Trattamento della CIN:
c’è un ruolo per il ‘see and treat’?

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A.G.E.O. corso di aggiornamento in ginecologia e ostetricia

Bologna, 22-23 Novembre 2019

Rationale

* 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[2,3]

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

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
No 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)

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Results

≤30-year-olds

	6 months			12 months			24 months		
	Regression	Persistence	Progression	Regression	Persistence	Progression	Regression	Persistence	Progression
No 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

Results
Progressions

* 3 studies reported a total of 15 cases of adenocarcinoma in situ (AIS) diagnosed during the follow-up period
  * 14 of these in <25-year-olds
* 4 studies reported a total of 15 cases of invasive cervical cancer
  * 13 of these were stage 1A1; 2 cases of more advanced disease
  * At least 7 were found in women >40 years of age
* Overall invasion rate: 15/3160 women, 0.5%

Discussion
In light of other evidence

* Risk of CIN 2 progression to invasion has been previously reported as 5%[1]
  * 0.5% in our study
* Risk of invasion in untreated CIN 3 has been reported to be 17%[2]; Östör 12%[1]
  * Marked difference in natural history of CIN 2 and 3
* Regression rates from our study higher than previously reported (50% vs. 44%[1]) and even more substantially in young women (60%)

[1]Östör 1993; [2]McCredie 2008

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?

Treatment

Overtreatment

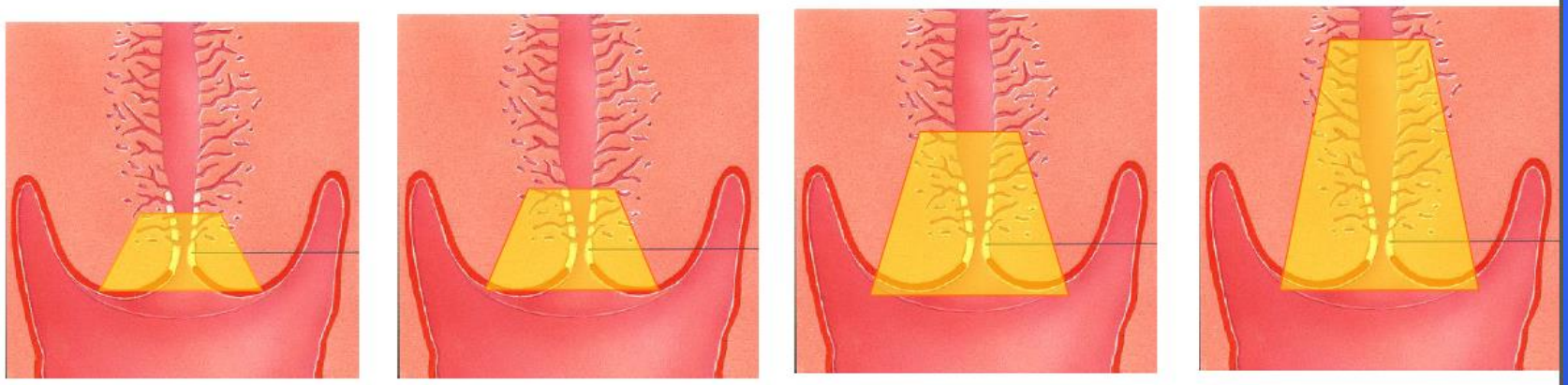
Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

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..

TRATTAMENTO DELLA CIN

TRATTAMENTO DELLA DONNA AFFETTA DA CIN

TERAPIA DELLA CIN

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

MANAGEMENT OF CIN

While some 60–70% of histologically spected cases will revert to normal over time, some 15% will persist.

Between 0% and 30% will ultimately reveal CIN2-3 and less than 1% will lead to invasive carcinoma.

Pertanto..

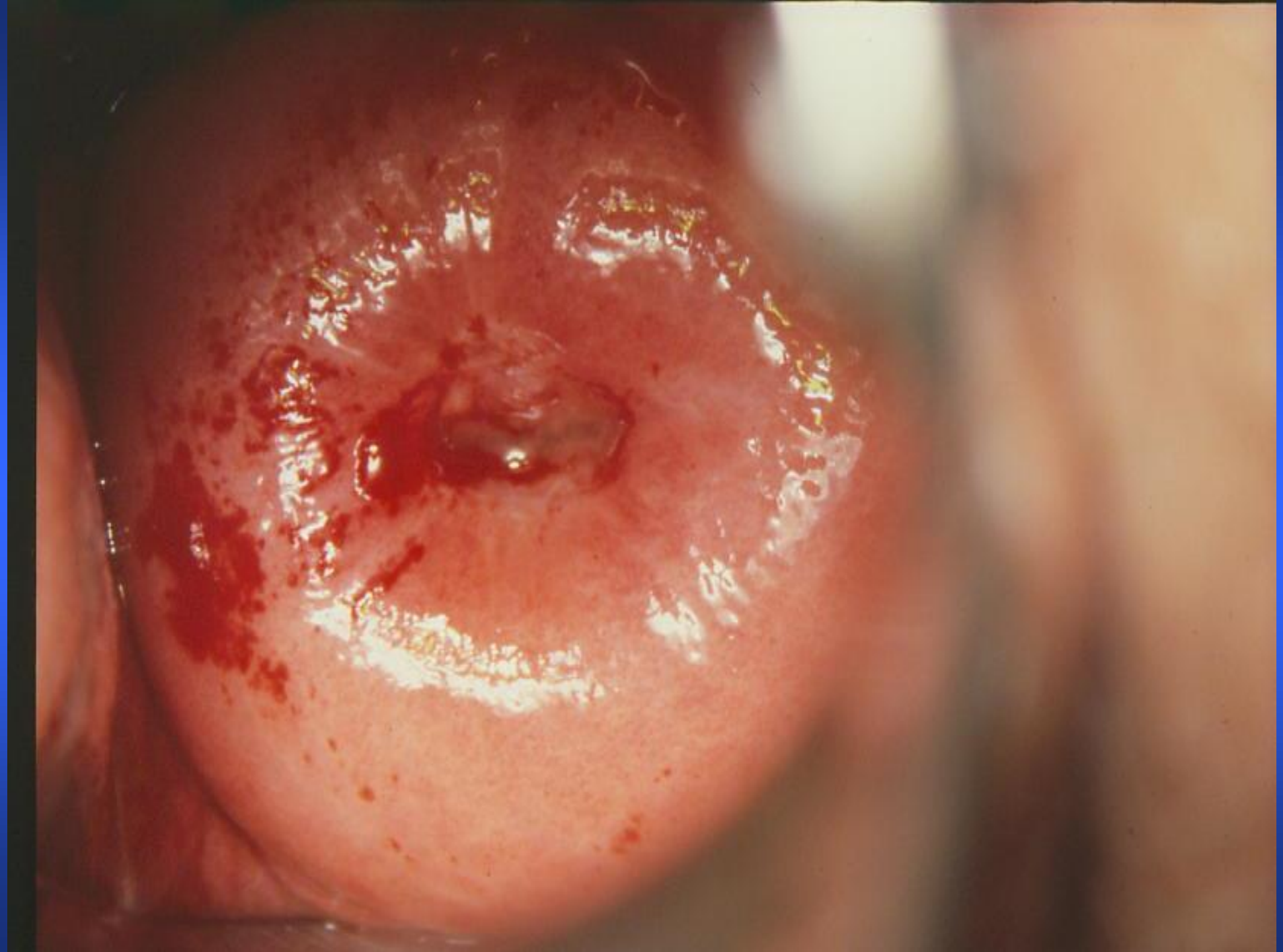
- Cautela nel decidere un trattamento
- Scegliere il trattamento meno invasivo
- Terapia efficace
- Follow up necessario

MANAGEMENT OF CIN > 50 ANNI

- La zona di trasformazione tende a ritrarsi entro l'endocervice in più del 40% delle donne sopra i 50 anni.
- L'epitelio squamoso diviene atrofico
- Viene persa la glicogenazione
- Frequente stenosi dell'OUE

↓

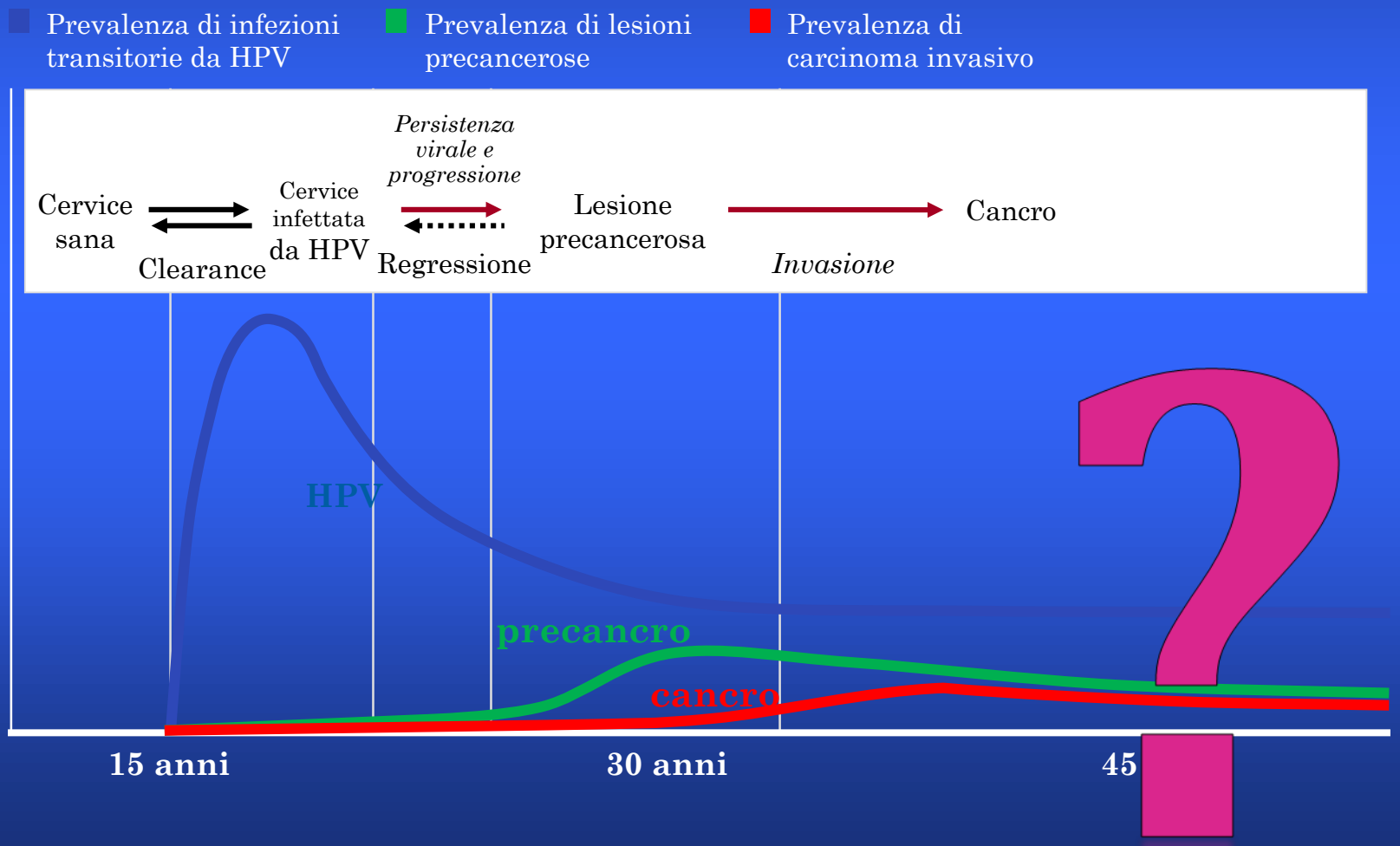
COLPOSCOPIA NON CONCLUSIVA



Pertanto..

- Ripetizione PAP TEST
- Colposcopista esperto
- Terapia estrogenica locale
- Trattamento escissionale
- Ago
- Follow-up intensivo

STORIA NATURALE DEL CERVICOCARCINOMA



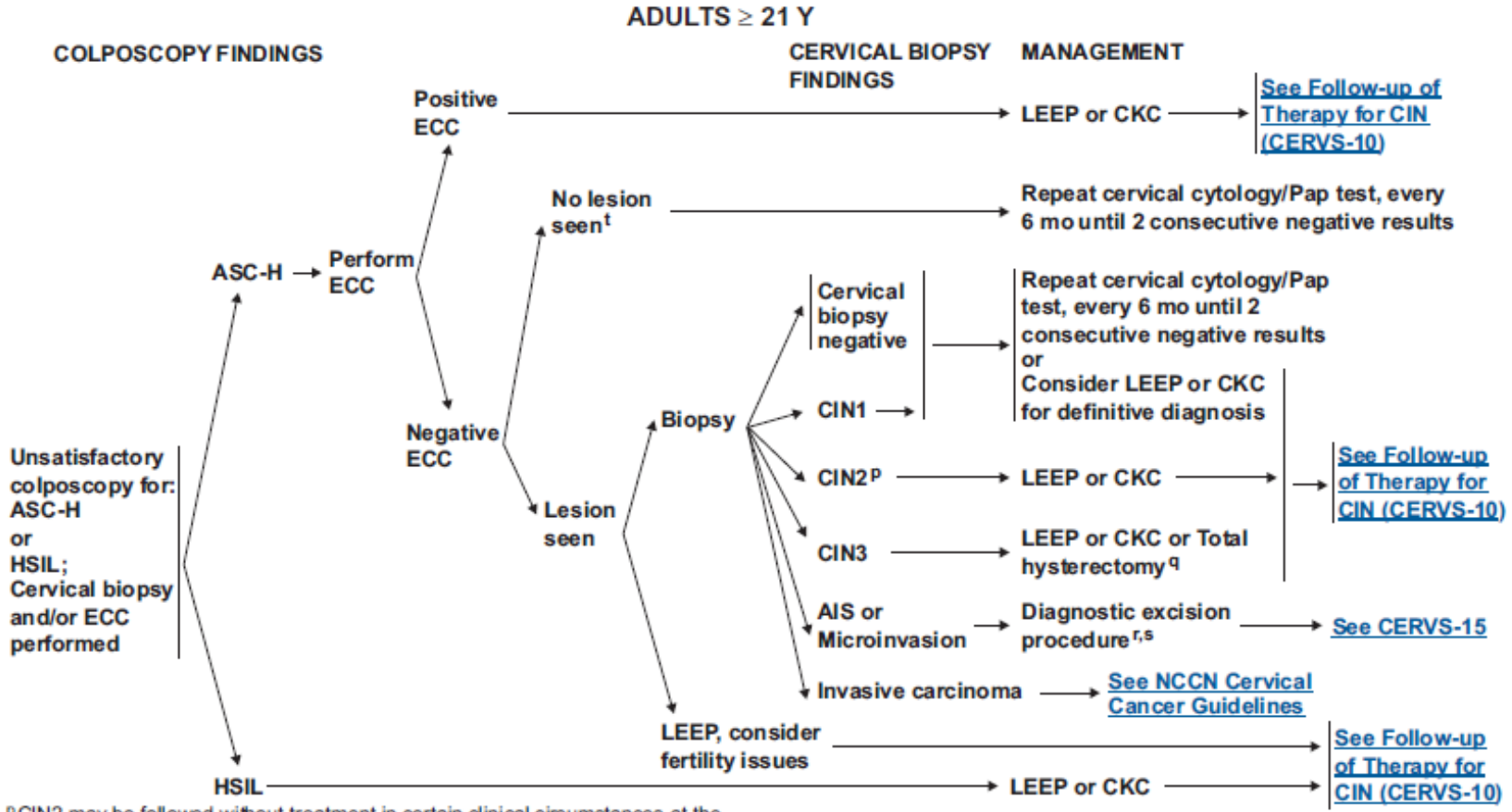
LINEE GUIDA SICPCV

HSIL → COLPOSCOPIA → BIOPSIA MIRATA

↓

TRATTAMENTO

NCCN Guidelines Version 2.2012
Cervical Cancer Screening



[p] CIN2 may be followed without treatment in certain clinical circumstances at the discretion of the physician.

[q] If appropriate for preexisting pathologic condition or quality of life.

[r] CKC is preferred. However, LEEP is acceptable provided attention is given to adequate margins.

[s] If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done.

[t] Perform vaginal and vulvar colposcopy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

152 West Washington St • Hagerstown, MD 21740 • 301-733-3640 • 800-787-7227 • 301-733-5775 (fax)

ASCCP

AMERICAN SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY

The society for lower genital tract disease since 1964

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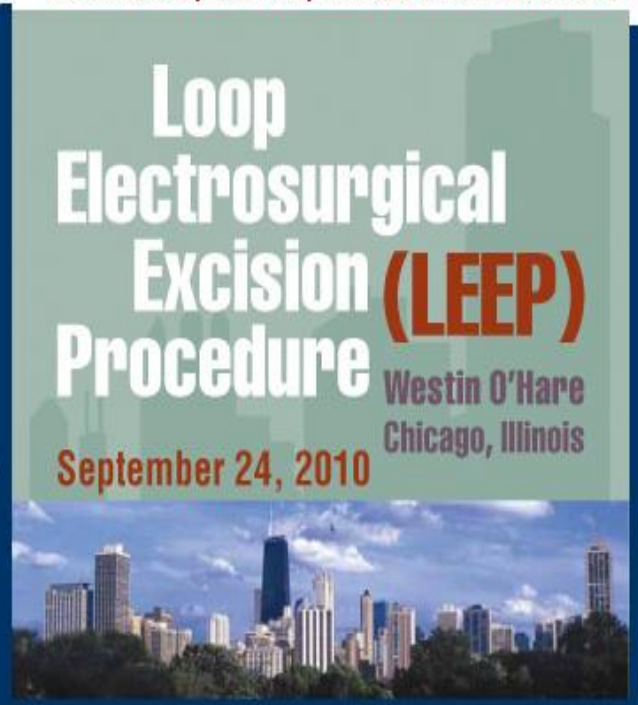

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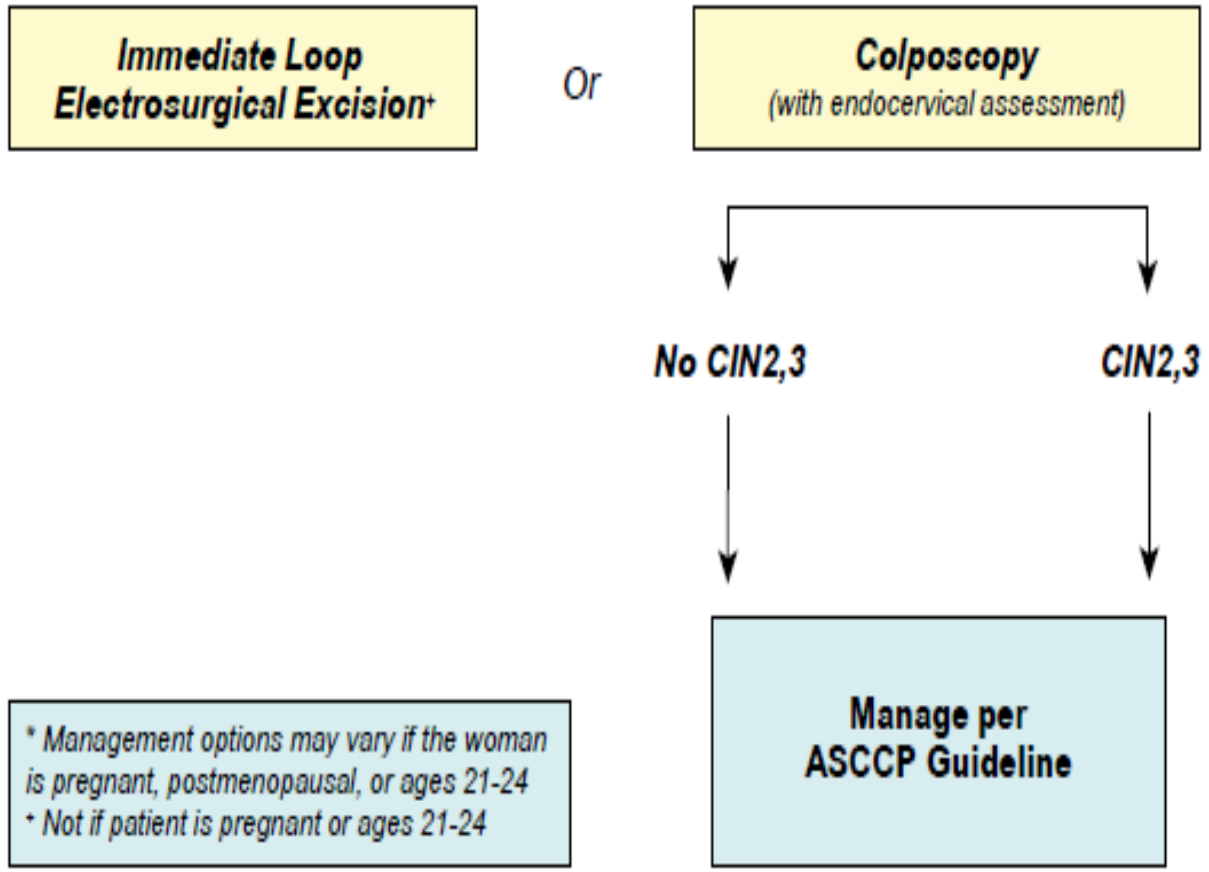
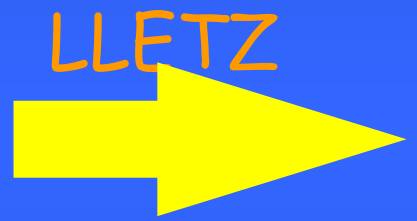
Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)*



H-SIL: QUALE ISTOLOGIA ?

100 casi H-SIL

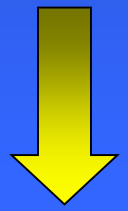


94% CIN 2 - 3
2% CIN 1
1% NO CIN
3% MICROINV

Dunn TS 2003

SEE AND TREAT

CITOLOGIA ANORMALE



COLPOSCOPIA

TRATTAMENTO

SEE AND TREAT

ASSENZA DI ANOMALIE ISTOLOGICHE	5 %	Luesley,	1990
	5 %	Bicrilg,	1990
	10 %	Howe,	1991
	14 %	Ferenczy,	1996

…. Loop electrosurgical excision procedure using the “see and treat” approach should be limited to cytologically and colposcopically unequivocal intraepithelial lesion….

…. Loop electroexcision represents an attractive means of diagnosing and treating cervical cancer precursors.

Conclusions

Implications for research

We would advocate a large multi-centre trial of sufficient power to evaluate the role of primary “see and treat” versus LLETZ or Laser Ablation after confirmation of disease by representative biopsy

”Evidence supporting see-and-treat management of cervical intraepithelial neoplasia: a systematic review and meta-analysis” RMF Ebisch at all, BJOG Jul 2015

3732 pubblicazioni → **13 studi**

4611 pazienti

OVERTREATMENT → **NO CIN- CIN1**

OVERTREATMENT

HSIL + COLP. G II → 11,6%

HSIL + COLP. G I → 29,3%

LSIL + COLP. G II → 46.4%

LSIL + COLP. G I → 72.9%

TWO STEP 11-35%

CONCLUSIONI

SEE AND TREAT → HSIL+ COLP. G II

In accordo con ASCCP

EFC

NHSCSP

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**

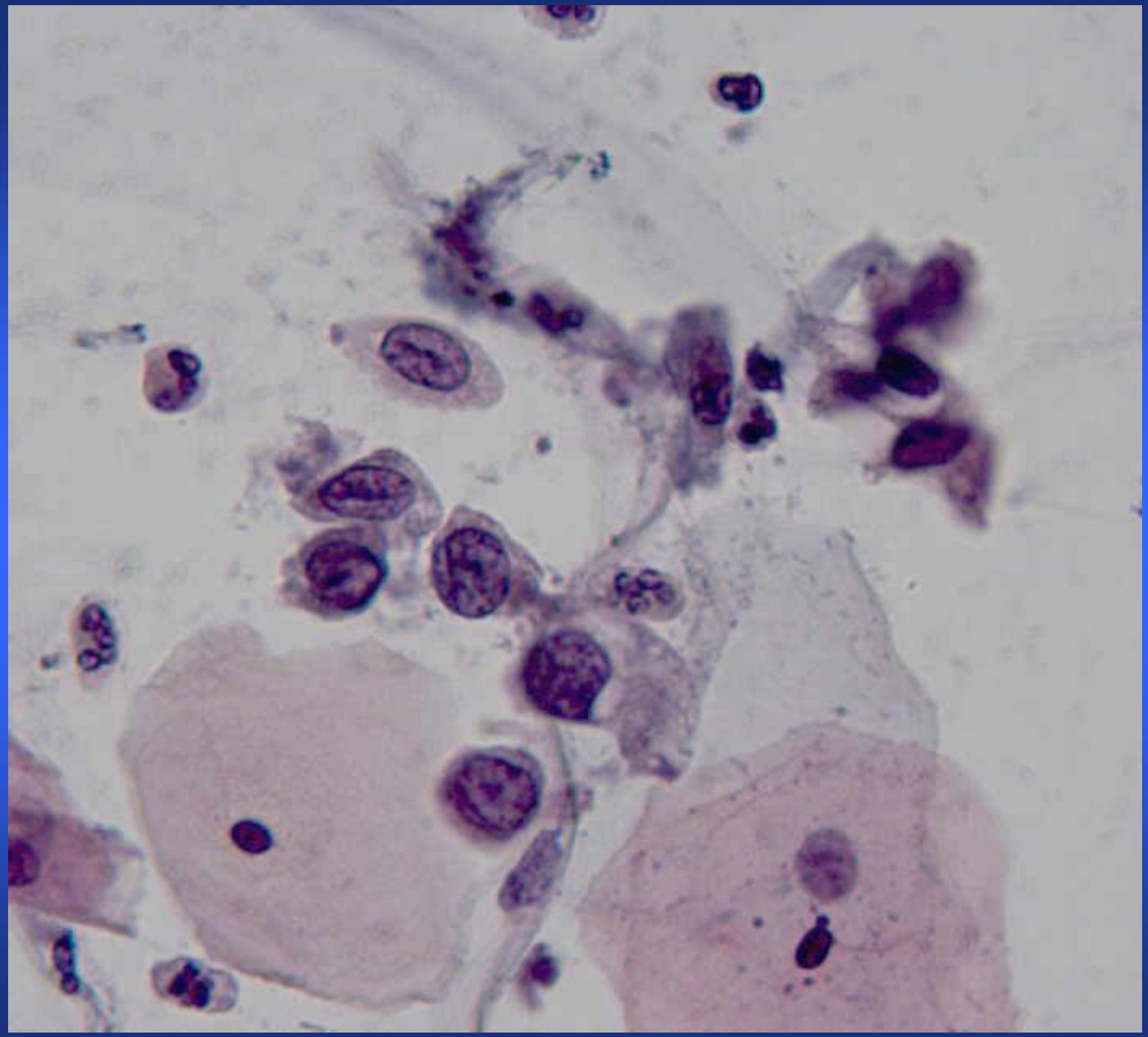
Correlazione tra esame citologico ed **esame istologico da biopsia mirata:**

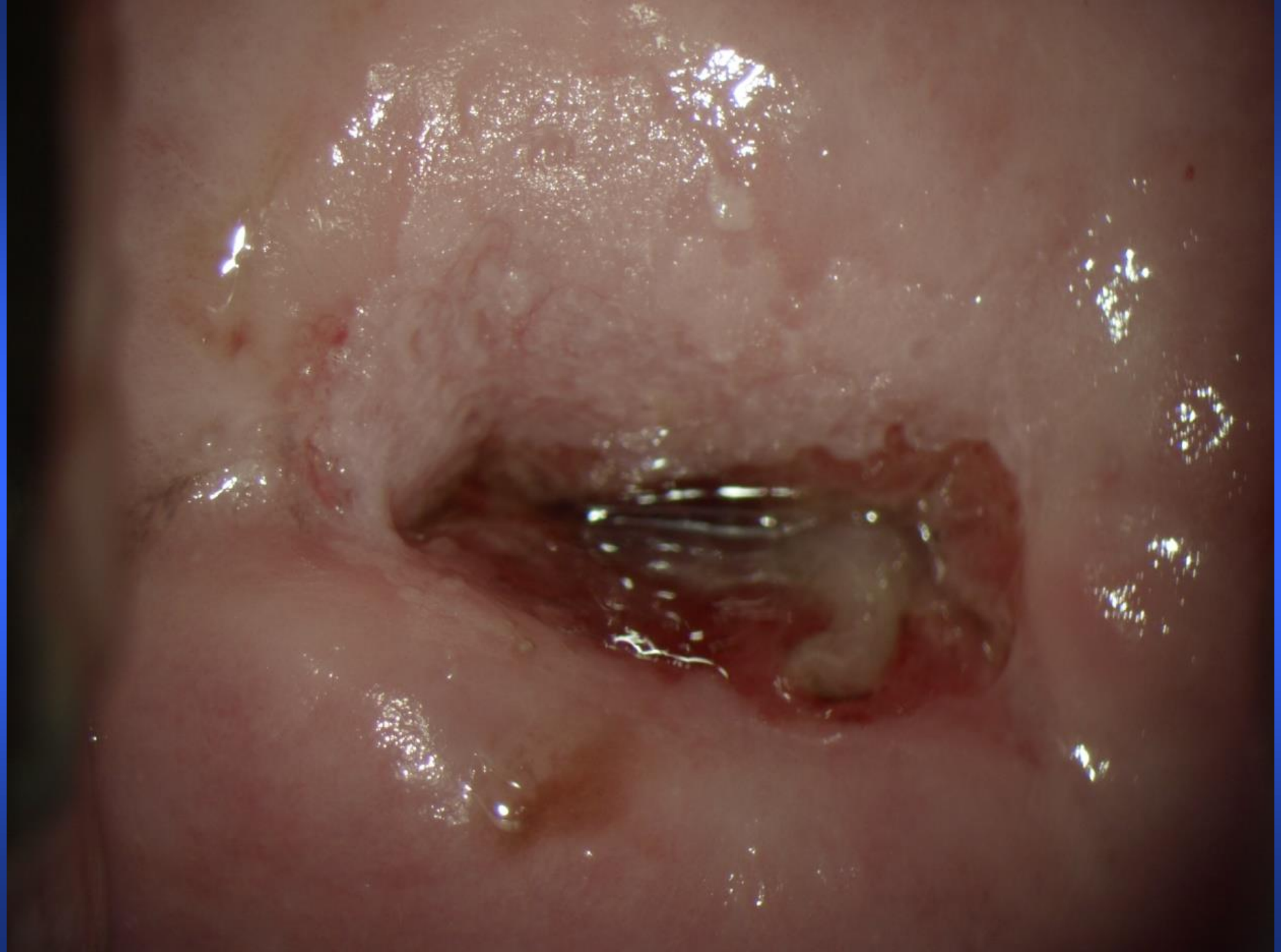
372 casi HSIL:

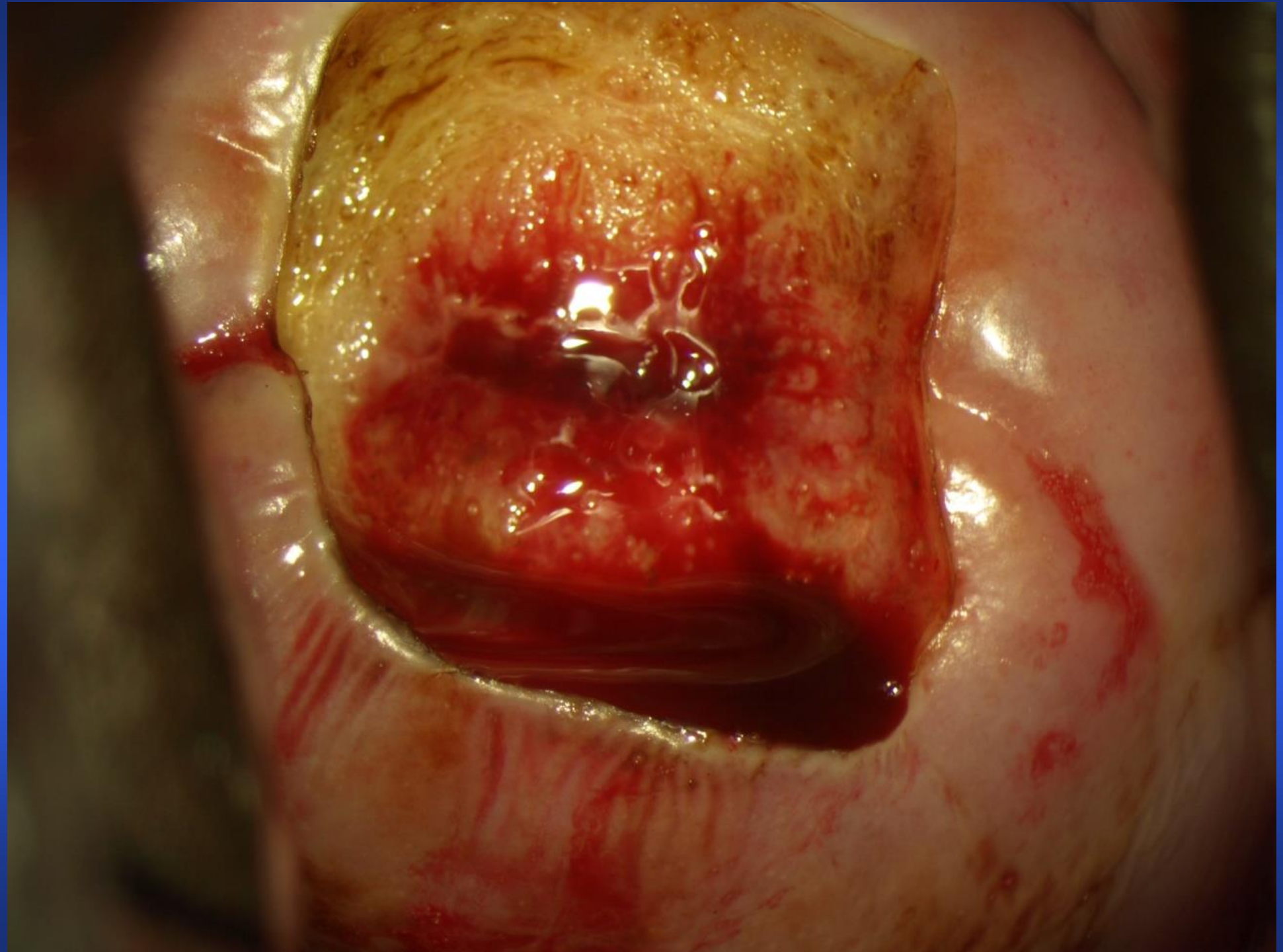
- 2.7% negativi (10 casi)
- 7.5% CIN 1 (28 casi)

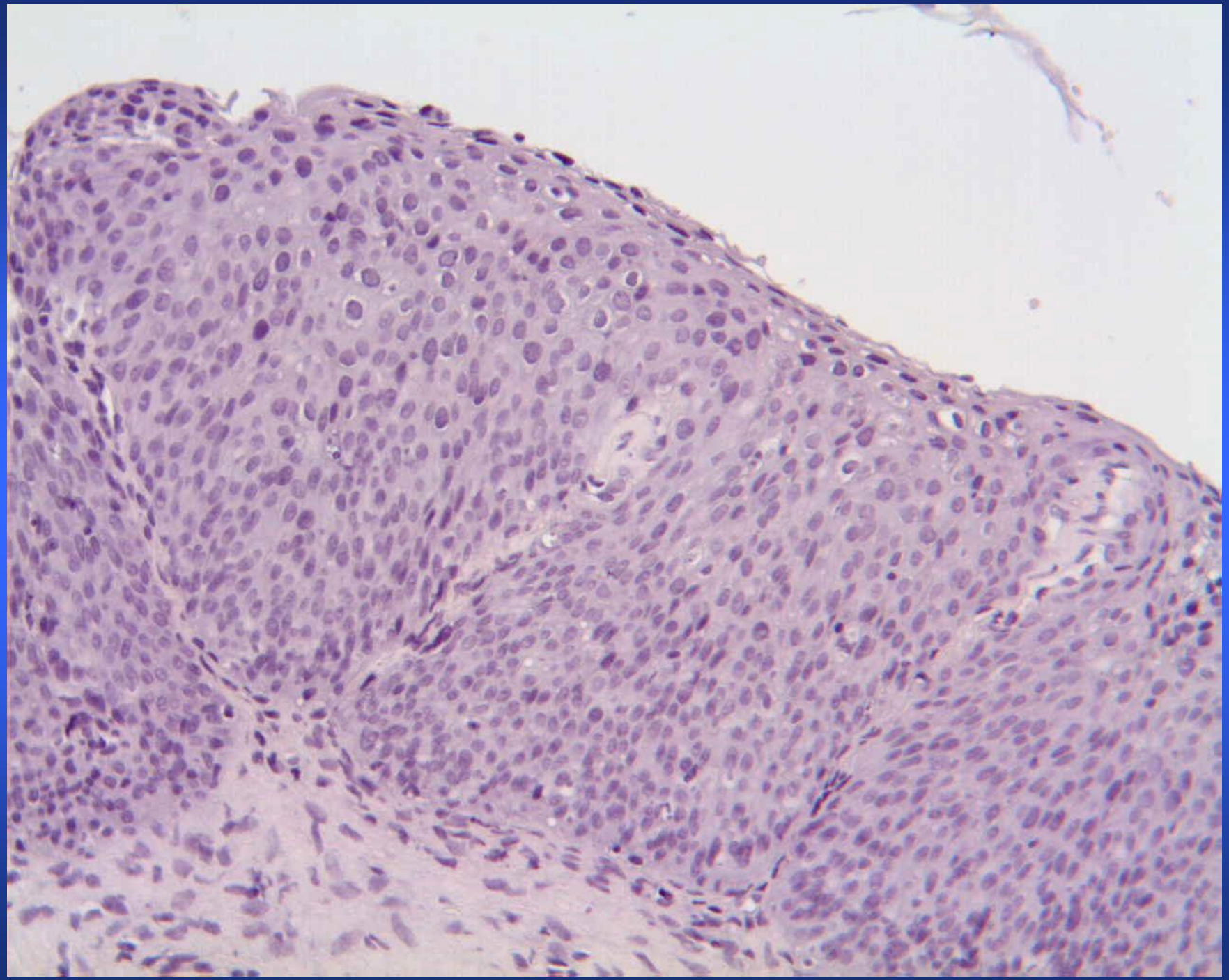
POSSIBILE RUOLO DEL SEE AND TREAT

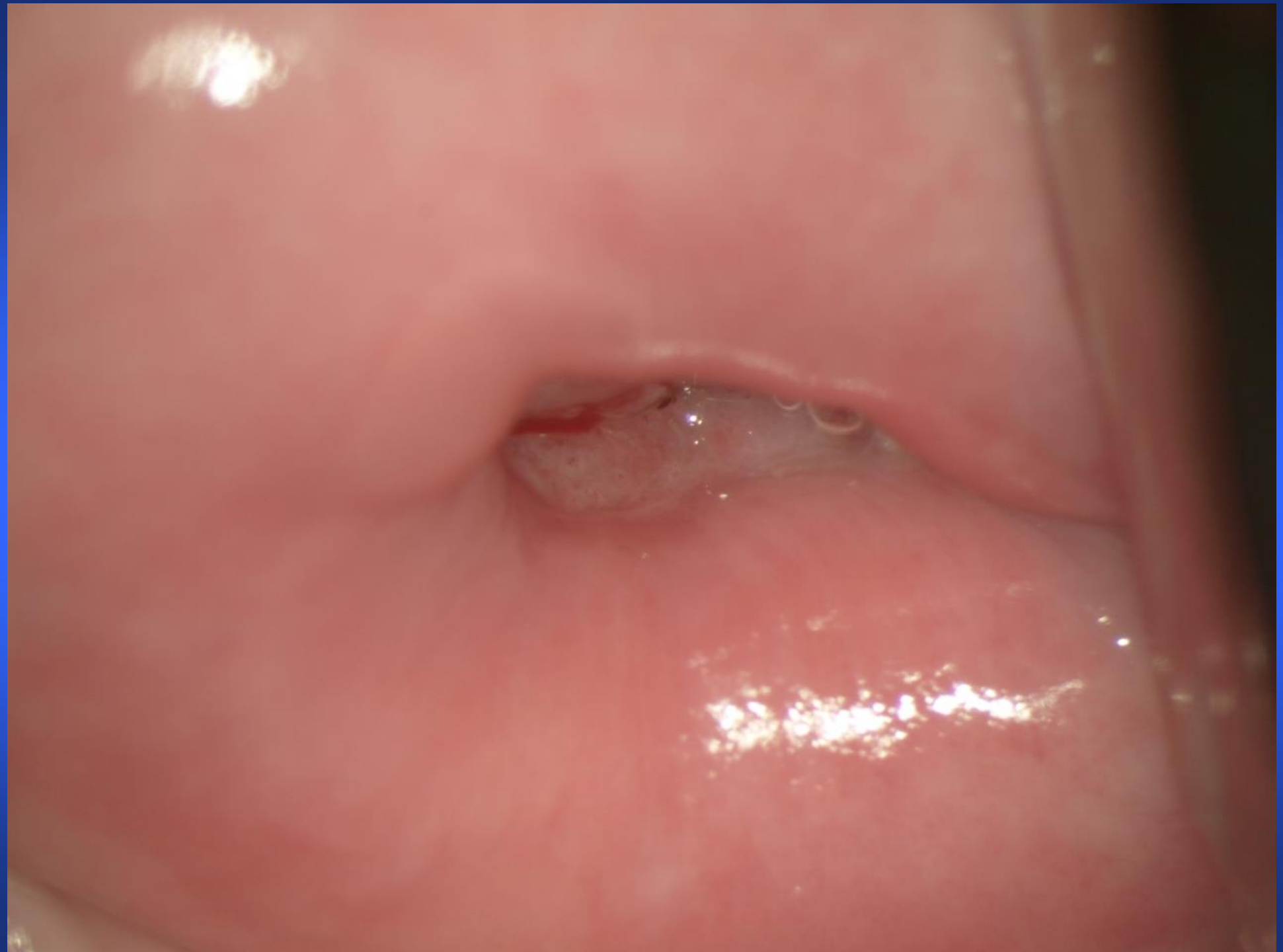
- Citologia H-SIL, Colposcopia G2
- Citologia H-SIL, Lesione endocervicale
- Nel follow-up di pazienti trattate per H-SIL, con colposcopia e citologia positiva
- Nel follow-up di pazienti trattate per ca invasivo, con colposcopia e citologia positiva
- Pazienti non affidabili
- Pazienti in situazioni ambientali e sociali disagiate











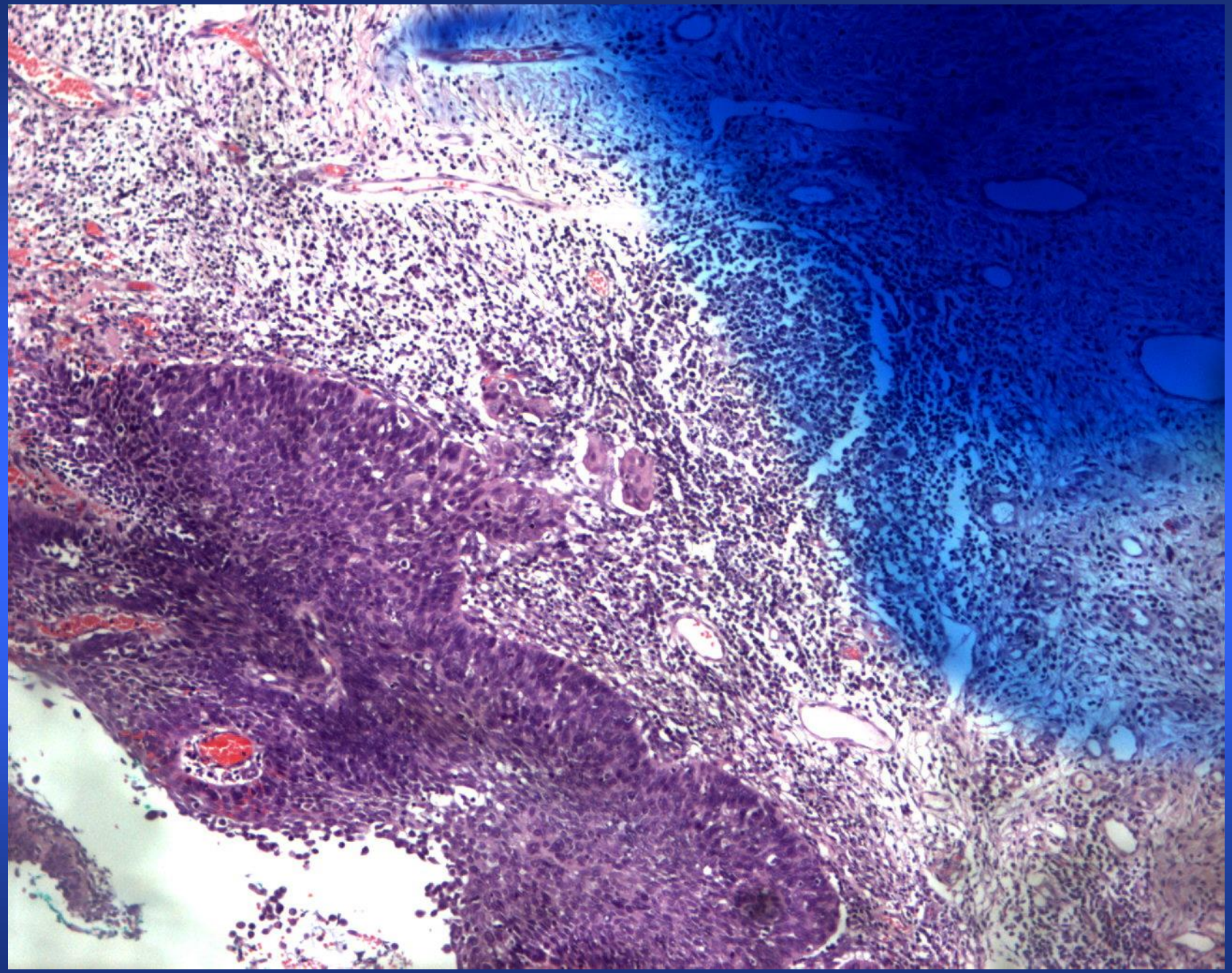
CASO CLINICO

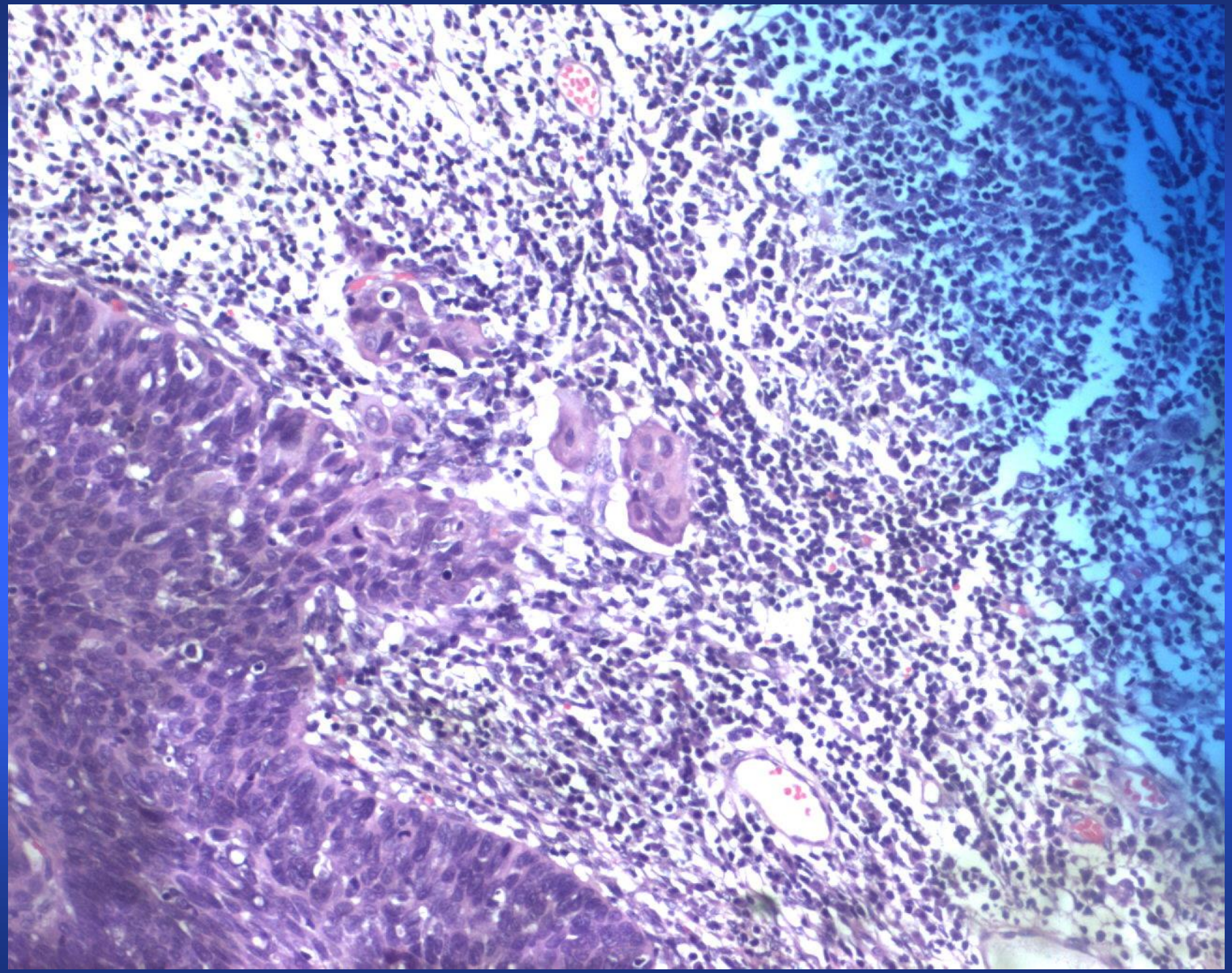
J.N. 21/06/1964

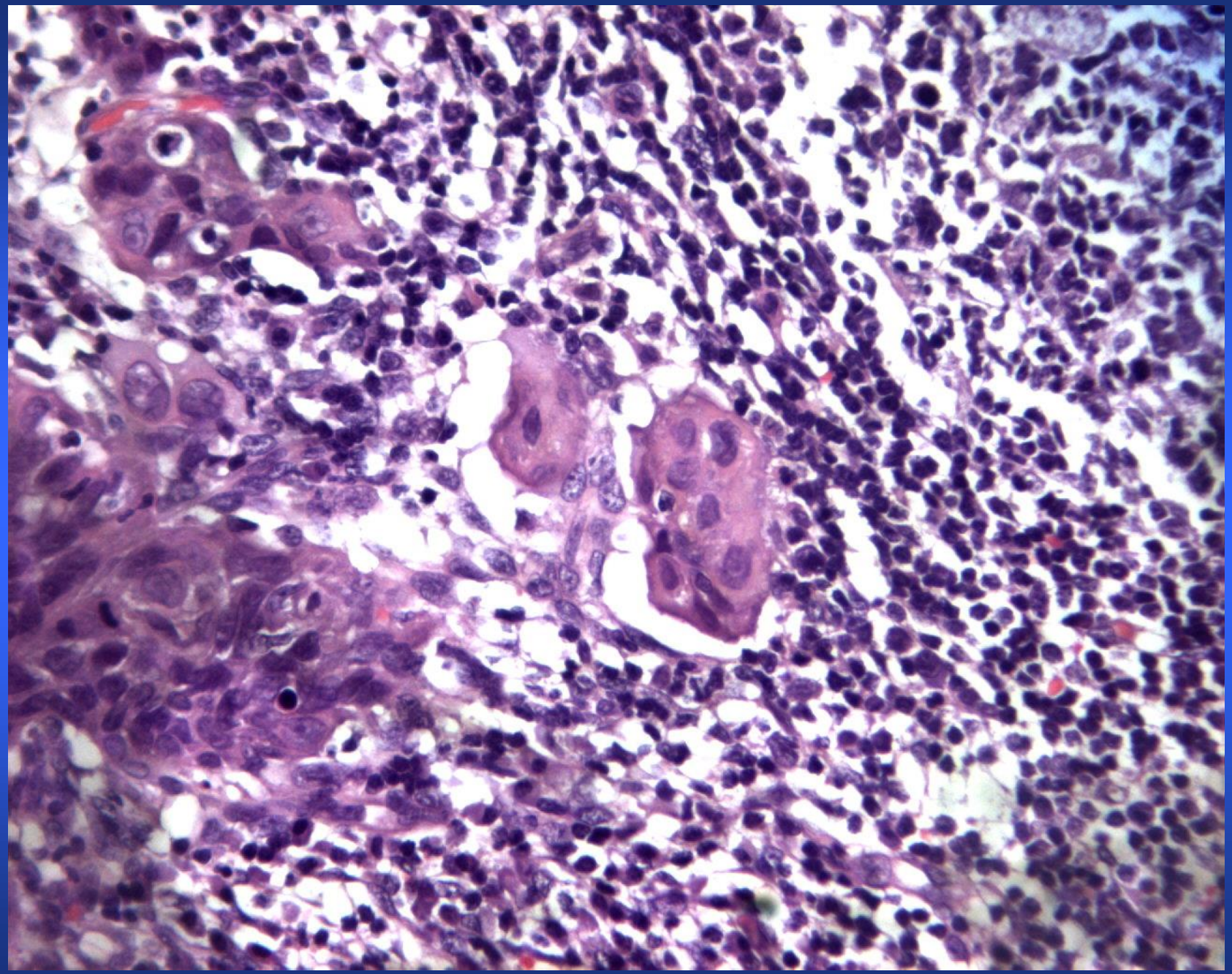
Nel 2000 36 anni Ansa a RF PER CIN III
altezza 1,8 cm

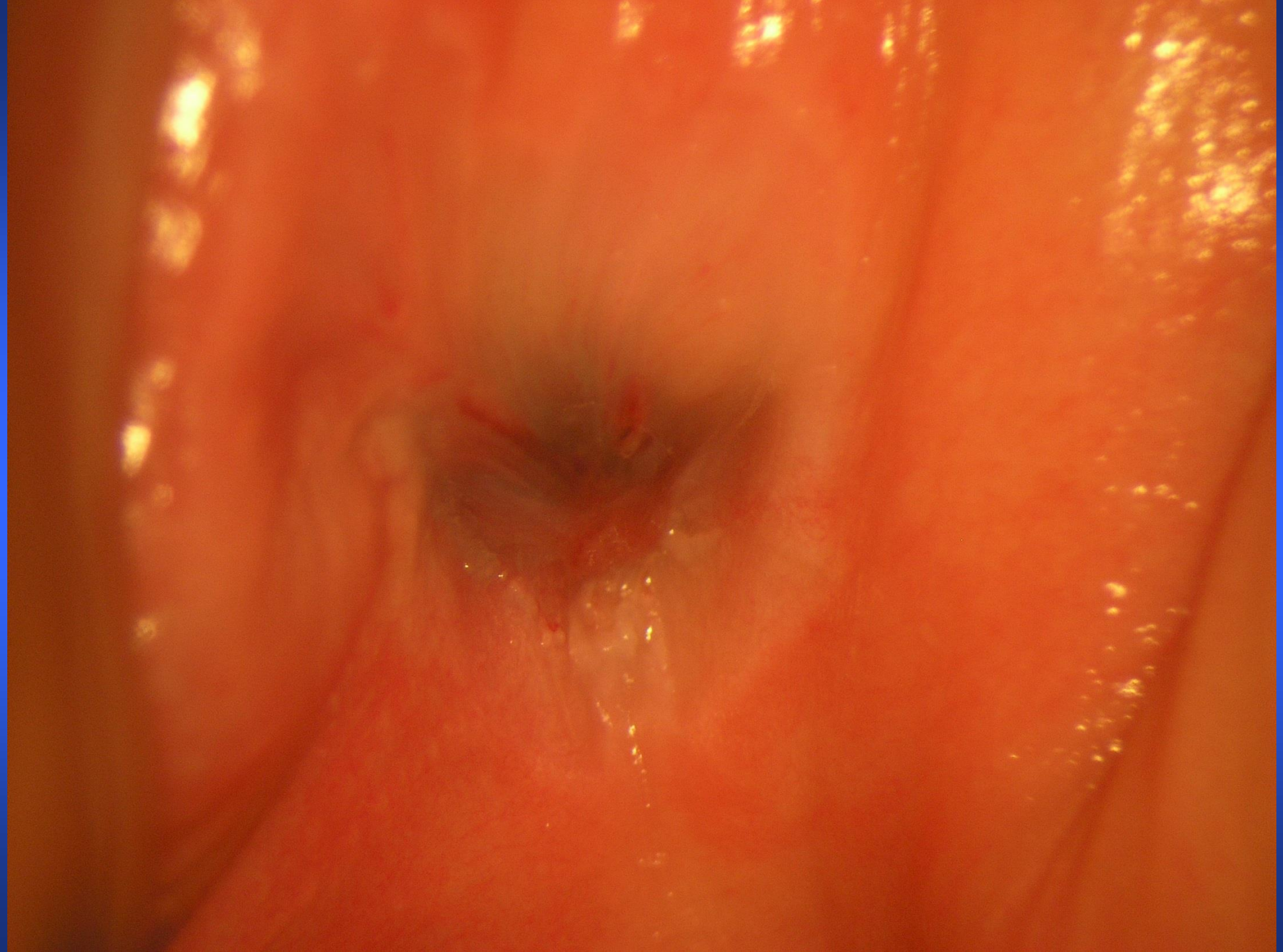
Nel 2012 47 anni Ansa a RF PER CIN III
altezza 2 cm

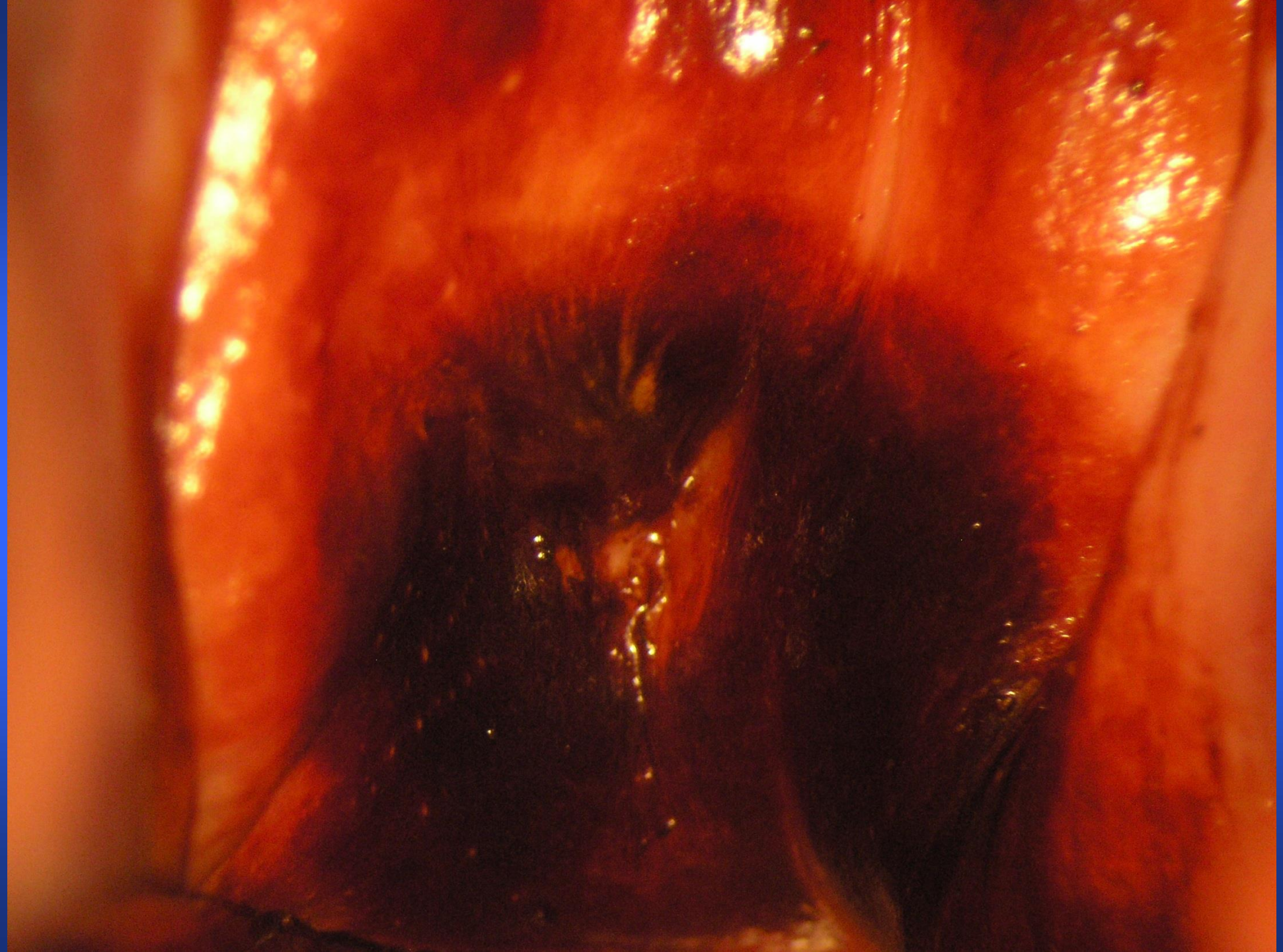
Nel 2013 49 anni Ansa a RF per CA microinvasivo (<1mm)
altezza 2,2 cm











CASO CLINICO

A.D. 29/04/1972

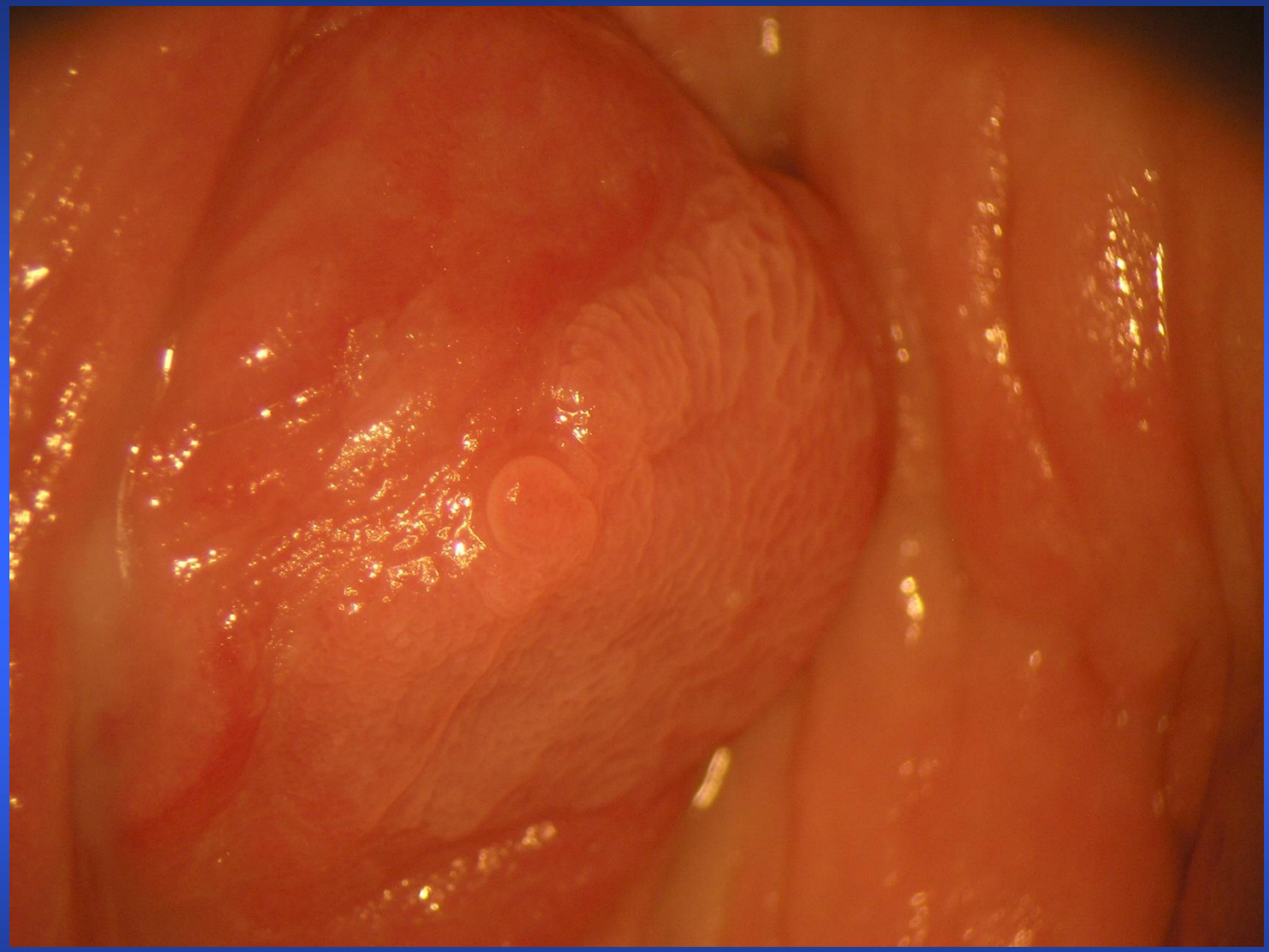
Nel 2013 41 anni - gennaio/luglio 2 Coniz. per CIN 3

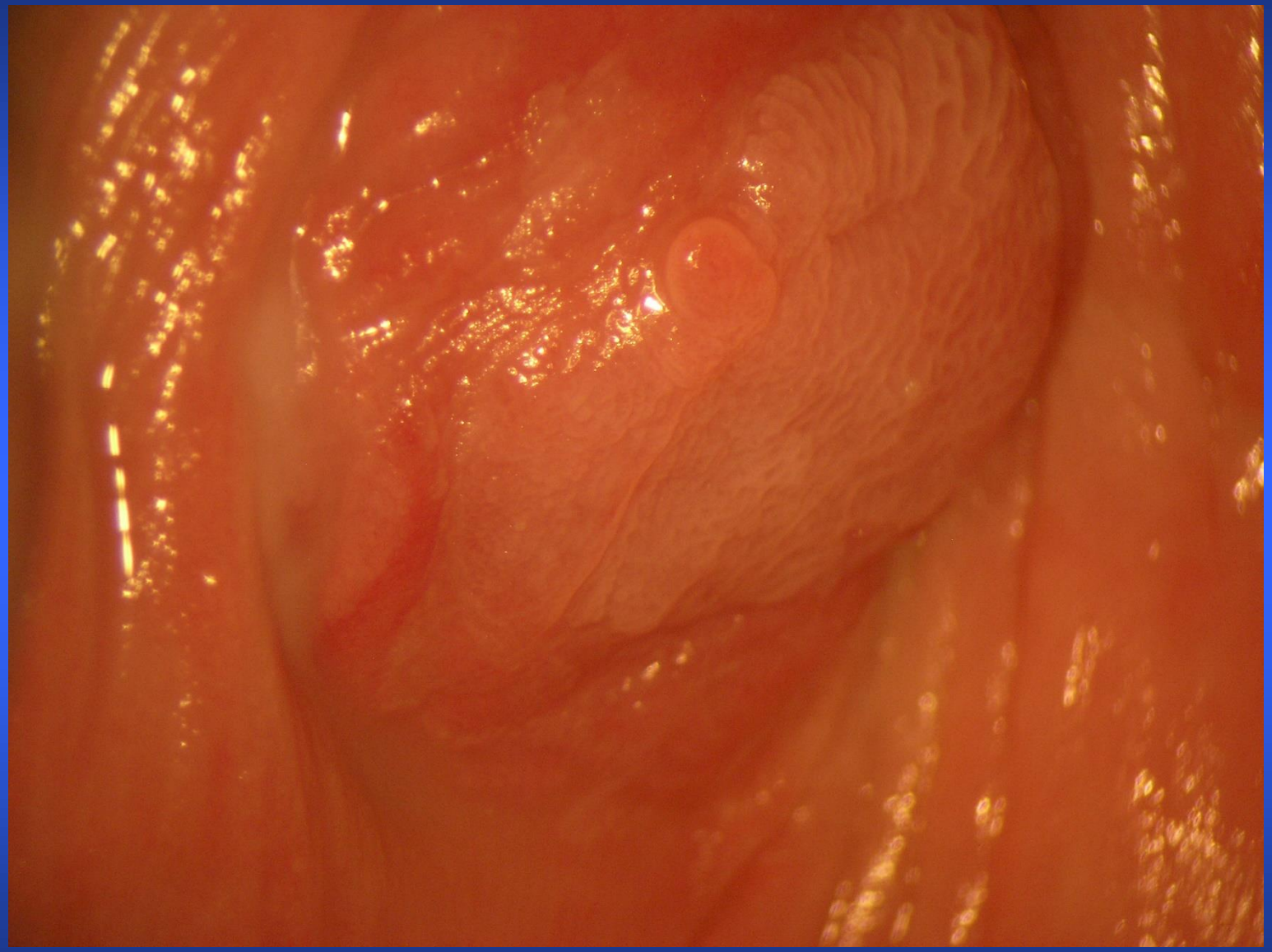
Nel 2013 – ottobre – H-SIL/CIN 3

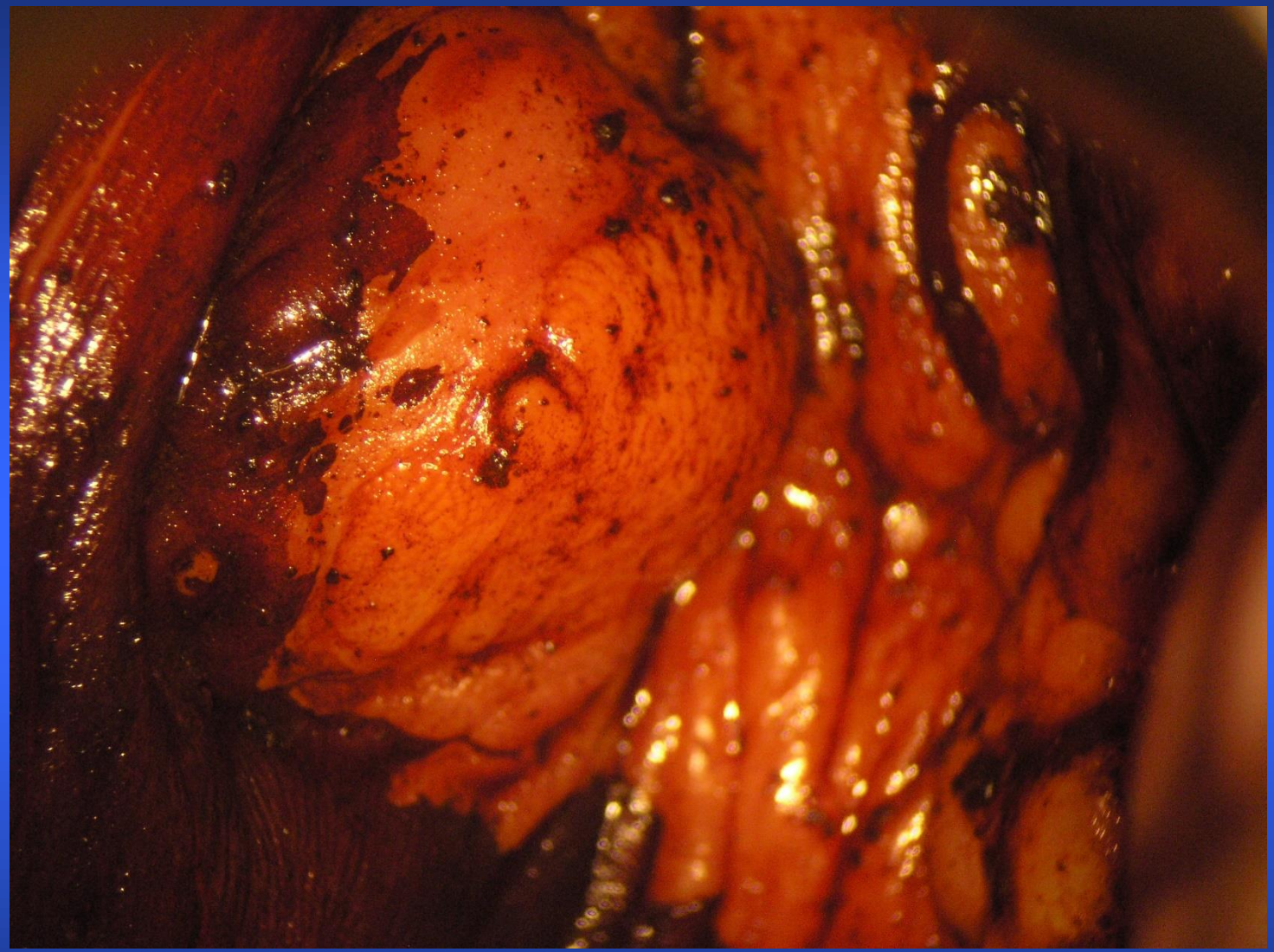
Nel 2013 – dicembre - isterectomia laparoscopica
E.I.: CIN 3 sul margine esocervicale

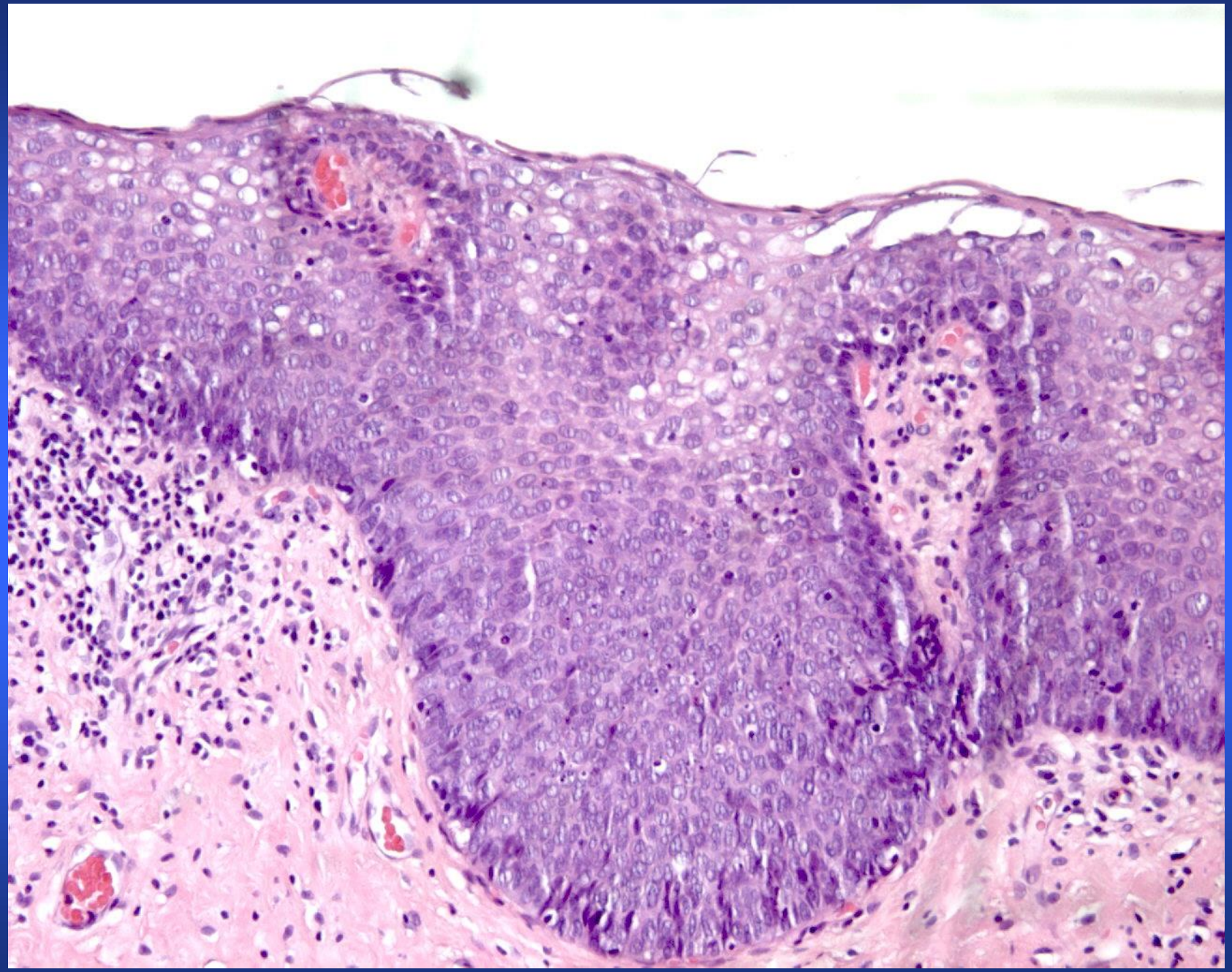
Nel 2014 – marzo- HSIL/VaIN 3

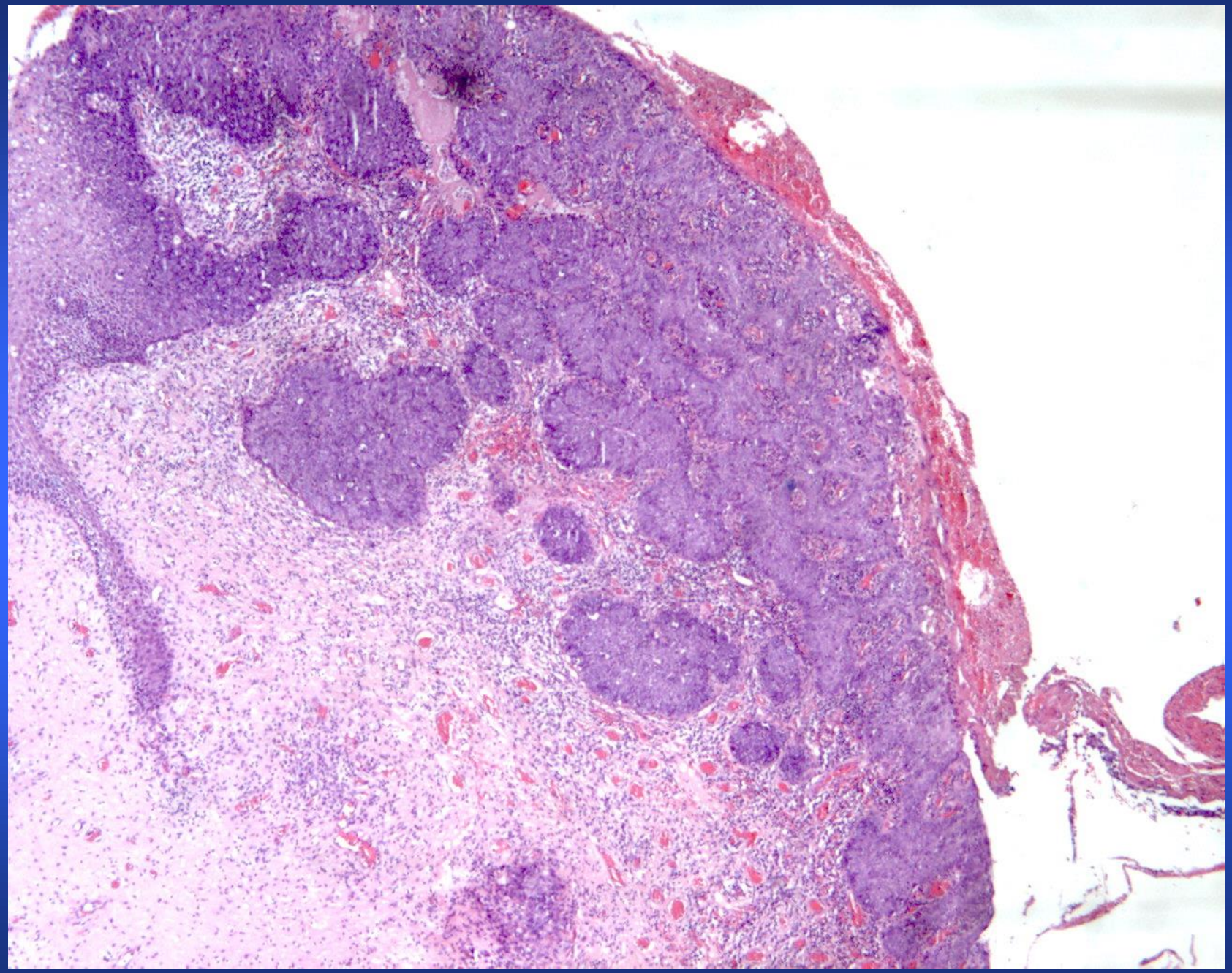
Nel 2014 – settembre – Escissione cupola vaginale con ago a RF

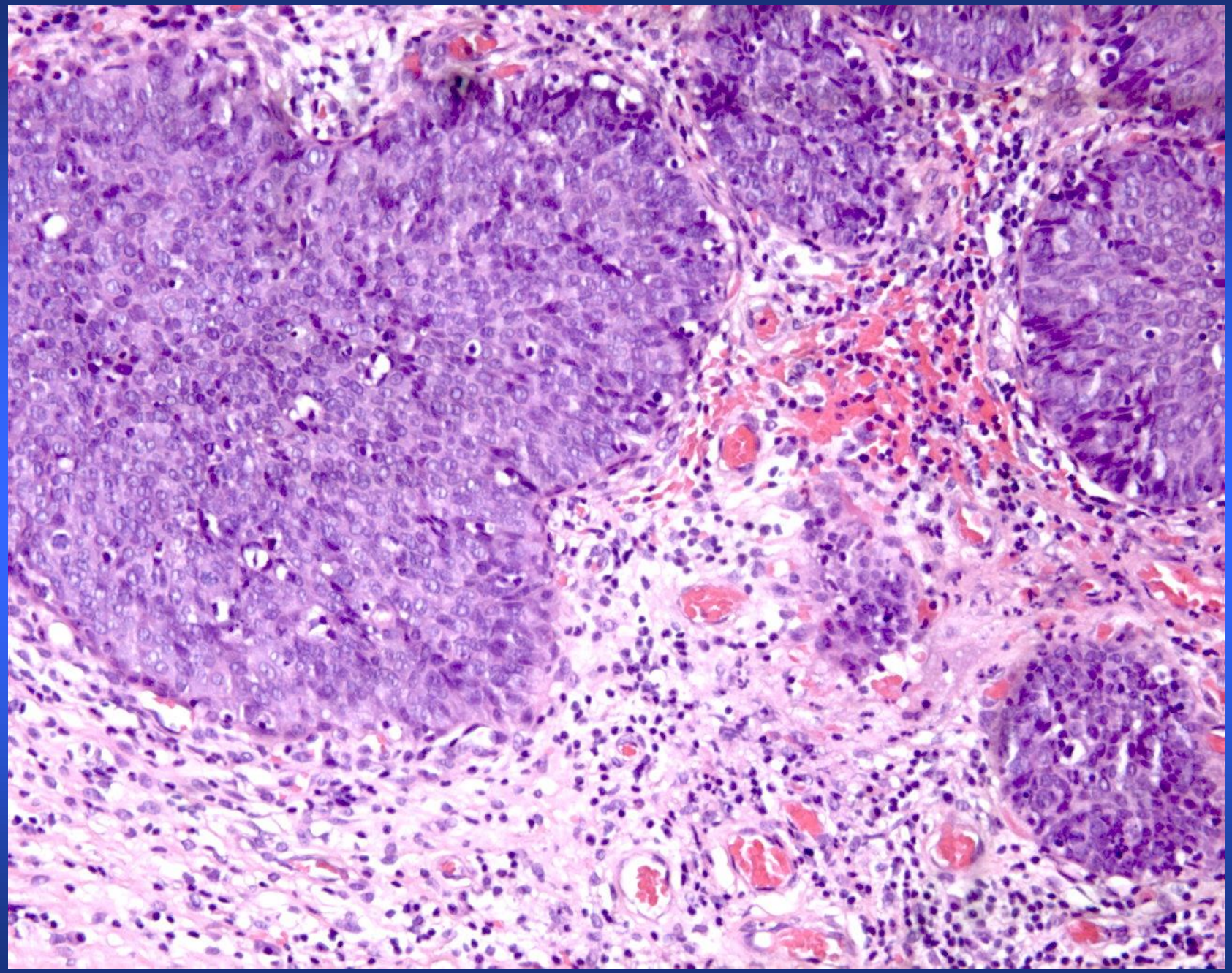


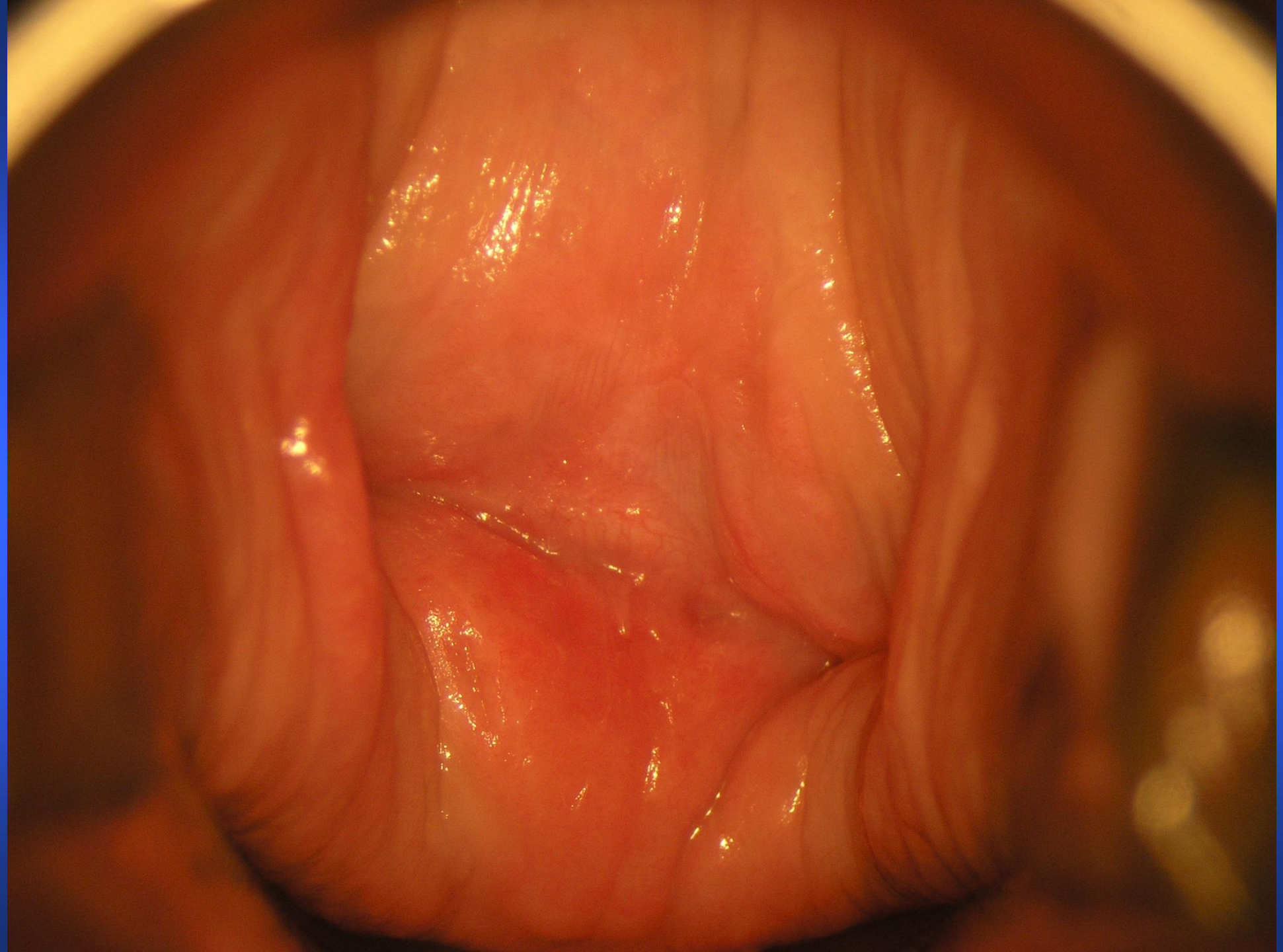


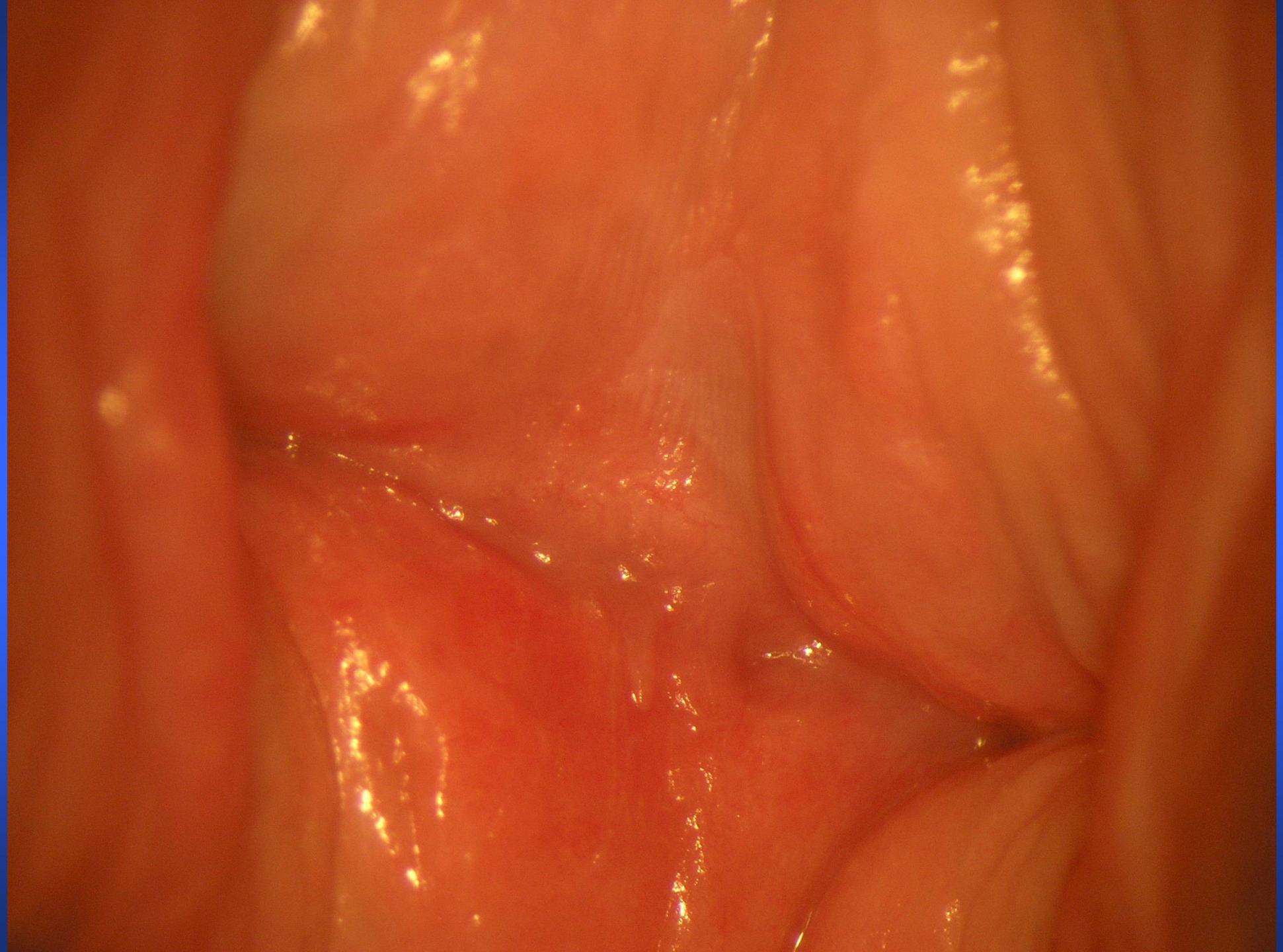


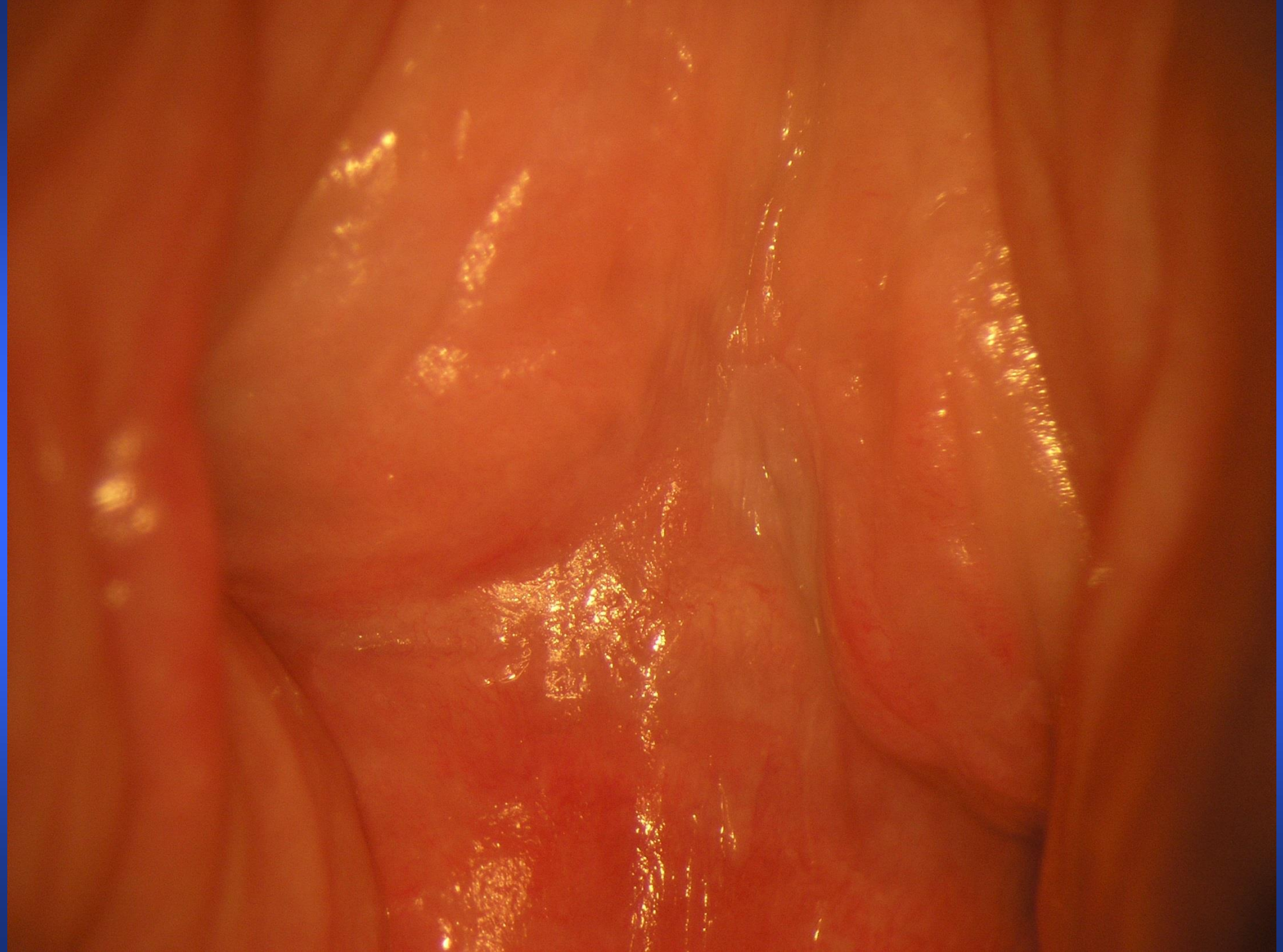


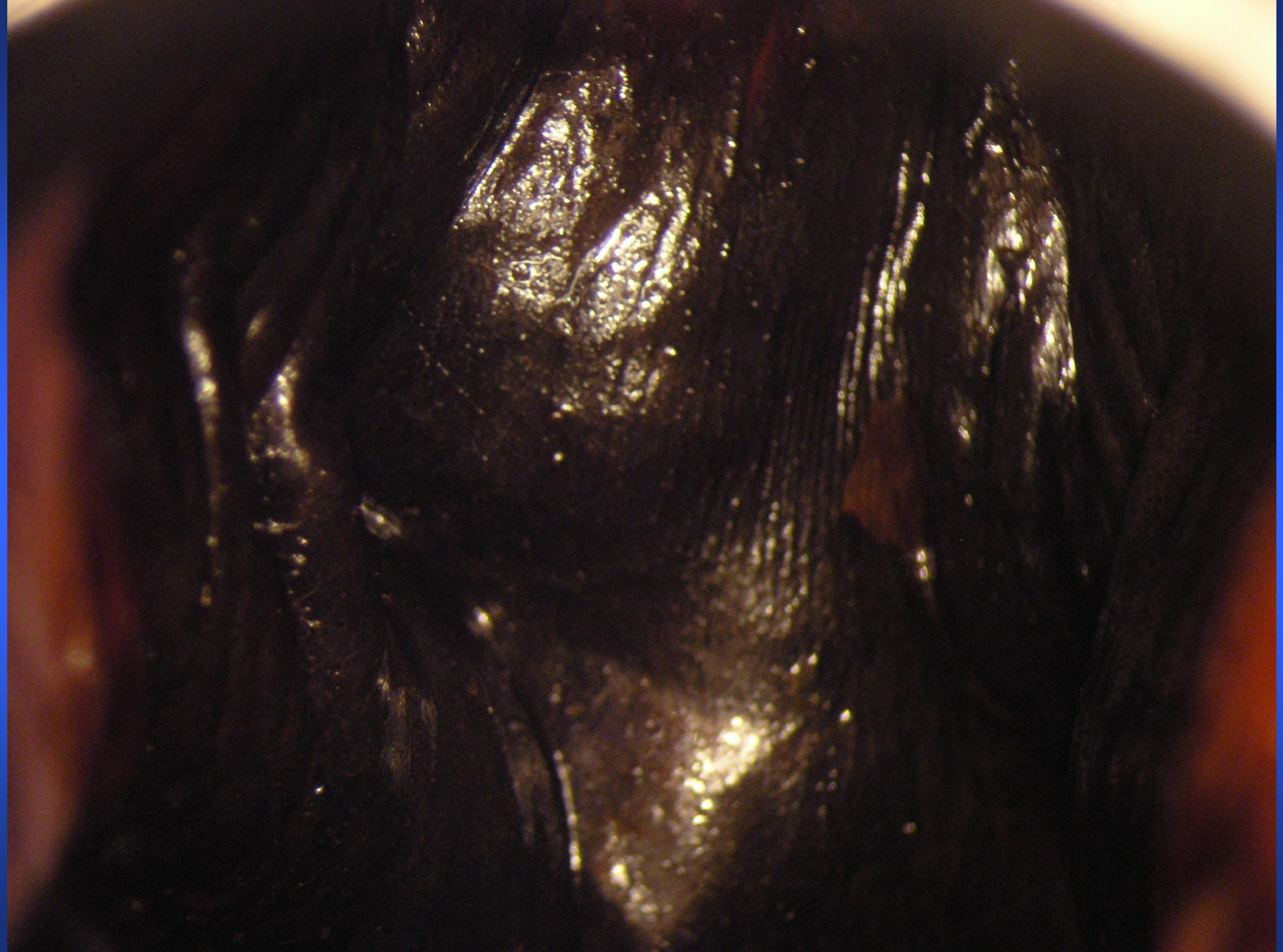






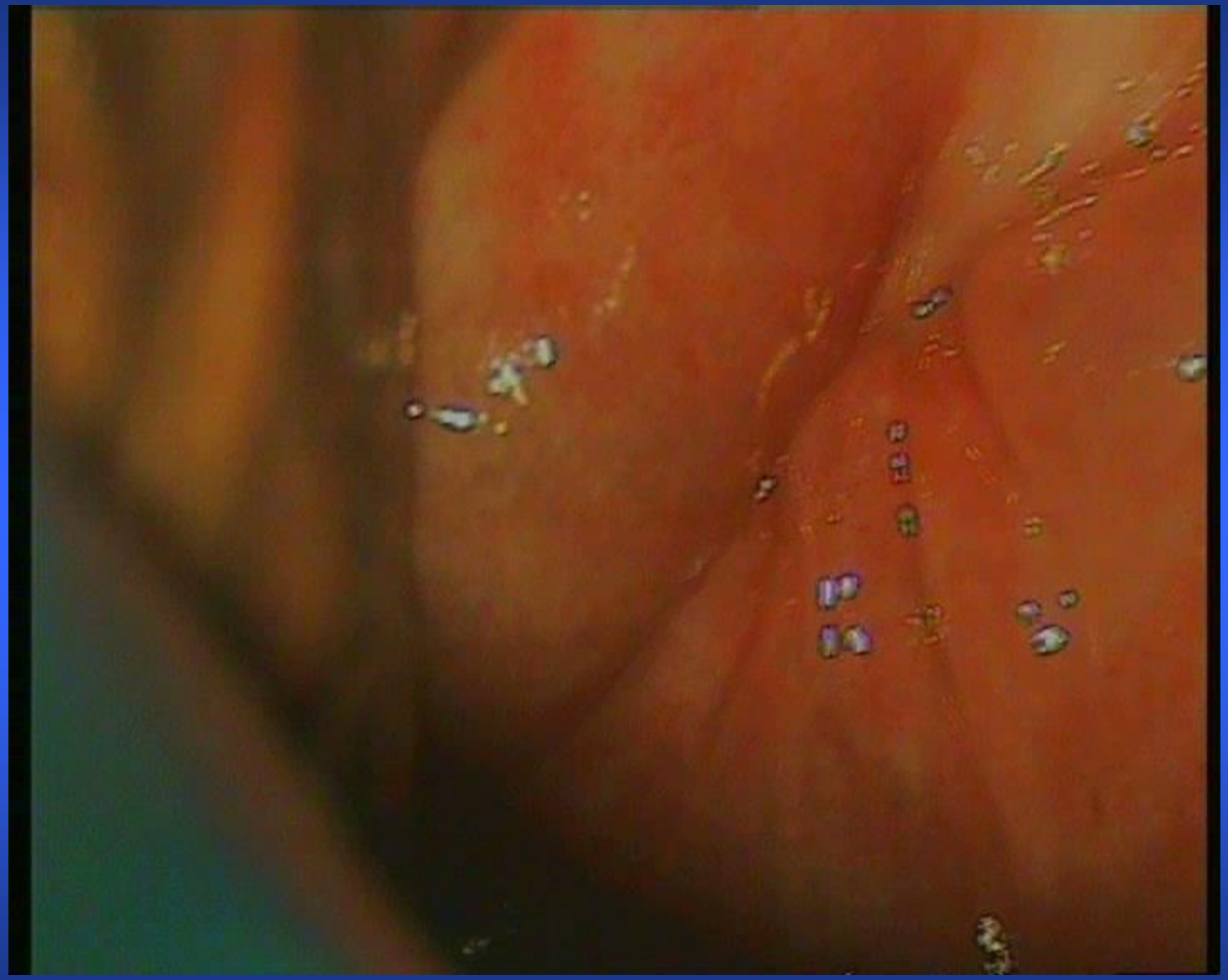


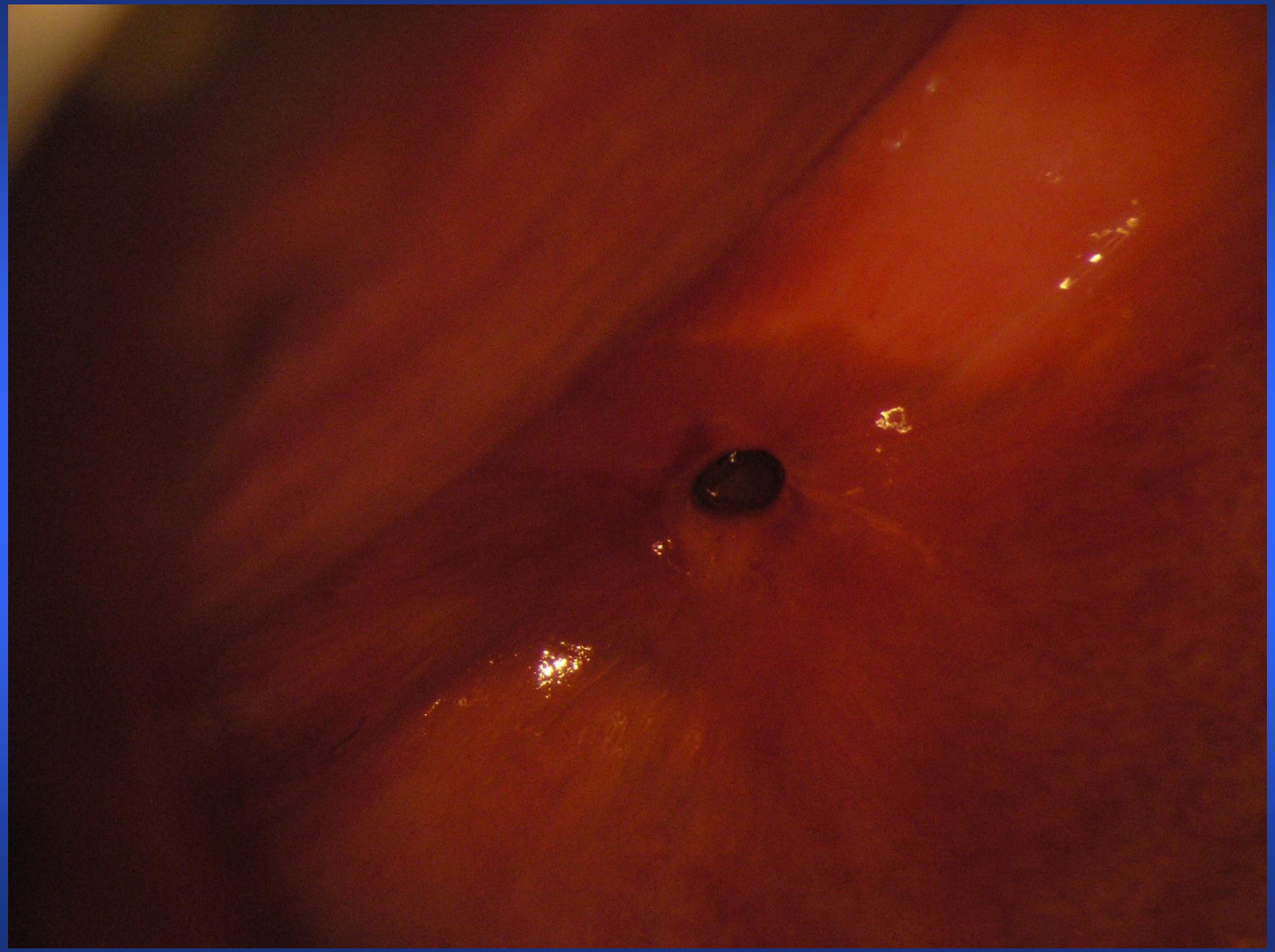


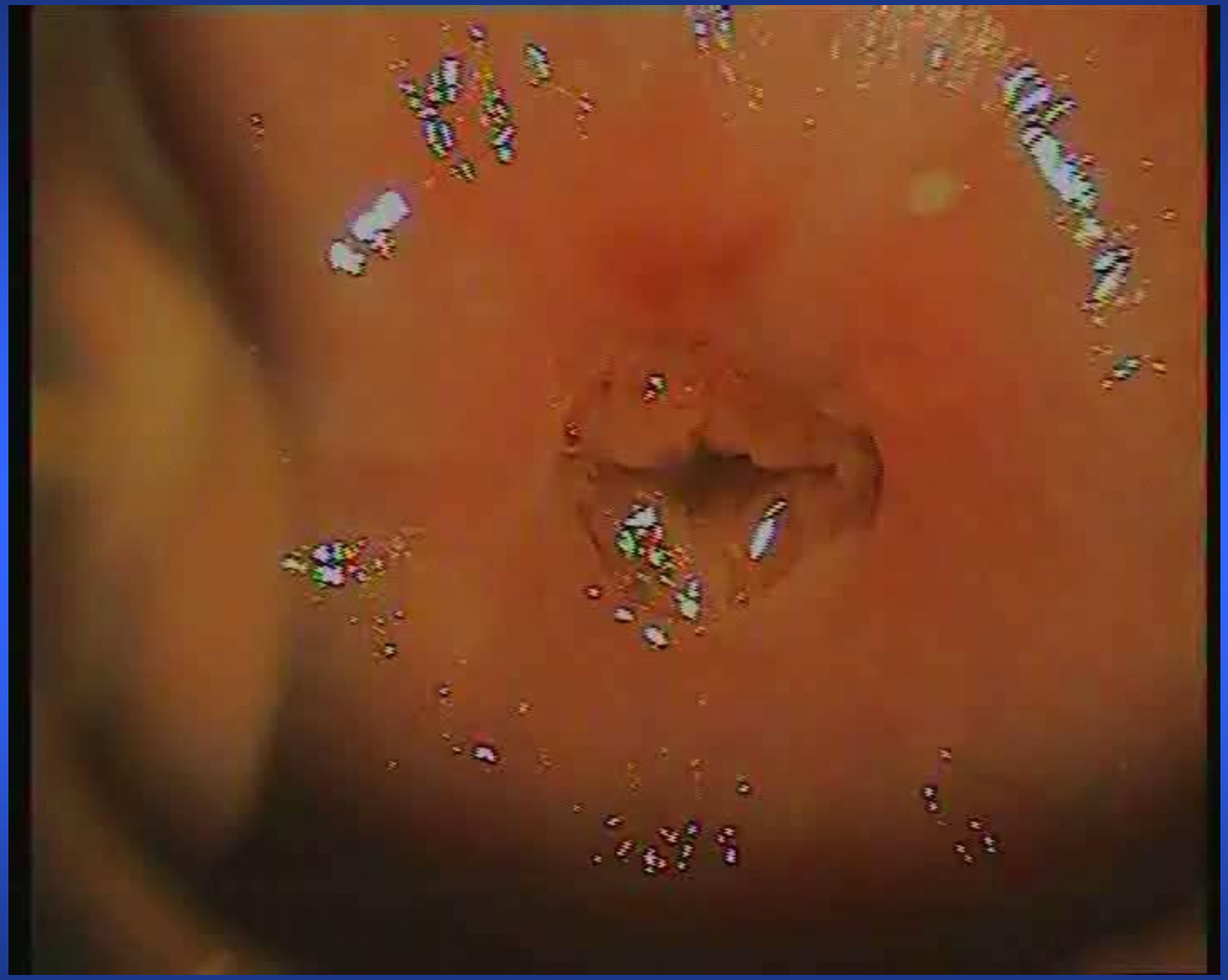


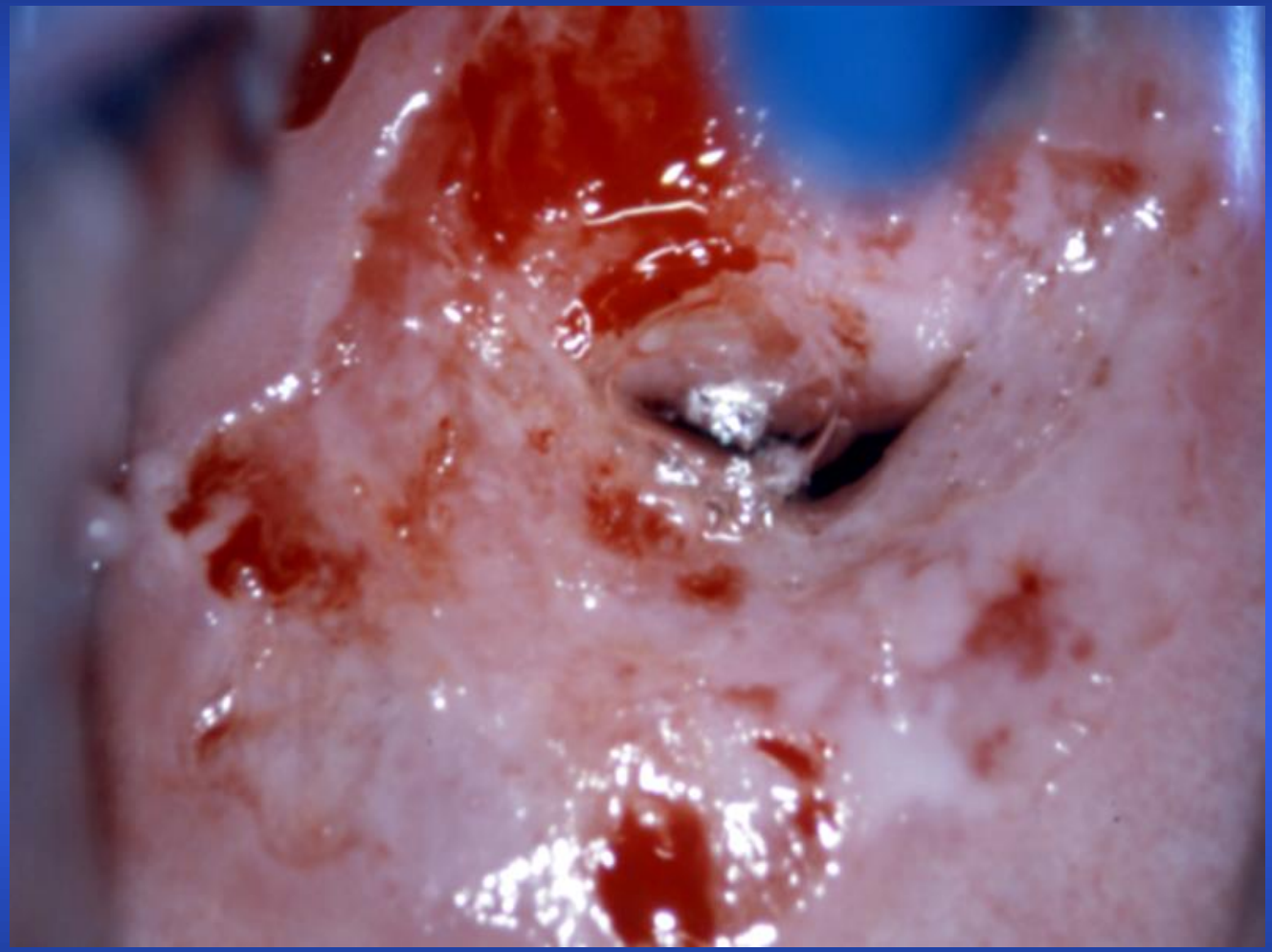
PUNTI FERMI

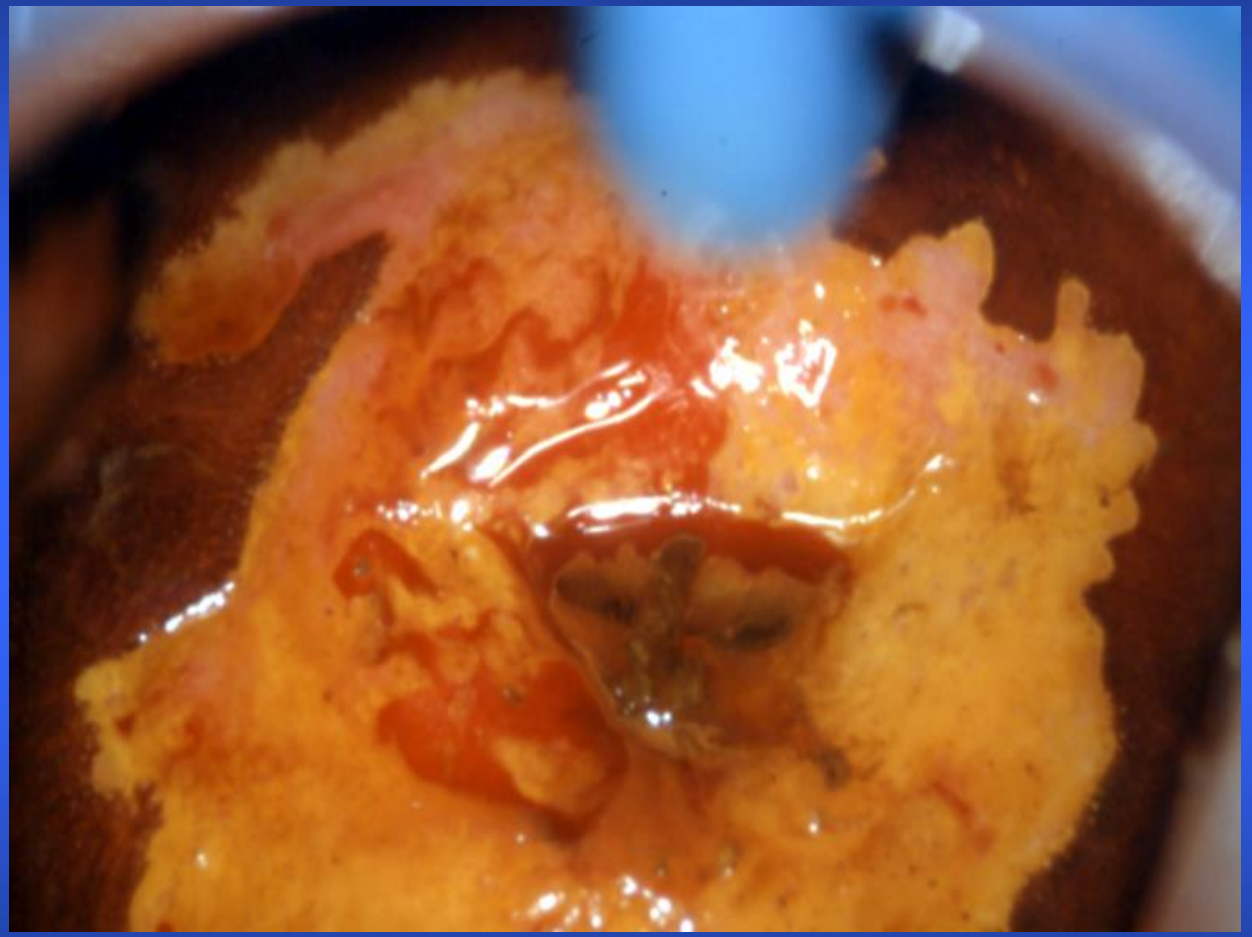
- Importanza dell’età
- Importanza del follow-up
- Importanza trattamento escissionale
- Biopsia mirata non sempre necessaria (selected and treat)
- Ruolo fondamentale della Colposcopia
- Controindicata l’Isterectomia

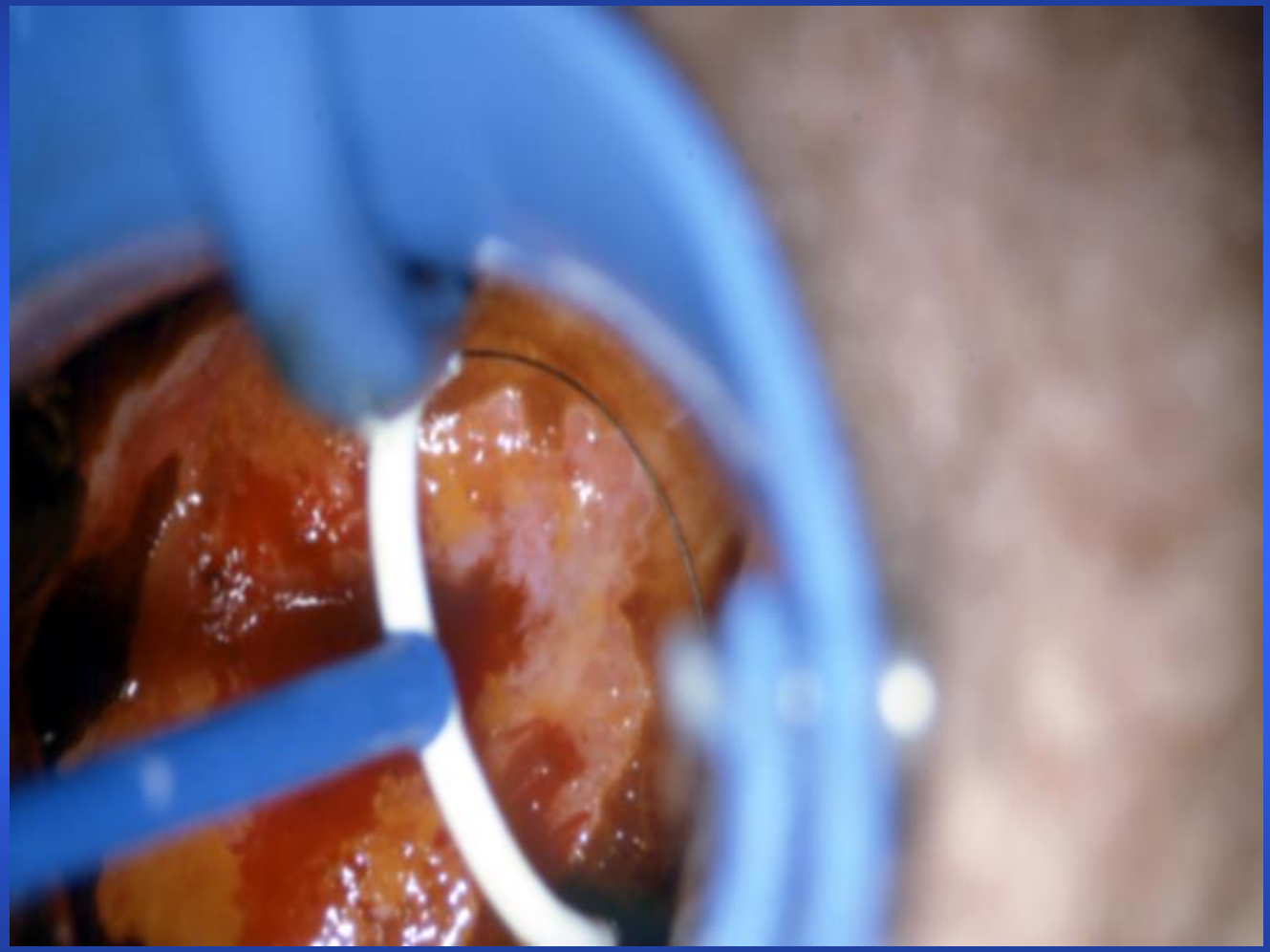


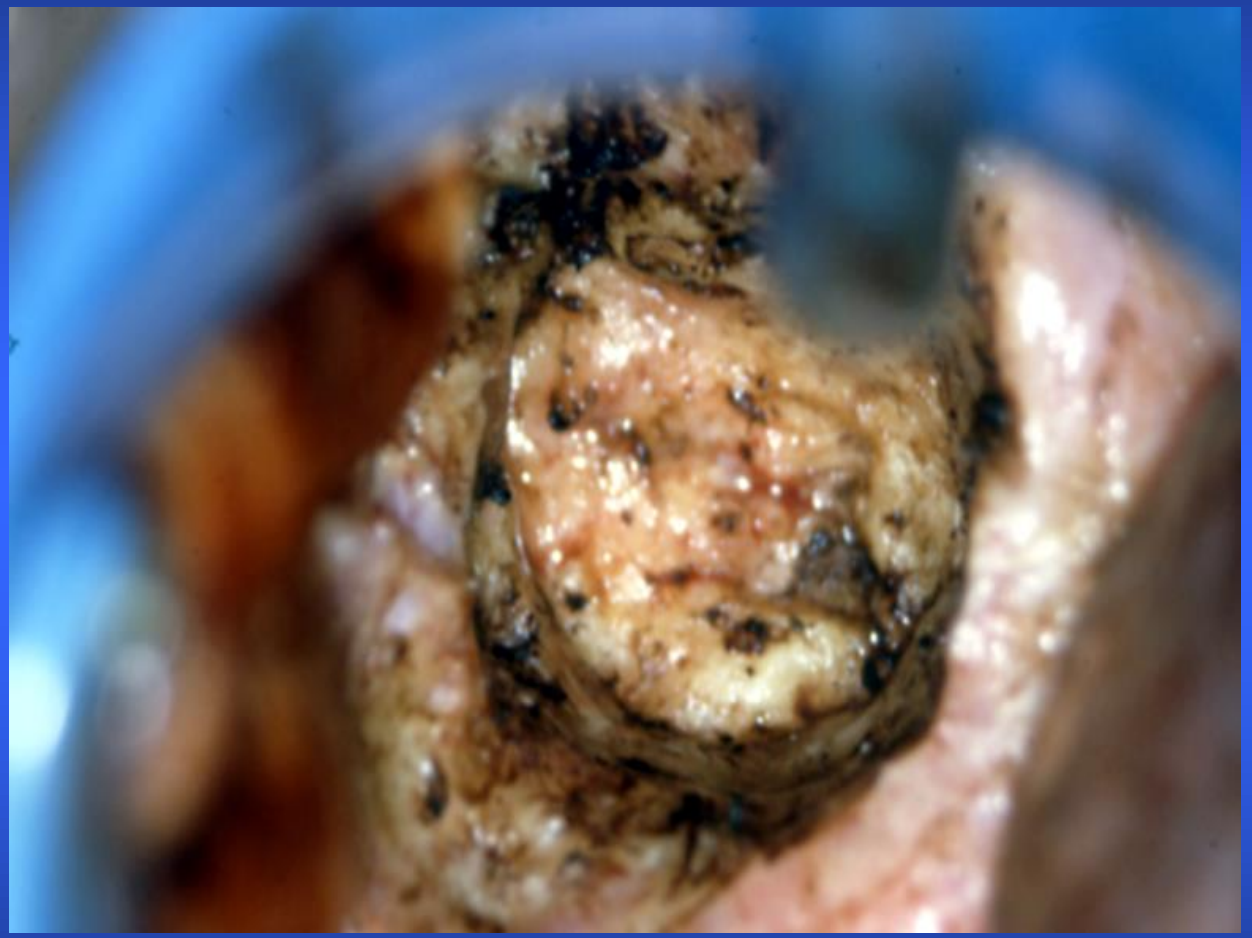


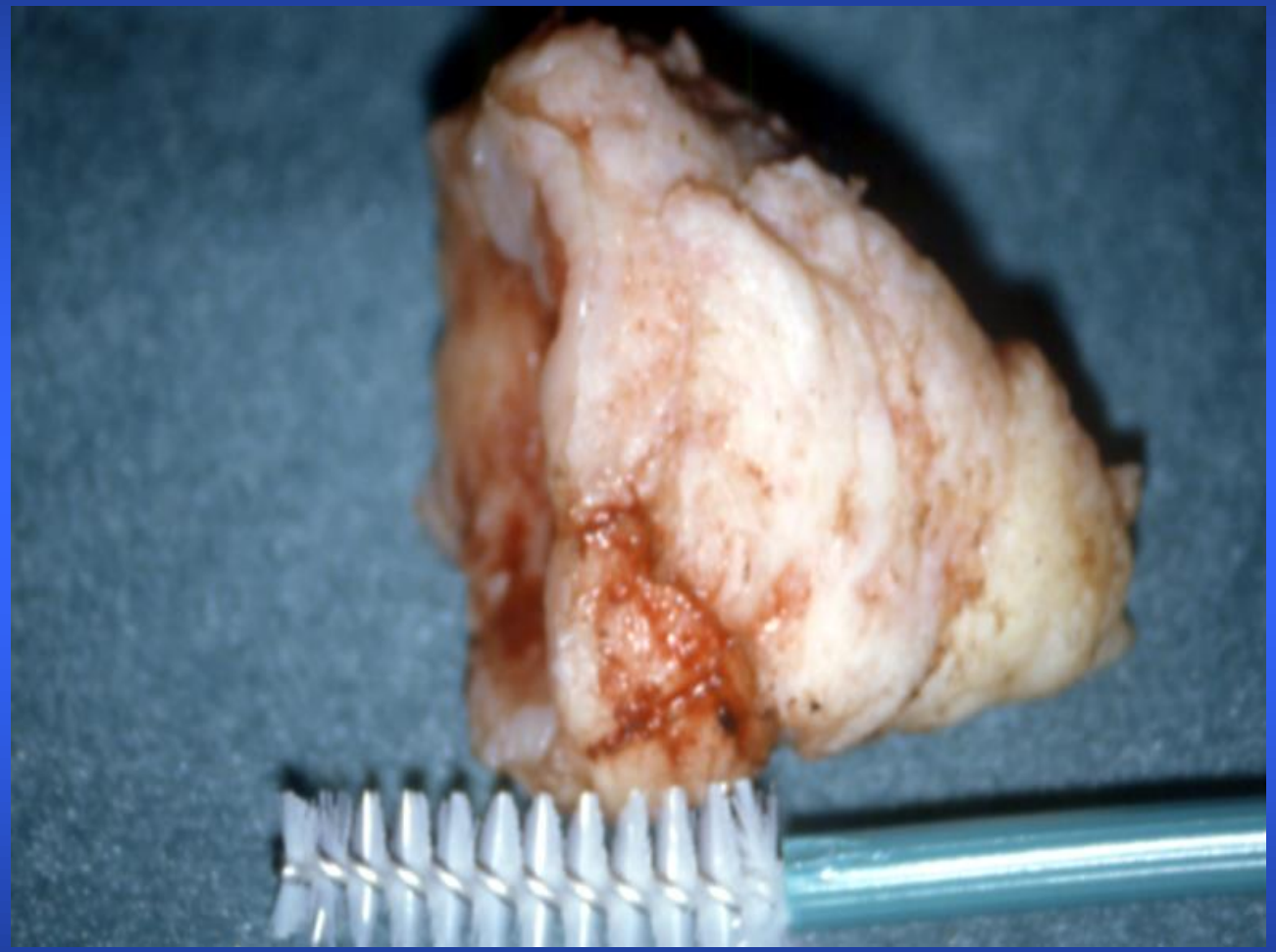


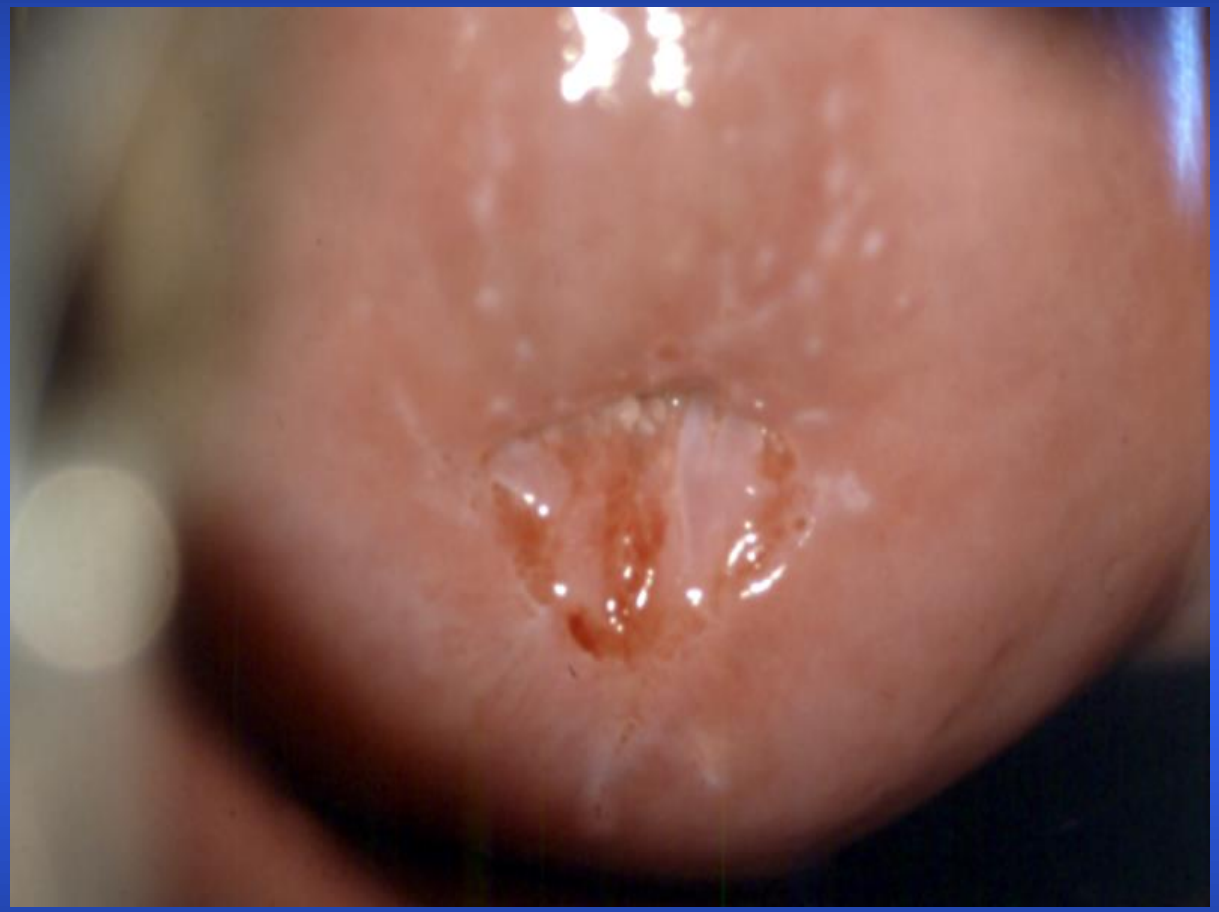


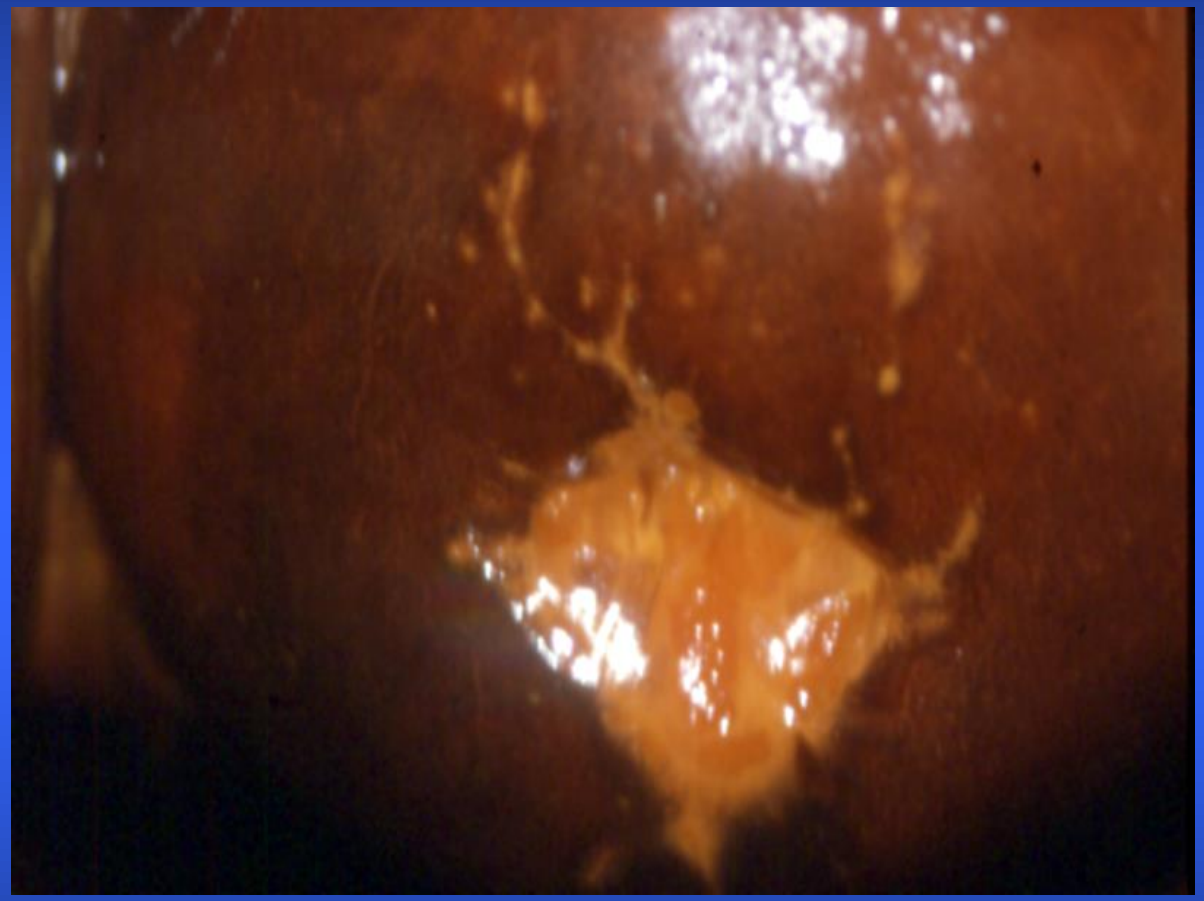


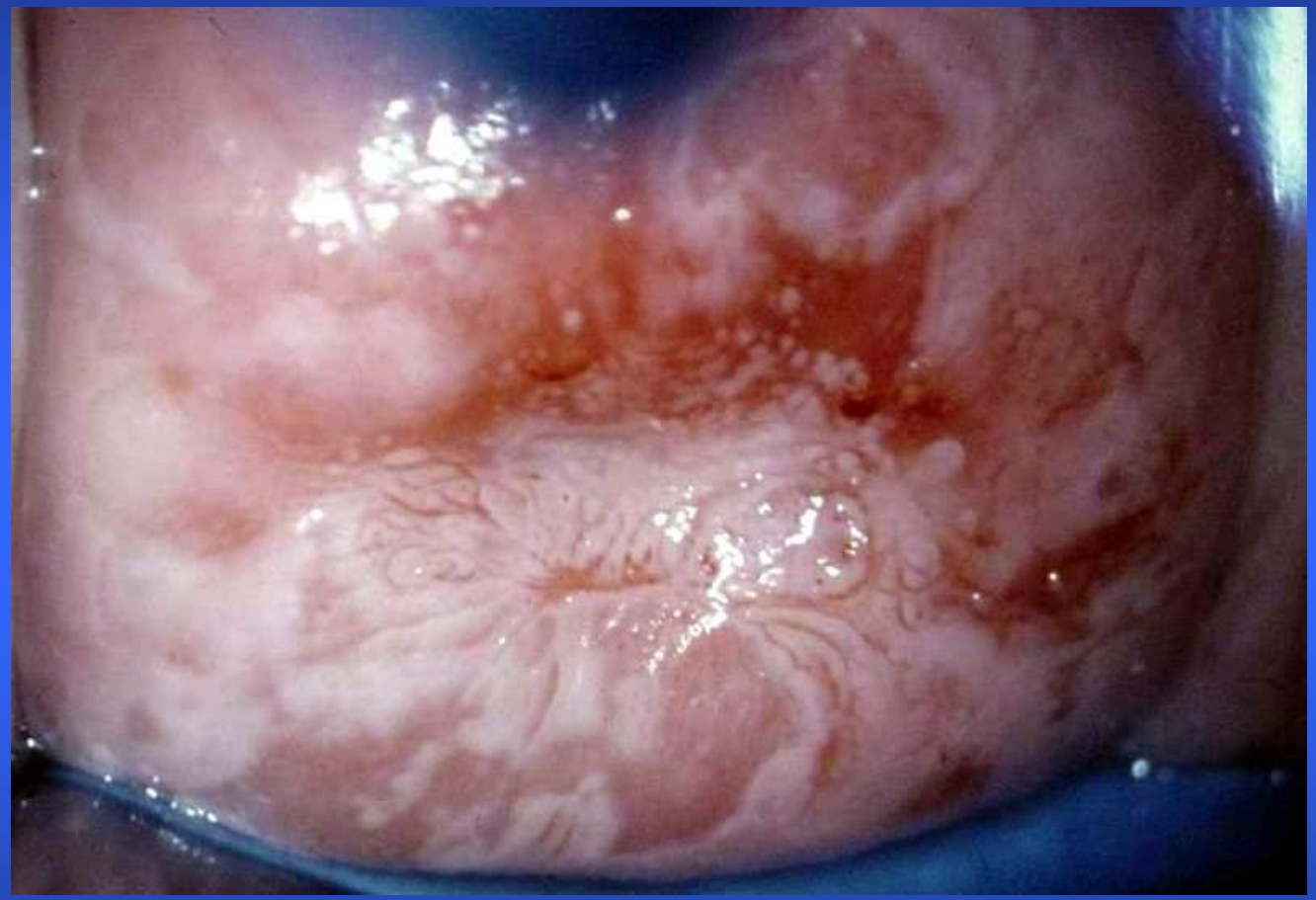


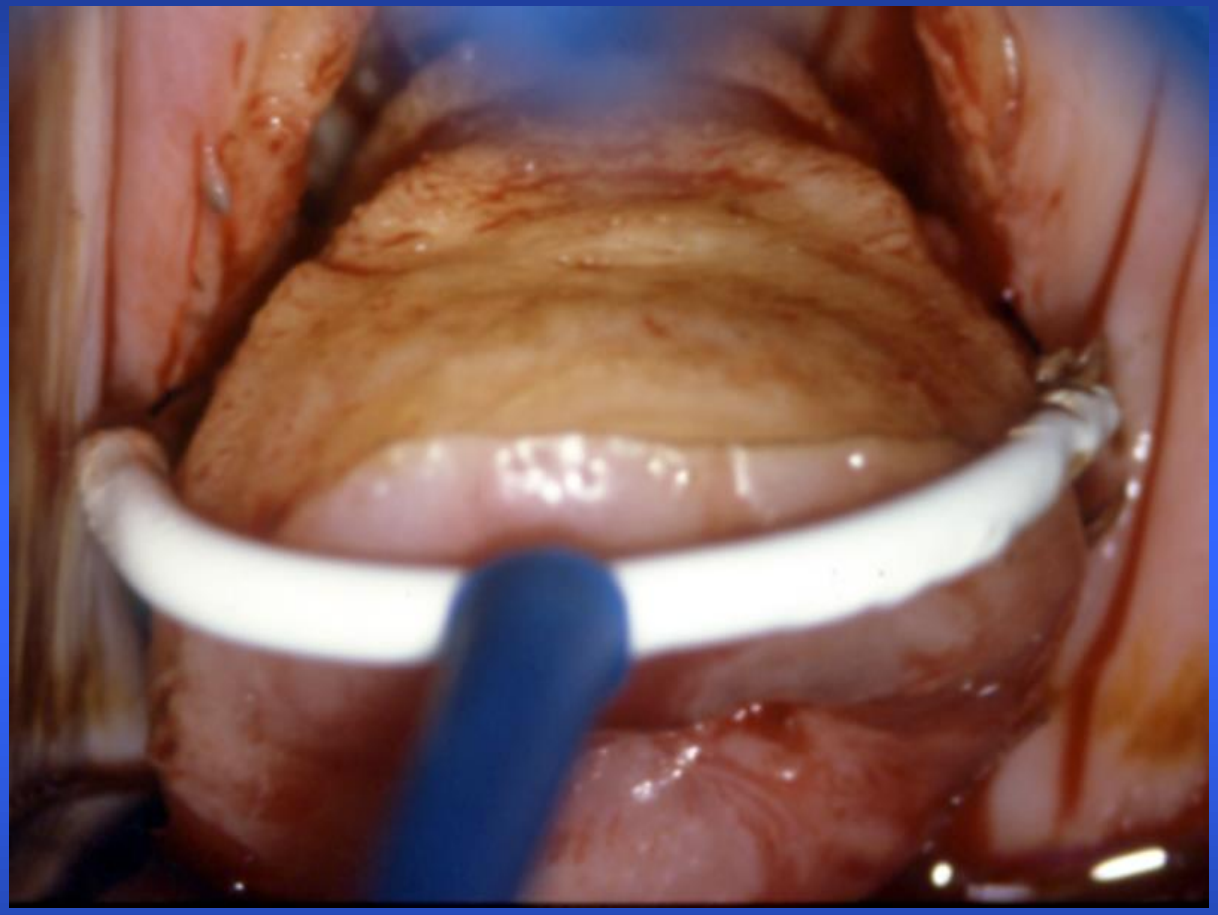


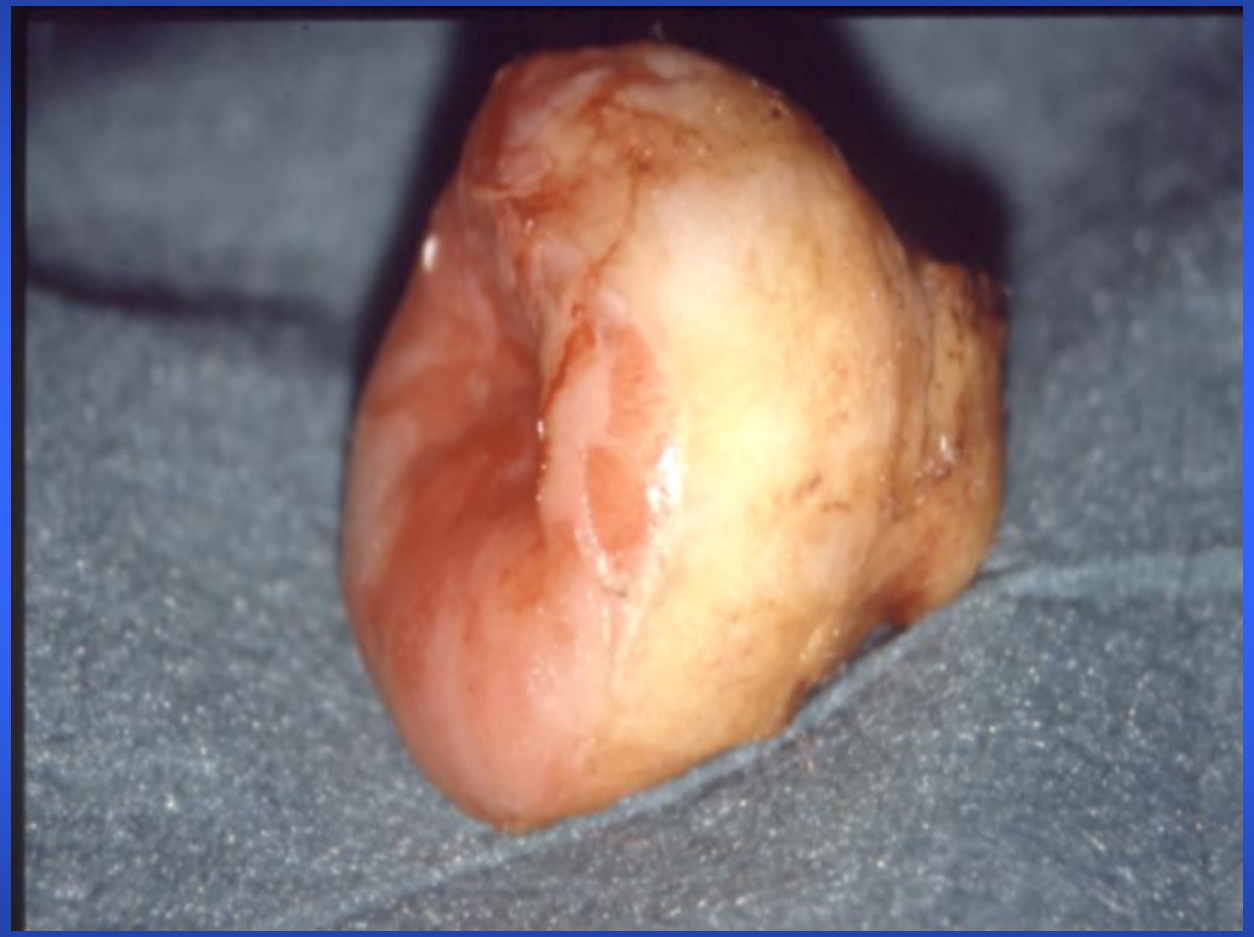


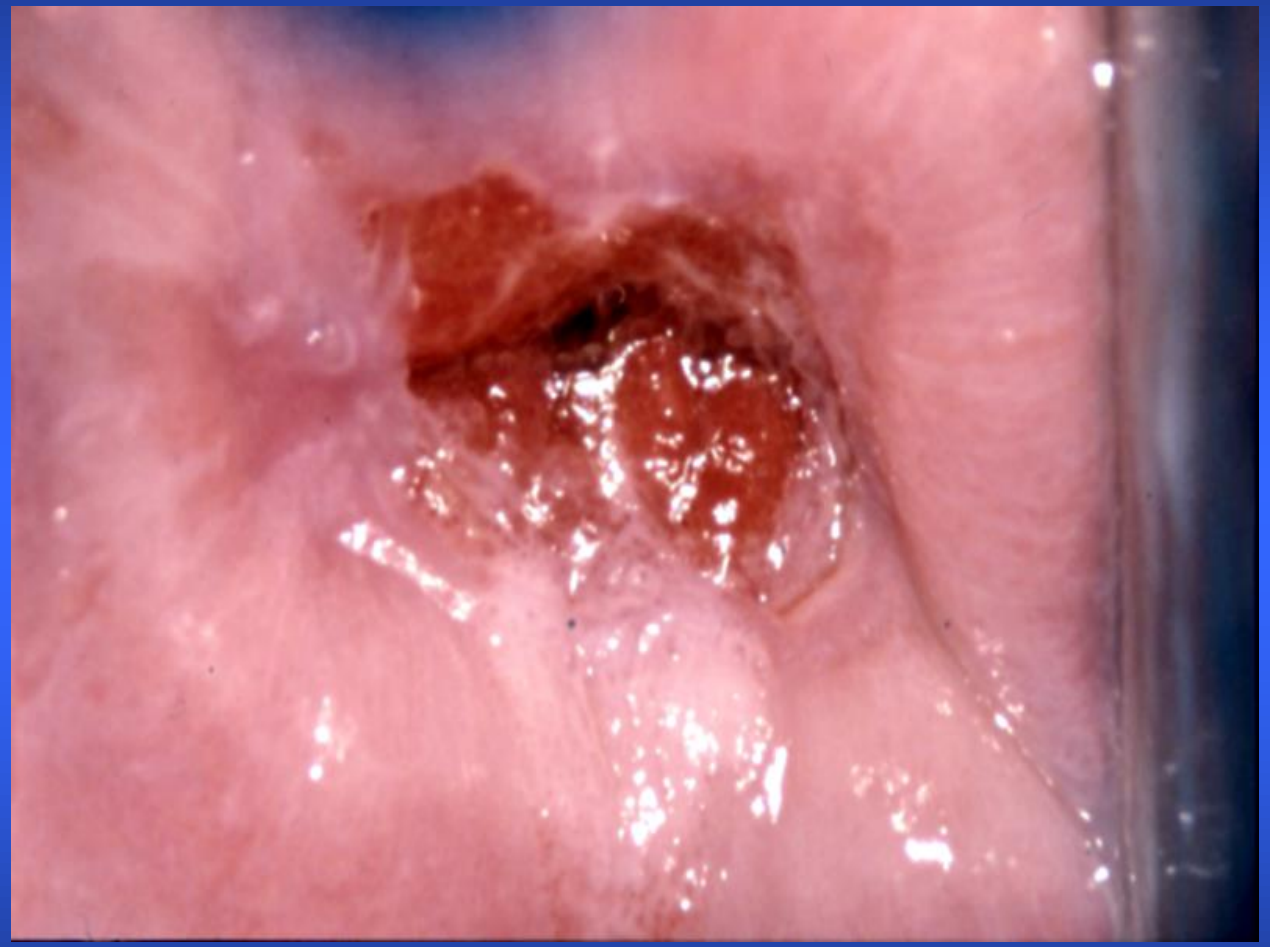


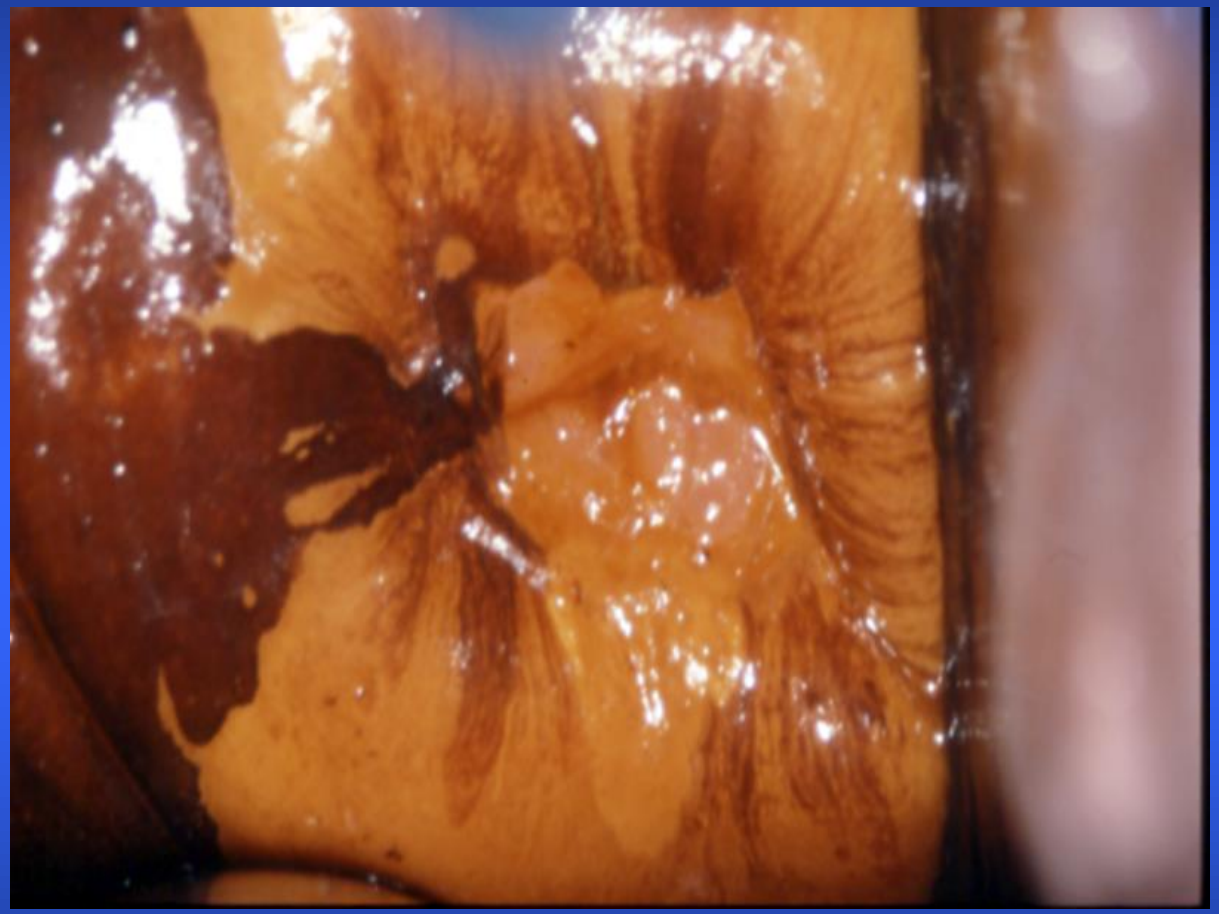


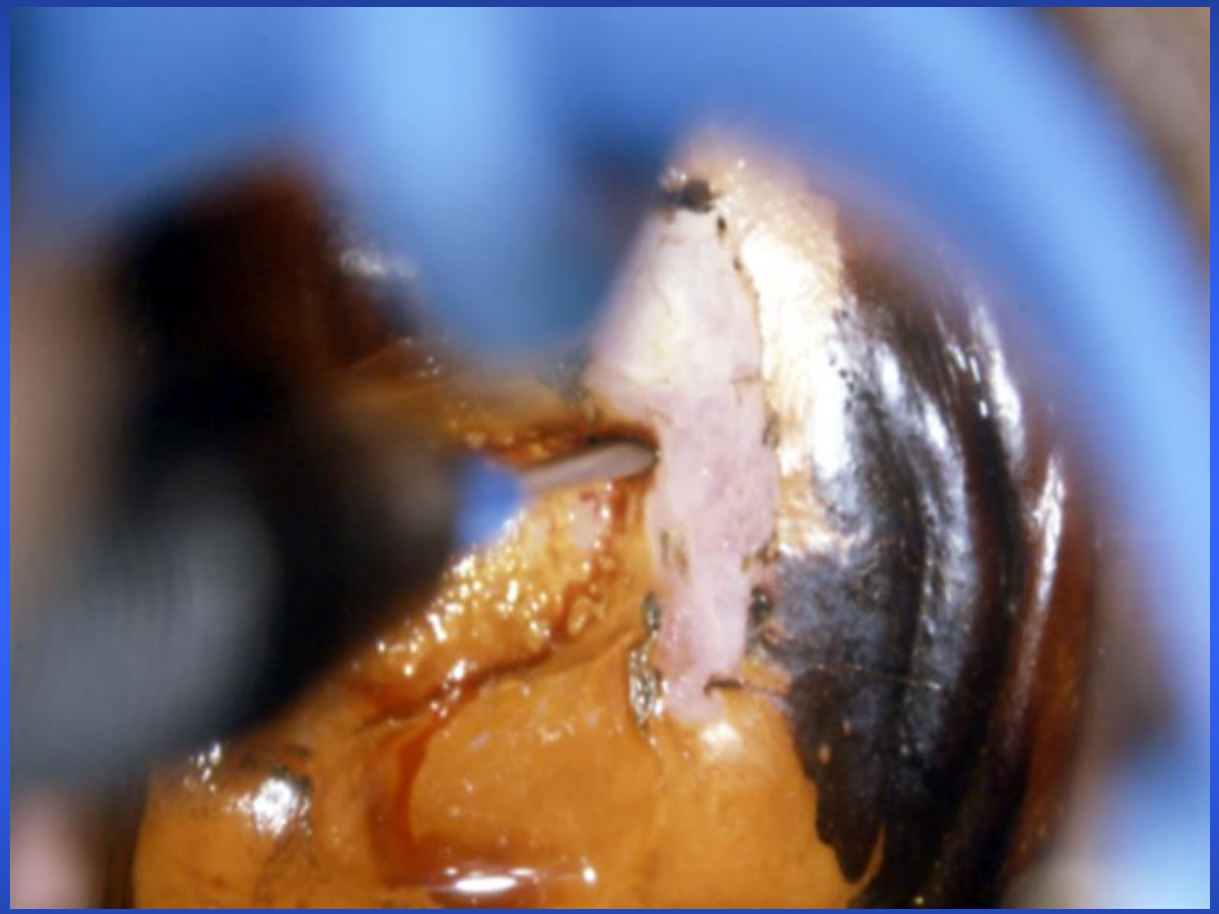


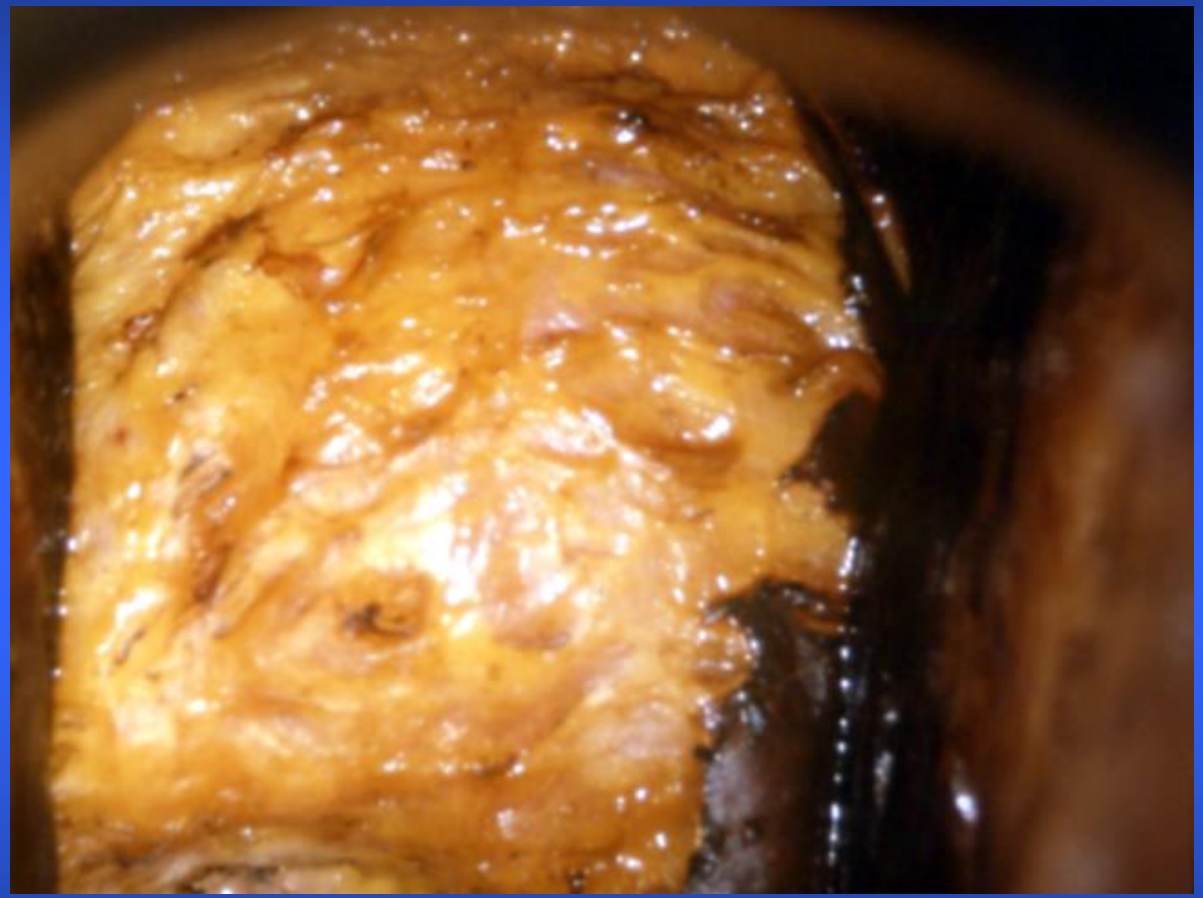


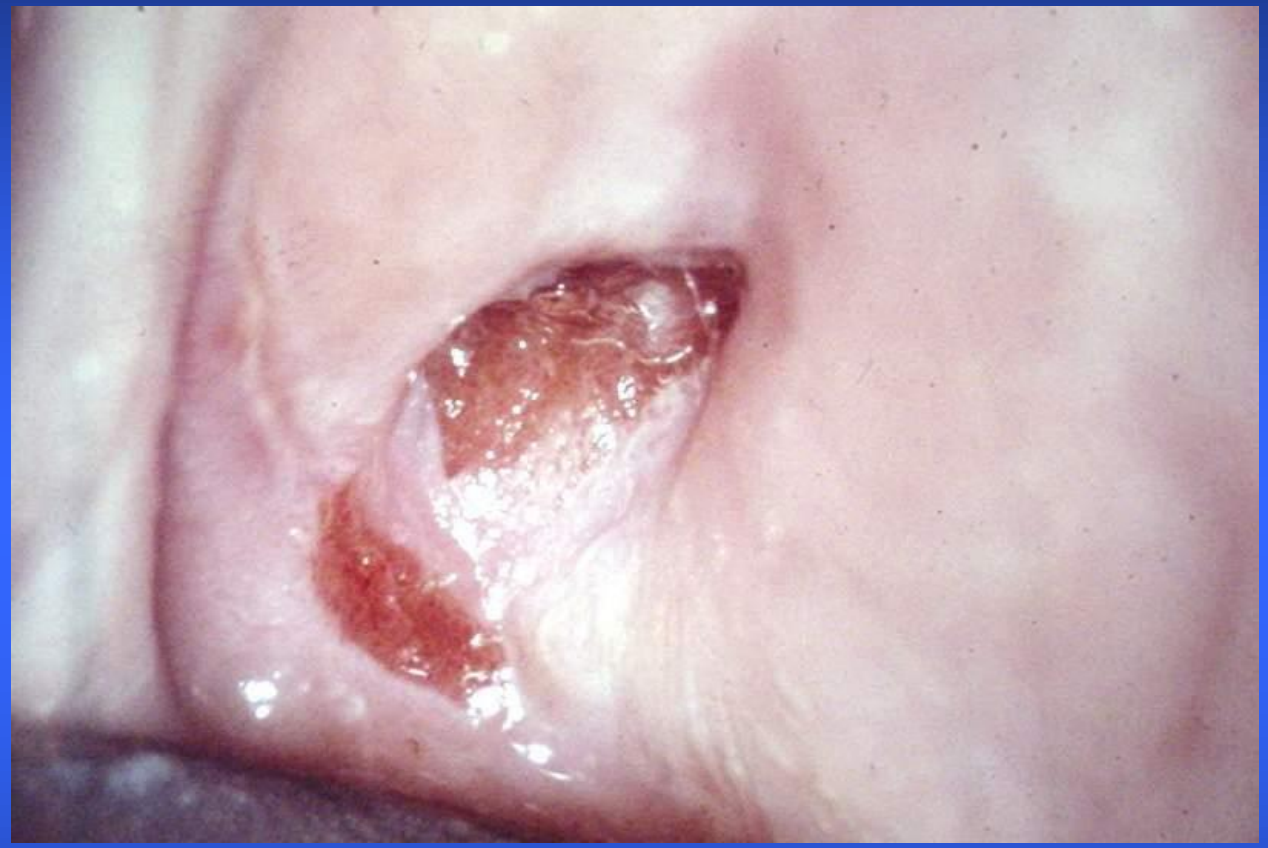


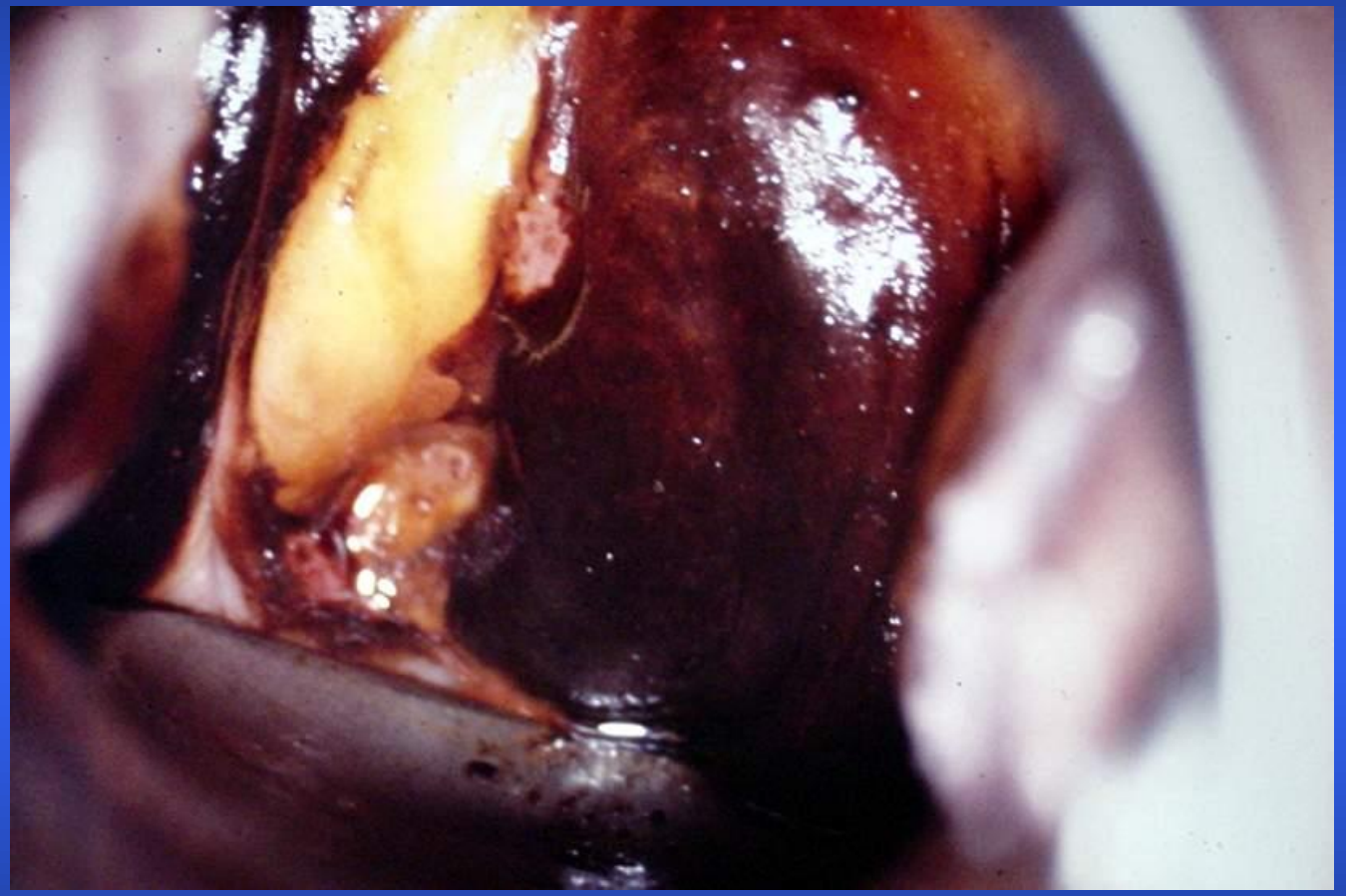






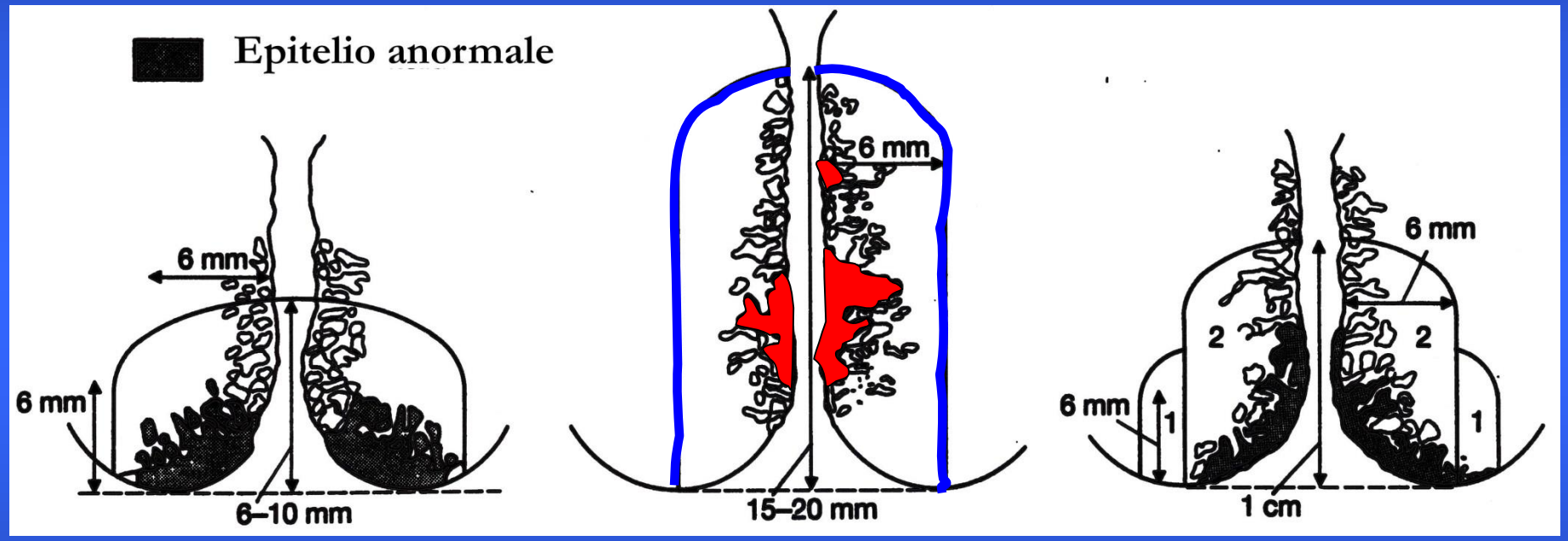






ENDOCERVICOSCOPIA

VARIABILITA'



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

ESCISSIONE CON AGO