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HPV AND ANAL CANCER

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HPVWorld

HPV WORLD (HPW) is an independent publication edited by selected teams of editors and authors in the HPV-related field with the purpose of disseminating scientific information that may have an impact in the prevention, diagnostic or treatment of HPV related malignancies and other conditions.

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Anal cancer is one of the most highly stigmatized diseases associated with HPV.

It is linked to human sexual behaviors and sexually transmitted infections, including HIV. Anal cancer incidence is on the increase in both genders in many countries, but has identified high-risk groups. It is being actively investigated to determine the best options for diagnosis, prevention and treatment. Introduction of routine gender-neutral vaccination against HPV is one of most important prevention approaches.

Yet, anal cancer is a poorly known consequence of the HPV pandemic. Information and health education are critical aspects to encourage prevention, medical consultation, early diagnosis, and prompt treatment.

The selection of newsletters, articles and references hereby edited by HPW has been conceived to disseminate state-of-the-art information to the wider circle of professionals who are not HPV specialists but who advise the general population and are on the front line of care.

If you find it useful please forward the link to your areas of influence.

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Screening for anal high-grade squamous intraepithelial lesions and anal cancer- has its time come?

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The incidence of anal cancer is rising and has been clearly doing so among both women and men in the general population since the 1970s.[1,2] The incidence of anal cancer is particularly high among those with HIV and other forms of immune suppression, and among women there is a clear relationship between history of cervical or vulvar cancer and anal cancer.[3,4] In some populations of women, the incidence of anal cancer exceeds that of cervical cancer. The natural history of anal HPV infection to the anal cancer precursor, anal high-grade squamous intraepithelial lesion (HSIL) to cancer is similar to that for cervical HPV infection to cervical HSIL and cancer. Screening for and treating cervical HSIL is well known to reduce the risk of cervical cancer, so why is it not yet standard of care to do so for anal HSIL?

There is one major reason for this- in this era of evidence-based medicine, there is a need for high quality evidence that treating anal HSIL reduces the risk of anal cancer. The ANal Cancer/HSIL Outcomes Research (ANCHOR, U01CA121947), funded by the U.S. National Cancer Institute, is a large randomized controlled trial to determine if treatment of anal HSIL reduces the incidence of anal cancer compared with active monitoring without treatment. This study is focused on the group at highest risk of anal cancer, men and women living with HIV over 35 years of age with biopsy-proven anal HSIL. If a meaningful level of anal cancer reduction can be demonstrated in the treatment arm of this very high risk, challenging population, it is expected that anal HSIL treatment will become standard of care for this group, as well as for the other groups at increased risk of anal cancer.

However the challenges don't stop there. If treating anal HSIL becomes standard of care, then optimal screening algorithms to detect it will need to be defined. Anal cytology has many of the same limitations as cervical cytology, primarily low sensitivity and tendency to under-call the severity of disease. As in the cervix, HPV testing offers better sensitivity than cytology but lower specificity, particularly in men and women living with HIV who have an especially high prevalence and incidence of

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anal HPV infection. The optimal combination of cytology and HPV genotyping, and second tier tests such as methylation markers, HPV oncoprotein detection and other methods still needs to be defined, and the best algorithms will likely vary depending on the risk group.

Another issue that will need to be addressed is optimal treatment for anal HSIL. The ANCHOR study will be by far the largest study examining the efficacy of anal HSIL treatment, but it is a "treatment strategy" study and is not designed to compare one treatment to another. There are very few published randomized controlled trials of anal HSIL to date, and all of the data published to date point to serious challenges with each of the modalities studied thus far. These include low efficacy and recurrence at treatment sites.[5,6] HPV is likely to be a "field infection" particularly in immunocompromised individuals, and consistent with this, there is also a high rate of incident lesions at untreated sites, known as metachronous disease.

Then there is an issue of numbers. If treatment of anal HSIL becomes standard of care in high-risk groups, a very large proportion of men and women in those groups may need HSIL treatment at some point. It is currently estimated that half or more of men living with HIV and about a third of women living with HIV will have anal HSIL in cross-sectional analyses.[7-9] Even though there may be spontaneous regression of some HSIL, there will also be incident HSIL over time in many. Given the limited numbers of individuals trained in high resolution anoscopy (HRA) and HRA-guided treatment of HSIL, it is easy to imagine that the existing pool of HRA providers will be quickly overwhelmed. There will be a need for a rapid expansion of the pool of well-trained HRA providers, necessitating expansion of high-quality training programs guided by rigorous metrics and practice standards. There is also urgent need for more scientific investigation of progression from anal HSIL to cancer and identification of biomarkers of progression to cancer. Not all HSIL is the same, and it may well be that some, but not all HSIL need to be treated. The ANCHOR Study includes a specimen biorepository that will be of great value for understanding anal cancer pathogenesis and identification of biomarkers of progression. Given the similarity between cervical cancer and anal cancer, identification of biomarkers of progression from anal HSIL to anal cancer could also be relevant to identification of similar biomarkers in the cervix. Perhaps in the future, with this information, we can limit our treatment of HPV-associated HSIL at any anatomic location only to those understood to be at highest risk of progression to cancer.

If treatment of anal HSIL becomes standard of care in high-risk groups, 1) optimal screening algorithms to detect HSIL will need to be defined and 2) a very large proportion of men and women in those groups may need HSIL treatment at some point.

Given the limited numbers of individuals trained in high resolution anoscopy (HRA) and HRA-guided treatment of HSIL, it is easy to imagine that the existing pool of HRA providers will be quickly overwhelmed.

There is of course the good news that HPV vaccination works very well to prevent anal

HPV infection and likely anal cancer among those not yet exposed to the relevant HPV types. This will be the key to anal cancer prevention in the future, and should be aggressively implemented in a gender-neutral manner wherever possible.

HPV vaccination works very well to prevent anal HPV infection and likely anal cancer among those not yet exposed to the relevant HPV types. This will be the key to anal cancer prevention in the future.

But for those who remain at high risk of having anal HSIL, has the time come to screen for and treat it? Based on the considerations listed above, the answer may be "not yet". One approach would be to wait for the answers that ANCHOR will provide: don't screen for it or treat it unless ANCHOR tells us that doing so is effective in reducing the incidence of anal cancer. In the absence of treatment for anal HSIL, we recommend that all individuals at high risk of anal cancer undergo digital anorectal examination (DARE) at regular intervals to palpate masses that could indicate the presence of anal cancer.

However, like many experts around the world, at the University of California, San Francisco Anal Neoplasia Clinic, Research and Education Center we take a different approach. In addition to performing DARE, until we get the answers from ANCHOR, we choose to actively treat anal HSIL given its known precancerous potential and the high incidence of cancer in our high-risk populations. We will consider other approaches only if the ANCHOR Study tells us that treating anal HSIL with our currently available methods is futile. One way or the other, we need to be ready to implement HSIL treatment as standard of care, and/or to continue to develop the infrastructure needed to explore other approaches to prevent anal cancer in high-risk populations.

Each of these issues will be explored further in this issue of HPV World. ■

DISCLOSURE
The author declares nothing to disclose.

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Anal HPV infection: risk groups and natural history

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Anal cancer shares biologic similarities with cervical cancer, including association with high-risk HPV and similar natural history from HPV infection to precancerous lesions to cancer. HPV has been detected in about 90% of anal cancers with HPV16 detected in about 80% of anal cancers, in comparison to HPV being detected in virtually all cervical cancers, and HPV 16 detected in about 50-60% of cervical cancers. The natural history of cervical HPV infection has been well characterized over the past 3 decades whereas the natural history of anal HPV is not as well studied. The majority of studies investigating anal HPV infection are cross-sectional data of men who have sex with men (MSM) and/or people living with HIV (PLWH).

Among men, anal HPV prevalence varies substantially by HIV status and sexual orientation; anal HPV prevalence in men does not vary by age.

Among men, anal HPV prevalence varies substantially by HIV status and sexual orientation; anal HPV prevalence in men does not vary by age. Figure 1 summarizes the findings from a recent systematic review and meta-analysis.[1] MSM living with HIV have the highest rates of prevalent anal HPV as well as anal HPV16. Interestingly, men who have sex with women (MSW) living with HIV have similar rates of prevalent anal HPV (43%), anal HPV16 (11%) compared with immune-competent MSM. Immune-competent MSW have substantially lower rates of anal HPV compared with all other males (12% prevalence of anal HPV, 3% prevalence of anal HPV 16).

Incident anal HPV16 infection rates are also strongly associated with HIV status and sexual orientation. MSM and MSW living with HIV have 9.1 and 4.4 incident anal HPV16 infections/1000 person-months (p-m) respectively whereas HIV-negative MSM and MSW have 4.7 and 1.4-2.7 incident HPV16/1000 p-m.[1] Among HIV-negative MSW, a history of genital HPV16 infection (i.e., penile or scrotal infection) is associated with a 4-fold increased incidence of anal HPV16 infection (in the absence of anal receptive sex).[2]

In women, anal HPV prevalence differs by

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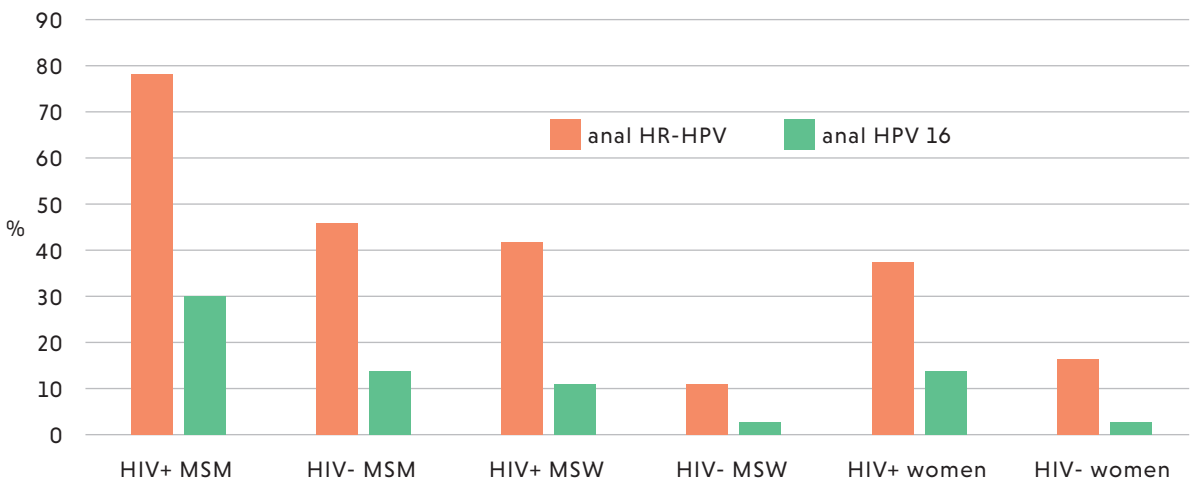
HIV status (with women living with HIV (WLHIV) being the best studied), and cervical HPV infection or cervical cytopathology. As summarized in a recently published collaborative pooled analysis, WLHIV are approximately twice as likely as HIV-negative women to have prevalent anal HR-HPV and 4 times more likely to have anal HPV16 (Figure 1).[3] WLHIV are more likely to have HPV detected in the anus than the cervix (38% vs 33% respectively) whereas women without HIV are less likely to have HPV detected in the anus than the cervix (17% vs. 22% respectively).[3] In HIV-negative women, the prevalence of anal HPV 16 increases significantly with higher grade cervical cytopathology; anal HPV16 is detected in 4% of women with normal cervical cytopathology, 10% with cervical LSIL, 22% with cervical HSIL and 44% with cervical cancer.[3] A large Hawaiian cohort of healthy women aged 18 or older found that the mean duration of incident anal HR-HPV infection was 5 months (compared with cervical HR-HPV infections that lasted a mean of 8 months).[4] Risk factors for anal HPV detection in all women included detection of cervical HPV, history of perianal and/or vulvar condyloma, smoking and for HIV-negative women, age younger than 30 years. Lower CD4 counts in WLHIV and history of anal intercourse in all women were not consistent risk factors for anal HPV.[4]

In women, anal HPV prevalence differs by HIV status and cervical HPV infection or cervical cytopathology.

Figure 1

Anal high-risk (HR) HPV and anal HPV16 prevalence by HIV status, and sexual preference (men) and women.



HR: High-risk; MSM: Men who have sex with men; MSW: Men who have sex with women.
Sources of data: HIV+ MSM [1], HIV- MSM [1], HIV+ MSW [1], HIV- MSW [1], HIV+ women[3], HIV- women[3].

Anal receptive intercourse is not necessary for anal HPV. For HIV-negative men and women, genital HPV infection has been found to precede anal HPV infection.

Anal receptive intercourse is not necessary for anal HPV. For HIV-negative men and women, genital HPV infection has been found to precede anal HPV infection.[2,4,5]

Differences in rates of anal HPV16 infection may help to explain the increased rates of anal cancer seen in PLHIV but it is likely only a part of the story.

Differences in rates of anal HPV16 infection may help to explain the increased rates of anal cancer seen in PLHIV but it is likely only a part of the story. Data are maturing that may allow us to better understand the natural history of anal HPV infections. ■

DISCLOSURE
The author declares nothing to disclose.

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Groups at High Risk of Anal Cancer

Similar to other HPV-related cancers, persistent anal high-risk HPV infection (HR-HPV) leads to precancerous anal high-grade squamous intraepithelial lesions (HSIL) that in a small number of patients over time may progress to anal cancer.[1,2] The molecular events that contribute to progression of HSIL to cancer are unclear, but immunosuppression and other factors may facilitate the common denominator, persistent HR-HPV infection. Consistent with its role as the precursor to anal cancer, groups at high risk of anal cancer also have a high prevalence of anal HSIL. Identifying these groups may guide targeted screening if current studies demonstrate efficacy of treating HSIL to prevent cancer.[3]

Trends in anal cancer in the US analyzed during 2001-2015 are disturbing.[4] Anal cancer occurred more commonly in women than men in the general population, comprising 66% of the 28,236 cases diagnosed between 2011 and 2015. Anal cancer incidence increased by 2.2% for men, and 3.1% for women. Anal cancer mortality increased by 3.1% in men and women consistent with an observed doubling of the proportion of advanced regional and distant cancers. The sexual revolution of the 1960s and 70s has had a lasting impact. Birth cohort analyses reflect a two-fold increase in anal cancer cresting for white or black women born in 1961. The incidence is five times higher for black men born around 1986 compared with men born in 1946, with at least some of this increase likely attributable to the high incidence of HIV reported in young black men. Anal cancer is also increasing among older women. Based on continuing trends over the next decade, anal cancer may become the most common HPV-related cancer affecting older US women.

Although women from the general population constitute the majority of anal cancer patients, women with a prior history of HPV-related lower genital tract lesions or immunosuppression are at higher risk of anal cancer than those in the general population (Table 1). From 1973-2007, there were 255 cases of anal cancer among 189,206 women diagnosed with lower genital tract neoplasia, but this represents fewer than 1% of the 26,030 women diagnosed with anal cancer from 2001-2010.[4,5]

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The molecular events that contribute to progression of high-grade squamous intraepithelial lesions to cancer are unclear, but immunosuppression and other factors may facilitate the common denominator, persistent high-risk-HPV infection. Consistent with its role as the precursor to anal cancer, groups at high risk of anal cancer also have a high prevalence of anal high-grade squamous intraepithelial lesions.

Table 1

Anal cancer incidence (approximated in the absence of definitive data) coupled with anal HPV and anal HSIL prevalence.[5,8-17]

	Anal cancer incidence per 100,000	SIR (cases observed/ cases expected)	% HR-HPV prevalence	% HPV16	% anal HSIL prevalence
MSM living with HIV	77.8 - 131	80.3	73.5	35.4	43
Women living with HIV	24.2 - 30	10.1	85	24	27
MSW living with HIV	31.9 - 46	26.7	50**	-	18
MSM	5 - 16.6	NA	37.2	12.5	25
Women with vulvar HSIL	48.9*	22.2[5]	-	-	-
Women with vulvar cancer	38.3*	17.4[5]	-	-	-
Women with cervical HSIL	9.8 – 36.1*	4.47[13] -16.4[5]	-	-	-
Women with cervical cancer	8.4 – 13.6*	3.82[13] – 6.2[5]	-	-	-
Women with cervical HPV 16	NA	NA	43-62	41-46	26***
Solid organ transplant patients	11.6	5.8	-	-	-
Crohn's disease/other immunosuppression	5.9*/2.5*	3.1[16]/1.3[16]	-	-	-
History of genital warts in men	34.4*	21.5[5]	-	-	-
History of genital warts in women	24.4*	11.1[5]	-	-	-
Women	2.2	1	9	2	-
Men	1.6	1	6.8	2.2	-

SIR: Standardized Incidence Ratio; HR: high-risk; MSM: men who have sex with men; MSW: men who have sex with women; HSIL: high-grade squamous intraepithelial lesions

* SIR multiplied by anal cancer incidence in women (2.2) or in men (1.6).

** overall HPV, not just high-risk-HPV.

*** over age 45.

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Although women from the general population constitute the majority of anal cancer patients, women with a prior history of HPV-related lower genital tract lesions or immunosuppression are at higher risk of anal cancer than those in the general population.

There is a latency period after diagnosis of 11-16 years after cervical cancer or HSIL, respectively, before diagnosis of anal cancer.[5] Older age at diagnosis of lower genital tract neoplasia is associated with a shorter interval to progression to anal cancer. A collaborative pooled analysis showed that women over the age of 45 with cervical HPV16 infection had a prevalence of HSIL of 38%.[3]

Iatrogenic immunosuppression for solid organ transplantation or due to HIV infection leads to increased rates of anal cancer compared with the general population.

Iatrogenic immunosuppression for solid organ transplantation or due to HIV infection leads to increased rates of anal cancer compared with the general population.[6] Patients who were more than 5 years out from transplantation had an anal cancer incidence rate ratio of 3.8 (2.2–6.9) compared with less than 2 years. Similarly, patients transplanted at an earlier age compared with those over 50 had a more than 2-fold increase in anal cancer.[7]

People living with HIV have the highest incidence of anal cancer, particularly men who have sex with men.

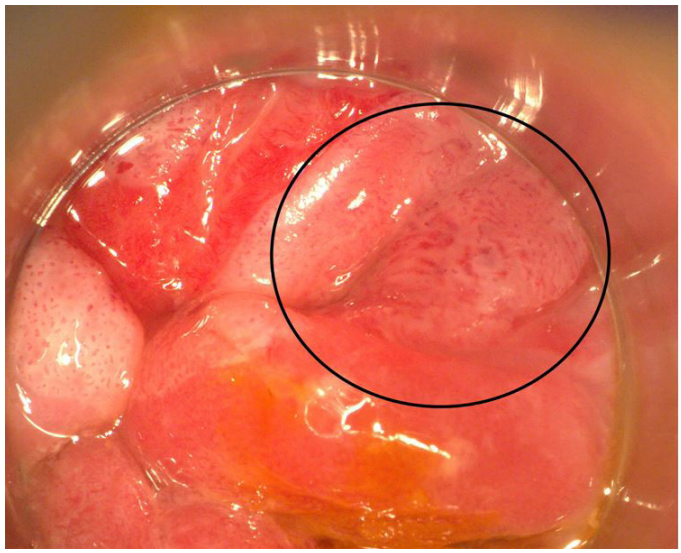
People living with HIV have the highest incidence of anal cancer, particularly men who have sex with men (MSM) (Table 1). The incidence of anal cancer increased substantially in this group after introduction of antiretroviral therapy for HIV in 1996 but the increase has levelled in recent years, with a possible decline, albeit to levels that remain very high.[8] Patients with a diagnosis of AIDS (as opposed to living with HIV) and lower CD4 lymphocyte count nadir are associated with increased risk of anal cancer, further emphasizing the role of immunosuppression.[9] HIV is responsible for the increase in incidence of anal cancer among men (28% of cases) but not women (1% of cases) of anal cancer. Anal cancer occurs at a younger age among those living with HIV by about 10 years. Until primary HPV vaccination is more widespread, we must improve our secondary prevention efforts. ■

DISCLOSURE

The author has no conflict of interests to disclose.

Figure 1

A superficially invasive squamous cell carcinoma was found during excision of this area seen with high-resolution anoscopy (black circle): the area is acetowhite and raised from the surface, and shows a highly atypical vascular pattern.



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Digital anal rectal examination (DARE) for anal cancer prevention

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Anal cancer prevention includes vaccination (primary prevention), screening and detection of precursor lesions (secondary prevention) and early detection of cancers (tertiary prevention). Cancers < 2 cm diameter at diagnosis typically have an 80% five year-survival, compared with 45-65% when cancers are > 2 cm, and 20% for cancers that have metastasized.[1] Unfortunately, over 85% of anal cancers are ≥ 2cm at the time of diagnosis.[2] Early detection of anal cancers therefore has a key role to play in improving clinical outcomes.

When conducted properly, digital anal rectal examination (DARE) has the potential to detect anal cancers ≥ 0.3cm diameter.[3] It is simple and safe, with no major adverse effects.[4] DARE is therefore the mainstay of tertiary prevention of anal cancer and annual DAREs are recommended in a number of jurisdictions for men who have sex with men living with HIV. Table 1 lists other populations at increased risk of anal cancer, for which DARE may be of value.[5] DAREs may also be used to evaluate anal cancer persistence or recurrence following initial treatment. They may be conducted by health professionals from a variety of backgrounds, and self-DARE has been advocated in high-risk individuals, such as HIV-positive men who have sex with men (MSM). Systematic performance and careful monitoring of outcomes are important to ensure the quality of examinations.[5]

When conducted properly, digital anal rectal examination (DARE) has the potential to detect anal cancers ≤ 0.3cm diameter. It is simple and safe, with no major adverse effects.

Digital anal rectal examination (DARE) may also be used to evaluate anal cancer persistence or recurrence following initial treatment.

Clinicians typically place the patient undergoing DARE in the left lateral decubitus position, with the knees up towards the chest, but sometimes may use the lithotomy, prone or right lateral decubitus positions. Swabbing for anal cytology and/or HPV DNA and STIs should always be performed before the DARE, as lubricant may interfere with testing technologies.

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Table 1

Groups who may potentially benefit from digital anal rectal examination (DARE), with proposed frequencies

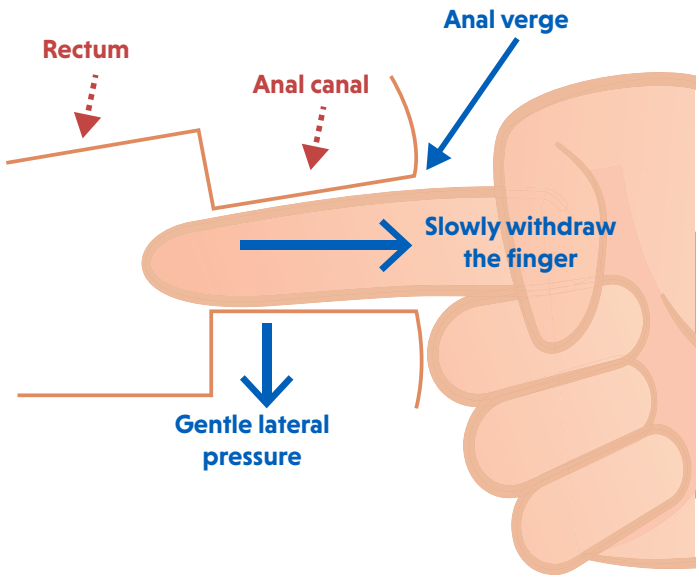
Group	Possible DARE frequency
Those with symptoms suggesting anal cancer such as: bleeding, anal/perianal mass, tenesmus, pain, altered bowel habit[6]	Immediately, with referral for anoscopy, high-resolution anoscopy, or to a colorectal specialist if the initial DARE is negative
HIV-positive men who have sex with men	At least annually
Those with demonstrated, current, histologic anal high-grade squamous intraepithelial lesions	At least annually
Those with a history of treated anal squamous cell carcinoma	Every 3–6 months for a period of 2 years, and 6–12 monthly until 5 years, with clinical examination including DARE and palpation of the inguinal lymph nodes[7]
Other immunosuppressed populations, such as other groups with HIV infection and recipients of solid organ transplants	Annually
HIV-negative men who have sex with men	Every two to five years, depending on further risk assessment, such as age and smoking status
Women with a history of cervical, vulvar or vaginal neoplasia or cancer	Every two to five years, depending on further risk assessment. Consider including at each cervical cytological review.

DARE specifically emphasizes palpation of the entire anal canal and visualization/palpation of the perianus (defined as 5cm distal to the anal verge). Details of how to perform a DARE can be found elsewhere.[5] Essentially it involves a thorough inspection of the perianus, followed by the insertion into the anal canal of a gloved, lubricated, index finger. The examination is then conducted in a systematic fashion, ensuring that all octants are palpated, extending from the rectal space to the external anal sphincter. This is illustrated in Figure 1.

Digital anal rectal examination (DARE) specifically emphasizes palpation of the entire anal canal and visualization/palpation of the perianus (defined as 5cm distal to the anal verge).

Figure 1

How to perform a digital anal rectal examination (DARE)

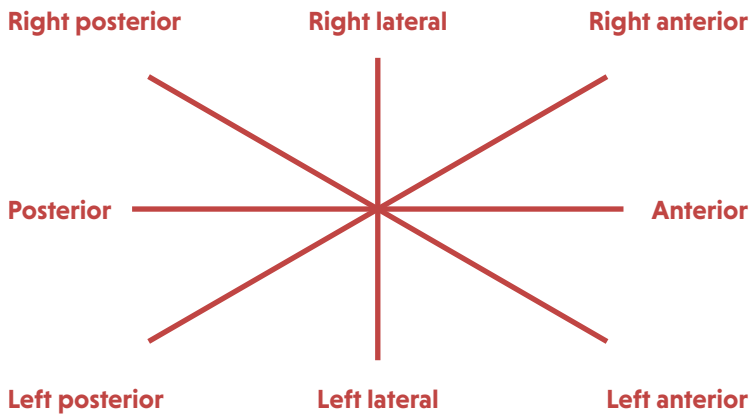


Once the digital anal rectal examination (DARE) has been completed, a precise description of the findings should be recorded, including the following components:

- The exact location of any abnormality, using standard anatomic location reporting, as is illustrated in Figure 2, together with a note of whether the lesion is in the proximal, mid canal, distal canal, protruding or extending to the perianus.
- Lesions may be masses, linear (such as a fistula tract), or a focal area of thickening or granularity.
- The size of the lesion should be estimated, if it is possible to feel the proximal limit.
- The contour should be described in terms of, for example, whether it is smooth or irregular, hard or compressible, superficial or submucosal, fixed or mobile.
- The inguinal regions should be palpated for any evidence of lymphadenopathy.
- Finally a note should be made of whether there is any blood on the withdrawn finger, and location of any tenderness experienced by the patient.

Figure 2

Location descriptors (for patient in the left lateral position)



Note: these descriptors are markedly different if the patient is in a prone, lithotomy position or right lateral position.

False-negative examinations are a major concern, as they potentially lead to incorrect reassurance of the absence of an anal cancer. These can be reduced by conducting thorough, systematic examinations regularly, and by encouraging patients to re-present promptly if any new symptoms develop. Because of the risk of false-negatives, self-DARE should only be offered to select high-risk individuals who have undergone thorough training.

In summary, DARE is a cheap and simple procedure that has the potential to save lives. Competent practitioners should be able to find most anal cancers. Failure to perform DAREs in at-risk individuals increases the likelihood of late presentation, with consequent poor outcomes. ■

Digital anal rectal examination (DARE) is a cheap and simple procedure that has the potential to save lives. Competent practitioners should be able to find most anal cancers.

DISCLOSURE

The author declares nothing to disclose.

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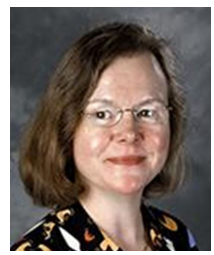
Pathology of anal squamous intraepithelial lesions and cancer: similarities and differences from cervical pathology

Nearly ten years ago, my colleague and friend, the late Dr. Barbara Winkler, and I penned a commentary on the key differences between anal cancer and cervical cancer screening.[1] My work with colleagues at UCSF and her work with colleagues in New York City helped to increase the understanding of this nascent field of HPV-associated anal disease. She facilitated much of the early work on anal cytology. We joked about calling anal cytology the "DarWin test" for Darragh-Winkler. She will be sorely missed.

Microscopically, the similarities between the diagnosis of HPV-associated lesions of the anal canal and the perianus outweigh the differences in their counterparts in the cervix and vulva. Productive HPV infection is detected on biopsy as a low-grade squamous epithelial lesion (LSIL) and the potential precancer – the result of cellular transformation by viral oncogenes – is manifested as high-grade squamous epithelial lesion (HSIL).[2] [Figure 1]

Histopathology provides a diagnosis based on a morphologic interpretation of a tissue sample. Biopsy diagnoses are often considered the gold standard for directing clinical management. Yet, any morphologic interpretation or diagnosis will have interobserver variability – be it an impression on high-resolution anoscopy, a cytologic interpretation, or a histologic diagnosis. Similar to gynecologic pathology, pathologists frequently agree on the diagnosis of anal high-grade lesions -- previously called anal intraepithelial neoplasia (AIN)3.[3] However, some diagnoses are more challenging morphologically. Pathologists employ p16 immunohistochemistry to help support a



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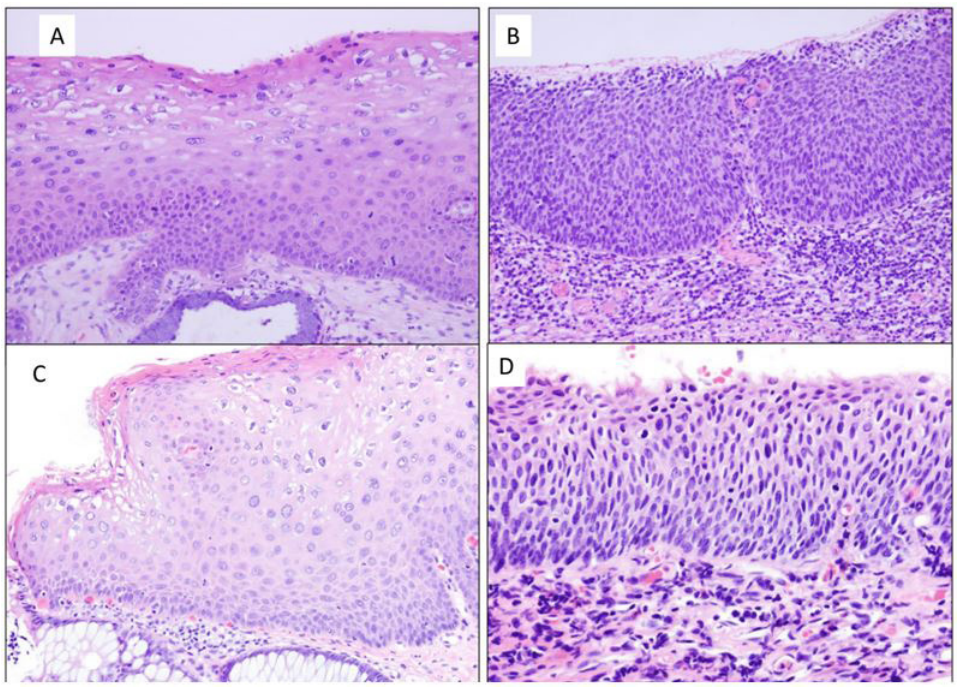
Microscopically, the similarities between the diagnosis of HPV-associated lesions of the anal canal and the perianus outweigh the differences in their counterparts in the cervix and vulva.

Figure 1

A. Cervical low-grade squamous intraepithelial lesion (LSIL), B. Cervical high-grade squamous intraepithelial lesion (HSIL), C. Anal LSIL, D. Anal HSIL.



There is a high burden of HPV in the anus – more so than in the cervix – especially in populations at greatest risk for anal cancer. Yet, anal cancer is a rare disease.

diagnosis of HSIL for biopsies that are equivocal on routine hematoxylin and eosin (H and E) stains with initial diagnoses such as atypical squamous metaplasia or the poorly reproducible diagnosis of AIN2. p16 is an oncoprotein that is paradoxically overexpressed when high-risk HPV has transformed host cells via the effect of viral E7 on another host oncoprotein, pRB. A positive p16 immunostain supports the diagnosis of HSIL in the appropriate morphologic context on H and E staining [Figure 2]. A negative p16 immunostain is consistent with a diagnosis of LSIL [Figure 3] or a reactive process [Figure 4] depending on the H and E morphologic differential diagnosis.

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Figure 2: Atypical anal squamous epithelium.
The differential diagnosis on Hematoxylin-Eosin is high-grade squamous intraepithelial lesion (HSIL) vs. a reactive process. The positive p16 immunostain (inset) supports a diagnosis of HSIL.

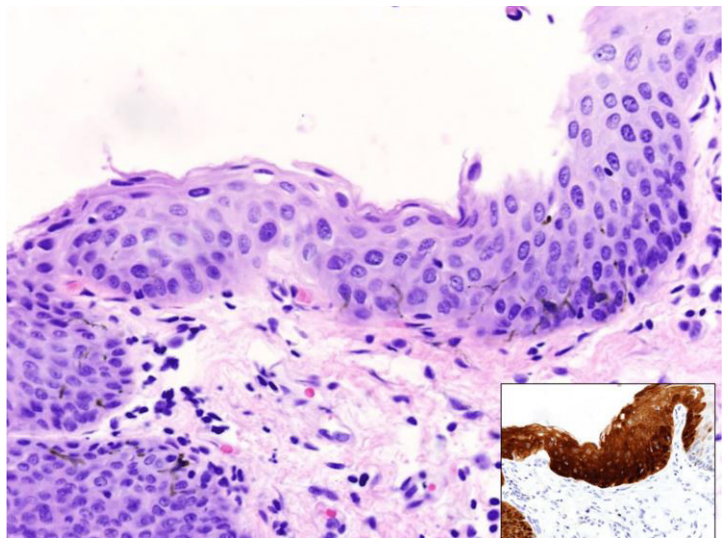


Figure 3: Morphologically, this is an HPV-associated lesion of the anal canal.
The differential diagnosis on Hematoxylin-Eosin is high-grade squamous intraepithelial lesion (anal intraepithelial neoplasia grade 2) vs. low-grade squamous intraepithelial lesion (LSIL, anal intraepithelial neoplasia grade 1). The p16 immunostain (inset) is negative; thus, the final diagnosis is LSIL -- a transformed (high-grade) lesion is not supported.

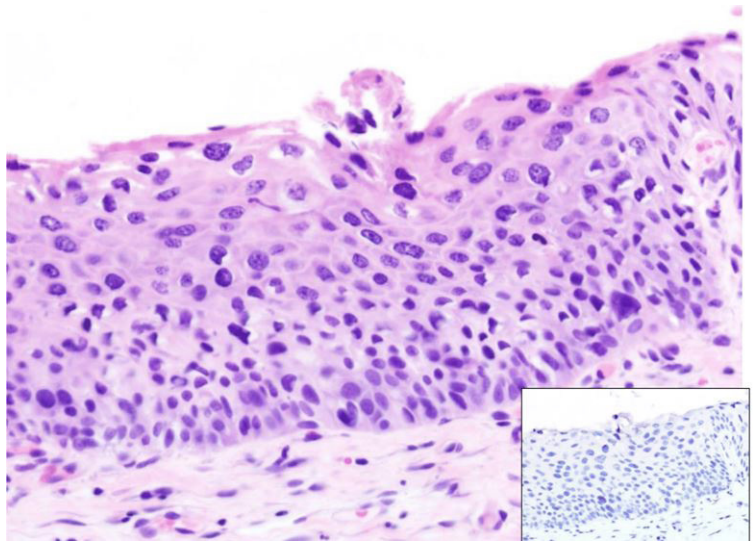
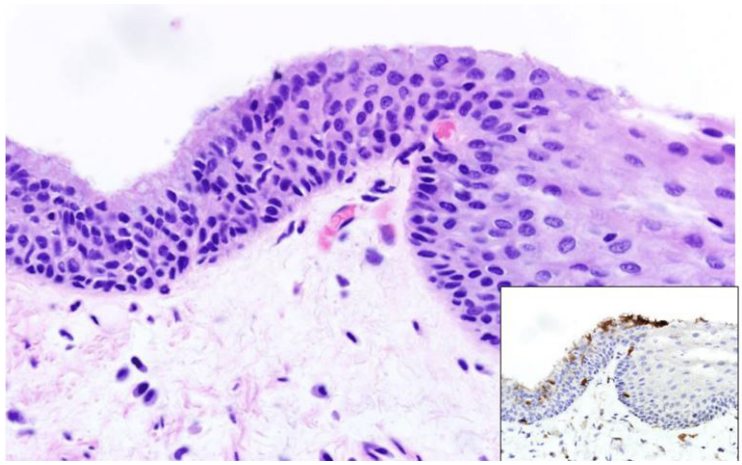


Figure 4: Atypical squamous metaplasia at the anal squamocolumnar junction.
The differential diagnosis is high-grade squamous intraepithelial lesion vs. reactive squamous metaplasia.
Given the negative p16 immunostain (inset), the final diagnosis is reactive squamous metaplasia.



Another interesting difference between the cervix and anus is the essential lack of HPV-associated glandular lesions of the anal canal.

There is a high burden of HPV in the anus – more so than in the cervix – especially in populations at greatest risk for anal cancer. Yet, anal cancer is a rare disease. Hit for viral hit, the anal canal may be less susceptible to malignant transformation than the cervix even in the face of persistent oncogenic HPV infection. Interesting work by Herfs et al has provided some intriguing clues to the issue.[4] There are key differences in the molecular markers expressed by the cells at the junction between the squamous epithelium and the glandular epithelium of the transformation zones in the cervix and anus.

Another interesting difference between the cervix and anus is the essential lack of HPV-associated glandular lesions of the anal canal. There is no well recognized anal counterpart to endocervical adenocarcinoma in situ. Almost all adenocarcinomas of the anal canal are actually misclassified rectal adenocarcinomas that have extended distally to the anus.[5] Similarly, squamous cell carcinomas of the rectum are HPV-associated cancers of the anus that have extended proximally. Herfs et al[6] have also identified a very rare HPV-associated adenocarcinoma of the anus; however, most of the rare adenocarcinomas of the anus are derived from malignant transformation of the anal sacs and are not caused by HPV. For animal lovers, you may have noticed the two dots at 3 o'clock and 9 o'clock on your pet's anus– these are the openings to the anal sacs. And beware the lowly

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skunk, who can rotate its anal glands like an anti-aircraft gun, while adjusting the spray like a hose nozzle, and aim a jet at its threat! Phew. ■

DISCLOSURE

The author declares nothing to disclose.

The anal canal may be less susceptible to malignant transformation than the cervix even in the face of persistent oncogenic HPV infection.

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Cytology and HPV Testing for Anal HSIL Screening

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Anal cancer disproportionately affects certain groups like men who have sex with men (MSM), people living with HIV (PLWH), and women with a history of lower genital tract neoplasia (LGTN). Interest exists in determining how to identify and treat those with the anal cancer precursor, high-grade squamous intraepithelial lesion (HSIL), prior to malignancy. Anal cytology has traditional been used to identify individuals at-risk for HSIL. The presence of any abnormality is followed by referral for high-resolution anoscopy (HRA), a procedure that uses a colposcope to examine the anal canal and perianus. When identified, treatment of anal HSIL typically involves ablation with electrocautery or infrared coagulation.

Cytology remains the mainstay of anal high-grade squamous intraepithelial lesion screening, although molecular testing may perform better in populations with lower prevalence of anal high-risk HPV.

Studies describing the performance of anal cytology have focused on MSM, particularly MSM living with HIV (MSMLWH). One recent such study compared anal cytology with same-day HRA in 375 MSM without HIV and 213 MSMLWH.[1] Results were consistent with previous reports and notable for low specificity and positive predictive value (PPV), but reasonable sensitivity and negative predictive value (NPV) (Table 1). Low specificity and PPV reflects the use of any cytological abnormality including atypical squamous cells of undetermined significance (ASC-US) as the threshold for HRA referral. Increasing the severity required for referral would improve these values but at the expense of sensitivity and NPV. Performance data are more limited in other at-risk populations, although a recent study of 636 women with LGTN also reported limited PPV but reasonable NPV (Table 1).[2] Thus, while a negative cytology does not entirely exclude HSIL, its use is considered acceptable given the slow progression of anal HSIL and that overall NPV will increase with serial cytologies over time. These studies also show a high PPV for biopsy-proven HSIL when the cytology shows HSIL. 59% of MSM and 42% of women had abnormal cytologies in the aforementioned studies, reflecting the large number of HRA referrals generated by cytology. This has prompted interest in determining whether newer molecular techniques like high-risk HPV (hr-HPV) testing can improve performance, particularly specificity.

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Table 1

Performance of Anal Cytology and High-Risk-HPV Testing to Detect Anal HSIL

Study	No.	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
MSM without HIV					
Jin 2016 [ref. 1]	375	83 (74-90)	55 (49-61)	40 (33-47)	89 (84-94)
MSM living with HIV					
Jin 2016 [ref. 1]	213	83 (74-91)	47 (38-56)	53 (45-62)	79 (68-88)
Dias 2019 [ref. 3]					
■ Anal cytology	2825 (pooled)	83 (72-90)	45 (31-60)	36 (23-50)	87 (78-93)
■ Hr-HPV	1855 (pooled)	91 (80-96)	27 (21-35)	37 (20-57)	87 (79-93)
Women with LGTN					
Albuquerque 2018 [ref. 2]	323	71 (61-79)	73 (66-79)	55 (46-64)	84 (78-89)

HSIL: High-grade squamous intraepithelial lesion; MSM: men who have sex with men; LGTN: women with a history of lower genital tract neoplasia; CI: Confidence interval.

Hr-HPV testing has been primarily studied for anal HSIL detection in MSMLWH, despite the absence of FDA-approval for use in the anus. A meta-analysis reported limited specificity and PPV but high sensitivity and NPV (Table 1).[3] This reflects the ubiquitous nature of anal hr-HPV in MSMLWH such that its identification does not add significant discriminatory power. While biomarkers of cellular proliferation like p16/Ki-67 or E6/E7 mRNA could theoretically improve test characteristics, their use was similarly not associated with improved performance compared with cytology alone.[3] Thus, cytology remains the mainstay of anal HSIL screening, although molecular testing may perform better in populations with lower prevalence of anal hr-HPV. It may also be a valuable alternative when access to pathologists for cytology interpretation is limited. Other approaches to testing including combinations of cytology with detection of specific HPV genotypes such as HPV 16 or 18 may be useful. There is also interest in other molecular markers of HSIL that could be used in combination with cytology or HPV testing, such as E6/E7 oncoprotein detection or methylation markers.

Existing guidelines are focused on high-risk groups. The HIV Medicine Association recommends anal cytology for certain people living with HIV: men who have sex with men, women with a history of receptive anal intercourse or abnormal cervical cytology, and people living with HIV with genital warts.

Despite our ability to identify and treat anal high-grade squamous intraepithelial lesion, there are no national guidelines recommending screening.

Despite our ability to identify and treat anal HSIL, there are no national guidelines recommending screening. This is partly due to the absence of trials demonstrating the efficacy of anal HSIL treatment in preventing anal cancer. Furthermore, the absolute incidence of anal cancer remains low in the general population such that widespread screening may be of limited benefit. Existing guidelines instead are focused on high-risk groups. The HIV Medicine Association recommends anal cytology for certain PLWH: MSM, women with a history of receptive anal intercourse or abnormal cervical cytology, and PLWH with genital warts.[4] In women, expert opinion concluded that HIV and LGTN were the most compelling indications for screening.[5] Thus, it is reasonable to perform anal cytology in these groups with prior counseling about the high probability of abnormal results and HRA referral. Cytology or other tests to detect anal HSIL should be avoided if the infrastructure to treat anal HSIL is unavailable, and instead, a yearly digitoanorectal exam to detect palpable anal cancer can be performed. ■

DISCLOSURE
The author declares nothing to disclose.

In women, expert opinion concluded that HIV and women with a history of lower genital tract neoplasia were the most compelling indications for screening. Thus, it is reasonable to perform anal cytology in these groups with prior counseling about the high probability of abnormal results and high-resolution anoscopy referral.

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Practicing and Training for High Resolution Anoscopy

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High-resolution anoscopy (HRA) is the examination of the anal canal and perianus using a colposcope and the adjunctive vital stains 5% acetic acid and Lugol's strong iodine. The intense light and magnification of the colposcope allow for visualization of lesions highlighted by tissue reactions with the vital stains, resulting in epithelial and vascular changes (Figure 1). Similar to their utility for identification of cervical precancers for diagnosis and treatment, these tools have been validated for identification of HPV-associated anal canal lesions.[1,2] The term high-resolution anoscopy first appeared in the literature in 2001, but reports of colposcopic evaluation of the anal canal appeared as early as 1977.[3] HRA has been used in limited research and clinical settings since the early 1990's, initially in the United States and United Kingdom. It is a growing field with clinics providing HRA established in more than 30 countries and in a variety of practice settings including colo-rectal and general surgery, dermatology, gastroenterology, gynecology, infectious disease, sexual health and primary care.

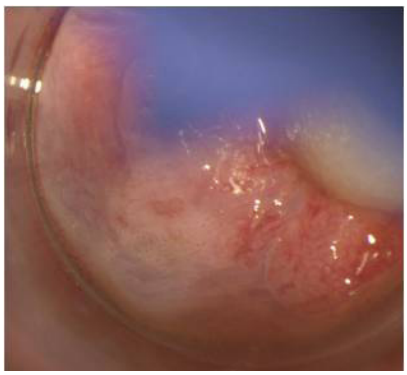
Standard anoscopy provides gross visualization of obvious lesions that may be large and thickened, but many more subtle lesions would be unappreciable without HRA (Figure 2). Lesions can potentially be found with random 4-quadrant biopsy of the anal mucosa, particularly among high-risk populations such as people living with HIV. However, this is an inefficient approach and HRA may differentiate types of lesions including high-grade squamous intraepithelial lesions (HSIL), low-grade (LSIL) and cancers. This allows for targeted biopsy for diagnosis and more precision in treatment. Prevention of progression to cancer from HSIL is predicated on removal of all HSIL and this may not be possible without the precise visualization provided by HRA.

HRA is an office-based procedure, though it can be used adjunctively for surgical procedures.[4] Incorporation of HRA in clinical practice requires an investment in equipment, training and clinician time. Necessary equipment includes a good colposcope with photo capability, an image management system and treatment equipment. Photographic capability to document lesion findings for follow up and/or referral is a necessary component of good HRA practice. It is also important to have a plan for treatment of abnormal findings, whether it will be referral to a collaborating specialist or in-office ablative therapy. An HRA practice also requires adequate investment in clinic and provider time. A consistent schedule dedicating

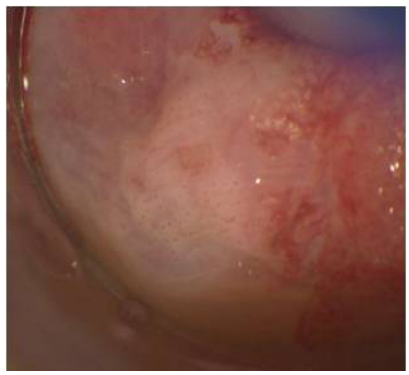
Standard anoscopy provides gross visualization of obvious lesions that may be large and thickened, but many more subtle lesions would be unappreciable without high-resolution anoscopy.

Figure 1

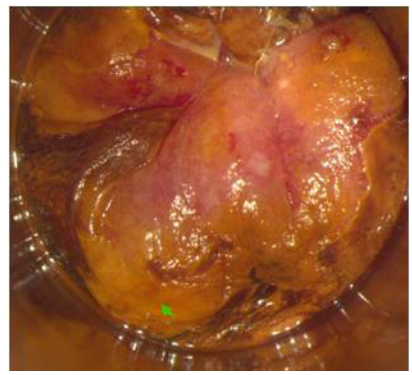
Anal lesion shown in low (A) and high (B) magnification and then highlighted by Lugol's staining (C). The magnification allows for better appreciation of vascular changes indicating HSIL, and the Lugol's staining defines the margins for treatment. The histology result confirmed HSIL.



A. Acetowhite lesion with low magnification.



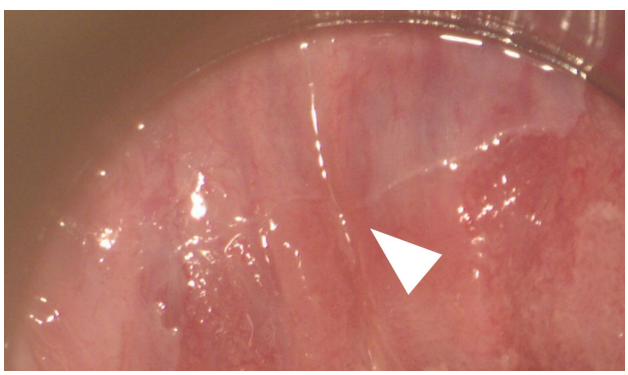
B. Lesion in A with higher magnification, showing changes in borders and vessels consistent with HSIL.



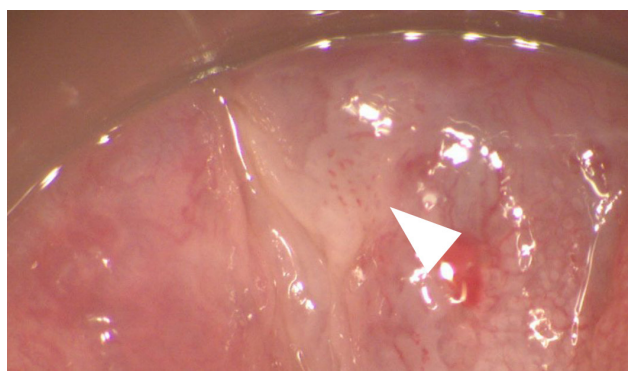
C. Lesion in A and B, outlined with Lugol's staining prior to biopsy.

Figure 2

A small, subtle lesion (A) becomes easily identified once acetic acid is applied along with increased magnification (B). The histology result confirmed HSIL in a woman with prior treated anal cancer.



A. Anal lesion with acetic acid applied, but only scantly.



B. Lesion in A with additional acetic acid and higher magnification. Now the lesion is apparent, showing vascular changes consistent with HSIL.

Incorporation of high-resolution anoscopy in clinical practice requires an investment in equipment, training and clinician time.

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a minimum of one day or session per week to HRA helps develop competency and maintain optimal skills. The clinic infrastructure should also include identification of collaborating colleagues for referral sources – depending on the provider's background, these may include a colorectal surgeon, dermatologist, gynecologist, infectious disease, or oncologist. In particular, a close working relationship with a pathologist is essential for management and interpretation of results in difficult cases.

Providers from a variety of specialties and backgrounds have received training in HRA. In most countries, medical doctors and advanced practice clinicians can perform HRA. Ideally training will include a didactic course followed by hands-on mentorship and observation with an experienced provider. Courses are offered annually through the International Anal Neoplasia Society. Unfortunately, as a young field, there is a shortage of expert clinicians to provide mentorship for hands-on training. Practice standards have been published as a guideline for establishing minimal proficiency.[5] While the difficulties of attaining a level of expertise has been documented in many studies, these same studies indicate that expertise will develop with practice.[6] There is a steady increasing demand for HRA in clinical care and research. Providers who choose to establish HRA in their practice will be rewarded by involvement in a young, growing field as well as the opportunity to serve patients seeking these much-needed services. ■

Practice standards for high-resolution anoscopy have been published as a guideline for establishing minimal proficiency. While the difficulties of attaining a level of expertise has been documented in many studies, these same studies indicate that expertise will develop with practice.

DISCLOSURE

The author declares nothing to disclose.

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Anal squamous intraepithelial lesions: risk groups and natural history

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Broadly the two groups of people who are at higher risk of anal high-grade squamous intraepithelial lesions are those with increased exposure to anal HPV infection, such as men who have sex with men, and those with immunodeficiency.

High-grade squamous intraepithelial lesions (HSIL), the precursor lesions to anal cancer, are caused by persistent infection with anal high-risk HPV (HRHPV). Like anal cancer, HPV16 is the causative type in over 80% of HPV-related anal HSIL.[1] Low-grade anal SIL is almost always the result of active viral replication of low-risk rather than high-risk HPV types and has been shown to be at extremely low risk of progressing to cancer. LSIL does not necessary precede HSIL in the anal cancer pathway.[2]

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Certain populations - people living with HIV, men who have sex with men (MSM), women with previous lower genital tract disease and solid organ transplant recipients - have increased risk of anal cancer. MSM living with HIV are at the highest risk. The logical, and accurate, assumption is that these groups also have a higher risk of anal HSIL. Much of the current understanding of anal HSIL and its natural history derives from cervical cancer research, but there are important differences between HSIL at these two anatomical sites.

There are several well-defined groups at particular risk of anal HSIL. Broadly the two groups of people who are at higher risk are those with increased exposure to anal HPV infection, such as MSM, and those with immunodeficiency. Estimates of one in five HIV-negative MSM and up to one in two HIV-positive MSM have prevalent anal HSIL.[3] This greatly exceeds the less than 2% prevalence of cervical HSIL in the general population.[4] In women, anal HSIL has been shown to be associated with cervical HRHPV and HSIL.[5] Numerous studies have reported that HIV-positive women have higher rates of abnormal anal cytology and histopathology than HIV-negative women, with an anal HSIL prevalence of 28% reported in HIV-positive women.[6] There is strong epidemiological evidence demonstrating an increased risk of anal HSIL in women with previous precancers and cancers of the cervix, vagina, and vulva compared with the general population.[7] A small number of studies have examined anal HSIL prevalence in organ transplant recipients, where prevalence ranged between 3 and 12%. The US Transplant Cancer Match Study observed a standardised incidence ratio of 11.6 for "in situ" anal cancers, which correspond to HSIL, compared with the general population.[8]

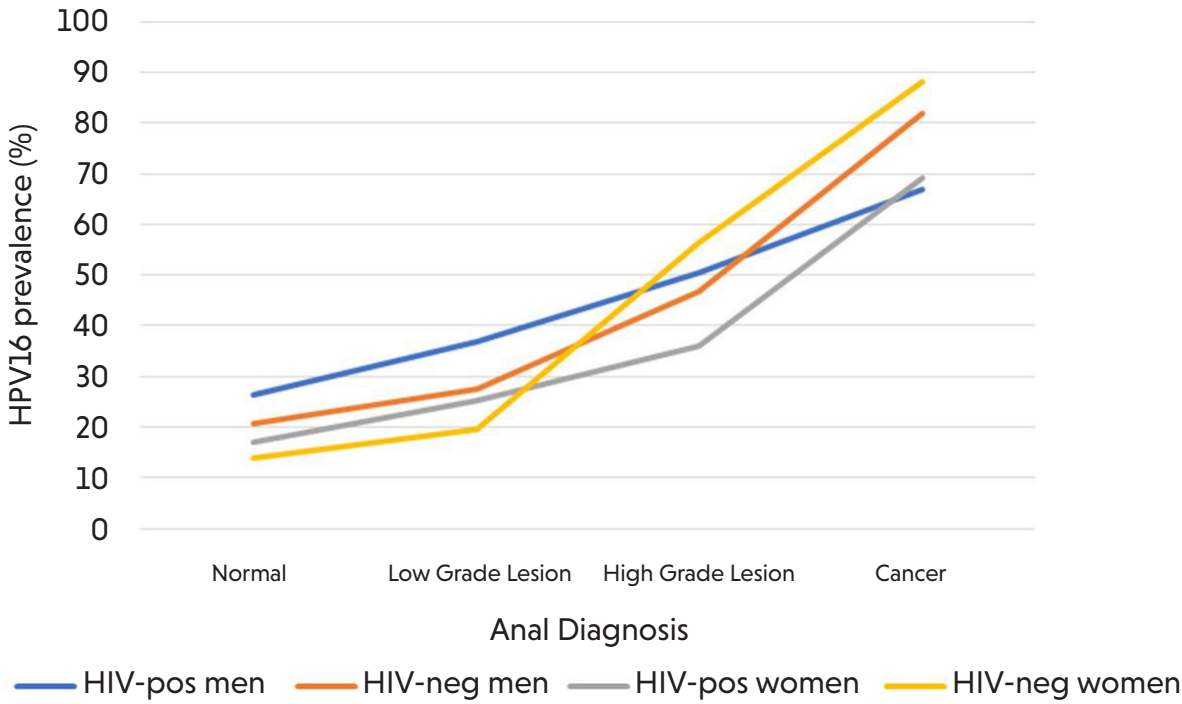
There is strong epidemiological evidence demonstrating an increased risk of anal high-grade squamous intraepithelial lesions in women with previous precancers and cancers of the cervix, vagina, and vulva compared with the general population.

The important differences in the natural history of HSIL of the anus compared with that of the cervix may be a result of biological factors, such as patterns of HRHPV prevalence, site-specific viral defences, effectiveness of immune control, and/or behavioural factors. A meta-analysis demonstrated that with increasing histological severity of HPV-related anal disease, an increasing proportion of disease is related to HPV16, irrespective of sex and HIV status (Figure 1). Non-HPV16 HRHPV type positivity was high for all groups with normal and intermediate anal diagnoses but was lower in anal cancer. In HIV-positive women, non-HPV16 types were more prevalent in anal HSIL than in HIV-negative women.[1] Based on limited data, it appears that progression rates from HSIL to cancer may be substantially lower for anal as compared with cervical HSIL.[2] In the Study of the Prevention of Anal Cancer, a cohort study of MSM aged 35 and older, there was one incident anal cancer in an HIV-negative participant, resulting in a progression rate from anal HSIL to cancer of one in 446 person-years (PY).[9] There were high rates of HSIL incidence (11.3 per 100PY), and incidence was higher among younger men, HIV-positive men, and in those with persistent HRHPV infection. HSIL clearance was also frequent (22.0 per 100PY) and was more common among younger men, after an AIN2 than an AIN3 diagnosis, smaller lesions, incident HSIL and in those not persistently infected with HRHPV. The high incidence and

A meta-analysis demonstrated that with increasing histological severity of HPV-related anal disease, an increasing proportion of disease is related to HPV16, irrespective of sex and HIV status.

Figure 1

Prevalence of HPV16 by anal diagnosis, gender and HIV status. Adapted from Lin et al[1]



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clearance of histological lesions likely reflected a high underlying rate of new HRHPV infections and subsequent clearance.

In summary, anal HSIL is common in anal cancer high-risk groups and is highly associated with HPV16, which reflects its role on the biological pathway to anal cancer. HSIL is a dynamic condition in MSM due to continued new exposures to HRHPV late into life, with high rates of spontaneous resolution. ■

High-grade squamous intraepithelial lesions is a dynamic condition in men who have sex with men due to continued new exposures to high-risk HPV late into life, with high rates of spontaneous resolution.

DISCLOSURE
The authors declare nothing to disclose.

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Treatment for Anal High-Grade Squamous Intraepithelial Lesions

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Treatment options for anal high-grade squamous intraepithelial lesion include topical therapy and targeted destruction under high-resolution anoscopy guidance. Mapping with wide local excision, historically favored by colorectal surgeons, is no longer appropriate and is associated with serious morbidity and unacceptably high recurrence rates.

High-grade squamous intraepithelial lesion (HSIL) is the invasive cervical cancer precursor, and excision or destruction of cervical HSIL significantly reduces cervical cancer. Jay et al. showed us how to identify anal HSIL, and some clinicians began treating anal HSIL with the hope that they might reduce progression to anal squamous cell carcinoma (SCCA).[1–3]

Treatment options for anal HSIL include topical therapy and targeted destruction under high-resolution anoscopy (HRA) guidance. Mapping with wide local excision, historically favored by colorectal surgeons, is no longer appropriate and is associated with serious morbidity and unacceptably high recurrence

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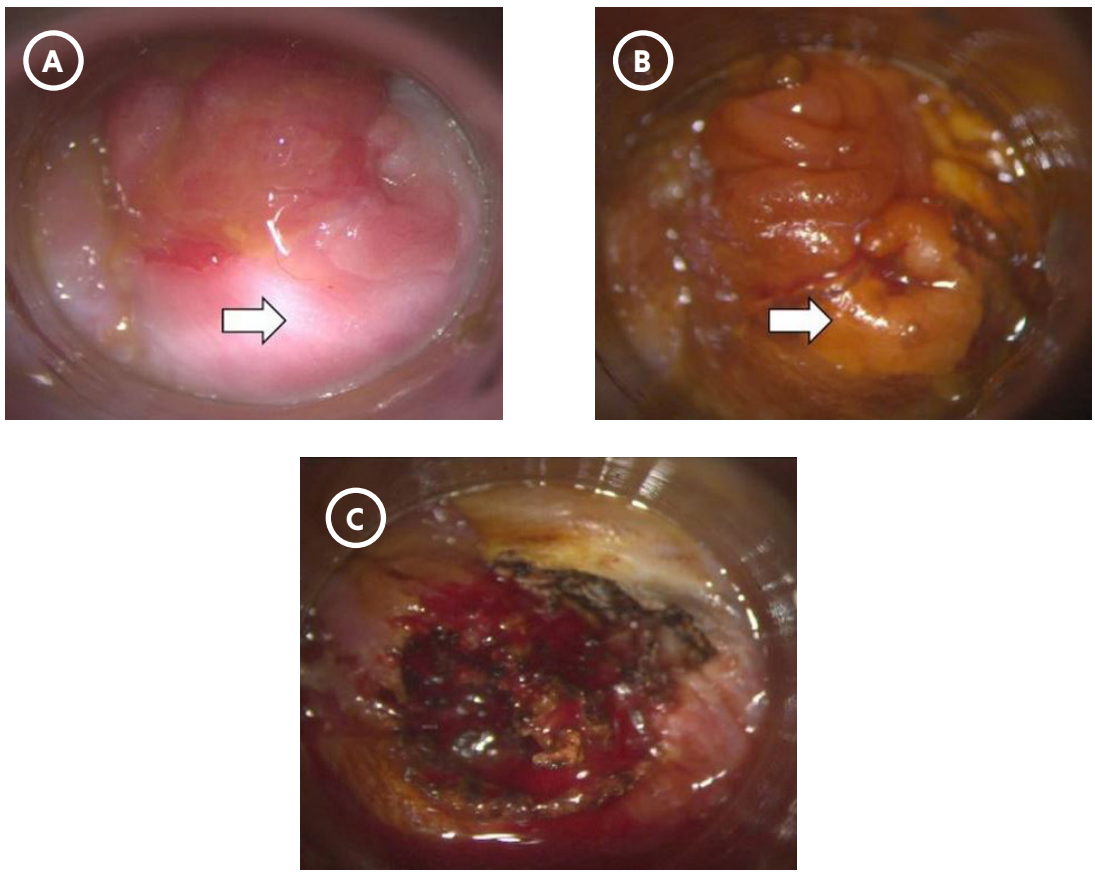
rates.[2] Topical therapies can decrease disease burden for those with extensive HSIL, or for individuals who cannot undergo ablative therapy. Clinician-applied trichloroacetic acid is efficacious particularly in small lesions.[4] One recent small study utilizing imiquimod suppositories to treat intra-anal HSIL and condyloma in people living with HIV (PLHIV) reported only a 3% complete response and 59% no-response rate.[5] The authors felt that topical therapy was useful in debulking disease prior to ablation.

Figure 1

(A.) High-resolution anoscopy view of an acetowhite lesion with coarse punctation at the squamocolumnar junction. (B.) After the application of Lugol's iodine solution, the boundaries of the high-grade squamous intraepithelial lesion (HSIL) become apparent. (C.) The HSIL was completely ablated, to the level of the submucosal vessels, using the hyfrecator at 15 watts.



In 2005, Goldstone et al first described the technique of high-resolution anoscopy-guided ablation for intra-anal high-grade squamous intraepithelial lesion. They reported a 72% individual lesion cure rate and an overall recurrence of 65% after a median of 217 days. None of the study participants developed anal squamous cell carcinoma during the follow-up period.

In 2005, Goldstone et al first described the technique of HRA-guided ablation for intra-anal HSIL.[6] HRA was performed to identify and biopsy all potential HSIL. After histologic confirmation, each lesion was re-identified using HRA and individually ablated (Figure 1). Most treatments were done in-office, using only a small amount of local anesthetic. In this initial study, ablation was performed using infrared coagulation (IRC). They reported a 72% individual lesion cure rate and an overall recurrence of 65% after a median of 217 days. Recurrence decreased as the authors gained experience over three years. None of the study participants developed SCCA during the follow-up period.

Nine years later, Goldstone et al published a comparison of IRC, electrocautery ablation (ECA) and laser ablation for anal canal HSIL in over 700 patients with up to 13 years follow-up.[2] Regardless of treatment type, Kaplan-Meier probability of recurrent HSIL at 1 year was approximately 50% in PLHIV and those without, rising to 77% and 66% by 3 years, respectively (Figure 2). Although recurrence was common, the number of recurrent lesions was low (median of 1 lesion for HIV-negative patients and 2 lesions for PLHIV). Risk factors for recurrence were living with HIV and increasing extent of disease. Five patients progressed to cancer during the follow-up period but only 1 was being actively treated for cure. Kaplan-Meier probability of SCCA in all participants was only 2% out to 10 years.

A recent clinical trial randomized 120 PLHIV subjects with small volume HSIL (maximum of 3 intra-anal lesions no larger than 15mm) to IRC ablation or observation without treatment. At one year, index lesion clearance was 62% in the treatment arm and 30% in the observation arm ($P<0.001$), and no participants progressed to SCCA.[7] A retrospective review published in 2020 reported a 50% cumulative probability of overall recurrence by 12 months after ECA in PLHIV, increasing to 68% at 36 months. Overall HSIL recurrence was associated with HIV RNA >100 copies/mL, multiple lesions at baseline, and infection with high-risk HPV strains. Of those who recurred, 95% had only 1 or 2 lesions on surveillance HRA. None of the participants progressed to SCCA.[8]

Topical and ablative therapies were compared in only one prospective, randomized trial in men who have sex with men living with HIV (MSMLWH). (...) The complete response rate at four weeks following treatment was 24% for imiquimod, 17% for 5-flurouracil, and 39% for electrocautery ablation (ECA). (...) The authors recommended ECA as the preferred method for treating anal squamous intraepithelial lesions in MSMLWH.

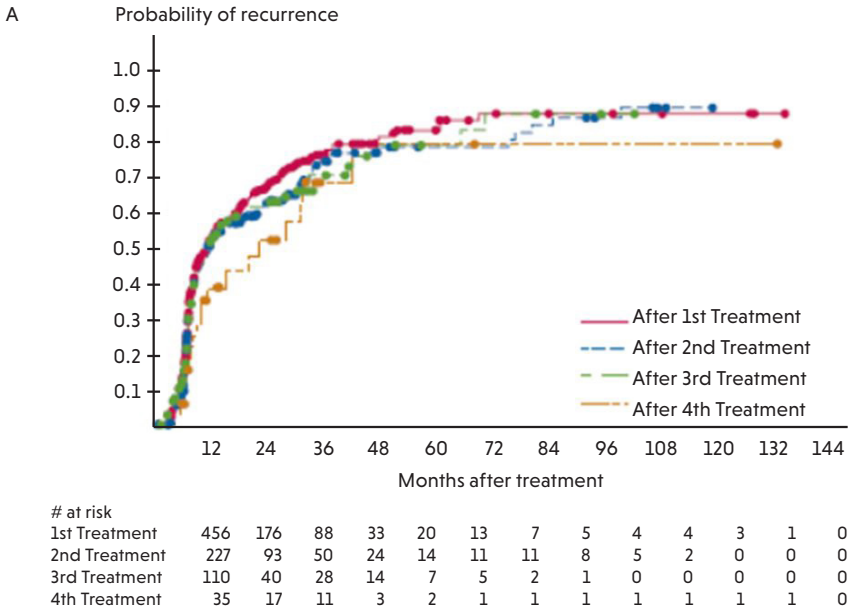
Topical and ablative therapies were compared in only one prospective, randomized trial. Men who have sex with men living with HIV (MSMLWH) with low-grade squamous intraepithelial lesions (LSIL) or HSIL were treated for 16 weeks with imiquimod or 5-flurouracil, or underwent HRA-guided ECA. The complete response rate at four weeks following treatment was 24% for imiquimod, 17% for 5-flurouracil, and 39% for ECA. Tolerability led to therapy interruptions with both topical therapies but not with ECA. No serious adverse event occurred in any of the patients. The authors recommended ECA as the preferred method for treating anal SIL in MSMLWH.[9]

We are several years away from obtaining results of the Anal Cancer/HSIL Outcomes Research study (ANCHOR, Clinicaltrials.gov NCT02135419), the first prospective, randomized trial evaluating the efficacy of treating anal HSIL to prevent SCCA. Until then, we recommend HSIL treatment, as multiple smaller studies have shown decreased SCCA when compared with observation alone.[10] ■

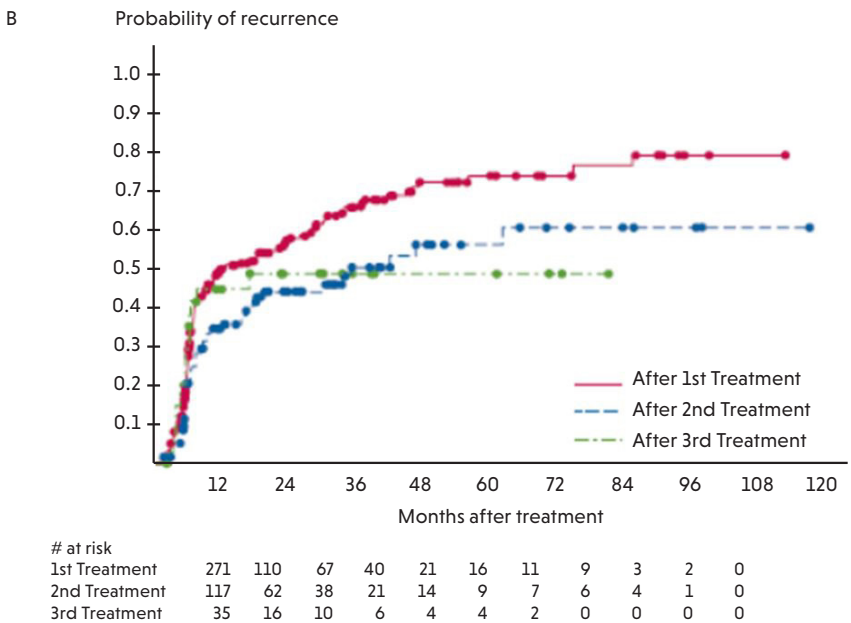
DISCLOSURE
The authors have no conflict of interests to disclose.

Figure 2

Kaplan-Meier curves for probability of recurrence in (A) People living with HIV and (B) HIV-negative individuals. Reproduced with permission from Goldstone et al, 2014.[2]



# at risk													
1st Treatment	456	176	88	33	20	13	7	5	4	4	3	1	0
2nd Treatment	227	93	50	24	14	11	11	8	5	2	0	0	0
3rd Treatment	110	40	28	14	7	5	2	1	0	0	0	0	0
4th Treatment	35	17	11	3	2	1	1	1	1	1	1	1	0



# at risk											
1st Treatment	271	110	67	40	21	16	11	9	3	2	0
2nd Treatment	117	62	38	21	14	9	7	6	4	1	0
3rd Treatment	35	16	10	6	4	4	2	0	0	0	0

We are several years away from obtaining results of the ANCHOR study, the first prospective, randomized trial evaluating the efficacy of treating anal high-grade squamous intraepithelial lesions (HSIL) to prevent anal squamous cell carcinoma. Until then, we recommend HSIL treatment, as multiple smaller studies have shown decreased anal squamous cell carcinoma when compared with observation alone.

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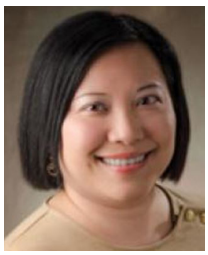
Treatment for anal cancer



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Anal cancers are mostly of squamous cell histology. They are separated into anal canal cancers and peri-anal cancers based on the location of the primary tumor. The location of the tumor in the anal region also affects the lymphatic drainage, with peri-anal and distal anal canal cancers draining mainly to the inguinal nodes, and anal canal cancers draining mainly to the anorectal, perirectal and nodes in the internal iliac system. The prognosis of anal cancer is related to the size of the primary tumor and presence of lymph node metastases.[1] If there are hypermetabolic or clinically/radiographically-enlarged lymph nodes, fine needle aspiration or excisional biopsy are recommended to confirm metastatic disease.

Surgical excision can be used to treat peri-anal cancers that are less than 2 centimeters and do not involve the anal sphincter. More advanced peri-anal cancers will need to be treated with concurrent chemoradiotherapy.

Surgical excision can be used to treat peri-anal cancers that are less than 2 centimeters and do not involve the anal sphincter. More advanced peri-anal cancers will need to be treated with concurrent chemoradiotherapy (CRT). Surgical excision can also be used to treat superficially invasive anal cancer (SISCCA), which is defined as anal cancer that is completely excised with at least 1mm margin clear of cancer, 3 mm or less depth of invasion, and horizontal spread of 7 mm or less.[2] To adequately treat SISCCA or stage 1 peri-anal cancer with surgery, surgeons need to have access to high-resolution anoscopy and the ability to treat high-grade squamous intraepithelial lesions (HSIL). SISCCA may be hard to diagnose without high resolution anoscopy and the surgical management of early anal cancer may be less definitive than chemoradiation and therefore have higher risk of recurrence. It would therefore be imperative to detect local recurrence of early anal cancer so patients can be referred for CRT or repeat surgery in a timely manner.

To adequately treat superficially invasive anal cancer or stage 1 peri-anal cancer with surgery, surgeons need to have access to high-resolution anoscopy and the ability to treat high-grade squamous intraepithelial lesions.

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For non-metastatic anal cancers that are not resectable, CRT with 5-fluorouracil (5-FU) infusion and mitomycin (or cisplatin) has been established as the standard-of-care regimen.[3,4] Mitomycin or cisplatin with capecitabine is an acceptable alternative. Most studies have delivered 5-FU as a 96-hour infusion during the first and fifth week of radiotherapy, and bolus injection of mitomycin is typically given on the first day of the 5-FU infusion. Capecitabine is given orally (Monday to Friday) for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiotherapy. CRT can provide 5-year overall survival of 60-70% for most patients. A compilation of the regimens, patient outcomes, and toxicities can be seen in Table 1.

For non-metastatic anal cancers that are not resectable, chemoradiotherapy with 5-fluorouracil (5-FU) infusion and mitomycin (or cisplatin) has been established as the standard-of-care regimen.

Table 1

Treatment regimens, patient outcomes, and toxicities for non-resectable, non-metastatic anal cancers

Trial	Number of patients	Grade 3-5 toxicities	Locoregional failure rate	Colostomy-free rate	Overall survival
UKCCCR (1996)[6]	585				
RT alone			61%		58%
RT with 5-FU/mitomycin			39%		65%
EORTC (1997)[7]	110				
RT alone			50%	40%	65%
RT with 5-FU/mitomycin			32%	72%	72%
RTOG/ECOG (1996)[8]	310				
RT with 5-FU		7%		78%	68%
RT with 5-FU/mitomycin		20%		75%	75%
RTOG 9811 (2008)[9]	644				
RT with 5-FU/mitomycin		87%	19%	75%	75%
5-FU/cisplatin followed by RT with 5-FU/cisplatin		83%	23%	70%	70%
ACT II (2013)[4]	940				
RT with 5-FU/mitomycin (+/- adjuvant 5-FU/cisplatin)		86%			78%
RT with 5-FU/cisplatin (+/- adjuvant 5-FU/cisplatin)		78%			78%

RT: radiotherapy; 5-FU: 5-fluorouracil

People living with HIV (PLWH) are at increased risk for developing anal cancer but most anal cancer clinical trials have excluded PLWH.

People living with HIV (PLWH) are at increased risk for developing anal cancer but most anal cancer clinical trials have excluded PLWH. Most evidence regarding anal cancer outcomes in PLWH are retrospective. Older case series have shown poor outcomes in terms of higher relapse rates and higher rates of treatment toxicities. However, more modern case series including PLWH with better CD4 and virologic control have demonstrated similar outcomes for PLWH with anal cancer that are comparable with their HIV-negative counterparts. Therefore, the most up-to-date national guidelines recommend that PLWH receive the same treatment for anal cancer as the general population.

Following the completion of CRT, digital rectal examination should be performed 8-12 weeks later to evaluate for presence of residual disease. Some experts also perform high resolution anoscopy to look for residual disease and high-grade squamous intraepithelial lesions. It is appropriate to wait up to 6 months post-CRT to determine if further treatment is needed because frequently residual anal cancer can resolve (as long as there is no evidence of progressive disease). If persistent residual cancer or recurrent cancer is diagnosed in the anal region, abdominoperineal resection will be needed. This surgery can be quite morbid, as anal cancer patients are prone to poor wound healing due to radiation exposure to the perineum, and a permanent colostomy is required.

If distant metastases are found, systemic chemotherapy with 5-FU/cisplatin or carboplatin/paclitaxel are usually used. These 2 regimens have similar response rates of about 60%, but carboplatin/paclitaxel may have lower rates of toxicities and higher relapse-free survival and overall survival.[5] For patients who do not respond to chemotherapy, immunotherapy with nivolumab or pembrolizumab are recommended. ■

DISCLOSURE
The author declares nothing to disclose.

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Early HPV vaccination could reduce anal cancer incidence

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Approximately 40,000 persons are diagnosed worldwide every year with anal cancer, with 88% (35,000) of cases attributable to HPV infection.[1] The United States Centers for Disease Control reports increasing incidence of anal cancer with rates of 1.8 cases of per 100,000 in 2016.[2] 84% to 88% of anal cancer is caused by HPV types contained in the currently available 9-valent vaccine (9vHPV) (6, 11, 16, 18, 31, 33, 45, 52, and 58).[1,2] Anal cancer screening strategies are being studied for some subgroups at high risk for anal cancer, but HPV vaccination remains the only accepted prevention modality for anal cancer.

HPV vaccine efficacy was studied in 602 men who have sex with men (MSM) who were randomized to receive 3 doses of the quadrivalent HPV vaccine (4vHPV) or placebo (Table 1).[3] Per protocol efficacy (PPE) was calculated in those who were seronegative at baseline and did not have detectable HPV DNA from the 4 types (6, 11, 16, and 18) from anal swabs or in anal biopsy specimens through the vaccination period (7 months). In the PPE group, 4vHPV prevented 75% of anal high-grade squamous intraepithelial lesions (HSIL) due to 4vHPV types and prevented 95% of persistent anal infection with these same HPV types. In a cross-sectional study of women exiting a clinical trial of the bivalent HPV vaccine (2vHPV), the prevalence of anal infection with HPV types 16 and 18 was 84% lower in women who were randomized to 2vHPV compared with the control group (hepatitis A vaccine) (Table 1).[4] The women included in this analysis were seronegative for HPV 16 and 18 and negative for HPV 16 and 18 DNA in the cervix prior to vaccination.

In a double-blind randomized control trial of 9vHPV versus 4vHPV in 14,215 young women, the 9vHPV was shown to be effective at preventing cervical disease and infection due to HPV 31, 33, 45, 52, and 58 and stimulated an immunogenic response to HPV 6, 11, 16, and 18 that was non-inferior to the response induced by 4vHPV.[5] On the basis of immunogenicity and prior demonstration of efficacy of 4vHPV, it is generally accepted that 9vHPV will lead to similar prevention of persistent infection and associated HSIL of the anus due to 9vHPV types in persons without prior infection.

Persons living with HIV (PLWH) have a much higher incidence of anal cancer than the general population. 4vHPV has been shown to produce long-lasting immunogenicity in PLWH[6] and 9vHPV immunogenicity and

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Table 1

Summary of referenced HPV vaccine efficacy studies.

Study	Population	Anal HPV Infection Outcome	Vaccine Efficacy on High-Grade Anal Squamous Intraepithelial Lesions
V501-020.[3] Randomized control trial of 4vHPV versus placebo in MSM without HIV aged 16 to 27.	402 of the 602 enrolled men received at least one dose of 4vHPV and did not have baseline serologic or PCR evidence of prior or prevalent HPV infection with types 6, 11, 16, or 18.	Vaccination prevented 94.9% (95% CI, 80.4 to 99.4) of persistent anal infection with HPV 6, 11, 16, or 18.	74.9% (95% CI, 8.8 to 95.4)
The Costa Rica Vaccine Trial.[4] Randomized control trial of 2vHPV versus Hepatitis A vaccination in Costa Rican Women without HIV aged 18 to 25.	Anal swabs were collected from 1,989 of the 7,466 women randomized in the study at study exit who were seronegative for HPV 16 and 18 and negative for HPV 16 and 18 DNA from cervical swabs prior to vaccination.	The cross-sectional prevalence of anal infection with HPV 16 or 18 was 83.6% (95% CI, 66.7 to 92.8) lower in women randomized to 2vHPV.	No anal biopsies were taken.
AIDS Clinic Trial Group A5289.[7] Randomized control trial of 4vHPV versus placebo in older (≤ 27 years) persons living with HIV.	575 adults were randomized regardless of baseline anal HPV infection and prevalent HSIL.	Vaccination prevented 22% (95% CI, -31 to 53) of persistent anal infection[a] with HPV 6, 11, 16, or 18 including single detection at the final visit.	0% (95% CI, -44 to 31%)[b]

HSIL: High-grade intraepithelial squamous lesions; MSM: men who have sex with men; 2vHPV: bivalent HPV vaccine; 4vHPV: quadrivalent HPV vaccine.

[a] Persistent infection in A5298 was defined as new detection of HPV 6, 11, 16, or 18 at 2 sequential 6-month visits. For this analysis (modified intent to treat) the single detection of one of these 4 HPV types at the final visit was included.

[b] Efficacy after 52 weeks. Among those with HSIL after week 52, 62% had HSIL in baseline biopsies.

efficacy in PLWH are transitively presumed. However, a double-blind randomized trial of 3 doses of 4vHPV versus placebo in PLWH ages 27 and older did not improve anal HPV disease outcomes or prevent persistent anal HPV infection (Table 1).[7] These results suggest that vaccination of older adults is not an effective strategy to reduce anal cancer rates.

Vaccination of children and adolescents with 9vHPV is expected to prevent a large majority of anal cancer cases while HPV vaccination of adults, after sexual debut, may not significantly affect anal cancer rates due to pre-existing infection.

Given the lack of other accepted anal cancer prevention modalities, widespread HPV vaccination is the best hope for reducing the burden of anal cancer worldwide.

Vaccination of children and adolescents with 9vHPV is expected to prevent a large majority of anal cancer cases while HPV vaccination of adults, after sexual debut, may not significantly affect anal cancer rates due to pre-existing infection. The impact of vaccinating children and adolescents on reducing the incidence of anal cancer will likely not be seen for decades given the time usually required to develop anal cancer after initial exposure to HPV. Given the lack of other accepted anal cancer prevention modalities, widespread HPV vaccination is the best hope for reducing the burden of anal cancer worldwide. ■

DISCLOSURE
The authors declare nothing to disclose.

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Current guidelines & recommendations for anal HPV-related disease screening

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There is no consensus in national and international guidelines regarding anal HPV-related disease screening. Recommendations can be conflicting and with low strength of evidence (expert opinion in many cases).

First, we should differentiate between anal cancer screening and screening for anal high-grade squamous intraepithelial lesions (HSIL), as recommendations for these might differ. Anal cancer screening consists of inquiring about anal symptoms, visual inspection and digital anorectal examination (DARE), with the objective of diagnosing cancer in early stages.[1] Several guidelines recommend anal cancer screening (Table 1), with variable periodicity (commonly repeating it annually). Most of the guidelines do not specify the age of starting or stopping screening. On the other hand, screening for anal HSIL consists of performing anal cytology, followed by high-resolution anoscopy (HRA) if the cytology is abnormal, with the objective of diagnosing HSIL through HRA-guided biopsy.[2,3] Regarding anal HSIL screening, there are divergent recommendations summarized in Table 1. These can be conditioned by sexual practices, concomitant diseases and/or medications, age or the presence of other HPV-related diseases. All guidelines coincide that cytology should not be done if there is no option of performing HRA if the cytology is abnormal.

Anal cancer screening consists of inquiring about anal symptoms, visual inspection and digital anorectal examination, with the objective of diagnosing cancer in early stages. (...) On the other hand, screening for anal high-grade squamous intraepithelial lesions (HSIL) consists of performing anal cytology, followed by high-resolution anoscopy (HRA) if the cytology is abnormal, with the objective of diagnosing HSIL through HRA-guided biopsy.

Table 1

Guidelines recommendations regarding anal cancer/dysplasia screening.

GUIDELINES Organization and year issued	RECOMMENDATIONS	EVIDENCE
NYSDHAI 2020[6]	Anal cancer screening* annually for all HIV ≥ 35 years old, regardless HPV vaccine status.	A2 (inquiring), A3 (inspection), B3 (DARE)
	Informed and shared decision-making with patient regarding anal cytology.	A3
	For HIV <35 years old only if anal signs/symptoms.	A3
	HRA and biopsy if abnormal anal cytology.	A2
HIVMA/IDSA 2020[7]	Annual DARE. Anal cytology in PLWH (only if HRA available): - People with receptive anal intercourse - Abnormal cervical Pap test - Genital warts	Weak recommendation. Moderate quality evidence.
	HRA if abnormal cytology.	
	No recommendation regarding periodicity.	
DHHS Nov 2018[8]	No national recommendations exist for routine screening for anal cancer.	
	Some experts recommend anal cytology or HRA for PLWH.	C3
	Annual DARE.	C3
	If abnormal anal cytology HRA + biopsy if visible lesions.	B3
EACS 10.1 October 2020[9]	DARE +/- anal cytology in PLWH: - MSM, - persons with HPV-associated dysplasia (anal and/or genital).	Expert opinion.
	HRA if abnormal cytology.	
	Screening interval: 1-3 years.	
GeSIDA 2019[10]	Annual anal cancer screening. *	A3
	Annual anal cytology in PLWH including: - MSM, - women with genital HPV-related dysplasia, - heterosexual men/women with genital warts.	B3
	HRA +/- biopsy if abnormal cytology.	B3
BHIVA 2014[11]	Role of annual anal cytology and HRA not proven yet; patients encouraged to check/report lumps in anal canal (recommendations from the 2008 guidelines).	Consensus or expert opinion.
	Advocate surveillance for AIN by HRA.	
DAIG 2015[12]	Annual anal cytology in all PLWH.	Not reported.
	HRA if abnormal cytology.	
	Consider the use of HPV typing.	
ASCRS 2018[13]	Anal cytology may be considered in high-risk population: PLWH, MSM, history of cervical dysplasia.	Weak recommendation. Moderate quality evidence.
	HPV testing may be used as an adjunct to screening for anal cancer.	
	HRA may be considered as a screening option for patients at high risk for cancer.	
ASTIDCP 2019[14]	Anal cytology in solid-organ transplant recipients if history of receptive anal intercourse, history of cervical dysplasia.	Weak recommendation. Low quality evidence.
	HRA if abnormal cytology.	
	Normal cytology repeated every 1-3 years.	

AIN: Anal Intraepithelial Neoplasia; HIV: human immunodeficiency virus; HPV: human papillomavirus; HRA: high-resolution anoscopy; MSM: men who have sex with men; PLWH: people living with HIV; DARE: digital anorectal examination.

Legend for Evidence Column:

A. Strong evidence, should always be offered. B. Moderate evidence, in general should be offered. C. Weak evidence, must be offered optionally. 1. Data from randomized clinical trials or metaanalysis; 2. Data from non-randomized trials or observational cohorts; 3. Expert opinion.

* Anal cancer screening includes inquiring about anal symptoms, performing visual inspection of the perianal region and digital anorectal examination (DARE).

The prevalence of anal cancer in the general population is low, and does not justify routine screening. However, it is much higher in specific populations, which primarily include people living with HIV, with the highest risk in men who have sex with men, followed by hererosexual men/women living with HIV, women with genital HPV-related dysplasia/cancer and men/women with genital warts.

The prevalence of anal cancer in the general population is low, and does not justify routine screening. This is reflected in guidelines issued by "general" societies (Colorectal Surgeons, Medical/Surgical Oncology, etc). However, the prevalence of anal cancer is much higher in specific populations and the recommendations in guidelines focusing on these high-risk individuals must be reviewed. These primarily include people living with HIV (PLWH), with the highest risk in men who have sex with men (MSM), followed by heterosexual men/women living with HIV, women with genital HPV-related dysplasia/cancer and men/women with genital warts. In recent years, other high-risk populations have been considered, including transplant recipients receiving immunosuppressive medication, but with low quality of evidence.[3]

A major caveat is that some of these guidelines were published many years ago (some more than a decade ago). For example, one of the pioneer guidelines regarding anal HSIL screening, the New York State Department of Health AIDS Institute, has just recently updated its recommendations in March 2020, the previous version being from 2007. However, guidelines revised on a yearly basis (national/international HIV guidelines) review all aspects of HIV clinical management but usually provide only generic recommendations regarding cancer screening in PLWH.

There are several aspects that explain the lack of consensus between guidelines. The low grade of evidence makes it difficult to establish screening programs, which in turn makes it difficult to generate solid data to increase the level of evidence, generating a vicious circle. We need data confirming that anal HSIL screening and treatment has an impact reducing anal cancer, and the Anal Cancer/HSIL Outcomes Research (ANCHOR) study will be crucial in this aspect. We also need cost-effectiveness studies to justify implementing screening programs, and these studies will need to be country-specific.

Finally, other guidelines to consider are the International Anal Neoplasia Society (IANS) guidelines for practice standards in the detection of anal cancer precursors and for the practice of digital anal rectal examination.[4,5] These guidelines give recommendations on how to adequately perform DARE; the minimum standards for performance of DARE, anal cytology and HRA; and the minimum competencies anoscopists should have and how to evaluate them . ■

DISCLOSURE

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We need data confirming that anal high-grade squamous intraepithelial lesion screening and treatment has an impact reducing anal cancer, and the ANCHOR study will be crucial in this aspect. We also need cost-effectiveness studies to justify implementing screening programs.

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The Modern Anal Neoplasia Clinic

Five essentials that comprise the modern anal neoplasia clinic are a colposcope, power exam table, table set up, image capturing system and a hyfrecator (Figures 1 and 2).

A colposcope is used to closely examine the anal canal for disease caused by HPV. It is a low-power, stereoscopic, binocular, field microscope with a powerful variable intensity light source that illuminates the area being examined.[1] The head of the colposcope contains the optic lens, two ocular lenses or eyepieces, a light source and a knob to change the magnification of the objective lens.[2] A colposcope can be fitted with halogen, xenon, tungsten or incandescent bulbs. Halogen is usually preferred as it gives off the whitest light. Modern colposcopes will have the ability to change magnification. To focus the colposcope, adjust the distance between the objective lens and the patient. Colposcopes are generally quite heavy and are either mounted to the wall or ceiling or mounted on the floor pedestal with wheels.

A hydraulic table with stirrups should be a central part of the examination and treatment room. Patients are placed in the left lateral decubitus position for examinations. The table should be able to be raised about three to four feet off the ground for good ergonomics while performing exams. The table should have bariatric specifications for heavy patients. Most tables will have storage capacity as well, which is where we usually store Tischler forceps.

An image capturing software program must be set up to capture images of the anal canal. Lesions that are noted during the exam and photographed are stored on a hard drive for comparison from visit to visit. This system can be used to capture video or still photos, but video is used sparingly because of the large amount of hard drive storage required.

A table set is up in easy proximity to the clinician, on which is placed a tray that has all the equipment needed to perform the exam. These include a nylon swab to collect an anal cytology and a Thinprep™ container to collect an anal cytology sample. An anoscope and lidocaine cream are available for insertion into the anal canal. A cotton tipped wooden applicator is wrapped with a four-by-four gauze to create a swab that can be soaked in vinegar (5% acetic acid) and inserted into the anal canal.[3] Cotton-tipped wooden applicators are used for applying supplemental vinegar and strong Lugol's iodine solution to the anal canal. These techniques enhance the visibility of anal

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A colposcope is used to closely examine the anal canal for disease caused by HPV. It is a low-power, stereoscopic, binocular, field microscope with a powerful variable intensity light source that illuminates the area being examined.

Figure 1

Modern anal neoplasia clinic room with colposcope, power table and video capturing software.

Figure 2

Table set up for examination with nylon swab, Thinprep™ vial, lidocaine cream, disposable plastic anoscope, cotton-tipped wooden applicators, scopettes, small cotton swabs, stick wrapped in gauze soaked in 5% acetic acid and strong Lugol's solution.

squamous intraepithelial lesions. If lesions are noted during the exam, they will be biopsied with the Tischler forceps.

An image capturing software program must be set up to capture images of the anal canal.

In the modern anal neoplasia clinic, an examiner using high-resolution anoscopy can identify potentially precancerous HSIL and anal cancer, and is used to target the most worrisome vascular changes or other signs for biopsy. If a biopsy shows HSIL, these can usually be treated in the modern anal neoplasia clinic as an outpatient. The most common treatment currently used is hyfrecation, a form of electrocautery. After injecting local anesthetic, typically 1 or 2% lidocaine with epinephrine, and buffered with 8.4% bicarb in a 5:1 lidocaine:bicarbonate ratio, the hyfrecator sends an electric current down a wand to a metal tip.[4] When electric current is supplied to the tip, tissue will be destroyed immediately. A smoke evacuator is needed, and a special hyfrecation tip is available that has a hollow tube that obviated the need to have an assistant holding a smoke evacuator hose and prevents the smoke from obstructing the view of the clinician, this procedure is usually tolerated very well. ■

The most common treatment currently used for high-grade squamous intraepithelial lesion is hyfrecation, a form of electrocautery.

DISCLOSURE

The author declares nothing to disclose.

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