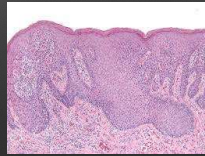


Anal Dysplasia: Diagnosis and Management

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MSMS 2020 Fall Meeting
October 22, 2020



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No Disclosures

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Objectives

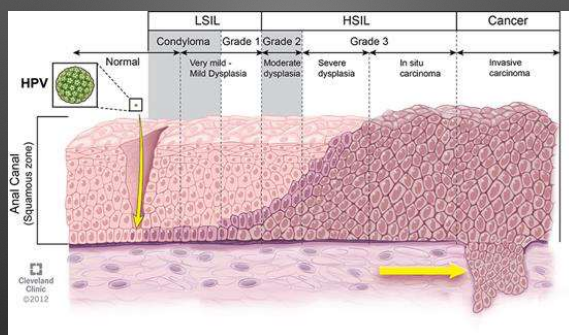
- Review nomenclature for various types of anal dysplasia
- Discuss importance of detecting these precancerous lesions and which populations this may affect most
- Consider how to screen and diagnose AIN lesions, and propose possible algorithm
- Review various treatment modalities that are available
- Discuss vaccination to protect against development of AIN and surveillance strategies once treated

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Nomenclature

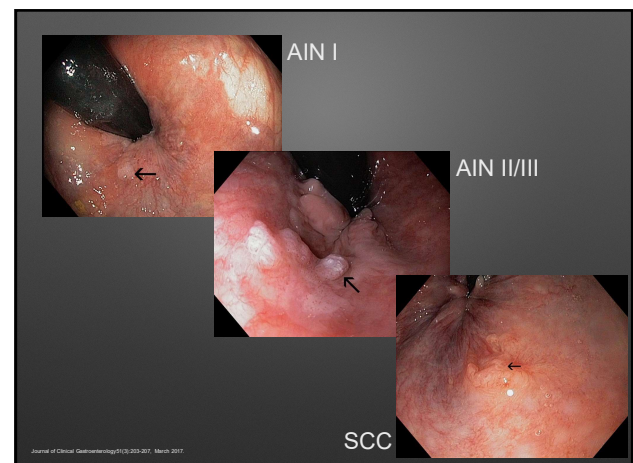
- Anal Intraepithelial Neoplasia (AIN)
- Dysplastic condition of the squamous tissue → premalignant
- Adapted from Bethesda classification for cervical neoplasia (CIN)
- Two-tiered system (adopted by CAP, AJCC, ASCCP and ASCRS)
 - AIN I → Low Grade Squamous Intraepithelial Lesion (LSIL)
 - AIN II and III → High Grade Squamous Intraepithelial Lesion (HSIL)
- *Terms no longer used: Bowen's disease, carcinoma in-situ*
- *Do not confuse with:*
 - Verrucous Carcinoma (giant condyloma acuminatum or Buschke-Lowenstein tumor) : locally aggressive
 - Perianal Paget Disease : intraepithelial adenocarcinoma

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From: my.clevelandclinic.org

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Incidence of AIN/SCC

- Increased from 0.7→2 cases/100,000 in recent decades*
- Anal precancerous lesions: highest in ages 40-49; increasing incidence 11%/year
- In US, new cases of anal SCC rose from 3900→5250 in women and 2200→2950 in men between 2012-2017**
- Progression of AIN to SCC
 - LSIL risk of progression to HSIL: 10% of cases in 2 years
 - HSIL risk: 9-13% conversion if untreated
 - HIV population: 1.2% at 12 months, 2.6% at 24 months, 3.7% at 36 months and 5.7% at 60 months* for AIN3
 - Spontaneous regression rates HSIL→LSIL of 17%

*Nelson RB, Levine AM, Bernstein L, Smith DD, La LL. Changing patterns of anal cancer in the United States. J Clin Oncol 2013;31 (12): 1500-1505
 **American Cancer Society. <http://www.cancer.org>

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Incidence (cont).

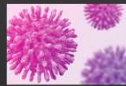
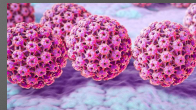
- Immunocompromised patients more susceptible**
 - Series of 138 HIV+ patients with HSIL - 72 pts (52%) developed SCC after an average of 5 years
- Possible decreased rates with proper surveillance and treatment of early lesions
 - Significant variability with screening guidelines, treatment and surveillance
- Watson et al - Observational study of 72 patients with untreated AIN:
 - 8 (11%) progressed to SCC over 8 years
 - 2 out of 10 patients with AIN2 (20%) progressed
 - 6 out of 45 patients with AIN3 (13.3%) progressed
 - AIN grade of 25 of their 72 patients (35%) REGRESSED***

*Aroni V et al. Risk of invasive anal cancer in HIV-infected patients with high-grade anal dysplasia: a population-based cohort study. Clin Gastroenterol Hepatol 2013
 **Chen S, Coombs RW (2005) Elevated progression of anal dysplasia to invasive anal cancer in HIV. Clin Gastroenterol Hepatol 3:45-50
 ***Watson AJ, Smith BB, Witschard SR, Sykes PH, Finkelstein EA. Histologic progression of anal intraepithelial neoplasia. BMJ 2000; 32 (701): 1123-1126

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Risk Factors for Contraction

- High risk sexual behavior (MSM), multiple partners
- Human Papillomavirus (HPV)
 - Presence of multiple subtypes (subtypes 16, 18, 31, 33)
 - Repeated exposures to HPV increases risk
 - DNA virus incorporates into the host, affects epithelial cells
 - Acquired by direct exposure
 - Prevalence of anal HPV: 12%→91% depending on country, gender, sexual orientation***
 - HPV detected in 88-91% of dysplastic lesions****
- Human Immunodeficiency Virus (HIV)
 - Higher prevalence of subtype 16
 - Higher prevalence of LSIL and greater likelihood that this will progress to HSIL
- Smoking
- Woman with presence of CIN3 or vulvar dysplasia (4x)



***Schon van der Laan MF, Meijer GJ, Witte DJ, de Witte NJ, Price AJ (2014) HPV and cancer in HIV-infected individuals: a review. Can J Infect Dis Rep 1(2):200-202
 ****Nelson RB, Pauly DA, Pinsky AJ, Smith BB, Smith DD, Levine AM, Bernstein L, Smith DD, La LL. Changing patterns of anal cancer in the United States. J Clin Oncol 2013;31 (12): 1500-1505

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Screening

- Guidelines for Screening by Infectious Disease Society in America (IDSA) in high risk patients*:
 - HIV+ individuals (especially MSM)
 - Patients with multiple partners
 - Women with prior HPV-related neoplasia
 - History of organ transplantation (immunocompromised)
- Screening recommended for high-risk individuals every 1-3 years

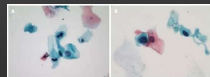


*Bong JA, Gallant JE, Charney KD, Ertterman P, Zingoni BS, Homburg MA. Infectious Diseases Society of America. Primary Care guidelines for the management of persons infected with HIV 2015 issued by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2014; 58 (5): 1-10

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Anal Pap Smear

- Anal Papanicolaou (pap) Smear (modeled after cervical screening)
 - Moistened swab to the anal transition zone
 - Office based procedure, CPT Q0091
 - Low specificity, suboptimal correlation with biopsy
 - Not shown to improve survival
 - Sensitivity (in MSM, HIV-) = 47-90%, specificity 16-92%*
 - Combination of HPV testing and cytology in HIV- patients improves sensitivity
 - Sensitivity higher in HIV+ and MSM -> 83%, may have some benefits as a screening tool in this population**
- Compared to HRA, may yield more false positives



Can SF, Winter DC. Perianal condylomas, anal squamous intraepithelial neoplasms and screening: a review of the literature. J Med Screen 2010; 17 (3):144-49
 **Jung J, et al. SPAN Study Team (2018) The performance of anal cytology as a screening test for anal HSIL in homosexual men. Cancer Cytopathol 124(3): 415-424.

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PRACTICE PARAMETERS

Practice Parameters for Anal Squamous Neoplasms

Scott R. Steele, M.D., Madhulika G. Varma, M.D., Genevieve B. Melton, M.D., Howard M. Ross, M.D., Janice F. Rafferty, M.D., W. Donald Buie, M.D., on behalf of the Standards Practice Task Force of the American Society of Colon and Rectal Surgeons

2. Anal Papanicolaou smear cytological examination may be useful in the detection and follow-up of LGAIN/HGAIN. Grade of Recommendation: Strong recommendation based on low-quality evidence, IC.

DISEASES OF THE COLON & RECTUM VOLUME 55: 7 (2012)

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Diagnosis

- Typically asymptomatic; incidental detection
- Has good prognosis if detected and treated early
- Clinical Exam
 - Detailed history: sexual habits, previous STIs
 - Head-to-toe (include all mucosal membranes and LN basins)
 - Both perianal and genital areas
 - Digital rectal examination
 - If concern, refer to colorectal surgeon for more in-depth evaluation
- Anoscopy
 - Important role in detecting lesions >6mm (no magnification)



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High Resolution Anoscopy (HRA)



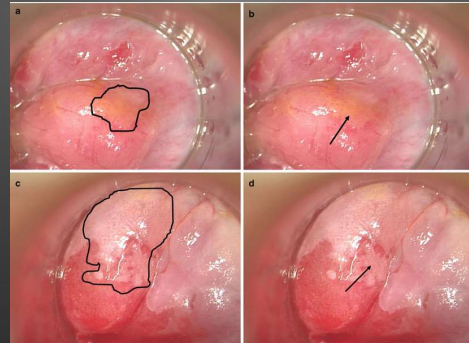
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High Resolution Anoscopy

- Magnified visualization of the distal rectal mucosa, anal mucosa and perianal skin
- Recommend proceeding with HRA if cytology positive (standard of care in some societies)
- Office based procedure, CPT 46607
- Technique:
 - Equipment: Operative microscope, colposcope or Loupes (no specific requirements)
 - First evaluation easiest in the operating room
 - 3-5% acetic acid is applied—> will see whitish change of abnormal tissue
 - Can add Lugol 2% solution (compound absorbed by normal tissue)
 - Absence of colorization after application of Lugol indicative of HPV-induced dysplasia
 - Biopsy and cautery/excision can then be used
- Availability and training of this technique vary
 - HRA competency standards - ?attend a specialized course with proctored cases

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LSIL in distal rectal mucosa



HSIL in distal rectal mucosa

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High Resolution Anoscopy

- Sensitivity and Specificity vary in literature (60-100%)
- Operator-dependent
- Learning curve
- More accurate in high-risk populations
- Crawshaw BP et al* found no difference in progression comparing HRA to expectant management, as long as patient compliant with follow-up
- No data comparing HRA over other methods of biopsy to say one method is superior



Crawshaw BP, Russ AJ, Stein SL, et al. High-resolution anoscopy or expectant management for anal intraepithelial neoplasia for the prevention of anal cancer: is there really a difference? Dis Colon Rectum 2015;58(9):1155-60

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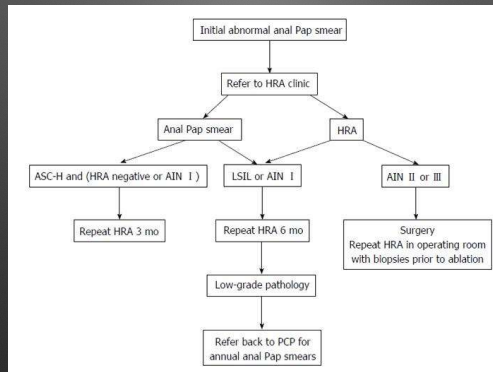
Screening and HRA

- Why has this not been more widely adopted?
 - Not well reimbursed
 - No procedural code (CPT)
 - Need for specialized course/training
 - Reported as a painful procedure
 - ?Lack of data to support that HRA can prevent progression to SCC
- Survey of colon and rectal surgeons through ASCRS
 - 90/1655 responded (18%), most board certified
 - 1/3 had performed anal cytology, 1/3 had performed HRA
 - 46% formally trained, 83% do HRA in the operating room, 82% use acetic acid with magnification
 - More likely to screen: women, more recent graduates, surgeons with HIV-patient population



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Johns Hopkins Algorithm



Leach N, Fang SH. Anal cancer and intraepithelial neoplasia: screening. *A review*. *World J Gastroenterol* 2010; 16(1): 41-51

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Management

- Many specialties involved: dermatologist, CRS, gastroenterologists, gynecologists
- No uniform accepted management guidelines
- "Watchful waiting" – observation alone with close clinical follow-up every 4-6 months
- Can consider with LSIL lesions given low rates of progression
- Increased morbidity associated with excision
- "Expectant management" = Reported clearance up to 80% with < 5% progression to high-grade lesions or invasive cancer on 10-year follow-up*
- Cytology
- High-resolution Anoscopy (HRA)
- Targeted biopsies
- Directed therapies
- HSIL lesions should be treated given their higher transformation risk

*Pindea CE, Berry JM, Jay N, Paley JM, Watson ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. *Dis Colon Rectum* 2008; 51 (05):829-835.

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Treatment -Topical

- Reasonable efficacy, may be good compromise to be used with "watch and wait" strategy
- **5% Imiquimod cream (Aldara)**
 - Immunomodulator - activates immune system to promote regression
 - Administered 3x/week for up to 16 weeks
 - Applied to perianal skin at night, then washes off in the AM
 - Lesion clearance of 80%
 - Side effects: burning and erosion, potential stenosis
 - Double-blind, randomized controlled trial of 53 HIV+ MSM
 - 28 pts in experimental group → 43 resolution or down-grading of their lesion
 - 61% responders achieved sustained response at 36 months*
- **5% 5-fluorouracil (5-FU)**
 - Pyrimidine analogue which inhibits DNA synthesis
 - Treatment of actinic keratosis, Bowen disease and superficial basal cell carcinoma
 - Administer twice weekly for a total of 16 weeks
 - Inferior to electrocautery to downgrade lesions
 - Less side effects, hypopigmentation



*Thompson R et al. Imiquimod for anal and anal intraepithelial neoplasia (abstract). *Colorectal Disease*. Sept 12, 2004.

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Treatment -Topical

- Cidofovir 1%
 - Acyclic nucleoside phosphonate with broad spectrum antiviral activity
 - Not as much follow-up with this, usually used in combination with surgery
- Trichloroacetic Acid (TCA) 85%
 - Recommended by CDC as first-line treatment of anogenital warts
 - Apply repeatedly to lesion until lesion turns a dense white color
 - AIN 2/3 lesions - study with 28 patients: 65% resolved completely, 29% down-graded to AIN 1**
 - Treatment more effective in younger and HIV+ patients
- Low cost, easy to use, safe



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Treatment - Ablative

- Initial response rates vary from 30-70%, however high recurrence rate
- HRA should be repeated every 3-4 months after treatment
- Methods:
 - **Electrocautery** best for intra-canal lesions
 - Compared to topical, higher rate of complete response
 - **CO2 Laser**
 - Low penetration depth of CO2+ no scarring with targeted destruction
 - Cure rates of 63%
 - **Infrared Coagulation (IRC)**
 - During HRA, lesion infiltrated with lidocaine, treated and debrided until reaching the submucosal vessels
 - Sierra et al report 87.5% (49/56 patients) resolution at mean follow-up of 25 months (12.5% recurrence at a year)*
 - **Photodynamic Therapy**
 - 5-aminolevulinic acid cream followed by treatment with nano-wave length laser (small case reports)
 - Can be painful and requires multiple treatments



*Sierra G et al. Long-term effectiveness of infrared coagulation for the treatment of anal intraepithelial neoplasia grades 2 and 3 in HIV-infected men and women. *AIDS* 2010; 24(10): 2705-2710

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Treatment - Wide Local Excision (WLE)

- Performed using multiple punch biopsies and analyzing frozen sections
- Negative margins (usually 1cm)
- Hard to tell if complete excision if extensive lesion, leading to high recurrence rates
- Can leave large defects; may need grafts or flaps
- Risks: anal stenosis, incontinence
- Watson et al. reported in 72 patients:
 - 55 HSIL (30% immunocompromised)- 11% progression to malignancy despite WLE
 - 9 developed fecal incontinence with 4 needing colostomy*
- Recurrence rates very high (9-90%) depending on risk factors
- Conclusion: Only consider in well-demarcated lesions occupying less than 1/3 circumference

*Watson AJ, Smith BB, Whithead MS, Spies PH, Fritzsche FA. Malignant progression of anal intraepithelial neoplasia. *BMJ* 2000; 320(7238): 1132-1136

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Vaccination



- Since 2006, two vaccines available targeting HPV 16 and 18:
 - Cervarix™ - bivalent
 - Gardasil™ - quadrivalent (qHPV); also targets 6 and 11
 - Gardasil 9 - multivalent vaccine developed in 2014 to include more subtypes
- DNA-free, virus-like particles (VLP); not infectious or oncologic
- Proven to protect against AIN and development of SCC
 - Could prevent 75.4% AIN2/3 lesions and 84.3% anal cancers*

*Armstrong L, et al. HPV VLPF Study Group (2015) Human papillomavirus DNA prevalence and type distribution in anal carcinoma worldwide. *Int J Cancer* 138(1): 98-107

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Vaccination



- Recommendations:
 - CDC: for children at age 11 up to age 26
 - Ideally prior to the onset of sexual activity
 - Advisory Committee on Immunization Practices (ACIP) for at-risk populations
- Prevention of recurrent premalignant anal lesions?
 - No effect on active dysplasia or HPV infection
 - May prevent recurrent high-grade AIN post-treatment**

**Santibañez VA, Factor SM, Goldstone SE (2012) Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men with men: a retrospective cohort study. *Clin Infect Dis* 54:891-898

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Surveillance



- No common consensus or guidelines
- After treatment, patient should be still considered high-risk
- Proposed surveillance: DRE, HRA and/or brush cytology
 - Q4 months in the first 3 years
 - Q6 months in the following 2 years
 - Annual exam if no lesions detected
 - Brush cytology Q1 year
 - HRA Q2-3 years



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Surveillance after SCC treatment

ORIGINAL CONTRIBUTION

High-Resolution Anoscopy Surveillance After Anal Squamous Cell Carcinoma: High-Grade Squamous Intraepithelial Lesion Detection and Treatment May Influence Local Recurrence

Caroline Caporaso, M.D.^{1,2} • Tamara Canning, F.R.C.S.¹ • Julie Bowring, M.B.Ch.B.¹
Adam N. Rosenthal, Ph.D.^{1,2} • Noreen Chindawi, B.Sc.¹ • Mayara Nathan, M.B.B.S., F.R.C.P.¹

¹ Department of Colorectal Surgery, St. James's University Hospital, Leeds, United Kingdom

² University College London Hospital, London, United Kingdom

See "Editorial" on page 1345.

BACKGROUND: Local recurrence is a significant risk after anal squamous cell carcinoma.

OBJECTIVE: This study aimed to examine the occurrence of high-grade squamous intraepithelial lesions and local recurrence after anal cancer at surveillance with high-resolution anoscopy.

DESIGN: Cohort study of patients with anal cancer.

PATIENTS: There were 76 anal/perianal cancers from 1998 to 2014. Sixty-three patients were eligible and 3 were excluded, for a total of 60 patients; 35 of 60 (58%) patients were male.

INTERVENTION: High-resolution anoscopy after chemoradiation or excision only for anal squamous cell carcinoma was performed.

MEASUREMENTS: The primary outcomes measured were local recurrence and high-grade

Methods

- 60 anal/perianal cancers over 10-year period (27% HRA)
- HRA after chemoradiation (57%) or excision only (43%) performed
- Surveillance over a median of 42 month follow-up

Results

- HGSL detected
 - Chemoradiation group – 13% (4 of 30), with one local recurrence of SCC
 - Excision only group – 74% (17 of 23)
- 95% of recurrent lesions then treated with ablation

Conclusions

- HGSL more common after excision-only treatment
- Local recurrence is low in this HRA surveillance group treated with ablation

Dissecta of the Colon and Rectum, vol 63 (10) (1003-1071), 2020

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Questions?



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