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Comparison between Cervical Cancer and Anal Cancer Screening

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Abstract

When it comes to simple anatomy, the colon, rectum and anus all seem to be part of the same gastrointestinal highway, so wouldn't the cancers that develop in these different...stretches, be the same? While colon and rectal cancers can be similar and are often referred to collectively as colorectal cancer, anal cancer is completely different in significant ways, including the cell type where cancer begins, the cause of the cancer, who gets this cancer, and how we treat it. Anal cancer is more similar to cervical cancer because the tissue that lines the anus (where anal cancer typically develops) is like the tissue that lines a woman's cervix. Most anal cancers are related to human papillomavirus (HPV) infection like cervical cancer, and the precancerous and cancerous changes that we see in the anal canal are also similar to cervical cancer. Cervical disease and anal-centric malignancy share numerous likenesses including causation by oncogenic human papillomaviruses; in any case, critical contrasts exist in their study of disease transmission, hazard factors, biologic conduct, the executives, and treatment. Albeit uncommon, the rate of anal-centric malignant growth is alarmingly high and keeps on expanding in high-hazard populaces, especially men who have intercourse with men paying little heed to their human immunodeficiency infection (HIV) status. There are no public evaluating rules for butt-centric malignancy. Utilizing the achievement of cervical malignant growth screening as a model, anal-centric disease screening approaches apply anal-centric cytology, high-goal anoscopy, and guided biopsy to direct treatment and the executives' techniques.

Keywords: Anal cancer • Anal dysplasia • HPV • HIV/AIDS

Abbreviations: HPV: Human Papilloma Virus • AIDS: Acquired Immunodeficiency Syndrome • HIV: Human Immunodeficiency Virus • HSIL: High-grade Histologic Lesions • aSCCA: Anal Cancer Squamous Cell Carcinoma • CD4: Cluster of Differentiation Four • HRA: High Resolution Anoscopy

Introduction

The incidence of anal cancer squamous cell carcinoma (aSCCA) is increasing both in the general population and disproportionally in high-risk groups [1,2]. The HIV epidemic has been partially responsible for this increase due a rise in chronically immunosuppressed hosts [3]. The advent of highly active antiretroviral therapy has not ameliorated the increased incidence of anal cancer, and instead may be indirectly contributing to the increase. The pathophysiology of anal cancer mimics that of cervical cancer in several respects. Both cancers are due to chronic infection with human papilloma virus (HPV) [4], which results in characteristic dysplasia that progress over years. Immunologic control of HPV infection results in regression of dysplasia, and while this can occur in high-grade lesions regression is difficult to predict prospectively [5].

Screening for cervical cancer through the use of cervical cytology (Papanicolaou or "Pap" smears) with subsequent colposcopy and biopsy of abnormal screening results and complete ablation of high-grade lesions has decreased the incidence of cervical cancer in the developed world [6]. Although never proven in a randomized, controlled fashion, epidemiologic evidence has demonstrated the efficacy of cervical cancer screening.

A similar paradigm has been established for anal cancer screening in high-risk groups. This involves screening with anal cytology followed by high-resolution anoscopy of patients with abnormal screening results and ablation of high-grade histologic lesions (HSIL). Performance characteristics of anal cytology are similar to cervical Pap smears in some respects but different in others [7].

Despite similarities, several differences exist between cervical cancer and anal cancer screening. These include the anatomy of the involved organs, rates of high-risk HPV positivity of target populations, progression rates of high grade dysplasia, and the efficacy of ablative therapies. As a result, there are several questions regarding anal cancer screening: Which groups should be targeted for screening? What is the optimal screening modality and frequency? How does anal cytology compare to cervical cytology? Most importantly: Does anal cancer screening prevent anal cancer?

Literature Review

As cervical cytology is a well-known, accepted practice among clinicians it serves as an important comparator for anal cytology. This review focuses on anal cytology and compares it to cervical cytology. It attempts to outline what is known and highlight areas needed for future research in order to more definitely establish anal cancer screening as standard of care.

Pathophysiology of anal dysplasia and anal cancer

Human papilloma virus (HPV) is a non-enveloped double stranded DNA virus. There are over 100 serotypes known to infect humans [8]. HPV infection of stratified squamous mucosa of the anal canal occurs as a result of direct exposure or as a "field effect"; i.e. from HPV infection elsewhere in the perineum [9]. The virus enters through microabrasions in the epithelial layer, and infects the rapidly dividing cells of the basal layer.

Viral replication in the perinuclear cytoplasm causes cytologic changes of koilocytosis, or perinuclear halos. Low risk serotypes cause dysplasia of the lower third of the epithelial layer; anal or cervical intra-epithelial neoplasia (AIN1 or CIN1) depending on the organ involved. These early histologic

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changes are driven by persistent viral replication in epithelial cells, and regression occurs upon immune recognition and control of the infection. Therefore while HPV infection is common in a sexually active virologically naïve population, the overwhelming majority of infections are transient and do not result in high grade dysplasia or cancer. Lack of immunologic control allows persistence of HPV infection, which in some patients infected with high-risk serotypes results in progression to high grade dysplasia [5,10]. With HIV coinfection, HPV persistence and progression occur more often [11]. With high-risk HPV serotypes this results in changes classified as high-grade squamous intra-epithelial lesion (HSIL). Histologically this correlates to anal or cervical dysplasia in the lower 2/3 (AIN2 or CIN2) of the epithelium or upper third (AIN3 or CIN3) to full thickness dysplasia (anal or cervical carcinoma in situ, AIS or CIS). Current guidelines group all of these histologic changes into HSIL, discouraging reliance on the previous grading system CIN or AIN 1, 2, or 3 [12].

In contrast to cervical disease, progression of anal dysplasia is not as well characterized. Data supporting the progression of HSIL to anal cancer are compelling but indirect. Long term follow-up of cohorts with HSIL shows variable rates of malignant transformation.

The most direct data for HSIL progression come from a retrospective chart review of anal cancer patients from the University of California, San Francisco with available biopsy reports. Previous anal HSIL (aHSIL) was found at the current anatomic location of anal cancer in 21/27 patients, and there was a history of HSIL but no recent biopsy in the remaining 6 [13]. The epidemiologic association between aHSIL and anal cancer coupled with limited direct evidence of aHSIL preceding anal cancer serve as evidence for the paradigm of high-risk HPV infection proceeding to HSIL which in turn proceeds to anal cancer in a subset of individuals.

Progression of aHSIL to SCCA rates vary depending on the cohort studied due to confounding variables such as selection bias. Matthews et al conducted a study which separated patients into high resolution anoscopy (HRA) cohort and a non-HRA cohort. The HRA cohort tended to have higher grade dysplasia and HIV viral load as well as more cytology tests and increased length of follow up appointments. The authors found transition rates to be overestimated in the HRA group further attesting to selection bias at referral clinics [14].

Cohorts have shown that aHSIL lesions can regress in a substantial minority of patients, possibly due to an immune E6 T cell response found in majority of the regressors [15]. Another study by Tong and colleagues showed a progression rate of 7.4/100 person years in comparison to regression rates at 23.5/100 person years. Persistence of HSIL was most likely associated with older age, HIV positive status, and low CD4 counts [16]. A randomized multicenter clinical trial found significantly increased rates of HSIL regression after treatment with infrared coagulation [17]. Larger and longer prospective studies are necessary to provide robust data on the rates of progression vs regression, risk factors, and if regression was sustained.

Comparisons between cervical and anal dysplasia are complicated by the fact that most cervical dysplasia studies are done on HIV negative women whereas a significant proportion of anal dysplasia data comes from HIV infected individuals. Furthermore, subsequent discovery of high-grade disease may result from a new infection with a high-risk HPV strain, from missed prevalent disease, or activation of latent HPV. The incidence rates of aHSIL in high risk groups remains high regardless of previous presence of dysplasia [18], this is likely due to new HPV acquisition as well as reactivation. The question of whether LSIL progresses to HSIL is another complicating factor; some data suggest that it may [19].

Epidemiology of HPV and anal dysplasia

HIV infection is associated with an increased incidence of virtually all common malignancies [20]. The reasons for this are multifactorial, and may include decreased immune surveillance for pre-malignant cells, decreased control of chronic infections that can result in malignancy (such as human herpes virus 8 and Epstein-Barr virus), and correlation with certain lifestyle factors (such as tobacco use) [20].

HIV alone is a risk factor for high grade anal intraepithelial neoplasia (HSIL) and anal cancer even in the absence of anal receptive intercourse [21,22], although HSIL rates are higher in the setting of anal intercourse with multiple partners. The MSM, HIV positive population has been especially affected by the anal cancer epidemic, with an incidence ranging from 75-137 per 100,000 person-years [23-25]. In this population HPV infection is common; and coinfection with multiple HPV types and high risk HPV types is also common [21,22]. A prospective cohort study by Clarke et al. evaluated MSM, HIV+ individuals and found the two and five year risk of anal cancer progression was greatest in those who tested positive for HPV 16/18 with E6/E7 [26]. Another multicenter cohort study, found HPV16 prevalence in HIV+ MSM to be 25% compared to 16% in HIV- MSM [27]. Risk factors for positive anal cytology included older individuals, seropositivity for HPV, low CD4 count, higher HIV viral load, and more receptive anal intercourse in the last year [27,28]. Studies focusing on the HIV positive, MSM population have found high rates of anal dysplasia, with prevalence as high as 59% to 81%. The prevalence of HSIL is also high, ranging from 31% to 52%.

Subset analysis of an HIV positive cohort in the French Hospital Database showed several risk factors for anal cancer. These included CD4 nadir, cumulative duration of CD4 count < 200, and cumulative duration of HIV viral load above 5 $\log_{10}$ [29]. In this cohort HAART had a protective effect for the development of cervical cancer; patients on HAART were half as likely to develop the disease. In contrast, nearly all of the patients with anal cancer were receiving HAART for greater than 6 months at the time of diagnosis. This may have been due to the fact that being on therapy was an indirect marker for a longer duration of immunosuppression, which is important in the pathogenesis of anal cancer. Current guidelines for the treatment of HIV encourage early initiation of treatment, mandating treatment regardless of CD4 count. It remains to be seen if earlier initiation of HAART and the prevention of low CD4 nadirs will decrease anal cancer incidence.

There was initial optimism that HAART therapy may have an ameliorative effect on anal cancer incidence, but this has not been shown. Since the natural history of HPV requires several years to progress from low grade to high grade dysplasia then cancer, increasing the life expectancy of the HIV positive population may increase anal cancer rates, as patients are now living long enough for lesions to fully progress. Two studies suggest that long term HAART and avoidance of low CD4 nadirs may decrease incidence of AIN2/3 [30,31]. More recent literature shows a plateau of anal cancer incidence rates in the past decade and a slight recent decline in anal cancer rates [32]. This may be attributed individuals receiving treatment at a younger age and advancements in HAART therapy.

Screening paradigm for anal cancer

In 2007, the state of New York issued guidelines recommending anal cancer screening in the HIV positive MSM population [33]; however, due to the paucity of data regarding the ability of screening to prevent anal cancer, no sub-specialty organizations have followed suit. The most accepted paradigm for anal cancer screening involves anal cytology (which is analogous to the cervical Pap smear) followed by high resolution anoscopy (which is analogous to colposcopy) in high risk patients with any cytologic abnormality.

The sensitivity and specificity of anal cytology varies across studies but is sub-optimal. A systematic review and meta-analysis of HIV positive women and men and HIV negative MSM showed that there is increased accuracy, sensitivity and specificity of anal cytology in the HIV positive population. Cytology alone had a sensitivity of 85% and specificity of 43.5% for the detection of HSIL (AIN II or worse) in comparison to LSIL (AIN I) groups [34]. Another cohort study in France showed that a co-test with standard anoscopy, HPV testing, and HPV genotyping detected significantly more high grade lesions than either method of testing alone [35]. ASCUS and LSIL ("low risk") cytologies in the anal canal are found to have increased HSIL on subsequent biopsy than cervical ASCUS and LSIL cytology. A recent study reported the progression of ASCUS/AIN I cytology to AIN II/AIN III to be 24.5% (10.5/100 person years) within high risk populations in 36 months [36]. Bekos and colleagues found that individuals with ASCUS/CIN I had a 14% of progressing to CIN II or higher [37]. The sensitivity and specificity of ASCUS and LSIL drive the difference in performance characteristics between anal and cervical cytologies [38].

Given that cervical Pap screening has been standard of care for several decades, studies that report cytologic-histologic correlation only in a population with cytologic abnormalities (such as women referred for cervical colposcopy) suffers from verification bias. This will tend to overestimate sensitivity and specificity compared to random cohorts where all women undergo cytologic screening with histologic verification of all results. One meta-analysis from twelve unbiased studies showed sensitivity ranging from 30% to 87% (mean 47%) and specificity ranging from 86% to 100% (mean 95%) [38]. When used as a binary test in a high risk population with ASCUS+ results proceeding to high resolution anscopy, performance characteristics of anal cytology approximate cervical cytology. This strategy ameliorates somewhat the underestimation of disease in ASCUS and LSIL anal cytologies, but it results in several patients who undergo anal cytology being ultimately referred to the more invasive HRA procedure.

Sub-optimal sensitivity brings up the question of how often to screen for anal dysplasia through anal cytology. A large cohort study showed that two years of recurrent screening with cytology increased the positive and negative predictive values to 78% and 79% respectively for HIV positive men; with values of 50% and 90% for HIV negative men [39]. Yearly screening is therefore likely to maximize positive and negative predictive values in the HIV positive cohort; but there are no studies indicating when anal cytology can be stopped or when the screening interval can be safely increased without compromising sensitivity. Without robust data, clinicians must rely upon expert opinion based on the risk factors of their patients to develop a screening protocol [40].

In contrast to anal cytology smears, the negative predictive value of a negative cervical Pap for development of cervical cancer in the next three years has been shown to be high [41,42]. This serves as the basis for guidelines allowing for less frequent cervical Pap screening. The data for the negative predictive value of anal Pap smears are not as robust, so formal recommendations cannot be made at this time.

Contrasts between cervical and anal dysplasia screening

The similarities between cervical and anal HPV disease outweigh the differences; although important differences remain. The first difference is that cervical cancer screening has been standard of care for over five decades. There are well established guidelines and algorithms, and for a given patient with a given result the next diagnostic or therapeutic step is well established. The same is not the case for anal cancer screening, which is largely driven by expert opinion at this time.

A second important difference between cervical cancer and anal cancer screening involves the populations at risk. Cervical cancer screening is indicated in the broad population of women between the ages of 21 and 65 [43], since the incidence of cervical cancer in the general population without screening and treatment is between 30-70 per 100,000 woman-years, depending on the country surveyed [44]. In contrast, the rate of anal cancer in the general population is approximately 0.8-1.5 per 100,000 person-years, which is too low to warrant a general screening program. Thus cervical cancer screening is indicated in the very broad population of women aged 21-65, whereas anal cancer screening should be limited to certain target populations where benefit is most likely.

The exact populations that warrant screening are still somewhat controversial. Anal cancer incidence data show that groups such as HIV negative MSM, HIV patients (men and women), or HIV positive MSM have anal cancer incidence rates as high as 35, 70, and 137 per 100,000 person-years respectively [24,25]. Anal cancer incidence varies from 1-2 per 100,000 py in the general population to 131 per 100,000 py in HIV positive MSM. A modeled incidence of anal cancer in HIV positive individuals peaked at 81 per 100,000 py in 2009 and has plateaued between 2010-2015. It is expected to further decrease in this population by 2030 with the widespread use of cART [45]. Other groups to consider are HIV positive women, HIV positive non MSM men, and HIV negative MSM. Although anal cancer incidence is elevated among these groups, the data are not as robust as for HIV positive MSM.

Despite these high incident rates of anal cancer, the rates of anal dysplasia vary considerably across studies, and the rate of progression of high-grade lesions to anal cancer is poorly characterized. The prevalence of ASIL on anal pap smears vary from 7.7 to 31% in HIV negative MSM and 27.8 to 75% in HIV positive MSM [46]; and there are at least two studies with a low prevalence of histologic HSIL in HIV positive populations [47,48]. Further studies better characterizing anal cytologic and histologic abnormalities and the progression to cancer in the risk groups of HIV negative MSM, HIV positive non-MSM men and women, and HIV positive MSM are crucial to help to develop evidence based screening guidelines. Given the goal of cancer diagnosis and prevention, the decision to initiate screening should be based on cancer incidence rates and not necessarily on the likelihood of finding HSIL.

Other groups, such as transgender women and those with immunosuppressive conditions (i.e., IBD) may be considered for testing as well based on individual patient risk factors. Risk factors stated by a retrospective chart review present in transgender women include age greater than 50, HIV positive status, smoking history, African American race, and male partner preference [49]. A cohort study of other conditions found that IBD, Crohn's disease and IBD presence of greater than ten years were risk factors [50]. A metaanalysis of AIN prevalence and anal cancer incidence in HIV positive and HIV negative men suggests that the progression of high grade dysplasia to cancer may be far lower for the anal canal than the cervix [44]. Despite limitations this represents one of the most comprehensive reviews of anal dysplasia data to date, and it highlights the need for more systematic research into the natural history of anal dysplasia progression and regression in HIV positive and negative patients.

Although poorly defined, spontaneous regression rates of high grade dysplasia likely vary between anal and cervical disease. Some cohorts show anal HSIL regressing at rates of 23 per 100 person years [16]. In contrast, one retrospective study of conization specimens from 635 women with CIN III found a regression rate of only eight cases while the remainder persisted at CIN II or III; there was more occult invasive cancer in this cohort than there was regression of HSIL. Increased regression was observed as time from procedure progressed [51].

HPV testing

HPV DNA testing by PCR or hybrid capture is a far more sensitive technique that has augmented cervical cytology in recent years. Studies evaluating HPV DNA as a primary means of screening have found it to be very sensitive but lacking in specificity [52-56]. HPV DNA testing has previously been used in conjunction with cervical cytology. This is typically used in one of two ways: to risk-stratify ASCUS cytology or to increase the negative predictive value of benign cytology in the 30-65 year old age group and allow for five years between negative tests [41,43]. More recent guidelines allow for the use of primary HPV based screening from cervical samples, from co-testing of cytology and HPV status [57]. Currently, there is only one model approved by the FDA for women older than 25 years which solely analyzes HPV DNA. The increasing reliance of HPV molecular testing in cervical cancer screening algorithms represents another difference between anal and cervical cytology.

HPV DNA testing differs in many important ways when applied to the anal canal due in part to epidemiologic differences in HPV prevalence in high-risk populations. While HPV DNA testing detects HPV infection of the anal canal, the extremely high prevalence of infection compromises the cost effectiveness and predictive value of this strategy. This is true in HIV positive MSMs, where anal HPV prevalence is extremely high [21,58,59]. In HIV negative MSMs and HIV positive non-MSM, anal HPV prevalence is lower [46,59,60], and there may be a role of combined cytology/HPV DNA testing in this group. Physicians should be cognizant about the HPV incidence and prevalence in groups and stratify patients in other populations based on individual risk (Table 1).

Anal HPV testing based on NAAT technology is very sensitive for HPV infection. High risk groups (such as HIV positive MSM) have a 90% anal HPV prevalence, with a high proportion of high risk HPVs (hrHPV) [61,62]. HPV16 plays a disproportionate role in oncogenesis in the anal canal compared to other hrHPVs. A study by Alemeny and colleagues found HPV 16 in 80.6% of anal cancers with HPV 18 following at 3.6% [62].

The high prevalence of HPV in high risk groups makes anal HPV testing

Table 1. HIV negative MSM, HIV patients (men and women), or HIV positive MSM have anal cancer incidence rates.

Risk Group	HSIL Prevalence	Anal SCC Incidence
HIV negative MSM	25%[3]	35[4]
HIV positive female	20%[2]	30[1]
HIV Positive male, non-MSM	18%[3]	46[1]
HIV positive MSM	43%[3]	131[1]

Table 2. Recurrence rates vary according to the modality used.

Ablative Modality	Population	Efficacy	References
85% TCA	35 HIV Positive 19 HIV Negative Men	32% AIN 2/3 cleared 71% AIN 2/3 decreased to AIN1 73% AIN 1 cleared	[70]
5-FU cream	8 patients (1 HIV positive)	87% clearance of Bowen's disease (AIN3) at one year	[71]
Imiquimod	53 HIV positive MSM (28 active, 25 placebo)	61% treated with imiquimod exhibited clearance or regression of HGAIN	[67]
Infrared Coagulation	68 HIV positive MSM	72% response rate per lesion 65% recurrence rate 58% to 40% recurrence after retreatment	[72]
Surgical Resection	37 patients total All male 29 HIV Positive All with HGAIN	79% recurrence in HIV positive patients No recurrence in HIV negative patients	[73]
Surgical Resection	246 patients total 182 HIV positive All HGAIN	Persistent Disease: 18.7% Recurrent Disease: 56%	[74]
Infrared Coagulation	75 HIV negative men	47%/72%/100% complete response after first/second/third treatments respectively	[66]
Infrared Coagulation	16 HIV positive men, 2 HIV positive women	37.5% recurrence rate (at one year?)	[75]
IRC/Laser/ Electrocautery	456 HIV positive MSM 271 HIV negative MSM	77% recurrence at three years HIV positive 66% recurrence HIV negative	[65]
Radiofrequency Ablation	21 HIV negative men	29% recurrence in treatment zone at one year	[76]

less useful as it compromises the positive predictive value. Future algorithms may be able to use demographic differences in HPV prevalence to increase performance characteristics of the test. A retrospective study showed a significant prevalence in the MSM HIV positive group in comparison to the non-MSM HIV positive group. This was followed by a significant difference in the positive predictive value between the two groups as well [61]. However, an HPV algorithm using NAAT may serve to be beneficial in other groups like HIV positive men (non-MSM) and HIV positive women due to differences in HPV prevalence [63]. There is yet to be definite consensus on the use of anal HPV testing in high risk populations. Thus, clinicians should be aware of the possible benefits and limitations of this test in specific groups and request it based on careful evaluation of a patient's demographic group and individual risk status.

Treatment of high grade disease

Another important difference between cervical and anal dysplasia involves treatment of high grade disease. Cervical dysplasia has several different treatment options, but they generally involve complete ablation of the transformation zone, thereby completely removing dysplastic epithelium. The paradigm for this approach is LEEP, and the ability to treat the entire transformation zone and examine margins to ensure clearance likely decreases recurrence rates. In contrast, complete circumferential ablation of the transformation zone of the anal canal with electrocautery would result in unacceptably high rates of stenosis. Thus, dysplastic lesions must be individually identified and ablated. This process is more technically demanding and more prone to missing small area of high grade dysplasia; this likely contributes to higher recurrence rates. However, the emergence of radiofrequency ablation as a treatment for high grade lesions offers the ability to treat the anal canal hemi-circularly or circumferentially. No serious adverse events, heavy bleeding, or strictures were observed, and preliminary data show a lower recurrence rate [64-69].

Although not definitively proven to reduce cancer rates, ablation of high-grade anal dysplasia is the standard of care according to most expert opinion. While recurrence rates vary according to the modality used, they remain high [64-69].

The response rates of cervical HSIL to Loop electrocautery excision procedure (LEEP) serve as a useful comparator to anal dysplasia recurrence rates. In one retrospective study, 760 women with CIN 2+ were followed for almost 7 years, and found to have an 8.8% recurrence rate after treatment with LEEP. Previously cited recurrence rates range from 5-30% [70-77] (Table 2).

The squamocolumnar junction visibility, lesion grade, and hrHPV status are important considerations to determine the response rates of cervical HSIL to therapy [77]. Bruno and colleagues recently conducted a retrospective review of the correlation of high risk HPV subtypes and regression after treatment with LEEP. Relapse after treatment occurred in 9.8% of patients and in a greater proportion of patients with persistent HPV16 (94.4%). Patients with hrHPV but negative margins were found to have increased risk for recurrent lesions; this risk was highest with persistent HPV16. Women negative hrHPV at 6 months were found to have a no recurrent disease [78]. Thus, it is imperative that future efforts are aimed at preventing and clearing HPV infections to minimize recurrence rates and improve regression of lesions.

Discussion and Conclusion

Squamous cell carcinoma of the anal canal represents another non-AIDS defining illness whose burden continues to increase, particularly in the HIV positive population. The highest risk group is HIV positive MSMs, particularly those with a low CD4 nadir and a long duration of HIV positivity. HAART is not alleviating this problem but paradoxically making it worse. While screening for anal dysplasia is effective at finding high background rates of dysplasia in high-risk populations, it remains to be seen if aggressive screening and treatment can decrease the incidence of anal cancer. Thus anal cancer screening is likely in a stage analogous to cervical cancer screening in the middle of the twentieth century. Landmark trials, such as the ongoing ANCHOR trial, will provide answers to critical questions in this area. This topic is an important area for future research to address the many unanswered questions and develop much-needed guidelines.

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