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Five-year cumulative incidence of invasive anal cancer among HIV-infected patients according to baseline anal cytology results: an inception cohort analysis

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Abstract

Objectives—The aim of the study was to estimate the cumulative incidence of, and rates of progression to, invasive anal cancer (IAC) according to baseline anal cytology screening category in an unselected HIV clinical care cohort in the antiretroviral era.

Methods—A retrospective cohort analysis of HIV-infected patients under care at the University of California at San Diego Owen Clinic was carried out. Patients were eligible for this analysis if they had at least two anal cytohistological results available for longitudinal analysis. Kaplan-Meier analysis was used to estimate the cumulative incidence of IAC over time according to baseline cytology category [less than high-grade intraepithelial lesion (HSIL) versus HSIL]. Cox regression analysis was used to adjust for the following covariates: antiretroviral use, level of HIV viraemia, smoking status and infrared photocoagulation (IRC) ablation therapy.

Results—Between 2000 and 2012, we followed 2804 HIV-infected patients for a median of 4 years under a clinic protocol requiring baseline anal cytology screening. Incident IAC was diagnosed in 23 patients. Patients with a baseline HSIL anal cytology had an estimated 5-year probability of progression to IAC of 1.7% and an estimated annual progression risk of 1 in 263. None of the examined covariates was significantly associated with IAC incidence when examined in separate unadjusted Cox models.

Conclusions—HIV-infected patients with a baseline HSIL anal cytology had a 5-year cumulative incidence of IAC of 1.65%, with an upper 95% confidence bound of 4.5%. This population-based study provides quantitative risk estimates that may be used for counselling patients regarding management options for abnormal cytology results.

Keywords

anal cytology; HIV; invasive anal cancer; natural history

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Introduction

The incidence of invasive anal cancer (IAC) is increasing among HIV-infected persons [1], and in response many centres have implemented programmes to screen for anal cancer and its precursor lesions [2]. In screening for precursors of IAC, one of the first steps is to obtain anal cytology [1]. A cytological diagnosis of high-grade squamous intra-epithelial lesion (HSIL) is considered a surrogate marker for histopathological categories including anal intraepithelial neoplasia (AIN) 2 and 3, precursor lesions for progression to IAC [1]. In the absence of guidelines for managing the results of anal screening cytology, most experts agree that patients with anal cytology HSIL should have priority for referral for a high-resolution anoscopy (HRA) procedure [3]. In considering the evidence base to support treatment of HSIL, the efficacy and risks of treatment should be examined with respect to the risk of progression to IAC in the absence of treatment for precursor lesions. Quantitative estimates of the risk of progression to IAC based on baseline anal cytology results are imprecise [4]. We therefore conducted this study: (1) to estimate the cumulative incidence and person-time rate of IAC in a cohort of HIV-infected adults under care during the highly active antiretroviral therapy (HAART) era, stratified according to baseline anal cytology results; and (2) to estimate the effect of antiretroviral use, HIV viraemia, smoking status and infrared photocoagulation (IRC) ablation on progression to IAC.

Methods

This was a retrospective inception cohort analysis of HIV-infected patients under care at the University of California, San Diego (UCSD) Owen Clinic between 2001 and 2012. To be eligible for inclusion, patients had to have at least two anal cytology results without diagnosis of IAC or at least one cytology result if subsequently diagnosed with IAC. Patients diagnosed with IAC within 180 days of the first anal cytology test were excluded from the analysis to avoid prevalence bias. The study was approved by the UCSD Human Research Protection Program.

Beginning in 2001, a clinic protocol was implemented by which every HIV-infected patient attending for care at the UCSD Owen clinic undergoes a digital rectal examination (DRE) and anal cytology collection as a routine component of their first clinical evaluation, and annually thereafter. Patients with any abnormal anal cytology result [atypical squamous cells of uncertain significance (ASCUS), atypical squamous cells cannot rule out high grade (ASC-H), low-grade squamous intraepithelial lesion (LSIL) or HSIL] are referred for HRA evaluation [2]. Because of limited availability of HRA appointments, those with HSIL lesions, symptoms or abnormal DRE are preferentially triaged to HRA. Cytology rather than histopathology was the primary independent variable for the current analysis in order to avoid selection bias introduced by restricting the analysis to patients who had undergone one or more HRA procedures. Starting in 2007, patients with histopathological HSIL lesions were offered ablative treatment using IRC. Following IRC therapy a patient undergoes a surveillance HRA 3 months after IRC and thereafter according to the management algorithm reported elsewhere [1].

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The anal cytology sample was collected with a moistened Dacron swab as previously described [2]. Starting in 2006, the slide fixation method was replaced by insertion of the swab into ThinPrep™ liquid cytology medium (Hologic Inc., Marlborough, MA, USA) and its processing according to the manufacturer's instructions. Cytology smears were reviewed at the UCSD pathology laboratory and classified according to the 2001 Bethesda classification system [5,6].

Uptake of the cytology screening algorithm was evaluated by comparing screened (at least one cytology result) with nonscreened patients according to sex, race, HIV transmission risk factor, age and the number of primary care visits during the study period.

For each eligible screened patient, follow-up time began on the date of the first anal cytology test and ended on the first of either the date of IAC diagnosis or the date of the last anal cytology test in the study period. IAC diagnosis was ascertained by linking the clinic cytology database to the UCSD Cancer Registry and verified using UCSD histopathology reports. Anal cytology was categorized as 'less than HSIL' (< HSIL) and HSIL. The < HSIL category included the following cytology results: no atypical or malignant cells, ASCUS and LSIL. The HSIL category also included ASC-H. Kaplan-Meier analysis was used to estimate the cumulative incidence of IAC over time according to baseline cytology category. The person-time incidence of IAC by baseline cytology category was estimated assuming a Poisson distribution of IAC incidence. Cox regression analysis with robust standard errors was used to estimate the effect of at least one IRC ablation as a fixed covariate and the following time-dependent covariates: antiretroviral use, level of HIV viraemia and smoking status. Analysis was performed using STATA version 13.0 (Stata Corp., College Station, TX).

Results

During the study period, 2804 patients met the eligibility criteria. At baseline the median age was 40 years [interquartile range (IQR) 34–46 years] with a median CD4 cell count of 384 cells/μL (IQR 217–572 cells/μL). Approximately 89% of patients were male and 38% nonwhite. The HIV transmission risk factor distribution was: men who have sex with men (MSM), 78%; injecting drug use (IDU), not MSM, 5%; heterosexual, not IDU, 13%; and other, 4%. Most patients (75%; $n = 2080$) were taking antiretroviral therapy, of whom 64% ($n = 1326$) had viral load ≤ 400 HIV-1 RNA copies/ml. Thirty per cent reported smoking at entry. At baseline, 305 patients (11%) had HSIL anal cytology.

Overall, 71% of patients receiving care in our clinic were screened for anal cytology at least once. However, the estimate of screening uptake was related to the number of primary care visits at the study clinic. Among those with only one visit, the proportion screened was only 32%, whereas among those with 10 or more visits, 86% were screened. To understand factors related to uptake of anal cytology screening, we fitted a multiple logistic regression model of screening status (ever versus never). We found that nonwhite patients were more likely to be screened [adjusted odds ratio (aOR) 1.25; 95% confidence interval (CI) 1.11 to 1.41], non-MSM were less likely to be screened (aOR 0.39; 95% CI 0.34 to 0.44), and older

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patients were less likely to be screened (aOR per 10 years 0.92; 95% CI 0.87 to 0.97). There was no difference in screening status according to sex.

Of 2804 patients with at least one anal cytology result, 629 (22.4%) underwent at least one HRA and 218 (7.8%) underwent one or more IRC procedures between 2007 and 2012. Of the 237 patients with initial HSIL cytology who underwent HRA, 62 (16%) underwent one or more IRC ablations. According to baseline cytology results, the proportion subsequently undergoing at least one HRA was 16.3% (392 of 2411) for < HSIL and 60.3% (237 of 393) for HSIL. Considering the most severe cytology category observed over each patient's follow-up period, the proportion undergoing at least one HRA varied from 0.4% (seven of 1691) for those never having HSIL cytology to 55.9% (622 of 1113) for those ever having HSIL cytology.

Patients were followed for a median of 4.0 years (IQR 2.0–7.1 years). During the follow-up period, the distribution of cytology ascertainment frequency (including baseline) was: two tests, 27%; three tests, 20%; four tests, 15%; five tests, 11%; at least six tests, 27%. The median (IQR) number of cytology tests per patient-year of follow-up was 1.1 (0.7–1.6). A total of 35 patients were diagnosed with IAC on or after the first cytology test date. Of these, 23 patients were diagnosed with IAC more than 180 days after the first cytology result. Patients with baseline HSIL anal cytology had an increased hazard of progression to IAC compared with the reference baseline category of < HSIL [hazard ratio (HR) 2.92; 95% CI 1.16–7.36; $P = 0.023$]. The estimated annual per-person risk of IAC by baseline cytology category was: 0.0038 (95% CI 0.0014–0.0082) for HSIL and 0.0015 (0.0009–0.0024) for < HSIL. None of the examined covariates was significantly associated with IAC incidence when examined in separate unadjusted Cox models: (1) IRC ablation (HR 1.52; 95% CI 0.51–4.51); (2) antiretroviral therapy (HR 1.39; 95% CI 0.20–9.96); (3) controlled HIV viraemia ≤ 400 copies/ml (HR 0.62; 95% CI 0.24–1.64); and (4) current smoking (HR 1.20; 95% CI 0.51–2.82). Table 1 presents the estimated unadjusted cumulative incidence of IAC according to baseline cytology category. It shows that HIV-infected patients with a baseline HSIL anal cytology had an estimated 5-year probability of incident IAC of 1.65%, with an upper 95% confidence bound of 4.5%. When adjusted for undergoing at least one IRC procedure, the 5-year IAC incidence among those with baseline HSIL cytology (1.65%) changed minimally from the unadjusted estimate.

Discussion

Recently, it has been demonstrated that human papillomavirus (HPV)-induced anal HSIL lesions are the direct precursors of IAC [7]. Few studies have reported rates of progression from HSIL to IAC. In a study that followed 55 patients with baseline HSIL (mostly women), eight patients (14.5%) with unknown HIV serostatus developed IAC after a median time of 42 months [8]. In a second study that included mostly women and no HIV-infected patients, three of 35 patients (8.5%) progressed to IAC after a median of 60 months of follow-up; the three patients were immunosuppressed as a result of different medical conditions [9]. In a study that enrolled only HIV-infected men ($n = 40$) all of whom had gross and histological evidence of squamous dysplasia of the anal canal and/or anal margin, three (7.5%) developed IAC after a median of 16 months of follow-up [10]. These three studies came

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from surgical cohorts with mostly referred symptomatic patients, and thus with considerable potential for referral bias involving patients selected with more advance disease.

In a recent meta-analysis, Machalek *et al*. [4] presented a *theoretical* progression rate from high-grade AIN to invasive anal cancer among HIV-positive men in the HAART era of 1 in 377 per year. Dalla Pria *et al*. recently reported on the experience of a cohort of 368 HIV-positive MSM in which HRA with intervention for HSIL was routinely offered [11]. Thirty-two per cent of patients had high-grade AIN (including AIN-2 and AIN-3). In this cohort of patients treated for HSIL, the cumulative risk of cancer from first AIN-3 diagnosis was 3.2% (95% CI 0–7.8%) at 5 years. Moreover, the estimated rate of IAC from first histopathological diagnosis of high-grade AIN ascertained at the first HRA was 6.1 per 1000 person-years (95% CI 4.2–7.8); this rate corresponds to a per person per year risk of 1/164. Our base case estimate of HSIL progression to IAC, from a cytology inception cohort observed during the HAART era, was 1 in 263 per year (95% CI 1/714 to 1/122). Results from an ongoing prospective study in which all participants undergo screening for anal HPV, cytology and HRA are awaited and will contribute to the understanding of the natural history of anal dysplasia in men [12].

Our study has limitations. First, it could be argued that the baseline cytology results reported here are subject to both misclassification and verification bias because, respectively, cytology is an imperfect screening test and not all patients underwent HRA [13]. Our models were not adjusted for the sensitivity and specificity of anal cytology [14]. Despite this limitation, patients with baseline cytology < HSIL had a lower hazard of progressing to IAC than if the baseline cytology was HSIL, as one would expect. This limitation is balanced by the strength of estimating progression rates in an inception cohort that, although subject to misclassification, is not subject to HRA or surgical referral bias. Secondly, our exclusion of IAC diagnoses occurring within 180 days after the first cytology test could be criticized for potentially excluding truly incident progressions rather than baseline prevalent cases of IAC. We performed a sensitivity analysis, including additionally 10 patients who were diagnosed with IAC between 30 and 180 days after the first cytology test. After including these 10 patients with early IAC diagnosis, we found that, among patients with baseline HSIL, the estimated 5-year cumulative incidence of IAC was 3.24% (95% CI 1.70–6.12%) with a corresponding annual progression risk of 1/133. These estimates are closer than those of our base case analysis to those reported by Dalla Pria *et al*. [11]. Thirdly, some patients could have been diagnosed with IAC outside our medical system and those with < HSIL cytology may have had underascertainment of IAC because of less frequent referral to HRA. To avoid outcome ascertainment problems from diagnosis outside our clinic, we linked our clinic registry with the UCSD cancer registry. Although it is possible that a few additional cases occurred outside our health care system and were not ascertained, because IAC is a rare disease, we believe that the impact of underascertainment by this mechanism would be small. Regarding possible differential underascertainment among those with < HSIL baseline cytology, we think this is unlikely because our clinic screening protocol combines annual cytology tests with DRE so that those with palpable abnormalities or transition to HSIL would be preferentially referred to HRA. Fourthly, although our clinic practice guideline recommended anal cytology screening for all patients, we observed that screening

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uptake was differentially associated with being MSM, nonwhite and older. We believe that the sociodemographic characteristics of our screened and eligible population should be taken into account when generalizing our results to cohorts of dissimilar composition. Fifthly, it might be argued that our inclusion of patients who underwent IRC ablation limits coherent inference by introducing treatment effects. We would argue, however, that exclusion of IRC patients would have introduced post-baseline selection bias, thereby threatening the integrity of an inception cohort; in addition, we were unable to detect an association between risk of the IAC outcome and IRC exposure despite having 82% power to detect an adjusted HR of 1.5 in post hoc analysis. Finally, the observed 5-year cumulative incidence of IAC among patients with baseline HSIL (1.65%) is low in comparison with historical reports of the natural history of cervical dysplasia [15]. Among women with histologically documented cervical intraepithelial neoplasia 3 (CIN 3), and who had HSIL cervical cytology collected at least 6 months after having different treatment modalities for CIN 3, 16% of women by 10 years and 25% by 20 years developed invasive cervical cancer in the absence of any subsequent treatment intervention [15]. Because our analysis evaluated the effect of cytological HSIL, a diagnostic category that corresponds to histological categories AIN 2–3 and carcinoma in situ, it is not directly comparable to studies evaluating the prognosis of CIN 3 or AIN 3 alone.

In summary, HIV-infected patients with a baseline HSIL anal cytology had an estimated 5-year probability of progression to IAC of 1.65%, with an upper 95% confidence bound of 4.5%. This population-based study provides quantitative risk estimates that may be used for counselling patients regarding management options for abnormal cytology results.

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Table 1

Estimated unadjusted cumulative incidence of invasive anal cancer according to baseline cytology category, by year of follow-up

Time (years)	No. patients at risk	Per cent developing IAC from baseline [% (95% CI)]
<HSIL		
1	2182	0.09 (0.02–0.36)
2	1827	0.14 (0.05–0.45)
3	1516	0.33 (0.15–0.73)
4	1223	0.47 (0.23–0.95)
5	983	0.47 (0.23–0.95)
HSIL		
1	320	0.30 (0.04–2.13)
2	266	0.65 (0.16–2.60)
3	217	1.03 (0.33–3.17)
4	176	1.03 (0.33–3.17)
5	141	1.65 (0.59–4.52)

CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; IAC, invasive anal cancer.