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Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men

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The incidence of anal cancer is elevated in human immunodeficiency virus (HIV)-infected men-who-have-sex-with-men (MSM) compared to the general population. Anal high-grade squamous intraepithelial lesions (HSIL) are common in HIV-infected MSM and the presumed precursors to anal squamous cell cancer; however, direct progression of HSIL to anal cancer has not been previously demonstrated. The medical records were reviewed of 138 HIV-infected MSM followed up at the University of California, San Francisco, who developed anal canal or perianal squamous cancer between 1997 and 2011. Men were followed up regularly with digital anorectal examination (DARE), high-resolution anoscopy (HRA) and HRA-guided biopsy. Although treatment for HSIL and follow-up were recommended, not all were treated and some were lost to follow-up. Prevalent cancer was found in 66 men. Seventy-two HIV-infected MSM developed anal cancer while under observation. In 27 men, anal cancer developed at a previously biopsied site of HSIL. An additional 45 men were not analyzed in this analysis due to inadequate documentation of HSIL in relation to cancer location. Of the 27 men with documented progression to cancer at the site of biopsy-proven HSIL, 20 men progressed from prevalent HSIL identified when first examined and seven men from incident HSIL. Prevalent HSIL progressed to cancer over an average of 57 months compared to 64 months for incident HSIL. Most men were asymptomatic, and cancers were detected by DARE. Anal HSIL has clear potential to progress to anal cancer in HIV-infected MSM. Early diagnosis is facilitated by careful follow-up. Carefully controlled studies evaluating efficacy of screening for and treatment of HSIL to prevent anal cancer are needed.

The incidence of anal cancer continues to increase annually in the general population.[1] Prior to the availability of effective antiretroviral therapy (ART), the estimated incidence of anal cancer among human immunodeficiency virus (HIV)-infected men-who-have-sex-with-men (MSM) was nearly 60-fold higher than men in the general population.[2] Although the incidence of other viral-associated malignancies has decreased in HIV-infected MSM as a result of ART, anal cancer incidence has increased, and its incidence in HIV-infected MSM is now estimated to be 80 times higher than men in the general

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What's new?

The elevated incidence of anal cancer seen among HIV-infected men-who-have-sex-with-men (MSM) is presumably linked to the common occurrence of anal high-grade squamous intraepithelial lesions (HSIL) in this population. This study provides some of the first evidence for direct progression of the postulated HSIL precursors to anal cancer. MSM were followed for a period of more than 20 years with high-resolution anoscopy and biopsy. The data provide conclusive evidence of the malignant potential of anal HSIL and underscore the potential to reduce anal cancer through targeted removal of anal HSIL.

population.[3–7] In 2012, the incidence of anal cancer among HIV-infected MSM in North America was 131/100,000.[7]

Anal high-grade squamous intraepithelial lesions (HSIL) are postulated to be the precursors to anal cancer. MSM and most HIV-infected persons, regardless of mode of acquisition of HIV, have a high prevalence and incidence of anal canal and perianal HSIL.[8–10] Similar to the lack of effect of ART in reducing squamous cell cancer of the anal canal and perianal region, most studies show that ART has had little effect on reducing HSIL. The prevalence of anal HSIL in HIV-infected MSM is reported to range from 30 to 52% in the ART era.[11,12]

The secondary prevention of cervical cancer through identification and eradication of cervical HSIL is an undisputed success of modern medicine.[13] Squamous cell carcinomas of the anus and cervix are histologically and biologically similar, sharing an etiologic association with oncogenic human papillomavirus (HPV) infection, as do anal and cervical HSIL.[14] Based on their similarities, a strategy to detect and ablate anal HSIL to reduce the incidence of anal cancer has been proposed.[15] However, anal cytology screening and preventative treatment programs have not yet been routinely adopted for several reasons. First, there is limited information on the natural history and rate of progression of HSIL to anal cancer in at-risk populations. In a report of six patients with untreated perianal HSIL who were immunocompromised due to autoimmune diseases or renal transplantation, 50% (3 of 6) progressed to anal cancer at a median of 5 years after diagnosis of HSIL.[16] Another group reported progression in eight of 55 (15%) patients with HSIL at a median time of 42 months and no progression among 17 patients with low-grade SIL (LSIL).[17] A second obstacle has been the lack of data on efficacy of anal HSIL treatment in reducing the incidence of anal cancer. However, two studies strongly suggest benefit. In a German study, HSIL was found in 156 of 446 (35%) HIV-infected MSM.[18] Progression to cancer was reported in five study participants who refused treatment at an average of 8.6 months after diagnosis of HSIL, but in none of the treated patients during a mean follow-up of 20.5 months. From our own series, only two of 182 (1%) patients treated with intraoperative high-resolution anoscopy (HRA)-guided ablation of HSIL progressed to cancer.[19] Finally, although HSIL, the presumed cancer precursor, is frequently found adjacent to anal cancers,[20] to date there are no data showing that HSIL directly progresses to anal cancer. In this study, we describe for the first time, direct progression of anal HSIL to anal cancer in the same location as previously biopsied HSIL among HIV-infected MSM being followed up prospectively. Our data definitively demonstrate that HSIL, both anal canal and perianal, can directly progress to anal cancer.

Material and Methods

Description of cohort

After obtaining approval of the Committee on Human Research at the University of California, San Francisco (UCSF), charts were reviewed of HIV-infected MSM who had been diagnosed with anal cancer and had been prospectively followed up in the UCSF Anal Neoplasia Study (ANS) or the UCSF Anal Neoplasia Clinic (ANC) from 1997 to 2011. Beginning in 1991, HIV-infected and HIV-uninfected MSM who had no history of HSIL were enrolled in the ANS.[10,11,21] Study recruitment concluded in January 2000, and the study ended in August 2003. The UCSF ANC was established as a resource for comprehensive management of anal SIL. Approximately 2,000 HIV-infected MSM were followed up in total. Men were examined at 3-, 6- or 12-month intervals depending on HIV status and presence of HSIL with anal cytology and digital anorectal examination (DARE), palpating for masses or areas of induration suspicious for cancer.[22] HRA was performed after applying 3–5% acetic acid. Digital images were captured, and abnormalities visualized at HRA were biopsied.[23] Lesions were selected for biopsy based on criteria used to identify the highest grade of lesion.[24] Biopsy diagnoses were categorized as benign, atypia, LSIL, HSIL or squamous cell carcinoma using criteria equivalent to cervical histopathology. Incident HSIL was defined in subjects who on their initial HRA examinations had no evidence of HSIL, but who then during subsequent examinations developed their first biopsy-documented HSIL. Prevalent HSIL was defined in subjects who had HSIL identified during their initial HRA.

Study design

Only HIV-infected men who developed documented anal cancer in the site of previously biopsied HSIL were included. Men were excluded if they presented with anal cancer at their first visit (prevalent cancer) or incident cancer without previously documented HSIL in the region where the cancer developed. Progression to cancer was clinically suspected when men presented with an anal mass, anal pain or bleeding, focal tenderness or induration associated with extensive perianal lesions or had findings on HRA that included abnormal vessels, friability, mucosal bulging or ulcerations.

To determine whether the cancer developed specifically from a site of previously biopsied HSIL, the location of the

cancer was determined by physical examination. Prior records were then reviewed to determine if this corresponded to the location of the previous biopsy site of HSIL documented on diagrams of the anal canal and perianus or by digital images, when available. If men were not directly examined at the time of cancer diagnosis, then the pathology and operative reports had to specifically indicate that HSIL had been diagnosed previously in exactly the same location as the cancer.

Treatment and follow-up of anal HSIL

At the end of the ANS, men were informed of the risks and warning signs of cancer and urged to consult with their provider or follow-up at the UCSF ANC. Although treatment of HSIL was recommended for all men in the ANS, for several reasons not all were treated. Men with HSIL were managed at the UCSF ANC according to treatment guidelines published by Chin-Hong and Palefsky[25] or by their local colorectal surgeon. Small lesions were treated using 85% trichloroacetic acid. Larger lesions were treated with infrared coagulation in the clinic or ablated or excised during outpatient surgery using HRA to guide identification of lesions.[19,23,26] Patients who declined therapy, had extensive lesions deemed too large and unlikely to respond to treatment, had significant comorbidities or who developed recurrences of HSIL shortly after treatment were followed up closely without treatment at 3- to 4-month intervals with anal cytology, DARE and HRA. Patients who developed signs and symptoms clinically suggestive of anal cancer were referred for examination under anesthesia and biopsy.[23] Patients diagnosed with invasive anal canal cancers were referred for combined modality therapy with chemotherapy and radiation. Those with superficially invasive anal canal and perianal (anal margin) cancers were treated with excision, followed by fulguration, and then intensive follow-up every 3 to 4 months with treatment of recurrent HSIL.[23,27]

Clinical correlations/statistical analysis

Data were collected on age at diagnosis, CD4 cell count within 6 months of the date of anal cancer diagnosis, date of first diagnosis of anal HSIL, duration of documented HSIL prior to developing cancer, location of HSIL with respect to cancer location, presenting signs and symptoms of anal cancer and stage and treatment of anal cancer. The *T*-test was used to test the difference between the mean values of CD4 cell counts for perianal *versus* anal canal cancers.

Results

From January 1997 through December 2011, 138 HIV-infected MSM were diagnosed with squamous cell cancer of the anal canal and perianus. Sixty-six men had anal cancer diagnosed at their first visit. Sufficient clinical information existed to determine that anal cancer developed in a previously biopsied site of HSIL in 27 men. An additional 45 men had documented HSIL prior to cancer diagnosis; however, concordance between the location of the HSIL and the cancer could not be definitively confirmed. The 66 men with prevalent cancer and the 45 men with insufficient documentation of prior HSIL at the site of cancer were excluded from our analysis. However, all of those excluded had biopsy-proven HSIL and most had HSIL overlying or immediately adjacent to their cancer. A summary of those included and excluded from our analysis is shown in Figure 1.

The appearance of HSIL and subsequent invasive anal cancer in two men are shown in Figures 2 and 3. Progression of HSIL to anal canal cancer was heralded in most men by detection of a hard mass palpated on DARE that occasionally was only submucosal, which means that although HSIL was present, the mass (cancer) was located deep to the mucosal surface. Perianal HSIL was clinically suspicious for cancer when progressive thickening, induration, ulceration or new abnormal vascular patterns were found. The presentation and stage of the 27 men included in the analysis are summarized in Table 1. Their median age at diagnosis of cancer was 51 years (range: 39–69 years). Two men were Hispanic, one was black and 24 were white. Seven men were from the ANS and 20 from the ANC. The average CD4+ cell count at the time of diagnosis of anal canal cancers (388 cells per microliter) was higher than that of perianal cancers (215 cells per microliter); however, this difference was not statistically significant ($p = 0.07$). HIV RNA level at time of cancer diagnosis was available for 24 of 27 participants. Sixteen participants (67%) had an HIV RNA level that was below the limit of detection of the tests in use at the time. In the remaining eight participants (33%), the mean HIV RNA level was 42,992 copies per milliliter with a median of 24,000 copies per milliliter (range: 95–138,743).

Superficially invasive squamous cell carcinomas (SISCCA) of the anal canal and perianus are currently defined as T1 cancers that are minimally invasive to a depth of less than or equal to 3 mm with less than or equal to 7 mm of lateral spread and that have been completely excised.[13] All of the men with perianal cancers and two of the men with anal canal cancers had only superficial invasion noted pathologically and can be identified in Table 1 as the subjects who were treated with excision and fulguration. The definition of SISCCA had not been formalized when these men were treated. Three subjects with perianal cancers had horizontal areas of invasion larger than the proposed definition, but were excised with clean margins. All subjects with SISCCA had overlying HSIL on histopathology (Figs. 4*a*–4*c*).

Findings indicative of cancer included palpable intra-anal masses, vascular changes detected during HRA and/or areas of perianal induration. Fourteen of 27 men (52%) presented with pain, bleeding and/or a mass, but 13 of 27 (48%) men were asymptomatic at the time of presentation. A mass, area of induration or ulcer could be palpated or seen in 23 of 27 men (85%). Two men with anal canal cancers (one shown in Fig. 4) and two men with perianal cancers had no palpable abnormalities and their cancers were detected solely by vascular changes visualized and biopsied during HRA.

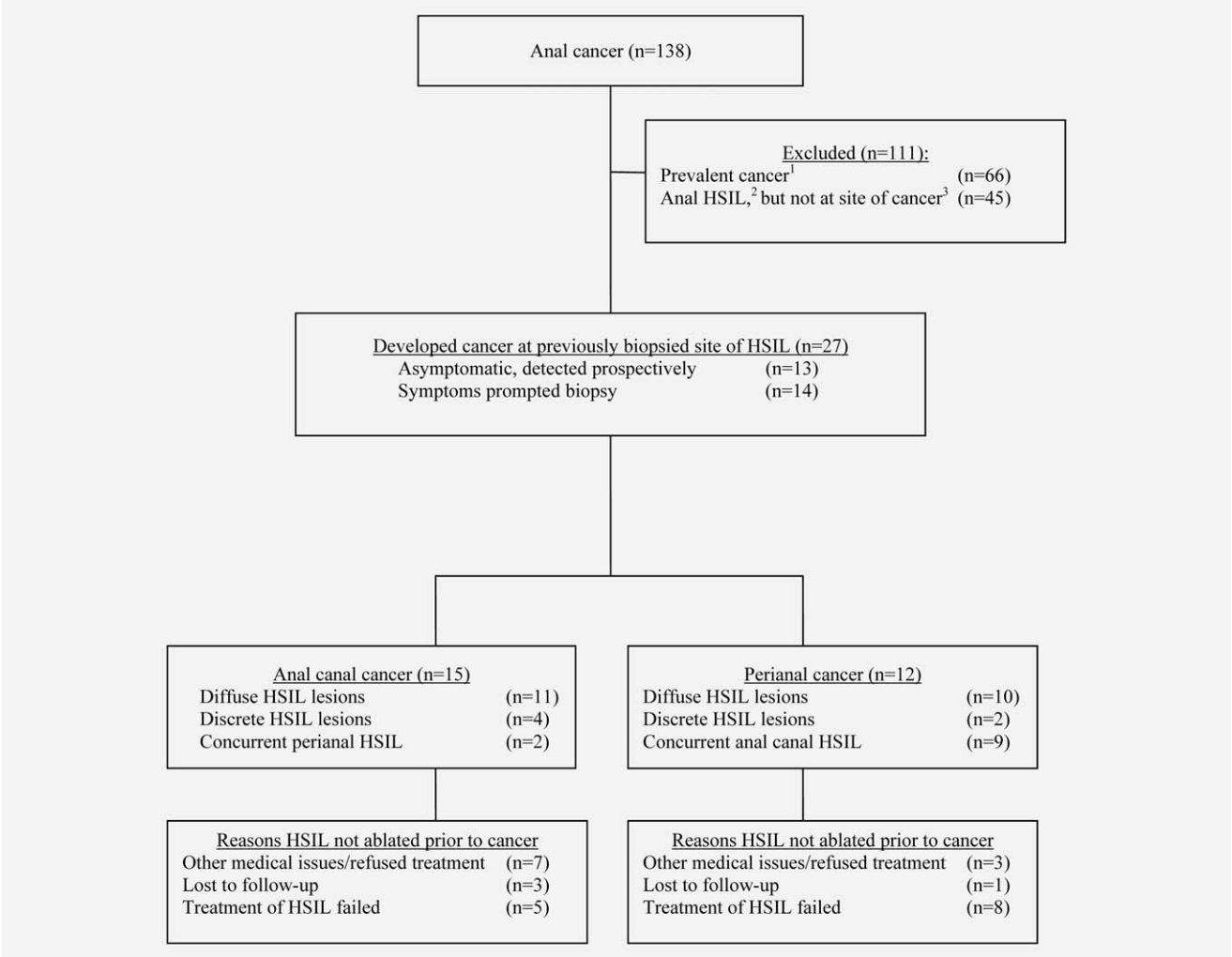

Figure 1. Flowchart of HIV-infected MSM with anal cancer included in and excluded from analysis. [1]Prevalent cancer, cancer that was diagnosed at a patient's first visit to the UCSF Anal Neoplasia Clinic. [2]HSIL, high-grade squamous intraepithelial lesions. [3]HSIL, but not at site of cancer, indicates men who had a history of HSIL; however, concordance between the location of the HSIL and the site of progression to cancer could not be definitively confirmed.

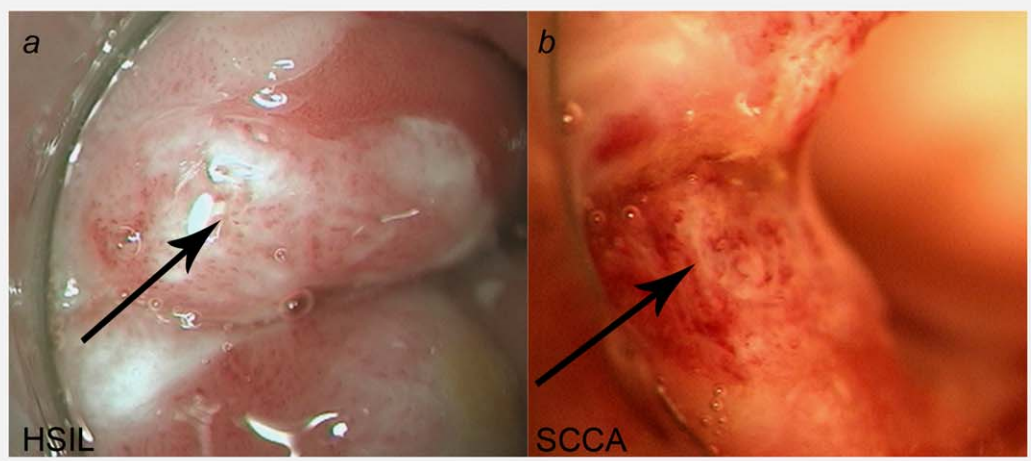

Figure 2. (*a*) Case 6. Arrow indicates anal high-grade squamous intraepithelial lesion (HSIL) biopsied in May 2001 at the end of Anal Neoplasia Study. Patient lost to follow-up. (*b*) The same man presented with a palpable mass in June 2002 in exactly the same area as previously biopsied HSIL; arrow indicates invasive squamous cell carcinoma (SCCA). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

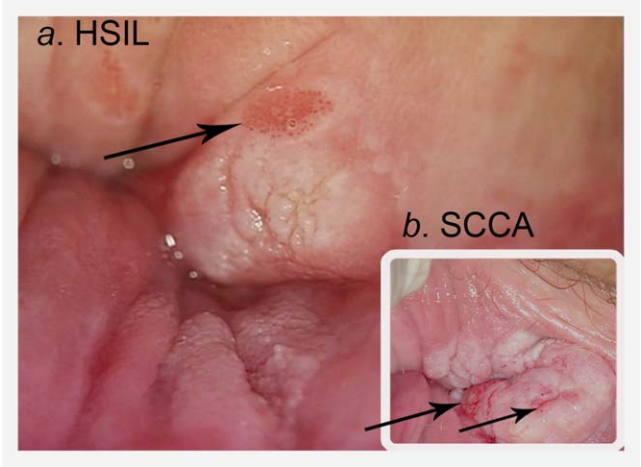

Figure 3. (*a*) Case 22. Patient had HSIL on histology indicated by arrow in April 2008. The lesion persisted despite treatment with trichloroacetic acid, 5% fluorouracil cream and infrared coagulation. (*b*) The lesion clinically evolved into an obvious mass with atypical vessels and ulceration. Histopathology was invasive cancer (SCCA) indicated by arrows in December 2008. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Fourteen of the 27 men were not being actively treated for HSIL prior to cancer diagnosis, including ten who refused treatment and four who were lost to follow-up until being diagnosed with cancer. Three of those four men who were categorized as lost to follow-up had previously been treated with HRA-guided surgery but never returned for a post-operative follow-up examination until they developed symptoms related to cancer. The remaining one of that four and one other of the 14 had no prior treatment of any kind prior to development of cancer.

Thirteen of the 27 men had prior treatment for HSIL in the same region as the subsequent cancer and were categorized as treatment failure. Men were categorized as treatment failure as opposed to lost to follow-up if they returned for planned follow-up visits. All of the men with perianal HSIL who progressed to cancer had advanced HIV disease, which coupled with multiple prior treatment failures for extensive condyloma, were the main reasons that HSIL was not aggressively treated. However, treatment of HSIL evolved during the time period of the study, including the addition of office-based ablation. Only three of these 13 men were treated with curative intent according to the approach currently used in 2013; details of treatment are summarized in Table 2. One of these three men progressed while being treated and was considered a true treatment failure. In the other two men, SISCCA was identified during follow-up and successfully excised.

Twenty of the 27 men presented with prevalent HSIL, and therefore, duration of HSIL prior to progression to cancer is not known; the average time to development of cancer in these men after initial documentation of HSIL was 57 months. Seven of the 27 men developed incident HSIL that progressed to cancer while being followed up prospectively; their clinical information is presented in Table 1. The index HSIL that progressed to cancer was present in these men for an average of 46 months before diagnosis of cancer (range: 10–103 months). Although diffuse multifocal HSIL was present in 21 men, only three men developed simultaneous multifocal cancers. Six of 27 study participants had discrete lesions that progressed.

Discussion

The earliest assumptions that anal HSIL is an anal cancer precursor were based on our knowledge of cervical carcinogenesis and identifying anal HSIL adjacent to invasive anal cancers. Additional evidence came from studies reporting HSIL in resection specimens from patients with anal squamous cell cancers but not in those with rectal adenocarcinoma, anal melanoma or inflammatory bowel disease.[20] Here, we report direct progression of both anal canal and perianal HSIL to invasive cancer in the area of previously biopsied HSIL in 27 men. In addition, most of the 111 men with cancer excluded from our analysis had HSIL overlying their cancer, suggesting that their cancers developed from HSIL. Taken together, our data strongly support the malignant potential of HSIL.

A direct implication of this observation is that, as with cervical cancer prevention, eradication of anal HSIL has the potential to reduce the risk of progression to anal cancer. Our study was not designed to evaluate the effectiveness of treatment of HSIL to prevent anal cancer. Many of the patients in this series who progressed to cancer refused treatment for HSIL. Anal cancer was diagnosed in several men prior to 2004 when office-based infrared coagulation was not in common use and patients with diffuse lesions were not routinely treated due to its associated morbidity. Several participants had widespread HSIL, and eradication of all disease was not always possible. Although we cannot prove a direct causative relationship, the majority of patients treated for HSIL in the UCSF ANC have not progressed to cancer.[19] Currently, most cases of anal cancer diagnosed in the ANC are identified in patients who have not been screened or treated previously for HSIL, but instead are referred to evaluate anal symptoms, manage anal HSIL or to initiate anal cancer screening. Ultimately, the most direct proof of the malignant potential of HSIL will come from randomized controlled trials demonstrating that treatment of HSIL reduces the incidence of anal cancer.

This series also describes for the first time the presentation of SISCCA of the anal canal and perianus. None of the patients with anal canal or perianal SISCCA were managed conservatively with local excision developed recurrent cancer; however, a discussion of efficacy is beyond the scope of our article. The importance of careful follow-up of patients with HSIL was clearly demonstrated. Cancers were palpable in almost all participants, except for the four participants whose cancers were first visualized during HRA. Nearly half of the participants were asymptomatic. Thus, at least in this cohort,

Table 1. Presentation and stage of anal cancer that progressed from anal HSIL in HIV-infected MSM at UCSF

Case no.	Age at cancer diagnosis (years)	CD4+ cells per microliter at cancer diagnosis	Location[1]	Number of months from HSIL to cancer[2]	Presenting signs[3]	Presenting symptoms	TNM[4]	Treatment[5]
1	42	175	AC	76	Mass	Pain	T1	CMT
2	56	49	AC	16	Mass	Pain/bleeding	T2	CMT
3	58	950	AC	14	Mass	Pain	T2	CMT
4	46	1,000	AC	71	Mass	Pain/bleeding	T2	CMT
5	40	308	AC	23	Mass	None	T1	CMT
6	47	NA	AC	45	Mass	None	T2	CMT
7	56	308	AC	**92/59**	Mass	Pain/bleeding	T2	CMT
8	50	131	AC	42	Mass	None	T1	CMT
9	53	300	AC	87	Mass	Mass	T1	CMT
10	43	470	AC	36	HRA	None	T1	E & F
11	61	253	AC	100	Mass	Pain/bleeding	T1	CMT
12	56	269	AC	113	Mass	None	T2	CMT
13	56	485	AC	70	Mass	None	T2	CMT
14	47	350	AC	11	HRA	None	T1	E & F
15	61	NA	AC	93	Mass	Pain/bleeding	T2	CMT
16	51	307	PA	**14/14**	Induration	None	T1	E & F
17	45	200	PA	8	Induration/ulcer	Pain	T1	E & F
18	46	132	PA	53	Induration/ulcer	None	T1	E & F
19	39	100	PA	107	Induration/ulcer	Pain/bleeding	T1	E & F
20	64	194	PA	**20/10**	Induration/ulcer	None	T1	E & F
21	52	150	PA	**107/101**	HRA	None	T1	E & F
22	69	400	PA	**16/16**	Mass	None	T2	E & F
23	53	316	PA	124	HRA	None	T1	E & F
24	44	220	PA	43	Induration/ulcer	Pain/bleeding	T1	E & F
25	48	220	PA	12	Induration/ulcer	Mass	T1	E & F
26	57	213	PA	**167/103**	Induration/ulcer	Pain/bleeding	T1	E & F
27	49	125	PA	**29/17**	Induration/ulcer	Itching/bleeding	T1	E & F

[1]AC, anal canal; PA, perianal.
[2]Bold values indicate subjects diagnosed with incident HSIL, which was defined in subjects who on their initial high-resolution anoscopy examinations had no evidence of HSIL, who then during subsequent examinations developed their first biopsy-documented HSIL. The second value indicates the time in months prior to diagnosis of cancer that the specific index HSIL lesion that progressed to cancer was identified and biopsied.
[3]HRA indicates cancers detected solely by visual signs detected during high-resolution anoscopy.
[4]TNM, TNM stage, T1, tumor less than 2 cm; T2, tumor more than 2 cm, but less than 5 cm in greatest dimension. No men had pathologically documented nodal or systemic metastases at diagnosis.
[5]CMT, chemotherapy and radiation therapy; E & F, excision and fulguration (all patients treated with E & F had superficially invasive squamous cell carcinoma).

it appears that patients with diffuse and/or persistent HSIL may benefit from close follow-up using DARE and HRA as early detection of invasive cancer may allow for conservative management with excision and fulguration instead of chemotherapy and radiation therapy.[27] As many SISCCA will not be palpable and this is likely the earliest recognizable sign of cancer, this further emphasizes the potential importance of specifically following up patients using HRA who have been diagnosed with HSIL.

The progression of persistent oncogenic HPV infection to cervical HSIL to cervical cancer typically takes many years. This long time provides an opportunity to intervene by identifying and eradicating the cervical cancer precursor, cervical HSIL. Histologically, increased cellular proliferation, angiogenesis and decreased apoptosis signify and herald progression in the cervix as normal mucosa progresses along the continuum of LSIL, HSIL and cancer. Anal mucosa demonstrates similar changes supporting the theory that carcinogenesis most likely occurs in a similar fashion.[28] In our study, time to progression to cancer from initial diagnosis of HSIL was quite variable even when considering only those with incident HSIL. Factors that may have affected this variability

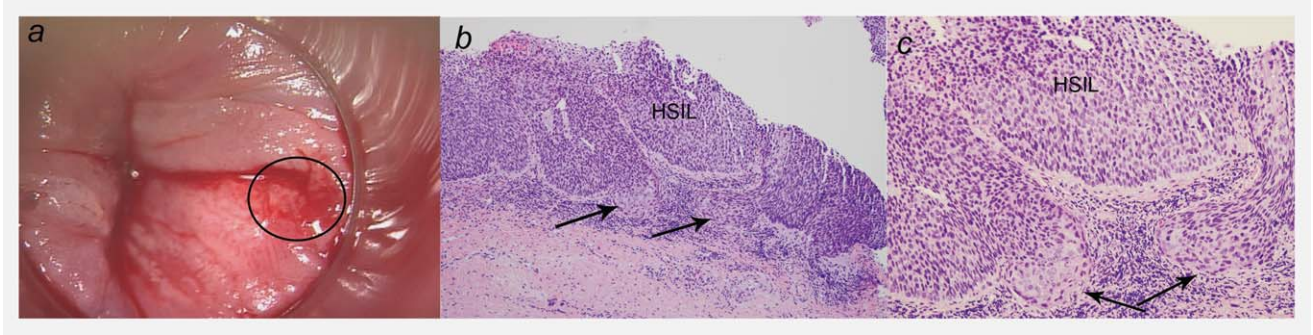

Figure 4. Case 14. Appearance of lesion during HRA that developed 3 months after HRA-guided surgery that was easily excised during second surgical procedure. Circle indicates biopsy site. (*b*) Low-power photomicrograph of superficially invasive squamous cell carcinoma arising focally from HSIL. Arrows indicate areas of superficial invasion in both pictures. (*c*) Higher power view of HSIL and superficially invasive carcinoma. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

include the presence of unrecognized or occult cancer in large HSIL lesions, underlying host immune response to HPV that was further diminished by HIV infection, the specific HPV type that was present and other cofactors such as smoking. In this series of HIV-infected MSM, cancers occurred at a younger median age compared to the general population, likely to be a direct effect of HIV-associated immunosuppression.[29] The relatively short time to progression observed in some individuals belies the uncertain natural history of HSIL and underscores the importance of closely following those diagnosed with and /or treated for HSIL.

In the cervix, it was reported that between 31.3 and 50.3% of women with cervical intraepithelial neoplasia will progress to cervical cancer over time if not treated adequately.[30] Our data do not allow us to define the annual rate of progression from HSIL to anal cancer. However, the progression rate from HSIL to anal cancer is likely to be lower.[12] It is also possible that the progression rate will increase with longer follow-up based on the relatively long latency period between the development of HSIL and cancer, the high prevalence of HSIL among HIV-infected men on ART and increased longevity of these men due to ART.[31] Methods to identify individuals at the highest risk of progression to anal cancer, including molecular markers, are clearly needed.

Cancers occurred at all levels of immunosuppression, and although not statistically significant, those with perianal cancers had lower CD4+ levels than those with cancers of the anal canal. CD4+ nadir and duration of HIV infection are predictors of anal cancer in HIV-infected persons[6]; however, these data were not available for this cohort. As cancers occurred at all levels of immunosuppression, CD4+ level should not be used as a criterion to prioritize screening in HIV-infected persons.

One of the strengths of our study is that 23 of 27 men were being followed up prospectively, allowing for the direct observation of the progression of HSIL to invasive cancer. The remaining four men were lost to follow-up until symptoms developed. A limitation is that our strict inclusion criteria permitted inclusion of only a relatively small number of men and no women in the analysis. As only HIV-infected MSM were included, clinical features such as presentation and time to progression may not be generalizable to other groups at risk of anal cancer. However, the basic biology and malignant potential of anal HSIL are likely to be similar in other groups at-risk for anal cancer such as solid organ transplant recipients, women with prior HPV-related lower genital tract neoplasia and those incidentally diagnosed with anal HSIL. Although most HSIL will probably not progress to cancer, we do not currently have any validated way of identifying those who are at greatest risk of progression, and to date, we have yet to prove that ablation of HSIL actually prevents progression. In a recent meta-analysis, the rate of progression from HSIL to cancer was calculated theoretically to be one in 377. Considering that many HIV-infected MSM are diagnosed at 30–40 years, this translates to a lifetime risk of anal cancer that may exceed 10%.[12,31] Based on the relative simplicity of treating HSIL *versus* the morbidity of radiation and chemotherapy, all patients diagnosed with HSIL should be considered for treatment, or at a minimum, be followed up closely for signs of progression to cancer.

Another potential limitation is that because there can be movement or rotation of the anal canal between HRA examinations, it is possible that the area shown to have HSIL was not the exact lesion that progressed to cancer. For this reason, we restricted the inclusion criteria listed in the methods to determine eligibility. Location was further substantiated by review of the digital images, whenever possible. If there were any doubts regarding whether the cancer developed from a previously biopsied area of HSIL, then the documentation was not considered sufficient and the subject was excluded from the analysis.

In summary, prior to our study, anal HSIL was assumed to be the putative precursor to anal cancer and the malignant potential of anal HSIL inferred from the analogy to cervical HSIL. Our study adds substantively to mounting evidence that anal HSIL can indeed progress directly to anal cancer. Further evidence of the role of HSIL as a cancer precursor

Table 2. Summary of prior treatment of HSIL among 27 men whose lesion progressed to anal cancer

Case number	Reason HSIL not ablated	Any prior treatment of HSIL	Most recent treatment of HSIL prior to cancer	Year of cancer diagnosis
1	Other medical issues/refused	Yes	Imiquimod[1]	2000
2	Other medical issues/refused	No	None	2000
3	Lost to follow-up	Yes	HRA surgery[3] 14 months	2000
4	Lost to follow-up	Yes	HRA surgery 8 months	2001
5	Treatment failed	Yes	Non-HRA[4] laser warts 10 months	2002
6	Other medical issues/refused	Yes	None	2002
7	Other medical issues/refused	Yes	None	2003
8	Treatment failed	Yes	TCA[5] 3 months	2004
9	Other medical issues/refused	Yes	None	2006
10	Treatment failed	Yes	HRA surgery 7 months	2006
11	Lost to follow-up	Yes	None	2007
12	Other medical issues/refused	Yes	None	2007
13	Treatment failed	Yes	IRC 3 months	2009
14	Treatment failed	Yes	HRA surgery 3 months	2010
15	Other medical issues/refused	No	None	2011
16	Treatment failed	Yes	Podophyllin[6]	1997
17	Treatment failed	Yes	Non-HRA surgery 8 months	2001
18	Other medical issues/refused	Yes	None	2001
19	Treatment failed	Yes	HRA surgery 29 months, TCA 18 months	2002
20	Treatment failed	Yes	Imiquimod followed by LN2[7]& TCA 7 months	2004
21	Other medical issues/refused	No	Non-HRA surgery warts 4 years	2008
22	Treatment failed	Yes	5 fluorouracil[8] 8 months	2008
23	Treatment failed	Yes	Cidofovir[9]	2009
24	Lost to follow-up	Yes	HRA surgery 36 months	2010
25	Other medical issues/refused	Yes	None	2009
26	Treatment failed	Yes	Non-HRA ablation 8 months, topical ointment[10]	2010
27	Treatment failed	Yes	TCA 11 months	2007

[1]Imiquimod, topical 5% imiquimod cream.
[2]Treatments without a time period were performed 1–2 months prior to diagnosis.
[3]HRA surgery indicates that surgery was guided by HRA at UCSF.
[4]Non-HRA indicates procedure was not performed at UCSF and was not guided by HRA.
[5]TCA, 85% trichloroacetic acid.
[6]Podophyllin, provider applied.
[7]LN2, cryotherapy with liquid nitrogen.
[8]5 fluorouracil, topical 5% fluorouracil cream.
[9]Cidofovir, topical 1% cidofovir gel.
[10]Topical ointment, placebo *versus* traditional Chinese herbal ointment.

and guidelines to establish anal cancer screening and management programs as standard of care will await the results of randomized controlled trials of treatment of HSIL to reduce the risk of subsequent cancer.

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