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Viszerale Chirurgie und Medizin

Perianale Veränderungen

38. SCHWEIZERISCHE KOLOPROKTOLOGIE-TAGUNG

14. JANUAR 2017 – BERN

Curdin Conrad
Lukas Brügger

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UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

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Case

- male, 40 years
- Smoker 20 py
- Msm, HIV-

Therapy

Recommended Patient-Applied Regimen	Dosing
Imiquimod 5% cream	Topically every night at bedtime for 3 times/wk up to 16 wk
Imiquimod 3.75% cream	Topically every night at bedtime up to 16 wk
Podofilox 0.5% solution or gel	Topically twice daily × 3 d followed by 4 d off for up to 4 cycles
Sinecatechins 15% ointment	Topically 3 times daily, for up to 16 wk
Bichloracetic acid 80%–90%	Applied once every 1–2 wk
Cryotherapy	Applied once every 1–2 wk
Surgical removal	
Trichloroacetic acid 80%–90%	Applied once every 1–2 wk

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Park IU. STD Treatment Guidelines: HPV Updates Clinical Infectious Diseases 2015

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Imiquimod

Study method	*Treated patients*	*Intervention*	*Results*	*Conclusion*
Double-blind randomized clinical trial (n = 64)	MSM HIV+HG-AIN	Imiquimod (n = 28) ---------- Placebo (n = 25)	Imiquimod: – Complete response: 14% – Partial response: 28% ---------- Placebo Complete response: 4%	Imiquimod is a safe and well tolerated treatment which can be useful for the treatment of HG-AIN

Fox PA. AIDS 2010

Imiquimod

Study method	*Treated patients*	*Intervention*	*Results*	*Conclusion*
Randomized clinical trial (n = 148)	HIV+, MSM, > 18 years LG-AIN or HG-AIN	Imiquimod (n = 54)	Complete response: 24% Recurrence: – At week 24: 19% – At week 48: 50% – At week 72: 71% Side-effects: 91% Stopped treatment: 9%	In cases of LG-AIN "watch and wait" could be adequate. Electrocautery is superior to topical Imiquimod or to topical 5-FU in the treatment of AIN in HIV-infected MSM. Imiquimod is the best option for perianal lesions
		5-FU (n = 48)	Complete response 17% Recurrence: – At week 24: 38% – At week 48: 50% – At week 72: 58% Side-effects: 92% Stopped treatment 4%	
		Electrocautery (n = 46)	Complete response 39% Recurrence: – At week 24: 14% – At week 48: 43 % – At week 72: 68% Side-effects: 93% Stopped treatment: 7%	

Richel O. Lancet Oncol 2013

Treatment
Ablation

- Electrosurgery (sling/cautery)
- CO2-laser vaporisation
- Cryotherapy

} no scarring

- Surgical excision

- RCT:
  - Electrosurgery vs CO2-laser: clearance 75 vs 64%
  - Surgical excision vs CO2-laser: no difference

- Recurrence high
  - 50% immunocompetent
  - 70% immunocompromised

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Ferenczy A. J Gynecol Surg 1995
Duus Br. Genitourin Med 1985

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UNITED MEDICAL PARTNERS AG

CRYOSUCCESS
LIQUIDFREEZING

Cryosurgery with „LIQUIDFREEZING“

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Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation

Elizabeth Thurgar, Samantha Barton, Charlotta Karner and Steven J Edwards

- **ablative techniques** are clinically **more effective**
- **Podophyllotoxin 0.5%** solution is likely to represent a cost-effective **first-line** treatment option
- **CO2 laser** therapy or **surgery**, may represent cost-effective **second-line** treatment options
- No treatment and podophyllin are unlikely to be considered cost-effective treatment options
- **uncertainty** around the cost-effectiveness of treatment with **imiquimod**, trichloroacetic acid and cryotherapy.

Health Technology Assessment 2016

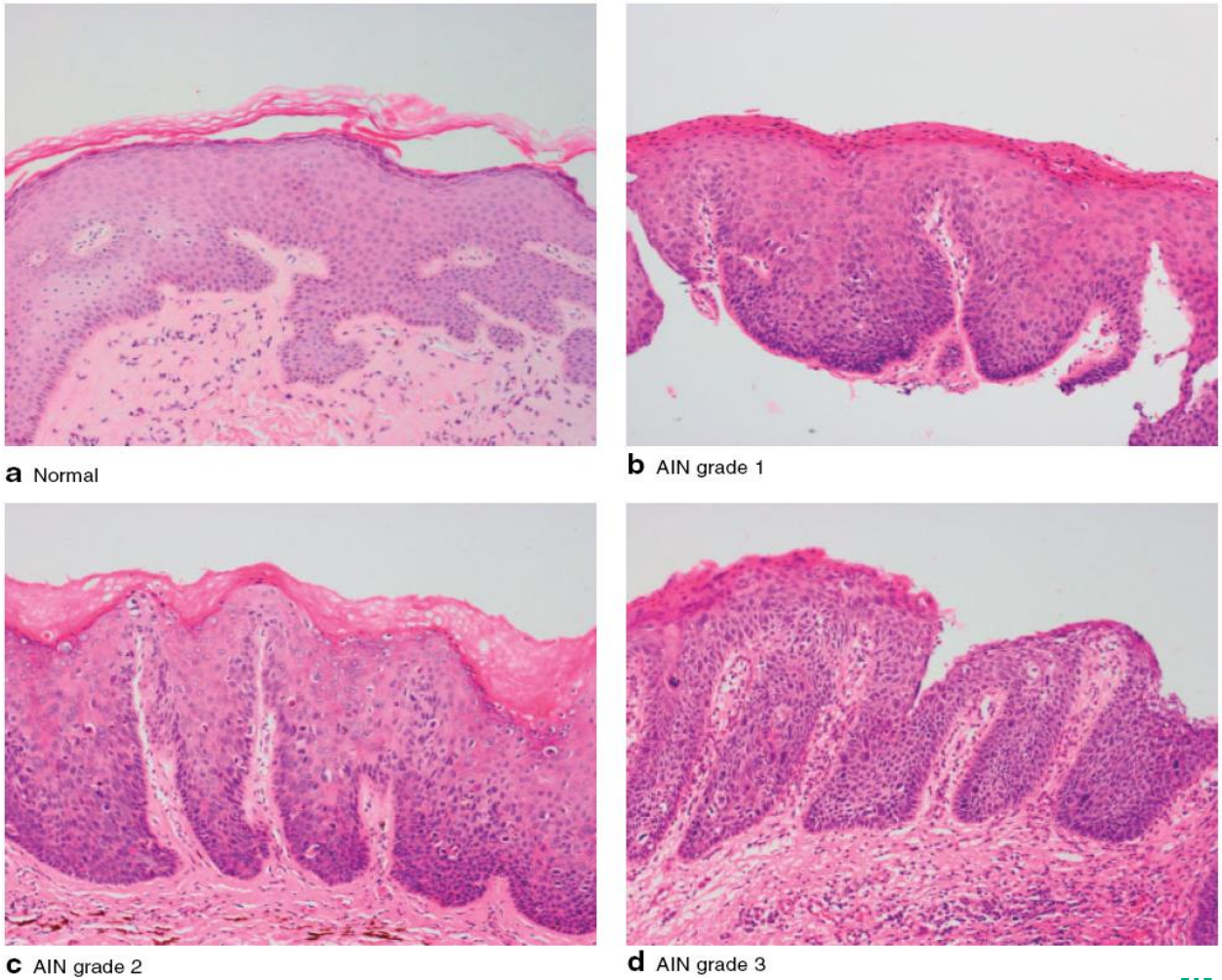
Case

- male, 40 years
- Smoker 20 py
- Msm, HIV-

Case

- male, 40 years
- Smoker 20 py
- Msm, HIV-
- Condyloma since 2001 (Laser, Imuiquimod, Electrocautery)
- Several times AIN II-III
- HPV 16
- Now (again) HSIL in Pap smear

AIN (Anal Intraepithelial Neoplasia)



a Normal

b AIN grade 1

c AIN grade 2

d AIN grade 3

Abbasakoor F. Br J Surg 2005

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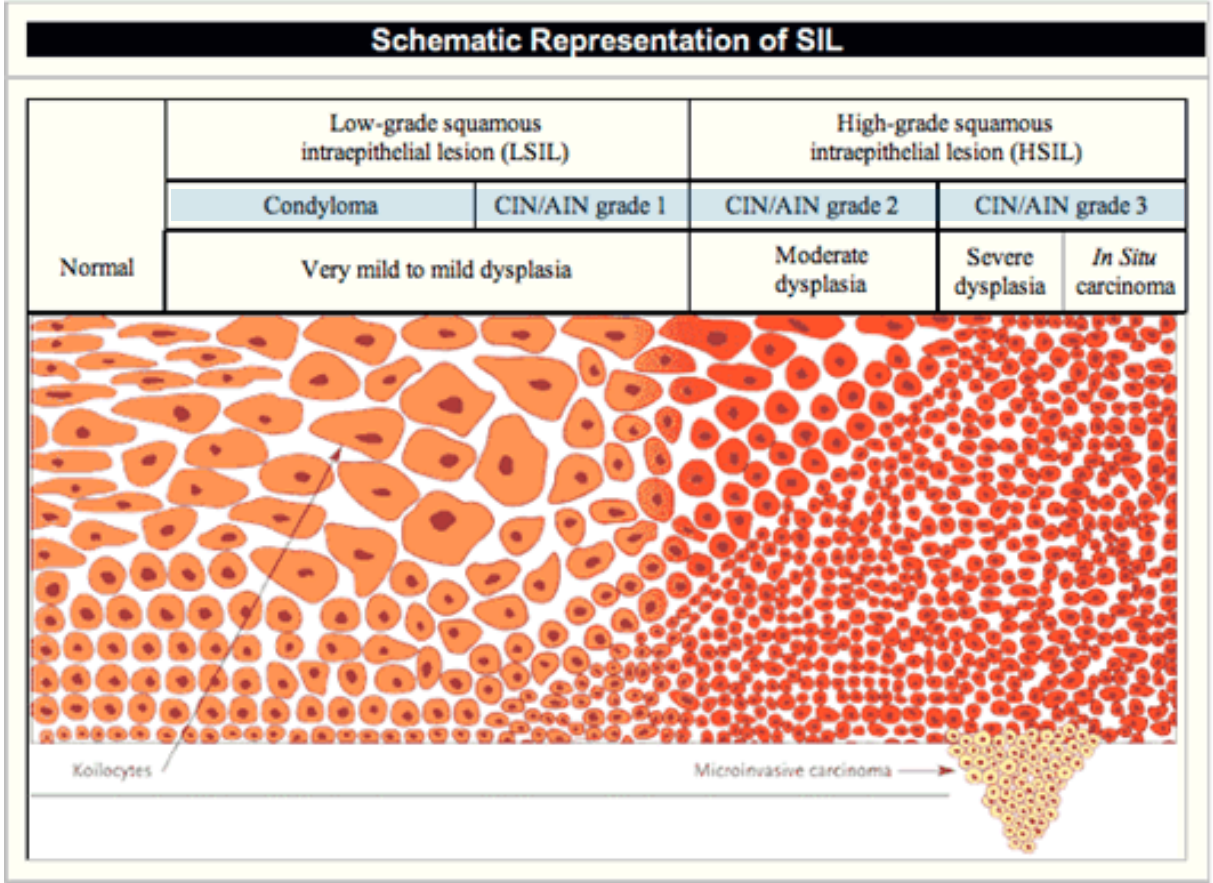
Terminology (Bethesda System)

- Low-grade squamous intraepithelial lesion (LISL)
- High-grade squamous intraepithelial lesion (HISL)



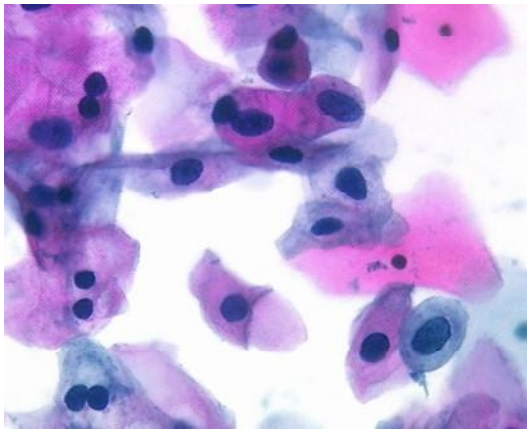
Solomon D. JAMA 2002

Diagnosis

Anal cytology (PAP)

- Identifies HSIL, not localisation
- Sensitivity 81-87%
- Specifity 39-41%

HPV testing poor Specifity for HSIL



Berry JM. DCR 2009
Salit IE. AIDS 2010
Matthews WC. PLoS One 2011
Nathan M. AIDS 2010
Salit IE. Cancer Epidemiol Biomarkers Prev 2009

Diagnosis

- Anal colposcopy / high resolution anoscopy
  - Acetic acid → „acetowhitening“ of AIN
  - Lugol‘s iodine → normal squamous epithelium brown

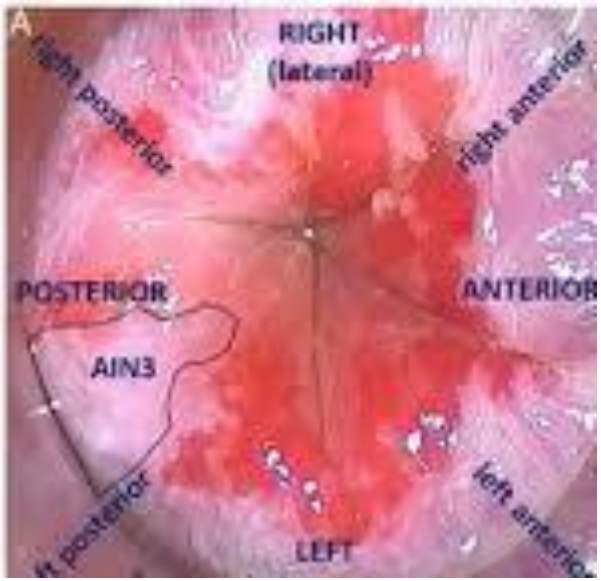


Table I. Prevalence of anal HPV infection, AIN and progression of anal carcinoma per year

	Anal HPV infection (any type)	*Abnormal citology or histology*	*High-grade AIN*	*Progression to anal carcinoma/year*
MSM HIV+	85-95% (3)	48% (7)	31% (3.7)	1/600 (3) 1/400 (7) 1/760 (13)
MSM HIV-	42-63% (2.8)		19% (3)	1/4,000 (3) 1/50,000 (13)
Heterosexual males	24% (14)			
HIV+ women	80% (9)	% (7.9)	6% (11)	1/204 (7) 1/3.000 (13)
HIV- women	6.2)	2-9%	1% (11)	1/770 (10) (women with a previous vulvar/ cervical carcinoma)

Infrequent!!

Elorza G, Rev Esp Enferm Dig 2016
Machalek DA, Lancet Oncol 2012
Weis SE, DCR 2011
Salaem AM, Obstet Gynecol 2012
Silverberg MJ, Clin Infect Dis 2012

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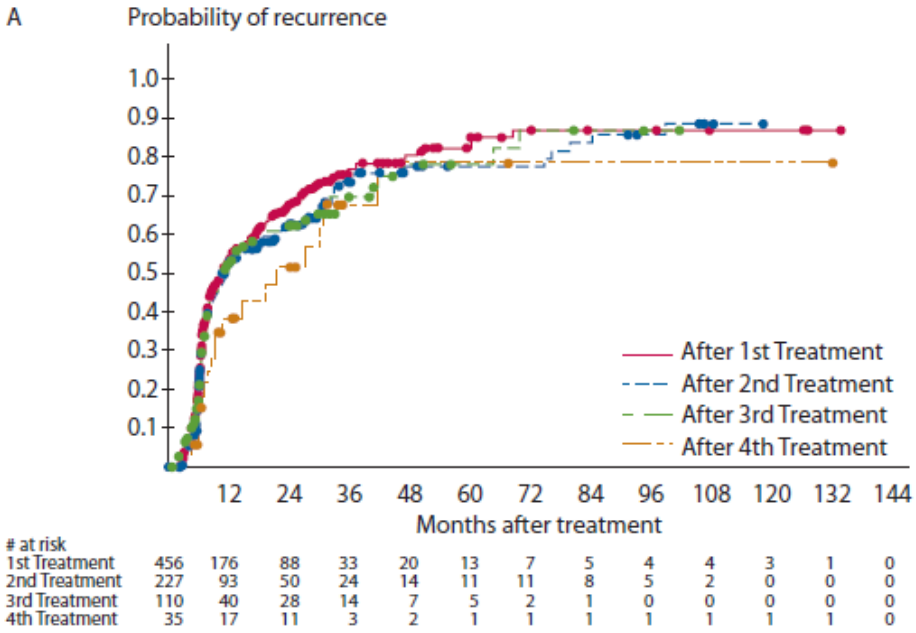
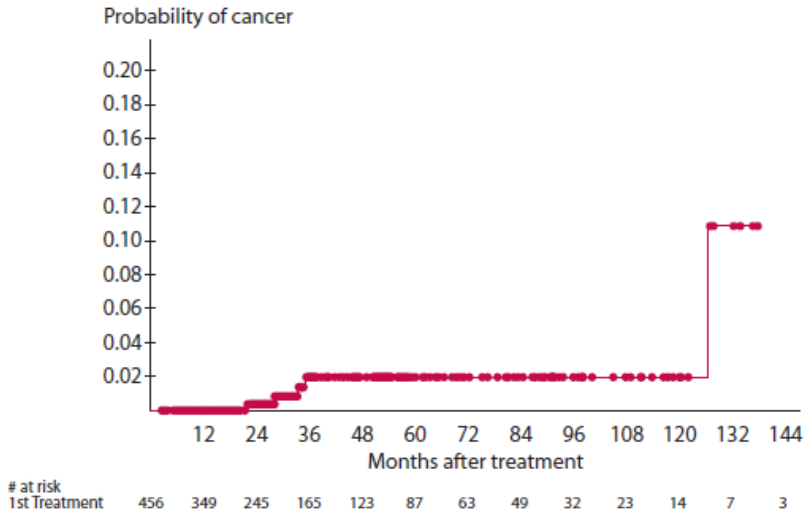
ORIGINAL CONTRIBUTION

Long-term Outcome of Ablation of Anal High-grade Squamous Intraepithelial Lesions: Recurrence and Incidence of Cancer

Stephen E. Goldstone, M.D.[1] • Andrew A. Johnstone, B.A[1] • Erin L. Moshier, M.S.[2]

1 Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, New York
2 Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, New York





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DCR 2014

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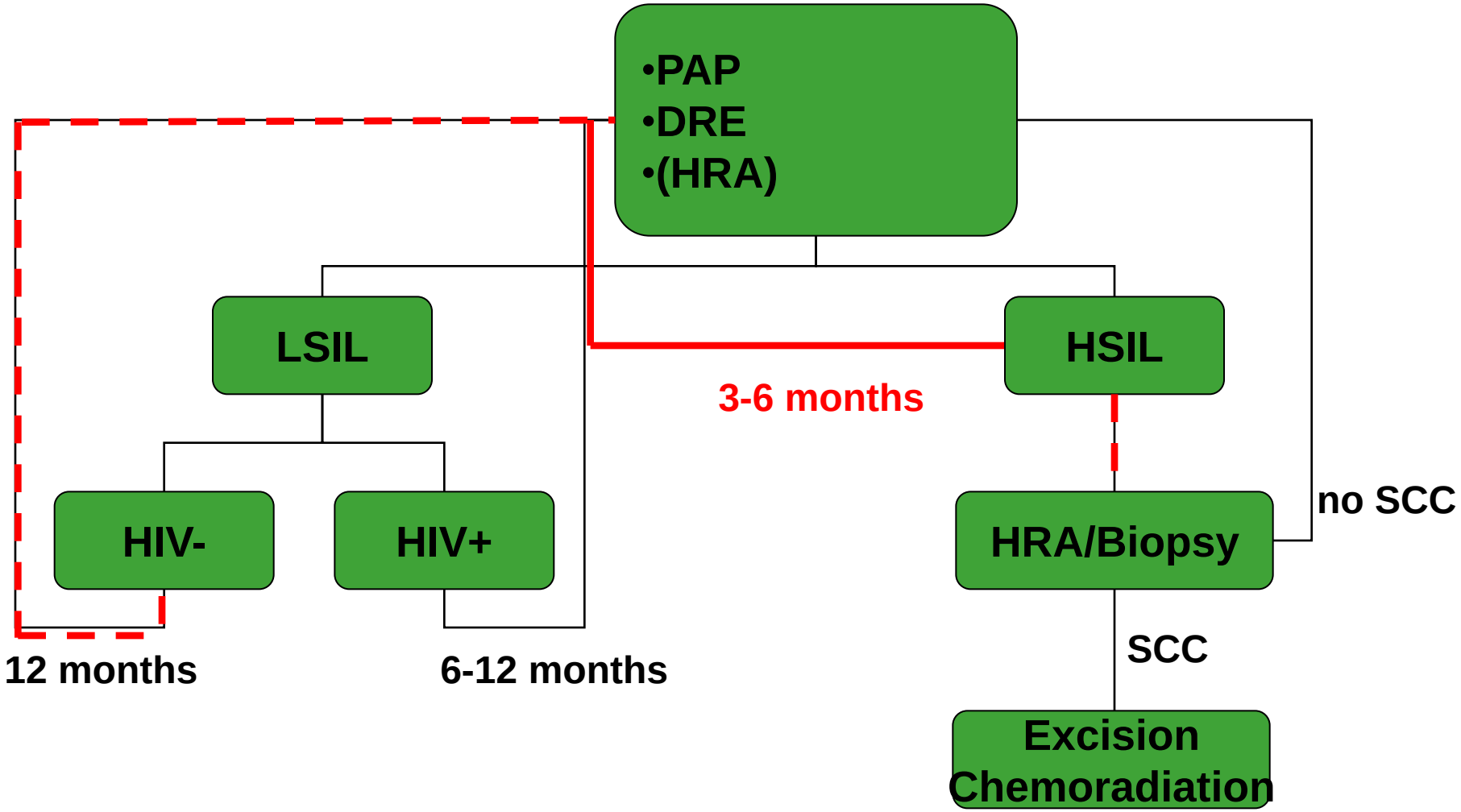
Screening Guidelines

	Recommendation	
European AIDS Clinical Society guidelines	Anal Pap smear, Anoscopy for MSM every 1-3 years	Evidence of benefit uncertain!
NY State Department of Health AIDS Institute	Pap screening and HRA when not normal for HIV+/MSM and history of anogenital condylomas or cervical/vulvar histology	
Center for Disease Control and Prevention (CDC)	No routine screening	Anal cytology for HIV+/MSM and women might be useful
British Guidelines	No routine screening	Patients with dysplasia should be monitored

Smyczek P, Int J of STD & AIDS 2013

Algorithm MSM



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Topical or Ablative Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions (ANCHOR)

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2016 by AIDS Malignancy Consortium

Sponsor:
AIDS Malignancy Consortium

Collaborators:
National Cancer Institute (NCI)
The EMMES Corporation
University of Arkansas
University of California, San Francisco

Information provided by (Responsible Party):
AIDS Malignancy Consortium

ClinicalTrials.gov Identifier:
NCT02135419

First received: May 8, 2014
Last updated: December 30, 2016
Last verified: July 2016
History of Changes

Case

- male, 40 years
- Smoker 20 py
- Msm, HIV-
- Condyloma since 2001 (Laser, Imuiquimod, Electrocautery)
- Several times AIN II-III
- HPV 16
- Now (again) HSIL in Pap smear

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Case

- male, 40 years
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- Msm, HIV-
- Condyloma since 2001 (Laser, Imuiquimod, Electrocautery)
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- HPV 16
- Now (again) HSIL in Pap smear

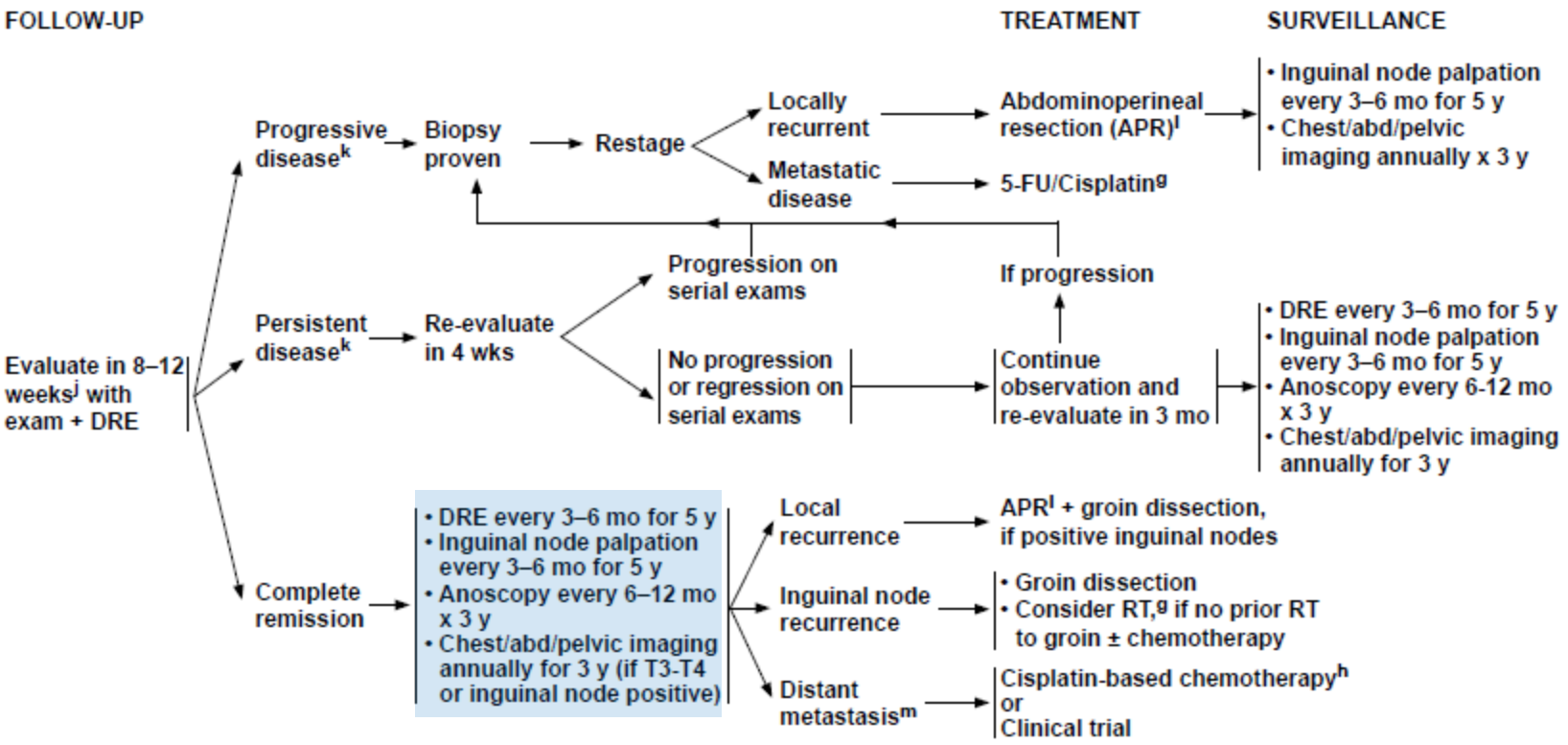
well differentiated

Anal CA in Biopsy

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Anal Carcinoma

NCCN Guidelines Index
Anal Carcinoma Table of Contents
Discussion



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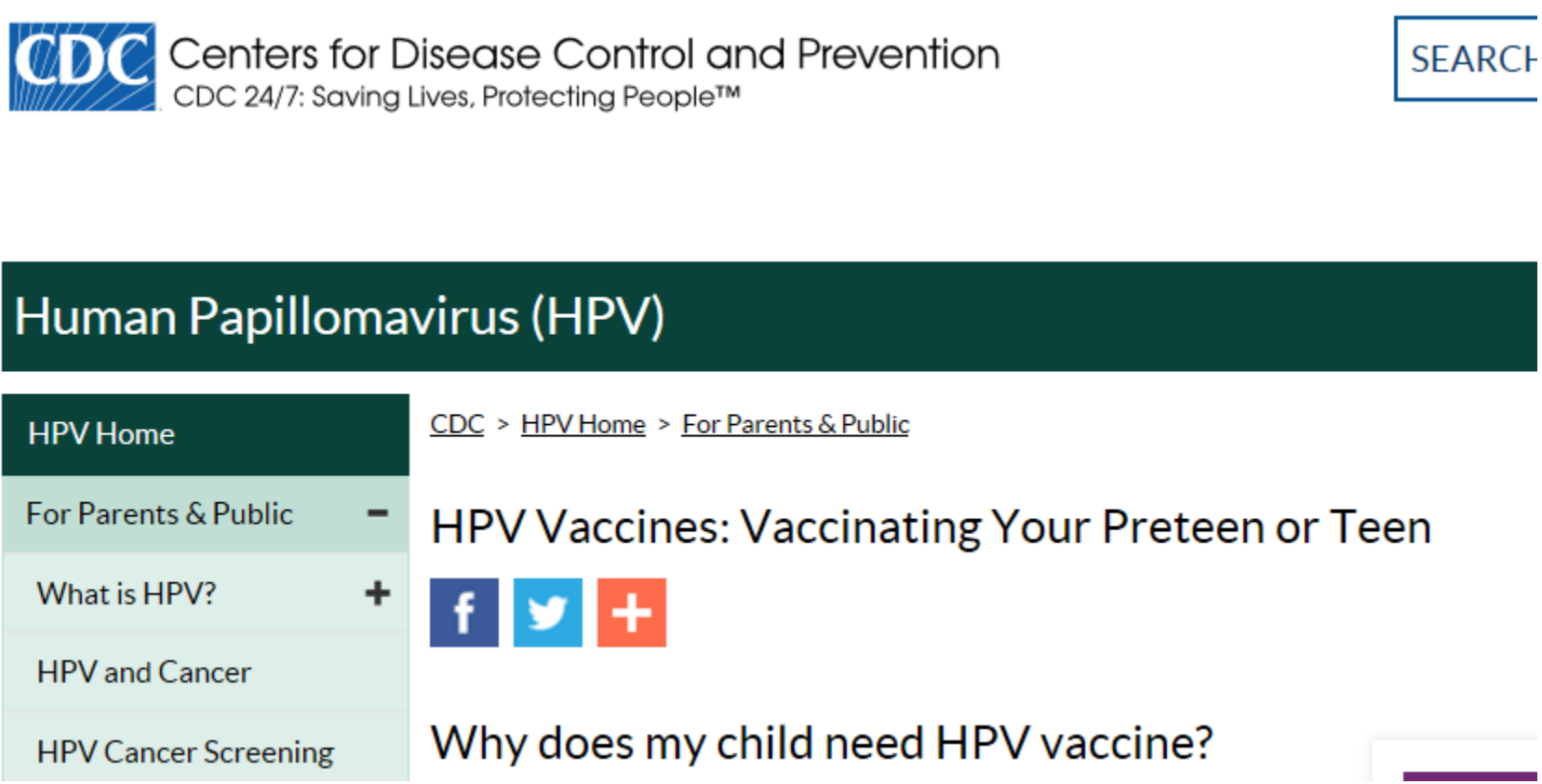

through age 26 when at risk (men and women)

- MSM
- Transgender
- Immunocompromising condition

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Don’t miss the Carcinoma!

Hidradenitis Suppurative Acne inversa)

Kohorst and colleagues (current study), 2015	Surgical excision, unroofing, or incision and drainage	590	24.4% (144/590 patients) recurrence; 11.7% (69/590 patients) repeat surgery following recurrence
Watson[9]	Surgical excision with primary closure, grafting, and local flap	72	54.2% (39/72 patients) recurrence in primary closure; 12.5% (9/72 patients) recurrence with skin graft; 19.4% (14/72 patients) recurrence with local flap
Lapins and colleagues[10]	Carbon dioxide laser excision	24	8.3% (2/24 patients) recurrence
Endo and colleagues[11]	Surgical excision (perianal)	12	0% (0/12 patients) recurrence
Ritz and colleagues[5]	Drainage, local surgical excision, radical surgical excision	31	100% (6/6 patients) recurrence after drainage; 42.9% (6/14 patients) recurrence after local excision; 27.3% (3/11 patients) recurrence after radical excision
Rompel and Petres[8]	Surgical excision	106	2.5% recurrence within operated fields*
Bohn and Svensson[4]	Surgical excision	116	32.8% (38/116 patients) recurrence
Lamfichekh and colleagues[12]	Surgical excision with primary closure, healing by second intention, Z-plasty, or flap	15	20.0% (3/15 patients) recurrence
Tanaka and colleagues[13]	Surgical excision with primary closure, graft, or flap	19	31.6% (6/19 patients) recurrence
Lapins and colleagues[14]	Carbon dioxide laser excision	34	11.8% (4/34 patients) recurrence
Bocchini and colleagues[15]	Surgical excision (abdominal and gluteal)	56	1.8% (1/56 patients) recurrence; 8.9% (5/56 patients) recurrence
Altmann and colleagues[16]	Radical surgical debridement with	20	15% (3/20 patients) recurrence
Kagan and colleagues[6]	Surgical excision	57	0% (0/57 patients) recurrence at 8-mo follow-up
Mandal and Watson[17]	Surgical excision with primary closure, split skin grafts, and flaps	96	4.9% recurrence with primary closure compared with 0% recurrence with either skin graft or flap†
Aksakal and Adisen[18]	Electrosurgery excision	12	16.7% (2/12 patients) no remission at 16 d
Bordier-Lamy and colleagues[19]	Surgical excision	93	33.0% (69/209 operations) relapse
Buimer and colleagues[20]	Surgical excision with placement of gentamicin sponge vs control	200	Absence of complications more often with gentamicin sponge (58.9% [73/124 patients]) compared with control (47.4% [36/76 patients])
Madan and colleagues[21]	Carbon dioxide laser excision	9	22.2% (2/9 patients) no remission at 1 yr
Balik and colleagues[22]	Surgical excision with open healing, flaps, and delayed grafting	15	0% (0/15 patients) recurrence at 5 yrs
Bieniek and colleagues[23]	Surgical excision with flap	57	31.6% (18/57 patients) had partial recovery (new lesions at operative or adjacent site); 8.8% (5/57 patients) had no improvement
Hazen and Hazen[24]	Carbon dioxide laser excision with marsupialization	61	1.1% (2/185 operations) recurrence
Mahmoud and colleagues[25]	Follicle destruction with Nd:YAG laser	22	72.7% (16/22 patients) had Sartorius score improvement on experimental side; 22.7% (5/22 patients) on control side
Menderes and colleagues[26]	Surgical excision	27	7.4% (2/27 patients) recurrence
van der Zee and colleagues[27]	Deroofing	88	17.0% (15/88 patients) recurrence at 34 mo; median time to recurrence, 4.6 mo

Biologicals

Reference	LOE	Type	No. of Patients	Treatment	Study Duration	Outcomes
Miller et al[35]	"Miller": II	Double-blind RCT vs placebo	21	80 mg then 40 mg ADL SC q.o.w (15) or placebo (6) for 12 wk	24 wk	Significant reduction in Sartorius score after 6 wk compared with placebo; no long-term curative effect observed
Grant et al[34]	"Grant": I	Double-blind RCT vs placebo then open-label	38	5 mg/kg IFX at wk 0, 2, 6 (15) or placebo (23), open-label at 8 wk	60 wk	25% of patients had >50% decrease in HSSI; IFX group also had significant improvement in DLQI, visual analog scale, ESR, and CRP compared with placebo
Blanco et al[36]	"Blanco": IV	Open-label prospective	6	40 mg ADL SC q.o.w	21.5 mo	Significant improvement in DLQI after 1 mo treatment for a mean duration of 21.5 mo
Pelekanou et al[37]	"Pelekanou": II	Open-label prospective	10	ETN 50 mg q.o.w 12 wk	120 wk	5 patients with favorable response, 3 had no relapse, 7 needed second course of ETN, and 2 failed treatments

ADL, adalimumab; CRP, C-reactive protein; DLQI, dermatology life quality index; ESR, erythrocyte sedimentation rate; ETN, etanercept; HSSI, hidradenitis suppurativa severity index; IFX, infliximab; RCT, randomized controlled trial; SC, subcutaneously.

Perianal Paget Disease

1. What is common is common
2. Don’t miss the carcinoma
3. Treatment without a clear diagnosis might be an option
4. Have strategies if treatment does not work

Benign Anal Tumors

Mesenchymal Tumors	• Lipoma • Leiomyoma • Neuroma • Angioma • Others…
Epithelial Tumors	• Perspiratory Gland Adenoma • Keratoakanthoma
Condylomata acuminata Molluscus contagiosus Condylomata lata (Lues II)	
Adenomatous Polyps Hyperplastic Polyp Juvenile Polyp Inflammatory Pseudopolyp Hypertrophic Anal Papilla (Fibroepithelial Polyp)	• Tubular Adenoma • Villous Adenoma • Tubulovillous Adenoma

Malignant Anal Tumors

- Squamous Cell Carcinoma
- Basalioma
- M. Paget
- Adeno-CA

- Digital anal palpation?
- Anoscopy?
- Biopsy?
- Swabs?
- Manometry?
- Exposition prophylaxis?
- Steroid cream?

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ST SPLEX

Fibroepithelial Polyp

- Present for some years
- Often more than one lesion
- Can become quite large
- Always benign

Treatment
Imiquimod (Aldara®)

- Immune response modifier
- 3x/week for 12 weeks
- Local inflammatory reaction: burning
- Metaanalysis Imiquimod vs Podophylin:
  - Recurrence 50 vs 56%, no sig. Difference
  - Less serious side effects for imiquimod

- Endoanal tampon prevents recurrence

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Yan J. Dermatology 2006
Kaspari M. Br. J Dermatol 2002

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Treatment
Imiquimod (Aldara®)

- RCT:

	Subjects no recurrence at 6 months (%)
ablation	73.6
imiquimod	93.7
ablation + imiquimod	91.5

Schöfer H. Eur J Dermatol 2006

Treatment Alternatives

- Podophyllin
- Trichloracetic acid 85% (TCA) → 80% cure
- Cryotherapy (63-88% cure)
- Photodynamic therapy
- Infra-red coaculation

Anal intraepithelial lesion (AIN)

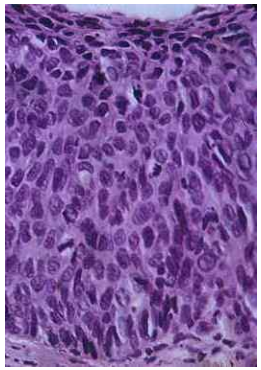
- HPV believed causative agent

  IARC Vol. 64. WHO: Lyon 1995
  Melbye M. Int J Cancer 1990

- Precursor of squamous cell carcinoma (SCC)

  Lacey HB. Sex Transm Infect 1999

- Nuclear abnormalities:



Grade 1

Grade 2

Grade 3

- Progression Grade 1 → Grade 3

Palefsky J. J Aquir Immune Defic Syndr Hum Retrovirol 1998
Lacey HB. Sex Transm Infect 1999

Table II. Prevalence of anal HPV in HIV-uninfected women and its relation with cervical cytology abnormalities (10)

	Anal HPV
No cervical dysplasia	6.2%
CIN 1	15.8%
CIN 2	27.8%
CIN 3	48.5%
In situ adenocarcinoma	33.3%
Micro-invasive cervical carcinoma	55.5%

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Elorza G, Rev Esp Enferm Dig 2016

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Int J Colorectal Dis (2014) 29:899–908
DOI 10.1007/s00384-014-1922-y

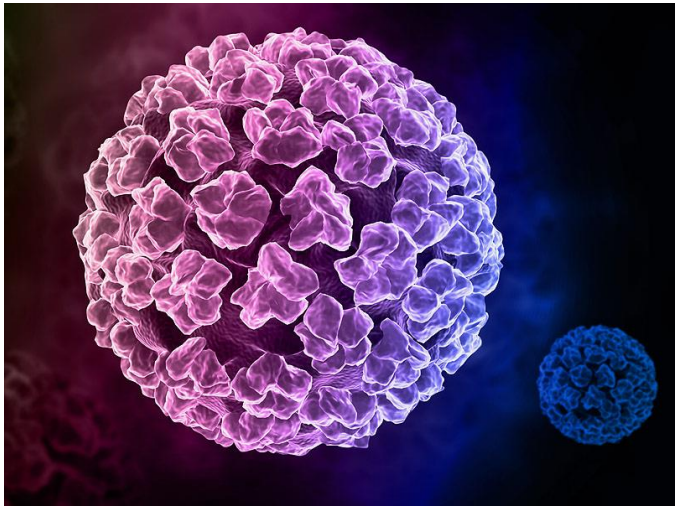
REVIEW

The impact of smoking on HPV infection and the development of anogenital warts

Reto Kaderli · Beat Schnüriger · Lukas E. Brügger

Results In both genders, smoking is associated with higher incidence and prevalence rates for HPV infection, whereas the latter responds to a dose-effect relationship. The overall HPV prevalence for smoking patients was 48.2 versus 37. 5 % for nonsmoking patients ($p<0.001$) (odds ratio (OR)=1.5, 95 % confidence interval (CI) 1.4–1.7). Smoking does also increase persistence rates for high-risk HPV infection, while this correlation is debatable for low-risk HPV. The incidence and recurrence rates of anogenital warts are significantly increased in smokers.

Anal HPV Infection



- >100 subtypes of HPV
- >23 subtypes for infection of anogenital mucosa

  – **Low-risk** subtypes → Condyloma, AIN 1

  ➢ HPV 6, 11, 42-44

  – **High-risk** subtypes → AIN 2-3, invasive cancer

  ➢ HPV 16, 18, 31, 33, 35, 39, 45, 50-53, 55, 56, 58, 59, 68

Zbar AP. Int J Colorectal Dis 2002
IARC Vol. 64. WHO: Lyon 1995
Friedman HB. J Infect Dis 1998

Epidemiology

- Prevalence of anal HPV infection in MSM
  - HIV-: 42-63%
  - HIV+: 80-95%

- Regression of warts common in women after 1 year
  - 60% HIV+
  - 80% HIV-

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Park IU. STD Treatment Guidelines: HPV Updates Clinical Infectious Diseases 2015

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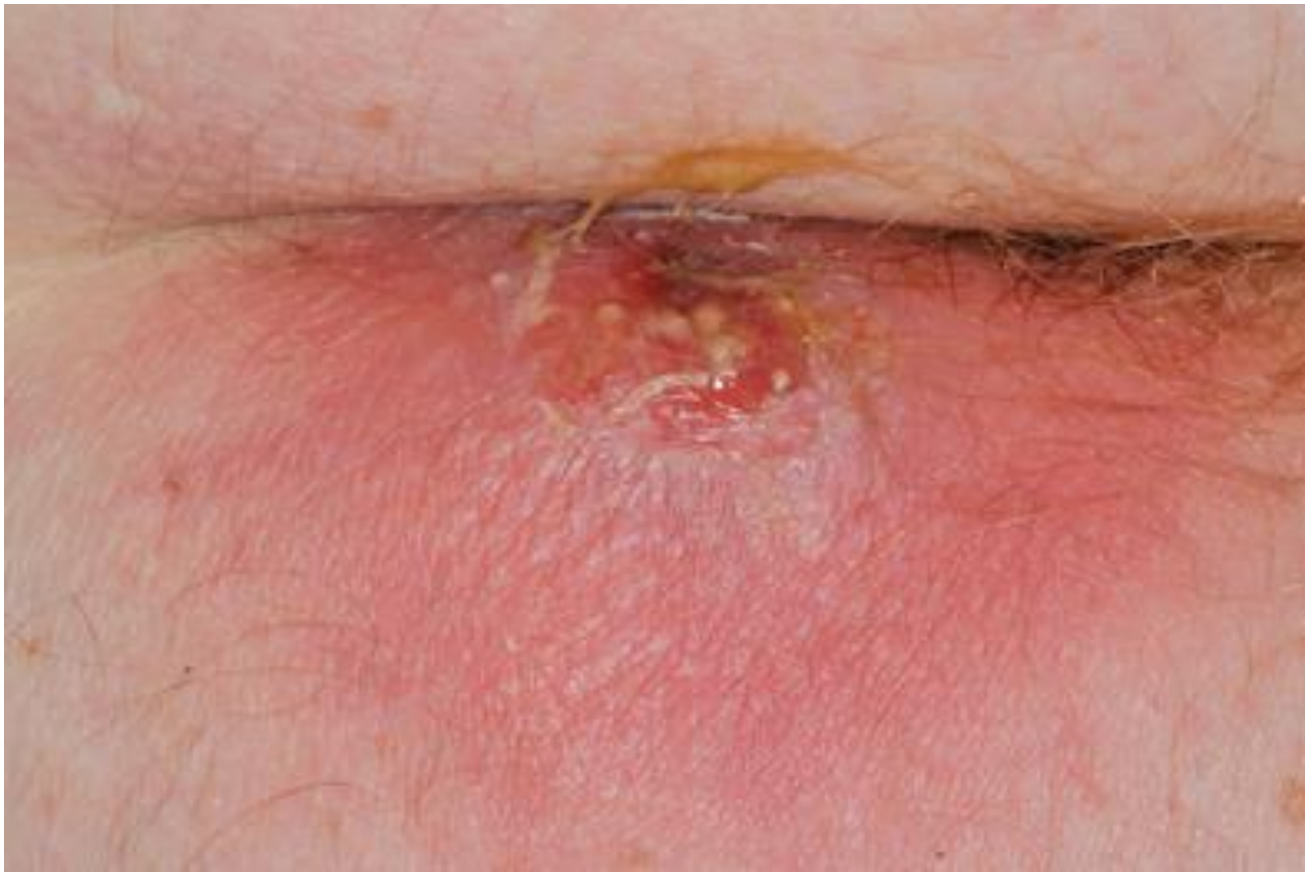
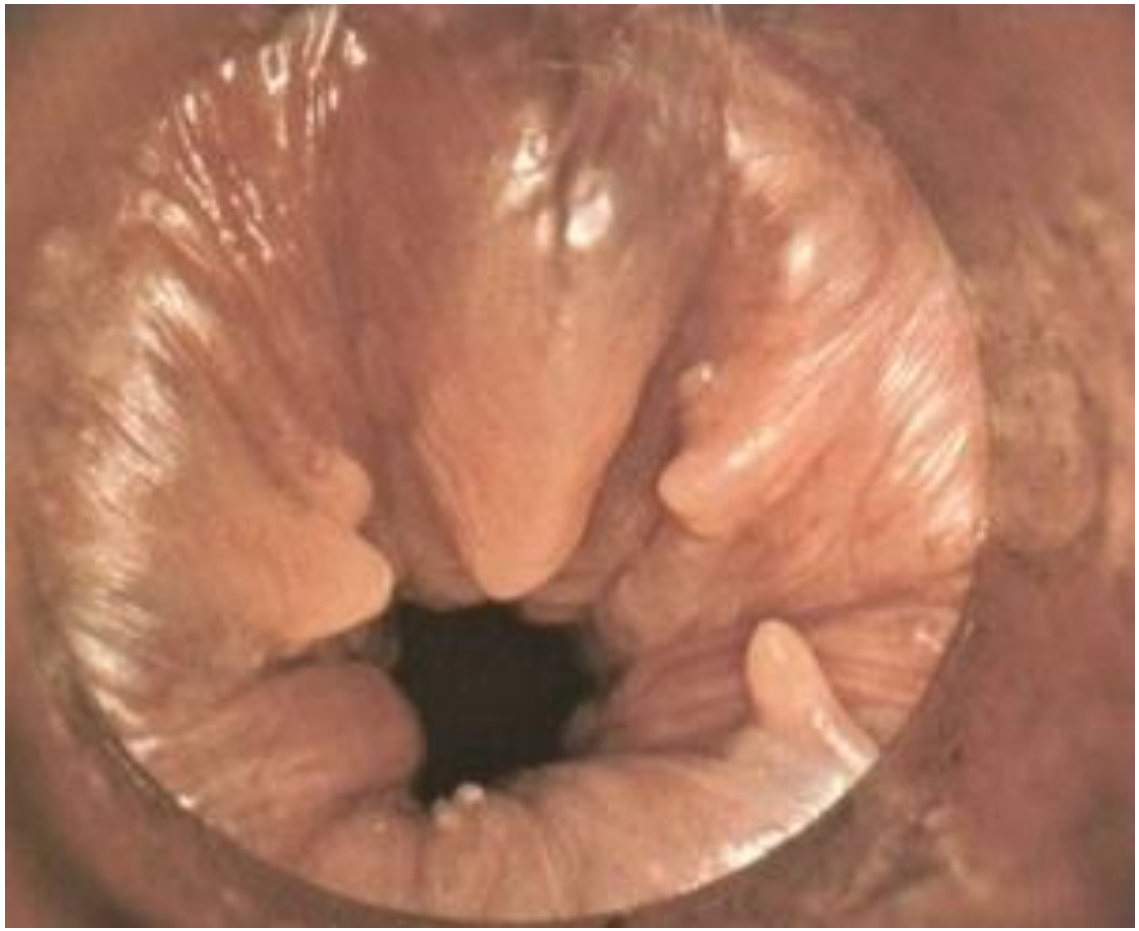


♀, 40 years, No Symptoms



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Hypertrophied Anal Papilla

- Fibroepithelial Polyp
- DD:
  - Adenomatous Polyp (less firm, not white)
    - Colonoscopy
  - Inflammatory Pseudopolyp (IBD)
- Classic triad of chronic fissure
- Should be removed during surgery for fissure?!

Treat when symptomatic!

Anal Skin Tag

- Often remnants of previously thrombosed external hemorrhoids
- Post Surgery (Hemorrhoidectomy)
- Morbus Crohn
- Diabetes, Adipositas
- Fissure triad

Treat when symptomatic!

- Removal in local anaesthesia ± primary closure

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Cancer risk

- Incidence of squamous cell cancer (SCC) in patients with anal condyloma: 3-4%

Metcalf A. Surgery 1995
Byars RW. Am Surg 2001

- 5% High-grade Squamous intraepithelial lesion (HISL) → SCC

Marfing TE. Dis Colon Rectum 1987
Marchesa P. Dis Colon Rectum 1997
Scholefield JH. Lancet 1992

Risk Factors AIN

- Immunosuppression (10-100 fold increase)

  Ogunbiyi O. Br J Surg 1994
  Adami. Br J Cancer 2003

- HIV (especially CD4 < 200/mm$^{3)}$

  Palefsky J. J Aquir Immune Defic Syndr Hum Retrovirol 1998
  Friedman HB. J Infect Dis 1998
  Palefsky J. J Acquir Immune Defic Syndr 1994

- Homosexual men (MSM)

  Critchlow CW. AIDS 1998

- Promiscuity

  Goldstone S. J Infectious Dis 2011

- Cigarette smoking

  Guiliano AR. Lancet 2011

- Not beeing cricumcised

  Albero G. Sex Transm Dis 2012

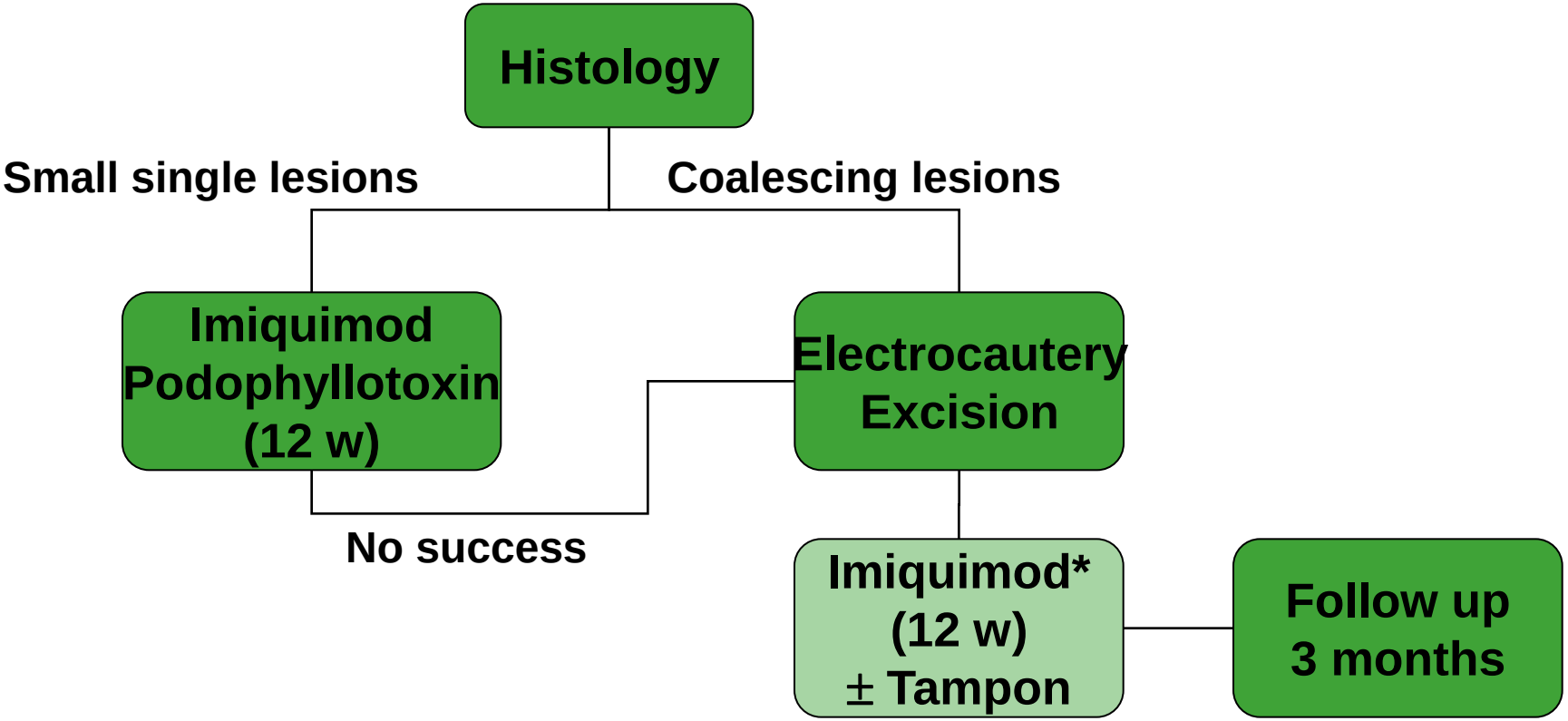
Epidemiology anal SCC (Incidence)

- ♂ 0.7/10^5/y
  (increase 96% last 20y)
- ♀ 0.9/10^5/y
  (increase 39% last 20y)

- MSM 5/10^5/y
- MSM / HIV+ 46/10^5/y (29% HSIL)

Palefsky JM. AIDS 1994
Maggard MA. Dis Colon Rectum 2003
Machalek DA. Lancet Oncol 2012

Algorithm (Condyloma)



*2 weeks after operation

Kaspari M. Br. J Dermatol 2002