

Cytopathology + More | Anal cytology: life-saving potential at low cost

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January 2016—Anal cancer incidence is on the rise in North America with rates of both invasive and in situ squamous carcinomas of the anus increasing sharply over the past several decades. While women have the highest overall likelihood of developing anal carcinomas, certain male subpopulations (namely men who have sex with men and those who are HIV positive) are at a dramatically increased risk of developing squamous precursors and carcinomas of the anal canal. As with the cervix, squamous carcinomas of the anus are associated with infection by oncogenic types of human papillomavirus.

Most precancerous and malignant squamous proliferations of the anus develop in the anal “transition zone,” which lies at and just proximal to the dentate line. This anatomic region is also known as the intermediate or cloacogenic zone, and its lining can include nonkeratinized squamous, transitional, basal, cuboidal, and columnar epithelial cell types. The anal transition zone is in many ways analogous to the transformation zone of the uterine cervix, where most cervical dysplasias and carcinomas arise.

Although there are no national guidelines addressing screening for anal cancer, progress is being made. In 2013, the Infectious Diseases Society of America published “Primary Care Guidelines for the Management of Persons Infected with HIV.” This document emphasizes that HIV-infected men and women with HPV infection are at increased risk for anal dysplasia and carcinoma. The IDSA guidelines for patients with HIV disease state that men who have sex with men, women with a history of receptive anal intercourse or abnormal cervical Pap test results (atypical squamous cells and above), and those with genital warts should have anal Pap tests.

In mid-2015, an excellent publication was put forth by a group of experts convened by the American Society for Colposcopy and Cervical Pathology and the International Anal Neoplasia Society. This group reviewed the literature on anal HPV infections, anal squamous intraepithelial lesions, anal cancers in well women, those with histories of HPV-associated disease, and the immunocompromised. Even though anal cancer is more common in women than in men, it is overall a rare disease and an unlikely target for cost-effective, population-based screening. Thus, when considering screening women for anal cancer, the main conundrum is whom to screen—who among the population of all women is at greatest risk? The ASCCP and IANS experts made recommendations based on a systematic review of more than 125 peer-reviewed studies, incorporating potential health benefits, adverse effects, and risks; a formal cost-benefit analysis was not possible, however, and was not performed.

One of their important recommendations is to screen all women at increased risk of anal cancer with digital anorectal examination, a cancer screening test in which the palpating finger can detect areas of hardness, induration, or pain that may be suspicious for carcinoma. In addition, screening for preinvasive squamous lesions by anal cytology can be considered in women with HIV disease, given the high incidence of anal cancer in this population. HIV-positive women screened by anal cytology and found to have abnormal results can then be referred for high-resolution anoscopy and targeted biopsies. The publication also suggests that women with high-grade vulvar, vaginal, or cervical HPV-associated lesions or cancers may benefit from anal cytology screening.

Another important advance in anal cancer screening is a recently launched multicenter prevention trial, the Anal Cancer HSIL Outcomes Research (ANCHOR) study. The primary objective of ANCHOR, which is funded by the National Cancer Institute, is to determine whether treating patients with biopsy-proven anal HSIL is effective in reducing the incidence of anal cancer in HIV-infected men and women. In this study, men and women 35 years of age and older with HIV disease and biopsy-proven HSIL are randomized to treatment versus active monitoring with

close surveillance (including high-resolution anoscopy) at least every six months, for up to five years. This study will provide evidence to determine if detection of anal precancer—and its subsequent treatment—changes the natural history of the disease and, by extension, where screening for intraepithelial lesions is worthwhile.

As persons with HIV disease live longer on highly active antiretroviral therapies, the durations of potential co-infections with HPV are prolonged, allowing time for comorbid conditions (like anal cancers) to develop. Results of studies like ANCHOR will contribute to informed decision-making and may support the evidence base that screening tests coupled with early disease management may decrease morbidity, mortality, and expense. Joel Palefsky, MD, ANCHOR principal investigator, has been quoted as saying, “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.” In many practice settings, non-HIV-infected men who have sex with men may also be screened for anal squamous intraepithelial lesions by anal cytology, depending on their individual clinical situations.

Sexual practice patterns and societal attitudes toward sexuality are changing in North America and elsewhere. A 2010 study by investigators at the Kinsey Institute of Indiana University, who surveyed more than 5,000 American women, confirmed that 20 to 25 percent of women between ages 20 and 40 reported engaging in receptive penis in anus intercourse. In another study, 20 percent of black and Latino adolescent females reported engaging in heterosexual anal intercourse, with an additional 50 percent reporting refusal of attempts at such. Heterosexual anal intercourse is a complex behavior that is viewed by some as a means to preserve virginity and prevent pregnancy. It can be a mechanism for spread of sexually transmitted infections, including HIV and HPV. Many primary care physicians and gynecologists do not discuss patterns of sexual behavior or specifically question patients regarding their participation in anal intercourse, and many people are not attuned to the concept that anal sex may be related to later development of anal carcinoma.

Pathologists may ask, “What can I do in my professional community to become involved with anal cancer prevention?” As with cervical cancer prevention, screening requires a multidisciplinary approach in which clinicians perform screening tests and manage abnormal screening results and laboratorians evaluate screening and diagnostic tests. The collection methods for anal cytology are simple and minimally invasive. (A concise and step-by-step algorithm for specimen collection is given in a March 2011 supplement to the *Journal of the American Osteopathic Association*.) Laboratory preparation and interpretation of specimens are analogous to those for cervicovaginal cytology. While some large hospitals and academic medical centers have anal neoplasia screening services in place, many smaller cities lack these services. Establishing a screening service in a smaller practice setting is feasible and can be accomplished by partnering with an interested clinician and referring patients to regional centers for necessary management. No matter what a pathologist’s geographic location, there may be patients who could benefit from a simple and inexpensive exfoliative anal cytology test.□

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