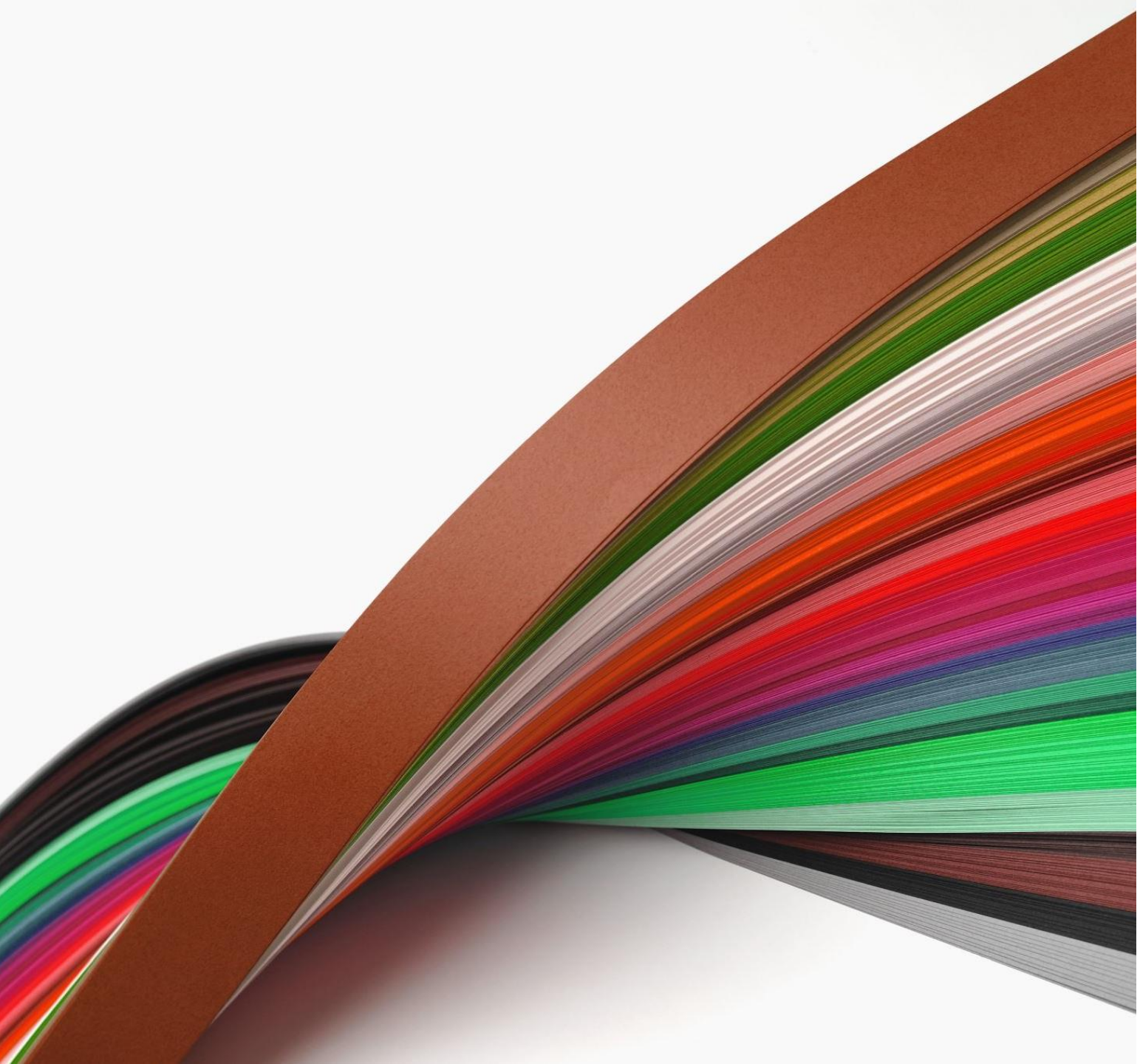


Elena Sendagorta

Servicio de Dermatología

Hospital La Paz

HSIL TREATMENT STATE OF THE ART

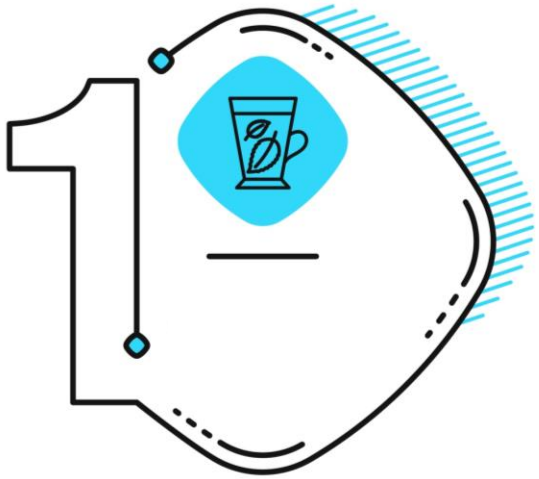
HPV The BCN HPV Course
Jornadas sobre el VPH

STATE OF THE ART?

WHAT IS THE BEST TREATMENT FOR HSIL?

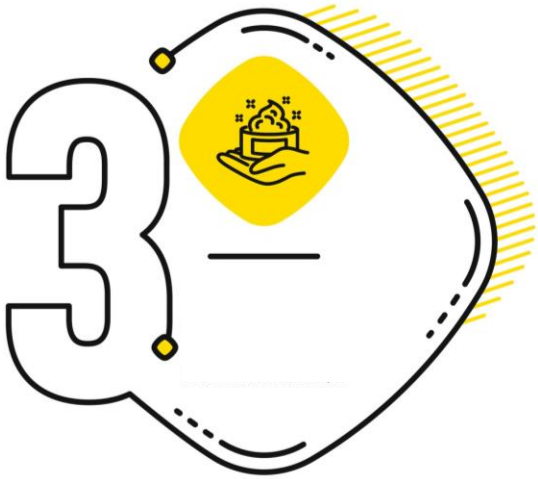
- Scarce clinical trials, only one comparing treatments
- Heterogeneous populations
- Metachronic/recurrent disease
- Strongest evidence ANCHOR study

INDEX

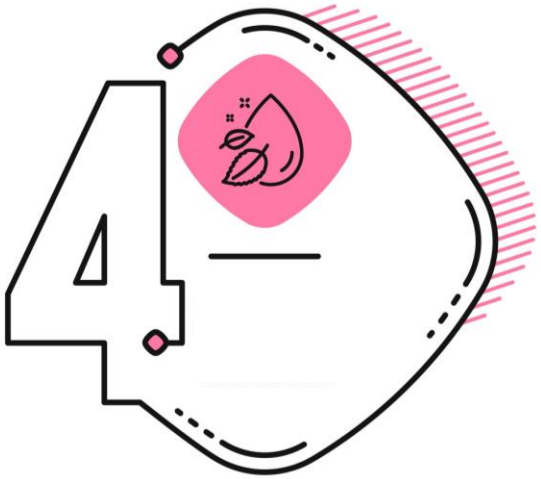


GENERAL PRINCIPLES

- **ABLATIVE**
- **TOPICAL**
- **OTHER**

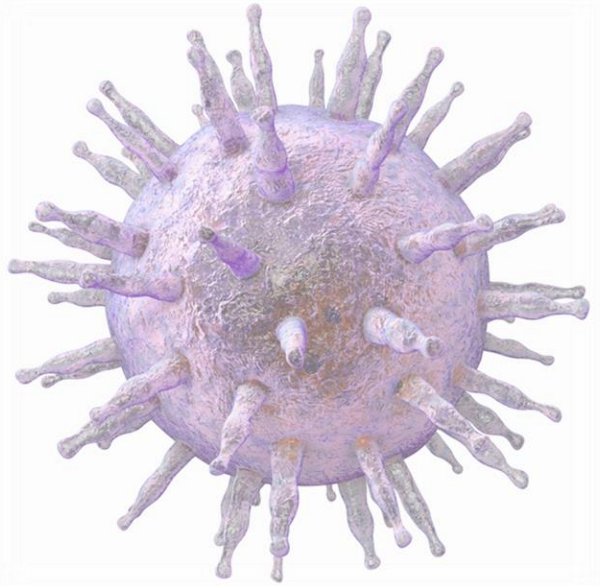


HOW TO CHOOSE TREATMENT



TAKE HOME MESSAGES

GENERAL PRINCIPLES

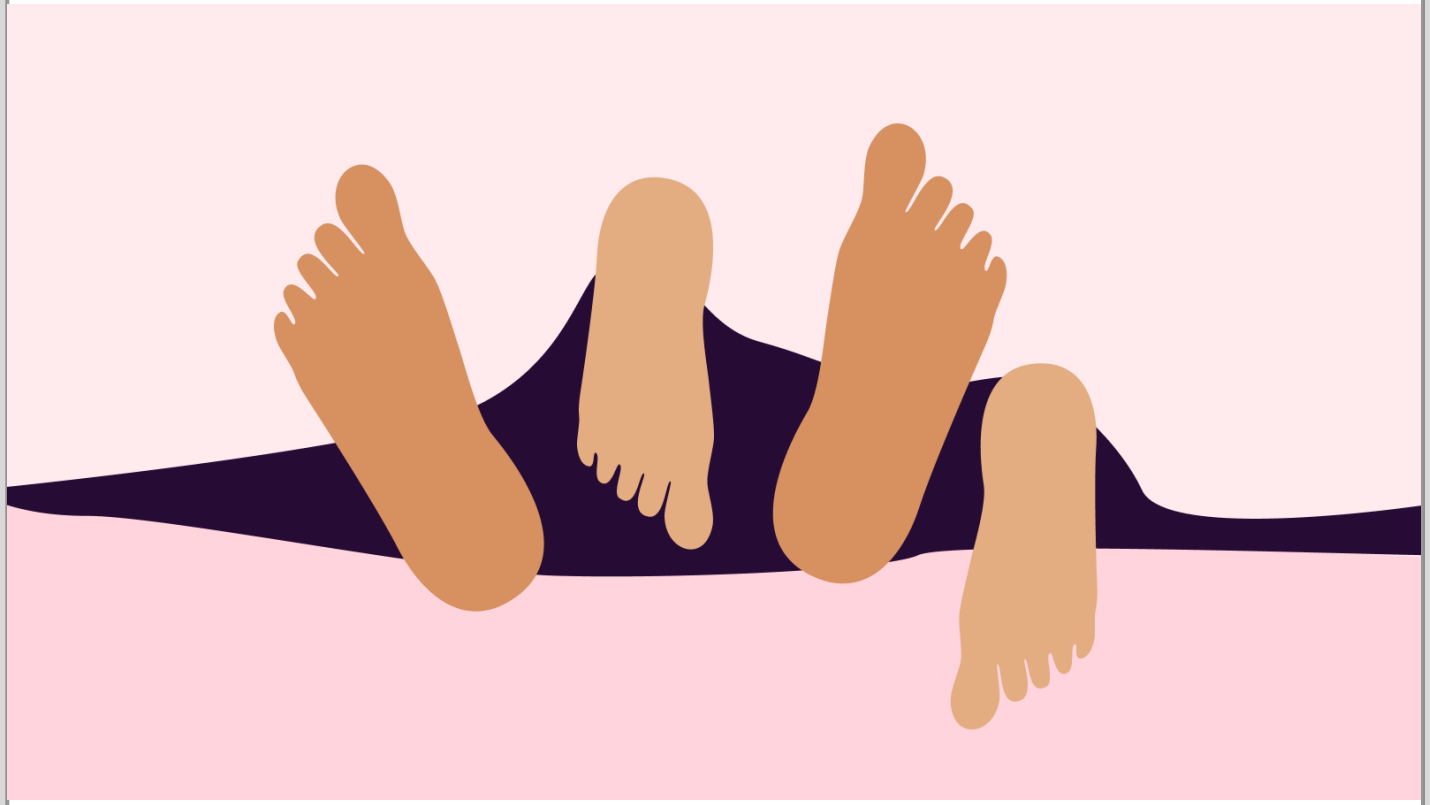


LESION TREATMENT

SYNCHRONOUS AND METACHRONOUS LESIONS

PERSISTENT AND INCIDENT HPV INFECTION

Sexual sphere



Costs

DISEASE BURDEN

What is the challenge?

- Discuss risks, uncertainties and risk of leaving untreated

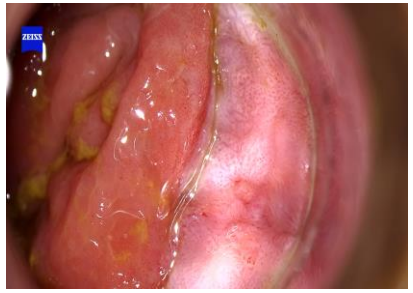
- **Treat HSIL to prevent anal cancer: Ablative**
  - Avoid excessive scarring and stenosis
  - Avoid incontinence
- **Treat HSIL to prevent anal cancer: Topical**
  - What to expect
  - How to improve treatment adherence
  - Avoid AEs

Individual decisions

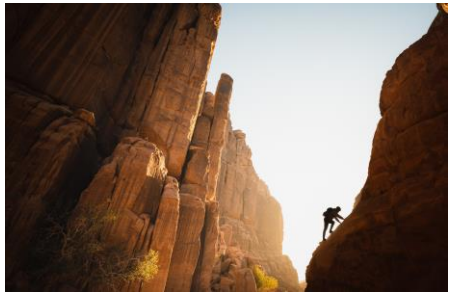
Multidisciplinary team

PERSONALIZE TREAMENT

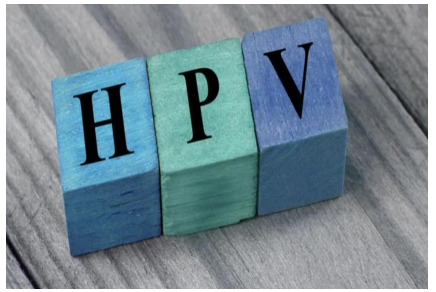
AGE



EXTENSION



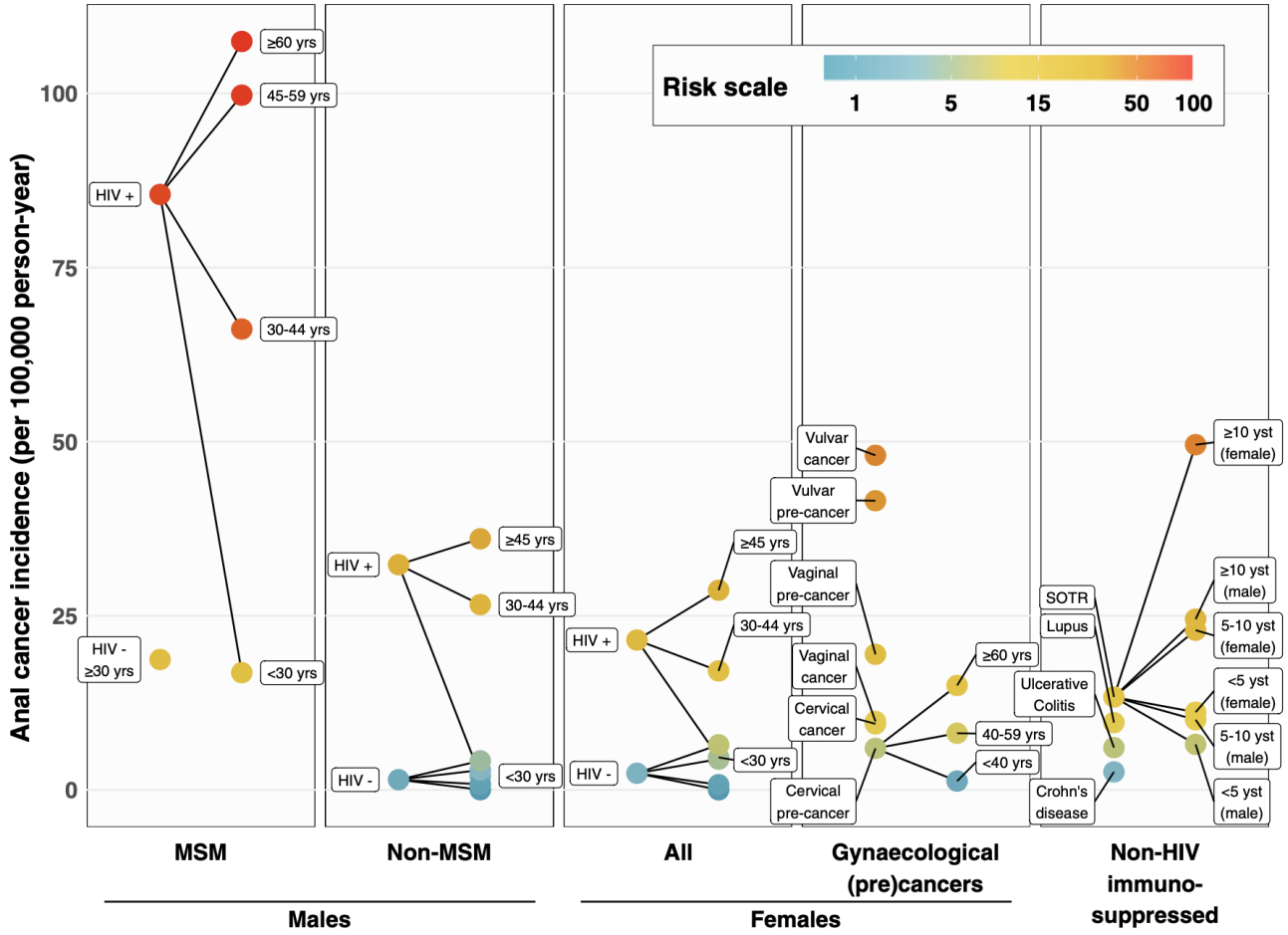
PERSISTENCE



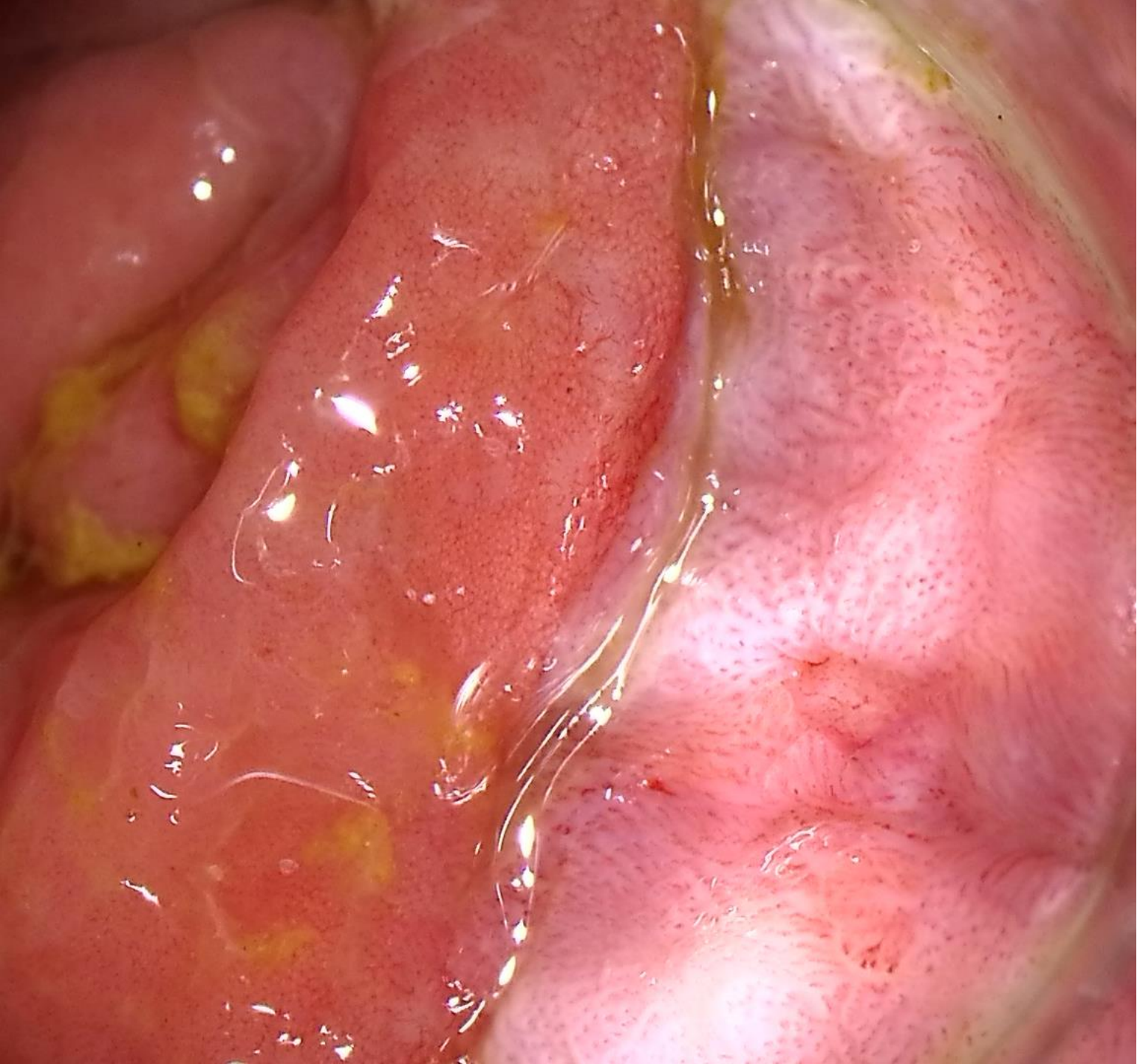
HPV GENOTYPE

IMMUNE STATUS

¿WHY IS AGE IMPORTANT?



Clifford et al Int J Cancer. 2021;148:38-47



¿WHY IS EXTENSION AND PERSISTENCE IMPORTANT?

ANCHOR:

- "Time to progression to anal cancer was associated with lesion size (hazard ratio, 5.26; 95% CI, 2.54 to 10.87)
- "The rate of progression to anal cancer was 1047 per 100,000 person-years among participants with a lesion size of more than 50% of the anal canal or perianal region and 185 per 100,000 person-years among those with a lesion size of 50% or less of the anal canal or perianal región"

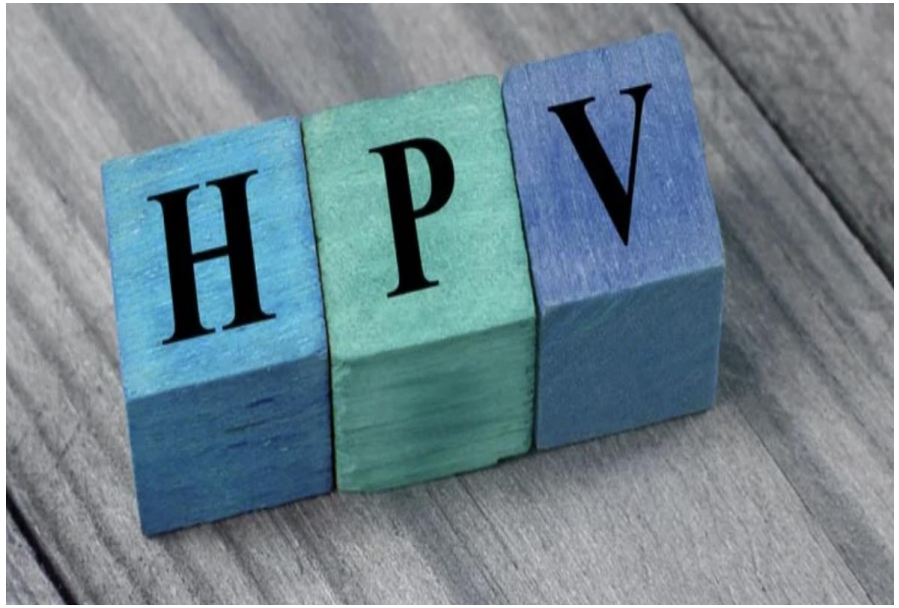
SPANC 617 MSM older than 35 years, median follow-up 3 years

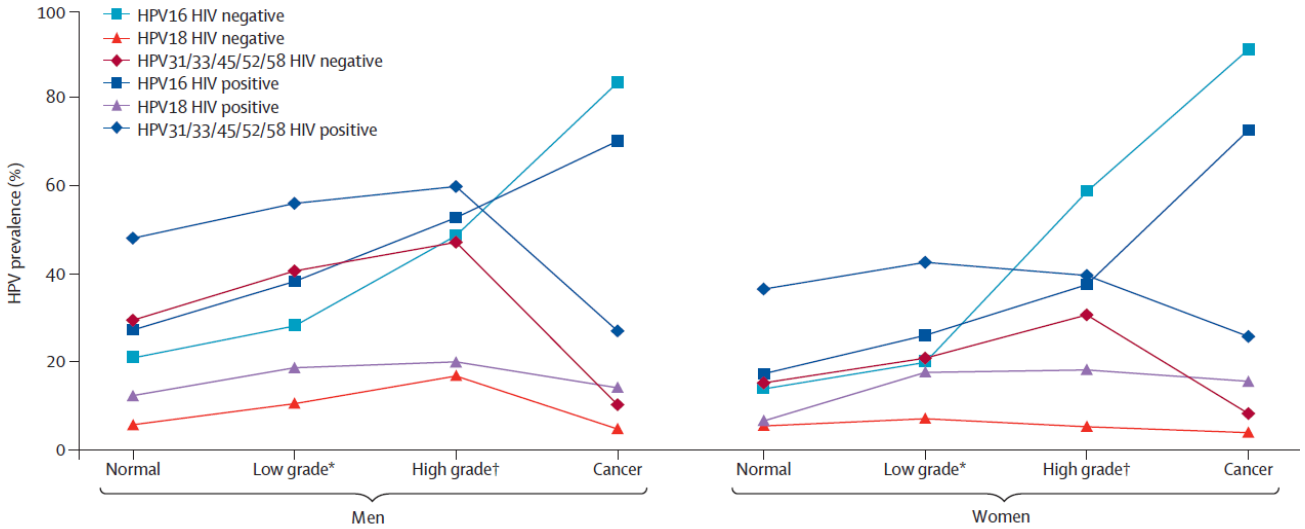
(SPANC: Poynten et al 2022 Clin Infect Dis)

24% histological clearance

Predictors of regression: AIN 2, Age <45 years, Small lesion, HPV16 negative

¿WHY IS HPV IMPORTANT?





Lin et al, Lancet Infect Dis 2018

1. Enrichment HPV 16 from SIL to AC
2. HPV 16 is related to persistent lesion

WHY IS THE PRESENT AND PAST IMMUNE STATUS IMPORTANT?

	Hazard ratio	95% CI	P-value
CD4 cell count,/100 cells/µL	0.72	0.59 – 0.88	0.002
Mode of transmission	Reference		
Heterosexual			
MSM	8.3	1.9 – 36.3	0.005
IDU	1.15	0.12 – 15.3	0.91
Other/unknown	2.32×10^{-19}	…	…
AIDS prior to anal carcinoma	2.7	1.1 – 6.6	0.035

Dis Colon Rectum 2023 Aug 3.**Incidence of Anal Cancer and Related Risk Factors in HIV-Infected Patients Enrolled in the National Prospective Spanish Cohort CoRIS** Elena Sendagorta Cudós[2], César Sotomayor De La Piedra , Mar Masia Canuto, Alfonso Cabello Úbeda , Adrian Curran Antonio Ocampo Hermida Marta Rava , Alfonso Muriel , Juan Macías , David Rial-Crestelo , Javier Martínez-Sanz , Lorena Martinez , María De La Villa López-Sánchez, José A Perez-Molina [2]

2. TREATMENTS

- There are few high-quality studies addressing the efficacy of various treatments for anal HSIL
- Selection remains largely empiric
- Modalities of treatment varies by clinical expertise

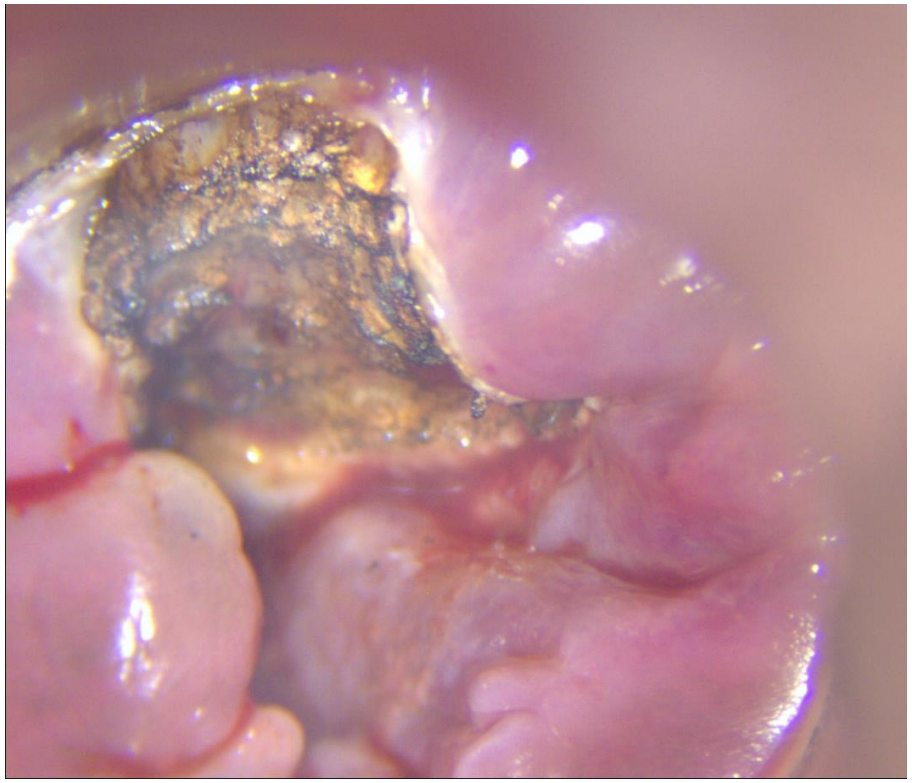
Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sara

- 32 studies
- Only 4 randomized clinical trials
- Risk of bias

International Journal of Colorectal Disease (2021) 36:213–226

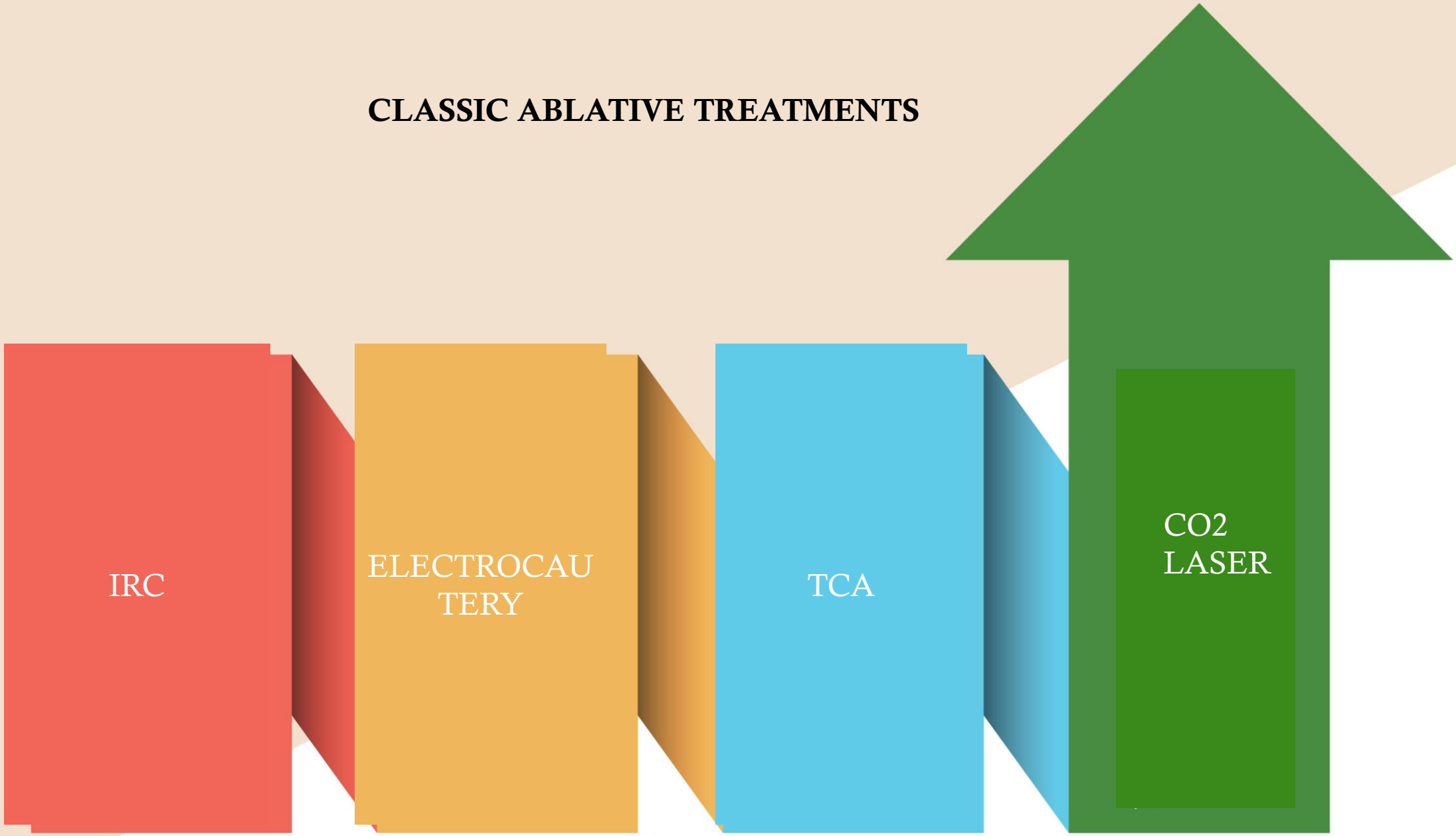
ABLATIVE TREATMENTS



- Very effective in treatment of individual lesion
- Applicated by physician
- Not field treatment/not immunomodulators
- Cost/material
- May need local anaesthesia
- Risk of scarring/stenosis

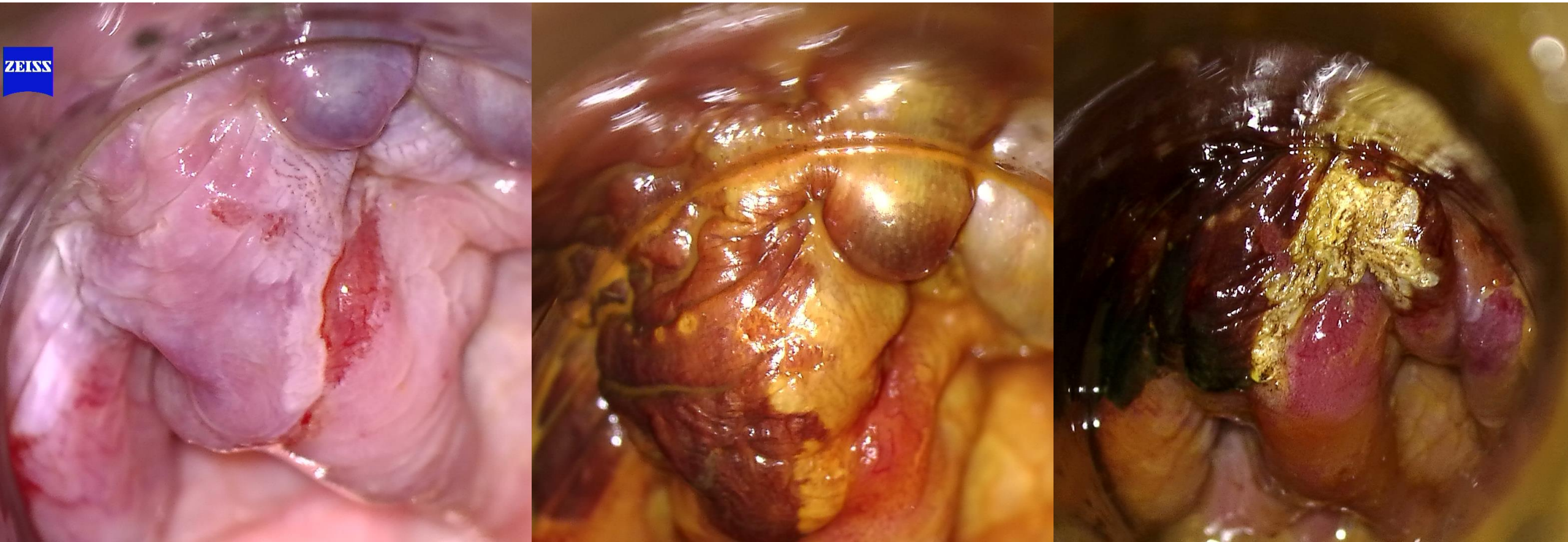
Cranston RD *et al*. Sex Transm Dis 2014;41:420–6// Goldstone RN *et al*. Int J Colorectal Dis 2017;32:357–65.// Burgos J *et al* HIV Med 2016;17:524–31.//Chang G *et al*. Dis Colon Rectum 2002;45:453–8. //Gaisa MM *et al*. Cancer 2020;1261470–9.//Burgos J *et al*. J Acquir Immune Defic Syndr 2018;79:612–6.

CLASSIC ABLATIVE TREATMENTS



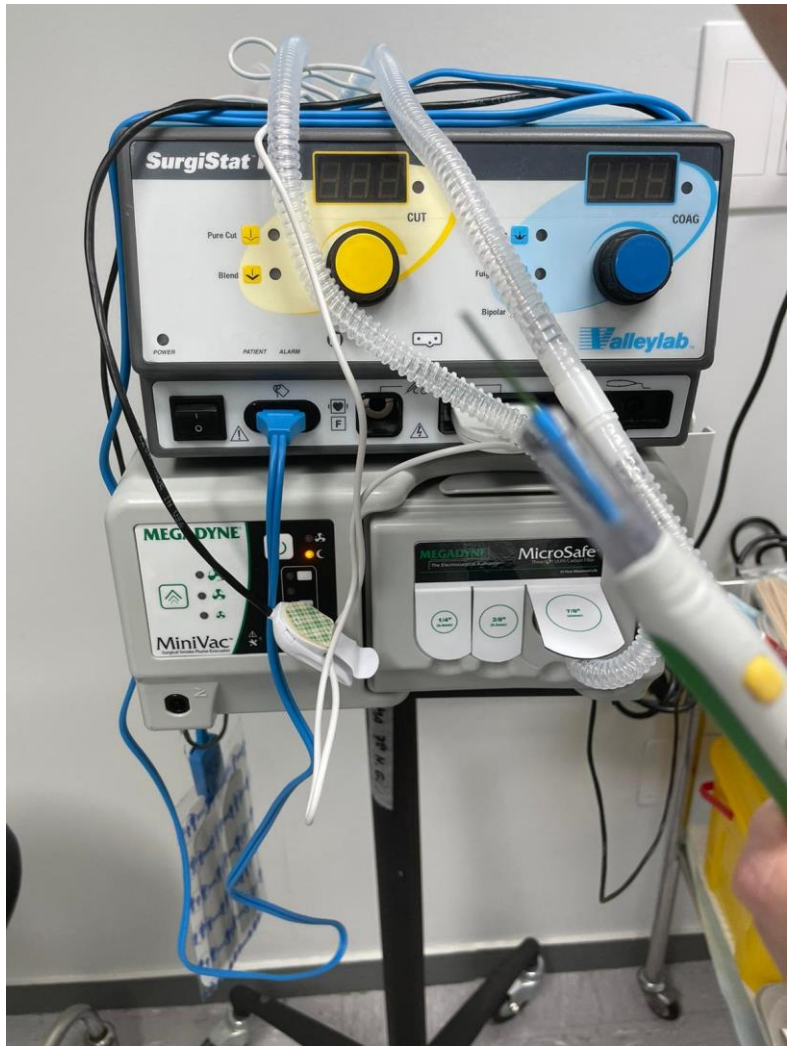
CASE 1.

53 YEARS-OLD, HIV+-MSM. ACETOWHITE, COARSE PUNCTATION, LUGOL NEGATIVE.
PERSISTENT LESION AFTER TCA



ELECTROCAUTERY

ADVANTAGES	DISADVANTAGES
Easy, quick to perform Faster tan IRC, better for PAIN	Risk inhalation
Affordable, widespread	AEs (pain, bleeding, synchronous lesions, stenosis)
Treatment with most evidence of efficacy(ANCHOR)	Does not allow extensive treatment



Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sarah C. Mills [1]

Table 2 Ablative treatments

Study	Design	*N*	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Treatment length	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
Electrocautery: HRA-guided destruction of AIN lesions															
Chang et al. 2002 [26]	Prospective non-randomised open-label pilot study	37	45	100	78	65	100	-	22	0	-	-	32.3 in HIV-negative and 28.6 in HIV-positive (mean)	4	Moderate +
Pineda et al. 2008 [25]	Retrospective chart review	246	44	84	74	-	100	One or multiple treatments if circumferential	78	-	57	0.4	42	4	Critical +
Marks et al. 2012 [29]	Retrospective chart review	232	43 HIV-negative, 49 HIV-positive (median)	-	57	100	100	Up to 4 treatments with 3–4 months follow-up periods	67 (after 4th treatment)	0	-	0.4	17.3 in HIV-negative, 13 in HIV-positive after 1st treatment	4	Moderate +
Richel et al. 2013 [12]	Open-label RCT	46	47 (median)	100	100	100	54	4 months	39 (40 HGAIN)	7 (12 HGA-IN)	28	0	4.5 (response) 16.5 (recurrence)	1b	Some con-cerns *
Assoumou et al. 2013 [27]	Retrospective chart review	80	42 (median)	100	56	100	90	1 treatment	53	-	-	0	-	4	Critical +
Burgos et al. 2016 [28]	Observational cohort study	108	-	100	100	100	100	2–4 treatments followed by HRA 6–8 weeks later. This was repeated until clearance.	25	26	13	0	12 (mean)	4	Moderate +
N = 749															
Infrared coagulation: after HRA, 1.5–1.6 second pulses under direct vision															
Cranston	Retrospective	68	45 (median)	100	100	100	97	1 treatment	11	66	-	0	4.6 (mean)	4	Moderate

CR 22-78%
PR 7-26%
2 STUDIES LESS RISK OF RECURRENCE HIV-
BURGOS ET AL: 39% RECURRENCE WERE METACHRONOUS DISEASE

6 STUDIES
N: 749

IJCD 2021

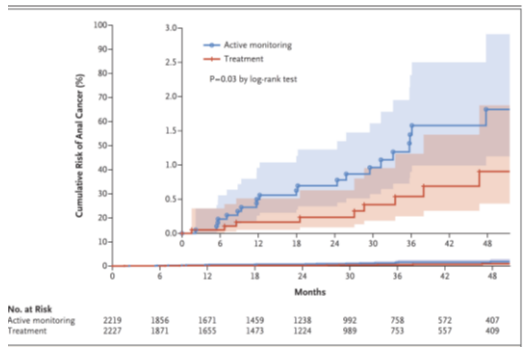
Open, Multicenter, Controlled Study
HIV+, proven HSIL at baseline

ARM 1- Active Treatment :2227

Topical or ablative treatment at the discretion of the clinician.
->Topical treatment apply imiquimod intra-anally, peri-anally or both thrice weekly for up to 16 weeks, fluorouracil twice daily for 5 days every 2 weeks for up to 16 weeks, or trichloroacetic acid every 3 weeks up to 12 weeks
->Ablative treatment using infrared coagulation, hyfrecation/electrocautery, or laser.

173/100000 PY

9 CA



Primary Outcome:
Time to Anal Cancer
Secondary Outcomes
Adverse effects

83% cauterization

ARM 2 - Comparator – Monitoring: 2219

II (active monitoring)
Patients undergo active monitoring with examinations every 6 months. Every 12 months, patients undergo biopsies of visible lesions. Patients have cytology sampling performed at every visit.

32 CA

402/100000 PY

Palefsky J. 2022. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer

Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial

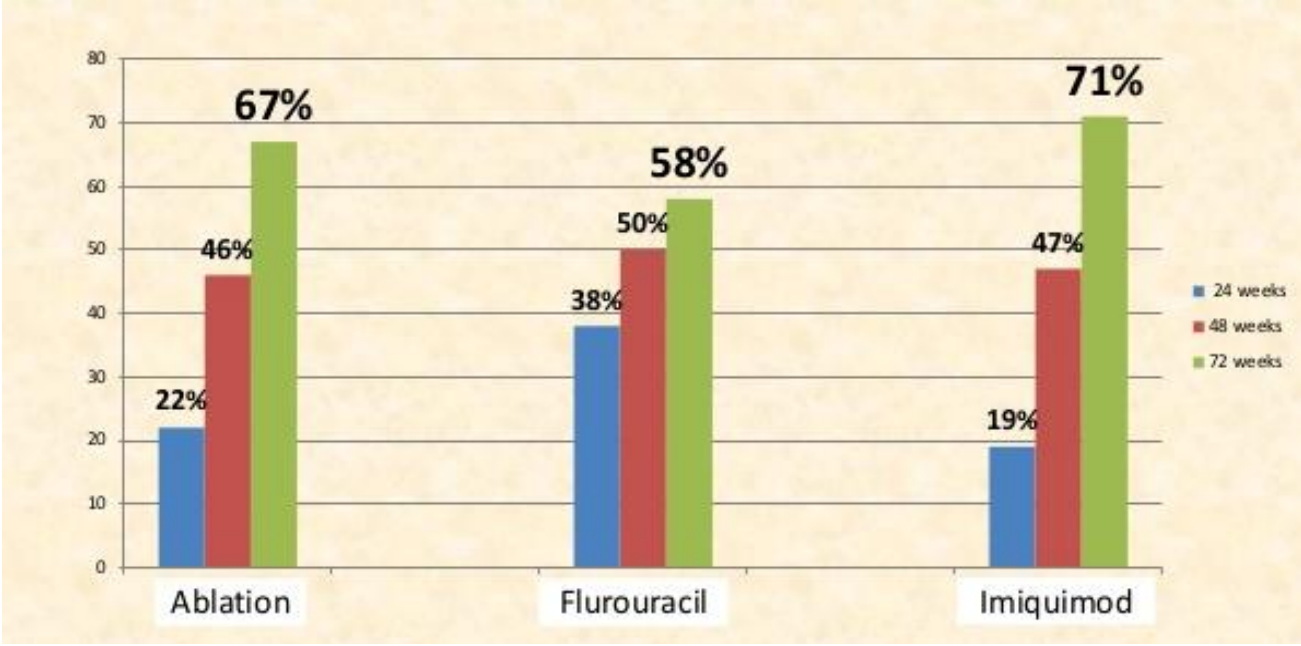
Olivier Richel, Henry J C de Vries, Carel J M van Noesel, Marcel G W Dijkgraaf, Jan M Prins

	Intra-anal lesions			Peri-anal lesions		
	Imiquimod	Fluorouracil	Electrocautery	Imiquimod	Fluorouracil	Electrocautery
Complete response						
n/N	9/41	7/42	16/34	9/9	4/7	3/4
% (95% CI)	22% (12–37)	17% (8–31)	47% (31–63)	100% (73–100)	57% (25–84)	75% (29–97)
Partial response						
n/N	6/41	7/42	3/34	..	..	..
% (95% CI)	15% (7–29)	17% (8–31)	9% (2–24)	..	..	..
No response						
n/N	26/41	28/42	15/34	0/9	3/7	1/4
% (95% CI)	63% (48–76)	67% (51–79)	44% (29–61)	0% (0–28)	43% (16–75)	25% (3–71)

Assessment of response by localisation. The cumulative number of peri-anal and intra-anal lesions exceeded the total number of patients, because some patients had both peri-anal and intra-anal lesions. For intra-anal lesions, groups differed significantly in complete response (p=0·0080) and overall (complete+partial) response (p=0·045). For peri-anal lesions, groups did not differ significantly in response (p=0·36).

Table 4: **Response to treatment (per protocol) for peri-anal and intra-anal lesions separately**

- EC best results in terms of effectiveness for intra-anal HSIL
- EC: higher percentage of mild AEs but lower percentage of severe AEs



Original Article

Electrocautery Ablation of Anal High-Grade Squamous Intraepithelial Lesions: Effectiveness and Key Factors Associated With Outcomes

Michael M. Gaisa, MD, PhD [1]; Yuxin Liu, MD, PhD[2]; Ashish A. Deshmukh, PhD, MPH[3]; Kimberly L. Stone, MPH[4]; and Keith M. Sigel, MD, PhD [4]

BACKGROUND: Electrocautery ablation (EA) is a common treatment modality for patients with anal high-grade squamous intraepithelial lesions (HSILs), but to the authors' knowledge its effectiveness has been understudied. The objective of the current study was to determine ablation outcomes and to identify clinicopathological factors associated with postablation disease recurrence. **METHODS:** A total of 330 people living with HIV with de novo intra-anal HSIL who were treated with EA from 2009 to 2016 were studied retrospectively. Using long-term, surveillance high-resolution anoscopy biopsy data, treatment failures were classified as local recurrence (HSIL noted at the treated site at the time of surveillance) or overall recurrence (HSIL noted at treated or untreated sites). The associations between these outcomes and clinical factors were analyzed using Cox proportional hazards models. **RESULTS:** Approximately 88% of participants were men who have sex with men. The median age of study participants was 45.5 years (range, 35-51 years) and approximately 49% had multiple index HSILs (range, 2-6 index HSILs). At a median of 12.2 months postablation (range, 6.3-20.9 months postablation), approximately 45% of participants had developed local recurrence whereas 60% had developed overall recurrence. Current cigarette smoking, HIV viremia (HIV-1 RNA ≥100 copies/mL), and multiple index HSILs were found to be predictive of local recurrence. Overall recurrence was more common in current smokers and those with multiple index lesions. In multivariable models that included human papillomavirus (HPV) genotypes, baseline and persistent infections with HPV-16 and/or HPV-18 were found to be significantly associated with both local and overall recurrence. **CONCLUSIONS:** EA is an effective treatment modality for anal HSIL in people living with HIV, but rates of disease recurrence are substantial. Multiple index HSILs, HIV viremia, current cigarette smoking, and both baseline and persistent infection with HPV-16 and/or HPV-18 appear to negatively impact treatment success. Ongoing surveillance is imperative to capture recurrence early and improve long-term treatment outcomes. ***Cancer* 2020;126:1470-1479**. © *2020 American Cancer Society*.

KEYWORDS: anal cancer precursors, electrocautery ablation, high-grade squamous intraepithelial lesion (HSIL), HIV, outcomes, recurrence.

- Multiple HSILs
- HIV detectable CV
- Current smoking
- Initial / Persistent HPV-16 and/or 18 infection
- High RR 50%12 m 68% 36 m

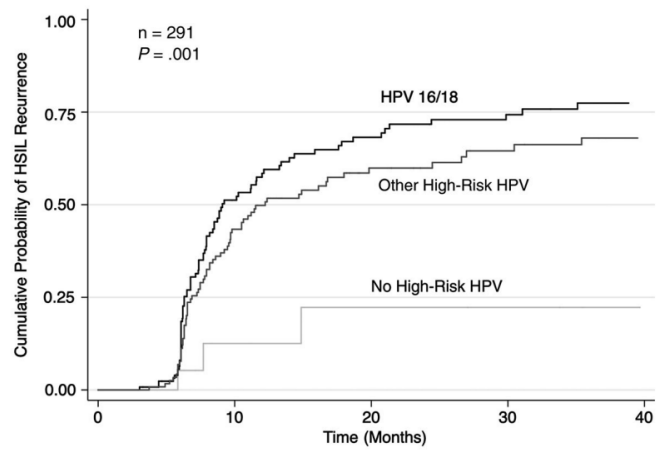
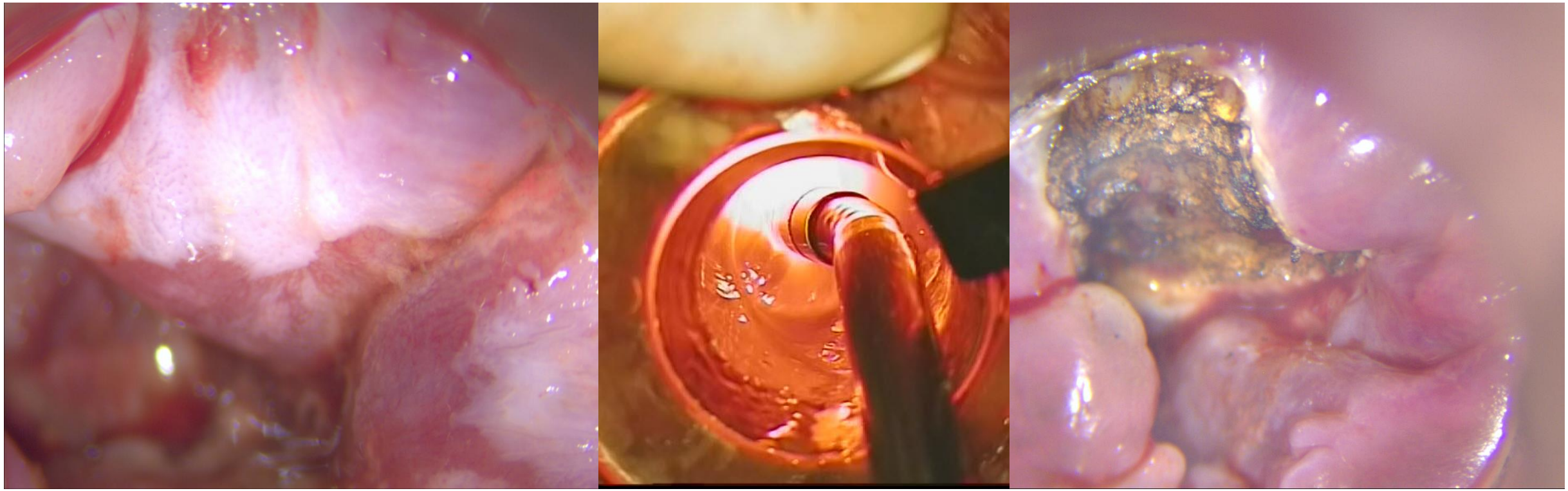


Figure 2. Cumulative probability of overall recurrence of high-grade squamous intraepithelial lesions (HSILs) after electrocautery ablation of anal HSILs among people living with HIV by baseline human papillomavirus (HPV) status.

CASE 2.

46 YEARS-OLD, HIV WSM. ACETOWHITE, MOSAICISM, LUGOL NEGATIVE.



INFRARED COAGULATION

- Device that delivers short pulses of visible and infrared light → necrosis
  - 1.5mm deep lesions
  - Very easy to use
- May require local anaesthesia
- Local side effects: pain and bleeding

Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden[1] · Una Walsh[1] · Gianluca Pellino[2,3] · Christos Kontovounisios[1] · Paris Tekkis[1] · Sarah C. Mills[1]

Study	Design	N	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
Infrared coagulation: after HRA, 1.5–1.6 second pulses under direct vision															
Cranston et al. 2008 [32]	Retrospective chart review	68	45 (median)	100	100	100	97 (lesions)	1 treatment	11	66	-	0	4.6 (mean)	4	Moderate +
Stier et al. 2008 [36]		18	44	89	100	-	44 (lesions)	1 treatment but retreated at 3 months if persistent disease	39	17	11	0	12	4	Moderate +
Goldstone et al. 2011 [33]	Retrospective cohort	143	42 HIV-positive; 36 HIV-negative	100	48	100	67	Up to 4 treatments	45 (after 4th treatment)	-	-	0	69 HIV-positive; 48 HIV-negative	4	Serious +
Weis et al. 2012	Prospective cohort	124	40	80	100	-	100	1 treatment	3	69	-	0	33	2B	Serious +
Sirera et al. 2013 [34]	Retrospective cohort	69	43	45	100	74	100	1 treatment, further treatment if recurrence	71	6	-	0	25 (mean)	4	Moderate +
Goldstone et al. 2019 [35]	Non-blinded multisite randomised control trial (IRC vs observation alone)	120	49 treated vs. 50.5 untreated	90 treated 97 vs. untreated	100	-	100	1–3 treatments depending on response	62 treated vs. 30 untreated	7 treated vs. 6 untreated	-	0 (both arms)	12	1b	Some concerns*

$N = 542$

Less severe side effects vs other ablative treatments
3-71% CR
6-69%PR

N:542

IJCD 2021

Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review

J. Corral[1,2] · D. Parés[1,2,3] · F. García-Cuyás[1,2] · B. Revollo[2,4] · S. Videla[2,5] · A. Chamorro[2,4] · M. Piñol[1,2] · B. Clotet[2,3,6] · G. Sirera[2,4]

Received: 2 April 2019 / Accepted: 16 July 2019 / Published online: 23 July 2019

Abstract

Background Anal intraepithelial neoplasia (AIN) (or low/high grade squamous intraepithelial neoplasia (L/HSIL)) is the precursor of anal of early invasive anal cancer. Different treatment options for local ablation of localized lesions have been reported. The aim of this study was to analyze the clinical efficacy and safety of infrared coagulation for the treatment of anal dysplasia.

Methods A search of the literature was performed in 2019 using PubMed and Cochrane to identify all eligible trials published reporting data on the treatment of anal dysplasia with infrared coagulation. The percentage of squamous cell carcinoma of the the anus that developed in the follow-up and results on major complications after treatment were the primary outcomes.

Results Twenty-four articles were identified from which 6 were selected with a total of 360 patients included, with a median age of 41.8 years. Three studies were prospective and 3 retrospective, only one was a randomized trial. All articles included males, 4 articles included HIV-positive women and only one article included non HIV infected males. No patient developed major complications after infrared coagulation therapy. Pain was the most common symptom found after the procedure in the different series and mild bleeding that did not require transfusion was the most common complication occurring in 4 to 78% of patients. Median follow-up was between 4.7 and 69 months. No patient developed squamous cell carcinoma after infrared treatment. Recurrent HSIL varied from 10 to 38%. Two studies reported results from follow-up of untreated patients showing that between 72 and 93% of them had persistent HSIL at last follow-up and 4.8% developed squamous cell carcinoma.

Conclusions Infrared coagulation is a safe and effective method for ablation of high-grade anal dysplasia that could help prevent anal cancer. Continued surveillance is recommended due to the risk of recurrence.

24 articles, 6 selected
Only 1 clinical trial
AEs PAIN, mild bleeding (4-78%)
No complications, No AC
Recurrent HSIL 10-38%

Clinical Infectious Diseases
MAJOR ARTICLE

A Randomized Clinical Trial of Infrared Coagulation Ablation Versus Active Monitoring of Intra-anal High-grade Dysplasia in Adults With Human Immunodeficiency Virus Infection: An AIDS Malignancy Consortium Trial

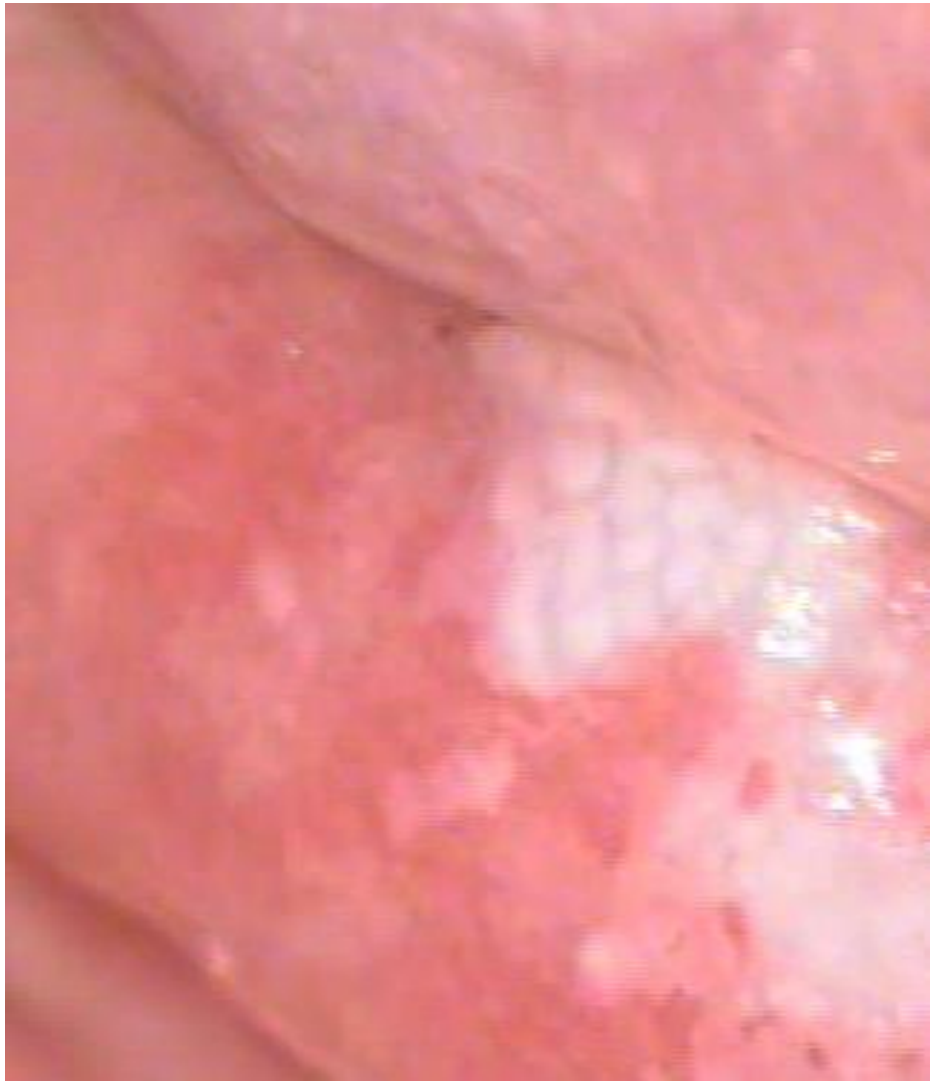
Stephen E. Goldstone,[1] Shelly Y. Lensing,[2] Elizabeth A. Stier,[3] Teresa Darragh,[4] Jeannette Y. Lee,[2] Annemieke van Zante,[4] Naomi Jay,[5] J. Michael Berry-Lawhorn,[5] Ross D. Cranston,[6] Ronald Mitsuyasu,[7] David Aboulafia,[8] Joel M. Palefsky,[4] and Timothy Wilkin[9]

- Open-label, randomised, multicentric clinical trial
- IRC vs active monitoring
- 120 HIV ≥27 years with 1-3 anal HSILs

	Infrared coagulation	Active monitoring
HSIL clearance 12 months	63%	30%

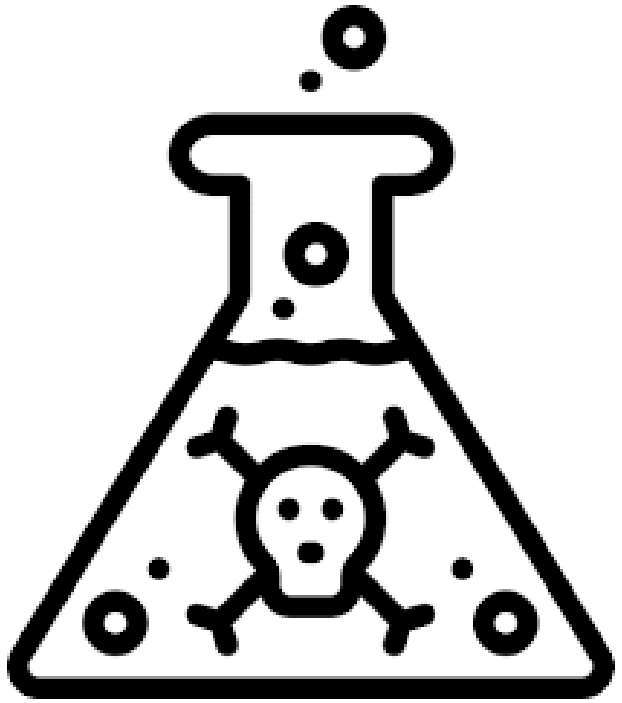
CASE 3

35 YEAR OLD, HIV MSM- SMALL LESIÓN
POOR PAIN TOLERANCE



TCA ACID

Topical Ablative Treatment	TCA 80-85%	4-5 touches
Applicated by healthcare personnel	No local anaesthesia required	Minimal training required
No risk of HPV inhalation	Inexpensive	More effective in small lesions/younger patients
Requieres many sessions	The only treatment approved for pregnacny women	



Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sarah C. Mills [1]

Study	Design	*N*	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
N = 112 80% Trichloroacetic acid - Cranston et al. 2014 - 5 Q-tips worth of TCA applied under direct vision at HRA × 1; Singh et al. 2019 - up to 4 applications of TCA (1–2 month intervals) on direct vision at HRA															
Cranston et al. 2014 [21]	Retrospective chart review	72	48	100	100	-	100	100	72	11	15 at index site (22.6 at index and adjacent 32 synchronous)	-	-	4	Serious +
Singh et al. 2009 [22]	Retrospective chart review	54	44 HIV-positive; 45 HIV-negative	100	65	-	52		28	14	28	-	12	4	Moderate +

RC 28-72%
RP 11-15%
RR 8-15%

N: 50

IJCD 2021

Retrospective
2-4 treatment sessions

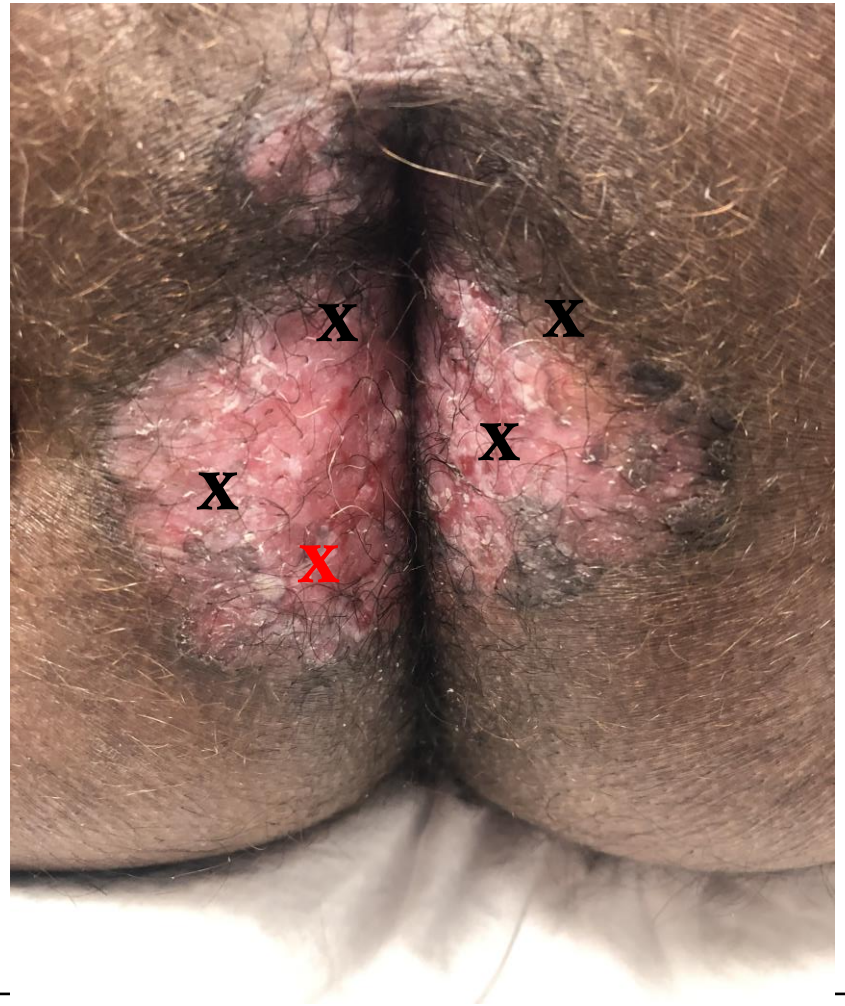
Effectiveness of Trichloroacetic Acid vs. Electrocautery Ablation for the Treatment of Anal High-Grade Squamous Intraepithelial Lesion in HIV-Infected Patients

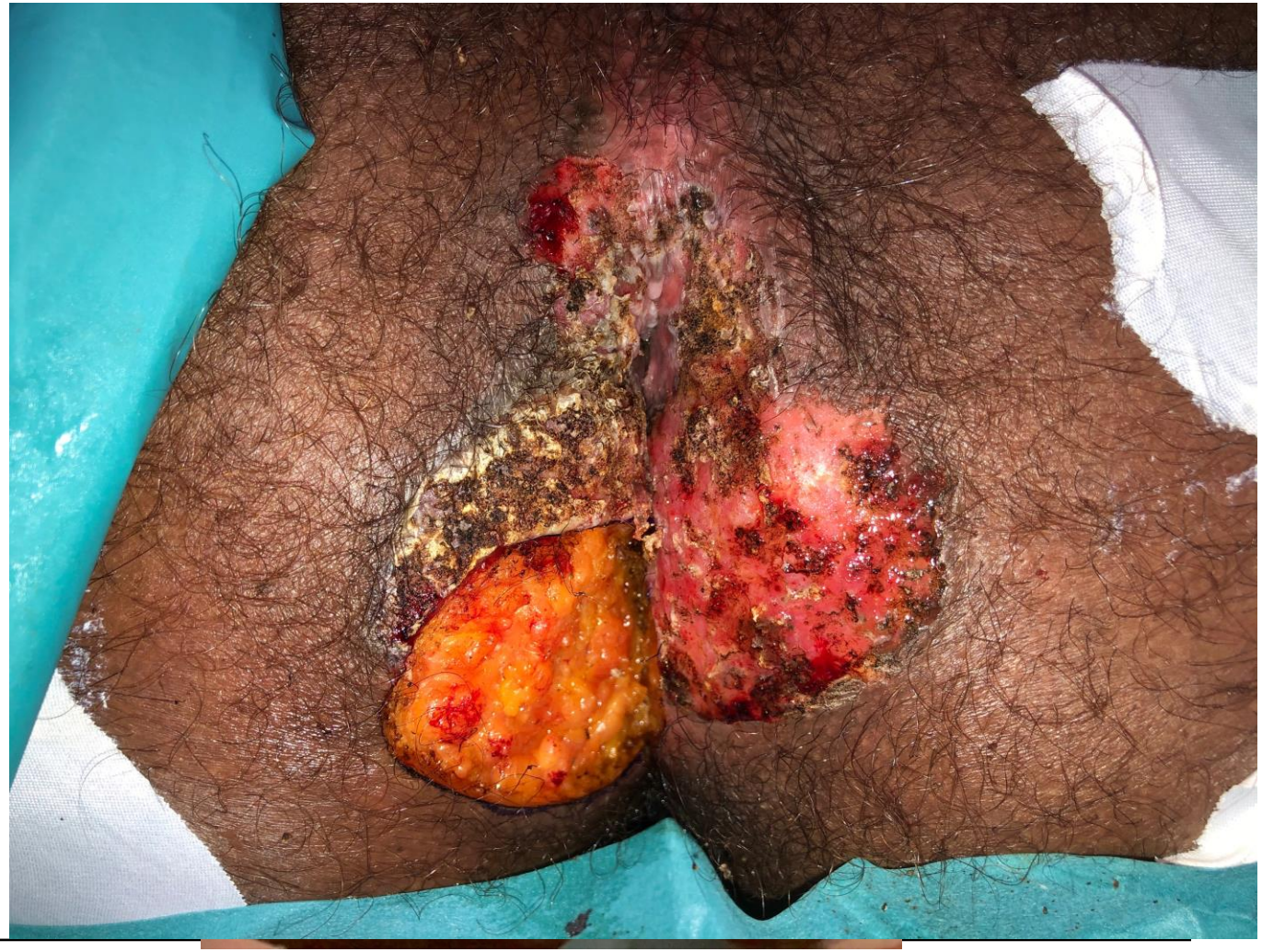
Joaquin Burgos, MD, PhD, Mario Martin-Castillo, MD,† Stefania Landolfi, MD,‡ Maria C. Dinares, MD,‡ Judith Villar, MD, PhD,‡§ Jordi Navarro, MD,* Esteve Ribera, MD, PhD,* Vicenç Falcó, MD, PhD,* and Adria Curran, MD, PhD**

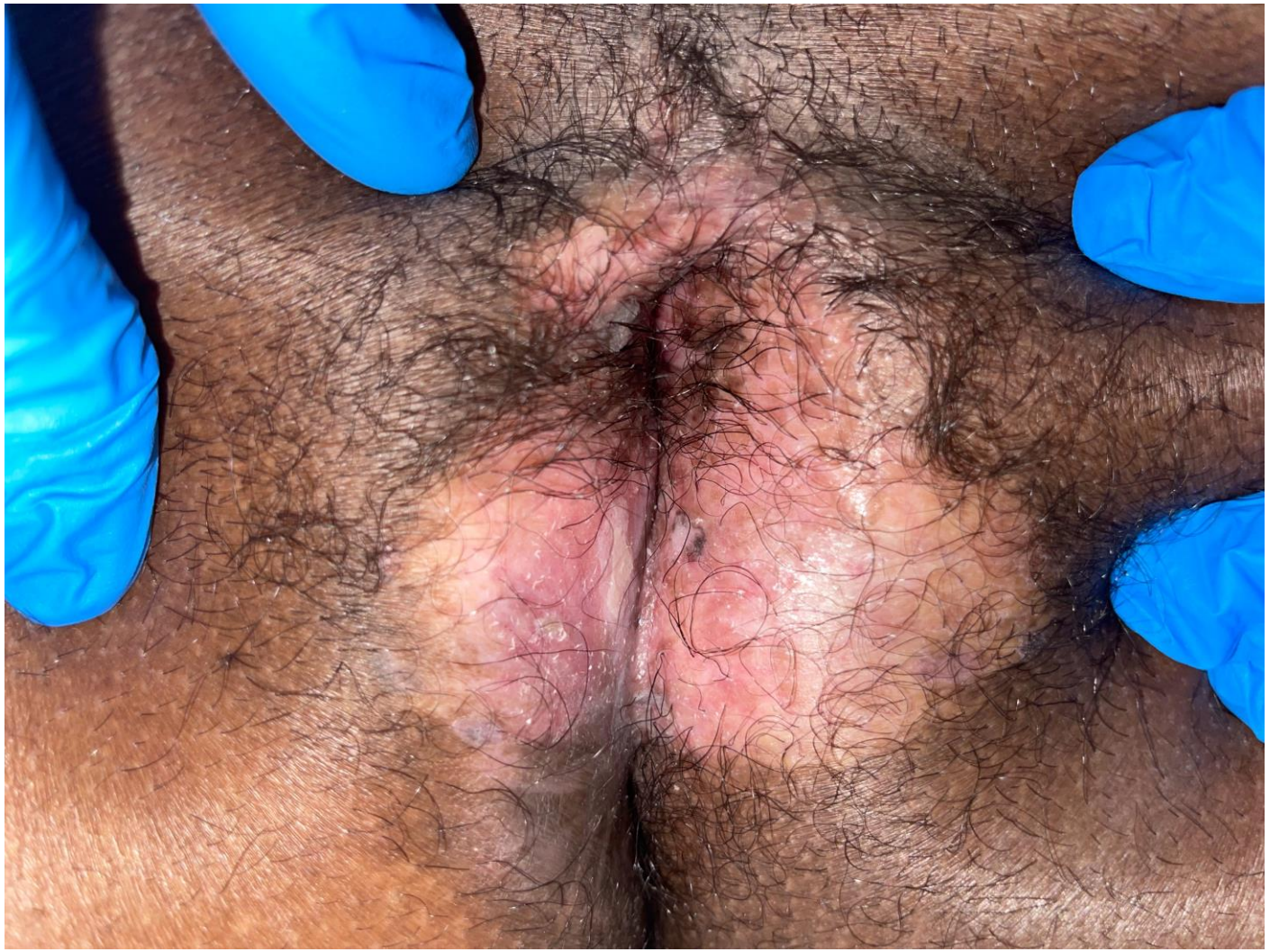
	ELECTROCAUTERY	TCA
HSH-VIH	182	56
Complete Response	33.5%	**60.7%**
Partial Response	28.0%	23.2%
Good tolerability	80.6% (more **bleeding**)	82.6% (more **itching**)
Recurrence 12m	**14.6%**	27.6%

CASE 4

46, HIV MSM, PAIN and microinfiltrant perianal carcinoma





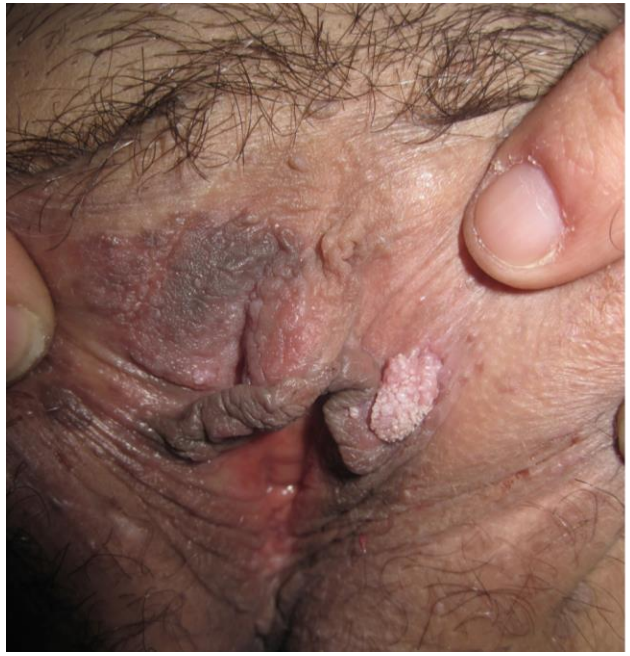


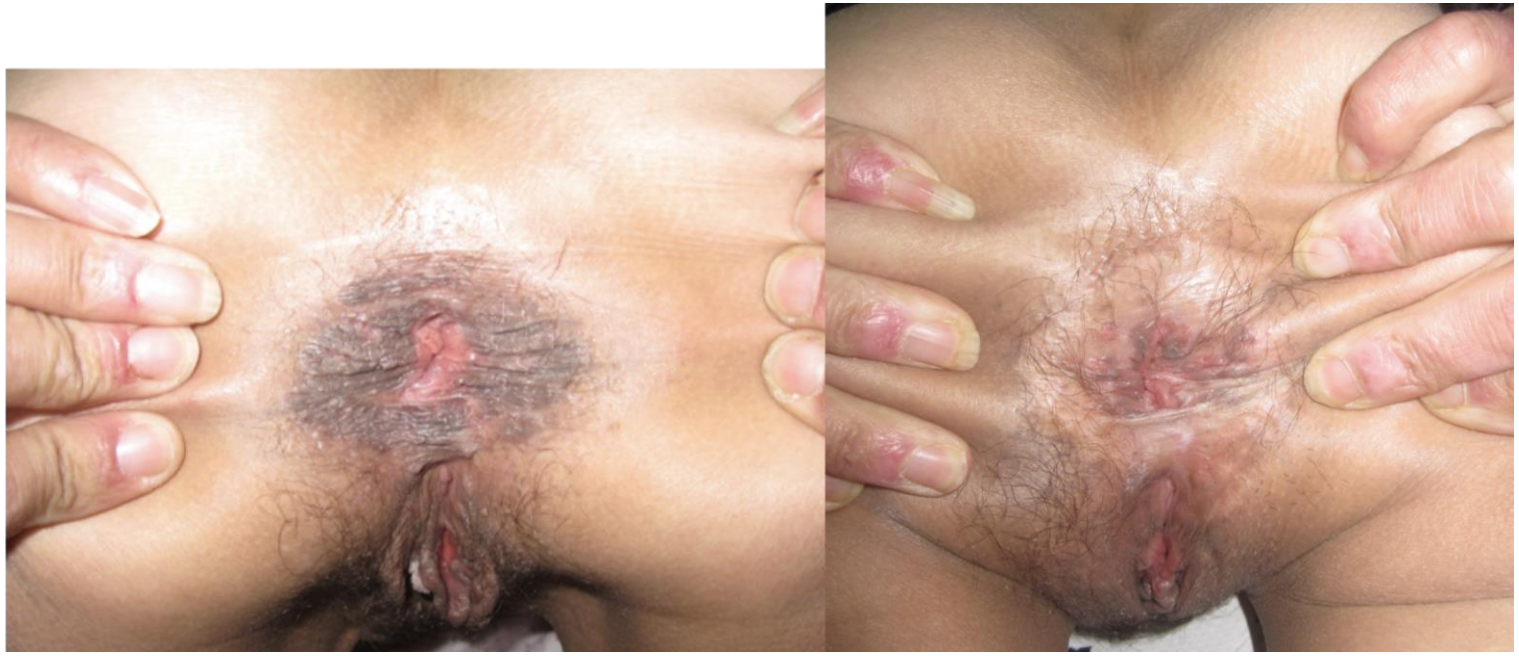
Co2 LASER

- Superficial vaporization of the epithelium
- Excellent for perianal/vulvar disease
- High precisión, very good cosmetic outcomes
- Minimal damage to adjacent tissues
- More bleeding tan EC
- Expensive, not widely available
- Applicated by healthcare personnel
- Risk of HPV inhalation
- Requires eye protection

CASE 5

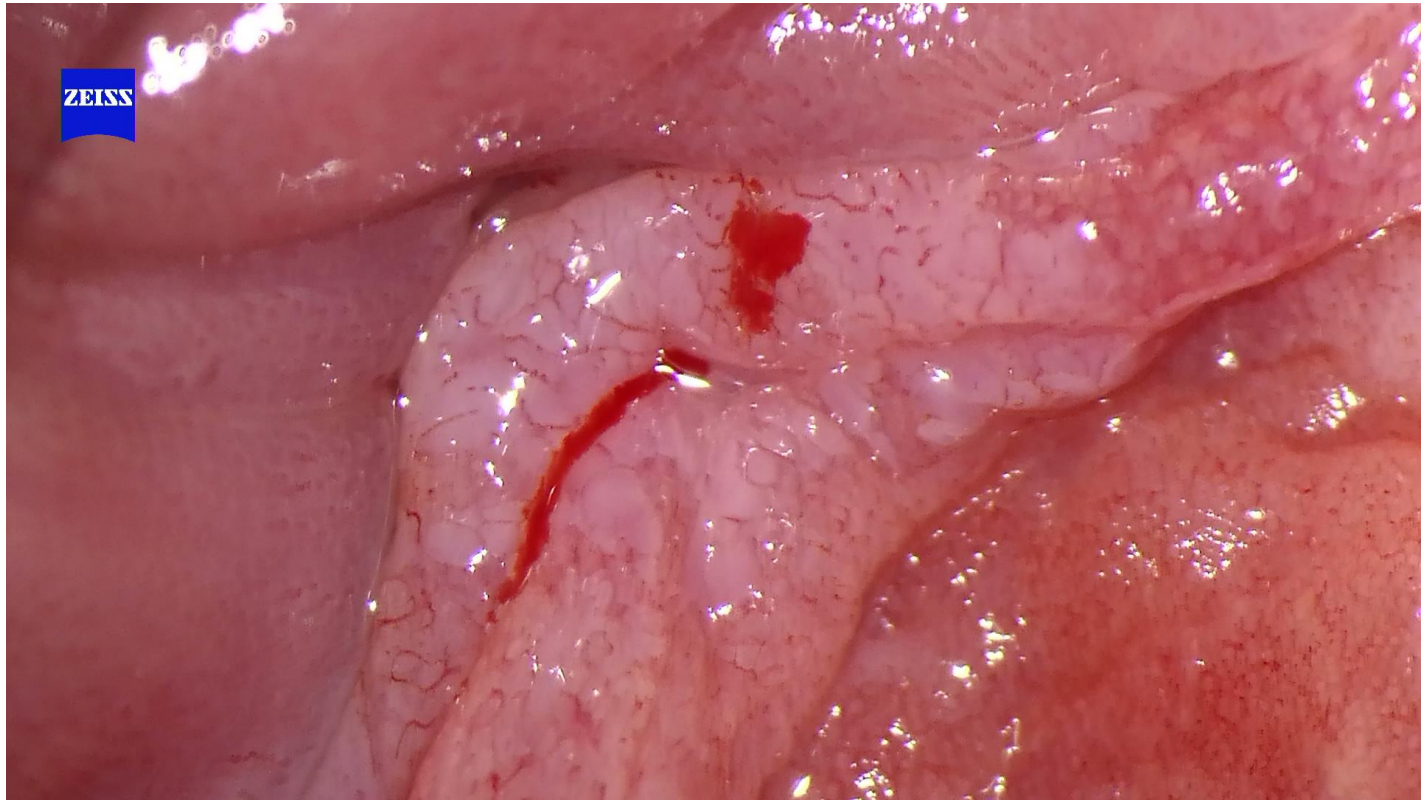
- WOMEN 45, LES TREATMENT WITH HIDROXICLOROQUINE AND AZATHIOPRINE
- PAIN, VAIN

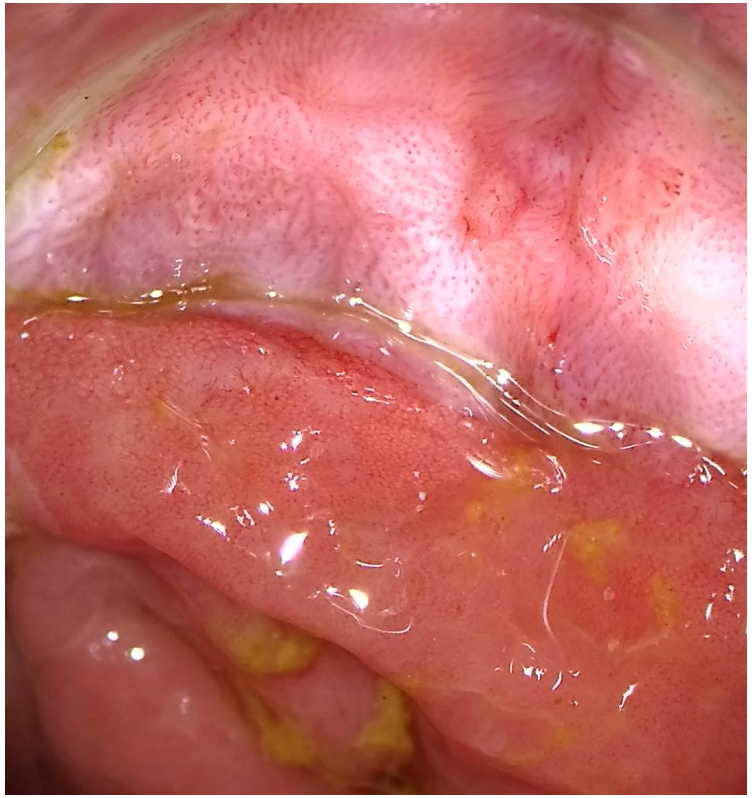




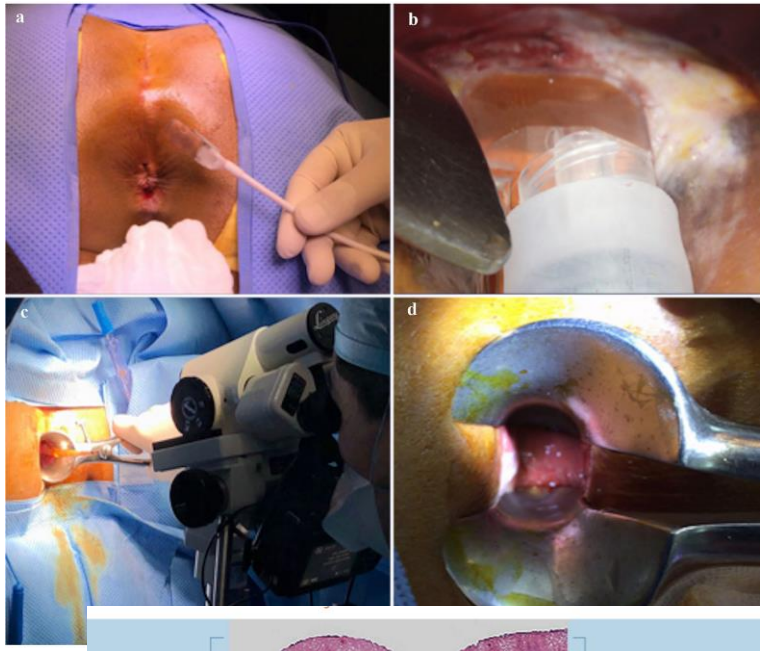
CASE 6

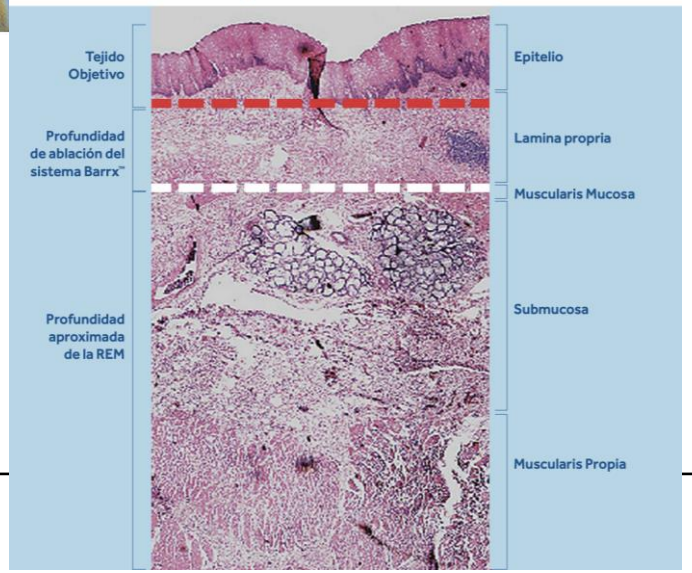
54 HIVMSM, ACETOWHITE PLAQUES WITH MOSAICISM AND COARSE PUNCTATION CIRCUNFERENTIAL 360, NOT ADHERENT TO TOPICAL TREATMENT





RADIOFREQUENCY ABLATION

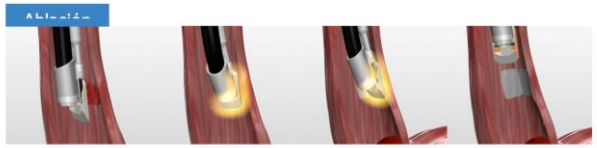




Radiofrequency ablation (RFA) is an endoscopic therapy used primarily to treat Barrett's esophagus.
RFA uses an array of parallel alternating electrodes to deliver radiofrequency energy that heats the lining of the gastrointestinal tract, destroying the tissue.

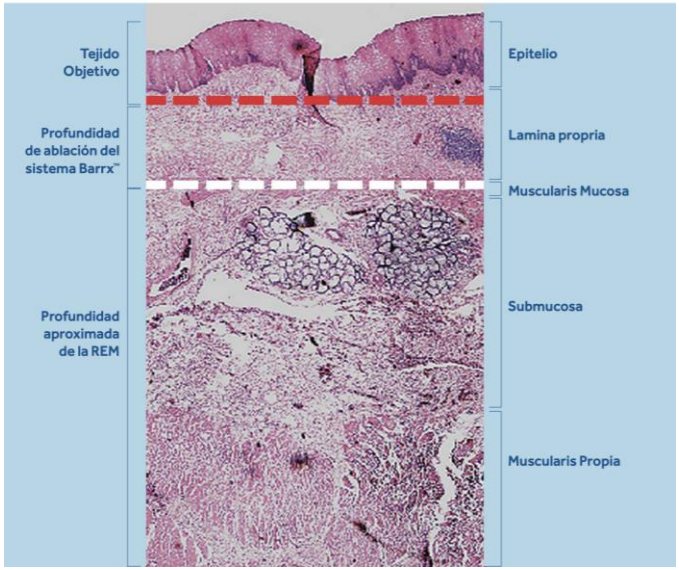
Advantages
FDA approved
Fast for extensive disease
Circunferential treatment
Less RR? Treats metachronous disease

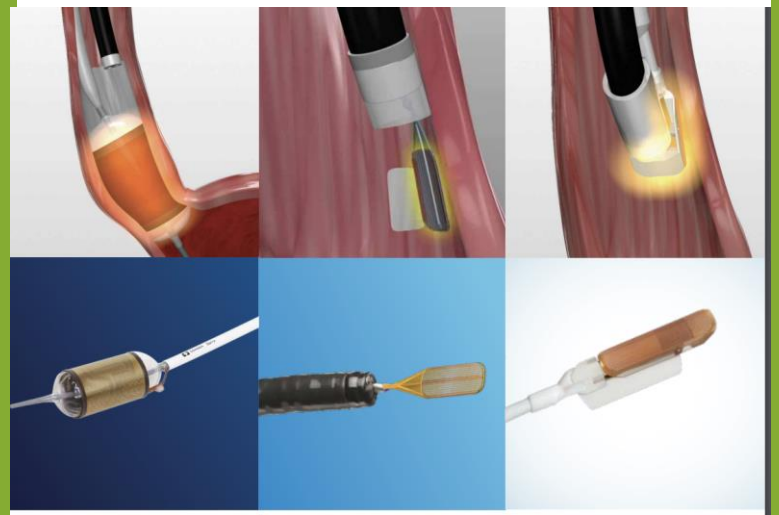
Proceso de catéter focal:



Tallas y Medidas

- Área de tratamiento: 150 mm²
- Longitud de tratamiento: 1,5 cm
- **Electrodo: longitud de 15 mm – ancho de 10 mm**
- Longitud del catéter: 160 cm
- Diámetro del catéter: 4 mm





Tratamiento de áreas circunferenciales y/o segmentos largos de esófago de Barrett por medio de un catéter con balón Barrx™

Tratamiento de casos complicados por medio de un catéter de canal Barrx™

Tratamiento de áreas patológicas pequeñas por medio de un catéter focal Barrx™

DISADVANTAGES

EXPENSIVE

MORE PAIN AND BLEEDING THAN TARGETED ABLATION

NEED ANESTHESIA

NEW PROCEDURE LEARNING CURVE

Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sarah C. Mills [1]

Study	Design	N	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
Radiofrequency ablation: intravenous sedation and local anesthetic, 3 applications of energy at 12 J/cm^2															
Goldstone et al. 2017 [37]	Prospective, non-randomised open-label pilot study; hemi-circumferential RFA	21	45	86	0	-	100	1 treatment. Further treatment if recurrence	52	-	14	0	12	4	Moderate +		
Goldstone et al. 2017[38]	Prospective, non-randomised open-label pilot study: circumferential RFA	10	52	100	90	-	100	1 treatment. Further treatment if recurrence	60	0	0	0	12	4	Moderate +		
$N=31$															

CR 58-100% at 12 months
RR 0-14%
No metachronous lesions at 12 months

N:31+12+52

IJCD 2021

Int J Colorectal Dis (2017) 32:357–365
DOI 10.1007/s00384-016-2679-2

ORIGINAL ARTICLE

A trial of radiofrequency ablation for anal intraepithelial neoplasia

Robert N. Goldstone[1] · Shirin R. Hasan[2] · Steven Drury[3] · Teresa M. Darragh[4] · Annemieke van Zante[5] · Stephen E. Goldstone[6]

- Prospective trial (2017)
- 21 participants (**no HIV+**)
- Hemi-circumferential anal canal RFA
- 3 pulses of 12 j/cm2 (Sedation)
- HRA control every 3 months
- Individual lesion cure rate after one RFA →88 %
- No metachronous lesions at 12 months
- Moderate-severe pain 24h

Brief Report: Clinical Science

Radiofrequency Ablation Therapy for Anal Intraepithelial Neoplasia: Results From a Single-Center Prospective Pilot Study in HIV+ Participants

Robert N. Goldstone, MD, Shirin R. Hasan, MSc, MS,† and Stephen E. Goldstone, MD‡*

- Prospective trial
- 10 participants (9 HIV+)
- Circumferential anal RFA (sedation)
  3 pulses of 12 j/cm2
- HRA control every 3 months
- All participants HSIL free by 12 months
- No serious AEs occurred
- *Average Anal pain peak level after RFA→ 7

Techniques in Coloproctology (2021) 25:701–707
https://doi.org/10.1007/s10151-020-02379-3

ORIGINAL ARTICLE

Outcomes of radiofrequency ablation for anal high-grade squamous intraepithelial lesions

O. Vergara-Fernandez[1] · D. Solórzano-Vicuña[1] · E. Coss-Adame[2] · M. Trejo-Avila[1]

Received: 16 April 2020 / Accepted: 20 November 2020 / Published online: 15 February 2021

Abstract

Background Radiofrequency ablation (RFA) of high-grade squamous intraepithelial lesions (HSIL) is a promising minimally invasive technique but its oncologic and functional outcomes are not well studied. The primary outcome was the efficacy of RFA, and the secondary outcomes were the functional and anatomical anal changes related to RFA.

Methods This was a retrospective analysis of our prospectively collected database of patients who had RFA for HSIL at our institution, between August 2018 and March 2020. To be eligible for RFA, all patients had impairment of their immune function. Targeted ablation was applied in all cases, with 5 overlapping pulsations at the targeted HSILs (delivering 12 J/cm^2 per application) followed by circumferential, 2-pulsation (12 J/cm^2) overlapping anal ablation, to cover the entire anal transition zone. Patients were assessed for recurrence or metachronous disease at 3-month intervals by means of high-resolution anoscopy (HRA) and targeted biopsies. Anorectal manometry, endoanal ultrasound, the 36-Item Short Form and Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ) were assessed at baseline and 12 months after intervention.

Results We included a total of 12 patients with anal HSILs. The mean age was 38.6 (±7.68) years, and 7 (58.3%) were males. Six were HIV positive, 2 had a primary immunodeficiency disease, and 4 were receiving immunosuppressive therapy. A mean of 2.1 anal HSILs per patient were treated. At 12 months, high-resolution anoscopy showed that 7/12 (58.3%) patients had normal high-resolution anoscopy, 3/12 patients had recurrent HSILs, and 2/12 had a persistent lesion. Those lesions were treated with electrocautery, and reached complete response in the following the 6 months (total of 18 months). In particular, there were no metachronous lesions detected. Patients reported moderate to severe pain during the first 24 h after RFA, but only mild discomfort was present at 30 days. Patients were asymptomatic at their 6- and 12-month visits. RFA was not associated with changes in anorectal manometry or ultrasound examination. The 36-SF survey reported improvement in the general health domain ($p = 0.038$), while the MGH-SFQ showed improvements in sexual function.

Conclusions In this study, targeted plus circumferential RFA had a 58.3% efficacy rate for the treatment of anal HSIL in immunocompromised patients, achieving 100% eradication after adding electrocautery ablation. No metachronous lesions were detected. Patients presented relatively mild symptoms after the procedure, no changes in anorectal anatomy or function, and some improvements in their sexual function. These results seem promising in light of the high recurrence reported after HSIL treatment. Larger studies are needed to validate our results.

- 12 patients HSIL, 50% HIV+, 50% IS
- 58% RC, 12 months after targeted and circunferencial RFA
- 3/12 recurrent, 2/12 persistent
- No metachronous lesions detected
- No changes in US, manometry

ORIGINAL CONTRIBUTION

A Prospective, Dual-Center Trial of Circumferential Radiofrequency Ablation of Anal High-Grade Squamous Intraepithelial Lesions Demonstrate Improved Long-term Efficacy Over Historical Controls of Targeted Ablation

Stephen E. Goldstone, M.D.[1] • Joseph P. Terlizzi, M.D.[1]
Rebecca A. Levine, M.D.[2] • Erin Moshier, M.S.[3] • Barbara Pereira Vera, B.S.[1]

1 Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, New York
2 Department of Surgery, Montefiore Medical Center, The Bronx, New York
3 Department of Population Health Science & Policy, Icahn School of Medicine at Mount Sinai, New York, New York

BACKGROUND: Targeted ablation of anal canal high-grade dysplasia results in high recurrence over time. Circumferential radiofrequency ablation might decrease recurrence.

OBJECTIVE: This study aimed to determine the safety and efficacy of circumferential radiofrequency ablation for anal high-grade dysplasia.

DESIGN: This was a dual-center, prospective trial of circumferential radiofrequency ablation with a 1-year follow-up with longer follow-up data abstracted from medical records of study patients returning after trial for surveillance. Ten participants from the identically conducted pilot circumferential radiofrequency ablation trial were included to improve sample size for longer-term analysis.

SETTINGS: This study included 3 surgeons at 2 sites.

PATIENTS: The study included 51 patients undergoing circumferential radiofrequency ablation for anal canal high-grade dysplasia.

INTERVENTION: Circumferential radiofrequency ablation of anal canal high-grade dysplasia and targeted radiofrequency ablation of recurrence.

MAIN OUTCOME MEASURES: The primary outcome measures were circumferential radiofrequency ablation efficacy and associated morbidity.

RESULTS: Fifty-one participants underwent circumferential radiofrequency ablation but 48 participants returned for 1 or more postprocedure high-resolution anoscopy and were evaluable. The mean age of participants was 43 years, most were male (94%), 33% were living with HIV, and 58% had 3 or more high-grade dysplasias treated. Sixty percent had no recurrence, whereas 19% had 1 recurrence, 15% had 2 recurrences, and 6% had 3 recurrences. Most recurrences (66%) developed within the first 6 months. Kaplan-Meier probability of recurrence combining both series was 19% at 3 months, 30% at 6 months, and approximately 40% after 6 months out to 30 months. Most common morbidities were pain (85.4%) lasting for a median of 21 (range, 4–91) days and bleeding (91%) lasting for a median of 21 (range, 5–87) days. Of those with pain and bleeding, 65% and 85%, respectively, described it as mild. No patients developed fistulas, stricture, or incontinence. No serious adverse events related to circumferential radiofrequency ablation occurred. Having a previous

Funding/Support: This trial was supported by Medtronic, Sunnyvale, California.

Financial Disclosure: Dr Goldstone is a consultant, speaker, and investigator for Merck and Co; an investigator and consultant for Inovio; and a consultant for THD America.

Presented at the virtual meeting of the American Society of Colon and Rectal Surgeons, April 24 to 28, 2021.

Correspondence: Stephen E. Goldstone, M.D., Department of Surgery, Icahn School of Medicine at Mount Sinai, 420 West 23rd St, New York, NY 10011. E-mail: goldstone.stephen@gmail.com

Dis Colon Rectum 2023; 66: 764–773
DOI: 10.1097/DCR.0000000000002365

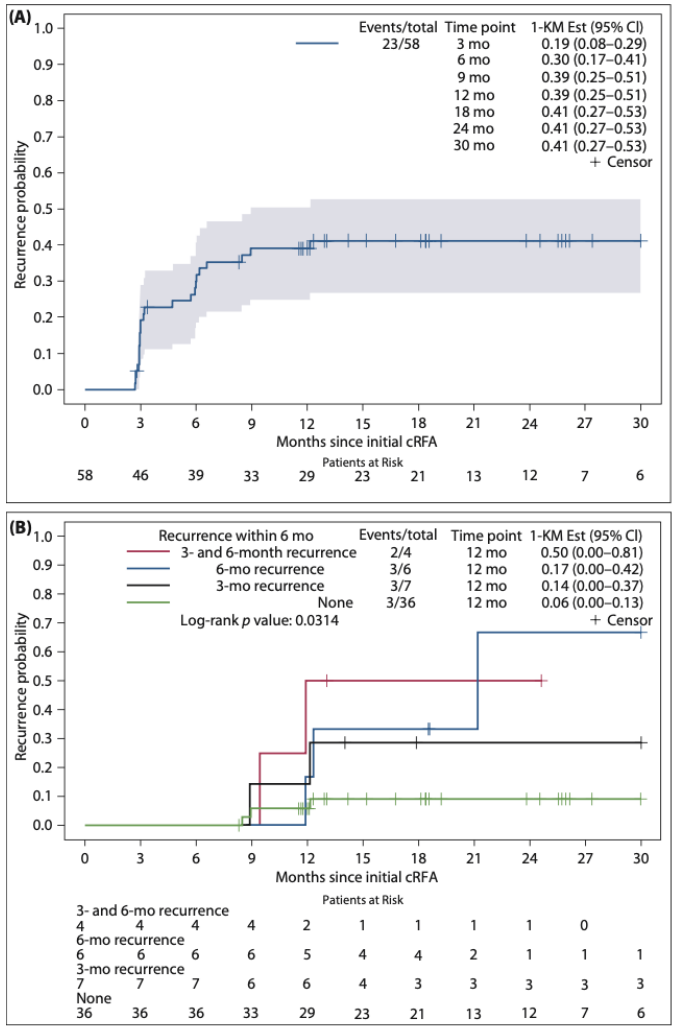


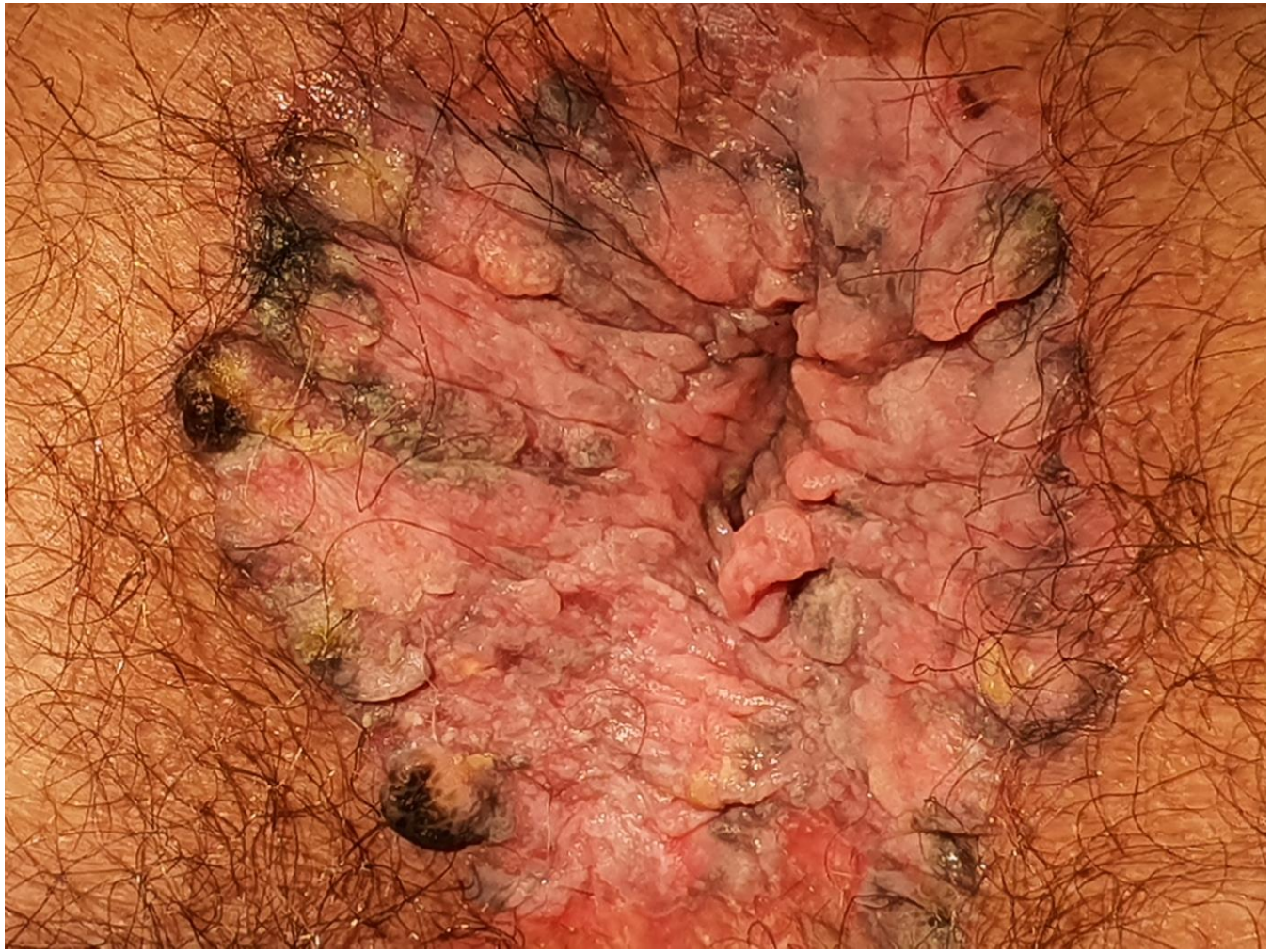
FIGURE 2. KM curves for the probability of recurrence over time. A, KM curve for the probability of recurrence over time combining participants with at least 1 after cRFA HRA from both cRFA trials (N = 58). Shaded area illustrates 95% CI. B, KM curves for risk of previous recurrence on future recurrence. Participants were stratified by those with no recurrence (green line) and those with recurrence at either 3 mo (black line), 6 mo (blue line), or both 3 and 6 mo (red line). cRFA = circumferential radiofrequency ablation; Est = estimate; HRA = high-resolution anoscopy; KM = Kaplan-Meier.

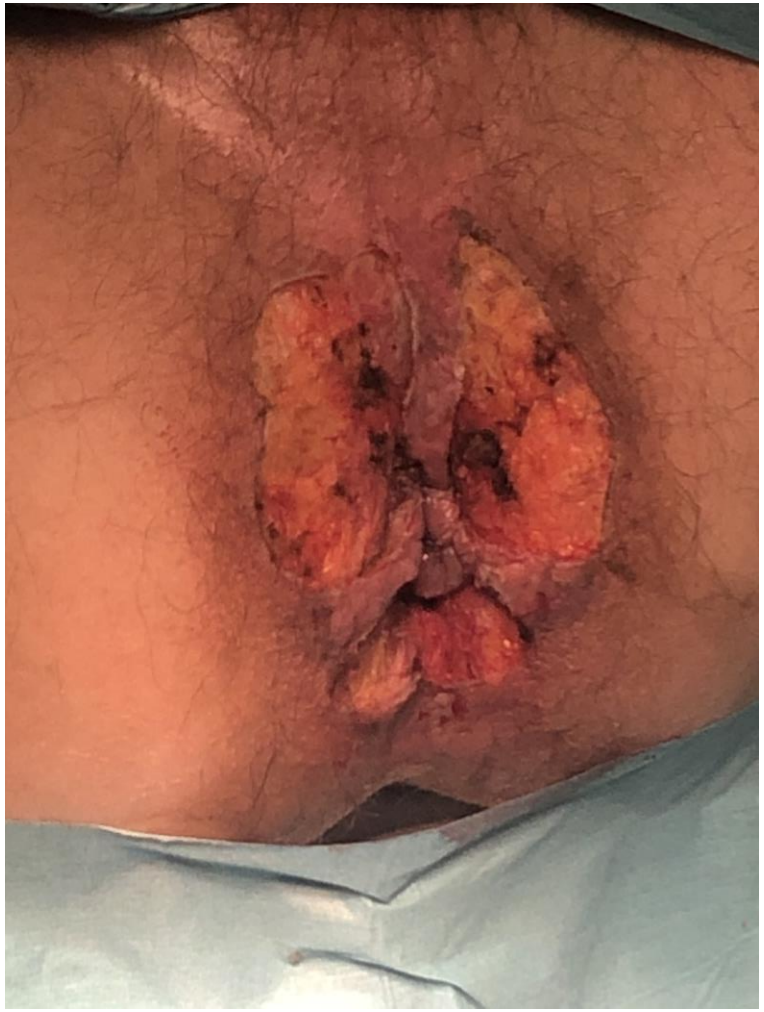
51 patients, 33% HIV
39% recurrence 12 m
85% pain
No severe AEs ,although more morbidity

Targeted ablation should destroy the entire HSIL to submucosa, but cRFA, with lower energy, might not penetrate the entire lesion.[9] This could translate clinically into rapid recurrence reported at 3 to 6 months. The plateauing much sooner and with lower probability of recurrence over targeted ablation could result from diminished metachronous recurrence because occult HSIL is destroyed before it grows large enough to be identified.[17] The fact that only a history of recurrence was a significant predictor of further

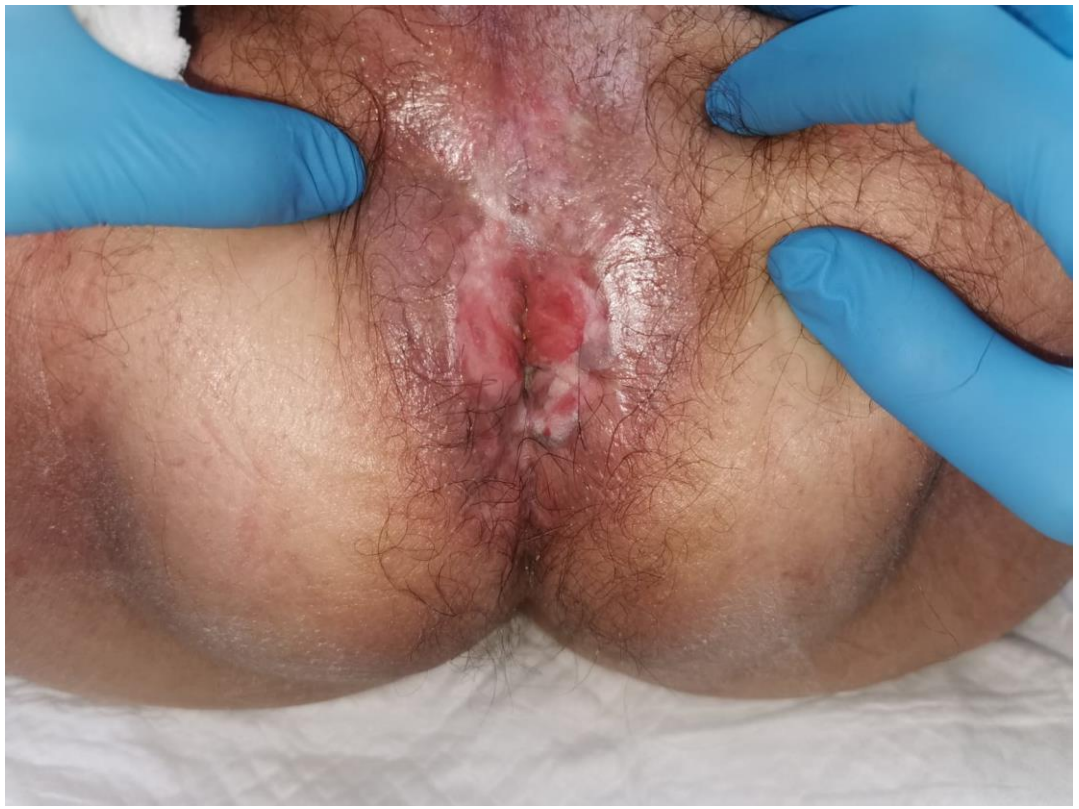
CASE 6.

63 YEARS-OLD TRASPLANT. 360 PAIN

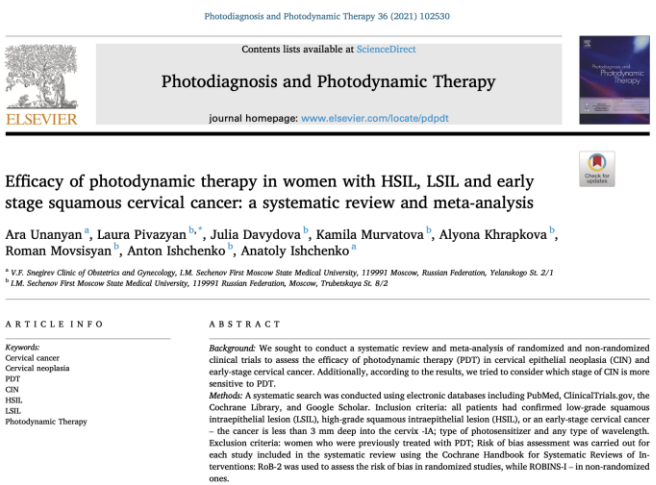




2 Sessions of TFD, red light at a wavelength of 630 nm .
ALA cream. IP 4 hours. 2 sessions of single dose of 100 J cm^{-2}



PHOTODYNAMIC THERAPY



Photodiagnosis and Photodynamic Therapy 36 (2021) 102530

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Photodiagnosis and Photodynamic Therapy

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

Efficacy of photodynamic therapy in women with HSIL, LSIL and early stage squamous cervical cancer: a systematic review and meta-analysis

Ara Unanyan [a], Laura Pivazyan [b,*], Julia Davydova [b], Kamila Murvatova [b], Alyona Khrapkova [b], Roman Movsisyan [b], Anton Ishchenko [b], Anatoly Ishchenko [a]

[a] V.F. Snegirev Clinic of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, 119991 Moscow, Russian Federation, Yelanskogo St. 2/1
[b] I.M. Sechenov First Moscow State Medical University, 119991 Russian Federation, Moscow, Trubetskaya St. 8/2

ARTICLE INFO

Keywords:
Cervical cancer
Cervical neoplasia
PDT
CIN
HSIL
LSIL
Photodynamic Therapy

ABSTRACT

Background: We sought to conduct a systematic review and meta-analysis of randomized and non-randomized clinical trials to assess the efficacy of photodynamic therapy (PDT) in cervical epithelial neoplasia (CIN) and early-stage cervical cancer. Additionally, according to the results, we tried to consider which stage of CIN is more sensitive to PDT.

Methods: A systematic search was conducted using electronic databases including PubMed, ClinicalTrials.gov, the Cochrane Library, and Google Scholar. Inclusion criteria: all patients had confirmed low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or an early-stage cervical cancer – the cancer is less than 3 mm deep into the cervix -IA; type of photosensitizer and any type of wavelength. Exclusion criteria: women who were previously treated with PDT; Risk of bias assessment was carried out for each study included in the systematic review using the Cochrane Handbook for Systematic Reviews of Interventions: RoB-2 was used to assess the risk of bias in randomized studies, while ROBINS-I – in non-randomized ones.

- Ablation by application of a light source to a previously photosensitised area (topical/systemic)
- PDT very suitable treatment for SIL for two reasons:
  - selectively eliminate lesions. Preserve healthy tissue
  - acts on its own against HPV ;PDT is useful for subclinical and latent human papillomavirus infections, decreasing recurrence rates dramatically
- Uniform application/ Field treatment/selective
- Ideal for multizonal disease
- No scarring in perianal área-excellent cosmetic outcome
- PDT has been used for VIN/CIN and early CC and condiloma
  - CR CIN 81% and 80.4% clear HPV

Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

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Study	Design		N	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)		PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
Photodynamic therapy																	
Van de Snoek et al. 2012 [39]	Prospective open-label pilot study	15	46		100	100	100	100	1 systemic treatment	20	27	20	0	-	4		Serious +
Welbourn et al. 2011 [40]	Retrospective chart review	15	52		47	-	-	-	1 systemic or topical treatment	40	20	20	0	19	4		Serious +
$N = 30$																	

CR 20-40%
PR 27%
RR 20%

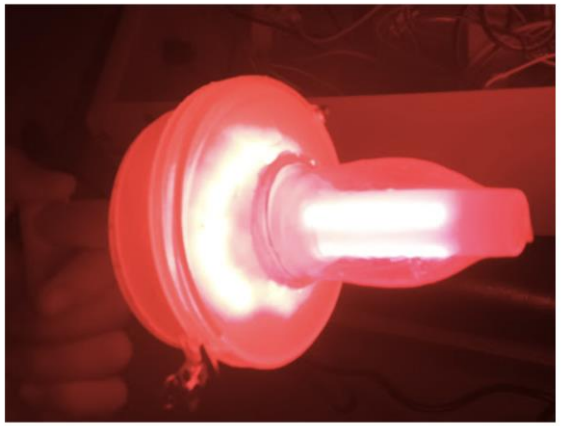
- **AEs**: 1 stenosis out of 15 patients, severe pain, suppuration…

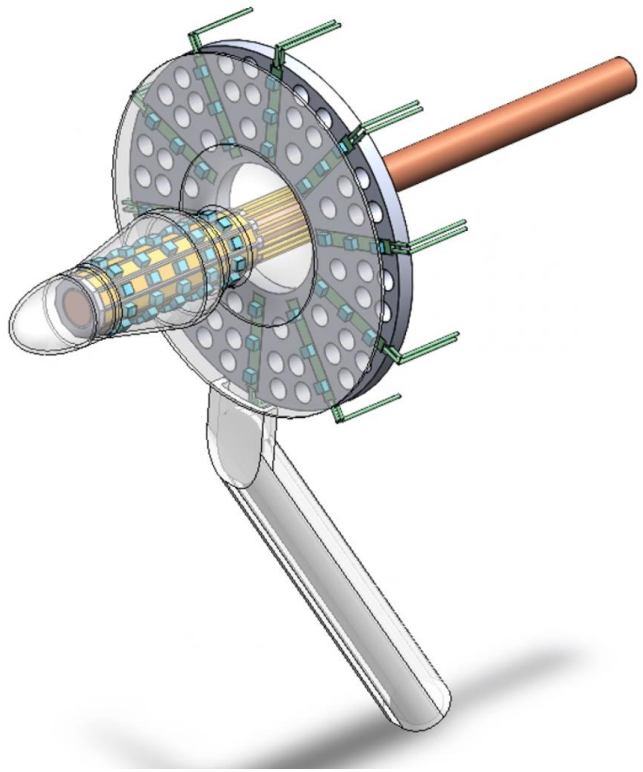
N:30

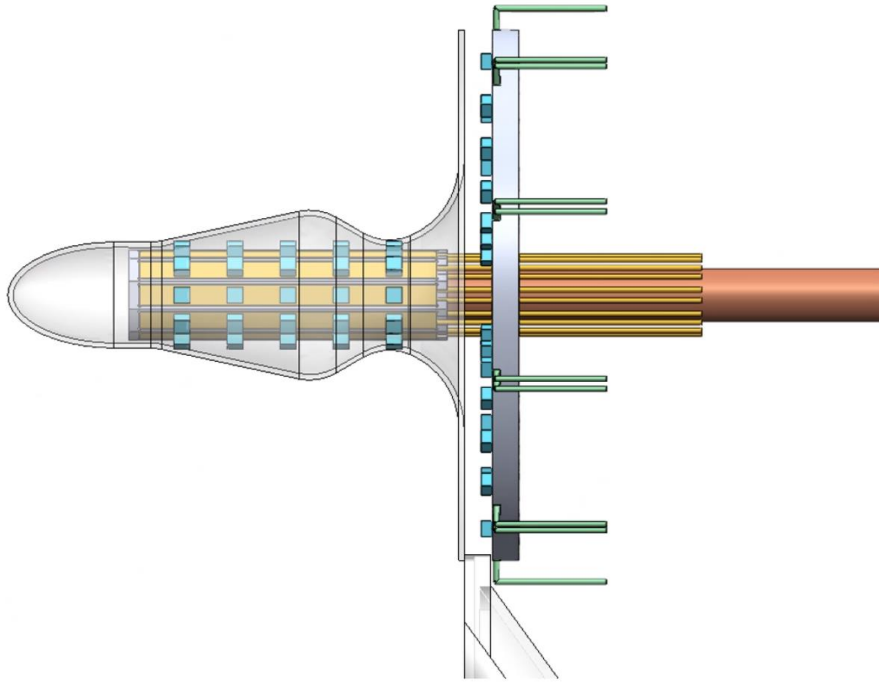
IJCD 2021

Possibility of treating multiple areas at the same time

Potentially combining the advatages
of field-treatment and selective treatment

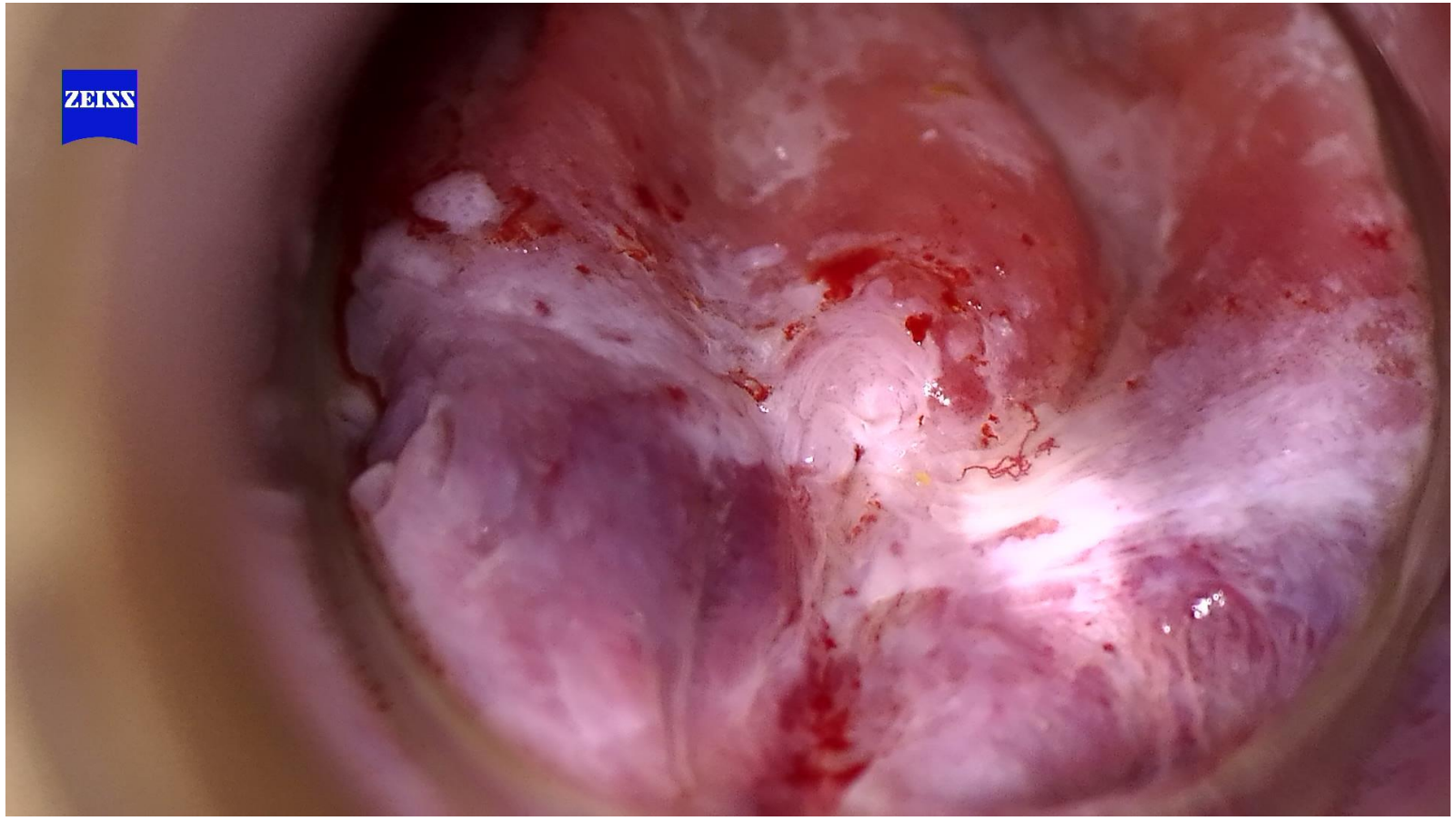






CASE 6

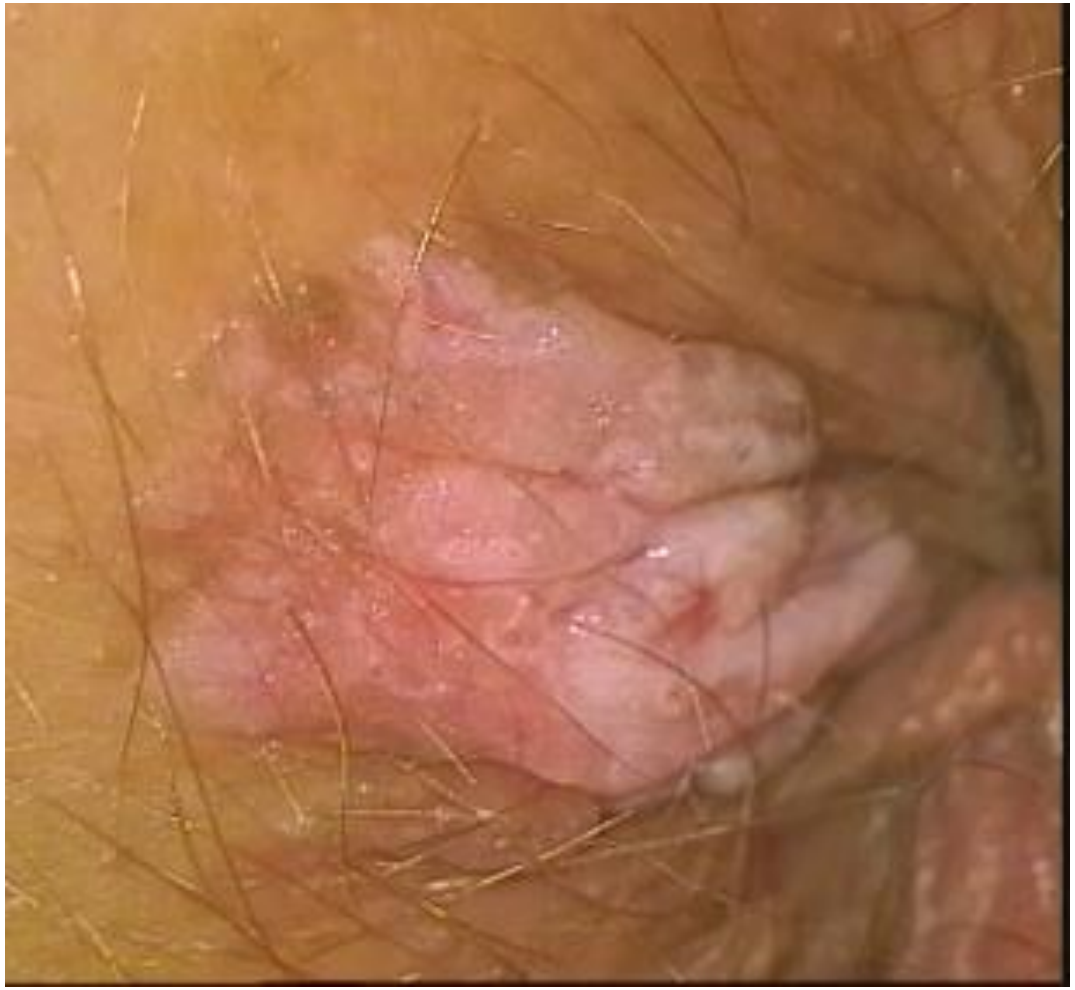
62 years-old MSM-HIV. Persistent HSIL disease in the same octant, atypical vessels, grade 3 dysplasia. Painful digital rectal exam

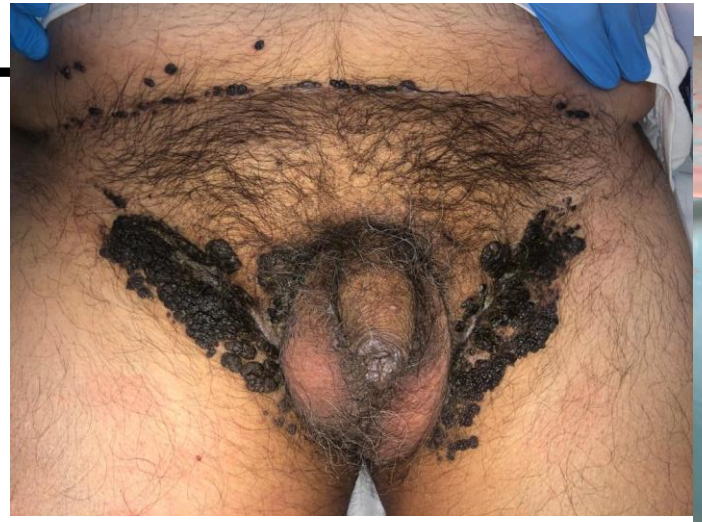


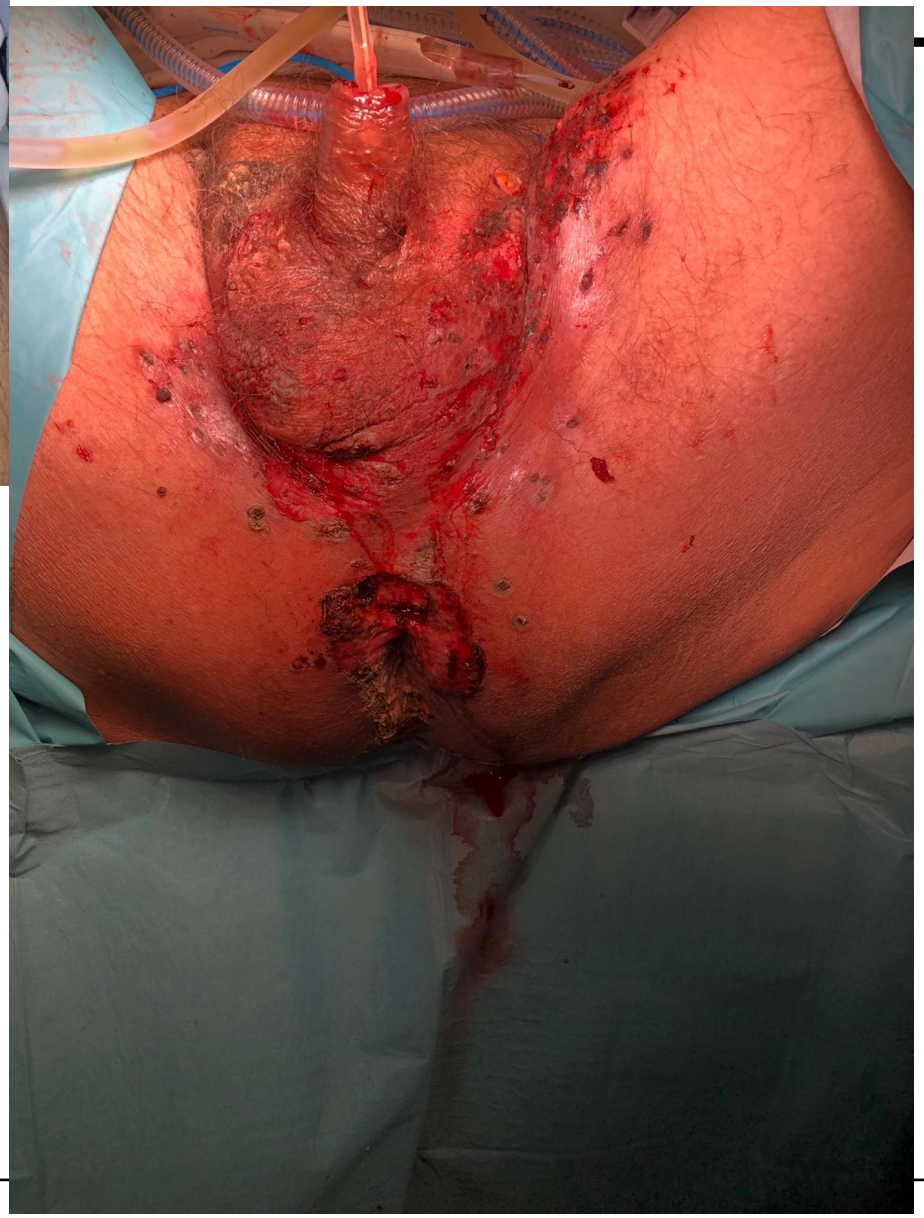
Plan:
Wide biopsy in the operating room, and cauterization under epidural anesthesia

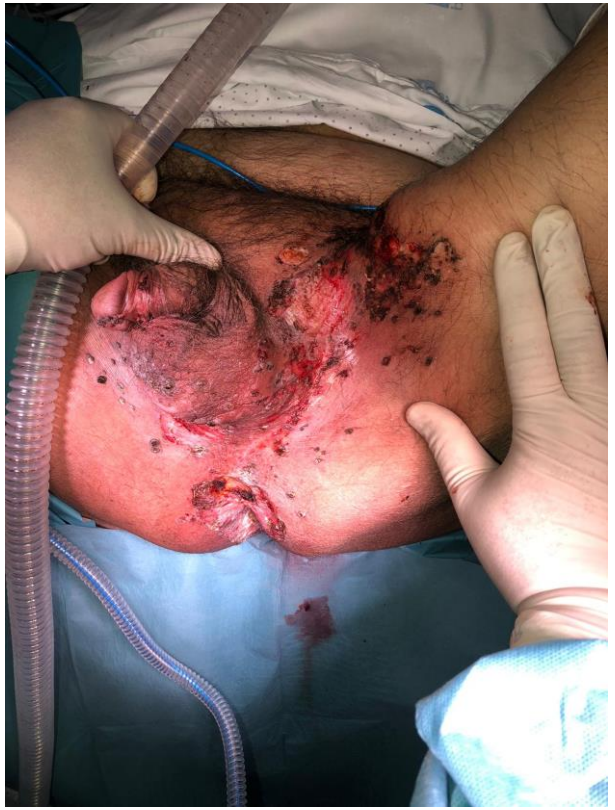
Lesions that are too large for office-based local ablation
Worrisome lesions that need larger biopsies(concern malignancy)

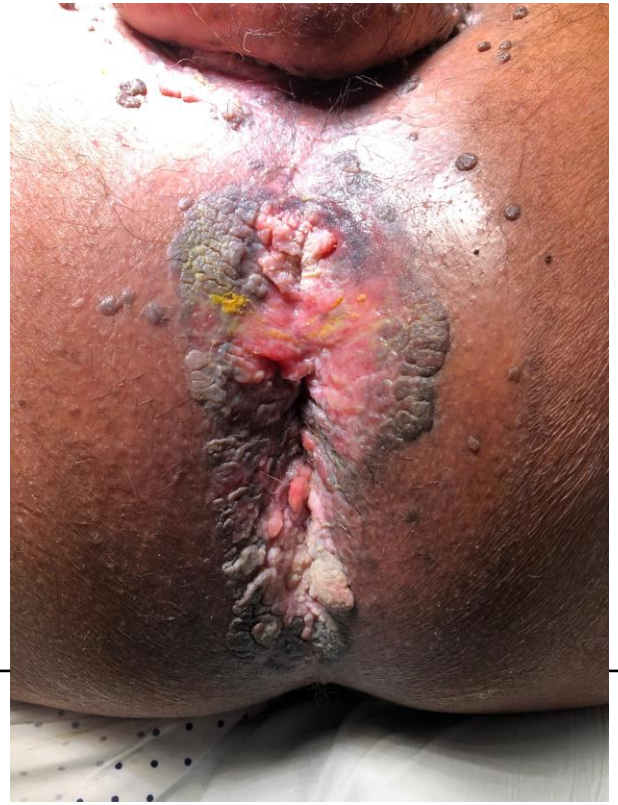
CASE 7. WLHIV, 52. PAIN











TOPICAL TREATMENTS

- Imiquimod, 5 Fu, Cidovir
- Actvity against HPV infection (less RR?)
- Self-applied / Outpatient
- Field treatment
- Local and systemic AEs
- Expensive, not for use in pregnant women

Semin Colon Rectal Surg. 2017 June ; 28(2): 86–90. doi:10.1053/j.scrs.2017.04.006.

Topical therapies for the treatment of anal high-grade squamous intraepithelial lesions

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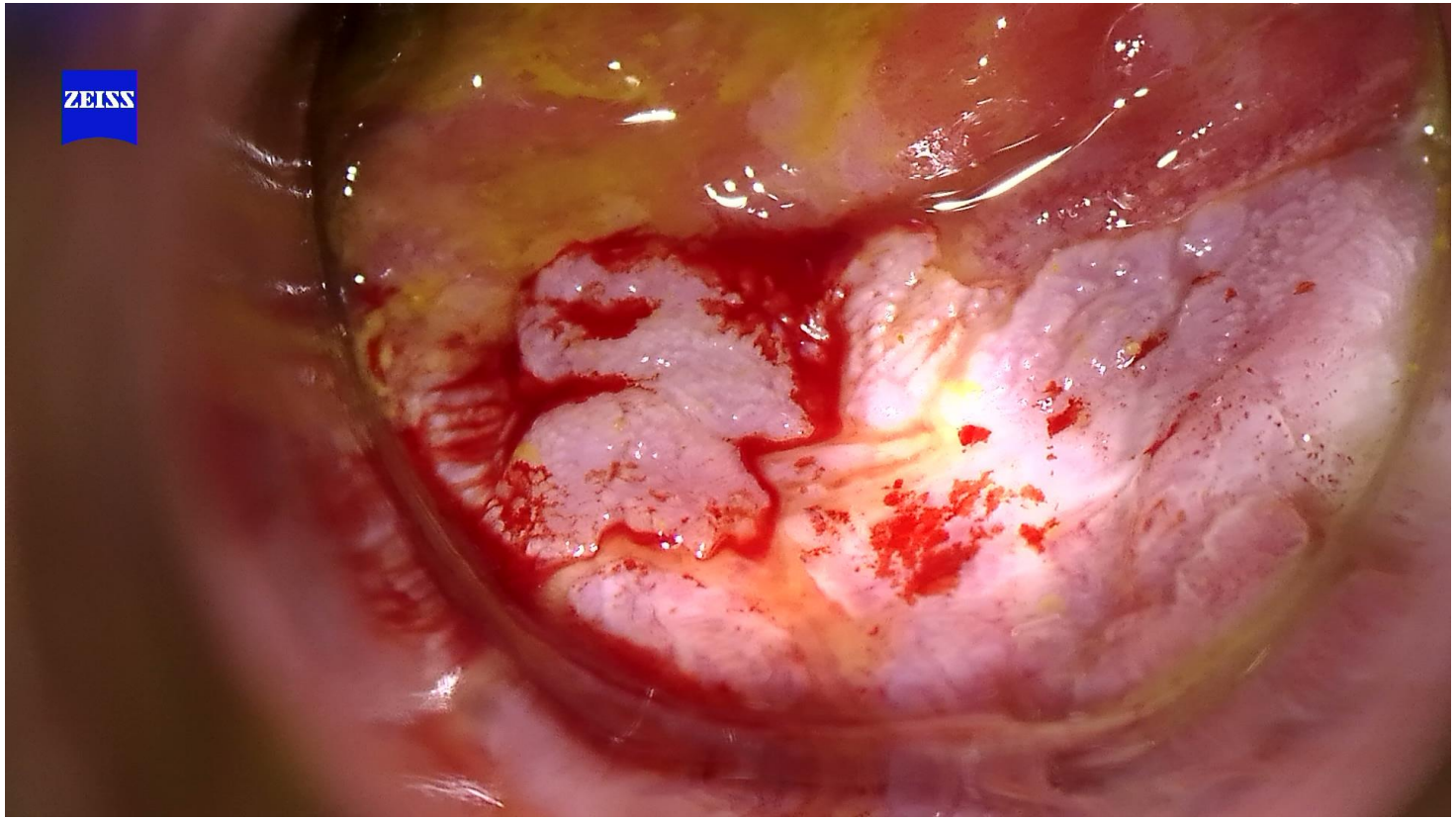
- Needs to be applied to the site of disease for optimal efficacy(SQJ)
  - Gloved finger, splitting dose right left hand to ensure complete coverage?)
  - No specific anal applicators/syringe, if used care must be taken to avoid inserting the cream beyond the anus into the rectum:
    - Loss efficacy and proctitis
- It may be reassuring for patients to know that side effects might indicate treatment efficacy
- If intermittent Schedule, consider calendar or electronic reminder
- Interim visit 4 weeks to survey for side effects and support adherence

DALL-E: “Cool doctor explaing topical anal treatment for anal HSIL to a very confused patient”

CASE 7

37 MSM, CO-EXISTING EXTENSIVE LSIL WITH FOCI OF HSIL. DIFFICULT TO DIFFERENTIATE BOTH



IMIQUIMOD

Imiquimod 12.5/supositorio
25 supositorios (máximo por receta)

Activates Toll like Receptor 7

- Antiviral, antitumoural and immunoregulatory effects

Off-label use for management of anogenital dysplasia

Available in 3.75 and 5% cream

- studies carried out with 5% dosage

Can be provided in suppositories/rectal rockets

Local and systemic side effects (more efficacy and worse tolerance in perianal)

Richel O, *et al*. Lancet Oncol 2013; 14: 346–353.
Wieland U *et al.* Arch Dermatol 2006; 142: 1438–1444.
Fuertes I *et al*. Int J STD AIDS. 2019 Oct;30(12):1194-1200.
Harvey G *et al*. Clin Exp Dermatol. 2019;44(4):e140–4

Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sarah C. Mills [1]

All studies investigating the use of a single treatment for AIN in any patients with a prior histological diagnosis of low-grade or high-grade AIN were included. To be included the papers required at least one of the end outcomes (partial or complete response to treatment, recurrence after treatment or ASCC diagnosis after treatment) to be reported. Any relevant peer-

Study	Design	*N*	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias scor
Imiquimod 5%: treated with cream or suppository 3 times a week × 16 weeks															
Weiland et al. 2006 [9]	Prospective non-randomised open-label - pilot study	28	43	100	100	100	64 (46)	79	54	17.9	16	0	9	4	Moderate -
Kreuter et al. 2008 [10]	Prospective follow-up study	19	-	100	100	100	68	100	74	-	26 at treated site (58 at untreated site)	0	32	4	Serious +
Fox 2010 et al. [11]	Double-blind RCT	53	42	100	100	100	100	83	14	29	39	2 (placebo arm)	33	1b	Low*
Richel et al. 2013 [12]	Open-label RCT	54	45 (median)	100	100	100	57	91	24 (16 HGAIN)	11	71	0	4.5 (response) 16.5 (recurrence)	1b	Some concerns*
Cranston et al. 2018* [13]	Prospective, non-randomised open-label pilot study	10	46 (median)	100	100	100	100	90	30		-	0	-	4	Moderate -

RC 14-86%

RP 5-35%

COMPL 75-100%

RR 39-71%

N:164

IJCD 2021

- 95 HIV patients retrospective analysis
- HSIL or condiloma
- 46.3% response to imiquimod(ITT), complete12.5%
- Poor response smokers
- Good tolerability 57%
- Systemic side effects 20%

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
2019, Vol. 30(12) 1194–1200
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DOI: 10.1177/0956462419864506
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SAGE

The effectiveness and tolerability of imiquimod suppositories to treat extensive intra-anal high-grade squamous intraepithelial lesions/ warts in HIV-infected individuals

Irene Fuertes[1,*], Carla Bastida[2,*], Carmen Lopez-Cabezas[2], Leonardo Rodríguez-Carunchio[3], Jaume Ordi[3,4], Josep Mallolas[5], Ross D Cranston[5] and Jose Luís Blanco[5]

Abstract

Topical imiquimod is a potential treatment for intra-anal condyloma and squamous intraepithelial lesions caused by human papillomavirus (HPV). We aimed to assess the effectiveness and tolerability of imiquimod suppositories for the treatment of anal high-grade intraepithelial lesions (HSIL) and condylomas in HIV-infected patients. We conducted a retrospective analysis in a prospectively followed cohort. High-resolution anoscopy was used for diagnosis and assessment following treatment. Patients' tolerability was assessed with a self-administered survey. Ninety-five patients (94.7% men) were analyzed. All were on combination antiretroviral therapy. Median CD4 T-cell count was 690 cells/mL, 89% had undetectable plasma viral load. Response to imiquimod was seen in 46.3% (complete: 12.5% partial: 33.8%) in the intent-to-treat analysis, and in 55.2% (complete: 14.9% partial: 40.3%) in the on-treatment analysis. Higher response rates were observed for anal condyloma compared with HSIL. A significantly poorer response rate was observed in smokers and in individuals with lower nadir CD4 T-cell counts. Imiquimod tolerability was "good" in 57.1% (n¼36), "acceptable" in 33.3% (n¼21), and "poor" in 9.5% (n¼6). Systemic side effects were reported in 20.7% (n¼13). There was no association between treatment effect and tolerability. In conclusion, imiquimod stands as a well-tolerated option for the treatment of HPV-associated intra-anal pathology in HIV-infected individuals.

Keywords

Anal dysplasia, effectiveness, HIV, human papillomavirus, imiquimod, tolerability

Date received: 26 February 2019; accepted: 25 June 2019

Introduction

Human papillomavirus (HPV) is a common viral infection responsible for a variety of disease processes that range from benign lesions, such as condylomas to dysplasia and invasive cancer. In the last decades, HPV-associated anal squamous cell carcinoma (ASCC) incidence has been increasing, particularly in human immunodeficiency virus (HIV)-infected men who have sex with men (MSM).[1,2] A higher prevalence and persistence of HPV infection, and a more frequent progression from low- to high-grade anal squamous intraepithelial lesions (LSIL, HSIL), the precursor of ASCC, has been reported in these patients compared to

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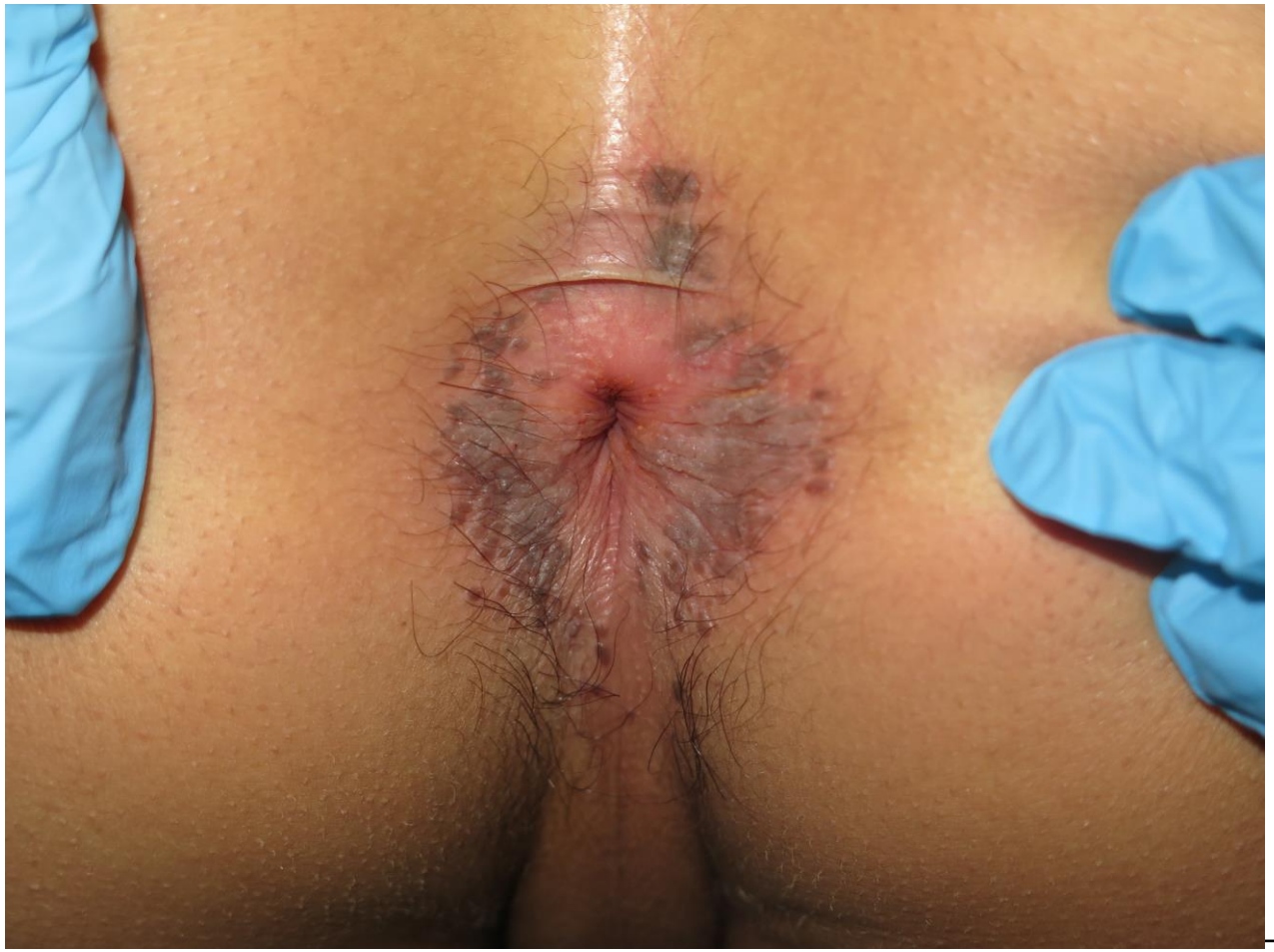
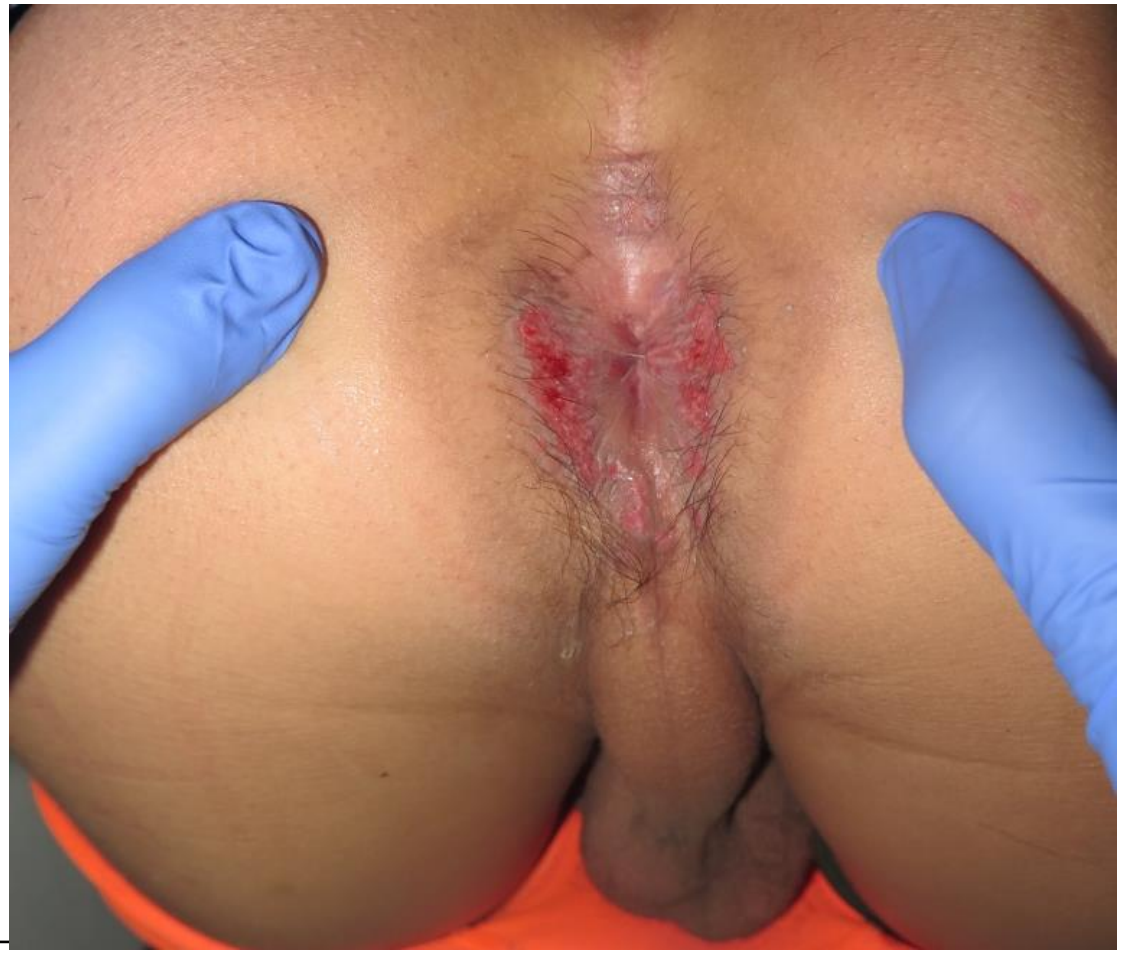
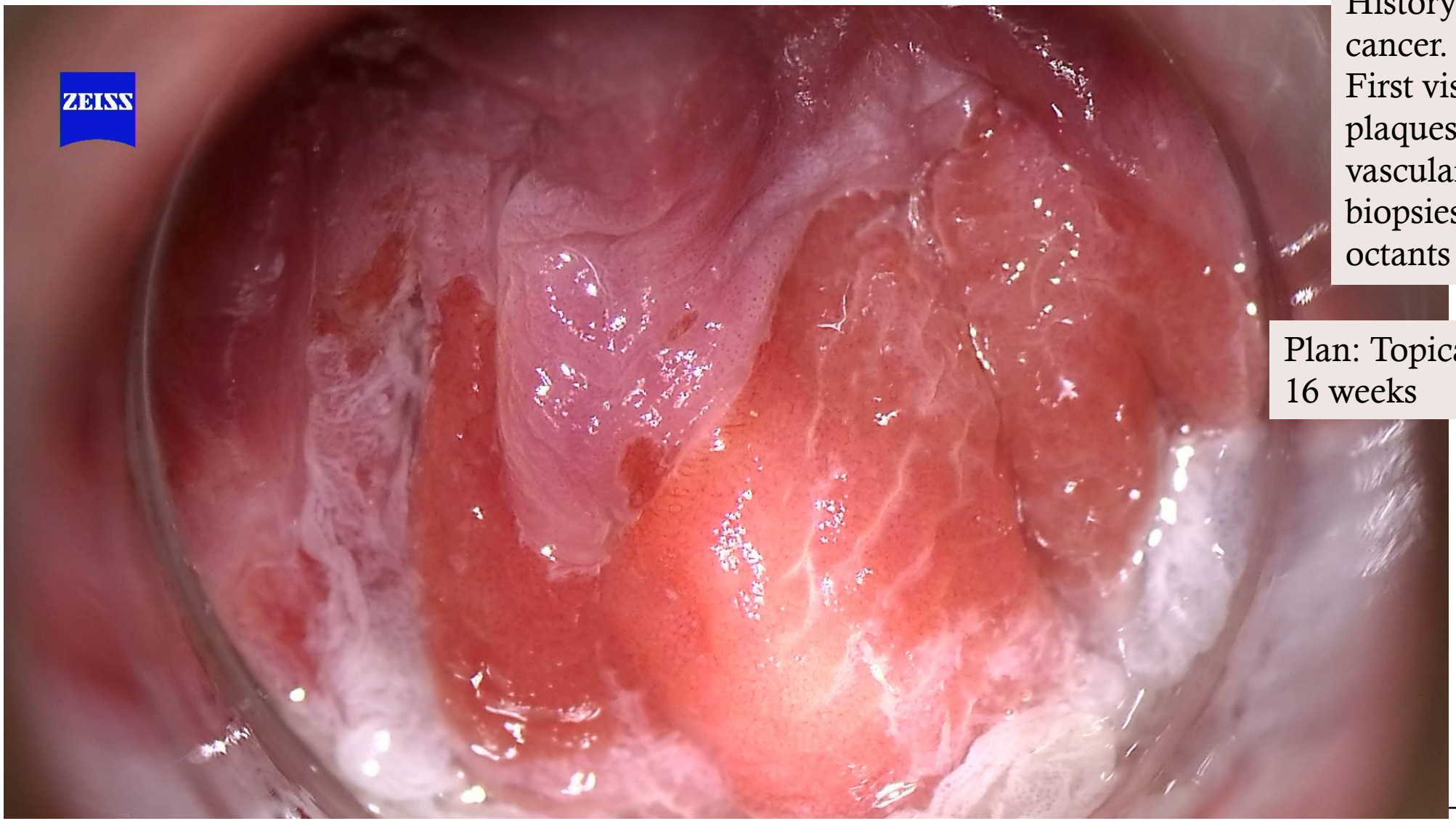
Email: cbastida@clinic.cat

Imiquimod 3.75%





CASE 8



Female patient
48 years old, HIV
History of cervical cancer.
First visit, acetowhite plaques with thick vascular punctation. 3 biopsies confirm HSIL 6 octants

Plan: Topical treatment 5 FU 16 weeks

5-fluoracil

- Pirimidine analogue, antitumoral effect
- Licensed for topical use in actinic keratosis and basal cell carcinoma
- Off label use for HSIL in four studies, 3 in HIV MSM
- 16 week 2 a week vs 5 days twice a day and rest for 9 days
- Formulated(3-5%) or commercial cream(5%, Tolak)

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Study	Design	N	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
5-Fluorouracil:16 weeks of treatment, 0.25 to 1 g self-administered, Synder et al 2011 treatment duration 9 weeks only															
Graham et al. 2005 [15]	Prospective, non-randomised open-label pilot study	7	48	45	9	-	100	100	86	0	0	0	39 (mean)	4	Serious +
Richel et al. 2010 [14]	Prospective, non-randomised open-label pilot study	46	46 (median)	100	100	100	74	93	39	17	50	0		4	Moderate +
Snyder et al. 2011* (remove star[16]	Retrospective single-intervention case review at a single center	11	45 (median)	100	100	100	82	100	9	27	-	0	-	4	Moderate +
Richel et al. 2013 [12]	Open-label RCT	48	47 (median)	100	100	100	60	96	17 (21 HGAIN)	12.5 (21 HGAIN)	58	0	4.5 (response) 16.5 (recurrence)	1b	Some concerns*

9-86% CR
0-27% PR
RR 9-58%
Decrease viral load(Richel 2010), 85% local side effects

N:112

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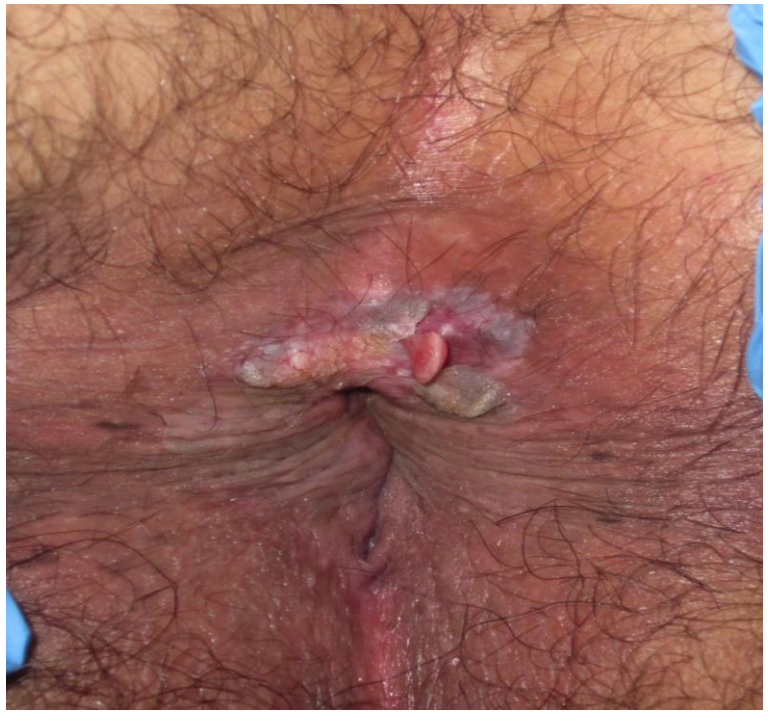
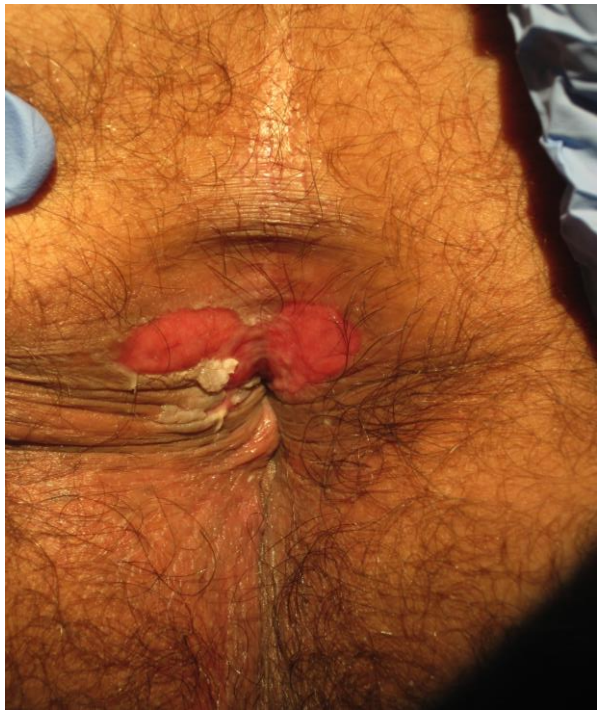
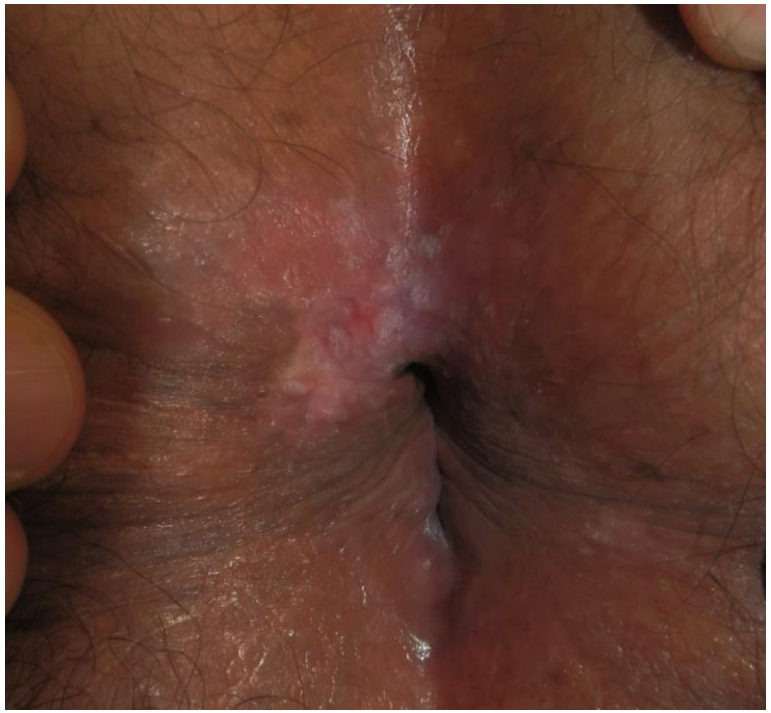
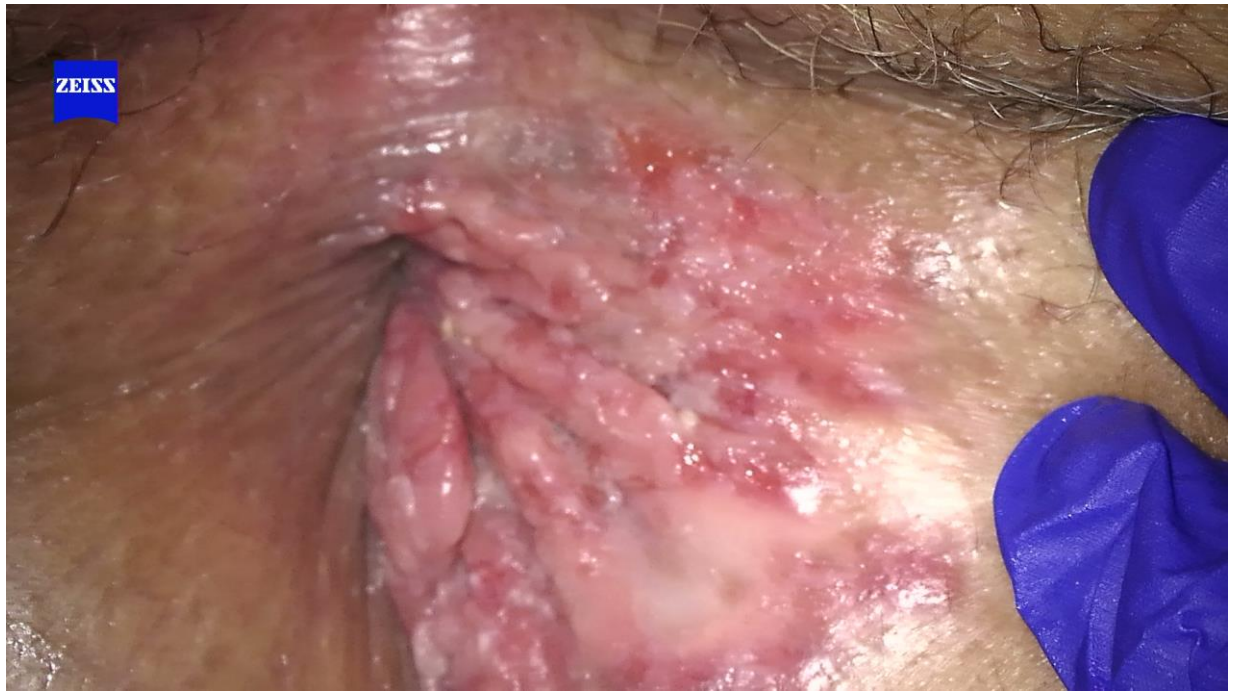
CASE 9

MSM-HIV, 59 YEARS-OLD. PAIN.





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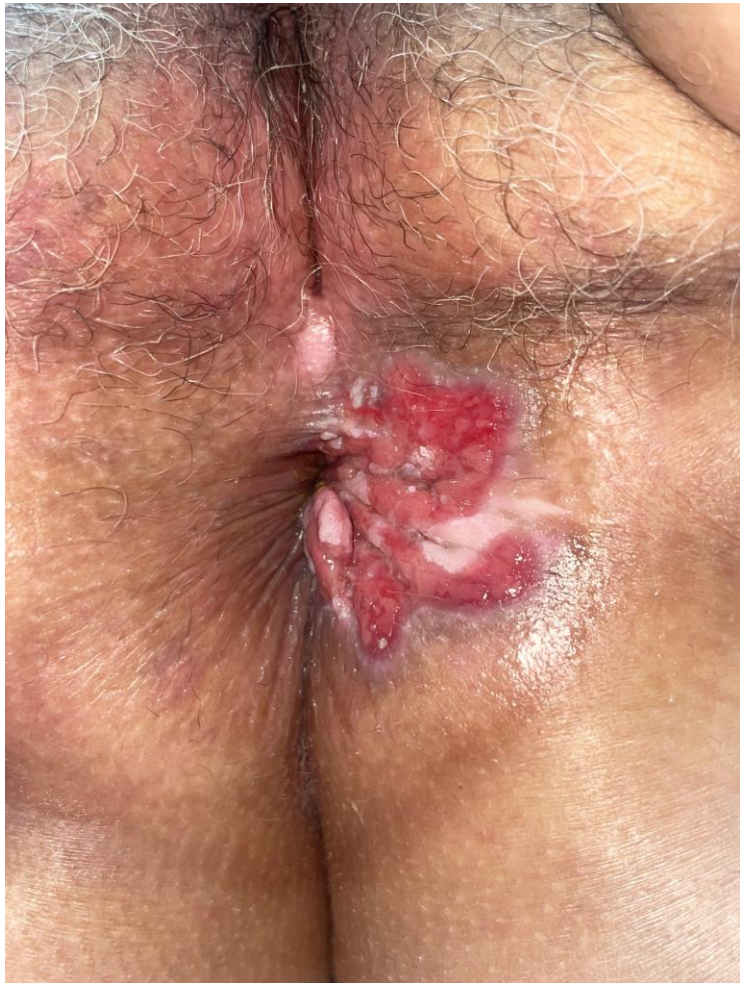

CIDOFOVIR

- Cidofovir is a nucleotide analog with activity against a wide range of DNA viruses
  - Induces of apoptosis only in HPV-infected cells
  - Antiangiogenic effect
  - Does not depend on immune status
- Off-label use for management of anogenital dysplasia
- Field treatment and patient self-application
  - Formulated in cream 1-2%
- Hospital dispensing
  - No cost for the patient

Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review

Danielle R. L. Brogden [1] · Una Walsh [1] · Gianluca Pellino [2,3] · Christos Kontovounisios [1] · Paris Tekkis [1] · Sarah C. Mills [1]

Study	Design	N	Mean age	Male (%)	HIV-positive (%)	MSM (%)	High-grade AIN (%)	Compliance (%)	CR (%)	PR (%)	Recurred (%)	ASCC (%)	Follow-up (median in months)	Level of evidence	Bias score
1% Cidofovir: [23] 2 g of self-applied cream three times a week for 4 weeks; [22] self-applied cream six 2-week treatment cycles (5 days ontreatment 9days off treatment)															
Sendagorta et al. 2016 [20]	Prospective, non-randomised pilot study	17	36	100	94	100	100	94	59	18	12	0	5.5	4	Moderate +
Stier et al. 2013 [19]	Phase 2a prospective multicentre trial open-label	33	44	73	100	-	100	79	15	36	-	3	1.4	4	Moderate +
$N = 50$															

CONCISE COMMUNICATION

Effectiveness of topical cidofovir for treatment of refractory anal high-grade squamous intraepithelial lesion

Joaquin Burgos[a], David Campany[b], Jorge Garcia[a], Stefania Landolfi[c], Vicenç Falcó[a] and Adrià Curran[a]

Objectives: Ablative electrocautery is effective treating anal high-grade squamous intraepithelial lesions (HSILs). However, persistence or recurrence of the HSIL despite ablative sessions is not uncommon. The aim of this study is to assess the feasibility of topical cidofovir as salvage therapy for the management of refractory HSIL.

Design: A prospective uncontrolled unicenter study of men and transgender people who have sex with men with HIV who had a refractory intra-anal HSIL after ablative treatments and who received topical cidofovir (ointment at 1%, auto-applicated, three times a week, a total of 8 weeks) as salvage therapy. Effectiveness was evaluated on-treatment defining response as resolution or regression to low-grade lesion of HSIL in the biopsy posttreatment. Tolerance and recurrences were recorded.

Results: From 2017 to 2022, 23 patients with refractory intra-anal HSIL (78.3% persistent lesions, 39% affecting > 50% of circumference, and a median of six previous ablative sessions) were treated with topical cidofovir. A response was observed in 16 of 23 patients [69.5% (95% confidence interval (95% CI) 50.8–88.4)]. Local tolerance was reported as regular or bad in 13 patients (52.2%), requiring modification of the treatment in eight patients (three early discontinuation and five dose reduction). Non-serious side effects were reported. After a median follow-up of 30.3 months, two of the 16 patients with a response developed recurrent HSIL [recurrence rate, 25.4% at 12 months (95% CI, 0–35)].

Conclusion: Topical cidofovir could be a good option in the management of anal HSIL due to its good effectiveness, low recurrence rate, and acceptable tolerance even in difficult-to-treat lesions.

AIDS 2023, **37**:1425–1429

CR 15-62%
PR 18-30%
RR 13-25%
AEs 81%

N: 73

IJCD 2021

CONCISE COMMUNICATION

Effectiveness of topical cidofovir for treatment of refractory anal high-grade squamous intraepithelial lesion

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AIDS 2023, **37**:1425–1429

2 grams cidofovir 1%, 3 times a week 8 week

23 patients refractory intra-anal HSIL

- 78% persistent lesions
- 39%>50% circumference
- Median 6 ablative treatments

Response in 69% patients (39%CR, 30% PR, 30% persitence)

52% regular/bad tolerance-modification treatment in 8 patients

No serious side effects

RR 25% 12 months lower recurence has also been observed in other studies

¿PROACTIVE SEQUENTIAL TREATMENT?

Prevention of Recurrent High-Grade Anal Neoplasia With Quadrivalent Human Papillomavirus Vaccination of Men Who Have Sex With Men: A Nonconcurrent Cohort Study

Kristin A. Swedish,[1] Stephanie H. Factor,[2] and Stephen E. Goldstone[3]

[1]Department of Preventive Medicine, [2]Division of Infectious Diseases, and [3]Department of Surgery, Mount Sinai School of Medicine, New York, New York

Background. Most squamous cell anal cancers and precancerous lesions are attributed to human papillomavirus (HPV) infection. By preventing HPV infection, quadrivalent HPV vaccine (qHPV) reduces risk of anal cancer/precancerous lesions in young men who have sex with men (MSM) without history of anal cancer/precancerous lesions. In our practice, many persons with history of precancerous anal lesions or high-grade anal intraepithelial neoplasia (HGAIN) have been vaccinated electively. We determined whether qHPV is effective at preventing recurrence of HGAIN.

Methods. This nonconcurrent cohort study evaluated 202 patients with a history of previously treated HGAIN. Eighty-eight patients were vaccinated, and 114 patients were unvaccinated. We determined the recurrence rate of histologic HGAIN in vaccinated versus unvaccinated patients.

Results. During 340.4 person-years follow-up, 12 (13.6%) vaccinated patients and 35 (30.7%) unvaccinated patients developed recurrent HGAIN. Multivariable hazards ratio (HR) analysis showed testing positive for oncogenic HPV genotypes within 8 months before study entry was associated with increased risk of recurrent HGAIN at 2 years after study entry (HR 4.06; 95% confidence interval [CI], 1.58–10.40; $P = .004$), and qHPV was associated with decreased risk of recurrent HGAIN (HR .50; 95% CI, .26–.98; $P = .04$). Among patients infected with oncogenic HPV, qHPV was associated with decreased risk of recurrent HGAIN at 2 years after study entry (HR .47; 95% CI, .22–1.00; $P = .05$).

Conclusions. qHPV significantly reduces HGAIN recurrence among MSM and may be an effective posttreatment adjuvant form of therapy. A randomized controlled trial is needed to confirm these results.

HPV vaccination to prevent recurrence of anal intraepithelial neoplasia in HIV+ MSM

Karien C.M. Gosens[a,b,*], Ramon P. van der Zee[a,b,c,*], Matthijs L. Siegenbeek van Heukelom[a], Vita W. Jongen[d], Irina Cairc Arne van Eeden[f], Carel J.M. van Noesel[g], Wim G.V. Quint[h], Hella Pasmans[i], Marcel G.W. Dijkgraaf[j], Henry J.C. de Vries[a,k] and Jan M. Prins[b]

See related paper on page 1863

Objective: Anal cancer precursor lesions high-grade anal intraepithelial neoplasia (HGAIN) are highly prevalent among HIV+ MSM. Treatment of HGAIN is frustrated by high recurrence rates. We investigated the efficacy of the quadrivalent human papillomavirus (qHPV) vaccine as posttreatment adjuvant in preventing HGAIN recurrence in HIV+ MSM.

Design: Randomized, double-blind, placebo-controlled, multicentre trial.

Setting: Three HIV outpatient clinics in Amsterdam, the Netherlands.

Subjects: HIV+ MSM with $CD4^+$ cell count more than 350 cells/μl, biopsy-proven intra-anal HGAIN successfully treated in the past year, and lesions still in remission at enrolment, as assessed by high-resolution anoscopy (HRA).

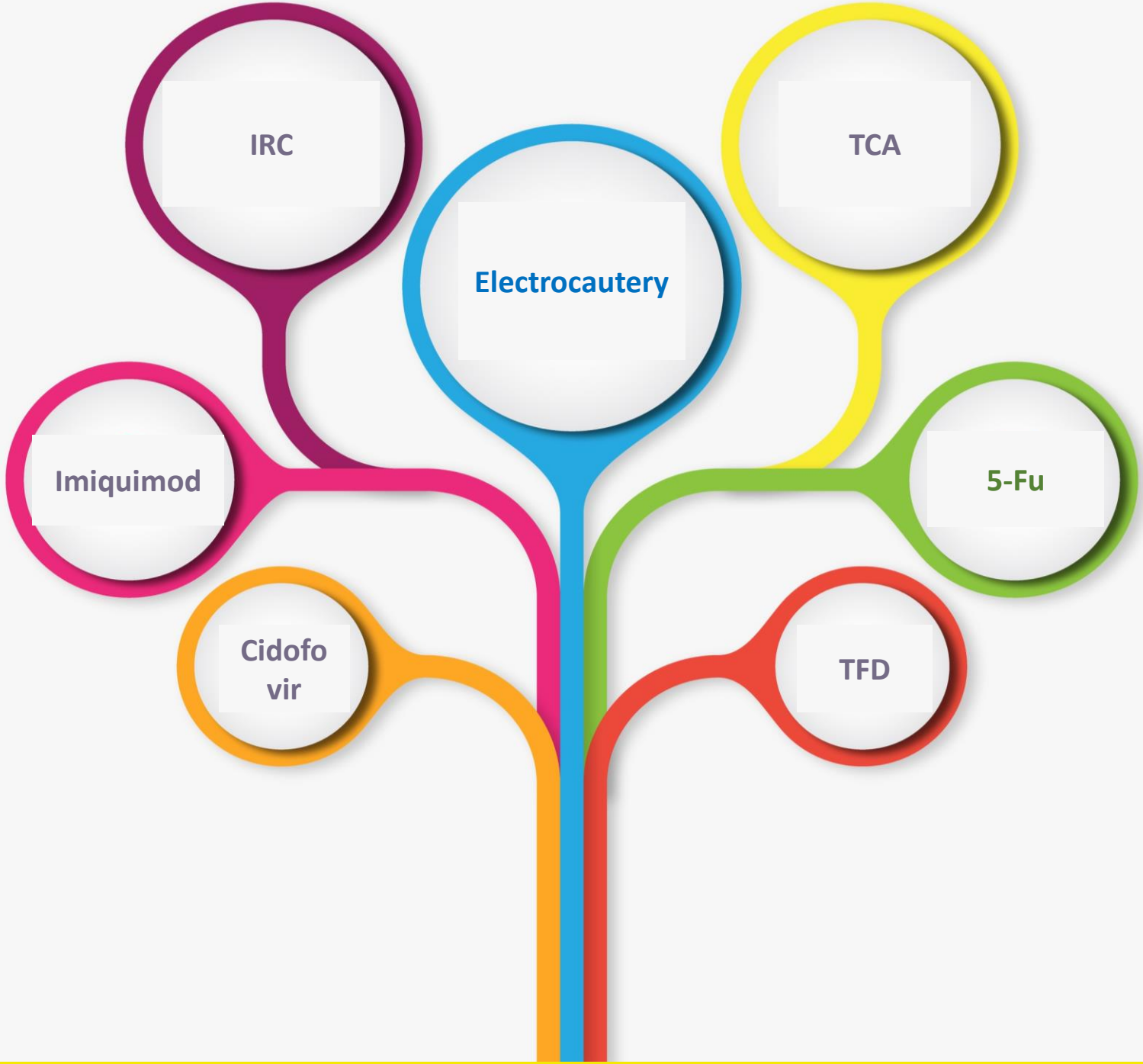
Intervention: Participants were randomized to three doses of qHPV (Gardasil-4, MSD) or placebo with vaccinations at 0, 2, and 6 months. HRA was repeated at 6, 12, and 18 months.

Main outcome measure: The primary outcome was cumulative, biopsy-proven HGAIN recurrence rate at 18 months, evaluated in an intention-to-treat (ITT) (received all vaccinations) and per-protocol analysis (all vaccinations and complete follow-up).

Results: We randomized 126 participants of which 64 (50.8%) received qHPV and 62 (49.2%) placebo. All participants received three vaccinations, and in both groups for two participants follow-up was incomplete. We found no difference ($P = 0.38$) in cumulative HGAIN recurrence rates between the qHPV (44/64, 68.8%) and placebo group (38/62, 61.3%) in the ITT analysis [absolute risk reduction −7.5 (95% confidence interval (CI) −24.1 to 9.2)]. This was similar in the per-protocol analysis.

Conclusion: Despite adequate serological responses to qHPV vaccination, short-term recurrence of HGAIN was not prevented. These findings do not support qHPV vaccination as a treatment adjuvant to prevent HGAIN recurrence in HIV+ MSM.

AIDS 2021, **35**:1753–1764


IRC
TCA
Electrocautery
Imiquimod
5-Fu
Cidofo
vir
TFD

What about sexual and life quality impact?

A-HRSI

VALUE IN HEALTH 21 (2018) 984–992

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ScienceDirect

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

Patient-Reported Outcomes

Initial Development and Content Validation of a Health-Related Symptom Index for Persons either Treated or Monitored for Anal High-Grade Squamous Intraepithelial Lesions

Jack E. Burkhalter, PhD[1], Thomas M. Atkinson, PhD[1,], J. Berry-Lawhorn, MD[2], Stephen Goldstone, MD[3], Mark H. Einstein, MD, MS[4], Timothy J. Wilkin, MD, MPH[5], Jeannette Lee, PhD[6], David Cella, PhD[7], Joel M. Palefsky, MD[2], ANCHOR HRQOL Implementation Group*

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ABSTRACT

Background: Anal cancer, caused by oncogenic types of human papillomavirus, is a growing problem in the United States. A key focus of anal cancer prevention has been screening for and treating precancerous high-grade squamous intraepithelial anal lesions (HSILs). **Objectives:** To develop a health-related symptom index for HSIL using qualitative techniques because anal HSIL and its treatment may have a negative impact on health-related quality of life (HRQOL), and no HRQOL measure specific to this condition and treatment currently exists. **Methods:** Expert consultation was used to guide one-on-one concept elicitation interviews with participants to identify HRQOL aspects they attribute to their anal HSIL and its treatment. This resulted in a draft instrument, which was administered to an independent participant sample, where cognitive interview techniques assessed comprehension. **Results:** Eighteen anal HSIL-related concepts were identified by the expert panel. Across the 41 concept elicitation interviews, 23 items representing physical symptoms, physical impacts, and psychological symptoms were identified to comprise the initial measure, which was then evaluated during three rounds of cognitive interviews (n = 45). Several questionnaire aspects were refined on the basis of participant input, with three additional items added per expert/participant recommendation. One item was removed because of poor comprehension, resulting in a 25-item measure. **Conclusions:** Using state-of-the-art qualitative methodology, we have established the content validity of this new instrument, the ANCHOR Anal HSIL Health-Related Symptom Index. Quantitative validation efforts are currently underway. The participant-driven process of developing this tool will facilitate a participant-centered evaluation of the impact on morbidity for treatment of anal HSIL or observation without treatment.

Keywords: ANCHOR trial, health-related quality of life, neoplasms, patient-reported outcomes.

Introduction

Anal cancer is a growing problem in the United States [1], with the incidence rising in the most common type of anal cancer, squamous cell carcinoma, from the year 1992 to 2011 [2]. In the US general population, the incidence of anal cancer from the year 2009 to 2013 was 1.8 of 100,000 among men and women [3], but there is a markedly higher incidence among subpopulations. The cumulative incidence of anal cancer among HIV-infected adults was reported to be 1.5% by age 75 years, compared with 0.5% among HIV-uninfected adults [4]. Human papillomavirus (HPV) infection is causally associated with the development of anal

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SHORT REPORT Open Access

Linguistic validation of the Spanish version of the Anal Cancer High-Grade squamous intraepithelial lesions outcomes Research Health-Related Symptom Index (A-HRSI): AMC-A04

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Abstract

Objectives The Anal Cancer High-grade squamous intraepithelial lesions (HSIL) Outcomes Research (ANCHOR) Health-Related Symptom Index (A-HRSI) is a 25-item measure that assesses physical symptoms and impacts, and psychological symptoms. To promote generalizability and equity in the capture of these concepts in Spanish-speaking participants, we linguistically validated a Spanish version of A-HRSI.

Methods Following independent forward translation and reconciliation of A-HRSI from English to Spanish, two rounds of cognitive interviews were completed with ANCHOR participants who had been diagnosed with anal HSIL in the prior nine months and preferred delivery of their healthcare in Spanish. Interviews were coded to highlight any items and concepts that were reported as being difficult for any reason by ≥ 3 participants, with such items revised during a research team panel discussion and tested in a second round of interviews if applicable.

Results Seventeen participants representing 8 nationalities were enrolled (Round 1 *n*=10, Round 2 *n*=7); 7 participants reported not completing high school (41.2%). No difficulties were reported with respect to the theoretical concepts measured by A-HRSI. We made modifications to the Spanish translation of eight items and two response option terms in cases where participants had difficulty understanding a term, experienced problems in discriminating between terms, or preferred the use of an alternative term to represent the concept(s).

Conclusion The Spanish version of A-HRSI is a linguistically valid tool that can be used to assess physical symptoms, impacts, and psychological symptoms related to anal HSIL.

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Table 2 Spanish A-HRSI modified terms and reasons for modifications

Domain	Item in English	Original item in Spanish	Revised item in Spanish	Reason(s) for the modification
Response Category				
	Very much- 4	Mucho- 4	Muchísimo- 4	Participants had difficulty discriminating between "bastante" (3) and "mucho" (4); these were overlapping and/or interchangeable terms (R1)
	Not at all- 0	Para Nada- 0	Nada- 0	Para nada seen as an "unusual" expression or difficult to distinguish from "Not applicable" (R2)
Physical Symptoms				
	I have pain during bowel movements	Tengo dolor durante la defecación	Tengo dolor cuando entro al baño a defecar	Participants had difficulty understanding the noun "defecación" (defecate/ defecating) (R1)
	I have urgency for bowel movements	Siento urgencia de defecar	Siento urgencia de entrar al baño a defecar	
Physical Impacts				
	I have problems taking care of myself (e.g., bathing, dressing, shaving)	Tengo problemas con mis deberes personales diarios (por ej., bañándome, vistiéndome, afeitándome)	Problemas con mi arreglo personal	"Problemas personales" ("problems with everyday duties") was unclear to participants—they did not interpret this to mean daily care activities such as bathing, brushing teeth, etc. (R1)
	I have problems with my physical ability to move around	Tengo problemas con mi capacidad física para movilizarme	Tengo problemas con mi capacidad física para moverme	"Movilizarse" is not specific enough to the act of physical movement (e.g. walking). Some participants interpreted this to mean "problems mobilizing myself", or motivation (R2)
	I have problems completing daily household chores (e.g., cleaning, cooking, laundry, house maintenance)	Tengo problemas terminando las tareas de la casa (por ej., limpiar, cocinar, hacer la colada, administrar la casa)	Tengo problemas manteniendo la casa (por ej., limpiar, cocinar, preparar el café, administrar la casa)	"Tareas" was initially confusing to participants; "hacer la colada" was seen as unfamiliar or "too regional"; "preparar el café" is a more widely understood example (R2)
	I have problems participating in leisure activities (e.g., watching television, relaxing)	Tengo problemas participando en actividades de ocio (por ej., mirar televisión, relajarme)	Tengo problemas participando en actividades de relajo (por ej., mirar televisión, relajarme)	"Ocio" viewed as an "archaic" phrase for "leisure", difficult to understand (R2)
Psychological Symptoms				
	I have a decreased enjoyment of anal sexual activity	Me ha disminuido el placer de la actividad sexual anal	Me ha disminuido el disfrute de la actividad sexual anal	Participants often interpreted these items in terms of desire, rather than physical pleasure. Changed to "placer" to "disfrute" to specify physical enjoyment (R2)
	I have a deceased enjoyment for any form of sexual activity other than anal sexual activity	Me ha disminuido el placer de cualquier forma de actividad sexual diferente a la actividad sexual anal	Me ha disminuido el disfrute de cualquier forma de actividad sexual diferente a la actividad sexual anal	

3. HOW TO CHOOSE TREATMENT??

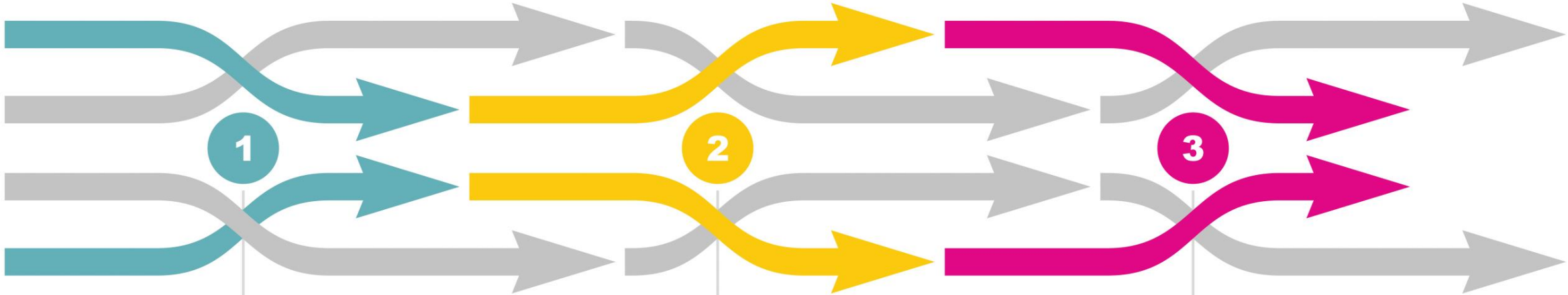
a. DOES THE PATIENT NEED TREATMENT?

b. DOES THE PATIENT AGREE TO BE TREATED/ANAL?

c. DOES THE PATIENT AGREE TO BE TREATED/PERIANAL?

a. DOES THE PATIENT NEED TREATMENT?

HOW OLD IS YOUR PATIENT?
Always treat patients>35

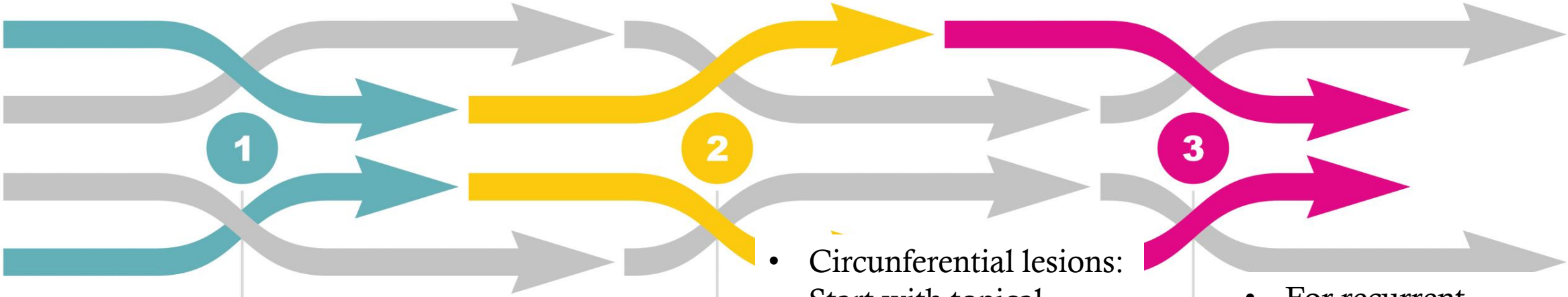


PERSISTENT/EXTENSIVE LESION?

SEVERE INMUNOSUPRESSION (CD4 NADIR, LOW CD4)

HPV16 POSITIVE?

b. DOES THE PATIENT AGREE TO BE TREATED/ANAL CANAL?

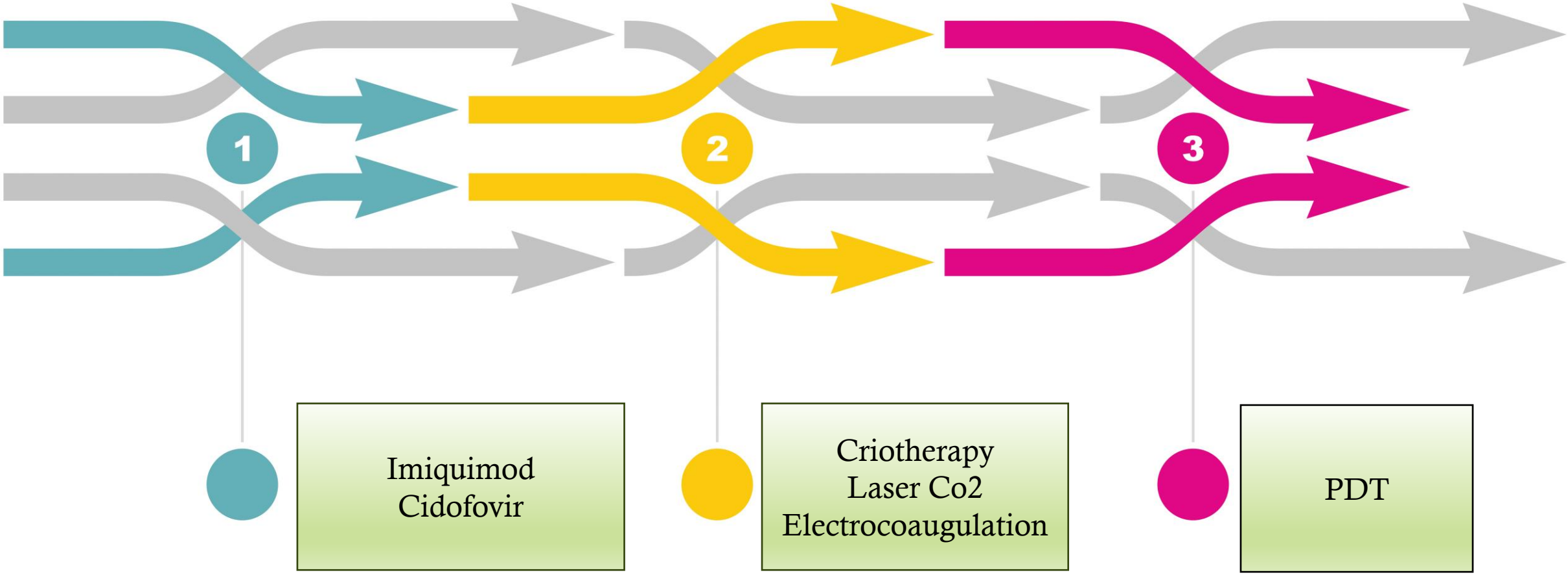


- For lesions scarce and small(<1 cm) TCA or ablation
- More than 1 cm, very atypical or old patients-cauterization

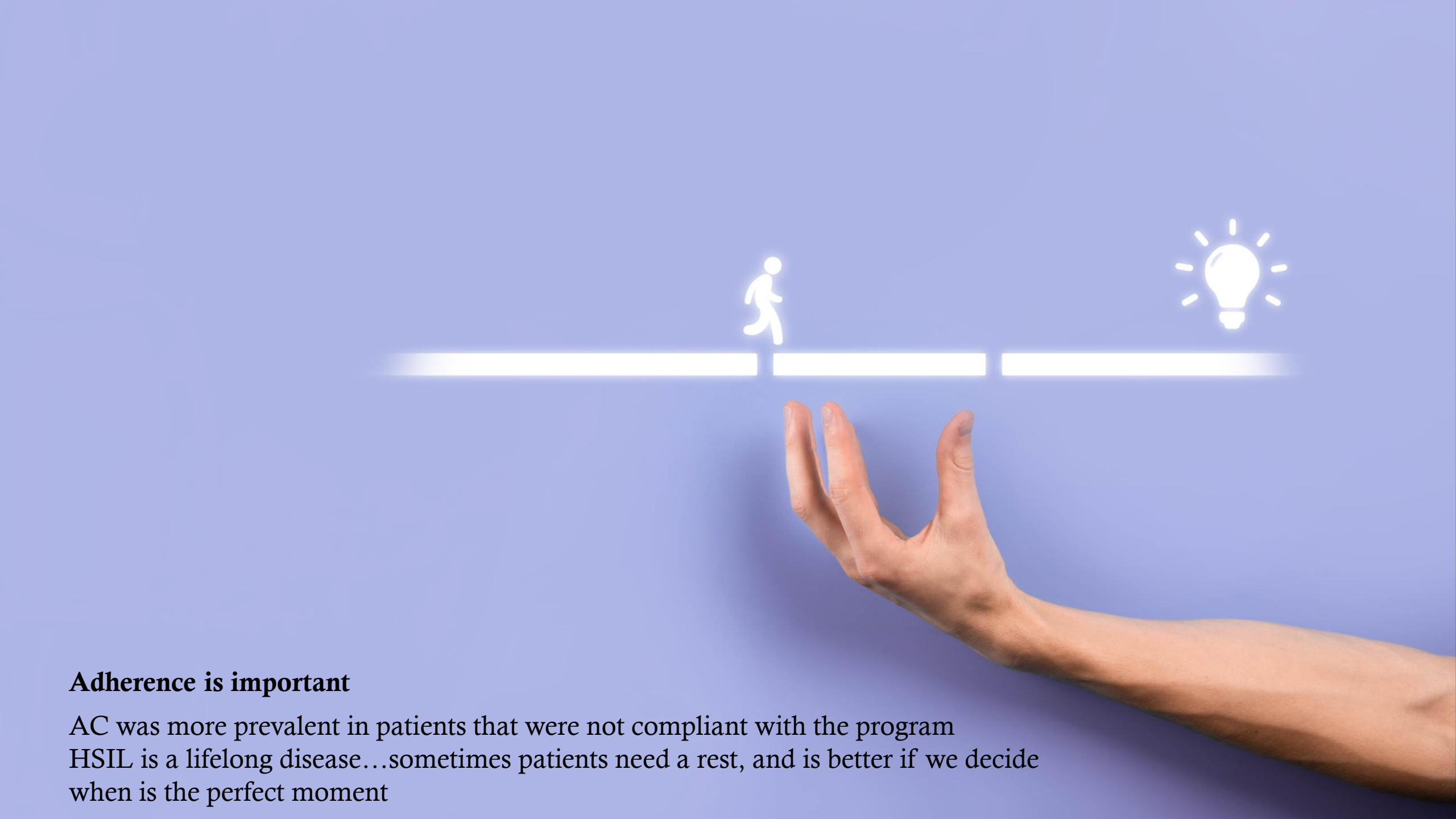
- Circunferential lesions: Start with topical treatment and combine with cauterization if needed
- If tolerance to treatment is low, cauterization under anesthesia in a stepwise manner
- Radiofrequency ablation/TFD

- For recurrent lesions add consider adding a topical treatment 3-4 months
- Stop smoking
- If posible lower inmunosupression

c. DOES THE PATIENT AGREE TO BE TREATED/ANAL CANAL?



¿IS THERE A WINDOW OF OPPORTUNITY TREATMENT?

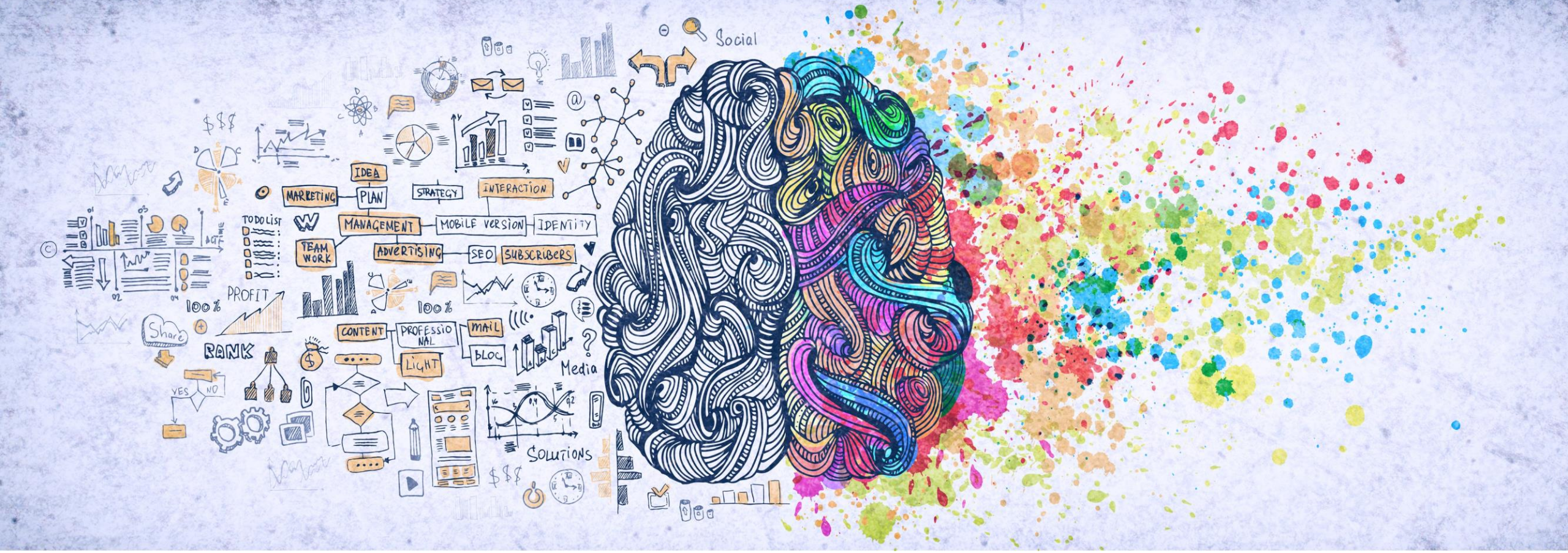


Adherence is important

AC was more prevalent in patients that were not compliant with the program
HSIL is a lifelong disease…sometimes patients need a rest, and is better if we decide when is the perfect moment

4. TAKE HOME MESSAGES

- Explain natural history of HSIL disease therapeutic possibilities with your patient
- Consider age, extension and persistence, HPV and inmunosupression in the timing and kind of treatment
- Explain warning signs to your patient, be accesible
- Consider multidisciplinary approach
- Consider sequential treatment



THANK YOU FOR YOUR ATTENTION

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