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Rectal squamous cell carcinoma in immunosuppressed populations: is this a distinct entity from anal cancer?

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Abstract

Objective—Squamous cell carcinoma (SCC) of the rectum is rare, but as with anal cancer, risk may be increased among immunosuppressed individuals. We assessed risk of rectal SCC in HIV-infected people.

Design—Population-based registry

Methods—We utilized the HIV/AIDS Cancer Match, a linkage of US HIV and cancer registries (1991–2010), to ascertain cases of anal SCC, rectal SCC, rectal non-SCC, and colon non-SCC. We compared risk in HIV-infected persons to the general population using standardized incidence ratios (SIRs) and evaluated risk factors using Poisson regression. We reviewed cancer registry case notes to confirm site and histology for a subset of cases.

Results—HIV-infected persons had an excess risk of rectal SCC compared to the general population (SIR=28.9; 95%CI 23.2–35.6), similar to the increase for anal SCC (SIR=37.3). Excess rectal SCC risk was most pronounced among HIV-infected men who have sex with men (MSM, SIR=61.2). Risk was not elevated for rectal non-SCC (SIR=0.88) or colon non-SCC (SIR=0.63). Individuals diagnosed with AIDS had higher rectal SCC rates than those with HIV-only (incidence rate ratio=1.86; 95%CI 1.04–3.31). Based on available information, one-third of rectal SCCs were determined to be misclassified anal cancer.

Conclusions—HIV-infected individuals, especially with advanced immunosuppression, appear to have substantially elevated risk for rectal SCC. As for anal SCC, rectal SCC risk was highest in MSM, pointing to involvement of a sexually transmitted infection such as human papillomavirus.

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Site misclassification was present, and detailed information on tumor location is needed to prove that rectal SCC is a distinct entity.

Keywords

HIV and cancer; rectal cancer; squamous cell carcinoma; HPV-associated cancer

INTRODUCTION

Colorectal cancer is a major cause of morbidity and mortality, with 132,700 incident cases and 49,700 deaths estimated for the US in 2015 [1]. The vast majority of colorectal cancer cases are adenocarcinomas [2]. In contrast, squamous cell carcinoma (SCC) in the colorectum is extremely rare. In the US, SCCs comprise only 1–2% of diagnosed rectal tumors with an annual incidence of 1.54 per 1,000,000 person-years in males and 3.00 per 1,000,000 person-years for females. [3]

Because of the rarity of rectal SCC, little is known about its etiology. To date, there are fewer than 100 published case reports since the first case described in 1919 [4–13]. Human papillomavirus (HPV) has been proposed as an etiologic agent for rectal SCC because of the proximity of the rectum to the anus and the known role of HPV in anal SCC, but results of HPV testing in rectal SCC tumors have been conflicting [7,9–12]. Reports published since 2000 often note the co-occurrence of ulcerative colitis [4, 8, 10, 11], pointing to inflammation as another possible co-factor. Although the rectum does not normally contain squamous epithelium, tumors might theoretically originate from areas of squamous metaplasia arising in the presence of inflammatory damage. The occurrence of such rectal squamous metaplasia has been documented in patients with ulcerative colitis, including a report of rectal squamous metaplasia occurring 7 years prior to the diagnosis of rectal SCC. [11, 14]

Two of the most recent case reports have described rectal SCC occurring in HIV-infected males [9, 12]. In preliminary data generated for a study describing cancer trends in HIV-infected people [15], we noted that approximately 30% of rectal cancers in HIV-infected persons were SCCs (unpublished observations). This high proportion, relative to the 1–2% observed in the general population, suggests that progressive immunodeficiency caused by HIV infection (i.e., acquired immunodeficiency syndrome [AIDS]) may be an unidentified risk factor for rectal SCC. Although HIV-infected people do not have an increased risk of colorectal cancer overall [16, 17], prior studies have not specifically examined the association with rectal SCC. Notably, HIV-infected persons have a strongly increased risk of anal cancer [16–18], and there may be etiologic similarity between rectal SCC and anal cancer (which is primarily also a SCC). However, because of the overall rarity of rectal SCC and the contiguous location of the rectum and the anal canal, there may also be site misclassification of anal SCC as rectal SCC.

In light of these possibilities, the objective of our study was to quantify the risk of rectal SCC in HIV-infected persons, both overall and within the group most likely to have anal HPV infection (i.e., men who have sex with men [MSM]). We used data from the HIV/AIDS Cancer Match (HACM) Study (http://hivmatch.cancer.gov/) [19], a linkage of HIV

and cancer registries, which provided information on cancer for a large population-based sample of HIV-infected people. We explored the possibility that rectal SCC may represent misclassified anal cancer through the examination of case notes collected by cancer registries. In addition, we estimated the risk of rectal SCC in solid organ transplant recipients, another immunosuppressed population, using data from the Transplant Match Study.

METHODS

The present study used data from HIV registries in the HACM Study that provided data on people registered with HIV infection with and without a prior AIDS diagnosis: Colorado, Connecticut, Florida, Georgia, Michigan, New Jersey, and Texas. We included cancers from cancer registries diagnosed during: (1) years when HIV infection and AIDS diagnoses were both reported to HIV registries and (2) years when cancer registries had completed ascertainment of cases at the time of the data linkage. Included registries (years of cancer diagnosis) were therefore: Colorado (1991–2007), Connecticut (2002–2010), Florida (1998–2002), Georgia (2004–2008), Michigan (1992–2010), New Jersey (1992–2007), and Texas (1997–2009).

We assessed rectal cancer (International Classification of Diseases for Oncology version 3 [ICD-O3] topography code C209) and, for comparison, colon cancer (ICD-O3 codes C180–189 or C260) and anal cancer (ICD-O3 codes C210–212 or C218). We further classified cases based upon their histological diagnosis, either as SCC or non-SCC. The following ICD-O-3 histology codes provided by the cancer registries were used to define SCC status: 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8077, 8078, 8083, and 8084. The remaining histologies were classified as non-SCC, excluding Kaposi sarcoma, lymphoma, mesothelioma, and poorly specified subtypes. The specific histologies classified as non-SCC among the identified HIV-infected cases and in the general population are included in Supplemental Table 1. We define outcomes as anal SCC, rectal SCC, rectal non-SCC, and colon non-SCC and consider only the first diagnosis for each cancer outcome.

We calculated standardized incidence ratios (SIRs) to compare cancer risk in HIV-infected people to risk in the general population, comprised almost entirely of HIV-uninfected individuals. SIRs are defined as the number of observed cases divided by the number expected based on general population rates (standardized to the HIV population by age, sex, race/ethnicity, calendar year, and cancer registry). We estimated SIRs overall and separately based on sex and HIV risk category (MSM, non-MSM male injection drug user [IDU], male heterosexual, female IDU, female heterosexual, other/unknown). We further used Poisson regression to estimate rectal SCC rates and assess potential risk factors for rectal SCC among HIV-infected people, including sex and HIV risk category, attained age, race/ethnicity, and degree of immunosuppression (prior AIDS diagnosis vs. no AIDS [i.e., HIV-only]). Follow-up for cancer diagnoses among the HIV-infected individuals accrued from the earliest of HIV report, AIDS diagnosis, or beginning of cancer registration. Follow-up ended at the earliest of death or end of cancer registration.

To examine potential misclassification of the cancer outcomes, we requested de-identified case notes from 4 of the participating registries (Colorado, Michigan, New Jersey, and Texas) on a proportion of anal and rectal cancer cases from HIV-infected people (i.e., cancer registry cases that matched to a record in the HIV registry), sampled according to the reported histology (SCC, non-SCC), as well as a comparison set of HIV-uninfected cases (i.e., cancer registry cases that did not match to the HIV registry). One cancer registrar, one HIV clinician, and two cancer epidemiologists (AC, EE, MS, and RR) independently reviewed the case notes for each individual and assigned a location (anus, rectum) and histology to the tumor. Reviewers utilized the available information on biopsy and tumor location as well as treatment administration to determine the most likely location. Detailed pathology reports and supporting medical records beyond the summary provided by the cancer registries were not available. Reviewers were blinded to the HIV status and risk category.

For any case that the reviewer classified as rectal SCC, a level of confidence was noted on a scale from 1–5 (1=very uncertain, 2=somewhat uncertain, 3=more likely than not, 4=somewhat certain, 5=very certain). Scores ≥4 were considered to indicate high confidence based on the amount of supporting information (e.g., rectum consistently listed as location in both diagnosis and treatment notes), and scores <4 were assigned to cases with little supporting data (e.g., rectum SCC listed but no supporting diagnostic or treatment notes). Rectal SCC cases with no conflicting information or information specifically pointing to an anal cancer diagnosis remained classified as rectal SCC cases. Any disagreements in the classification assigned between the 4 reviewers were resolved by consensus. According to patient HIV status, we report both: (1) the proportion of all reviewed cases in our sample for which either site or histology was reassigned by consensus and (2) the proportion of reviewed rectal SCC cases that were classified as such with ‘high confidence’ by at least one reviewer.

To determine whether misclassification could account for the excess of rectal SCC in HIV-infected persons, we recalculated the SIR using the results of the case review under two conditions. First, after estimating the proportion p_1 of reviewed rectal SCC cases that were potentially misclassified, we recalculated the SIR using only the remaining proportion of the observed rectal SCC cases ($1\text{-}p_1$). Secondly, we recalculated the SIR after removing the proportion of cases p_2 that were not scored as high confidence by at least one independent reviewer.

To further explore the potential association between immunosuppression and rectal SCC, we examined rectal SCC risk in solid organ transplant recipients (OTRs). OTRs are administered immunosuppressive medications to prevent graft rejection and represent a patient population with distinct risk factors from HIV-infected persons but who also experience immunosuppression. We evaluated the risk of rectal SCC in solid organ transplant recipients using data from the Transplant Cancer Match (TCM) Study. The TCM Study is designed similarly to the HACM Study, linking data from the U.S. transplant registry to multiple cancer registries (http://transplantmatch.cancer.gov/).[20] We calculated SIRs comparing the number of cancers occurring after transplant to the expected number based on general population rates.

RESULTS

We identified 295,738 HIV-infected people in these seven states, of whom 1,189 were diagnosed with anal cancer (64.4%), rectal cancer (18.8%), or colon cancer (16.7%). Notably, 89 (39.7%) of 224 HIV-infected cases of rectal cancer had a histological diagnosis of SCC, compared to only 1.3% of 209,775 HIV-uninfected rectal cases from these same states. For anal cancer, 92.0% of cases among HIV-infected people were SCCs in contrast to only 1.0% of HIV-infected colon cancer cases.

The incidence of rectal SCC cases in HIV-infected persons (5.61 per 100,000 person-years) substantially exceeded the rate in the general population (SIR = 28.9, 95% CI 23.2–35.6). (Table 1) Risk was elevated in both males and females, and for several HIV risk groups, although the excess was most marked in HIV-infected MSM (SIR = 61.2; 95% CI 47.8–77.2), with 79.8% of observed cases occurring in this group and an incidence equal to 10.2 per 100,000 person-years. This pattern was very similar to that observed for anal SCC (overall SIR= 37.3; 95% CI 34.6–40.2; MSM SIR= 65.6; 95% CI 60.2–71.5), with 75.0% of identified anal SCCs occurring in HIV-infected MSM. In contrast, incidence in HIV-infected persons was not elevated relative to the general population for rectal non-SCC (SIR=0.88; 95% CI 0.74–1.04) and was actually reduced for colon non-SCC (SIR=0.63; 95% CI 0.55–0.73). Similarly, in our analysis of immunosuppressed transplant recipients, we observed that the risk of rectal SCC exceeded that in the general population (SIR = 3.46, 95% CI 1.66–6.36, N=10 cases), whereas the risk of rectal non-SCC in transplant recipients was reduced (SIR=0.61; 95% CI 0.51–0.72, N=146 cases).

Among HIV-infected people, incidence of rectal SCC was higher in MSM compared to other HIV-infected groups (incidence rate ratio [IRR]=3.44; 95% CI 1.96–6.03), (Table 2). Persons ≥30 years of age had a higher risk for rectal SCC than those <30 years of age, as did whites compared to non-whites, although neither association was significant after multivariable adjustment. The incidence of rectal SCC did not appreciably change over time during the HAART era. Finally, people diagnosed with AIDS had higher rectal SCC incidence than those with HIV-only (IRR=1.92; 95% CI 1.08–3.42).

To explore the possibility that some rectal SCCs were misclassified anal cancers, we reviewed the case abstracts for 113 cases from four cancer registries, including 73 rectal SCC cases (55 HIV-infected, 18 HIV-uninfected). Examples of the information available on these cases along with some brief comments are given in Table 3. The level of detail varied, ranging from only a simple statement of the diagnosis to information on locations of biopsies and treatment received. For certain cases, information on the location of the tumor mass in different parts of the abstract was conflicting and often indicated that the tumor spanned the anorectal region; we classified these tumors as anal cancers because the site code for ‘anorectal lesion’ (C218) is classified as anal cancer [http://apps.who.int/classifications/icd10/]. Approximately one third of rectal SCC cases were determined to be potentially misclassified anal SCCs (HIV-infected cases: 34.5%, 95%CI 23.4–47.7%; HIV-uninfected cases: 33.3%, 95%CI 16.3–56.3%), (Table 4). After removal of these cases, the majority of cases assigned as rectal SCC by the consensus of reviewers were scored with ‘high confidence’ by at least one reviewer (58.3%, 95%CI 42.2%–72.9%).

Applying the same rectal SCC misclassification proportion (34.5%) in our sample of 55 HIV-infected cases with available case notes to all 89 HIV-infected rectal SCC cases in the HACM Study would result in the removal of 31 misclassified tumors, leaving 58 remaining rectal SCCs. Using this corrected approximation of the observed rectal SCCs in HIV-infected persons, the SIR would remain elevated (SIR=18.8; 95% CI 14.3–24.3). Furthermore, if we count only the proportion of rectal SCCs that were assigned as 'high confidence' (58.3%), leaving 34 remaining cases, there would still be a substantial excess of rectal SCC (SIR=11.0; 95% CI 7.64–15.4). Each of these revised SIR estimates is conservative because no misclassification of rectal SCCs among the HIV-uninfected general population was assumed (i.e., we did not change the expected rate in the denominator). For example, approximately 3 rectal SCC cases were expected based on counts observed in the general population. However, if one-third of the general population cases were misclassified anal SCC, then the observed count in HIV-infected persons (i.e., 89 cases) should have been divided by 2 rather than 3, which would have generated an ever more pronounced SIR for rectal SCC.

The level of detail for these more probable HIV-infected rectal SCCs varied in quality as well (Supplemental Table 2). Among the 21 'high confidence' cases, certain treatment details were provided for 11, with combination radiotherapy and chemotherapy most often listed. Specific location of the tumor within the rectum (i.e., proximal or distal rectum) was mostly missing, with the exception of case 21b, which was described as a tumor at 6–12cm from the anal verge. Advanced tumors may be more likely to span the anorectal region and be misclassified. Although detailed information on tumor size was not available, the stage distribution among this set of 21 cases did not appear to be heavily skewed towards advanced disease (11 local tumors, 4 regional tumors, 1 distant tumor, 5 unknown).

DISCUSSION

This is the first report to demonstrate that HIV-infected people have a markedly elevated risk for rectal SCC. This excess risk was most pronounced in HIV-infected MSM, a risk pattern very similar to that observed for anal SCC, which is caused by HPV. Notably, risk estimates for rectal SCC differed from those for rectal non-squamous rectal tumors and colon cancer. We eliminated obvious misclassification of anal SCC as rectal SCC. Some misclassification may have remained, but the extent to which this was the explanation for the excess incidence associated with HIV infection could not be determined without detailed information on tumor location.

Very little is known about risk factors for developing rectal SCC due to its rarity. Meta-analyses of studies of cancer risk in HIV-infected people show no consistent evidence of increased colorectal cancer risk, but these studies combined both colon and rectal cancers and did not separate histologic subtypes [16, 21]. The absence of an elevated risk is not surprising because, as we observed in this study, most colorectal cancers in HIV-infected people are still non-SCCs. Interestingly, the failure to evaluate colon and rectal tumors as distinct in prior studies may have also precluded the ability to observe a deficit of colon cancer in HIV-infected persons, as documented here.

In support of a role for immunosuppression as a risk factor for rectal SCC, we found a higher risk in HIV-infected people who had progressed to AIDS than in HIV-infected people who had not. In addition, we report here that rectal SCC risk was elevated among transplant recipients, another immunosuppressed patient population. Prior studies of transplant recipients have demonstrated a modest increase in colorectal cancer overall [20, 21] but the evaluation of all colorectal cancers together likely missed the stronger association specific to rectal SCC.

Given the anatomic continuity of the anal canal and the rectum, it is relevant to consider the etiology of anal cancer. Anal cancer is caused by infection with HPV-16 or, to a lesser extent, other oncogenic subtypes of HPV [22]. HIV-infected persons have an elevated risk of developing anal cancer [16–18], and long-term immunosuppression is a risk factor for anal cancer among HIV-infected individuals [23, 24]. Our data further confirm previous observations that MSM have a particularly increased risk of anal neoplasia [23, 25]. This high risk is largely due to a high prevalence of receptive anal sex practices, which increases the chance of HPV acquisition [26, 27].

In our study, the patterns for rectal SCC mirrored those for anal SCC, suggesting HPV infection could also be a contributing cause of rectal SCC. Specifically, HIV-infected MSM had the greatest elevation in rectal SCC risk. The elevation for rectal SCC was smaller in transplant recipients who, although immunosuppressed, may be less likely than HIV-infected MSM to have anal HPV infection. In addition, US population trends in anal and rectal SCC incidence have recently been reported to be similar, [3] providing further evidence that SCC etiology may be similar across the anorectal region. Prior studies have documented HPV DNA positivity in some rectal SCC tumors, as well as the presence of either HPV oncoprotein transcripts or altered levels of HPV-targeted tumor suppressor proteins [11–13]. However, these reports are limited to less than 10 cases, and two other studies using different assays, including *in situ* hybridization, reported negative results for the presence of HPV [8, 10].

Our observation of a strong association between HIV and rectal cancer specific to SCC histology may have been due in large part to misclassification of anal SCCs as rectal SCCs. The rectal and anal regions are continuous, and large tumors can span both regions, making them difficult to distinguish. Our greatest challenge was the limited data available in the cancer registries to assess the diagnoses. To some extent, the uncertainty is unavoidable, as there is inherent clinical ambiguity. It was reassuring that the rectal SCC cases that appeared to be misclassified anal cancers were equally present in both HIV-infected persons and the general population, pointing to non-differential misclassification. When we removed the cases that were probable anal cancers from the HIV-infected rectal SCC group, a nearly 20-fold excess risk of rectal SCC remained. Furthermore, we calculate that nearly 90% of the 89 rectal SCC cases reported in HIV-infected persons would have to have been misclassified, leaving fewer than 8 cases, to leave no excess risk compared to the general population (i.e., SIR ≤1). On the other hand, because rectal SCCs are not common, any misclassification would not substantially affect the SIRs for anal cancer. For instance, even if all of these 89 observed rectal SCCs were in fact anal SCCs, the SIR for anal SCC would only increase from 38 to 42. Future work requires a greater level of detail on tumor size and

location within the rectum, with demonstration of the presence of small, proximal SCCs of the rectum needed to conclusively prove that rectal SCC is a distinct entity from anal SCC.

Strengths of our registry-based study include a large enough HIV population to gather an adequate number of cancers classified by both tumor site and histology. This proved crucial for documenting previously unappreciated associations, which were masked by examination of colorectal cancer or rectal cancer overall. Our design also allowed us to compare across tumor sites, providing support for a similar etiology between rectal and anal SCC. Also unique to this study was access to cancer registry case notes, which allowed us to assess the potential misclassification of cancer sites. Limitations must also be noted, including a lack of conclusive details for some tumors due to factors such as clinical ambiguity and poor documentation. We also lacked data on HIV treatment and CD4 T-cell counts, which prevented more detailed examination of the role of immunosuppression. We did not have access to tumor tissues, which would have allowed us to test directly the hypothesis that HPV is etiologically relevant for rectal SCC as a distinct entity in the context of HIV infection.

We have shown that HIV-infected individuals are at an elevated risk of developing rectal SCC. The increased risk of rectal SCC among HIV-infected people occurred in a pattern very similar to anal cancer (i.e., particularly high in MSM), suggesting a sexually transmitted infectious etiology such as HPV. We also documented higher risk in people with AIDS than in other HIV-infected people, as well as elevated risk in transplant recipients, pointing to a role for immunosuppression. Although we observed ambiguity and misclassification between anal SCC and rectal SCC that could account for a proportion of the excess rectal SCC risk observed, the results are also consistent with squamous tumors with shared etiology (i.e., likely HPV) arising not only in the anal canal but also the rectum and occurring most frequently among HIV-infected MSM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Standardized incidence ratios for rectal, anal, and colon cancers in HIV-infected people

	Rectal SCC (N=89)		Rectal Non-SCC (N=135)		Anal SCC (N=705)		Colon Non-SCC (N=197)	
	Cases	**SIR (95% CI)**	**Cases**	**SIR (95% CI)**	**Cases**	**SIR (95% CI)**	**Cases**	**SIR (95% CI)**
Overall	89	28.9 (23.2–35.6)	135	0.88 (0.74–1.04)	705	37.3 (34.6–40.2)	197	0.63 (0.55–0.73)
Males, by risk group								
MSM	71	61.2 (47.8–77.2)	58	0.87 (0.66–1.13)	529	65.6 (60.2–71.5)	61	0.51 (0.39–0.66)
Non-MSM IDU	4	9.09 (2.48–23.3)	27	1.01 (0.66–1.46)	45	14.2 (10.4–19.1)	29	0.55 (0.37–0.79)
Heterosexual	2	8.7 (1.05–31.4)	12	0.95 (0.49–1.65)	24	16.7 (10.7–24.8)	23	0.83 (0.53–1.25)
Other/unknown	4	11.8 (3.21–30.1)	12	0.56 (0.29–0.98)	42	18.2 (13.1–24.6)	24	0.54 (0.35–0.80)
Females, by risk group								
IDU	3	11.5 (2.38–33.7)	8	1.03 (0.45–2.03)	21	16.4 (10.2–25.1)	14	0.73 (0.40–1.23)
Heterosexual	5	11.9 (3.87–27.8)	13	1.12 (0.60–1.92)	31	18.2 (12.4–25.9)	25	0.83 (0.54–1.23)
Other/unknown	0	0 (0–16.0)	5	0.72 (0.23–1.68)	13	13.8 (7.36–23.6)	21	1.12 (0.70–1.72)
Males and females, by risk group								
MSM	71	61.2 (47.8–77.2)	58	0.87 (0.66–1.13)	529	65.6 (60.2–71.5)	61	0.51 (0.39–0.66)
Non-MSM males	10	9.90 (4.75–18.2)	51	0.84 (0.62–1.10)	111	16.0 (13.2–19.3)	76	0.61 (0.48–0.76)
Females	8	8.79 (3.80–17.3)	26	0.99 (0.65–1.45)	65	16.5 (12.8–21.1)	60	0.88 (0.67–1.14)

Abbreviations: MSM (men who have sex with men), IDU (injection drug user), SCC (squamous cell carcinoma), SIR (standardized incidence ratio)

Analyses for anal cancer are restricted to the 705 of 766 cases with squamous histology; analyses for colon cancer are restricted to the 197 of 199 cases with non-squamous histology.

TABLE 2

Risk factors for rectal SCC among HIV-infected persons

	Cases	Incidence (per 100,000 py)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	p-value
MSM					
No	18	2.02	1.00	Referent	< 0.001
Yes	71	10.2	5.08 (3.03–8.52)	3.44 (1.96–6.03)	
Attained age					
< 30 years	3	1.66	1.00	Referent	0.15
30–40 years	25	4.94	2.99 (0.90–9.89)	2.08 (0.62–6.91)	
40–50 years	43	7.33	4.32 (1.34–13.9)	2.98 (0.91–9.75)	
≥ 50 years	18	5.77	3.29 (0.96–11.2)	2.44 (0.70–8.48)	
Race/ethnicity					
White	47	8.65	1.00	Referent	0.24
Black	24	3.27	0.38 (0.23–0.62)	0.64 (0.38–1.09)	
Hispanic	16	5.58	0.64 (0.37–1.14)	0.87 (0.49–1.55)	
AIDS status					
HIV-only	16	2.65	1.00	Referent	0.02
AIDS	73	7.43	2.80 (1.63–4.81)	1.92 (1.08–3.42)	
Calendar year					
1991–1995	1	1.06	0.17 (0.23–1.28)	0.48 (0.06–3.79)	0.41
1996–2000	24	6.13	1.00	Referent	
2001–2005	40	6.58	1.05 (0.63–1.74)	1.02 (0.60–1.74)	
2006–2010	24	4.88	0.76 (0.43–1.35)	0.68 (0.35–1.30)	

Abbreviations: py (person-years), MSM (men who have sex with men, SCC (squamous cell carcinoma), IRR (incidence rate ratio)

*Poisson regression model includes all covariates in Table 2 as well as cancer registry.

TABLE 3

Examples of case notes reviewed to evaluate misclassification of rectal cancers

Provided case abstracts (all dates are suppressed)	Original Diagnosis	Assigned Diagnosis	Comments
CASE 1A. PT IN FOR BX DUE TO COLON PRIMARY YEARS EARLIER WHEN NEW PRIMARY FOUND. PT IS OCC SMOKER/DRINKER W/PER HX OF COLON CA AND FAM HX OF PANCREATIC CA CT=LESS THAN 5MM PERI-RECTAL LN PRESENT/LESION ABOVE ILEORECTAL ANASTOMOSIS PET/CT=SPICULATED SMALL MASS RT MARGIN OF SURG STAPLE LINE SKIN ANUS EXCISION=SUPERFICIALLY INVASIVE SCC WELL DIFF W/HPV EFFECT. DEEP MARGINS ARE INDETERMINATE WITH SQUAMOUS CELL CARCINOMA STAGED BY xxxx MED ONC DR xxxx AS A T1.N0.M0 STAGE1 CA RT TX OF ANAL CANAL W/ IMRT=5400 CGY TOTAL IN 30 FRACT, CTV BOOST 40–50 CGY TO THE BILAT INGUINAL REGION IN 30 FRACT; NEULASTA, 5FU CHEMO, FLUROURACIL, MITOMYCIN	Rectal SCC	Anal SCC	The tumor location information was conflicting (i.e., peri-rectal, anus). Excision was reported for a lesion in the anus, and radiation therapy was directed at anal canal. On balance, evidence indicates the possibility of an anal lesion, so rectal SCC was reassigned to anal SCC.
CASE 2A. RECTAL PAIN AND BLEEDING. FAM HX BONE CA SMOKER, CURRENT USE OF ETOH. CT ABD/PELVIS: RECTAL/ANAL MASS C/W CA. COLON POLYP 20 CM BX: ADENOMATOUS EPITHELIUM. RECTAL MASS BIOPSIES: PD NONKERATINIZED SCC. T2N0M0, ANUS NONKERATINIZED SCC PELVIS 3600 RADS IN 20 FX REDUCED PELVIS 540 RADS IN 3 FX. ANAL BOOST 1800 RADS IN 10 FX.; CHEMO: NOS CONCOMITANT W/XRT	Rectal SCC	Anal SCC	The case notes referenced the presence of a colon polyp, and the biopsy describes a rectal mass, but the location in the CT scan was noted as rectum/anus. Radiation therapy boost was directed at the anus. To be conservative, rectal SCC was reassigned to anal SCC.
CASE 3A. SIGMOIDOSCOPY: BX OF SMALL POLYPOID RECTAL MASS 2CM FROM ANAL VERGE EXT JUST INSIDE ANAL CANAL; ONE FRAGMENT OF INVASIVE MD SQ CELL CA RECTUM EXT TO JUST INSIDE OF ANAL CANAL	Rectal SCC	Anal SCC	The specific location noted a mass spanning the rectum and the anal canal, so rectal SCC was reassigned to anal SCC.
CASE 4A. CT- SOFT TISSUE THICKENING IN LT PERIRECTAL FAT WORRISOME FOR PERIRECTAL SPREAD OF TUMOR. CXR NEG COLONOSCOPY- REVEALED 2 POLYPS IN THE RECTUM. RECTUM BX-INV M.D. SQUAMOUS CELL CARCINOMA. PROCTOSIGMOIDECTOMY- FOCAL FISTULA IN RECTUM EXTN INTO EXTRAMURAL MASS NO EVIDENCE OF CA. MARG NEG. 3 LNS NEG. T2- INV MUCOSA. N0, RECTUM SQUAMOUS CELL CARCINOMA RECTOSIGMOIDECTOMY W/LNS. 5040CGY TO THE PELVIS. CONCURRENT XRT WITH CHEMO - 5FU/CISPLATIN BASED.	Rectal SCC	Rectal SCC	Unlike the previous examples, the location of the polyps at colonoscopy and the biopsied mass are noted as in the rectum. A protcosigmoidectomy (i.e., removal of the rectum and sigmoid colon) was performed. On balance, evidence points to rectal SCC.
CASE 5A. PT W/BX OF RECTUM SHOWING HI GR DYSPLASIA SEEN FOR EXC BX TO R/O CARCINOMA. CXR: NEG COLONOSCOPY: RECTAL MASS (BX: HI GR DYSPLASIA) RECTAL BX (OP NOTE: LG ULCERATED MASS DEEP IN BOWEL WALL.CLEARLY ULCERATED, FIRM, HARD & MEASURES 3X2 CM. RECTUM (BX): INV PD SQUAMOUS CA W/INVASION RECTAL SUBMUCOSA & INV MUSCULARIS W/INVLV DEEP MARGINS OF EXCISION. STAGING FORM: cT4N1M0 STAGE 3B, RECTUM PD SQUAMOUS CARCINOMA EXTERNAL BEAM - NO SPECIFICS AVAILABLE, 5FU/MITOMYCIN C	Rectal SCC	Rectal SCC	The colonoscopy report, biopsy location, pathology report, and staging summary all consistently note the location as the rectum. All evidence indicates that this is rectal SCC.
CASE 6A. BIOPSY RECTAL MASS; BIOPSY TISSUE SAMPLE ONLY RECTAL MASS: MD KERATINIZING SQ CELL CA	Rectal SCC	Rectal SCC	Very few supportive data were available for review, but no conflicting data warranted reassignment.

Provided case abstracts (all dates are suppressed)	Original Diagnosis	Assigned Diagnosis	Comments
CASE 7A. PATHINVASIVE MOD DIFF SQ CELL CA, VASCULAR SPACE INVASION IDENTIFIED, RECTAL MASS:, INVASIVE MOD DIFF SQ CELL CA, RECTUM; RECTAL BX. NO OTHER TX KNOWN	Rectal SCC	Rectal SCC	Very few supportive data were available for review, but no conflicting data warranted reassignment.

TABLE 4

Reclassification of rectal and anal cancers following case review

	Cases reviewed N	Cases reassigned N(%)	New assignments	Remaining cases N	High confidence cases[a] N(%)
Rectal SCC					
HIV-infected	55	19 (34.5)	18 anal SCC, 1 rectal non-SCC	36	21 (58.3)
HIV-uninfected	18	6 (33.3)	5 anal SCC, 1 rectal non-SCC	12	8 (66.7)
Anal cancer					
HIV-infected	10	2 (20.0)	1 rectal SCC, 1 skin cancer	8	NA
HIV-uninfected	9	3 (33.3)	1 rectal SCC; 1 rectal non-SCC, 1 skin cancer	6	NA

Abbreviations: SCC (squamous cell carcinoma)

[a]High confidence diagnoses are rectal SCC cases scored as rectal SCC with a confidence rating of 4 or 5 by at least one reviewer