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ORIGINAL ARTICLE

Progression of anal intraepithelial neoplasia in HIV-positive individuals: predisposing factors

T. McCutcheon[1] · A. T. Hawkins[1] · R. L. Muldoon[1] · M. B. Hopkins[1] · T. M. Geiger[1] · M. M. Ford[1]

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Abstract

Background The aim of the present study was to evaluate patient factors that affect the progression of anal dysplasia in human immunodeficiency virus (HIV)-positive individuals.

Methods A retrospective cohort study of HIV-positive adults with human papilloma virus related anal lesions was performed from 2012 to 2017. All patients underwent surgical excision or biopsy and fulguration of lesions in the operating room without using high resolution anoscopy. Patients with initial presentation of squamous cell carcinoma were excluded. The study was designed to investigate progression between the first available histology and either the follow up histology or a negative examination. Patient files were reviewed and data was collected. A bivariate analysis of continuous and categorical variables was performed.

Results One hundred and sixty-one patients met the inclusion criteria. Ninety-seven percent were male. Mean age was 41 years. Thirty-five percent were African American and 47% were Caucasian. After a median follow-up interval of 331 days (IQR 120–615 days) 14 (9%) of patients had progression of disease. Visible lesions on initial presentation, as opposed to lesions found in patients undergoing examination under anesthesia because of HSIL on anal pap smear, was associated with progression ($p = 0.0.2$). A lower initial CD4 count ($p = 0.01$) and initial surgical pathology of anal condylomata ($p = 0.01$) were also associated with progression. High-risk serotype was associated with no change or regression ($p = 0.01$).

Conclusions In our large cohort of HIV-positive patients treated without high resolution anoscopy the rate of progression was low. Most notably, visible lesions at initial presentation and CD4 count when lower were associated with progression. Initial surgical pathology of anal condylomata was associated with progression, while high-risk serotypes correlated with regression or stability. Identification of risk factors has important implications concerning postoperative surveillance and counseling of HIV-positive patients with anal condylomata/ anal dysplasia.

Keywords Anal dysplasia · Anal intraepithelial neoplasia · AIN progression · HIV

Introduction

Although rare, the incidence of anal carcinoma has gradually increased over the past 3 decades, with a reported occurrence of 1 per 100,000 individuals within the general population [1]. However, human immunodeficiency virus (HIV)-positive individuals have a higher rate of development of anal carcinoma, with a reported incidence of 60–160 per 100,000 in HIV-positive men who have sex with men (MSM) [1]. This select population also has been shown to have higher rates of progression or recurrence of anal dysplasia [2].

Human papilloma virus (HPV) is an identifiable source in approximately 93% of anal carcinomas, with the most common associated high-risk oncogenic HPV strains being

Authors T. McCutcheon and A. T. Hawkins have contributed equally and are co-first authors.

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✉ A. T. Hawkins
alex.hawkins@vumc.org

[1] Department of General Surgery, Section of Colon and Rectal Surgery, Vanderbilt University Medical Center, 1161 21st Ave South, Room D5248 MCN, Nashville, TN 37232, USA

HPV 16 and 18 [3, 4]. These strains generate changes in the squamous epithelium, leading to anal intraepithelial neoplasia (AIN), which is a precursor to anal carcinoma [5].

The natural history of anal dysplasia is not fully understood. It is suggested that anal dysplasia develops in a progressive manner from onset of AIN 1 through AIN 3 and eventually to anal carcinoma [5]. Co-existing factors may influence the rate of progression along the neoplastic spectrum.

The purpose of this study was to evaluate patient factors that may affect the rate of progression of levels of anal dysplasia within the HIV-positive population. We hypothesize that there are important and potentially modifiable factors associated with progression of anal dysplasia.

Materials and methods

Study design

We performed a retrospective cohort study of all consecutive HIV-positive adults having an examination under anesthesia with pathological findings at a tertiary care hospital from January 1, 2012 to November 1, 2017. Exclusion criteria were as follows: patients without follow-up pathology or clinical examination, patients with initial diagnosis of squamous cell carcinoma, patients with a CD4 count < 200 cells/μL and patients who were HIV-negative. (Fig. 1) Of note, our practice does not in general operate on patients with a CD4 count lower than 200 cells/μl, as previous data have indicated that patients diagnosed with autoimmune deficiency syndrome (AIDS) have significant issues with wound healing when undergoing anorectal surgery [13]. The study was designed to investigate progression between the first available histology and either the follow up histology or a negative examination by either anoscopy or examination under anesthesia.

On presentation, a complete history was taken and a physical examination was carried out, including digital rectal examination and standard anoscopy. Treatment of patients seen in our clinic for AIN was based upon an existing protocol: those with grossly visible lesions on anoscopy would be scheduled for surgical excision and fulguration, as well as those without visible lesions in clinic who had an anal pap showing high-grade squamous intraepithelial lesion (HSIL), because our level of suspicion was high. Suspicious visible

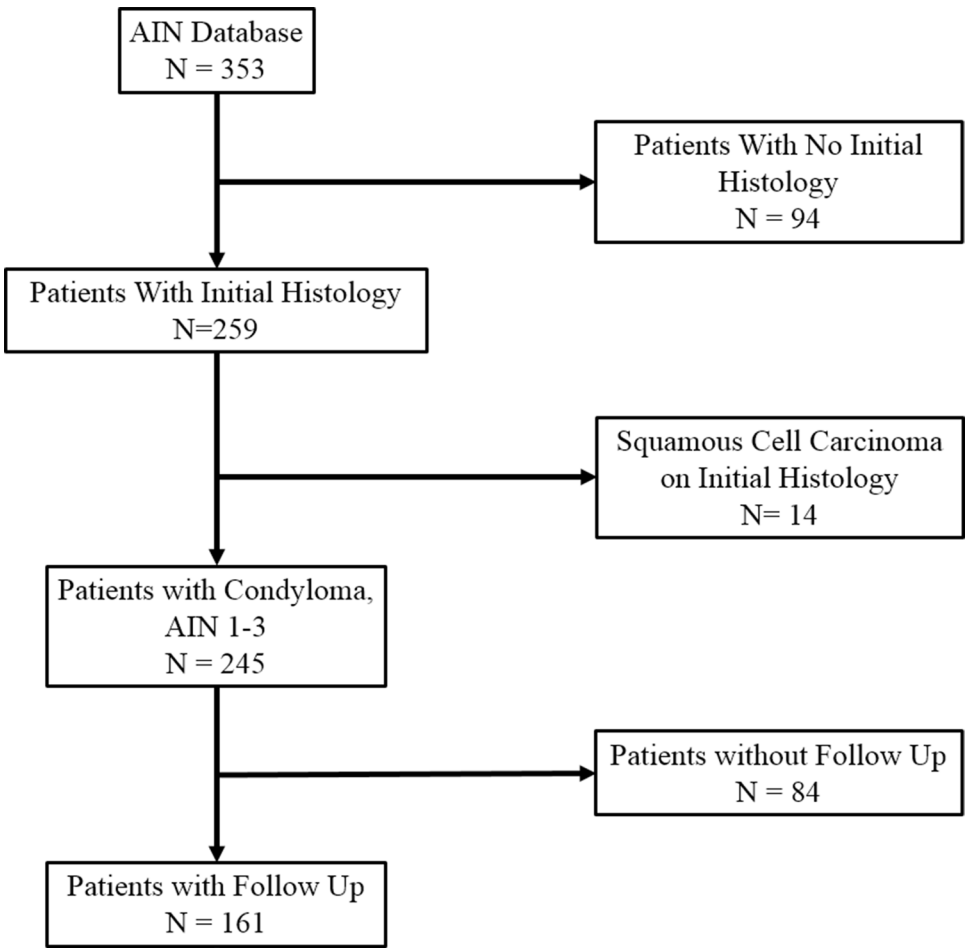

Fig. 1 Consolidated standards of reporting trials (CONSORT) diagram for cohort creation

lesions were defined as smooth papular, keratotic, or white plaque-like growths in the anal canal or perianal skin. High-resolution anoscopy (HRA) was not utilized, since this procedure is not an institutional protocol. To date, there have been no definitive data that has suggested HRA is superior to expectant management with close observation in the prevention of anal cancer. The American Society of Colorectal Surgeons (ASCRS) indicates HRA is a consideration for screening in high-risk patients if performed by trained providers, but the recommendation is a weak, based on moderate-quality evidence [6]. Each tissue sample was reviewed by two pathologists, with a low threshold for further evaluation. If the tissue was equivocal for high-grade lesions, a p16 stain was obtained. Pathology results were categorized as normal, anal condylomata (AC), AIN 1 (mild dysplasia), AIN 2 (moderate dysplasia), and AIN 3 (severe dysplasia) [7]. The authors did not distinguish between patients with AIN 2 and a positive p16 stain and patients with AIN 2 and negative p16 stain. All AIN 2 patients were considered high risk and were surveilled as such. Patients with a histologic diagnosis of anal condylomata or AIN 1 were scheduled to have surveillance with anoscopy every 6 months and patients with AIN 2 or AIN 3 were scheduled to have surveillance with anoscopy every 3 months. All patients with a histologic diagnosis of AIN 1, 2, or 3 were offered use of imiquimod cream postoperatively for 16 weeks (Fig. 2). Patients with recurrence of disease had excision and fulguration of lesions. For the purposes of this study, the interval between examinations was defined as the time between the first surgery and the second surgery or the next follow-up exam.

Patients were divided into two groups, those that progressed and those that did not. Progression was defined as a higher grade of AIN or progression to squamous cell carcinoma on follow-up surgical pathology. Patients with a clinical exam without any identifiable lesions were included in the non-progression group. Factors associated with progression were identified. The Vanderbilt University Institutional Review Board (Protocol 170799) reviewed and approved this study waiving informed consent. The study was also conformed to the preferred reporting of case series in surgery (PROCESS) checklist [8].

Data collection

Patient files were retrospectively reviewed and pertinent demographic, pathologic and surgical information was

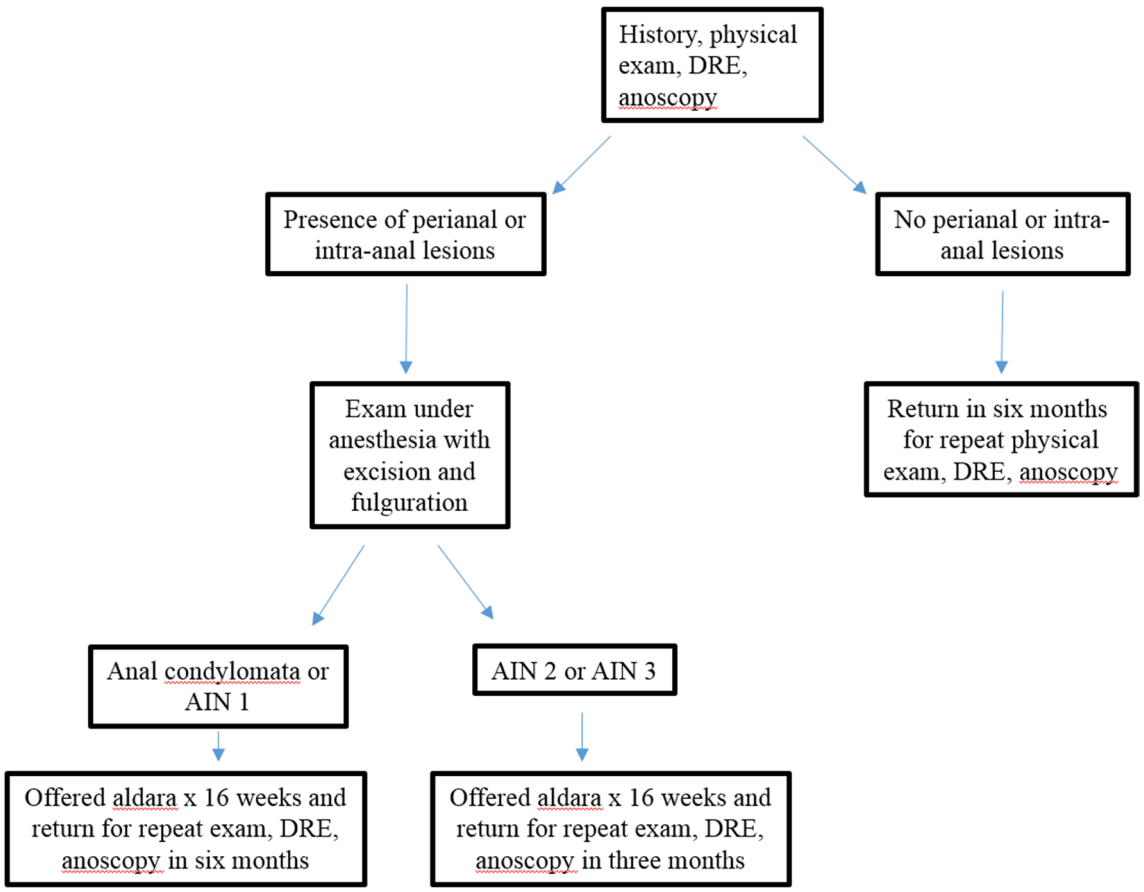

Fig. 2 Anal intraepithelial neoplasia (AIN) surveillance protocol

collected. Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center [9]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Covariates collected include: age, gender, ethnicity, presence of high-risk HPV serotypes, history of Gardasil (one, two, or three doses), history of sexually transmitted infections, HIV status, use of imiquimod postoperatively (defined as patient was given a prescription for 16 weeks of imiquimod cream), initial CD4 count (indicator of the patient's immunosuppression at the time of initial surgery), initial viral load, tobacco use, patient-reported history of anal or genital condylomata, patient-reported history of anal receptive intercourse, patient-reported number of lifetime sexual partners, patient-reported use of condoms, initial anal cytology, and initial surgical pathology. An additional covariate was the presence of a visible lesion on outpatient anal examination. If lesions were large enough to be detected on anal examination, then patients often did not undergo an anal pap test, as it would not have changed the plan for surgical excision.

Statistical analysis

Continuous and categorical variables are expressed as mean with standard deviation and proportions throughout the study, with the exception of continuous variables with grossly skewed distributions that are reported as the median with the interquartile range. Bivariate analysis of continuous and categorical variables was performed with either the Student's *t* test or the Wilcoxon rank-sum test, depending on distribution, and Fisher's exact test, respectively. For analysis of the clinical characteristics in relation to initial surgical pathology, proportional odd logistic regression modeling was used given the ordinal nature of initial surgical pathology. SAS statistical software (version 9.3; SAS Institute's Inc., Cary NC, USA) was used for all analyses. All tests were two sided with an alpha level of 0.05.

Results

Over the study period, 161 HIV-positive patients met the inclusion criteria and were analyzed. Of the entire group, 156 (97%) were male, 76 (47%) Caucasian, and the median age was 41 years (range 30–50 years). (Table 1) The mean initial CD4 count was 604 cells per microliter and 15% of patients had a detectable initial viral load. Fifty percent of patients tested positive for high-risk HPV. The median interval between the initial surgery and the second surgery or next follow-up visit was 331 days (IQR 120–615 days).

Progression was observed in 14 (9%) of patients, and 2 patients (1%) progressed to cancer (Fig. 3). A number of factors were associated with progression (Table 1). Patients who did not have initial anal pap cytology, but underwent examination under anesthesia (EUA) due to the presence of visible lesions alone were found to have progression of disease (progression 57%; no progression 24%; $p=0.02$). Initial CD4 counts were significantly lower in the group that experienced disease progression (progression 387; no progression 619; $p=0.02$) and those with a diagnosis of anal condylomata on initial surgical pathology (progression 62%; no progression 16%; $p=0.001$) were more likely to progress. Patients with high-risk HPV serotypes (progression 23%; no progression 54%; $p=0.03$) were less likely to progress. There was no difference observed in median interval between exams among the two groups (progression 404 days; no progression 303 days; $p=0.38$).

In an analysis of clinical characteristics in relation to initial surgical pathology, only two factors were associated with increasing grades of dysplasia: increasing age (OR 1.02; 95% CI 1.00–1.05) and tobacco use (OR 2.13; 95% CI 1.19–3.81) as seen in Table 2.

Discussion

In this retrospective cohort study, we evaluated HIV-positive patients with anal dysplasia looking for demographic or clinical factors associated with progression of anal dysplasia. An important finding was the high incidence of progression in patients with no initial anal pap cytology, but with visible lesions on exam at time of referral. Another notable finding was that patients with progression had a significantly lower initial CD4 count. Also, patients with anal condylomata on surgical pathology were found to have a higher risk of disease progression. Interestingly, we also noted that high-risk HPV serotypes were associated with a lower progression and that time to follow up did not seem to make a difference.

Progression of AIN is likely influenced by co-existing factors. Past research has indicated risks include anal receptive intercourse, the presence of oncogenic HPV infection, tobacco use, immunocompromised state, and abnormal anal cytology [3, 5]. Other reported risk factors for the progression of AIN have been mentioned in recent studies and include CD4 counts below 200 cells per microliter, a previous history of anal carcinoma, and MSM over than 40 years of age [5, 10, 11].

Patients in our cohort with no initial anal pap performed, but with visible lesions on exam had a higher rate of progression. No previous studies address visible lesions without associated cytology specifically. These patients also were found to have a high rate of AIN 3 (41% of the group of AIN 3) on initial exam, and it has been suggested that the rate of progression of high-grade perianal AIN to carcinoma is as high as 18% [11]. These results would suggest that surgical

Table 1 Demographics and progression of disease

Clinical characteristics	All ($n=161$)	Progression ($n=14$)	No change/regression ($n=147$)	p value
Age, years, median	41(30–50)	44 (35–54)	41 (30–50)	0.17
Male gender	156 (97%)	12 (86%)	144 (98%)	0.01
Race				0.39
African American	56 (35%)	7 (50%)	49 (33%)	
Caucasian	76 (47%)	6 (43%)	70 (47%)	
Other race	29 (18%)	1 (7%)	28 (19%)	
High-risk HPV serotypes	81 (50%)	3 (23%)	78 (54%)	0.03
History of Gardasil (1,2, or 3 doses)	20 (12%)	0 (0%)	20 (14%)	0.22
History of STI	74 (46%)	5 (35%)	69 (47%)	0.41
Use of imiquimod postoperatively	54 (33%)	4 (29%)	50 (34%)	0.80
Initial CD4 count	604 (357–830)	387 (232–603)	619 (380–835)	0.02
Detectable initial viral load	25 (15%)	1 (7%)	24 (16%)	0.69
Tobacco use	62 (38%)	6 (43%)	56 (38%)	0.90
History of anal or genital condylomata	58 (36%)	7 (50%)	51 (35%)	0.40
Anal receptive intercourse	62 (38%)	4 (29%)	58 (40%)	0.41
Lifetime sexual partners > 100	7 (4%)	1 (7%)	6 (4%)	0.50
Use of condoms	21 (13%)	1 (7%)	20 (14%)	0.69
Initial anal cytology				0.02
Initial anal cytology none	44 (27%)	8 (57%)	36 (24%)	
Initial anal cytology ASCUS	34 (21%)	1 (7%)	33 (23%)	
Initial anal cytology LSIL	70 (43%)	5 (36%)	65 (45%)	
Initial anal cytology HSIL	13 (8%)	0 (0%)	13 (9%)	
Initial surgical pathology				0.001
Initial surgical pathology normal	11 (7%)	0 (0%)	11 (7%)	
Initial surgical pathology anal condylomata	31 (19%)	8 (62%)	23 (16%)	
Initial surgical pathology AIN 1	47 (29%)	3 (23%)	43 (29%)	
Initial surgical pathology AIN 2	21 (13%)	0 (0%)	21 (14%)	
Initial surgical pathology AIN 3	51 (32%)	2 (15%)	49 (33%)	

HPV human papilloma virus, *STI* sexually transmitted infection, *ASCUS* atypical squamous cells of unknown significance, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion, *AIN* anal intraepithelial neoplasia

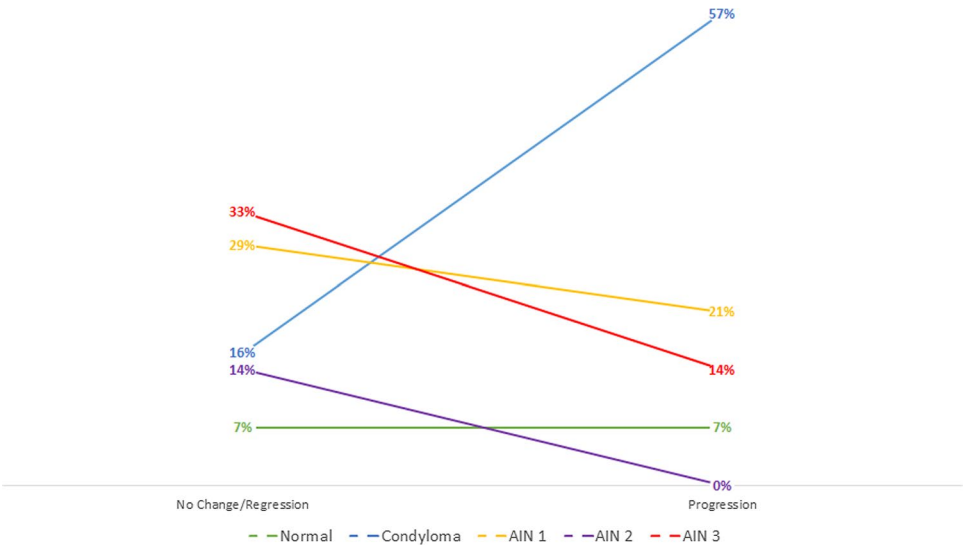

Fig. 3 Progression by initial surgical pathology

Table 2 Clinical characteristics in relation to initial surgical pathology

	Normal ($n=11$)	Condyloma ($n=31$)	AIN 1 ($n=46$)	AIN 2 ($n=21$)	AIN 3 ($n=51$)	OR (95% CI)	p value
Age,years, median (IQR)	36 (30–50)	40 (27–49)	34 (29–48)	49 (35–52)	45 (33–50)	1.02 (1.00–1.05)	0.04
Male gender	11 (100%)	30 (97%)	44 (96%)	21 (100%)	49 (96%)	0.80 (0.16–4.01)	0.79
Race							
African American	3 (27%)	13 (42%)	16 (35%)	5 (24%)	19 (37%)	REF	
Caucasian	7 (64%)	10 (32%)	26 (56%)	14 (67%)	18 (35%)	0.91 (0.49–1.70)	0.78
Other	1 (9%)	8 (26%)	4 (9%)	2 (9%)	14 (27%)	1.50 (0.66–3.38)	0.32
High-risk HPV serotypes	5 (45%)	13 (43%)	23 (51%)	11 (52%)	28 (56%)	0.73 (0.12–1.28)	0.28
Hx of Gardasil vaccine (completion of one dose, two doses, three doses)	1 (9%)	7 (22%)	6 (13%)	1 (5%)	5 (10%)	1.77 (0.76–4.11)	0.18
Hx of STIs	4 (37%)	14 (45%)	20 (43%)	9 (43%)	26 (51%)	0.79 (0.45–1.39)	0.41
Initial CD4	542 (385–761)	426 (293–681)	658 (492–835)	660 (422–850)	564 (281–830)	1.00 (1.00–1.00)	0.16
Tobacco use	1 (9%)	9 (29%)	18 (39%)	7 (33%)	26 (51)%	2.13 (1.19–3.81)	0.01
Hx of condyloma in the past (anal/ genital)	0 (0%)	14 (45%)	15 (33%)	12 (57%)	17 (33%)	1.21 (0.68–2.15)	0.51
Lifestyle risk							
Anal receptive intercourse	5 (45%)	13 (42%)	18 (39%)	5 (24%)	21 (41%)	0.90 (0.51–1.59)	0.72
Sexual partners > 100	0 (0%)	1 (3%)	4 (9%)	2 (9%)	0 (0%)	1.40 (0.36–5.43)	0.62
Use of condoms	1 (9%)	5 (16%)	6 (13%)	3 (14%)	6 (12%)	1.10 (0.48–2.51)	0.80
Initial cytology							
None	2 (18%)	11 (35%)	10 (21%)	3 (14%)	18 (35%)	REF	
ASCUS	0 (0%)	10 (32%)	11 (24%)	4 (19%)	9 (18%)	0.74 (0.33–1.65)	0.46
LSIL	6 (54%)	10 (32%)	24 (52%)	11 (52%)	6 (12%)	0.78 (0.39–1.54)	0.48
HSIL	3 (27%)	0 (0%)	1 (2%)	3 (14%)	6 (12%)	1.46 (0.47–4.57)	0.49
Interval, days, median (IQR)	389 (123–814)	413 (197–826)	210 (37–349)	350 (117–487)	396 (154–816)	1.00 (0.99–1.01)	0.95

HPV human papilloma virus, *STI* sexually transmitted infection, *ASCUS* atypical squamous cells of unknown significance, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion, *AIN* anal intraepithelial neoplasia

intervention, if lesions are visualized, is a more appropriate treatment than initial management with topical medications. This suggestion may be supported by an open-label randomized trial conducted by Richel et al. comparing electrocautery to 5-fluorouracil and imiquimod. The author's findings suggested electrocautery was a better treatment option for AIN than 5-fluorouracil or imiquimod [12].

In general, a low CD4 count has a known association with risk of acquiring opportunistic infections. However, we specifically demonstrated a difference in CD4 counts in patients who progress, as they had a significantly lower mean initial CD4 count. Progression with a very low CD4 count has been suggested in the past by Tinmouth et al., who found that a diagnosis of acquired immunodeficiency syndrome (AIDS) was associated with progression to carcinoma [11]. But our study looked at all patients who progressed and found that their mean CD4 count was 387 cells per microliter, versus the non-progressors or regressors with a CD4 count mean of 619. This should encourage providers to be more aggressive with surveillance regimens in patients with lower CD4 counts. Of note, our practice does not in general operate on patients with a CD4 count lower than 200 cells per microliter, as previous data have indicated that patients diagnosed with AIDS have significant issues with wound healing when undergoing anorectal surgery [13].

Our outcomes also suggested that anal condylomata had an elevated risk of disease progression compared to higher grade AIN. Fazendin et al. found similar results and reported anal condylomata and low-grade dysplasia exhibited a high risk of progression to moderate-grade dysplasia with surveillance by anoscopy every 6–12 months [14]. Patients within our study with a surgical pathology of anal condylomata, as well as AIN 1, were under planned surveillance with anoscopy every 6 months as compared to patients with AIN 2 or AIN 3 who were under planned surveillance with anoscopy every 3 months. However, despite our recommendations for follow-up, there was not a significant difference in follow-up periods between what we had initially deemed the low-risk group (condylomata, AIN1) and the high-risk group (AIN 2 and 3).

The overall rate of disease progression from AIN to anal cancer remains unclear. However, one reported estimation suggested a 1.3–3.2% rate of progression within a 5-year period [3, 15]. The rate of progression from AIN 1 to AIN 2 or AIN 3 to carcinoma is less well understood, but since many AIN 1 lesions are believed to be caused by low-risk HPV strains, the risk of progression to high-grade dysplasia and carcinoma has historically been thought to be lower. However, a counterintuitive finding in our study was a significant decrease in progression with identified high-risk HPV strains, meaning those without identified high-risk HPV showed progression. Although the literature is not definitive regarding this topic, Fazendin et al. also found that HPV genotypes did not affect the rate of progression of dysplasia [14]. This contrasts with Pokomandy et al. who suggested the risk of progression from a low-grade dysplasia to a high-grade dysplasia was greater in HIV-positive MSM older than 40 years of age with positive oncogenic HPV [10]. Similarly, Burgos et al. reported HIV-positive MSM with high-risk HPV serotypes were found to have a twofold increase in the risk of progression to high-grade dysplasia [5]. Our findings of decreased progression may be related to the overall low number of patients with disease progression or to more aggressive initial treatment for patients with identified high-risk HPV, going straight to surgical excision.

Although the findings were not statistically significant, it is important to mention that patients who had at least one dose of Gardasil were found to have no progression of disease (progression 0%; no progression 14%; $p = 0.22$). The low number of patients receiving Gardasil may be a factor in the insignificant findings. However, this information supports further study of the Gardasil vaccine in this setting.

The strengths of our study include the examination of a large non-HRA population, evaluation of patients with no initial anal pap cytology with visible lesions present on exam, analysis of CD4 counts in relationship to progression of AIN disease, and assessment of the effect of Gardasil on progression of AIN disease. To date, few studies have been done without the use of HRA and within this non-HRA study, no progression to anal carcinoma was found. Therefore, our findings may in fact suggest the acceptability of visual examination of the perianal and anal regions, which may prove to be less costly to patients as well as health care institutions.

HRA has been championed by some as the optimal modality for anal dysplasia screening [16]. Our institutional protocol does not include HRA in the treatment algorithm for AIN disease. Rather, the inspection of the anal canal with use of anoscopy on a regimented basis is utilized to visualize lesions and aid in the prevention of disease progression. To date, minimal data exists regarding the superiority of HRA or expectant management in prevention of progression of AIN disease. Crawshaw et al. compared HRA to expectant management in surveillance of AIN and prevention of anal carcinoma [17]. Results indicated that out of 424 patients (220 managed with HRA and 204 managed with expectant management), 3 patients progressed to anal carcinoma. Of the 3 patients, 2 were non-compliant with follow-up and HIV management and 1 was allergic to imiquimod, which was used postoperatively [17]. The researchers concluded the development of anal cancer is rare despite the method of treatment if patients are compliant with protocols [17]. Therefore, the importance of regimented surveillance and compliance with HIV treatment may be more of a factor as compared to the method of surveillance.

Limitations of this study include the low rate of progression that precluded building a multivariable model to assess risk factors. Because of this, we are unable to assess interaction between covariates in the progression of AIN lesions. Another limitation is the fact that follow up was limited to a single interval between baseline and follow up histology or negative exam. In the few patients with more than one histologic follow up only the result of the first follow up histology were examined, which in part explains our low rate of progression. Also, this study examined the progression of HPV related disease without emphasis on specific AIN lesions. This study was limited in that the data was obtained from a single institution and the majority of the population was male. Therefore, results may not be generalizable to other populations affected by AIN disease. Furthermore, this study looked at baseline data and did not track changes in CD4 counts and tobacco use over the course of the study. Finally, this select population of study was challenging in terms of continued surveillance. Many patients missed appointments or were lost to care, which in turn limited our ability to adequately examine time as a factor in the progression of AIN disease. Further studies that focus on the location of lesions in relationship to progression of disease may impart additional knowledge that could potentially drive future treatment for AIN disease.

In summary, factors that were shown to affect disease progression include visible lesions, low CD4 counts, anal condylomata on surgical pathology, absence of high-risk HPV serotypes and gender. As a result of these findings, we will modify our present practice by offering surgical intervention as a first-line treatment for visible lesions as well as provide additional counseling for patients with surgical pathology demonstrating anal condylomata about the risk of progression of disease and the importance of continued surveillance, shortening this interval for patients with anal condylomata. And finally, while our data did not find significance with use of Gardasil and/or imiquimod postoperatively, we will continue to gather data and expand our initial database in the hopes of answering these questions. Now with prospective collection of the data, we hope to provide greater longitudinal information with the eventual hope of

generating a multivariate model to create a predictive model for disease progression.

Conclusions

Most notably, visible lesions with no associated anal pap cytology correlated with progression and patients that did progress had a significantly lower CD4 count. Initial surgical pathology of anal condylomata was associated with progression, while high-risk serotypes correlated with regression or stability. At this time, there are no recommended surveillance guidelines or universal treatment protocols for this select population. Therefore, advocation for more aggressive surveillance intervals and treatment of visible lesions, anal condylomata and AIN disease is imperative.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest or off-label use.

Ethical approval This study was approved by the Vanderbilt University Medical Center IRB (Protocol 170799) with waiver of informed consent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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