Simple and Potentially Life Saving, Exfoliative Anal Cytology

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Disclosures for Dr. Sturgis

Consultant & Trainer for Ventana (PDL-1 IHC) 2015
Consultant for Philips (Pivotal Study – Digital Imaging) 2016

(No conflicts of interest with this teleconference).
Gross and micro-anatomic refresher and updates
Bethesda update and key references
Cytomorphologic tips
Biomarkers / adjunctive tests
Faces of anal cancer
Historical perspectives
Epidemiology and social - sexual demographics
Symptoms of anal HPV infection
Guidelines / recommendations for who should be screened
Management
ANCHOR and SPANC trials ongoing
Summary with emphasis on HPV vaccination.
The anal SCJ is nearly always “internal” within the anal canal and as with cervical disease is also generally the site of origin for high grade dysplasias and carcinomas.
Would it not make sense to think of all warts in the anogenital region as one disease process?

They are all caused by the same strains of the same DNA virus – HPV.
Genital Human Papillomavirus Infection in Men.

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Penile Condyloma
Fitzpatrick’s Dermatology in General Medicine

http://dermatlas.med.jhmi.edu/image/Genital_warts_2_040606
The **Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology**

Archives of Pathology and Laboratory Medicine Volume 136, Issue 10 (October 2012)

T Darragh; T Colgan; J Cox; D Heller; M Henry; R Luff; TMcCalmont; R Nayar; J Palefsky; M Stoler; E Wilkinson; R Zaino; D Wilbur; For members of the LAST Project Working Groups

**Abstract**

The terminology for human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract has a long history marked by disparate diagnostic terms derived from multiple specialties. It often does not reflect current knowledge of HPV biology and pathogenesis. A consensus process was convened to recommend terminology unified across lower anogenital sites. The goal was to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties. The Lower Anogenital Squamous Terminology (LAST) Project was cosponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology and included 5 working groups; 3 work groups performed comprehensive literature reviews and developed draft recommendations. Another work group provided the historical background and the fifth will continue to foster implementation of the LAST recommendations. After an open comment period, the draft recommendations were presented at a consensus conference attended by LAST work group members, advisors, and representatives from 35 stakeholder organizations including professional societies and government agencies. Recommendations were finalized and voted on at the consensus meeting. The final, approved recommendations standardize biologically relevant histopathologic terminology for HPV-associated squamous intraepithelial lesions and superficially invasive squamous carcinomas across all lower anogenital tract sites and detail the appropriate use of specific biomarkers to clarify histologic interpretations and enhance diagnostic accuracy. A plan for disseminating and monitoring recommendation implementation in the practicing community was also developed. The implemented recommendations will facilitate communication between pathologists and their clinical colleagues and improve accuracy of histologic diagnosis with the ultimate goal of providing optimal patient care.
The similarity of morphology between LAT sites and between sexes is shown. Each is an example of a precancerous HSIL. If reviewed without knowledge of biopsy site or sex of the patient, they would be impossible to distinguish from one another. A, CIN 3 (female); B, AIN 3 (female); C, AIN 3 (male); D, PeIN 3 (male).
A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.

The recommended terminology for HPV-associated squamous lesions of the LAT is:

*low-grade squamous intraepithelial lesion (LSIL)* and *high-grade squamous intraepithelial lesion (HSIL)*

These may be further classified by the applicable –IN subcategorization. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3.)

Concern was expressed that using the same terminology for cytology and histomorphology would not allow for distinction as to whether the diagnosis was associated with a cytologic or histologic specimen. On a written pathology report, the specimen type is clearly stated, so this confusion is minimized. However, in short-hand verbal communication, it may be important to designate reports as associated with cytology or histology specimens. The option of adding the specific –IN terminology with the basic 2-tiered classification would also help to identify these samples as histopathology.
Cervix.—It is thought that all SCCs of the cervix are attributable to HPV. There are abundant data that early invasive squamous carcinoma (SCC) of the cervix can safely be treated conservatively. Historically, a variety of terms, including microinvasive carcinoma, have been used to label this group. Criteria for defining patients amenable to conservative management have changed over the years.

Vagina.—Vaginal cancers are rare. Approximately 40% to 60% of SCCs of the vagina are attributable to HPV. In addition, vaginal squamous carcinomas are, in general, not amenable to local resection.

Vulva.—Approximately 40% to 50% of SCCs of the vulva are attributable to HPV.

Penis.—Cancers of the penis are rare in the United States. Approximately 40% of SCCs of the penis are attributable to HPV.

Anal Canal.—Approximately 90% to 93% of anal canal SCC is attributable to HPV. Historically, abdominoperineal resection was the primary management for anal canal cancer. In the 1980s, primary surgical therapy was supplanted by combined modality therapy which has achieved superior survival rates and reduced recurrence rates while preserving the anal sphincter.

Perianus.—The proportion of SCC of the perianus attributable to HPV are different between women and men, with 80% of female and 29% of male perianal cancers associated with HPV. The perianus is currently defined as the region extending 5 cm from the anal opening or verge. This region overlaps anatomically with the vulvar perineum.

The LAST Standardization Project for HPV Associated Lesions Consensus Recommendations
This study thus reveals two fundamental differences between the anus and the cervix:
(1) the anal transition zone does not harbor a single monolayer of residual undifferentiated embryonic cells
(2) the dominant tumor immunophenotype is in keeping with an origin in metaplastic (CK7-negative) squamous rather than squamocolumnar junction (CK7-positive) epithelium. The implication is that, at birth, the embryonic cells in the anal transition zone have already begun to differentiate, presenting a metaplasia that—similar to vaginal and vulvar epithelium—is less prone to HPV-directed carcinogenesis. This in turn underscores the link between cancer risk and a very small and discrete population of vulnerable squamocolumnar junction cells in the cervix.
Anal cytology first included in 2001 Bethesda System
Updated in the 2015 publication.

Anal squamous carcinomas are uncommon malignancies.
>90% attributable to persistent HPV infections.
HPV 16 most predominant viral type.

ACS 2014 statistics: 7,210 new case in US and 950 deaths
M:F = 1:1.8

Incidence increasing over last several decades,
Especially in “high risk groups” including:
MSM
Persons with HIV (both men and women)
Organ transplant recipients
Women with histories of lower genital tract SIL.

Incidence of anal carcinoma in HIV infected men 30X higher than for general population.
N = 126 MSM from San Francisco, USA
87% White
Median age: 44 years (24-73)
### Screening HIV-Infected Individuals for Anal Cancer Precursor Lesions: A Systematic Review

Chiao, Giordano, Palefsky, Tyring, El Serag  
(A meta-analysis from authors at Baylor, UT Houston, and UCSF).

#### Table: Cytological Examination Data

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of subjects</th>
<th>Liquid cytological examination or conventional histological examination</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palefsky et al. [32]</td>
<td>1997</td>
<td>407</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>69</td>
<td>59</td>
</tr>
<tr>
<td>Lee et al. [34]</td>
<td>2004</td>
<td>192</td>
<td>Not stated</td>
<td>95</td>
<td>Not stated</td>
</tr>
<tr>
<td>Matthews et al. [33]</td>
<td>2004</td>
<td>154</td>
<td>Conventional</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>Panther et al. [35]</td>
<td>2004</td>
<td>153</td>
<td>Not stated</td>
<td>93</td>
<td>33</td>
</tr>
<tr>
<td>Fox et al. [36]</td>
<td>2005</td>
<td>99</td>
<td>Conventional</td>
<td>83</td>
<td>38</td>
</tr>
<tr>
<td>Salit et al. [37]</td>
<td>2005</td>
<td>246</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>84</td>
<td>32</td>
</tr>
<tr>
<td>Arain et al. [30]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2005</td>
<td>200</td>
<td>Liquid (SurePath; Medical Solutions)</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Papaconstantinou et al. [31]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2005</td>
<td>37&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>42</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only patients with abnormal Pap smear results underwent high-resolution anoscopy and biopsy; therefore, sensitivity and specificity may be biased.

<sup>b</sup> Did not include atypical squamous cells of uncertain significance in definition of abnormal Pap smear.

<sup>c</sup> All patients had condyoma.

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**Anal Pap sensitivity:** ranges from 69 to 93%  
**Anal Pap specificity:** ranges from 32 to 59%

Sensitivity and specificity of a single anal cytology test are similar to those for a single cervical cytology test.
Sampling

Target: entire anal canal from the rectal vault to the anal verge

Samples usually obtained without direct visualization of anal canal. Some reports of using small anoscope to introduce collection device.

Both conventional smears and liquid-based preparations can be used. Liquid-based preparations may reduce compromising factors such as obscuring fecal material, air-drying and mechanical artifacts.
Obtaining Specimens for Anal Cytology:

Obtaining an adequate anal cytology specimen involves the following steps:
1. **Moisten a Dacron swab with water. It is important to use a Dacron swab, not a cotton swab, because cells cling to cotton swabs.**
2. **Insert the swab 4 to 5 cm (2 inches) (the length of the patient’s 5th finger) into the anal canal and proceed through the dentate line and transitional zone between the squamous and columnar epithelia.**
3. **Rotate the swab firmly with lateral pressure while slowly inserting and withdrawing in a tight spiral motion for 15 to 20 seconds.**
4. **Place the swab in liquid-based medium (ThinPrep CytoLyt solution) and swish the swab vigorously for 15 to 20 seconds.**
5. **Dispose of the swab; cap and label the specimen jar.**

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Anal cancer and Screening Guidelines for Human Papillomavirus in Men

Ortoski JR DO and Kell CS PhD, J Am Osteopath Assoc, March 2011 111:S35

From the Departments of Family Medicine and Microbiology, Lake Erie College of Osteopathic Medicine, Erie, Pennsylvania.
Adequacy

Usual Epithelial Cell Types:
- Anucleated squamous cells (distal anal canal).
- Superficial squamous cells.
- Intermediate squamous cells.
- Squamous metaplastic cells.
- Rectal columnar cells.

Rectal columnar cells / squamous metaplastic cells should be reported as a quality indicator, not a measure of overall specimen adequacy.

NILMs lacking transformation zone cells are more likely to be false negatives.

Minimum cellularity for adequacy: 2,000 to 3,000 nucleated squamous cells.
- 1-2 NSC per HPF for ThinPrep
- 3-6 NSC per HPF for SurePath

Samples obscured by fecal material or bacteria may be unsatisfactory.
Terminology, morphologic criteria, and guidelines for the evaluation of anal cytologic specimens parallel those for cervical cytology.

Bethesda terminology is used to report anal cytology and includes a cytologic interpretation and a statement of specimen adequacy.

The Bethesda System is modified to reflect the particulars of the body site (example: rectal columnar cells are substituted for endocervical cells as a measure of transformation zone sampling).
Bethesda Terminology

**Atypical Squamous Cells:**
- ASC-US (undetermined significance), morphologic differential LGSIL, approx 10% CIN II or greater on bx.
- ASC-H (cannot exclude HSIL), morphologic differential HGSIL, 30 to 40% CIN II or greater on bx.
- DOES NOT REPRESENT A SINGLE BIOLOGIC ENTITY.

**Epithelial Cell Abnormality, Squamous:**
- LSIL (low grade squamous intraepithelial lesion), correlates to HPV change and CIN 1.
- HSIL (high grade squamous intraepithelial lesion), correlates to CIN 2 and CIN 3.
- Squamous carcinoma.
Cytomorphologic Tips

NILM:
Reactive keratotic changes (hyperkeratosis and usual parakeratosis) common.
Reactive tight perinuclear halos and small nucleoli common.
Repair changes less common than in cervicovaginal cytology.

ASC:
Degenerative nuclear karyorrhexis more common in anal than cervical cytology.
Cytoplasmic orangeophilia more common in anal than cervical cytology.

SIL:
The presence of mixture of both LSIL and HSIL cells is more common in anal than cervical cytology.

Carcinoma:
Tumor diathesis may be less prominent in anal cytology than cervical cytology and may be difficult to distinguish from fecal material.
45M, NILM, HIV+, Anal HR HPV+
Unsatisfactory, obscuring fecal material
Conventional preparation
NCI Bethesda System Web Atlas
Histopathologic and Cytologic Follow-Up in High Risk Males with Unsat Anal Cytology
JASC, Vol4, Iss6, Nov/Dec 2015
Platform presentation at ASC 2015, Chicago
Zaccarini & Khurana
SUNY Upstate, Syracuse, NY

143 Unsat Anal Cyto Patients
57% of patients had AIN on Bx
(39% AIN1 & 18% AIN2/3)
Histopathologic, Cytologic and Molecular Follow up on Unsatisfactory Anal Cytology Cases – Collaboration with Ruba Khattab, M.D.

- Total anal cytology cases: 1276 (2001 - 2015)
- Total unsatisfactory cases: 130 (10%)
- 111 males, 19 females
- 130 cases represent 115 patients as 13 patients had 2 unsatisfactory cases each and one patient had 3 unsatisfactory cases.
- Clinical history:
  - HIV positive (100/130 = 77%)
  - Anal / perianal condylomas
  - Cervix dysplasia & anal condyloma
  - Genital herpes
  - VIN 3
  - Chrons disease
Histopathologic, Cytologic and Molecular Followup on Unsatisfactory Anal Cytology Cases

- Cotested: 116/130 (89%), 82 with HIV.
- Of those cotested, 40 (34%) HPV DNA +.
- 49 (42%) were HPV DNA + within one year.
- 26 of the 130 (20%) cases had a follow up of ASC or SIL within 2 years.
- 8 cases (6 %) had biopsy proven AIN-II or above within 2 years.
Conclusions

- 34% of cytomorphologically unsatisfactory samples are positive by HPV DNA testing, resulting in triage in our center.

- There is value in performing both tests (cytology and HPV DNA).

- Cost benefit analysis: not performed

- Patients with unsatisfactory anal pap smears are at risk of epithelial cell abnormalities.
Anal human papillomavirus (HPV) infections are common, and the incidence of anal cancer is high in HIV-infected men who have sex with men (MSM). To evaluate the performance of HPV assays in anal samples, we compared the cobas HPV test (cobas) to the Roche Linear Array HPV genotyping assay (LA) and cytology in HIV-infected MSM. Cytology and cobas and LA HPV testing were conducted for 342 subjects. We calculated agreement between the HPV assays and the clinical performance of HPV testing and HPV genotyping alone and in combination with anal cytology. We observed high agreement between cobas and LA, with cobas more likely than LA to show positive results for HPV16, HPV18, and other carcinogenic types. Specimens testing positive in cobas but not in LA were more likely to be positive for other markers of HPV-related disease compared to those testing negative in both assays, suggesting that at least some of these were true positives for HPV. Cobas and LA showed high sensitivities but low specificities for the detection of anal intraepithelial neoplasia grade 2/3 (AIN2/3) in this population (100% sensitivity and 26% specificity for cobas versus 84% sensitivity and 28.9% specificity for LA). A combination of anal cytology and HPV genotyping provided the highest accuracy for detecting anal precancer. A higher HPV load was associated with a higher risk of AIN2/3 with HPV16 ($P_{\text{trend}} < 0.001$), HPV18 ($P_{\text{trend}} = 0.07$), and other carcinogenic types ($P_{\text{trend}} < 0.001$). We demonstrate that cobas can be used for HPV detection in anal cytology specimens. Additional tests are necessary to identify men at the highest risk of anal cancer among those infected with high-risk HPV.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity AIN2/3</th>
<th>Specificity AIN2/3</th>
<th>PPV AIN2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobas</td>
<td>100%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>LBC</td>
<td>84%</td>
<td>52%</td>
<td>29%</td>
</tr>
<tr>
<td>LBC</td>
<td>40%</td>
<td>87%</td>
<td>43%</td>
</tr>
</tbody>
</table>

(ASC-US and above cut point) (HSIL cut point)
52M, NILM (HK), HIV+,
Rectal glandular component, helping to ensure specimen quality, but not “adequacy”.
BACKGROUND: In a cytology-based screening program intended to prevent anal cancer, the anal transformation zone (TZ) should be adequately sampled because it is the site most susceptible to the development of the cancer precursor, high-grade squamous intraepithelial lesion (HSIL). An adequate TZ component is defined as comprising at least 10 rectal columnar or squamous metaplastic cells. In the current study, the authors examined whether the presence of a TZ component in anal cytology correlated with the detection of histological HSIL.

METHODS: In a natural history study of anal human papillomavirus infection in homosexual men, all participants underwent liquid-based cytology and high-resolution anoscopy (HRA) with or without biopsy at each visit. True-negative cytology (negative cytology with non-HSIL biopsy or negative HRA), false-negative cytology (negative cytology with HSIL biopsy), and true-positive cytology (abnormal cytology with HSIL biopsy) were compared with regard to the presence or absence of a TZ component.

RESULTS: Of 617 participants, baseline results included 155 true-positive results, 191 true-negative results, and 31 false-negative results. The absence of an adequate TZ component was found to be significantly higher for false-negative (32.3%) than for either true-positive (11.0%; P < .0034) or true-negative (13.1%; P < .0089) results.

CONCLUSIONS: Significantly more false-negative cases lacked a TZ component compared with either true-positive or true-negative cases. TZ cells may be an important indicator of sample quality for anal cytology because, unlike cervical sampling, the anal canal is not visualized during cytology sampling.

Anal HSIL
Invasive squamous carcinoma

Squamous carcinoma
Background: The ThinPrep Imaging System (TIS) is an accurate time-saving method of reading cervical ThinPrep slides in screening programs. As anal and cervical cytology are morphologically similar, TIS can potentially be used for anal cytology. We assessed the performance of TIS on anal ThinPrep slides from homosexual men in a natural history study of human papillomavirus-related anal abnormalities.

Methods: Four hundred nineteen anal cytology slides were processed by TIS and classified by a cytologist as either No further review (slide archived) or Manual review (slide requiring full manual screen). The results were compared with the original manual screening report for all slides and specifically for those screening episodes accompanied by a high-grade squamous intraepithelial lesion (HSIL) on concurrent biopsy.

Results: One hundred seventy six of 419 (42.0%) slides were classified as No further review, with a trend of decreasing proportions as the degree of severity of the cytological abnormality increased. Thirteen (27.7%) slides with an original unsatisfactory report were classified as No further review. Eighty two (92.1%) of those with biopsy HSIL and cytological abnormality were classified for Manual review, including all 45 (100%) with cytological HSIL.

Conclusion: The cervical algorithm of TIS performed best on anal samples when HSIL was present both cytologically and histologically. The 27.7% unsatisfactory slides classified as No further review may indicate need for use of different criteria from cervical cytology. Because of the high prevalence of abnormalities, and hence the large proportion of slides needing manual review, the cytologist time-saving would compare unfavorably with use of TIS in cervical screening.


Anal: manual review rate + rejected rate: 60%.
Cervical: manual review rate + rejected rate: 16%.
Faces of Anal Cancer

Gwen Welles
Star of Robert Altman’s hit film *Nashville*, 1975
Died of anal cancer at age 42 in 1993.

Farrah Fawcett
Star of Television’s *Charlie’s Angels*, 1976-1980
Died of anal cancer at age 62 in 2009.
In the 1940s, cervical cancer was the #1 cause of cancer death for American women.

Between 1955 and 1992, the incidence of cervical cancer in the United States decreased by 74%.

Today, carcinoma of the uterine cervix ranks 14th in frequency in American women.
## Historical Perspectives

<table>
<thead>
<tr>
<th>Women's Cancers, Cancer Estimates (US)</th>
<th>Estimated 2007 Incidence</th>
<th>Estimated 2007 Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Sites</strong></td>
<td>678,060</td>
<td>270,100</td>
</tr>
<tr>
<td><strong>Cancers:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>178,480</td>
<td>40,460</td>
</tr>
<tr>
<td>Colorectal</td>
<td>74,630</td>
<td>26,180</td>
</tr>
<tr>
<td>Ovarian</td>
<td>22,430</td>
<td>15,280</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>26,030</td>
<td>2,890</td>
</tr>
<tr>
<td>Cervical</td>
<td>11,150</td>
<td>3,670</td>
</tr>
</tbody>
</table>

Dr. Papanicolaou’s simple test has saved countless lives, and the medical community has done a wonderful job, but people still die from this “preventable” disease.
FUTURE Perspectives

Might ALL or nearly all anal cancers also be “preventable”? 
Epidemiology of Anal Cancers: Incidence trends are increasing in both men and women.

**TABLE 1**
Rates of Invasive and In Situ Anal Carcinoma Incidence Reported to the Surveillance, Epidemiology, and End Results Program, 1973–2000, Overall and According to Tumor Behavior and Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Overall</th>
<th>In situ</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1979</td>
<td>1.06 (390)</td>
<td>0.09 (34)</td>
<td>0.97 (356)</td>
</tr>
<tr>
<td>1980–1986</td>
<td>1.26 (530)</td>
<td>0.13 (60)</td>
<td>1.12 (470)</td>
</tr>
<tr>
<td>1987–1993</td>
<td>1.60 (792)</td>
<td>0.24 (139)</td>
<td>1.36 (653)</td>
</tr>
<tr>
<td>1994–2000</td>
<td>2.04 (1176)</td>
<td>0.45 (291)</td>
<td>1.59 (885)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1979</td>
<td>1.39 (637)</td>
<td>0.12 (52)</td>
<td>1.27 (585)</td>
</tr>
<tr>
<td>1980–1986</td>
<td>1.69 (900)</td>
<td>0.13 (67)</td>
<td>1.56 (833)</td>
</tr>
<tr>
<td>1987–1993</td>
<td>1.84 (1109)</td>
<td>0.14 (81)</td>
<td>1.70 (1028)</td>
</tr>
<tr>
<td>1994–2000</td>
<td>2.06 (1369)</td>
<td>0.22 (143)</td>
<td>1.84 (1226)</td>
</tr>
</tbody>
</table>
In Washington, average age for anal cancer is about 10 years older than average age for cervical cancer.

Keep in mind: Cervix “screened” Anus not “screened”

Also keep in mind: Vaccination may impact future generations.
Majority of anal cancer patients are female. (approximately 2-3:1)
It is possible to implement and then maintain anal cytology screening programs in small non-academic medical centers by collaborating with an interested clinical colleague and building a referral network with a regional follow up center.
How many sexually active American women between the ages of 20 and 40 engage in anal intercourse?

I asked this question of several female coworkers including physicians, nurses, technologist, and lab clerical staff.

Responses ranged from 5% to 60%.

The real answer is...
20 - 25% of sexually active American women between 20 & 40 years of age have engaged in receptive penile – anal intercourse in the last year.
Symptoms of Anal/Perianal HPV Infection:

Most people asymptomatic!

A lump near the anus
Itching or discharge from the anus

Bleeding from the anus or rectum
Pain or pressure in the area around the anus

Unfortunately, detectable symptoms are often not present until the lesion is invasive or even metastatic...
HPV-Mediated Carcinogenesis

Episomes are closed circular DNA molecules.

The guidelines are intended for use by healthcare providers who care for HIV-infected patients. Since 2009, new antiretroviral drugs and classes have become available, and the prognosis of persons with HIV infection continues to improve. However, with fewer complications and increased survival, HIV-infected persons are increasingly developing health problems that also affect the general population. Some of these conditions may be related to HIV infection itself or its treatment. HIV-infected persons should be managed and monitored for all relevant age- and sex-specific health problems. New information based on publications from the period 2009–2013 has been incorporated into this document.

**Recommendation**

HIV-infected men and women with human papillomavirus (HPV) infection are at increased risk for anal dysplasia and cancer. MSM, women with a history of receptive anal intercourse or abnormal cervical Pap test results, and all HIV-infected persons with genital warts should have anal Pap tests (*moderate quality evidence*).
Human papillomavirus (HPV), the primary cause of cervical cancer, is also associated with the development of anal cancer. Relatively little is known about the epidemiology of anal HPV infection among healthy females and its relationship to cervical infection. We sought to characterize anal HPV infection in a cohort of adult women in Hawaii. Overall, 27% (372 of 1,378) of women were positive for anal HPV DNA at baseline compared with 29% (692 of 2,372) with cervical HPV DNA. Among women with paired anal and cervical samples, anal infection without accompanying cervical infection was observed in 14% (190 of 1,363). Concurrent anal and cervical HPV infections were observed in 13% (178 of 1,363) of women. Women with cervical HPV infection had >3-fold increased risk of concurrent anal infection. Concurrent anal and cervical HPV infection was most prevalent among the youngest women and steadily decreased through age 50 years. By contrast, the prevalence of anal infection alone remained relatively steady in all age groups. Compared with cervical infections, the overall distribution of HPV genotypes in the anus was more heterogeneous and included a greater proportion of nononcogenic types. A high degree of genotype-specific concordance was observed among concurrent anal and cervical infections, indicating a common source of infection. Nevertheless, the association of anal intercourse with anal HPV infection was limited to those women without accompanying cervical infection. The relationship of anal to cervical infection as described in this study has implications for the development of anal malignancies in women.
**TABLE 1. Summary of Recommendations**

<table>
<thead>
<tr>
<th>Risk group category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected women</td>
<td>Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Given their high incidence of anal cancer, some experts recommend routine screening for, and treatment of, AIN2/3 in this population in an effort to reduce their risk of anal cancer. Screening may include anal cytology with referral for HRA-guided biopsies, followed by treatment of biopsy-proven AIN2/3. The efficacy of this approach to prevent anal cancer has not yet been studied; a clinical trial is in progress to determine if screening and treatment of anal AIN2/3 in this population should become standard of care.</td>
</tr>
<tr>
<td>Women with organ transplant</td>
<td>Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Further research is recommended on screening for, and treating AIN2/3 to reduce the risk of anal cancer in this population.</td>
</tr>
<tr>
<td>Women with systemic lupus erythematosus and Crohn disease</td>
<td>Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Further research is recommended on screening for, and treating AIN2/3 to reduce the risk of anal cancer in this population.</td>
</tr>
<tr>
<td>Women with vulvar cancer or high-grade VIN</td>
<td>Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Some experts recommend routine screening for, and treatment of, AIN2/3 in an effort to reduce the risk of anal cancer in this population. The efficacy of doing so has not yet been shown in this population and screening is not yet standard of care.</td>
</tr>
<tr>
<td>Women with cervical or high-grade CIN or VaIN</td>
<td>Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Some experts recommend routine screening for, and treatment of AIN2/3 to reduce the risk of anal cancer in this population. The efficacy of doing so has not yet been shown in this population and screening is not yet standard of care.</td>
</tr>
<tr>
<td>Healthy women with none of the risk factors above</td>
<td>No screening for anal cancer or AIN2/3 is recommended at this time. Prompt referral for further diagnostic work-up if symptoms of anal cancer (pain and bleeding) are present.</td>
</tr>
</tbody>
</table>

*Providers should screen with cytology only if referrals to HRA and HRA-guided treatment are available.*
Patients with any level of abnormal anal cytology result are at significant risk of the presence of histopathologically verifiable high-grade anal intraepithelial lesions.

Anal Cytology Categories with AIN 2/3 on Biopsy:
- ASC-US: 47%
- LSIL: 57%
- ASC-H: 65%
- HSIL: 81%

Table 2. Correlation between abnormal anal cytologic tests and anal biopsy results

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Biopsy</th>
<th>AIN1</th>
<th>AIN2/3</th>
<th>Negative</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>162</td>
<td>43 (26.5)</td>
<td>18 (41.9)</td>
<td>20 (46.5)</td>
<td>5 (11.6)</td>
<td>4 (0.2–21)</td>
</tr>
<tr>
<td>ASC-H</td>
<td>17</td>
<td>6 (35.3)</td>
<td>1 (16.7)</td>
<td>4 (86.6)</td>
<td>1 (16.7)</td>
<td>7.7 (1–19)</td>
</tr>
<tr>
<td>LSIL</td>
<td>183</td>
<td>83 (45.4)</td>
<td>32 (38.6)</td>
<td>47 (56.6)</td>
<td>4 (4.8)</td>
<td>6.3 (0.4–24)</td>
</tr>
<tr>
<td>ASC-H/LSIL</td>
<td>23</td>
<td>14 (60.9)</td>
<td>5 (35.7)</td>
<td>9 (7.1)</td>
<td>0</td>
<td>7.7 (0.3–26)</td>
</tr>
<tr>
<td>HSIL</td>
<td>74</td>
<td>52 (70.3)</td>
<td>8 (15.4)</td>
<td>42 (58.9)</td>
<td>2 (3.8)</td>
<td>4.9 (0.3–24)</td>
</tr>
<tr>
<td>Summary</td>
<td>459</td>
<td>198 (43.1)</td>
<td>64 (32.3)</td>
<td>122 (61.6)</td>
<td>12 (6.1)</td>
<td>4.1 (0.2–16)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages or ranges.

1 One case with superficial invasive squamous cell carcinoma.
Cleveland Clinic 2015 Anal Cytology Data

- Unsat 44 (13%)
- NILM 121 (35%)
- ASC-US 86 (25%)
- ASC-H 20 (6%)
- LSIL 62 (18%)
- HSIL 10 (3%)
- Carcinoma 0
- Total 343

52% referral
High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus.

Panther, Wagner, Proper, Ugelso, Chatis, Weeden, Nasser, Doweiko, & Dezube
Beth Israel Deaconess Medical Center

<table>
<thead>
<tr>
<th>Cytological category</th>
<th>No. of specimens</th>
<th>Histological grade, no. (%) of specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>19</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Minimally abnormal</td>
<td>102</td>
<td>21 (21)</td>
</tr>
<tr>
<td>High-grade abnormal</td>
<td>32</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>33</td>
</tr>
</tbody>
</table>

NOTE. Histological specimens are high-resolution anoscopy–guided biopsy specimens that were obtained during the same examination as the anal Papnicolaou (Pap) smear; if biopsy was not performed at this time, histological specimens represent surgical pathology findings, if they were recorded within 3 months of the anal Pap smear. AIN, anal intraepithelial neoplasia.

Relatively poor correlation between cytology and histology from HRA biopsy.

Cytology often underestimates the grade of ASIL compared to biopsy.

More than 1/3 of LSIL on cytology show HSIL on biopsy.
High-Resolution Anoscopy: Clinical Features of Anal Intraepithelial Neoplasia in HIV-positive Men

Olivier Richel, M.D.1•2 • Nora D. L. Hallensleben, M.Sc.3 • Alexander Kreuter, Ph.D.4 Carel J. M. van Noesel, Ph.D.5 • Jan M. Prins, Ph.D.1,2 • Henry J. C. de Vries, Ph.D.2,3,6

RESULTS: Three hundred four biopsies were taken from 163 patients. One hundred sixty-eight biopsies (55%) showed anal intraepithelial neoplasia, and 67/304 (22%) showed high-grade anal intraepithelial neoplasia. The $\kappa$-coefficient was 0.65 for condylomatous lesions, 0.14 for surface configuration, 0.54 for punctuation, 0.08 for mosaicism, and 0.43 for atypical vessels. Condylomatous lesions showed high-grade anal intraepithelial neoplasia in 18% (95% CI, 11%–27%). In lesions with flat leukoplakia, punctuation, and atypical vessels, high-grade anal intraepithelial neoplasia was seen in 25%, 30%, and 23%. In lesions with the combination punctuation/atypical vessels and punctuation/flat leukoplakia/atypical vessels, high-grade anal intraepithelial neoplasia was found in 38% and 40%.

CONCLUSIONS: A moderate to substantial interobserver agreement was demonstrated in recognizing condylomas, punctuation, and atypical vessels. Furthermore, high-grade anal intraepithelial neoplasia is present in a high proportion of intra-anal condylomata. A combination of punctuation, flat leukoplakia, and atypical vessels is the best predictor for high-grade anal intraepithelial neoplasia.
Detection of anal dysplasia is enhanced by narrow band imaging and acetic acid

M. D. Inkster*, H. O. Wiland† and J. S. Wu*

*Departments of Gastroenterology/Hepatology and Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio, and †Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, Ohio, USA

Received 1 June 2015; accepted 17 August 2015; Accepted Article online 4 November 2015

Abstract

Aim Anal intraepithelial neoplasia precedes the development of anal squamous cell carcinoma. Detection of the lesion is essential to management. This paper describes a prospective study to detect and ablate anal squamous intraepithelial lesions (SILs) using white light narrow band imaging (NBI) and NBI with acetic acid (NBIA).

Method Sixty patients with abnormal anal cytology and risk factors for anal dysplasia underwent examination of the anoderm with a high definition gastroscope and NBI. Targeted biopsies were taken and the lesions were ablated and characterized histopathologically. Visualization of the anal transitional zone was facilitated by retroflexion and examination through a disposable anoscope.

Results Targeted biopsies were taken from lesions in 58 patients. No lesion was seen in two patients. Histopathology showed SIL in 48 (80.0%) of 60 biopsies. One biopsy showed lymphoid aggregates. Biopsies in nine (15%) of the 60 patients showed normal mucosa. Lesions were seen in white light in 27 (45%) of the 60 cases, NBI in 39 (65%) and NBIA in 57 (95%). There was no major morbidity. Sensitivity analysis showed that all methods were significantly different from each other.

Conclusion Anal SIL in the anal transitional zone and anal canal can be identified by NBIA. Patient selection influences findings. Limitations include small sample size and non-randomization.

Keywords Anal dysplasia, anal transitional zone, human immunodeficiency virus, human papillomavirus, narrow band imaging, squamous intraepithelial lesion

What does this paper add to the literature?

Individual facets of narrow band imaging with acetic acid are not new. What is new is the application of this technique to identify and destroy anal intraepithelial lesions. The procedure can be done by any practitioner familiar with endoscopy in a single setting with high yield and good patient tolerance.

Figure 1 (a) Cross-sectional depiction of the anal canal (after Tanaka et al. [8]). The anal transitional zone is located between the dentate line and anorectal line. (b) Retroflexion with white light shows the dentate line, the anal transitional zone and the anorectal line.

Figure 2. ATZ lesion in the left anterior position illuminated with NBI. Note the enhanced punctuation (black arrow) and mucosal (white arrow). Figure shows a left anterior raised lesion with punctuation and mucosal erosion from the ATZ; pathology showed HNE.
Objective: To estimate the cost-effectiveness of screening for anal cancer in the high-risk HIV-positive population [in particular, men who have sex with men (MSM), who have been identified as being at greater risk of the disease] by developing a model that incorporates the national screening guidelines criteria.

Data Sources: A comprehensive literature search was undertaken. 2006-2012.

Study selection: Published literature identified by the search strategy was assessed by four reviewers. Papers that met the inclusion criteria contained the following: data on population incidence, effectiveness of screening, health outcomes or screening and/or treatment costs; defined suitable screening technologies; prospectively evaluated tests to detect anal cancer. Foreign-language papers were excluded. Searches identified 2102 potential papers; 1403 were rejected at title and a further 493 at abstract. From 206 papers retrieved, 81 met the inclusion criteria. A further treatment paper was added, giving a total of 82 papers included.

Results: The reference case cost-effectiveness model for MSM found that screening for anal cancer is very unlikely to be cost-effective. The negative aspects of screening included utility decrements associated with false-positive results and with treatment for high-grade anal intraepithelial neoplasia (HG-AIN). Sensitivity analyses showed that removing these utility decrements improved the cost-effectiveness of screening. However, combined with higher regression rates from low-grade anal intraepithelial neoplasia (LG-AIN), the lowest expected incremental cost effectiveness ratio remained at over £44,000 per quality-adjusted life-year (QALY) gained. Probabilistic sensitivity analysis showed that no screening retained over 50% probability of cost-effectiveness to a QALY value of £50,000.

Conclusions: Many of the criteria for assessing the need for a screening programme were not met, and the cost-effectiveness analyses showed little likelihood that screening any of the identified high-risk groups would generate health improvements at a reasonable cost. Further studies could assess whether the screening model has underestimated the impact of anal cancer, the results of which may justify an evaluative study of the effects of treatment for HG-AIN.

Limitations: Limited knowledge is available about the epidemiology and natural history of anal cancer, along with a paucity of good-quality evidence concerning the effectiveness of screening.
Introduction: Anal cancer in men who have sex with men (MSM) living with HIV is an important issue but there are no consistent guidelines for how to screen for this cancer. In settings where screening with anal cytology is unavailable, regular anal examinations have been proposed in some guidelines but their cost-effectiveness is unknown.

Methods: Our objective was to estimate the cost-effectiveness of regular anal examinations to screen for anal cancer in HIV positive MSM living in Australia using a probabilistic Markov model. Data sources were based on the medical literature and a clinical trial of HIV-positive MSM receiving an annual anal examination in Australia. The main outcome measures for calculating effectiveness were undiscounted and discounted (at 3%) lifetime costs, life years gained, quality-adjusted life years (QALY) gained and incremental cost-effectiveness ratio (ICER).

Results: Base-case analysis estimated the average cost of screening for and management of anal cancer ranged from $195 for no screening to $1,915 for lifetime annual screening of men aged >= 50. Screening of men aged >= 50 generated ICERs of $29,760 per QALY gained (for screening every four years), $32,222 (every three years) and $45,484 (every two years). Uncertainty for ICERs was mostly influenced by the cost (financially and decrease in quality of life) from a false-positive result, progression rate of anal cancer, specificity of the anal examination, the probability of detection outside a screening program and the discount rate.

Conclusions: Screening for anal cancer by incorporating regular anal examinations into routine HIV care for MSM aged >= 50 is most likely to be cost-effective by conventional standards. Given that anal pap smears are not widely available yet in many clinical settings, regular anal exams for MSM living with HIV to detect anal cancer earlier should be implemented.

DARE is cost-effective.
Objective: To determine the lifetime and phase-specific cost of anal cancer management and the economic burden of anal cancer care in elderly (66 y and older) patients in the United States.

Patients and Methods: For this study, we used Surveillance Epidemiology and End Results-Medicare linked database (1992 to 2009). We matched newly diagnosed anal cancer patients (by age and sex) to noncancer controls. We estimated survival time from the date of diagnosis until death. Lifetime and average annual cost by stage and age at diagnosis were estimated by combining survival data with Medicare claims. The average lifetime cost, proportion of patients who were elderly, and the number of incident cases were used to estimate the economic burden.

Results: The average lifetime cost for patients with anal cancer was US $50,150 (N = 2227) (2014 US dollars). The average annual cost in men and women was US $8025 and US $5124, respectively. The overall survival after the diagnosis of cancer was 8.42 years. As the age and stage at diagnosis increased, so did the cost of cancer-related care. The anal cancer–related lifetime economic burden in Medicare patients in the United States was US $112 million.

Conclusions: Although the prevalence of anal cancer among the elderly in the United States is small, its economic burden is considerable.
Collaboration of:
- AIDS-Associated Malignancy Clinical Trials Consortium HPV Working Group
- University of California San Francisco

Sponsored by:
- National Cancer Institute Office of HIV and AIDS and Malignancy (OHAM).

Enroll >5,000 M & W, 35 and older who have HIV and biopsy-proven HSIL at baseline. Eligible participants will have no history of anal cancer, or treatment or removal of HSIL. Eligible participants will be randomized to treatment or active monitoring at baseline.

Treatment arm includes excision / imiquimod / fluorouracil / cautery / laser therapies. Monitoring are includes exams every six months for HSIL outcomes for up to five years.

The incidence of invasive cancer in both arms will be monitored, and biospecimens and associated participant data will be collected for correlative science studies.
Living with HIV has gotten a lot easier. With longer lifespans; however, persons with HIV face a new set of challenges.

Anal cancer rates are rising among people living with HIV.

The goal of the ANCHOR study is to find the best way to prevent anal cancer among HIV positive men and women.

"No one knew that cervical cancer was preventable before the use of Pap smears became widespread in the 1960s and cut the incidence of the disease by 80 percent."
- JOEL PALEFSKY, M.D., PRINCIPAL INVESTIGATOR
Study of the Prevention of Anal Cancer.

Funded by the National Health and Medical Research Council of Australia and Cancer Council NSW (2010 to 2018).

Examine the overlapping roles of DARE, HPV testing, anal Pap, and HRA.

Provide a major contribution on how to best utilize the various anal cancer screening modalities.
Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2010

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
Bethesda and Cytomorphologic Correlates

“Older linear” paradigm for individuals developing anogenital dysplasia / carcinoma.

“Newer nonlinear/bidirectional” paradigm with modern concepts of HPV mediated carcinogenesis.
Objective: To evaluate the prevalence of anal cytology (ACyt) abnormalities among HIV-infected and HIV-uninfected men who have sex with men (MSM).

Design: Multicenter cohort study of 723 HIV-infected and 788 HIV-uninfected MSM with ACyt, with a second ACyt collected 2 years later. A referral for high-resolution anoscopy was suggested for abnormal ACyt.

Methods: ACyt samples were collected using a polyester swab and liquid cytology media and read in a central laboratory.

Results: Prevalence of any abnormal ACyt was 25% in HIV uninfected MSM and increased to 38%, 41%, and 47% among HIV infected MSM with current CD4+ T-cell counts $500, 350–499, and ,350 cells/mm3 (P , 0.001), respectively. Anal HPV16 DNA was also more common in HIV-infected than HIV-uninfected MSM (25% versus 16%, P , 0.001). Abnormal baseline ACyt together with prevalent HPV16 DNA detection was present in only 7% of HIV-uninfected MSM compared to 18% of HIV-infected MSM with current CD4 , 350, P , 0.001. Among HIV-infected men, 56% of the men with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions ASCs-US/LSILs and 81% of men with atypical squamous cells cannot exclude high grade (ASC-H)/high-grade squamous intraepithelial lesions (HSIL) had lower grade ACyt findings 18–30 months later (“regressed”). However, 19% of untreated HIV-infected men with ASC-H/HSIL cytology maintained that same grade of cytology in their second test approximately 2 years later, and 15% with ASCUS/LSIL “progressed” to ASC-H/HSIL. Abnormal ACyt had high sensitivity (96%) but low specificity (17%) for biopsy proven HSIL.

Conclusions: Prevalence of abnormal ACyt remains elevated in HIV-infected men during the current antiretroviral therapy era. (J Acquir Immune Defic Syndr 2016;71:570–576)
Rates of Anal Cancer Compared to Other Cancers

Cancer incidence rates are measured as the number of cases each year per 100,000 people.

The incidence rates of the most common cancers are compared in the chart below.

The first three bars show the very different rates in anal cancer among HIV positive men, HIV positive men who have sex with men (MSM), and HIV negative men.

The anal cancer incidence rate among HIV positive MSM is even higher than the rates of much more common cancers that are routinely screened for in the general population.
Why the “No-Brainer” HPV Vaccine Is Being Ignored

Rita Rubin, MA  

Why should thousands of men and women develop precancerous or cancerous lesions that could have been prevented had they been vaccinated against the human papillomavirus (HPV) as 11- or 12-year-olds.

Studies have found that parents, like physicians, sometimes delay immunization because they think their child is years away from becoming sexually active and possibly contracting HPV. In addition, the HPV vaccine requires 3 trips to the physician’s office, which might prove daunting to busy families.

These vaccination rates fall far short of the Healthy People 2020 initiative’s target goal to have 80% of 13- to 15-year-old girls and boys fully immunized with all 3 HPV doses.

Pediatricians tend to regard the HPV vaccine as a different breed from the other preteen vaccines because the virus is sexually transmitted, and some of them aren’t comfortable talking about sexual health.
Cleveland Clinic

Every life deserves world class care.