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High-resolution anoscopy: Is it necessary in the management of anal epithelial neoplasia

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A B S T R A C T

The prevalence of anal cancer has more than doubled in the United States over the past 30 years. Consequently, there is a need to develop effective screening, treatment, and surveillance programs for patients at increased risk for anal cancer. Many of these approaches have been borrowed from cervical cancer due to the shared pathology involving the human papillomavirus and successful screening and surveillance methods developed with the use of high-resolution magnification. However, there is limited evidence to support the use of high-resolution anoscopy for populations at increased risk for anal cancer. In this review, we will examine the literature evaluating the use of high-resolution anoscopy and its role in the screening, surveillance, and treatment of patients at risk for developing anal cancer.

Introduction

The incidence of anal cancer has been growing in the United States. In the past 30 years, the prevalence of anal cancer has increased from 0.7 to 2 cases per 100,000 people.[1] However, the mortality associated with anal cancer has remained relatively constant at 0.2 per 100,000 people since the early 1990s.[2] The human papillomavirus (HPV) is detected in over 90% of anal cancers and is believed to play a critical role in anal carcinogenesis.[3] The prevalence of HPV in the world population is estimated to be 11–12% with 79 million infections detected annually in the United States.[4] However, of the 610,000 cancers attributable to HPV worldwide, only 13% are anal cancer.[4]

The majority of HPV-associated cancers are cervical in nature. Cervical cancer has a well-heralded screening, treatment and prevention program that has dramatically reduced the incidence of cervical cancer, the leading cause of death in women of childbearing age, by more than 60%.[5] Prevention of anal cancer is a more recent phenomenon, and when creating an anal cancer screening, treatment and prevention program, much of the data has been extrapolated from data on cervical cancer.[6]

One of the tools used successfully for screening, treatment, and surveillance in cervical cancer is high-resolution magnification. The use of colposcopy has been quickly extrapolated to use in anal cancer screening.[7] But data regarding the availability, cost-effectiveness, and quality of high-resolution anoscopy (HRA) is still sparse. By comparing the use of colposcopy in cervical cancer prevention to HRA in anal cancer prevention, the questions and issues that stymie the successful implementation of HRA into a prevention program can be well elucidated.

Similarities and differences between cervical cancer and anal cancer

There is no doubt that the relatively young field of anal cancer prevention can derive benefits from drawing parallels from a successful cervical cancer prevention program. There are many similarities between cervical and anal cancer. Histologically, both diseases are intimately associated with HPV infections, where early detection and treatment of dysplasia can prevent progression of disease into cancer.[6] The location of dysplasia and cancer effects both external and internal tissue, requiring some degree of invasive exam for evaluation, diagnosis, and treatment. These similarities make extrapolations from a successful cervical cancer prevention program to anal cancer prevention tempting.

However, there are also significant differences. HPV prevalence peaks in women with cervical intraepithelial neoplasia (CIN) in the third decade, but then tends to be cleared through natural processes, reducing the risk of dysplasia over time.[8] There is no such “clearing of HPV” in human immunodeficiency virus (HIV)-negative men who have sex with men (MSM). The average age of diagnosis of a patient with anal cancer is in the 60s.[6] While cervical dysplasia does affect immunosuppressed patients, the

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risks are similar to those of the general population; in contrast, in anal cancer, patients infected with HIV, MSM, patients on immunosuppression following organ transplantation, and those with a history of genital intraepithelial neoplasia are disproportionately at risk.[9,10] MSM are at highest risk of developing anal cancer regardless of their HIV status.[11]

History of colposcopy screening and treatment in cervical cancer

The history of screening and treatment in cervical cancer begins with the introduction of colposcopy, a form of high-resolution microscopy, in 1925 and invention of the Papanicolaou (Pap) smear in 1928. Pap testing was standardized in the 1950s, and colposcopy was implemented regularly for treatment of cervical dysplasia in the United States in the 1970s.[12] Between 1955 and 1992, the incidence of cervical cancer and death rates decreased by over half.[5]

While colposcopy is considered the gold standard, there is a great deal of operator-related discrepancy in the quality of exam. This affects the ability to fully identify key landmarks, the decision to biopsy lesions, as well as confirm pathological diagnosis after biopsy. Studies, demonstrate sensitivities for identification of neoplasia (CIN2 or higher) of 80–90%, but specificities of closer to 60%, with most experts "overestimating" the incidence of advanced neoplasia.[13] A second study evaluating colposcopists' diagnostic assessment noted that underdiagnosis occurred in 16–25% of cases and overdiagnosis in 20–44% of cases when compared to pathologic findings.[14] Basing decisions on colposcopically noted lesions alone may not be appropriate. A recent study demonstrated that, in expert hands, colposcopy-guided biopsies alone had a sensitivity of only 61% for CIN3 and concluded that obtaining additional "colposcopy negative" biopsies (random biopsies) were just as important in the identification of cervical dysplasia.[15]

Recent recommendations have curtailed the routine use of colposcopy. Based on cost, risk, and population data, a consensus statement from American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening recommended colposcopic evaluation only in patients with LSIL or more severe on cytology, or normal cytology with positive co-testing for HPV 16[16] These recommendations decreased the use of colposcopy from a diagnostic to a treatment tool and decreased the lifetime frequency of the procedure to 760 colposcopies per 1000 women.

Screening, treatment, and surveillance in anal cancer

These parallels between anal and cervical cancer have led to the adoption of similar policies for screening, treatment, and surveillance. There is no doubt that screening, treatment, and surveillance of anal dysplasia makes sense, particularly in high-risk populations.

Early literature that simply watched the progression of anal intraepithelial neoplasia (AIN), and demonstrated in the absence of early treatment a high risk of progression to anal squamous cell carcinoma (ASCC), which provided data to parallel cervical cancer data. Untreated AIN progresses to ASCC in rates ranging from 4.7% to 11%.[17–19] Data from these studies is generally limited to small case cohorts and retrospective series.

The retrospective study by Watson et al.[17] found that of 72 patients diagnosed with AIN, 11% of patients progressed to ASCC at a median of 42 months follow-up. Unfortunately, their surveillance methods are poorly described with respect to the use of Pap smear, vital staining, or microscopy.

Another small series by Devaraj and Cosman[18] included 40 patients over an 8-year period. Patients were seen every 6 months for a physical exam but abnormal areas that appeared stable were monitored and not treated. They reported that 3 patients (7.5%) developed ASCC during this time period. Of these patients, 2 had severe, multifocal dysplasia on initial evaluation and developed ASCC at 10 months and 16 months after initial biopsy. The remaining patient also had severe, multifocal dysplasia at initial biopsy and developed ASCC at 84 months after initial evaluation. A separate study by Weis et al. followed 42 patients with high-grade AIN (equivalent to high-grade squamous intraepithelial lesions, HSIL) defined as AIN2 or AIN3, who also did not receive treatment. Less than 5% of patients developed ASCC at 28 months of follow-up.[19]

When patients are monitored closely and treated, they demonstrate significantly lower rates of progression.[19–23] Pineda et al.[24] used HRA to evaluate and monitor 246 patients with evidence of HSIL. These patients were closely surveyed every 4–6 months with cytology, digital anorectal examination, and HRA. Only 3 (1.2%) patients progressed to cancer and 2 of them were lost to close follow-up. One patient had treatment limitations due to anal stenosis.

A large study of over 700 patients by Goldstone et al. underwent close follow-up with most patients undergoing digital anorectal examination with standard anoscopy at 3 months, and HRA surveillance at 6 months. Patients without evidence of HSIL were seen every 6 months for 2 years and if they had no evidence of dysplasia at that time, they were then seen annually. HRA was only performed during this period if a patient had a visual lesion, a palpable lesion on digital anorectal exam, or abnormal cytology. In this study, only 5 patients progressed to ASCC, of whom 3 had been lost to follow-up, and 1 developed HIV-related comorbidities requiring termination of HSIL treatment.[23]

Additionally, Dalla Pria et al.[25] evaluated 368 HIV MSM who were asymptomatic for AIN (without pain, bleeding, or other lesions noted by the patient) and were screened using anal cytology and HRA with biopsies of visual lesions. They found that during the surveillance period, only 1.4% ($\underline{n} = 5$) of patients developed invasive ASCC. Of note, 1 of these patients was unable to undergo anoscopy at first presentation, and the other 4 patients had AIN2 or AIN3 at initial evaluation. Median time from most recent HRA to diagnosis of anal cancer was only 4 months, demonstrating the risk of progression, even within a surveillance program.

This data demonstrates commonality that when patients are noncompliant with treatment of either AIN or HIV, as well as close surveillance, they are more likely to develop ASCC. This data highlights the necessity of surveillance and treatment programs in patients with known AIN. Surveillance of AIN, as in cervical neoplasia, appears to be key to limiting progression of disease. Multiple studies have demonstrated that progression of disease is associated with failure of treatment, compliance, and follow-up.[23,25] The question remains whether more patients should undergo more frequent surveillance, rather than limiting surveillance to practitioners trained and competent in HRA.

How critical is HRA in a screening program?

These studies failed to separate treatment and surveillance, from the use of HRA in treatment and surveillance. To date, only one study has evaluated structured surveillance programs with and without HRA. Crawshaw et al.[26] demonstrated that rates of progression do not differ in a retrospective series of 424 patients in which 2 physicians performed HRA and the other 3 performed surveillance without HRA. Median follow-up was at least 3 years in