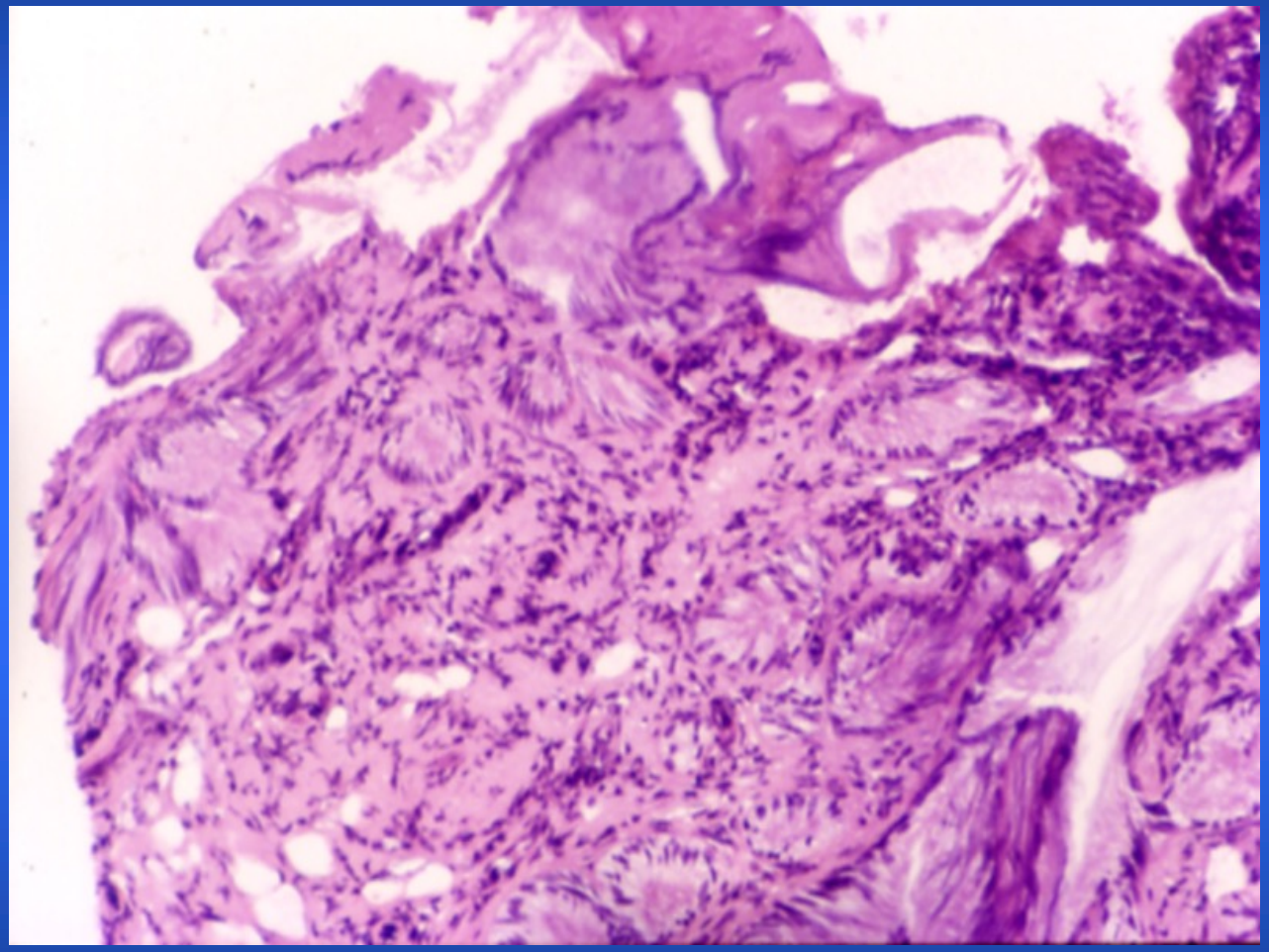
DIAGNOSI

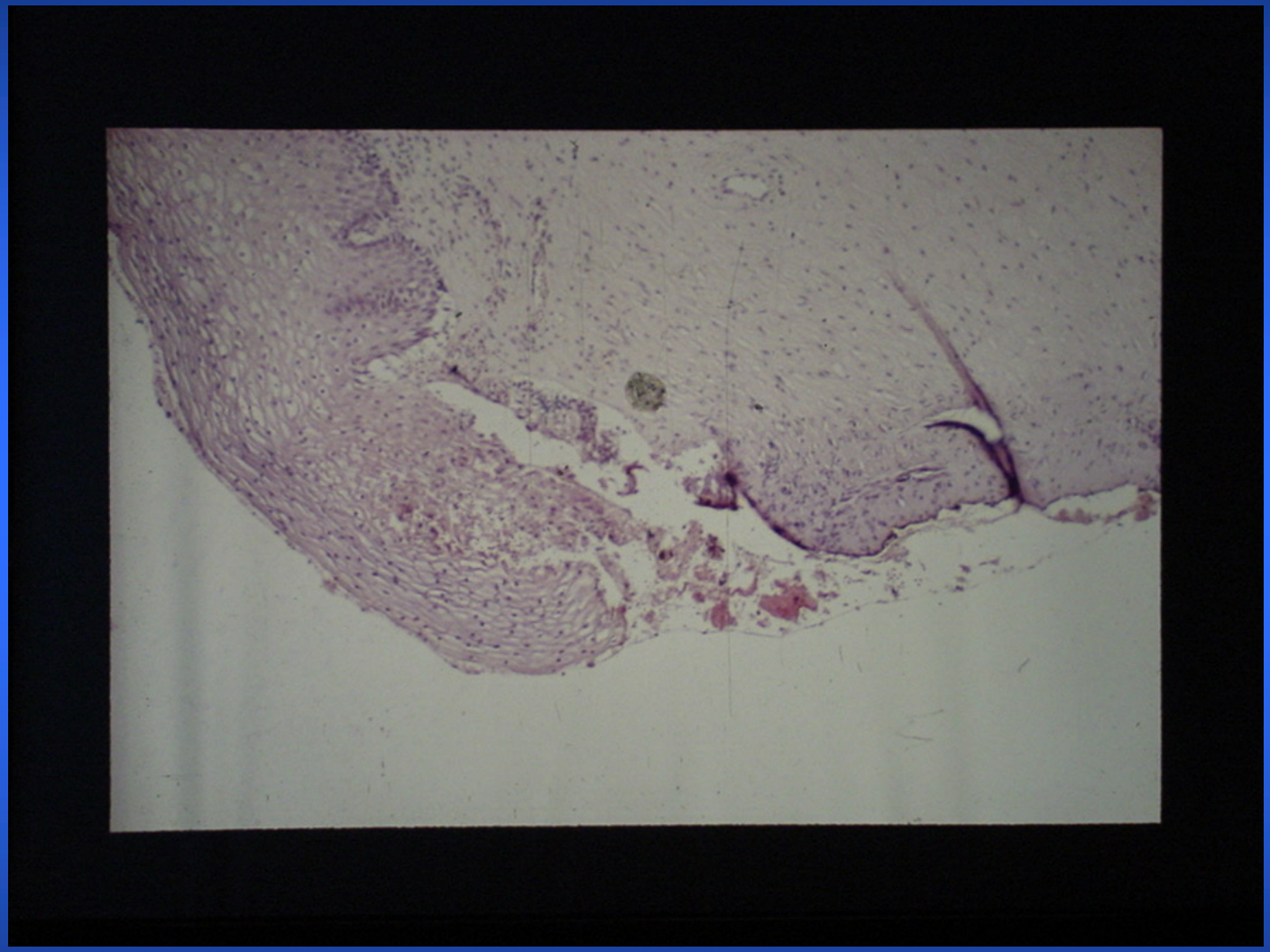
METODICHE ESCISSIONALI

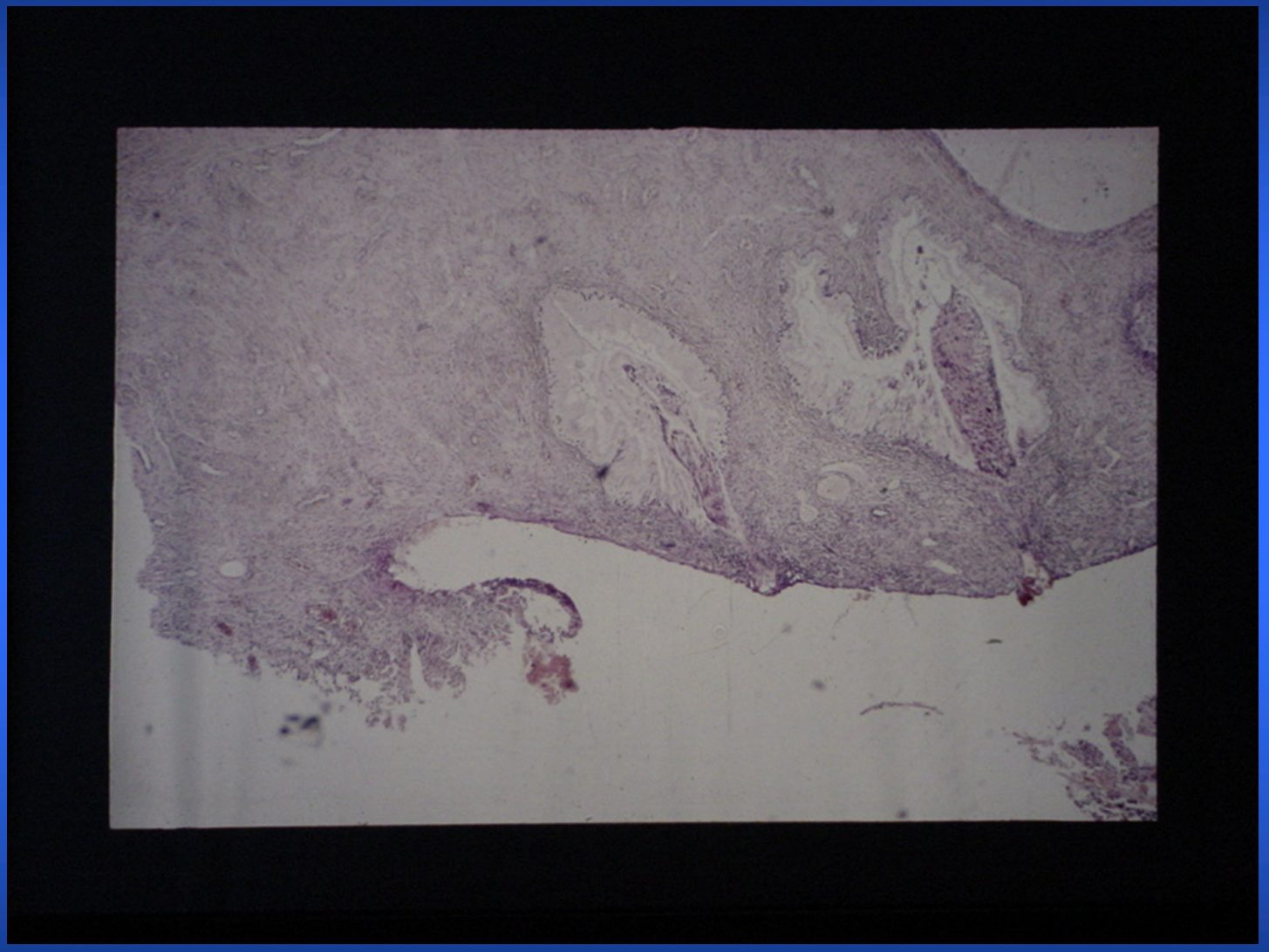
- **CONIZZAZIONE A "LAMA FREDDA"**
- **CONIZZAZIONE LASER**
- **CONIZZAZIONE A RADIOFREQUENZA**
- **ESCISSIONE A RADIOFREQUENZA**

TECNICA ESCISSIONALE

- **Tecnica ambulatoriale**
- **Intervento mirato**
- **Tempi di guarigione rapidi**
- **Buoni esiti anatomo - funzionali**
- **Ottima compliance**







…. Vi sono molti motivi per preferire metodi escissionali anziché distruttivi nel trattamento della CIN e per usare l'Ansa diatermica anziché il Laser….

M. Anderson, 1993

(TRATTAMENTI ESCISSIONALI NEL BASSO TRATTO GENITALE, W. Prendiville)

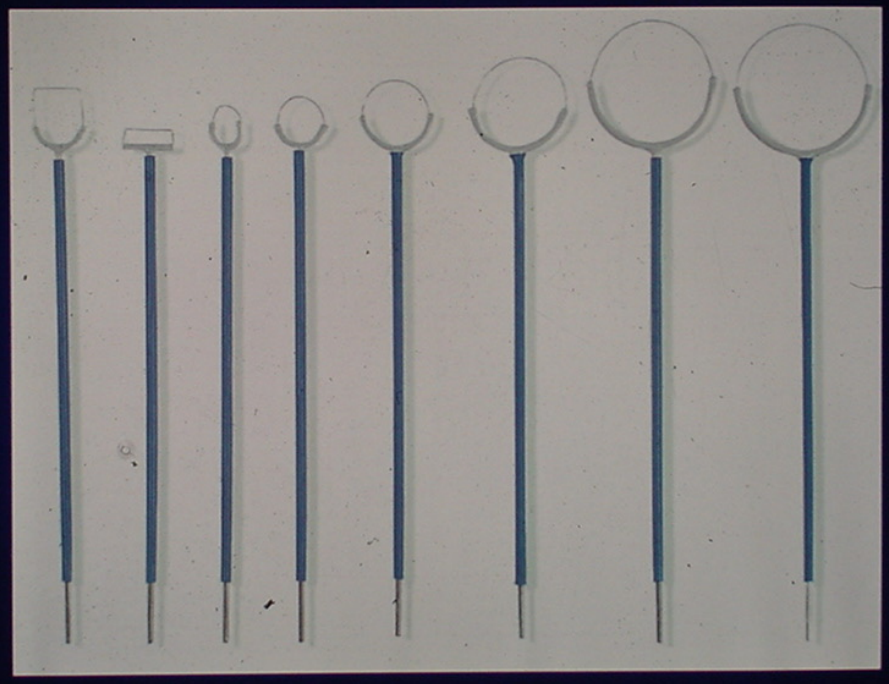
RISULTATI DEL TRATTAMENTO

Grado CIN	N° casi	Guarigione	Persistenza	Neoplasia
I	702	660 (94%)	42 (6%)	1 Adenoca i.m.
II	778	735 (94,5%)	44 (5,5%)	1 Adenoca i.m
III	520	488 (94%)	31 (6%)	30 Microinv. 4 Adenoca i.m. 4 Adenoca inv.
TOTALE	**2000**	**1883 (94,3%)**	117 **(5,7%)**	**40**

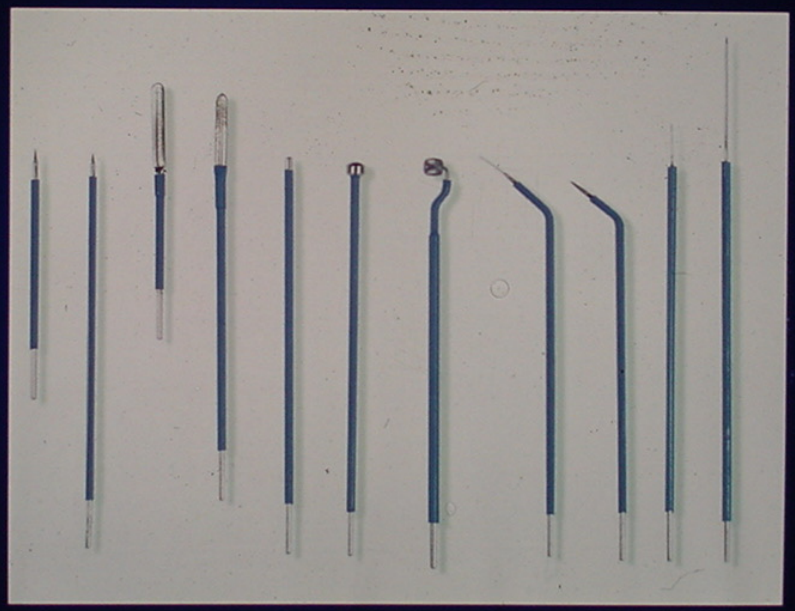
CARATTERISTICHE ISTOLOGICHE DEI CAMPIONI ESAMINATI

Lunghezza media	16 mm
Percentuale di casi con endocervice interessata	80%
Interessamento endocervicale medio	5,5 mm
Distanza media della displasia dal margine di resezione	2 mm

Anse



Elettrodi: lama, punte, filo, pallina



RADIOFREQUENZA

ESCISSIONE

COAGULAZIONE

VAPORIZZAZIONE

Microinvasive cervical carcinoma: FIGO Stage IA

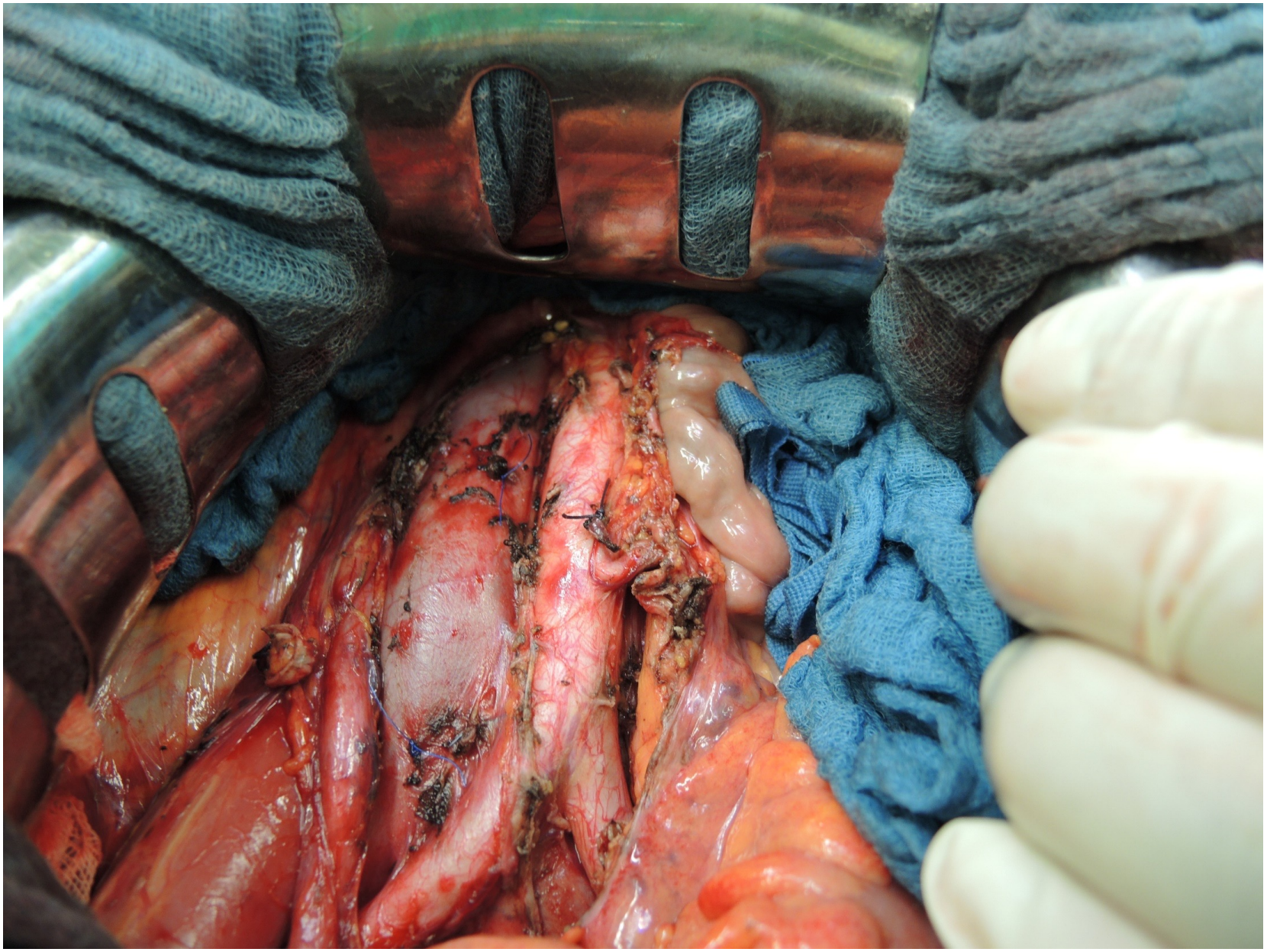
• Stage IA1

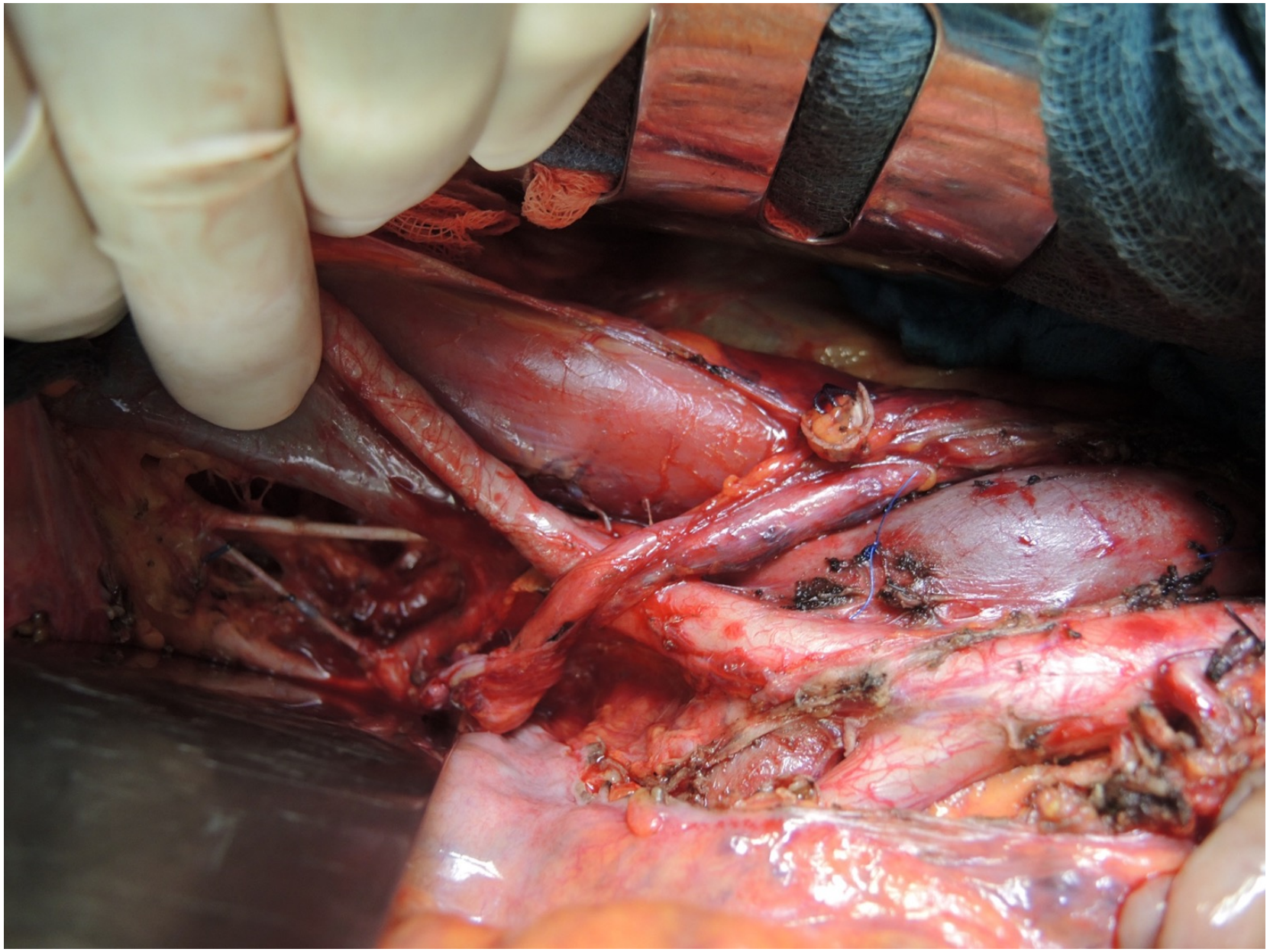
- Conization can be considered a definitive treatment as hysterectomy does not improve the outcome
- Lymph node staging is not indicated in LVSI-negative patients, but can be considered in T1a1 LVSI-positive patients.

Stage IA2

- Conization alone or simple hysterectomy.
- Lymph node staging should be performed in LVSI-positive patients.

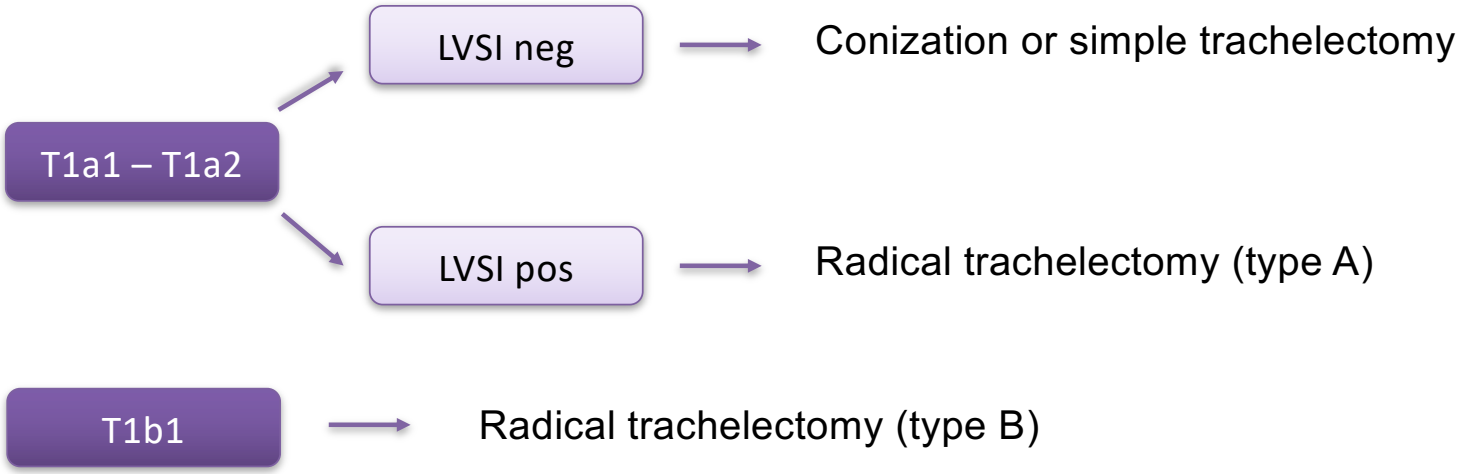
Sentinel lymph node biopsy alone (without additional pelvic lymph node dissection) appears to be an acceptable method of LN staging.





Fertility sparing treatment

- Squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma
- Tumor size **≤ 2 cm**
- Negative pelvic lymph node status (lymph node staging should always be the first step)



Routine hysterectomy after finishing fertility plans is not necessary.

Rischio di Carcinoma cervicale e Carcinomi HPV correlati

in **20 anni** di follow-up post trattamento di CIN 1-2-3

Rischio a lungo termine !

Sede del Carcinoma successivo	Rischio Assoluto	Rischio Relativo Rispetto alla Popolazione
Cervice	39 su 100.000	3 volte
Vagina		10.8 volte
Vulva		3.34 volte
Ano		5.11 volte

Kalliala Rev Syst 2020

Ipotesi per i carcinomi a lungo termine , nel post trattamento HSIL

2021

European Journal of Obstetrics & Gynecology and Reproductive Biology 264 (2021) 56–59

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/euro

Full length article

Invasive cervical cancer following treatment of pre-invasive lesions: A potential theory based on a small case series

Evangelos Paraskevaidis [a,*], Antonios Athanasiou [b], Ilkka Kalliala [b,c], Anna Batistatou [d], Maria Paraskevaidi [b,e], Evripidis Bilirakis [f], Maria Nasioutziki [g], Minas Paschopoulos [a], Deirdre Lyons [h], Marc Arbyn [i], Margaret Cruickshank [j], Pierre Martin-Hirsch [k], Maria Kyrgiou [b]

Casi

9 Carcinomi stadio da 1A1-IIIB
Insorti tra il 1997 e il 2020
Dopo 7-17 anni di Follow-up
Esclusi se comparsi nei primi < 2 anni , terapie ablative, no follow-up

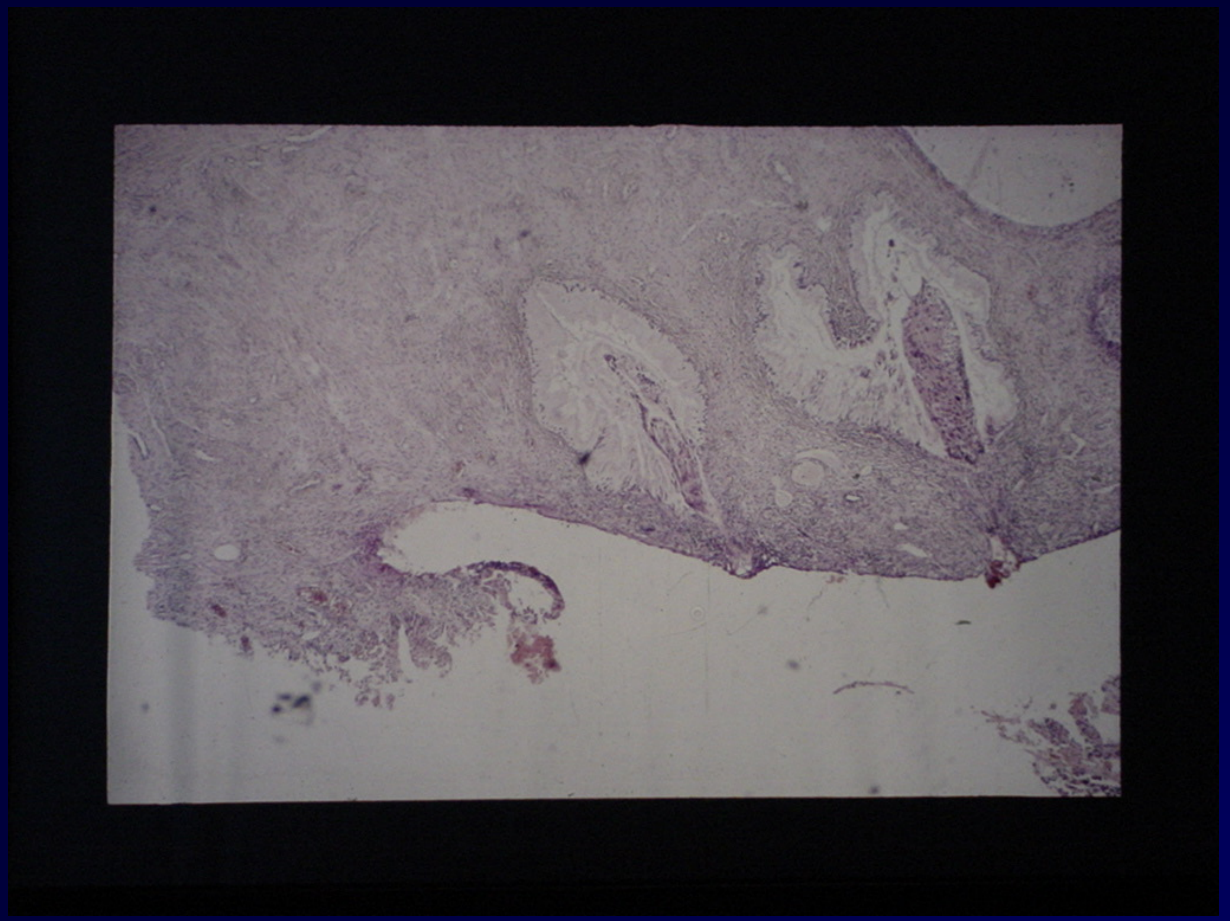
Margini ***negativi***
Follow-up citologico e colposcopico ***negativi***

«Teoria della cripta»

E' probabile che il cancro derivi dal processo di carcinogenesi di precursori non rimossi e rimasti *intrappolati nelle cripte*, nascosti dalla placca termica e poi dalla metaplasia.
La citologia e la colposcopia non possono rilevarli.
L'ipotesi di nuovi HPV è meno probabile perché si dovrebbe rilevare prima la CIN

Raccomandazione:

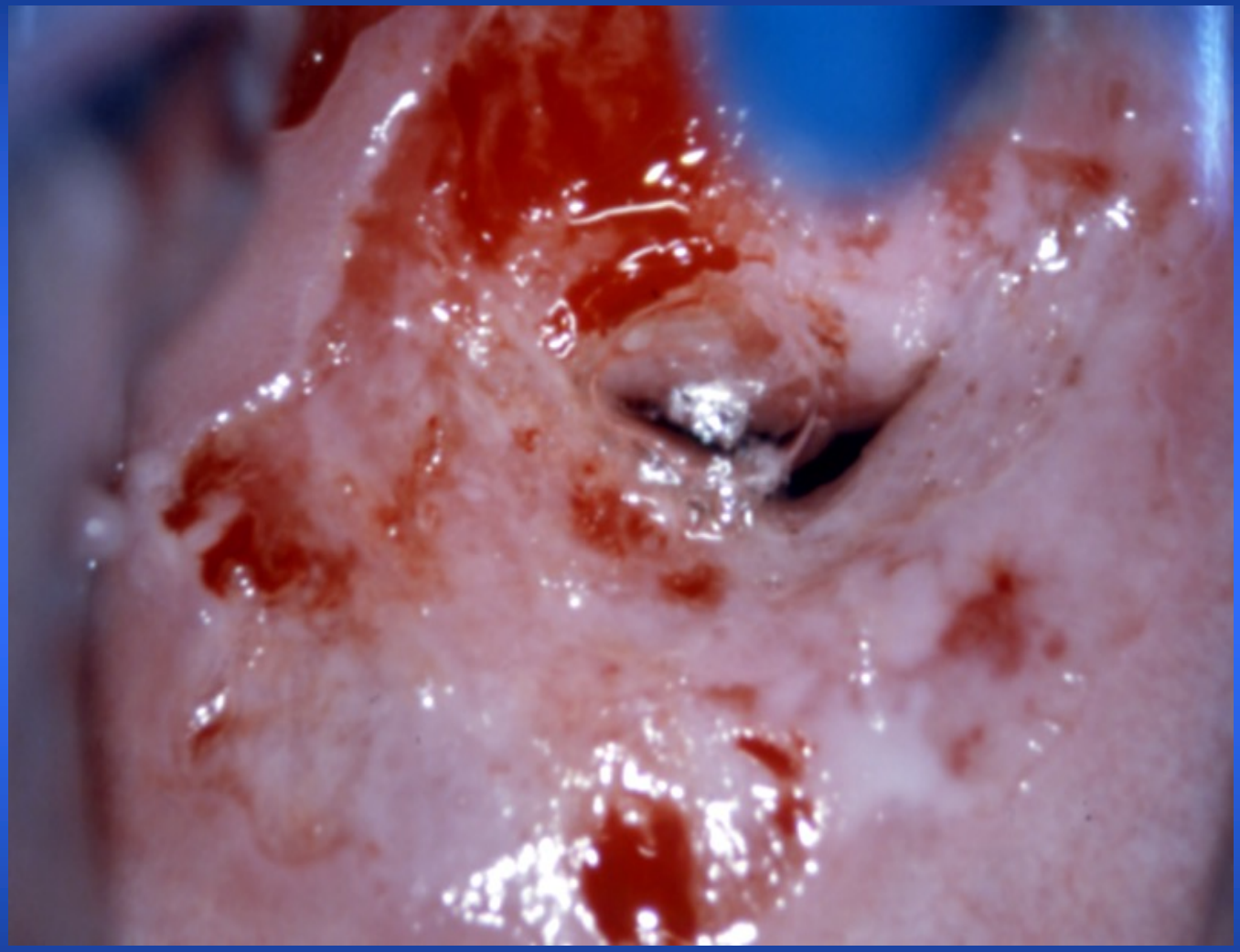
Limitare la cauterizzazione al minimo indispensabile e solo per eliminare le cripte residue
Follow-up accurato soprattutto per coni con cripte positive anche se margini negativi

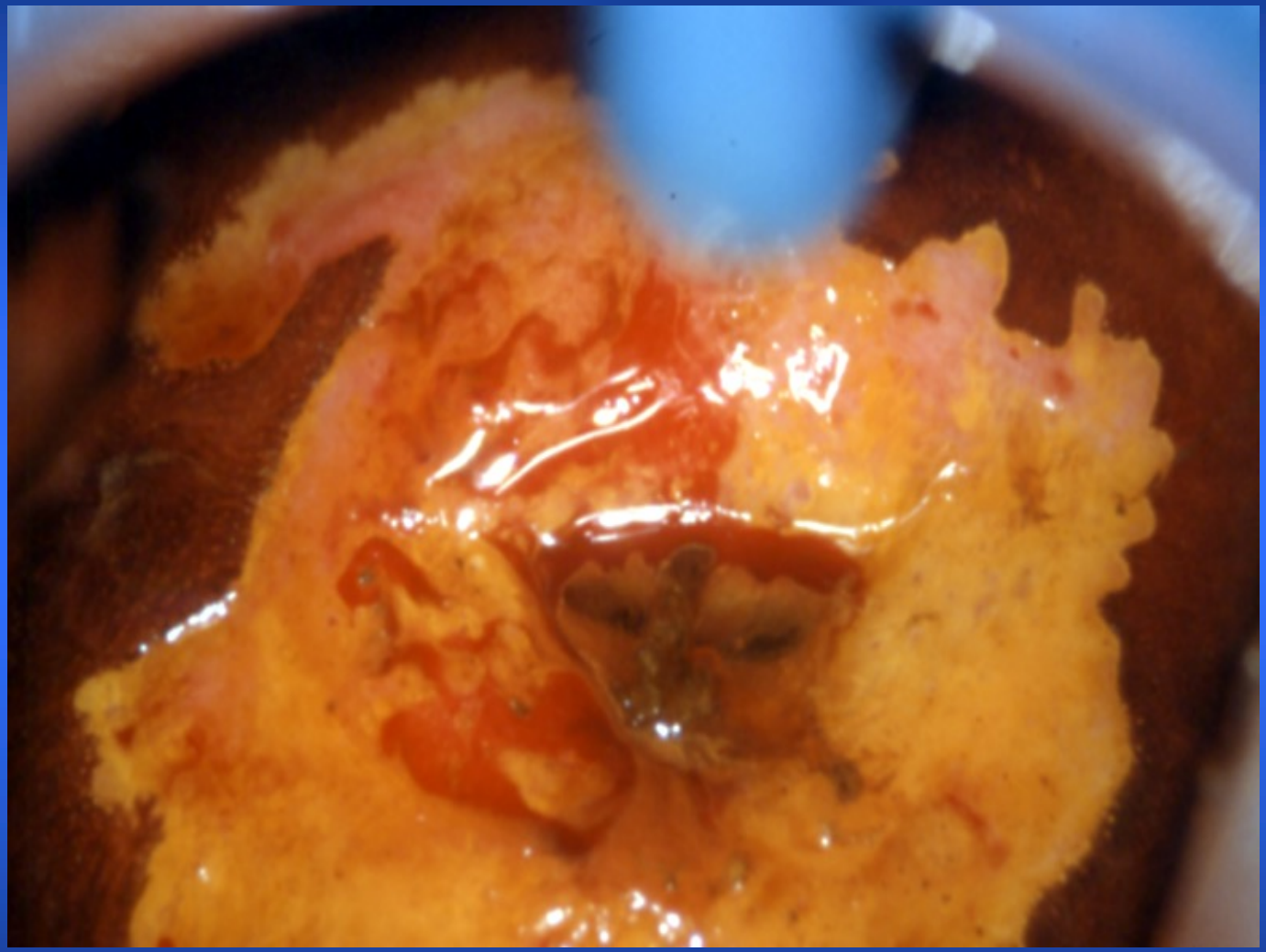


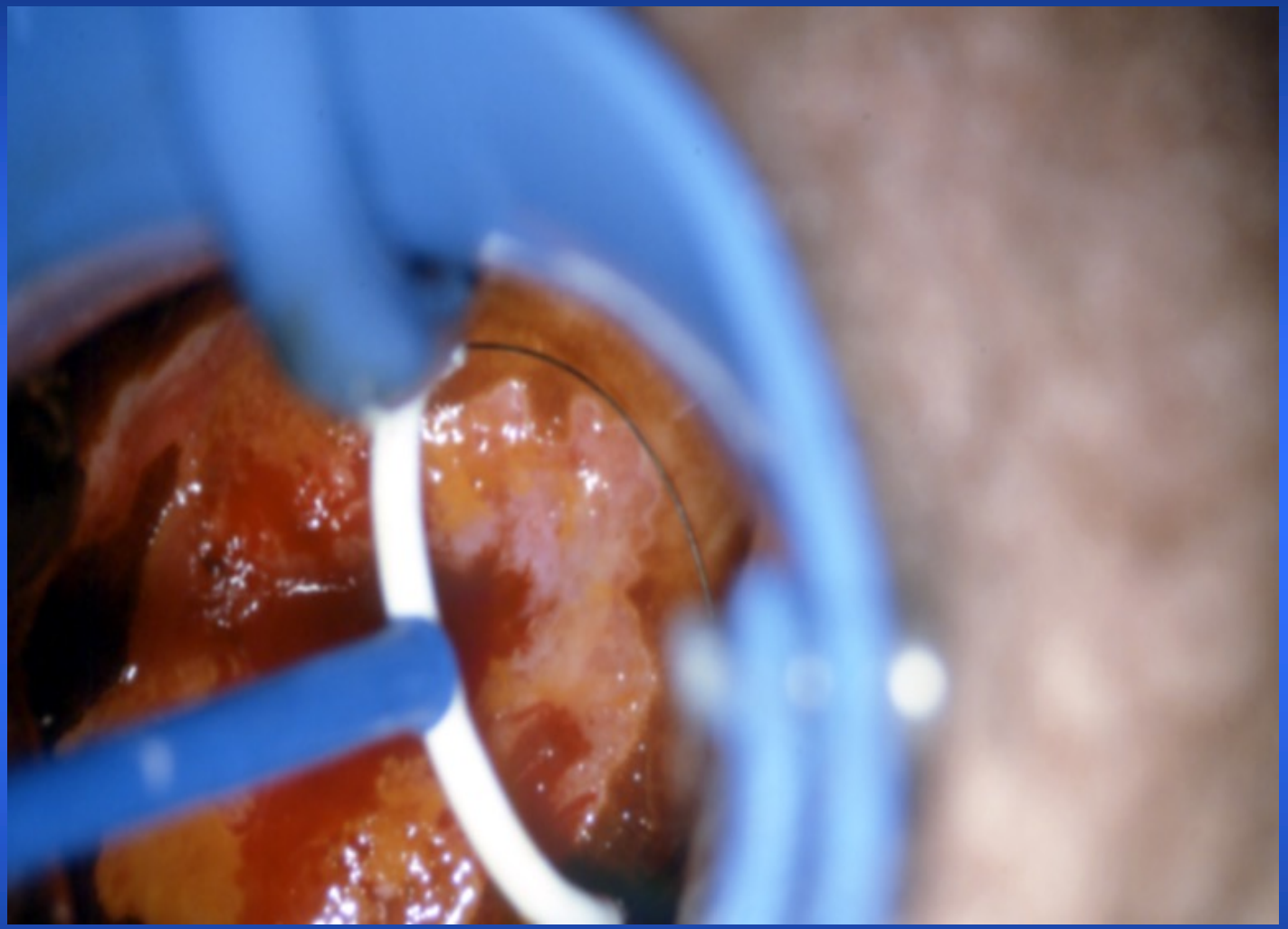
“

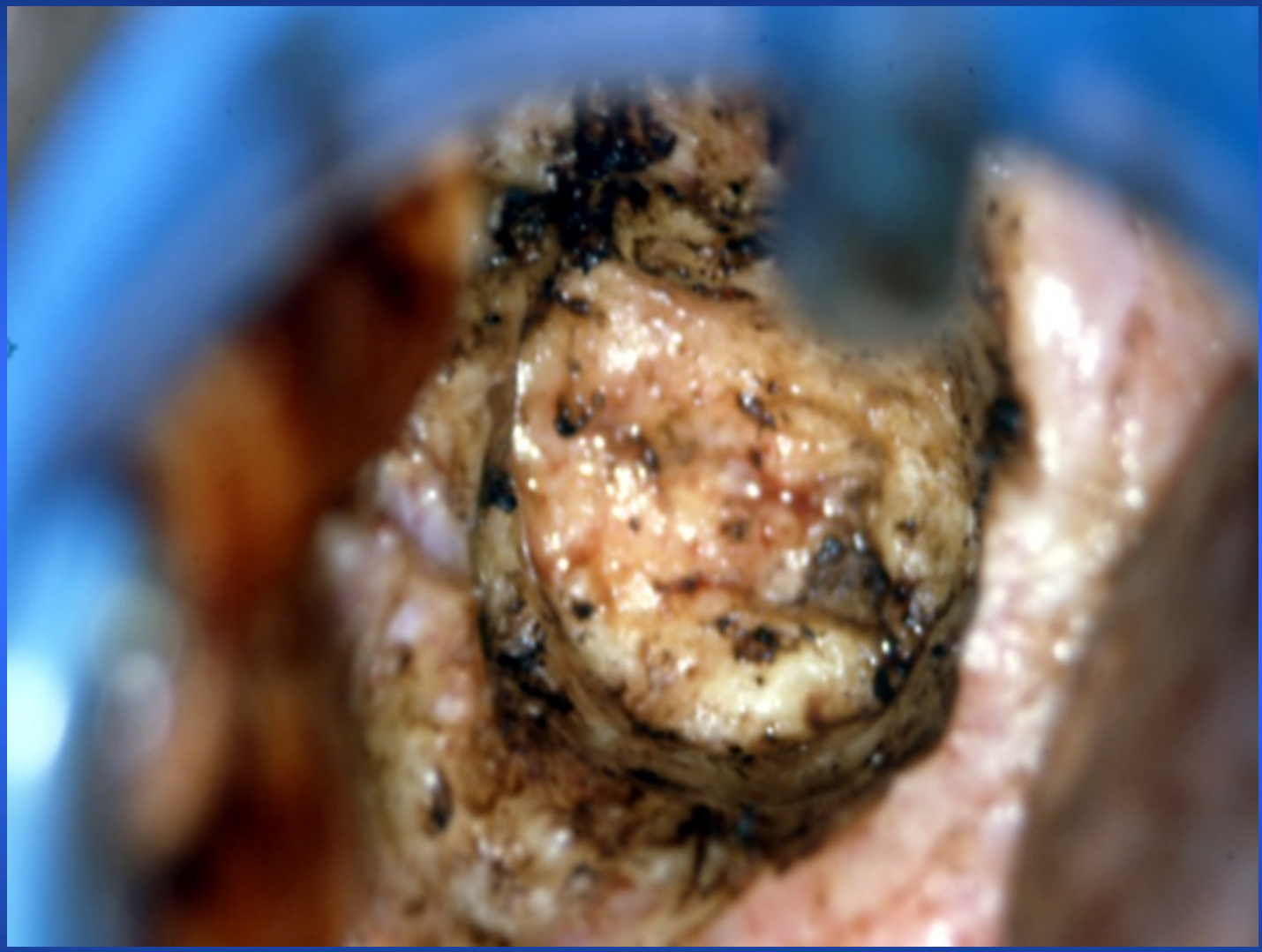
Le donne trattate per lesione di alto grado HSIL (CIN2-3) necessitano di **sorveglianza dopo il trattamento** perché sono a maggior rischio di ricorrenza e di carcinoma.

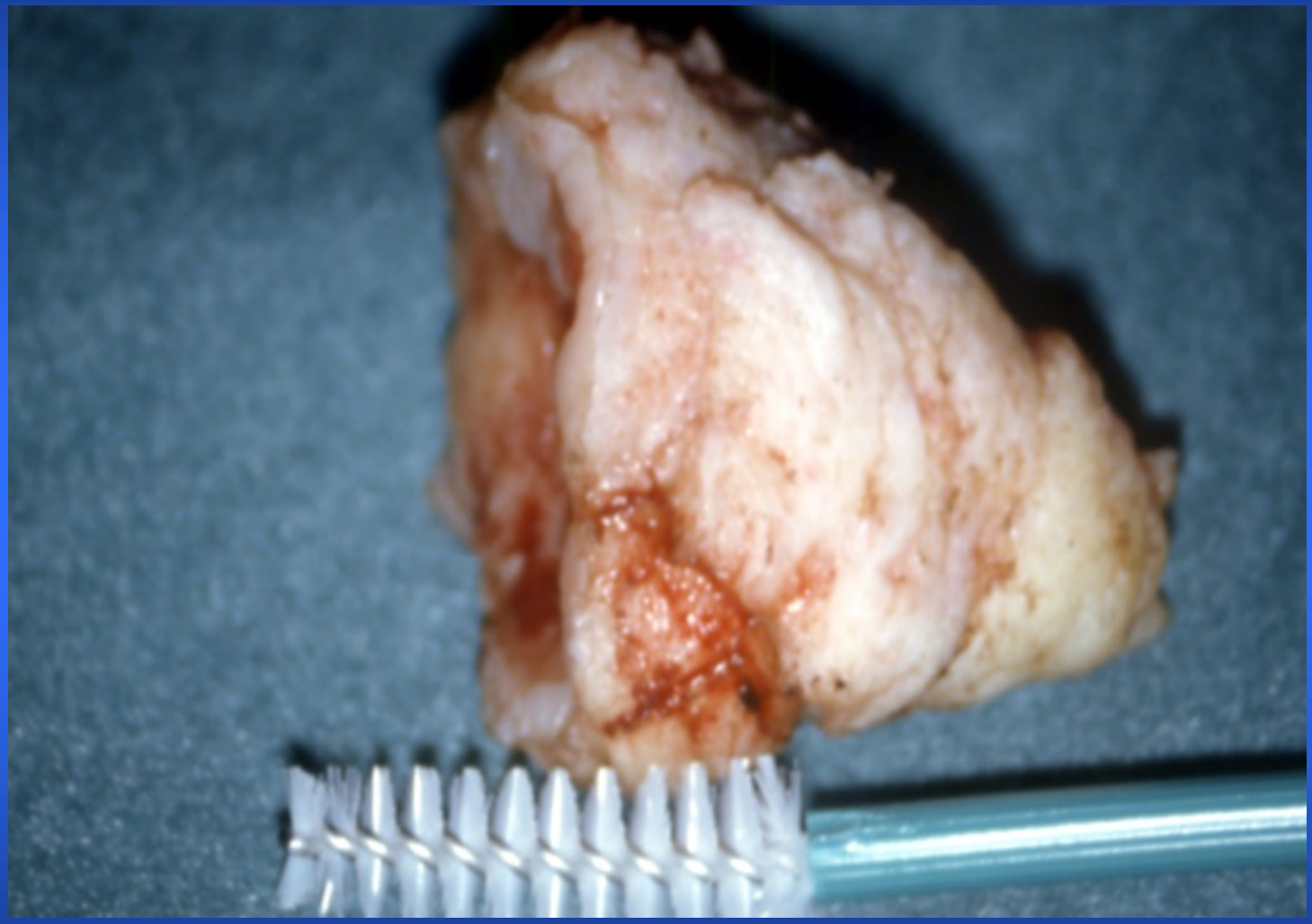
Il rischio rimane a breve e a lungo termine “

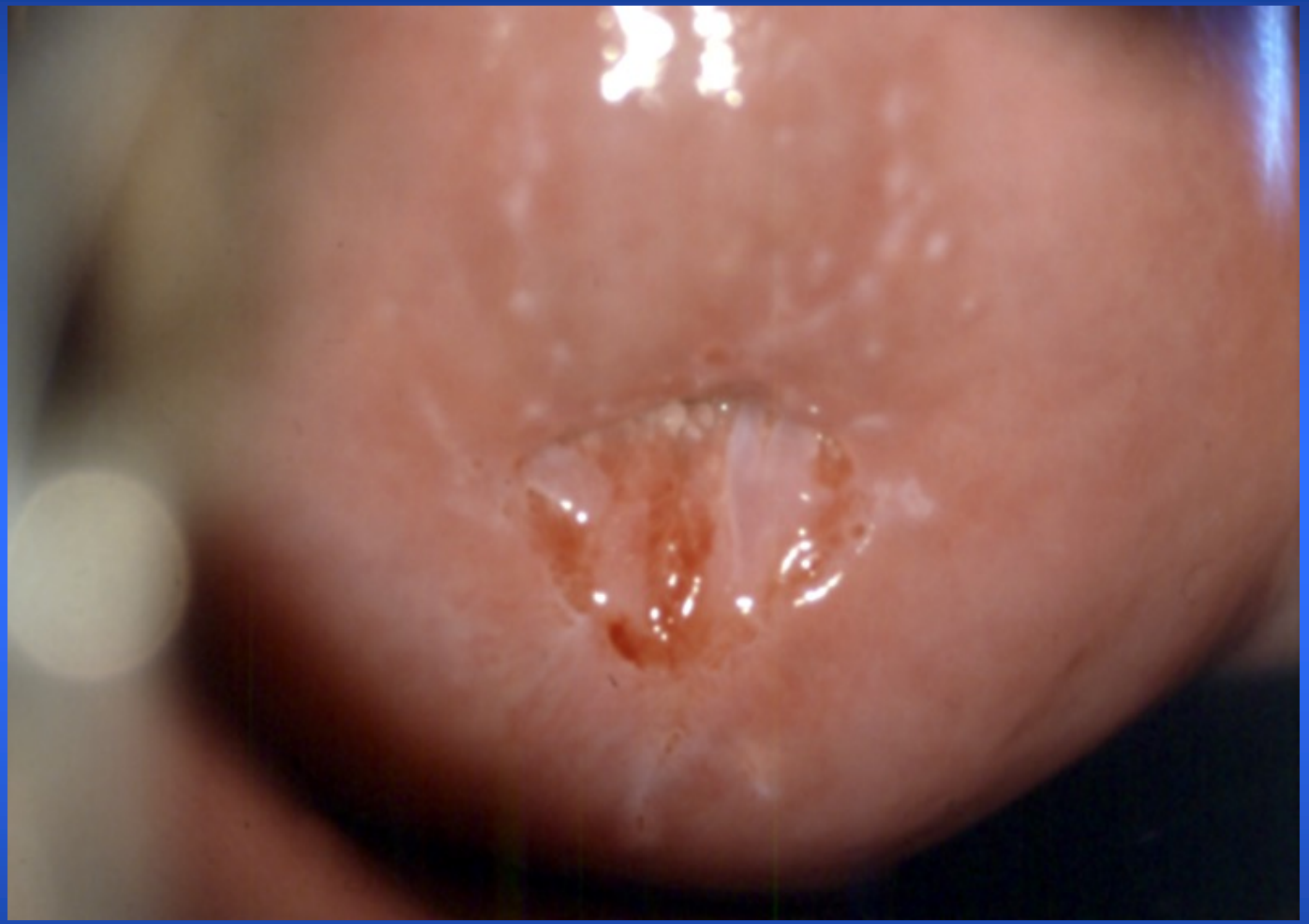


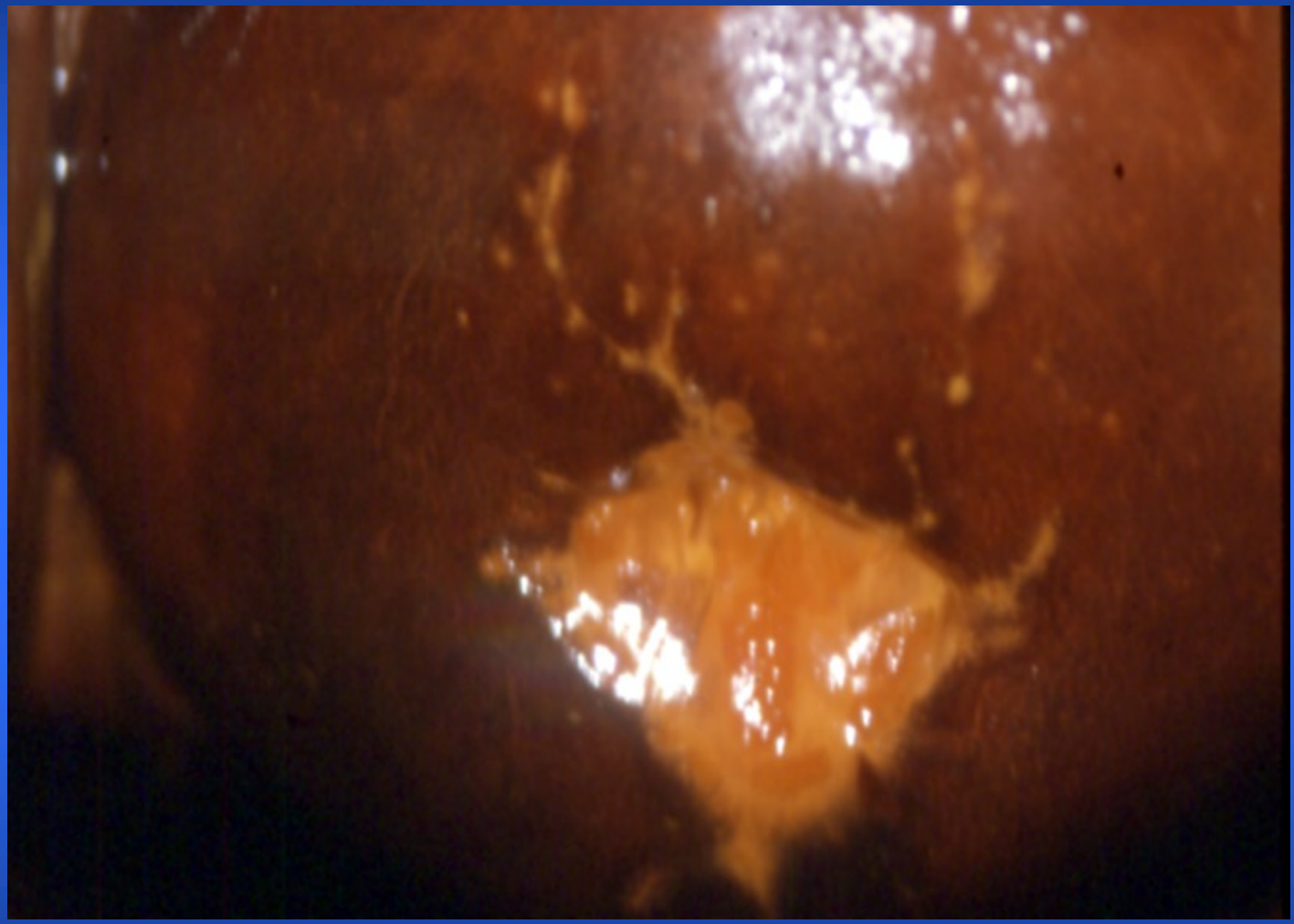


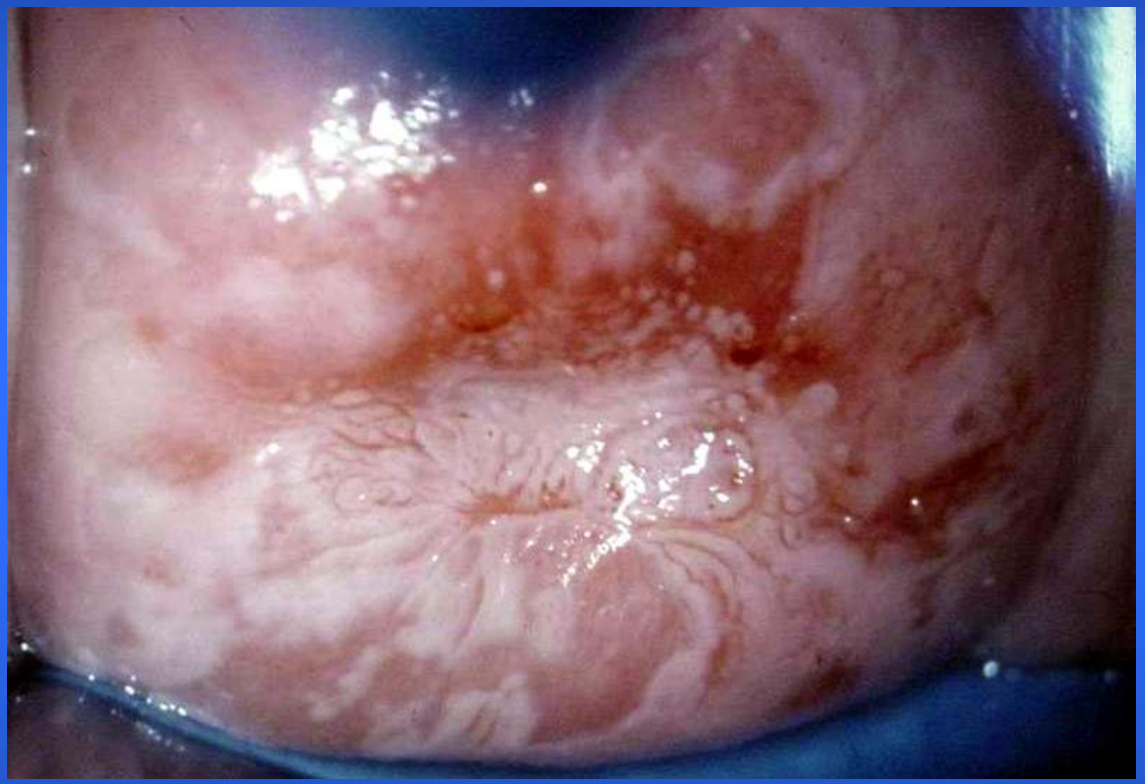


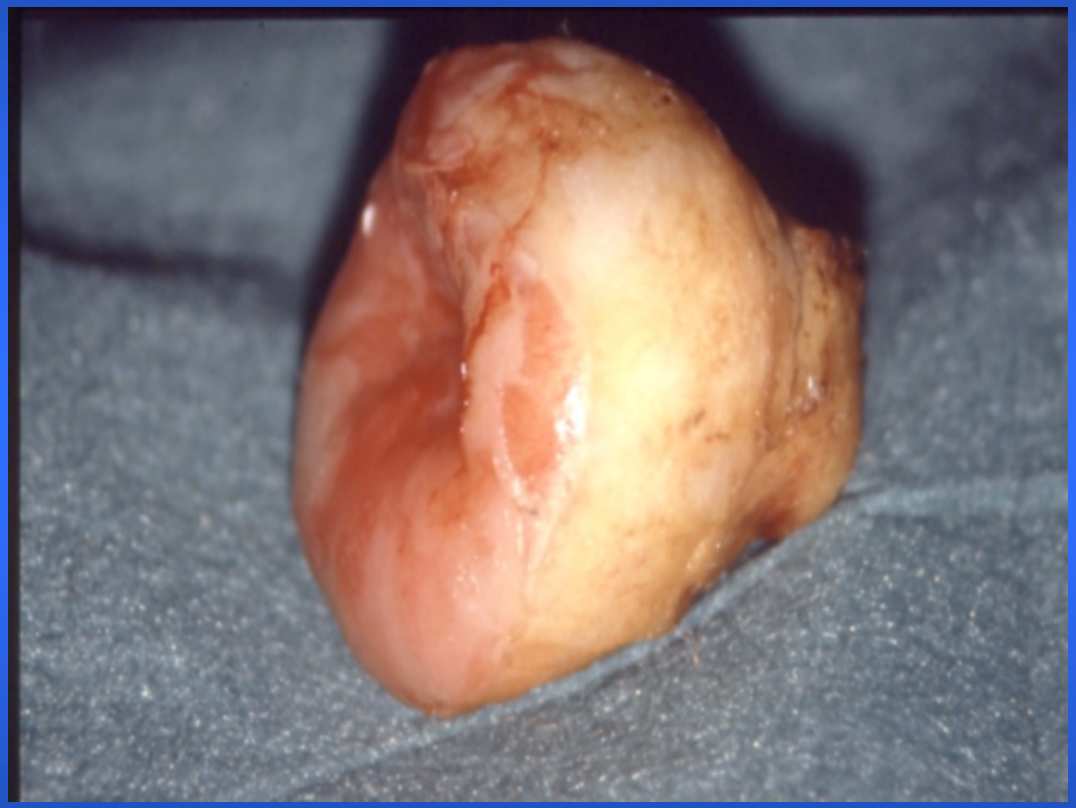


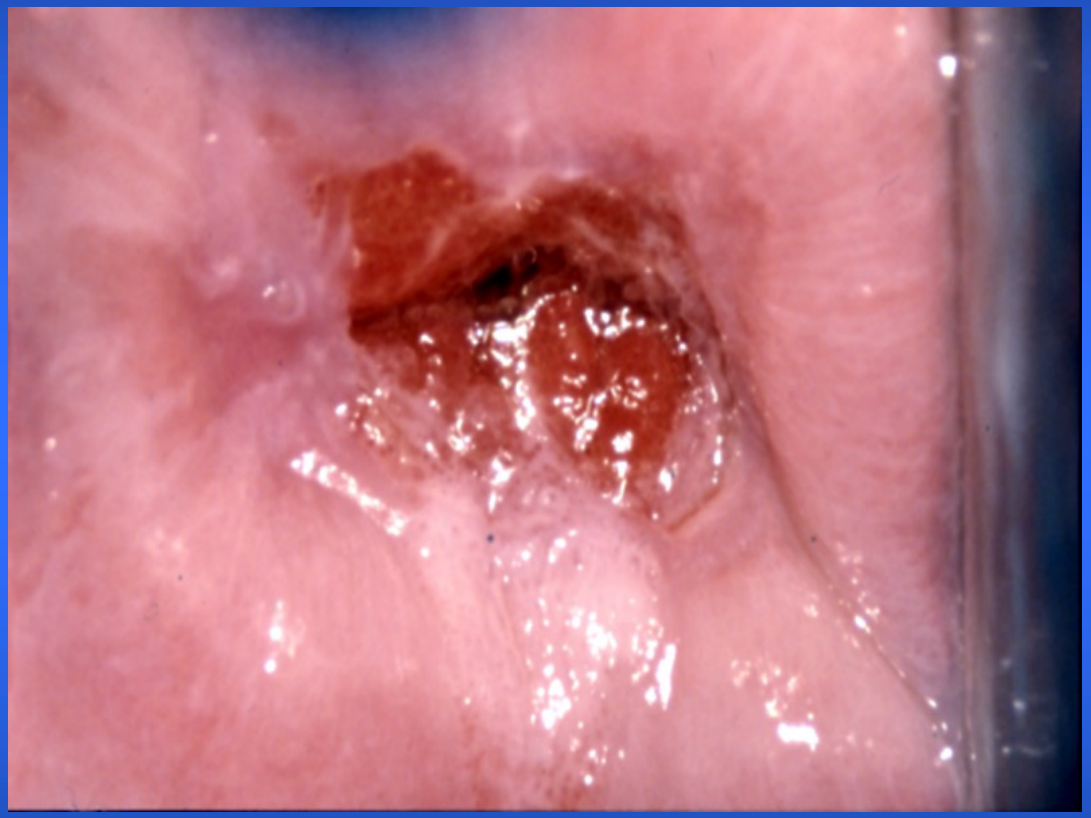


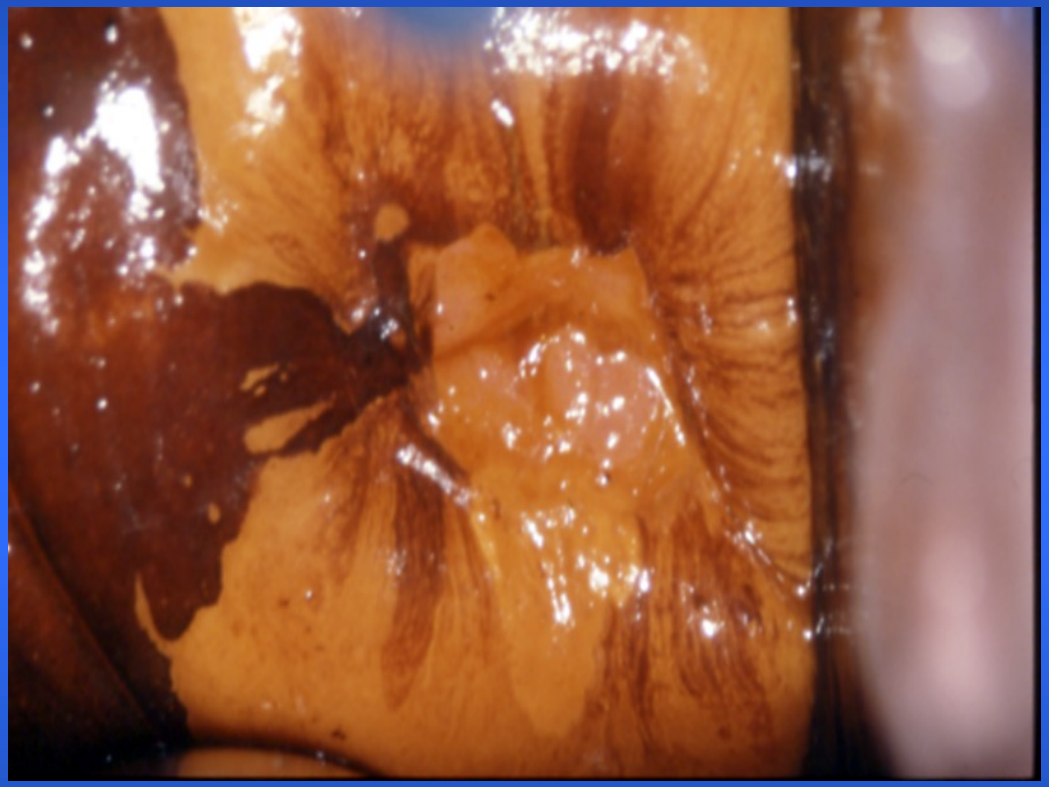


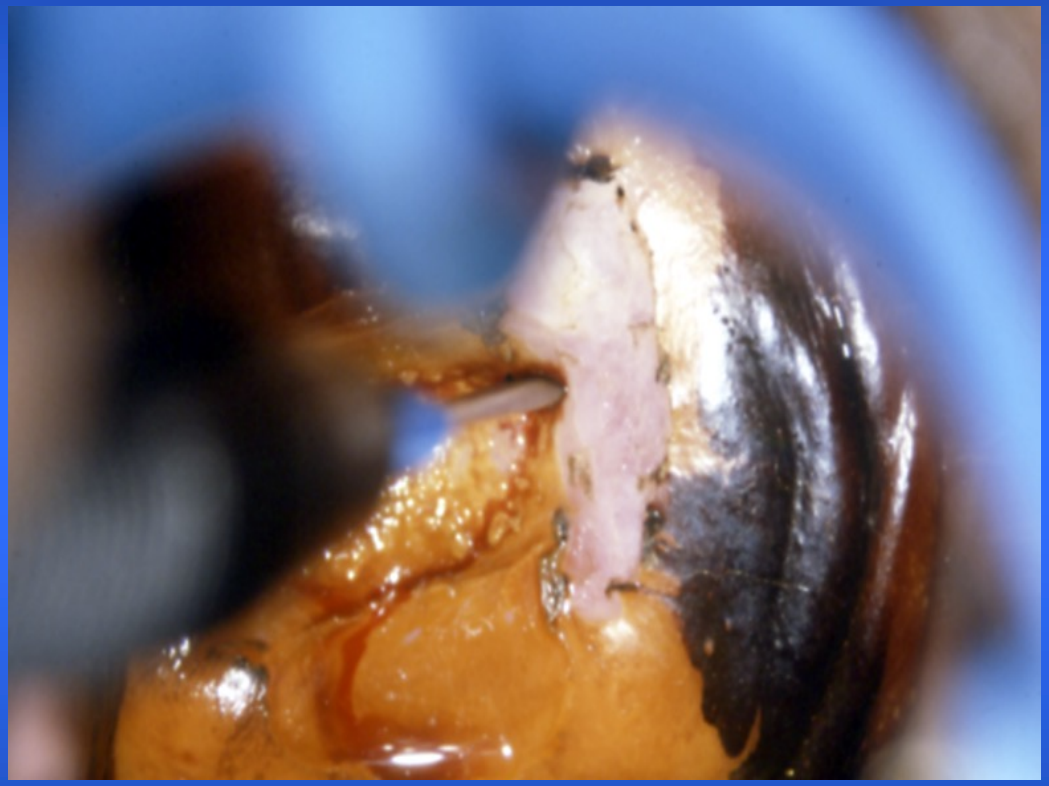


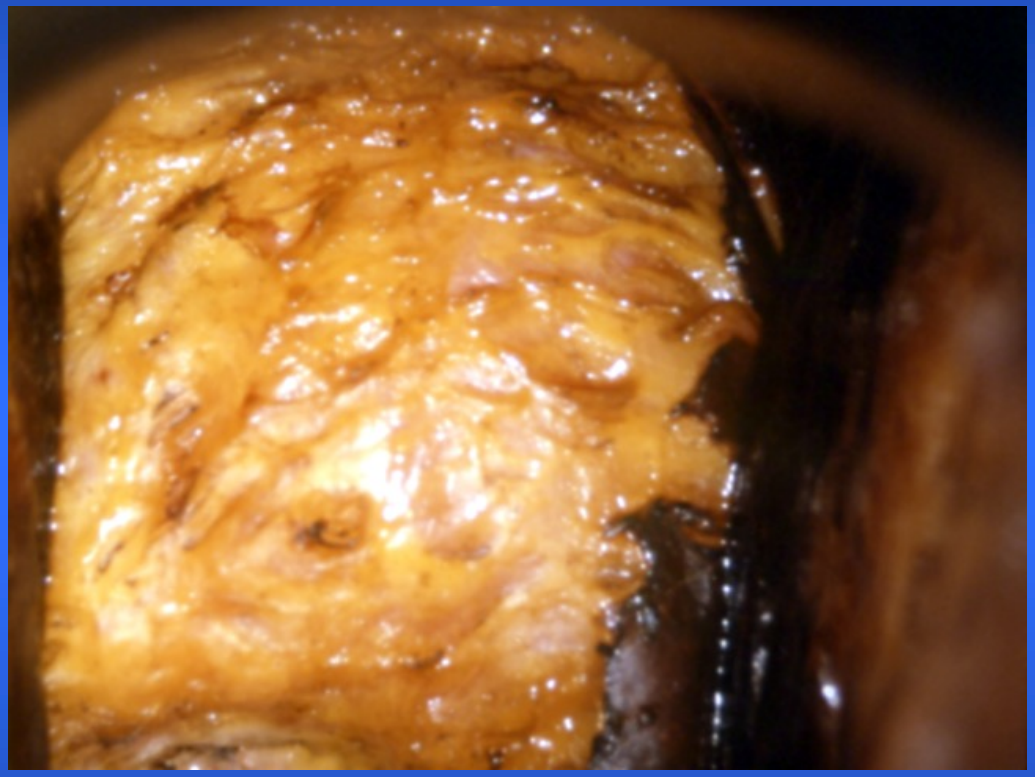


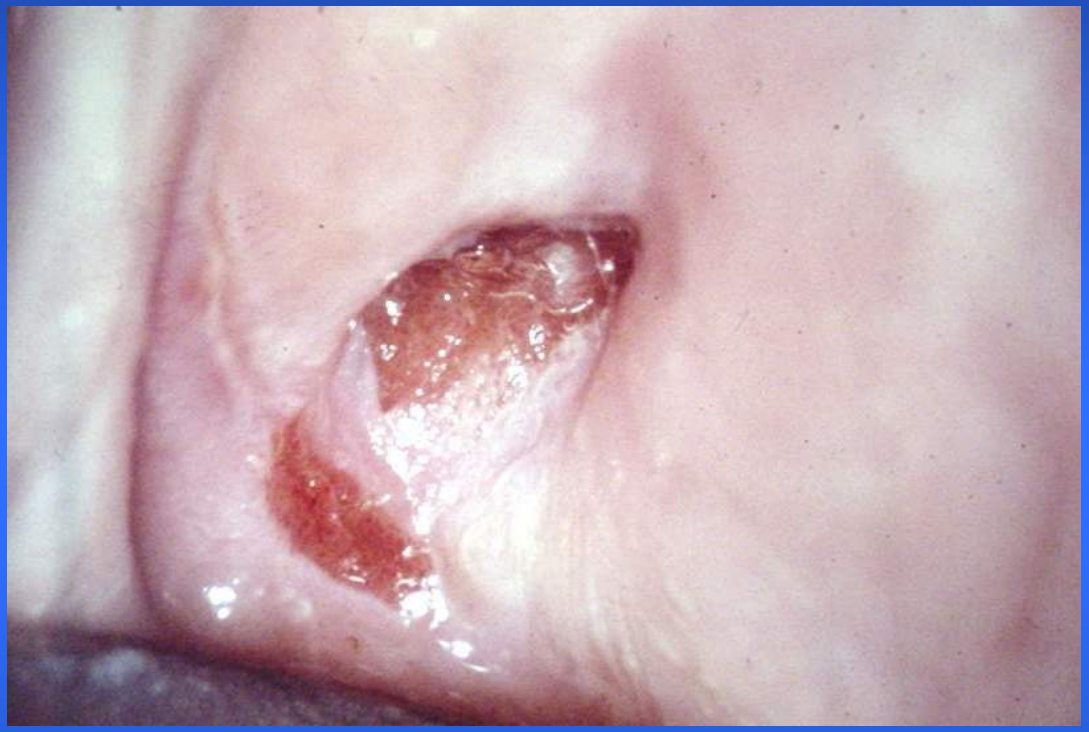


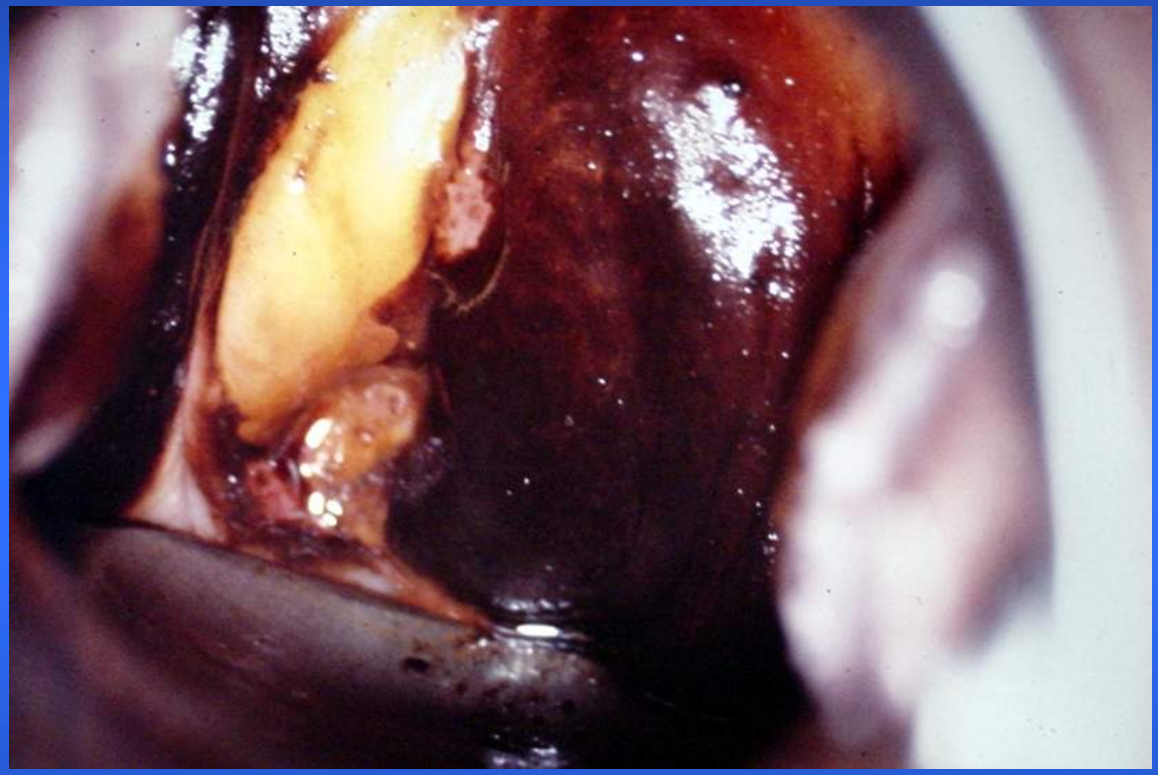






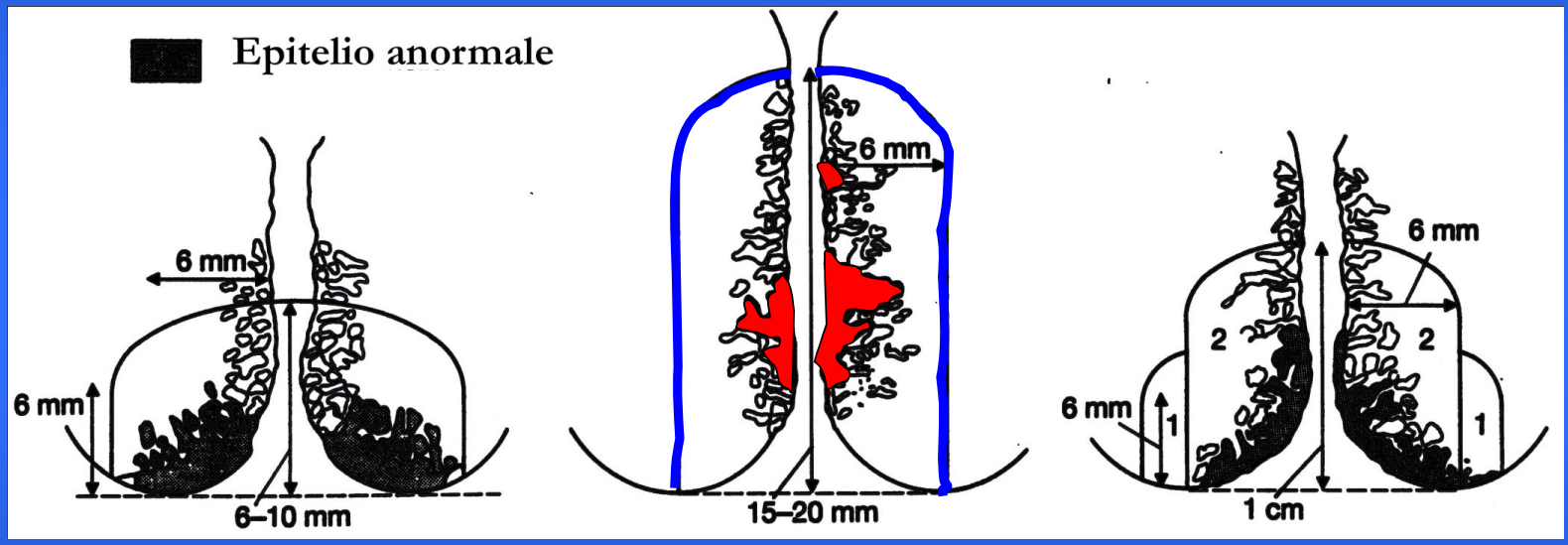






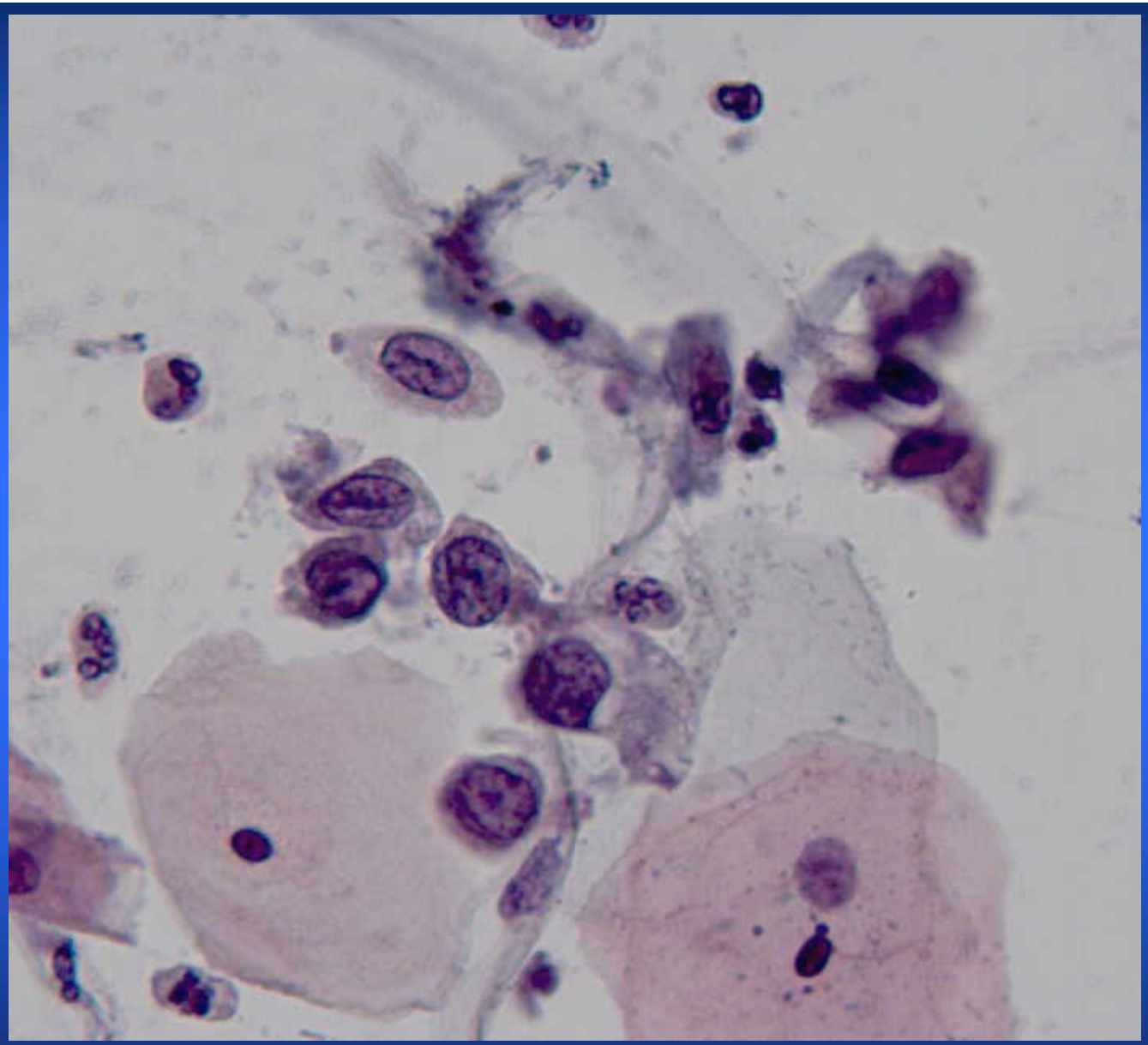
ENDOCERVICOSCOPIA

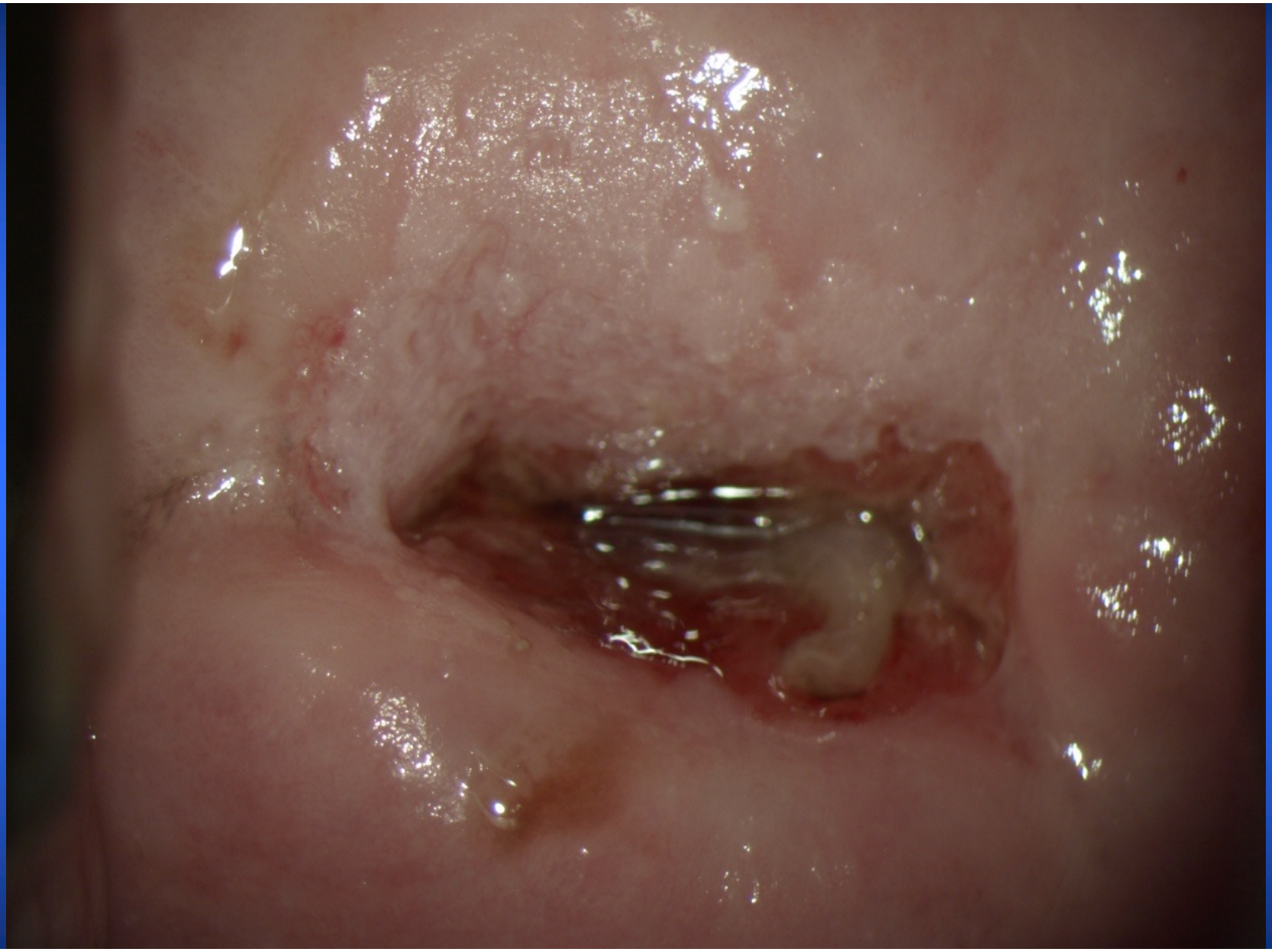
VARIABILITA'

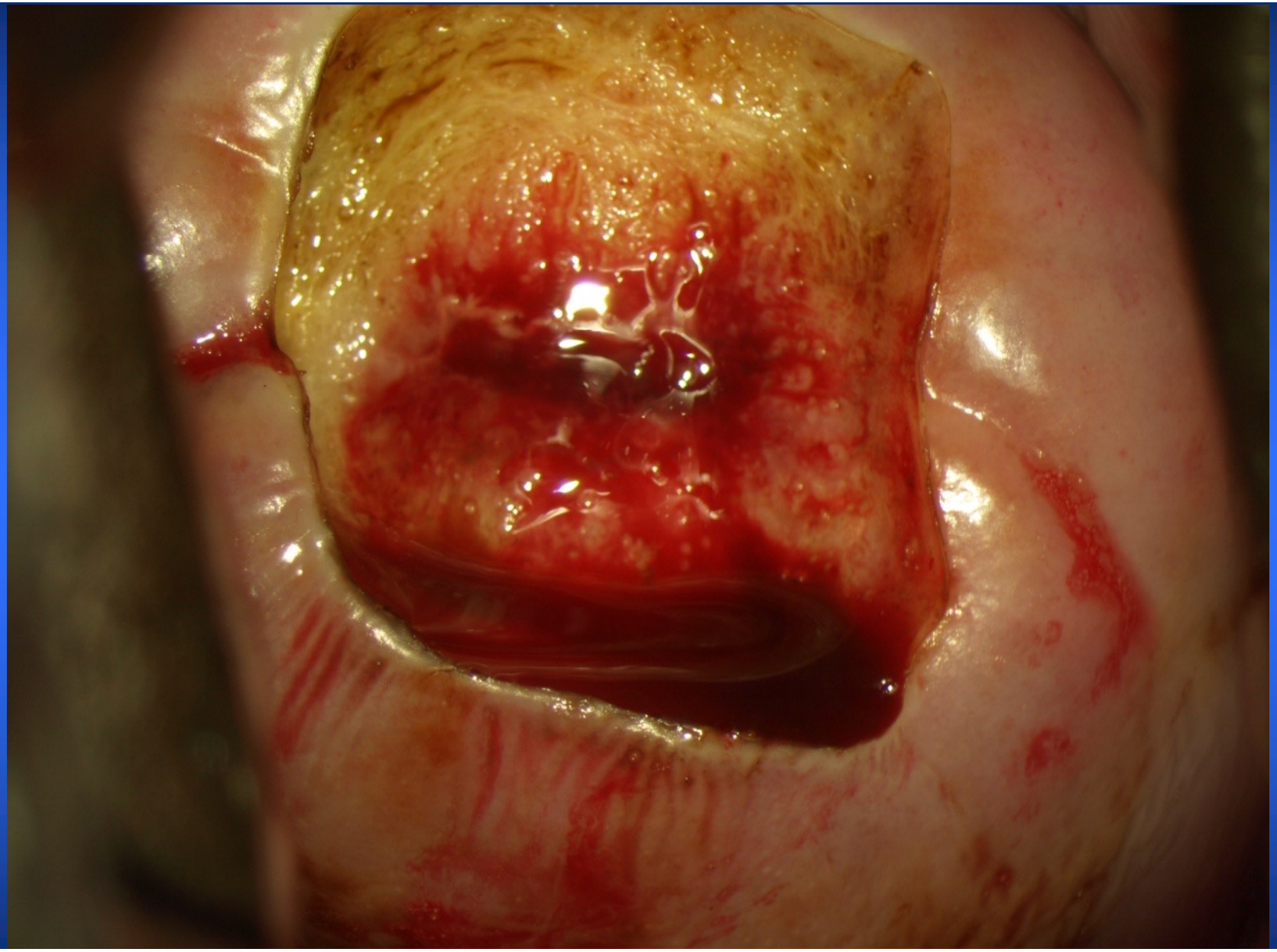


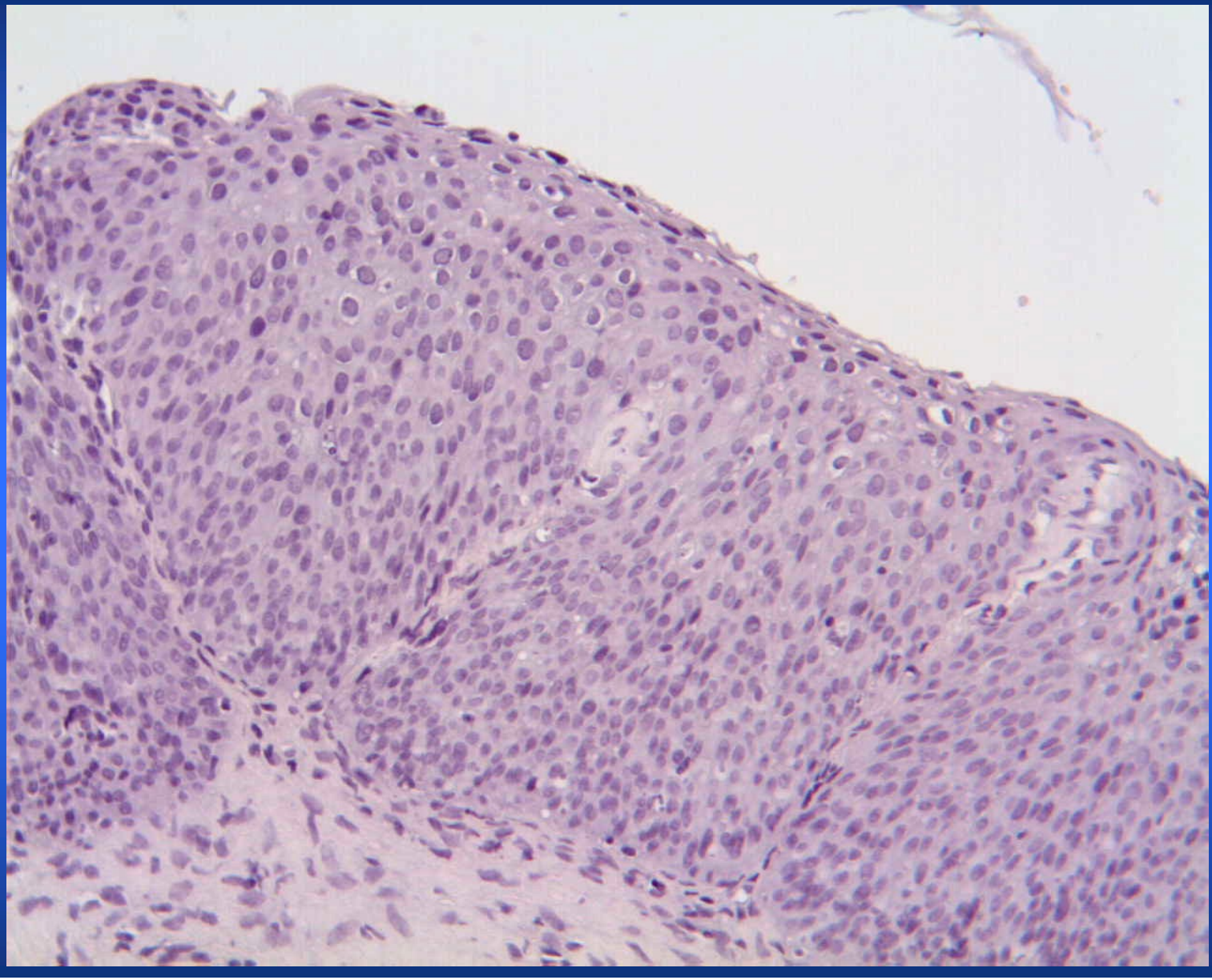
Modificata da:
Singer A & Monaghan JM "Lower genital tract precancer. Colposcopy, pathology and treatment

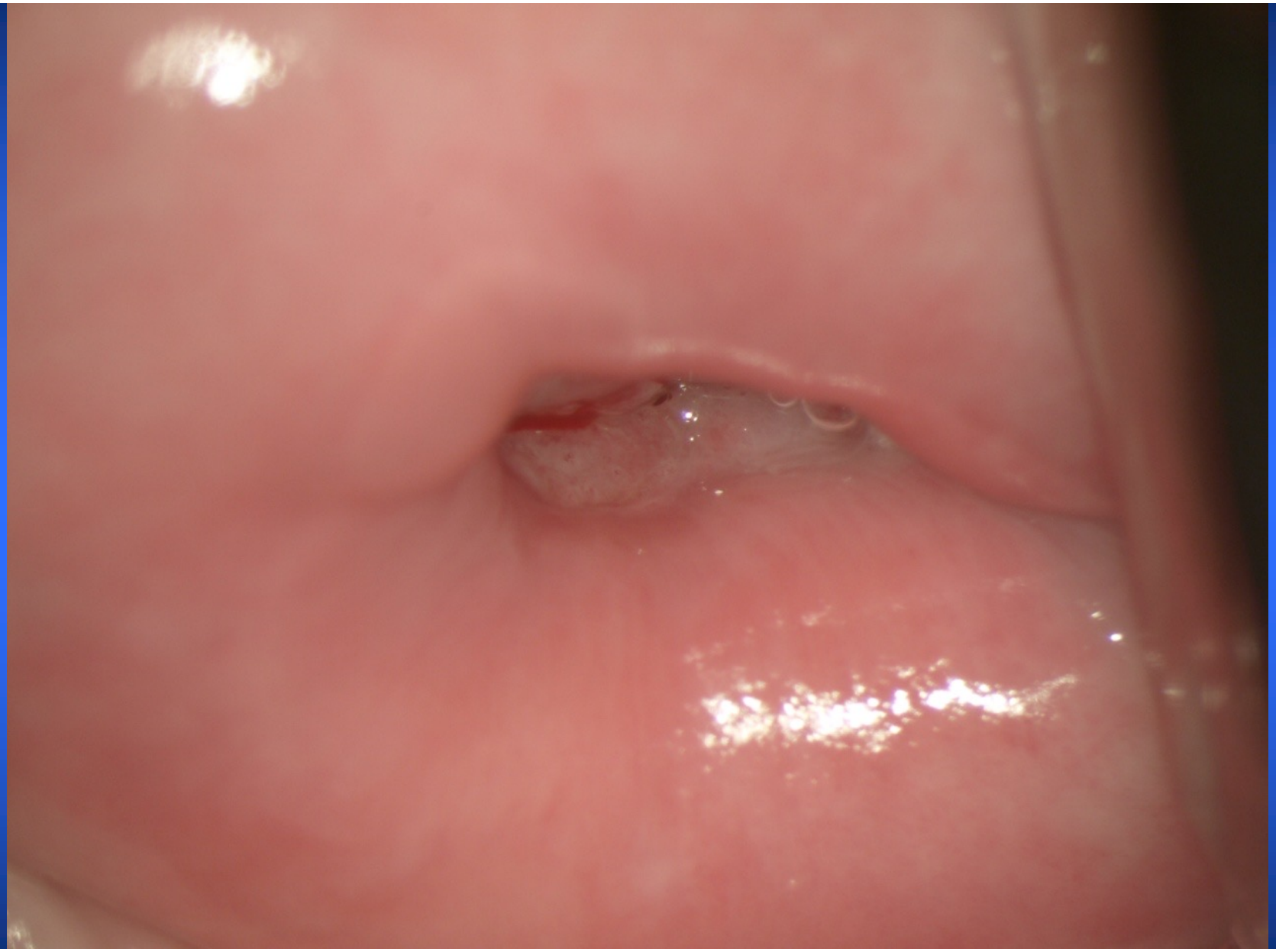
ESCISSIONE CON AGO











CASO CLINICO

A.D. 29/04/1972

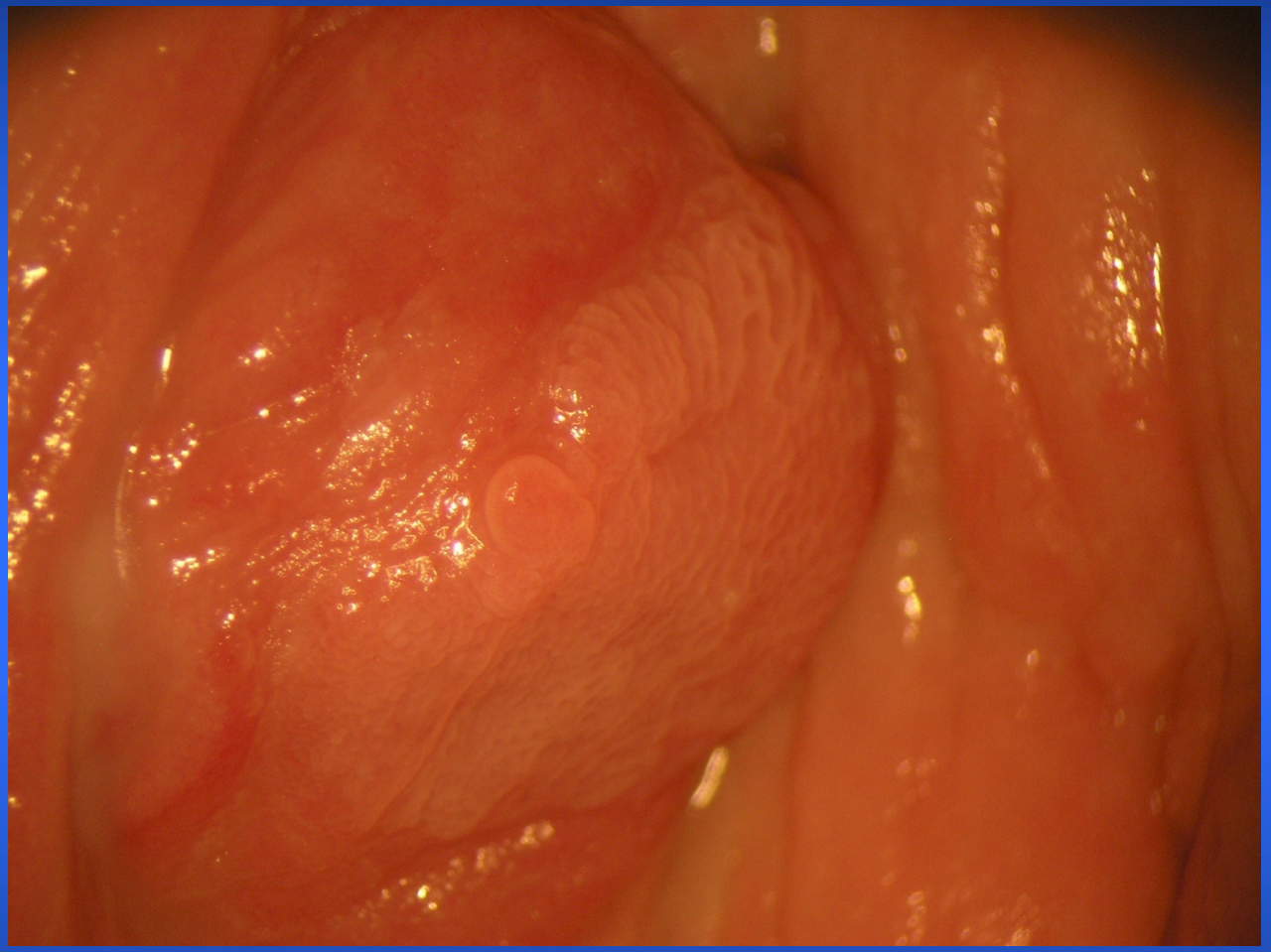
Nel 2013 41 anni - gennaio/luglio 2 Coniz. per CIN 3

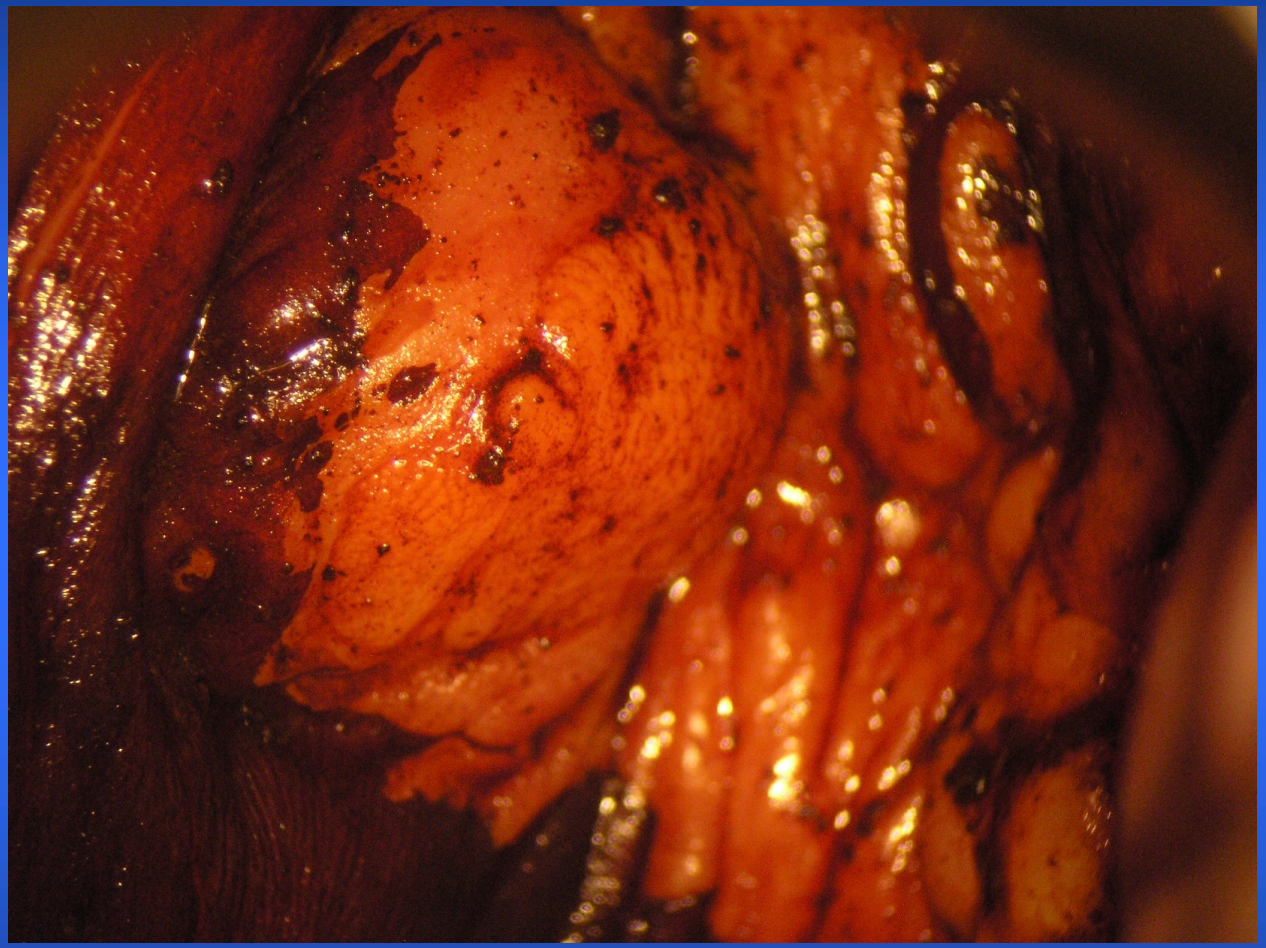
Nel 2013 – ottobre – H-SIL/CIN 3

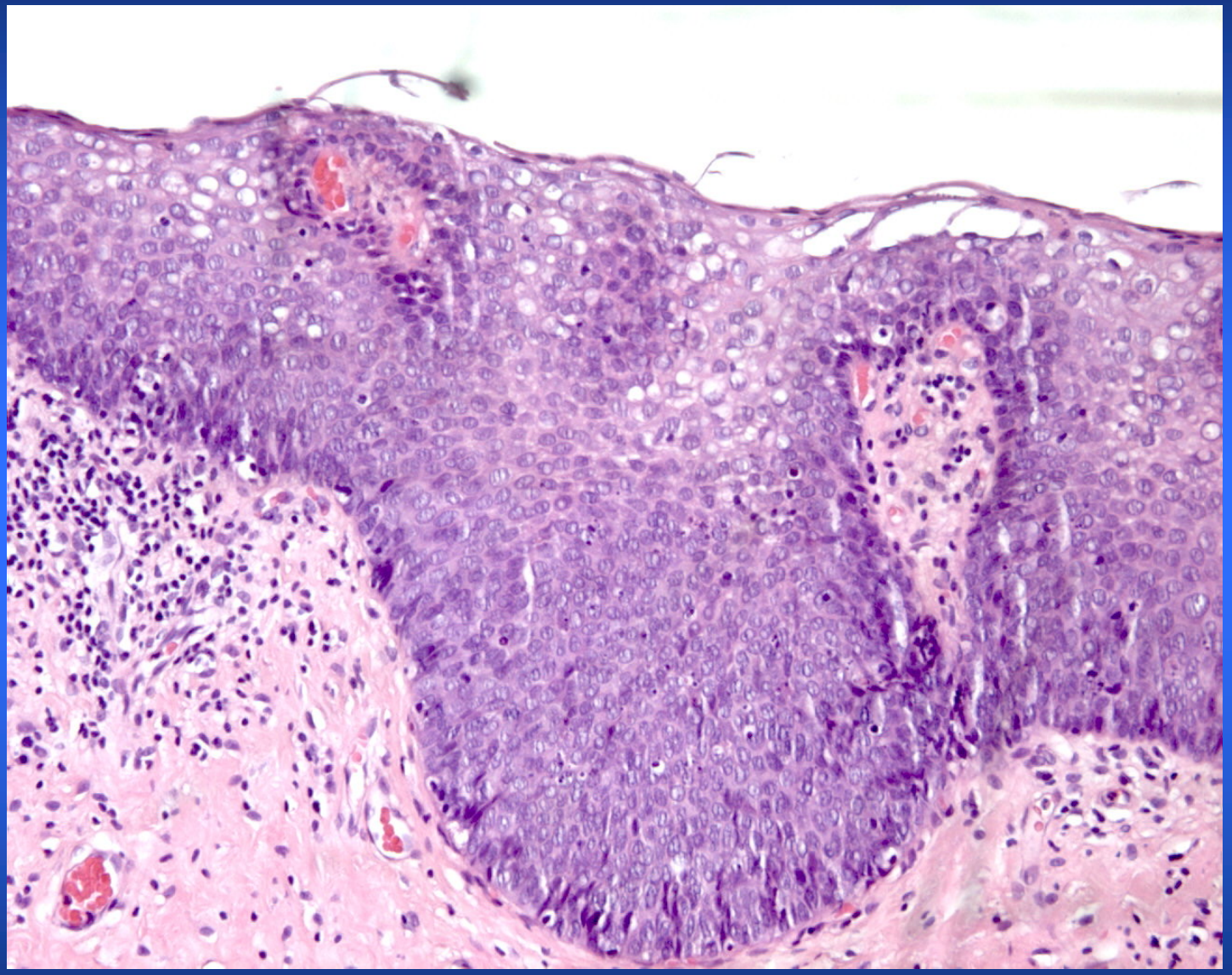
Nel 2013 – dicembre - isterectomia laparoscopica
E.I.: CIN 3 sul margine esocervicale

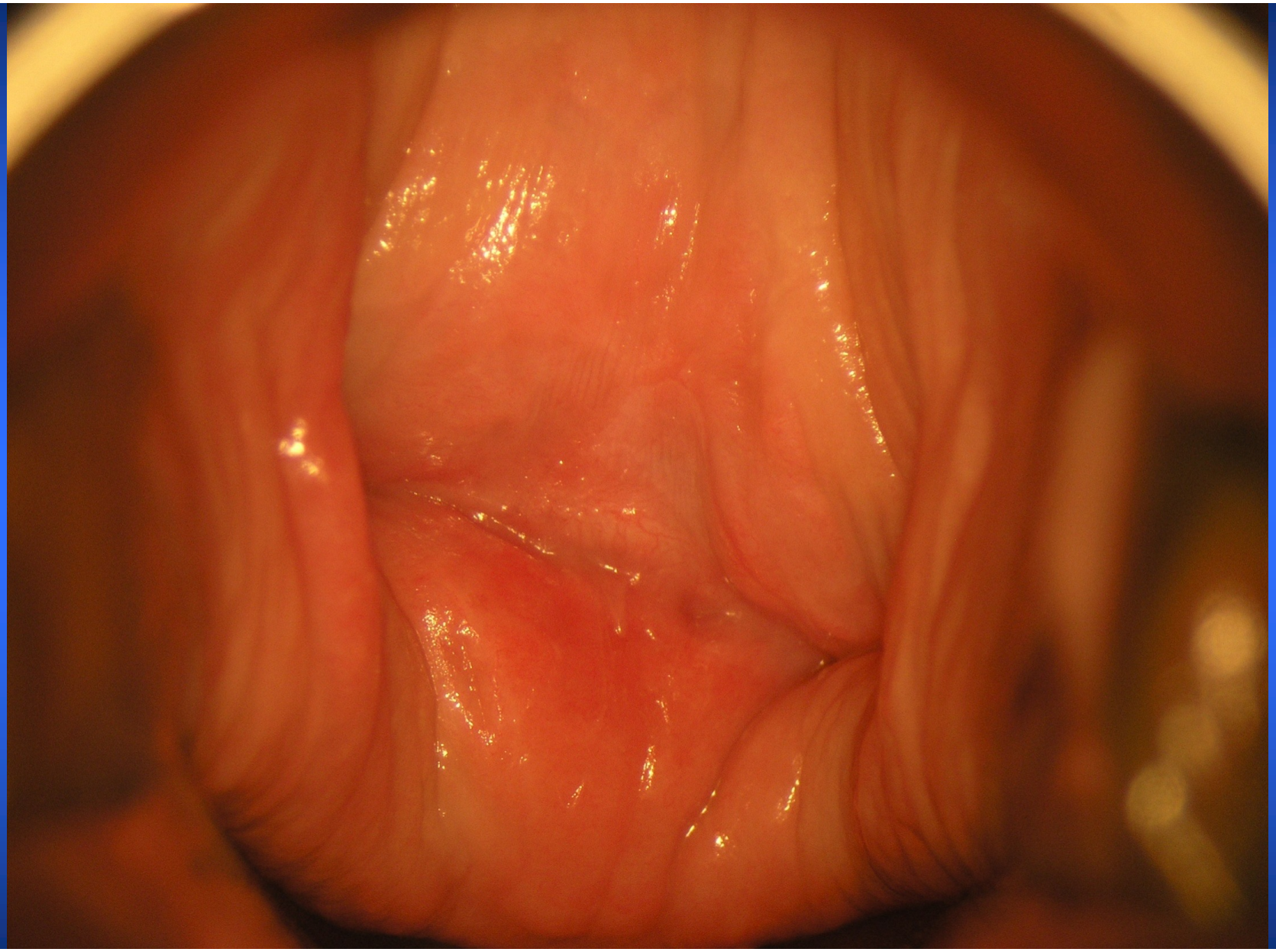
Nel 2014 – marzo- HSIL/VaIN 3

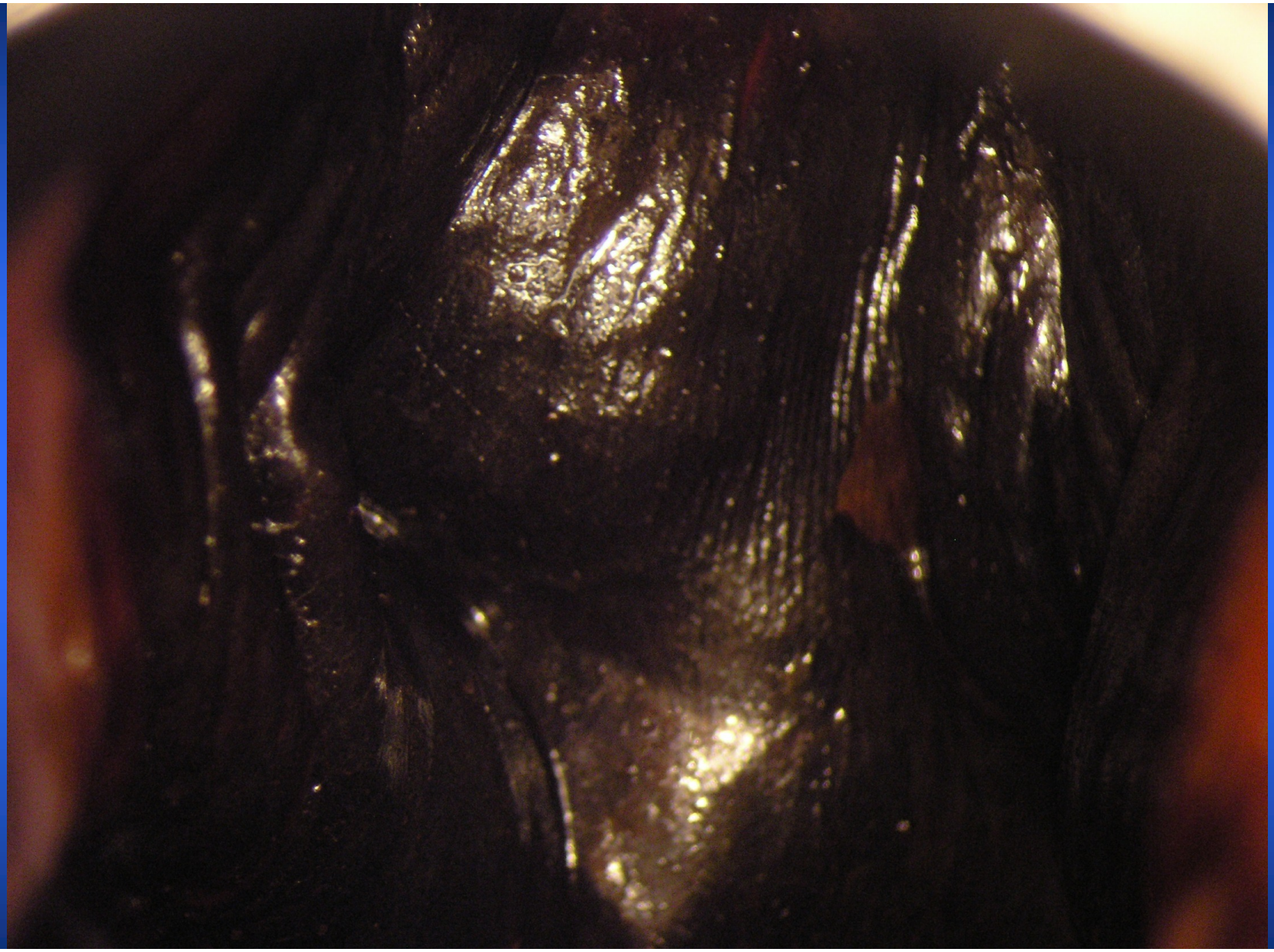
Nel 2014 – settembre – Escissione cupola vaginale con ago a RF











EXCISION OF THE TZ

- *LASER EXCISION IS EMPIRELY REASONABLE*
- Expensive
- Useful for vaginal disease
- Similar success and complications profile to LLETZ, with perhaps an incresed risk of subsequent perinatal mortality

- W. Prendiville – Praagues 5-7 september 2013

EXCISION OF THE TZ

- *LLETZ*
  - Usualy an outpatient procedure
  - Relatively inexpensive
  - Simple to perform
  - Accomodates all case of CIN and microinvasive disease and glandular disease
- If performed inexpertly may be associated with excess morbidity
-

CONCLUSIONI

- ***Il trattamento escissionale a radiofrequenza è:***

- ***Sicuro***
- ***Rapido***
- ***Bassa morbilità***
- ***Ripetibile***
- ***Difficoltà relativa***

L’isterectomia non è indicata!


Welcome
18th World
IFCPC
Congress
15 to 18
November
2023
Hotel Las Américas
Cartagena de Indias
Colombia
I.F.C.P.C


IFCPC
PARIS 2026
WELCOME TO PARIS !
World Congress of
the International Federation for
Cervical Pathology and Colposcopy
4th to 6th June 2026
The International Federation
of Cervical Pathology and Colposcopy

XXXVII CONGRESSO NAZIONALE della SOCIETA' ITALIANA di COLPOSCOPIA e PATOLOGIA CERVICO-VAGINALE (S.I.C.P.C.V.)

In memoria di Fausto Boselli

Modena

28, 29 e 30 novembre 2023