Original Article

Electrocautery Ablation of Anal High-Grade Squamous Intraepithelial Lesions: Effectiveness and Key Factors Associated With Outcomes

Michael M. Gaisa, MD, PhD [1]; Yuxin Liu, MD, PhD[2]; Ashish A. Deshmukh, PhD, MPH[3]; Kimberly L. Stone, MPH[4]; and Keith M. Sigel, MD, PhD [4]

BACKGROUND: Electrocautery ablation (EA) is a common treatment modality for patients with anal high-grade squamous intraepithelial lesions (HSILs), but to the authors' knowledge its effectiveness has been understudied. The objective of the current study was to determine ablation outcomes and to identify clinicopathological factors associated with postablation disease recurrence. **METHODS:** A total of 330 people living with HIV with de novo intra-anal HSIL who were treated with EA from 2009 to 2016 were studied retrospectively. Using long-term, surveillance high-resolution anoscopy biopsy data, treatment failures were classified as local recurrence (HSIL noted at the treated site at the time of surveillance) or overall recurrence (HSIL noted at treated or untreated sites). The associations between these outcomes and clinical factors were analyzed using Cox proportional hazards models. **RESULTS:** Approximately 88% of participants were men who have sex with men. The median age of study participants was 45.5 years (range, 35-51 years) and approximately 49% had multiple index HSILs (range, 2-6 index HSILs). At a median of 12.2 months postablation (range, 6.3-20.9 months postablation), approximately 45% of participants had developed local recurrence whereas 60% had developed overall recurrence. Current cigarette smoking, HIV viremia (HIV-1 RNA ≥100 copies/mL), and multiple index HSILs were found to be predictive of local recurrence. Overall recurrence was more common in current smokers and those with multiple index lesions. In multivariable models that included human papillomavirus (HPV) genotypes, baseline and persistent infections with HPV-16 and/or HPV-18 were found to be significantly associated with both local and overall recurrence. **CONCLUSIONS:** EA is an effective treatment modality for anal HSIL in people living with HIV, but rates of disease recurrence are substantial. Multiple index HSILs, HIV viremia, current cigarette smoking, and both baseline and persistent infection with HPV-16 and/or HPV-18 appear to negatively impact treatment success. Ongoing surveillance is imperative to capture recurrence early and improve long-term treatment outcomes. ***Cancer* 2020;126:1470-1479**. © *2020 American Cancer Society*.

KEYWORDS: anal cancer precursors, electrocautery ablation, high-grade squamous intraepithelial lesion (HSIL), HIV, outcomes, recurrence.

INTRODUCTION

The incidence of human papillomavirus (HPV)–related anal squamous cell carcinoma in the United States has risen by approximately 2.2% per year over the last decade, with 8300 new cases projected to occur in 2019.[1,2] Anal high-grade squamous intraepithelial lesions (HSILs) are the immediate cancer precursors and are highly prevalent among people living with HIV (PLWH), particularly among men who have sex with men (MSM) and women.[3-6] Given the paucity of data regarding the natural history of anal HSIL and its treatment outcomes, there has been ongoing debate as to whether HSIL treatment is justified and cost-effective.[7,8] With guidance from a prospective clinical trial still years away,[9] specialized anal dysplasia clinics are screening and treating anal HSIL proactively in high-risk populations, with the goal of eradicating these precursors and prevent malignant transformation.[10,11]

Treatment options for anal HSIL include topical immune modulators, chemotherapeutics, surgical excision, and targeted ablation using cryotherapy or thermocoagulation.[12,13] Among these options, high-resolution anoscopy (HRA)–guided electrocautery ablation (EA) has gained popularity as a fast, office-based procedure that produces favorable results with a low rate of complications. EA destroys individual lesions by inducing localized tissue necrosis to the depth of the submucosa while sparing adjacent benign-appearing tissue.[14] EA has been shown to be superior to topical immune modulators or chemotherapeutics for the treatment of anal HSIL.[15] In a retrospective study, adding HPV vaccination to HSIL treatment (adjuvant HPV vaccination) improved treatment outcomes among HIV-uninfected MSM and a mathematical

Corresponding author: Michael M. Gaisa, MD, PhD, Division of Infectious Diseases, Department of Medicine, Mount Sinai Health System, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl, Box 1090, New York, NY 10029; michael.gaisa@mssm.edu

[1]Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York; [3]Department of Management, Policy and Community Health, University of Texas School of Public Health, Houston, Texas; [4]Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

See editorial on pages 1376-8, this issue.

DOI: 10.1002/cncr.32581, **Received:** February 12, 2019; **Revised:** May 6, 2019; **Accepted:** May 16, 2019, **Published online** January 24, 2020 in Wiley Online Library (wileyonlinelibrary.com)

modeling study found adjuvant vaccination to be cost-effective[16,17]; however, a recent randomized clinical trial did not confirm such synergy among PLWH.[18]

Studies regarding ablation efficacy have been heterogeneous with regard to cohort characteristics and surveillance strategies, yet HSIL clearance after infrared coagulation (IRC) and/or EA has been consistently high, ranging from 53% to 87% in HIV-infected and HIV-uninfected MSM.[19-24] However, HSIL recurs frequently after ablation and necessitates ongoing surveillance and repeated treatments.[25]

In the current study, we summarized our experience using EA combined with HRA surveillance to manage anal HSIL in a large real-world cohort of PLWH, the majority of whom were MSM. The objectives were to determine the effectiveness of ablation and to identify key clinicopathological factors associated with postablation HSIL recurrence.

MATERIALS AND METHODS

Patient Selection

Institutional review board approval first was obtained from the Icahn School of Medicine at Mount Sinai in New York City. The anal dysplasia database at Mount Sinai was searched from January 2009 to December 2016 for PLWH who were referred for anal cancer screening either with or without previously obtained anal cytology and who met the following inclusion criteria: 1) de novo, biopsy-proven intra-anal canal HSIL; 2) EA within 6 months of diagnosis; and 3) ≥1 surveillance HRAs with biopsy after ablation. Patients with a history of anal cancer or prior treatment for HSIL were excluded. Electronic medical records were reviewed for clinical characteristics such as age, sex, race/ethnicity, history of an AIDS diagnosis (as evidenced by a nadir CD4-positive [CD4+] T-cell count <200 cells/mm^3 or clinical evidence of AIDS), HIV-1 RNA level and CD4+ T-cell count within 6 months prior to HRA, as well as smoking history.

HRA and Biopsy

All patients underwent a digital anorectal examination and HRA at the time of the initial and follow-up visits. Unless previously obtained, anal cytology samples were collected immediately prior to HRA. All HRA and biopsy procedures were performed by author M.M.G. using previously described techniques.[26] After treatment with 5% acetic acid and Lugol's iodine, the squamocolumnar junction, distal anal canal, and anal margin were visualized under 15x magnification to look for abnormal vascular patterns and other potential signs of HSIL or cancer, including ulceration, mass effect, and mucosal friability. Areas suspicious for HSIL or cancer were biopsied. If no suspicious mucosal changes were identified, then no biopsy was obtained and the patient was scored as having a "benign" examination. Random biopsies of healthy-appearing tissue were not performed during the current study.

Electrocautery Ablation

All EA procedures were performed by author M.M.G. using a hyfrecator (ConMed Corporation, Utica, New York). Under HRA guidance, index HSILs were identified and the hyfrecator was used to ablate the lesions after achieving local anesthesia using 1% lidocaine hydrochloride with epinephrine at a ratio of 1:100,000. The hyfrecator was used at a setting of 15 watts. Lesions were fulgurated and debrided with blunt and sharp dissection to healthy tissue and submucosal vessels were coagulated.[23] All HSILs detected at baseline were ablated concomitantly during the same treatment visit.

Classification of Ablation Outcomes

The anal canal was divided into octants and biopsy sites were recorded as anterior, right anterior, right lateral, right posterior, posterior, left posterior, left lateral, or left anterior. To account for potential mucosal shifts in between HRA procedures, lesions from any 3 adjacent octants were considered as the same location for the purposes of surveillance analyses. Based on surveillance HRA and biopsy results, ablation outcomes were classified as overall recurrence (any HSIL detected at the time of follow-up) or no recurrence (no evidence of HSIL). Recurrence then was subclassified further as local recurrence or metachronous recurrence according to lesion location. Local recurrence was defined as HSIL recurring in the same location as the index lesion. Metachronous recurrence was defined as HSIL recurring in a location independent from that of the index lesion. For time-to-event analyses, we calculated time to disease recurrence by measuring the time from the date of ablation until the occurrence of the outcome of interest (ie, a recurrence event); subjects with no recurrence were censored at the time of their latest surveillance HRA. For recurrence events, we also collected data regarding the number of HSIL lesions detected at the time of surveillance HRA.

Pathology Review

All biopsies were processed following standard histological protocols, serially sectioned into 6 levels, and stained

with hematoxylin and eosin. Surgical pathologists at the Mount Sinai Hospital rendered diagnoses based on standard morphological criteria for low-grade squamous intraepithelial lesions and HSILs. Consensus review was conducted by ≥2 pathologists in approximately 80% of the biopsies to confirm histological diagnoses. p16 immunohistochemistry was used in selected cases (approximately 40% of the biopsies) to grade morphologically ambiguous lesions wherein strong and diffuse positive immunoreactivity supported the diagnosis of HSIL.[27]

Results of HPV genotyping from liquid cytology fluid were obtained from the pathology database and were limited to samples collected concurrently or within 3 months of the index HRA beginning in February 2012 (HPV testing was performed in approximately 92% of cases after this date). We also collected data on HPV status at the time of each surveillance HRA. Oncogenic HPV subtype analysis was performed using the Roche cobas 4800 system HPV kit (Roche Diagnostics, Indianapolis, Indiana), which is capable of detecting 14 types of high-risk HPV (types 16 and 18 and other types including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV status was categorized as no high-risk HPV, HPV-16 and/or HPV-18 with or without other high-risk HPV, or non–HPV-16 and/or HPV-18 high-risk HPV.

Statistical Analysis

We first used descriptive statistics to summarize the baseline characteristic of the study population. To estimate the difference in HSIL recurrence on follow-up by patient characteristics, we used the Wilcoxon test for continuous variables (age and CD4+ T-cell count measures) and the chi-square test for categorical variables. Kaplan-Meier methods were used to estimate the cumulative risk of 2 primary outcomes: local and overall HSIL recurrence. We also compared the cumulative risk of recurrence by baseline HPV status; the difference in risk was compared using the log-rank test. Hazard ratios (HRs) and associated 95% CIs were computed by fitting multivariable Cox proportional hazards regression models to evaluate significant predictors from univariate testing, adjusted for demographic factors and other potential confounders. We first evaluated the association between HIV viremia (HIV RNA level <100 copies/mL vs ≥100 copies/mL to differentiate between viral "blips" and more significant viremia[28]; obtained within 6 months prior to index HRA), smoking status, and HSIL burden at baseline (solitary vs multiple) with local and overall recurrence. Because HPV typing only was available after early 2012, we fitted separate multivariable models to include baseline HPV infection status excluding subjects who were seen prior to February 2012. Because HPV-16 and/or HPV-18 status was found to be predictive of the outcomes of interest in univariate and multivariable analyses, we fitted additional models including individuals with longitudinal HPV information to assess the impact of HPV-16 and/or HPV-18 persistence on HSIL recurrence by categorizing HPV-16 and/or HPV-18 infection as always negative, intermittent (positive at some surveillance HRAs), or persistent (positive at all surveillance HRAs). Data were missing for baseline HPV status (8% in models excluding individuals who were included prior to the start of routine testing), smoking status, and race/ethnicity (<3%). We used multiple imputation methods in multivariable models to account for missing data (including baseline HPV status); these results are presented and did not differ significantly from those of complete case analyses. All analyses were performed using Stata statistical software (version 15; StataCorp LLC, College Station, Texas).

RESULTS

Patient Characteristics

A total of 330 PLWH met the inclusion criteria. The median age at the time of index HSIL diagnosis was 45.5 years (interquartile range, 35-51 years); approximately 88% were MSM, 12% were women, and 28% were current smokers (Table 1). At baseline, approximately 51% of patients were found to have a solitary index HSIL whereas 49% harbored 2 to 6 HSILs. Among patients with baseline HPV genotyping results (268 patients), oncogenic HPV types were detected in 93%, including 48% who tested positive for HPV-16 and/or HPV-18 with or without other high-risk types, and 45% who tested positive for only non–HPV-16 and/or HPV-18 high-risk types. All participants were prescribed antiretroviral therapy during the study period and had a median CD4+ T-cell count of 633 cells/μL. Approximately 82% of subjects had HIV-1 RNA <100 copies/mL within 6 months of the index HSIL diagnosis.

Ablation Outcomes and Predictors

The median follow-up after ablation was 12.2 months (interquartile range, 6.3-20.9 months). Overall, 148 patients (45%) developed local recurrence at the ablated site (Table 2). A total of 142 patients (43%) developed metachronous lesions. Overall, 198 patients (60%) experienced recurrent HSIL. None of the patients progressed to invasive cancer during the study period. Among patients who experienced HSIL recurrence, approximately

TABLE 1. Comparison of Baseline Demographic and Clinical Characteristics Between Ablation Outcome Groups

Patient Characteristics	Baseline Cohort Characteristics N = 330	Outcomes on Any Follow-Up		P^a
		No HSIL Recurrence N = 132	Overall HSIL Recurrence N = 198	
Median age (IQR), y	45.5 (35-51)	46 (35.5-52)	45 (34-53)	.7
MSM, no. (%)	290 (88)	118 (89)	172 (87)	.4
Race/ethnicity, no. (%)				
White	124 (38)	42 (32)	82 (41)	.5
Black	65 (20)	28 (21)	37 (19)	
Hispanic	105 (32)	47 (36)	58 (29)	
Other	28 (9)	11 (8)	17 (9)	
Unknown	8 (2)	4 (3)	4 (2)	
Smoking status, no. (%)				
Current smoker	93 (28)	25 (19)	68 (34)	.02
Former smoker	81 (25)	36 (27)	45 (23)	
Never smoker	153 (46)	69 (52)	84 (42)	
Unknown	3 (1)	2 (2)	1 (<1)	
AIDS diagnosis, no. (%)	131 (40)	56 (42)	75 (38)	.4
HIV RNA, no, (%)				
>100 copies/mL	59 (18)	16 (12)	43 (22)	.03
Median CD4+ T-cell count, (IQR), cells/μL	633 (459-828)	610 (443-771)	647 (460-869)	.3
Median no. of follow-up HRA examinations (range)	1 (1-8)	2 (1-8)	1 (1-4)	<.001
Lesion burden at baseline, no. (%)				
Solitary	167 (51)	57 (43)	110 (56)	.03
Multiple	163 (49)	75 (57)	88 (44)	
HR HPV types, no. (%)				
Total no.	268	106	162	
Negative	19 (7)	16 (15)	3 (2)	<.001
HPV type 16/18	128 (48)	43 (41)	85 (52)	
Other HR HPV[b]	121 (45)	47 (44)	74 (46)	

Abbreviations: CD4+, CD4 positive; HPV, human papillomavirus; HRA, high-resolution anoscopy; HR HPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; MSM, men who have sex with men.
[a]*P* values for comparisons between the "No HSIL Recurrence" and "Overall HSIL Recurrence" columns.
[b]Other HR HPV types included HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

TABLE 2. Postablation Disease Recurrence at a Median Follow-Up of 12.2 Months Among the 330 Study Patients

Recurrence	No. (Percentage)
Local	148 (45%; 95% CI, 39%-50%)
Metachronous	142 (43%; 95% CI, 38%-49%)
Overall	198 (60%; 95% CI, 54%-65%)

Definitions: local, high-grade squamous intraepithelial lesion detected in the location of the index lesion at the time of follow-up; metachronous, high-grade squamous intraepithelial lesion in a location different from that of the index lesion at the time of follow-up; overall, a combined outcome of local recurrence and metachronous lesions.

67% were found to have a solitary lesion on surveillance HRA, 28% had 2 lesions, and 5% had ≥3 lesions. In unadjusted analyses (Table 1), overall HSIL recurrence after EA was found to be significantly associated with HIV RNA >100 copies/mL ($P = .03$), multiple index lesions at baseline ($P = .03$), and infection by high-risk HPV types ($P < .001$). A greater percentage of patients with HSIL recurrence also were current smokers (34% vs 19%; $P = .02$). HSIL recurrence was highest for patients infected with HPV-16 and/or HPV-18 (52%), followed by those infected with other high-risk HPV types (46%) and was lowest for those with undetectable high-risk HPV types (2%; $P < .001$). We found no statistically significant difference with regard to postablation disease recurrence by age, race, AIDS diagnosis, and CD4+ T-cell count.

Unadjusted time-to-event analyses demonstrated a cumulative probability of local HSIL recurrence of 8% at 6 months (95% CI, 5%-12%), 38% at 12 months (95% CI, 33%-44%), and 53% at 36 months (95% CI, 47%-60%) (Fig. 1). The cumulative probability of overall HSIL recurrence was 50% at 12 months (95% CI, 44%-55%) and 68% at 36 months (95% CI, 62%-74%). In unadjusted time-to-event analyses of overall HSIL recurrence by baseline HPV status, HPV-16 and/or HPV-18 infection was associated with the greatest risk of HSIL recurrence ($P = .001$) (Fig. 2).

In multivariable analyses (Table 3), local HSIL recurrence after EA was found to be independently associated with HIV infection with viremia (hazard ratio [HR], 1.5; 95% CI, 1.0-2.2), as was current smoking (HR, 1.7 [95% CI, 1.1-2.4] compared with never having smoked) and the presence of multiple baseline

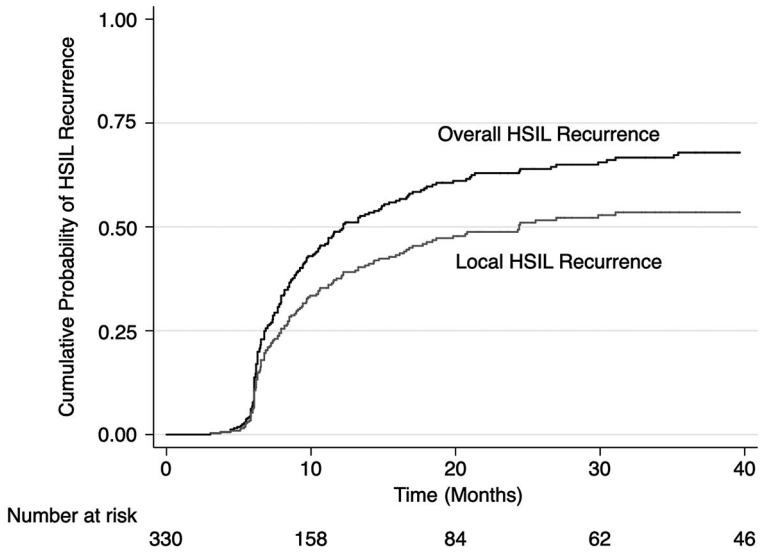

Figure 1. Cumulative probability of overall and local disease recurrence after electrocautery ablation of anal high-grade squamous intraepithelial lesions (HSILs) among people living with HIV.

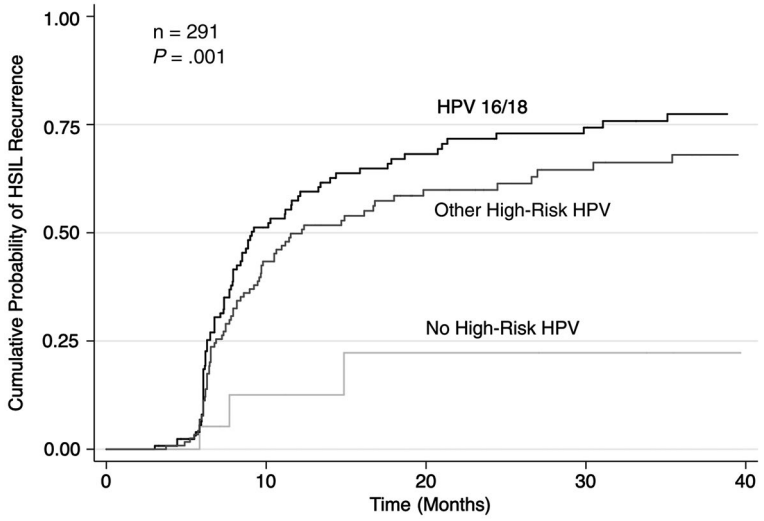

Figure 2. Cumulative probability of overall recurrence of high-grade squamous intraepithelial lesions (HSILs) after electrocautery ablation of anal HSILs among people living with HIV by baseline human papillomavirus (HPV) status.

lesions (HR, 1.8; 95% CI, 1.3-2.5). Current smoking and multiple baseline lesions also were found to be significantly associated with overall HSIL recurrence. In subgroup analyses when comparing outcomes by high-risk HPV infection at baseline (291 patients), detection of HPV-16 and/or HPV-18 (HR of 4.7 for local recurrence and HR of 5.6 for overall recurrence) or other high-risk HPV types (HR of 3.4 for local recurrence and HR of 4.3 for overall recurrence) were independently associated with an increased risk of HSIL recurrence compared with patients with a negative high-risk HPV test (each $P < .05$). HPV genotyping results on surveillance were available for 184 patients. In adjusted analyses of patients with longitudinal HPV genotyping results, persistent infection with HPV-16 and/or HPV-18 was found to be associated with both

TABLE 3. Multivariable Analysis of Predictors of Postablation Local and Overall Disease Recurrence

	Entire Study Cohort N = 330		HPV Testing–Eligible Cohort N = 291		Longitudinal HPV-16/HPV-18 Cohort N = 184	
	HR for Local Recurrence (95% CI)	HR for Overall Recurrence (95% CI)	HR for Local Recurrence (95% CI)	HR for Overall Recurrence (95% CI)	HR for Local Recurrence (95% CI)	HR for Overall Recurrence (95% CI)
Age	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Female	0.9 (0.4-2.0)	1.3 (0.8-2.1)	0.9 (0.4-1.9)	1.2 (0.7-2.2)	0.8 (0.3-2.1)	0.8 (0.3-2.1)
Race/ethnicity						
White	Reference	Reference	Reference	Reference	Reference	Reference
Black	0.7 (0.5-1.2)	0.6 (0.4-1.0)	0.9 (0.5-1.5)	0.7 (0.4-1.1)	1.1 (0.5-2.2)	0.7 (0.4-1.2)
Hispanic	0.8 (0.5-1.2)	0.7 (0.5-1.0)	0.9 (0.6-1.5)	0.8 (0.5-1.2)	1.2 (0.7-2.2)	0.7 (0.4-1.2)
Other	1.1 (0.6-2.0)	0.8 (0.5-1.4)	1.0 (0.5-2.0)	0.8 (0.4-1.2)	1.7 (0.6-4.7)	0.8 (0.3-2.0)
Smoking status						
Never smoker	Reference	Reference	Reference	Reference	Reference	Reference
Former smoker	1.1 (0.7-1.7)	1.0 (0.7-1.4)	1.0 (0.7-1.7)	0.9 (0.6-1.4)	1.1 (0.6-2.0)	1.2 (0.7-1.9)
Current smoker	1.7 (1.1-2.4)	1.8 (1.3-2.5)	1.3 (0.9-2.1)	1.7 (1.2-2.5)	1.2 (0.7-2.2)	1.8 (1.1-2.9)
HIV viremia						
Nonviremic	Reference	Reference	Reference	Reference	Reference	Reference
Viremic	1.5 (1.0-2.2)	1.3 (0.9-1.8)	1.3 (0.9-2.0)	1.2 (0.8-1.7)	1.9 (1.1-3.3)	1.4 (0.8-2.3)
Lesion burden at baseline						
Solitary	Reference	Reference	Reference	Reference	Reference	Reference
Multiple	1.8 (1.3-2.5)	1.4 (1.1-1.9)	1.8 (1.2-2.6)	1.3 (0.9-1.8)	1.7 (1.1-2.8)	1.3 (0.9-2.0)
High-risk HPV types						
No high-risk HPV	—	—	Reference	Reference	—	—
HPV-16/HPV-18	—	—	4.7 (1.1-19.5)	5.6 (1.7-17.9)	—	—
Other high-risk HPV	—	—	3.4 (0.8-14.1)	4.3 (1.3-13.7)	—	—
HPV-16/HPV-18 longitudinal positivity						
Always HPV-16/HPV-18 negative[a]					Reference	Reference
Intermittent HPV-16/HPV-18 positivity[b]					1.9 (0.6-6.3)	2.2 (0.8-6.3)
Persistent HPV-16/HPV-18 positivity[c]					2.3 (1.4-3.7)	2.0 (1.3-3.1)

Abbreviations: HPV, human papillomavirus; HR, hazard ratio.

[a]Always HPV-16/HPV-18 negative indicates that HPV-16 and/or HPV-18 was neither detected at baseline nor at follow-up.

[b]Intermittent HPV-16/HPV-18 positivity indicates that HPV-16 and/or HPV-18 was detected only once, either at baseline or at follow-up.

[c]Persistent HPV-16/HPV-18 positivity indicates that HPV-16 and/or HPV-18 was detected at both baseline and follow-up.

local HSIL recurrence (HR, 2.3; 95% CI, 1.4-3.7) and overall HSIL recurrence (HR, 2.0; 95% CI, 1.3-3.1).

DISCUSSION

In the current retrospective study, we evaluated the effectiveness of EA as an initial treatment of patients with anal HSIL. The current study cohort comprised 330 PLHW, predominantly MSM, with a de novo diagnosis of intra-anal HSIL. After a single ablation treatment, approximately 62% of study participants were free of HSIL at the ablation site 12 months after treatment and 47% maintained remission at the treated HSIL site 36 months after EA. Although the rate of overall postablation HSIL recurrence was substantial (50% at 12 months and 68% at 36 months), no patient progressed to cancer during the study period. We further demonstrated that HSIL burden at baseline, being an active smoker, HIV viremia, and HPV-16 and/or HPV-18 infection had a strongly negative impact on treatment effectiveness, suggesting that more vigilant posttreatment surveillance may be warranted for patients with these risk factors.

The results of the current study are in agreement with those of others regarding the effectiveness of ablation in eradicating anal HSIL. Cranston et al reported an HSIL clearance rate of 64% among 68 HIV-infected MSM who were treated with IRC.[22] Recently, Goldstone et al published what to the best of our knowledge is the first randomized, prospective trial comparing IRC ablation with active monitoring in 120 HIV-infected participants with 1 to 3 anal HSILs.[29] Complete index HSIL clearance was 62% for participants treated with IRC compared with 30% in the active monitoring group at a follow-up of 1 year, a result that demonstrated a clear treatment benefit in patients with limited disease as well as the potential for spontaneous regression. A decision analytic model that was developed based on Surveillance, Epidemiology, and End Results data also has affirmed the cost-effectiveness of HSIL treatment, particularly for HIV-infected MSM aged ≥38 years.[8]

When patients are treated with EA, index HSIL clearance rates are similarly high, but there remains significant concern over response durability and disease recurrence. In the current study, we observed an overall HSIL recurrence rate of 50% within 1 year and 68% within 3 years of ablation, thereby underscoring the need for ongoing, active surveillance after initial ablation. The findings of the current study are consistent with what to our knowledge is the largest retrospective study on long-term outcomes published to date, one that used a variety of ablative techniques (laser, IRC, and EA).[21] The authors estimated the probability of recurrence within 1 year, 2 years, and 3 years as 53%, 68%, and 77%, respectively, for HIV-infected patients, with slightly lower estimates for individuals not infected with HIV (49%, 57%, and 66%, respectively, at 1 year, 2 years, and 3 years).

High postablation recurrence largely is attributed to the targeted treatment approach whereby only visibly abnormal tissue is ablated under HRA guidance. Microscopic residual disease that is left untreated may pave the way for disease recurrence, and multiple index HSILs likely exacerbate that risk. This is supported by the current study finding that a high volume of baseline disease is a significant risk factor for disease recurrence. In addition, some experts have speculated that ablative therapy might promote activation of latent HPV in nondysplastic tissue surrounding ablated HSIL sites and thereby catalyze recurrence.[29] Reassuringly, although approximately 49% of subjects in the current study cohort had multiple index HSILs (range, 2-6 index HSILs) prior to EA, approximately two-thirds of all recurrences presented as a solitary lesion, suggesting a reduction in disease volume when ablative therapy is administered.

It is important to note that none of the study participants who underwent EA of anal HSIL progressed to anal cancer after a median follow-up of 12.2 months. Two recently published articles reported that anal HSIL progresses to invasive anal cancer at rates of 1.3% to 1.9% per year.[30,31] Despite slight variations in patient cohort characteristics and a longer median follow-up in these series, one would expect to note 4 to 6 patients progressing to cancer within 12.2 months by adopting similar progression rates to the current study cohort. The latest practice guidelines for colon and rectal surgeons have provided only a weak recommendation for both screening and surveillance of populations at risk of anal dysplasia.[32] In contrast, the data from the current study strongly suggests that for PLWH whose anal HSIL is treated and properly surveilled, the risk of progression to cancer is diminished, despite significant post-EA recurrence rates.

HIV infection is considered to be one of the major risk factors for postablation disease recurrence. In the current study cohort, a 50% increase in local HSIL recurrence rates was associated with HIV viremia, even after adjusting for potential confounders. Nevertheless, in contrast to previous evidence, we did not find any association between prior severe immunosuppression (AIDS diagnosis or a nadir CD4 count <200 cells/mm^3)

and EA outcomes.[25] Because the majority of viremic patients in the current study had relatively robust CD4 counts, this finding suggests that low-level or intermittent viremia leads to subtle immunosuppression or other immunological disturbances that may be more conducive for HPV infection to persist and progress.[33] This is corroborated by previous work our group has published regarding the immune microenvironment of anal HSILs. We found that anal HSILs among PLWH harbored excess mucosa-infiltrating CD8+ T lymphocytes, and this was significantly associated with ablation resistance.[34] HIV infection may disrupt the anal mucosa, thereby facilitating HPV infection.[35] Furthermore, the HIV Tat protein has been shown to increase expression of the HPV oncoprotein E6 and to reduce activity of the tumor suppressor gene p53, thereby providing a direct link between an HIV viral protein and the HPV carcinogenic pathway.[36]

Active cigarette smoking is an established risk factor for persistent anogenital HPV infection, HSIL, and anal cancer.[6,37,38] Furthermore, anal oncogenic HPV viral loads have been shown to be significantly higher in smokers compared with nonsmokers.[39] Consistent with these observations, both local and overall HSIL recurrences in the current study cohort were associated with being a current smoker.

To the best of our knowledge, there are limited data regarding the impact of specific high-risk HPV types on HSIL treatment outcomes. In the current study, we found that high-risk HPV infection, particularly persistent infection with HPV-16 and/or HPV-18, conferred a significant risk of postablation HSIL recurrence. We recently reported that baseline HPV-16 and/or HPV-18 infection was associated with an increased likelihood of progression from anal low-grade squamous intraepithelial lesion to HSIL compared with baseline infection with non–HPV-16 and/or HPV-18 high-risk HPV types.[40] Taken together, the findings of the current study underscore the importance of HPV-16 and HPV-18 in anal carcinogenesis, suggesting a potential role for HPV genotyping for risk stratification in anal cancer screening.[41,42] Studying the role of high-risk HPV infection and HIV-related local immune disturbance in the continuum of disease progression, screening effectiveness, HSIL treatment, and continued surveillance may help to formulate more targeted anal cancer prevention algorithms that will maximize the value of screen-and-treat approaches.

As previously reported, the quality of HRAs and the technical proficiency of ablative treatments are subject to a lengthy learning process with significant interoperator variability.[43,44] Quality can vary even within the same operator depending on a variety of factors: patient anxiety and discomfort can render the examination challenging, rushed, or abbreviated. Anatomic challenges such as preexisting scar tissue, postoperative or radiation changes, hemorrhoids, bleeding, and/or mucosal prolapse can have a significant impact on the quality of the examination. Such factors likely affect the detection rate of HSIL as well as ablation efficacy, thereby influencing overall recurrence rates.

The current study has several strengths. To the best of our knowledge, it is one of the largest clinical data sets published to date assessing the treatment effectiveness of EA for anal HSIL in PLWH and factors associated with treatment outcomes. Despite its retrospective design, it used a meticulous, longitudinal database capturing clinical and epidemiological variables and was unique in that it contained high-risk HPV infection and clinical HIV data. A single operator with significant experience performed all HRAs and ablative treatments, thereby preventing interoperator variability. Last, we used HRA-guided biopsy as a surveillance strategy, providing definitive histopathological confirmation of any disease recurrence. With regard to notable limitations, treatment adverse events were not systematically captured. Furthermore, the size and morphology of index HSILs were not recorded and may have had an impact on recurrence risk.

The results of the current study corroborate that EA is an effective treatment for anal HSIL in PLWH and achieves high index HSIL clearance rates. HSIL recurrence is a considerable downside of the targeted ablative approach. HIV viremia, smoking, HPV-16 and/or HPV-18 infection, and the number of index HSILs appear to have a negative impact on treatment success. Careful, ongoing surveillance using HRA and biopsy is imperative to capture disease recurrence early and to improve long-term treatment outcomes.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Keith M. Sigel receives funding through National Cancer Institute grant K07CA180782. Ashish A. Deshmukh has acted as a paid consultant for Merck for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors were involved in the study design, planning, conduct, and reporting of the work described in the article. **Michael M. Gaisa** and

Keith M. Sigel assumed responsibility for the overall content. **Michael M. Gaisa** conducted all relevant clinical procedures and was involved in the collection, analysis, and interpretation of the data as well as article preparation. **Yuxin Liu** read the clinical pathology specimens and was involved in the collection, analysis, and interpretation of the data as well as article preparation. **Ashish A. Deshmukh** and **Kimberly L. Stone** were involved in the statistical analysis and interpretation of the data as well as article preparation. **Keith M. Sigel** assumed final responsibility for the statistical rigor of the data analysis and was involved in the collection and interpretation of the data as well as article preparation.

REFERENCES

1. National Cancer Institute. SEER Cancer Factsheets: anal cancer. Accessed January 5, 2019. http://seer.cancer.gov/statfacts/html/anus.html
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.
3. Berry JM, Jay N, Cranston RD, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. *Int J Cancer*. 2014;134:1147-1155.
4. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS*. 2005;19:1407-1414.
5. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol*. 2012;13: 487-500.
6. Gaisa M, Ita-Nagy F, Sigel K, et al. High rates of anal high-grade squamous intraepithelial lesions in HIV-infected women who do not meet screening guidelines. *Clin Infect Dis*. 2017;64:289-294.
7. Orchard M, Roman A, Parvaiz AC. Anal intraepithelial neoplasia—is treatment better than observation? *Int J Surg*. 2013;11:438-441.
8. Deshmukh AA, Chiao EY, Cantor SB, et al. Management of precancerous anal intraepithelial lesions in human immunodeficiency virus–positive men who have sex with men: clinical effectiveness and cost-effectiveness. *Cancer*. 2017;123:4709-4719.
9. Burkhalter JE, Atkinson TM, Berry-Lawhorn J, et al; ANCHOR HRQOL Implementation Group. Initial development and content validation of a health-related symptom index for persons either treated or monitored for anal high-grade squamous intraepithelial lesions. *Value Health*. 2018;21:984-992.
10. Palefsky JM. Screening to prevent anal cancer: current thinking and future directions. *Cancer Cytopathol*. 2015;123:509-510.
11. Nathan M, Sheaff M, Fox P, Goon P, Gilson R, Lacey C. Early treatment of anal intraepithelial neoplasia. *BMJ*. 2011;343:d7717.
12. Fox PA. Treatment options for anal intraepithelial neoplasia and evidence for their effectiveness. *Sex Health*. 2012;9:587-592.
13. Megill C, Wilkin T. Topical therapies for the treatment of anal high-grade squamous intraepithelial lesions. *Semin Colon Rectal Surg*. 2017;28:86-90.
14. Terlizzi JP, Goldstone S. Ablative therapies for the treatment of anal high-grade squamous intraepithelial lesions. *Semin Colon Rectal Surg*. 2017;28:81-85.
15. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. *Lancet Oncol*. 2013;14:346-353.
16. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. *Clin Infect Dis*. 2012;54:891-898.
17. Deshmukh AA, Chiao EY, Das P, Cantor SB. Clinical effectiveness and cost-effectiveness of quadrivalent human papillomavirus vaccination in HIV-negative men who have sex with men to prevent recurrent high-grade anal intraepithelial neoplasia. *Vaccine*. 2014;32:6941-6947.
18. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus–infected adults aged 27 years or older: AIDS Clinical Trials Group protocol A5298. *Clin Infect Dis*. 2018;67:1339-1346.
19. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. *Dis Colon Rectum*. 2008;51:829-835; discussion 835-837.
20. Stier EA, Goldstone SE, Berry JM, et al. Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: an AIDS Malignancy Consortium pilot study. *J Acquir Immune Defic Syndr*. 2008;47:56-61.
21. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. *Dis Colon Rectum*. 2014;57:316-323.
22. Cranston RD, Hirschowitz SL, Cortina G, Moe AA. A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. *Int J STD AIDS*. 2008;19:118-120.
23. Marks DK, Goldstone SE. Electrocautery ablation of high-grade anal squamous intraepithelial lesions in HIV-negative and HIV-positive men who have sex with men. *J Acquir Immune Defic Syndr*. 2012;59:259-265.
24. Burgos J, Curran A, Landolfi S, et al. The effectiveness of electrocautery ablation for the treatment of high-grade anal intraepithelial neoplasia in HIV-infected men who have sex with men. *HIV Med*. 2016;17:524-531.
25. Burgos J, Curran A, Landolfi S, et al. Risk factors of high-grade anal intraepithelial neoplasia recurrence in HIV-infected MSM. *AIDS*. 2017;31:1245-1252.
26. Jay N, Berry JM, Miaskowski C, et al. Colposcopic characteristics and Lugol's staining differentiate anal high-grade and low-grade squamous intraepithelial lesions during high resolution anoscopy. *Papillomavirus Res*. 2015;1:101-108.
27. Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med*. 2012;136:1266-1297.
28. Fidler S, Olson AD, Bucher HC, et al. Virological blips and predictors of post treatment viral control after stopping ART started in primary HIV infection. *J Acquir Immune Defic Syndr*. 2017;74:126-133.
29. Goldstone SE, Lensing SY, Stier EA, et al. A randomized clinical trial of infrared coagulation ablation versus active monitoring of intra-anal high-grade dysplasia in HIV-infected adults: an AIDS Malignancy Consortium trial. *Clin Infect Dis*. 2019;68:1204-1212.
30. Cajas-Monson LC, Ramamoorthy SL, Cosman BC. Expectant management of high-grade anal dysplasia in people with HIV: long-term data. *Dis Colon Rectum*. 2018;61:1357-1363.
31. Lee GC, Kunitake H, Milch H, et al. What is the risk of anal carcinoma in patients with anal intraepithelial neoplasia III? *Dis Colon Rectum*. 2018;61:1350-1356.
32. Stewart DB, Gaertner WB, Glasgow SC, Herzig DO, Feingold D, Steele SR; Prepared on Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for Anal Squamous Cell Cancers (Revised 2018). *Dis Colon Rectum*. 2018;61:755-774.
33. Critchlow CW, Hawes SE, Kuypers JM, et al. Effect of HIV infection on the natural history of anal human papillomavirus infection. *AIDS*. 1998;12:1177-1184.
34. Liu Y, Gaisa MM, Wang X, et al. Differences in the immune microenvironment of anal cancer precursors by HIV status and association with ablation outcomes. *J Infect Dis*. 2018;217:703-709.
35. Tugizov SM, Herrera R, Chin-Hong P, et al. HIV-associated disruption of mucosal epithelium facilitates paracellular penetration by human papillomavirus. *Virology*. 2013;446:378-388.
36. Barillari G, Palladino C, Bacigalupo I, Leone P, Falchi M, Ensoli B. Entrance of the Tat protein of HIV-1 into human uterine cervical carcinoma cells causes upregulation of HPV-E6 expression and a decrease in p53 protein levels. *Oncol Lett*. 2016;12:2389-2394.
37. Vaccarella S, Herrero R, Snijders PJ, et al; IARC HPV Prevalence Surveys (IHPS) Study Group. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. *Int J Epidemiol*. 2008;37:536-546.

38. Bertisch B, Franceschi S, Lise M, et al; Swiss HIV Cohort Study Investigators. Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study. *Am J Epidemiol*. 2013;178:877-884.
39. Wieland U, Hellmich M, Wetendorf J, et al. Smoking and anal high-risk human papillomavirus DNA loads in HIV-positive men who have sex with men. *Int J Med Microbiol*. 2015;305:689-696.
40. Liu Y, Sigel K, Gaisa MM. Human papillomavirus genotypes predict progression of anal low-grade squamous intraepithelial lesions. *J Infect Dis*. 2018;218:1746-1752.
41. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18:198-206.
42. Sambursky JA, Terlizzi JP, Goldstone SE. Testing for human papillomavirus strains 16 and 18 helps predict the presence of anal high-grade squamous intraepithelial lesions. *Dis Colon Rectum*. 2018;61:1364-1371.
43. Hillman RJ, Gunathilake MP, Jin F, Tong W, Field A, Carr A. Ability to detect high-grade squamous anal intraepithelial lesions at high resolution anoscopy improves over time. *Sex Health*. 2016;13:177-181.
44. Siegenbeek van Heukelom ML, Marra E, Cairo I, et al. Detection rate of high-grade squamous intraepithelial lesions as a quality assurance metric for high-resolution anoscopy in HIV-positive men. *Dis Colon Rectum*. 2018;61:780-786.