

# HIV positivity and anal cancer outcomes: A single-center experience

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## KEYWORDS:

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## Abstract

**BACKGROUND:** Anal cancer remains common among human immunodeficiency virus (HIV) patients. Chemoradiation has had mixed results. We evaluated outcome differences by HIV status.

**METHODS:** We retrospectively analyzed 14 HIV+ and 72 HIV- anal cancer patients (2000 to 2013). Outcomes included chemoradiation tolerance, recurrence, and survival.

**RESULTS:** HIV+ patients were more often male (100% vs 38%,  $P < .001$ ) but diagnosed at similar stages ( $P = .49$ ). They were less likely to receive traditional chemotherapy (36% vs 86%,  $P < .001$ ). Recurrence ( $P = .55$ ) and survival time ( $P = .48$ ) were similar across groups. HIV+ patients had similar colostomy-free survival ( $P = .053$ ). Receipt of 5-fluorouracil/mitomycin C (MMC) chemotherapy predicted recurrence-free and overall survival (Hazard ratios .278, .32). HIV status did not worsen recurrence ( $P = .71$ ) or survival ( $P = .57$ ).

**CONCLUSIONS:** HIV+ patients received more non-MMC-based chemoradiation but had equivalent colostomy-free, recurrence, and overall survival. Use of 5-fluorouracil/MMC chemotherapy increased after 2008.

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Anal canal squamous cell cancer (ASCC) is a rare but increasingly prevalent cancer, with 7,210 new cases reported in the United States in 2014.<sup>1</sup> Human immunodeficiency virus (HIV) positivity is a significant risk factor, and the incidence of ASCC in the HIV-positive population is 40 to 122 fold higher than that of the general

population.<sup>2,3</sup> The increase in anal cancer cases diagnosed in the United States has correlated with the rise of the HIV epidemic. Anal carcinoma is strongly linked with persistent human papillomavirus (HPV) infection, which is likely facilitated by HIV-induced immunosuppression in the anal region.<sup>4</sup> Although effective drug treatment for HIV has decreased the risk for many AIDS-related cancers, ASCC remains common in HIV-infected patients, even after the introduction of highly active antiretroviral therapy (HAART) in 1996.<sup>5-7</sup>

The treatment for ASCC includes a multimodality approach.<sup>8</sup> Traditional treatment is concurrent mitomycin C (MMC), 5-fluorouracil (5FU) chemotherapy, and radiation therapy, which has been validated by several

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randomized controlled trials.<sup>9–13</sup> Combined chemoradiotherapy (CRT) can pose significant harm to HIV-positive patients, who are generally immunosuppressed. Some evidence suggests that chemotherapy can lead to prolonged suppressed CD4 counts.<sup>14</sup>

Early reports indicated that HIV-positive patients had worse outcomes and lower tolerance to standard treatment than HIV-negative patients; many of these, however, were conducted before the widespread use of HAART.<sup>15–17</sup> Since then, retrospective studies have shown contradictory outcomes with CRT in HIV-positive patients.<sup>3,18–23</sup> The presence of HIV may influence physician selection of chemotherapeutic agents and lead to empiric alteration of chemotherapy regimens in this population.<sup>2,7,17</sup> Very few studies have evaluated trends in treatment regimens at their institution by HIV status.<sup>24</sup> The National Comprehensive Cancer Network guidelines are not based on level I data that have included the impact of HIV status on outcomes.

Hence, our working hypothesis is that there are no differences in outcomes between HIV-positive and HIV-negative patients with ASCC. The objective of this study was to evaluate the impact of HIV on the treatment and outcomes of anal cancer at our institution in the post-HAART era and to evaluate temporal trends in treatment regimens.

## Methods

We performed a retrospective data analysis of the records of patients with anal cancer treated from 2000 to 2013 at Oregon Health and Science University (OHSU) Hospital and Clinics. The institutional review board at OHSU approved this study (IRB#10668). Our analysis included data from hospital records, outpatient charts, and tumor registry data. Our sample included patients with a histologic diagnosis of ASCC of the anal canal and documented HIV status. We also extracted data regarding CD4 counts at diagnosis and use of HAART at diagnosis. We excluded patients not meeting inclusion criteria and patients with in situ disease (Tis).

## Treatment modalities

The diagnosis of ASCC was made by digital rectal examination, anoscopy with or without EUS, and confirmed with anal biopsy in all patients. Metastatic workup included CT of the chest, abdomen, and pelvis.

We excluded stage IV disease. Only patients undergoing definitive chemoradiation were included. We defined definitive CRT as combined treatment with chemotherapy and radiation. “Current first line chemotherapy” consisted of continuous infusion of 5-FU and boluses of MMC, as recommended by current guidelines.<sup>25</sup> “Other chemotherapy” was defined as non-MMC based, for example, cisplatin. Radiation therapy was all given via an external beam approach and predominately included an intensity-modulated radiation

therapy-based treatment planning and delivery approach.<sup>26</sup> A full dose of radiation was defined as 45 to 54 Gy in total. The intensity-modulated radiation therapy-based algorithm closely paralleled the guidelines of RTOG-0529 (since 2007) and RTOG-9811 (before 2007).<sup>27,28</sup>

## Follow-up

All patients were evaluated 8 to 12 weeks after treatment with a physical examination, including digital rectal examination. Clinical response to CRT was evaluated 12 weeks after completion by clinical examination and anoscopy. Patients were routinely followed every 3 to 6 months for 5 years with a physical examination and anoscopy. They also underwent an annual CT of the chest, abdomen, and pelvis for 3 years.

## Outcomes measures

Main outcome measures included CRT tolerance and/or compliance, complete clinical response (CR) after CRT, recurrence status, colostomy-free time, and overall survival (OS) time.

CRT tolerance issues were defined as (1) treatment breaks due to toxicities and/or (2) grade 3 or 4 toxicities requiring hospitalization. Treatment-related toxicities were recorded according to the Common Terminology Criteria for Adverse Events (version 4.0). Compliance issues to treatment were considered present if there was failure to receive entire dose of radiation and/or dose reduction of chemotherapeutic agents.

CR was defined as an absence of mass on examination at the follow-up visit and absence of recurrent disease within 6 months of the end of treatment. Patients were categorized as complete responders or incomplete response and/or persistent disease. Recurrence status was determined after 6 months of completion of CRT and further delineated into persistence of disease, locoregional recurrence, distant recurrence, or no recurrence. Colostomy-free survival was defined as the time from end of treatment to death or abdominoperineal resection (APR) for recurrent or persistent disease. OS was defined as the time from end of treatment to death.

## Temporal trends in chemotherapy use

Given that the current first-line chemotherapy regimen was defined as 5FU/MMC over 5FU/cisplatin by the RTOG-9811 trial in 2008,<sup>12</sup> we determined the proportion of patients receiving definitive CRT with 5FU/MMC before and after 2008.

## Statistical analysis

Group differences in age were assessed with a Wilcoxon rank-sum test, and relationships between categorical data

were assessed via Pearson chi-squared and Fisher exact tests of association. We performed log-rank tests to compare group differences for survival, time until APR, and time to recurrence. We constructed multivariable Cox proportional hazards models of recurrence-free time and OS controlling for age at diagnosis, ASCC stage, standard vs nonstandard chemotherapy, and tolerance issues. All statistics were performed with R statistical software (R Core Team, Vienna, Austria), version 3.1.3.

## Results

### Patient characteristics and tumor factors

A total of 86 patients (14 HIV positive, 72 HIV negative) were treated for anal cancer at OHSU from 2000 to 2013. Before our exclusions, there were 26 HIV-positive patients treated for ASCC in the study period; 12 were excluded, however, as 10 patients underwent local tumor treatment only for early disease and 2 patients had stage IV disease. Median follow-up was 29.2 months (interquartile range [IQR] 15.9 to 55.7). Follow-up time did not differ between the HIV-positive and HIV-negative cohorts (median 39.1 vs 28.0,  $P = .49$ ). HIV-positive patients were more likely male (100% vs 38%,  $P < .001$ ) but were diagnosed at similar stages ( $P = .49$ ).

	HIV positive, <i>N</i> = 14	HIV negative, <i>N</i> = 72	<i>P</i> value
Median age at diagnosis	52	59	.105*
Gender			
Male	100% (14)	38% (27)	<.001†
Race			.118†
White	86% (12)	94% (68)	
Hispanic	7% (1)	0% (0)	
Other	7% (1)	6% (4)	
Insurance			.757†
None	0% (0)	10% (7)	
Medicare	36% (5)	32% (23)	
Medicaid	7% (1)	15% (11)	
Private	36% (5)	28% (20)	
Other/unknown	21% (3)	15% (11)	
Histologic grade			.574†
1	17% (2)	8% (5)	
2	58% (7)	58% (38)	
3	25% (3)	34% (22)	
Clinical stage			.493†
I	21% (3)	10% (7)	
II	50% (7)	54% (39)	
III	29% (4)	36% (26)	

HIV = human immunodeficiency virus.  
\*Wilcoxon test.  
†Fischer exact test.

Patient demographics and tumor characteristics are presented in Table 1. Among HIV-positive patients, median CD4 was 238, and all but 2 patients were on HAART, both of whom were started on HAART at or shortly after diagnosis. One patient was diagnosed with HIV at the time of anal cancer diagnosis and initiated on HAART, and the other had a history of noncompliance and was restarted on HAART therapy shortly after anal cancer diagnosis.

There was no difference in histologic grade ( $P = .57$ ); 14.3% of the patients in the HIV-positive group and 9.7% of patients in the HIV-negative group, however, had unknown histologic grades.

### CRT and CRT tolerance

The HIV-positive cohort was less likely to receive MMC-based chemotherapy (36% vs 86%,  $P < .001$ ). Alternative chemotherapy regimens received by the HIV-positive patients were 5FU alone ( $n = 2$ ) and 5FU/cisplatin ( $n = 7$ ). CRT treatment duration did not differ significantly between the cohorts (median 96.5 days, IQR 73.0 to 118.8 for HIV-positive cohort and 88.5 days, IQR 73.0 to 118.8, for HIV-negative cohort,  $P = .57$ ).

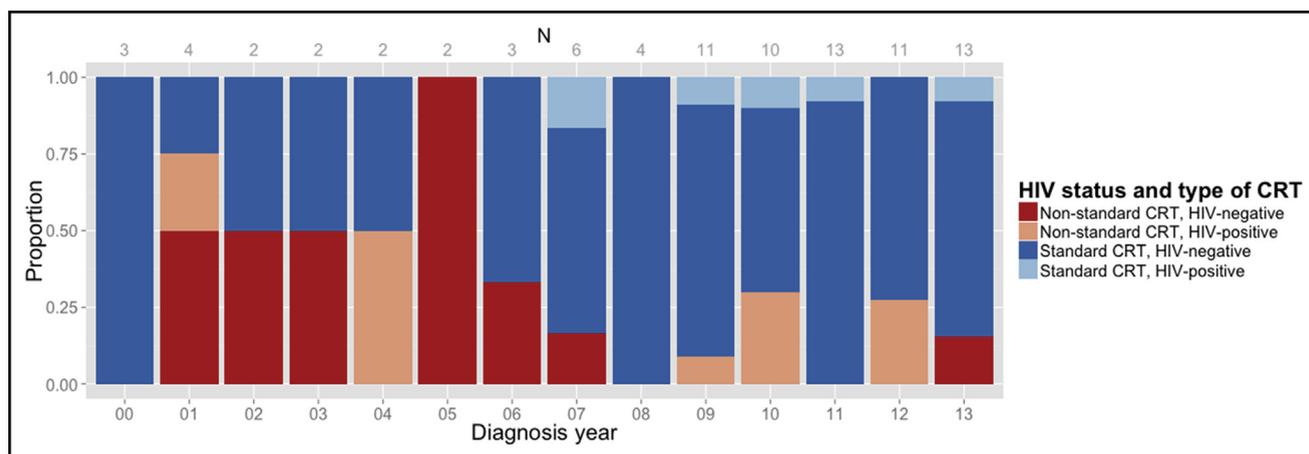
Overall, there was no difference in tolerance issues in the HIV-positive cohort, when compared to the HIV-negative patients, (64% vs 42%,  $P = .15$ ). There was no difference in dose reduction of chemotherapy or radiation completion among the cohorts (36% vs 25%,  $P = .51$ ; 86% vs 78%,  $P = .72$ ). On subset analyses of patients who received non-5FU/MMC chemotherapy, treatment tolerance issues were similar for the HIV-positive and HIV-negative patients (78% vs 40%,  $P = .17$ ).

### Temporal trends in chemotherapy use

The proportion of patients who received standard chemotherapy vs nonstandard chemotherapy as part of definitive CRT is shown in Fig. 1. When compared to pre-RTOG-9811 era, use of MMC-based chemotherapy increased significantly in all patients (85.5% after 2008 vs 58.3% before 2008,  $P = .009$ ). The increased use of standard chemotherapy was more pronounced in the HIV-negative group (96.1%, 49/51 after 2008 vs 61.9%, 13/21 before 2008,  $P < .001$ ) compared to the HIV-positive group (36.4%, 4/11 after 2008 vs 33.3%, 1/3 before 2008,  $P = 1$ ). The HIV-positive cohort, however, was limited by small numbers.

### Outcomes following definitive CRT

Outcome measures for both cohorts are presented in Table 2. Both cohorts had high complete CR (71% in HIV-positive group vs 90% in HIV-negative group,  $P = .06$ ). Only 1 patient in the HIV-negative cohort had an unknown clinical response and was excluded from the analysis. Recurrence status did not significantly differ between the 2 groups ( $P = .36$ ), nor did recurrence-free time (log-rank  $P = .55$ ). Two patients



**Figure 1** Temporal trends in chemotherapy use.

(including the patient with unknown CR status) in the HIV-negative group transferred care after CRT, and recurrence status was thus unknown. These patients were excluded from the subsequent survival analyses. APR for recurrent or persistent disease was similar among the cohorts (29% vs 10%,  $P = .075$ ). Details regarding patients with failure of tumor control after definitive CRT are presented in Table 3. All the patients with tumor control failure in both cohorts who died in follow-up died of their disease.

OS and colostomy-free survival from date of treatment completion were not significantly different between the 2 cohorts ( $P = .48$ ; Fig. 2). Median OS was 68.8 months for the HIV-positive group and 110.9 months for the HIV-negative patients. Overall 5-year survival was 61.9% for the HIV-positive group and 74.0% for the HIV-negative group.

On multivariate logistic regression analysis, receipt of MMC-based chemotherapy positively predicted recurrence-

free and OS (Hazard ratio [HR] .278, .082 to .946,  $P = .07$ ; HR .32, .094 to 1.096,  $P = .04$ ). Tolerance issues were negative predictors for both (HR 5.264, 1.376 to 20.142,  $P = .02$ ; HR 4.181, 1.136 to 15.389,  $P = .03$ ). HIV status did not worsen recurrence (HR .78,  $P = .71$ ) or OS (HR .67,  $P = .57$ ).

## Comments

ASCC is increasing in incidence in HIV-infected patients, even in the HAART era. Treatment approaches and outcomes for this patient population continue to evolve. Existing reports have shown contradictory use of chemoradiation regimens in this population, and outcomes in this population have had mixed results, when compared to HIV-negative patients.<sup>3,20,22,23</sup> In our study, HIV-positive patients were diagnosed at similar stages and received less 5FU/MMC-based chemoradiation therapy. Although

**Table 2** Outcomes after definitive CRT

	HIV positive, $N = 14$	HIV negative, $N = 72$	$P$ value
Treatment duration (in days)	96.5	88.5	.569*
CRT tolerance issues	64% (9)	42% (30)	.149 <sup>†</sup>
CRT compliance issues			
Completion of RT	86% (12)	78% (56)	.724 <sup>†</sup>
Chemotherapy dose reduction	36% (5)	25% (18)	.510 <sup>†</sup>
Complete clinical response (CR) <sup>‡</sup>			.057 <sup>†</sup>
Yes	71% (10)	90% (64/71)	
Recurrence <sup>§</sup>			.507 <sup>†</sup>
Distant	0% (0)	3% (2)	
Locoregional	14% (2)	6% (4)	
Never Disease Free	14% (2)	9% (6)	
None	71% (10)	83% (57)	
APR for persistent/recurrent disease	29% (4)	10% (7)	.075 <sup>†</sup>

APR = abdominoperineal resection; CRT = chemoradiotherapy.

\*Wilcoxon test.

<sup>†</sup>Fischer exact test.

<sup>‡</sup>One patient in HIV-negative cohort was lost to follow-up and CR was unknown.

<sup>§</sup>Two patients, both in HIV-negative cohort, were missing data for recurrence status.

**Table 3** Tumor control failure after CRT by HIV status

	HIV positive			HIV negative		
	Persistent	Local	Distant	Persistent	Local	Distant
N (% of total cohort)	2 (14)	2 (14)	0 (0)	6 (9)	4 (6)	2 (3)
Clinical response (CR)	0	0	0	0	4	2
Tolerance issues	2	2	4	4	3	2
CRT compliance issues						
Dose reduction chemo	2	1	2	2	1	0
Failure to complete RT	0	1	2	2	2	0
APR for recurrent/persistent disease	2	2	3	3	4	0
Time to recurrence or APR (range in months)	4–7	17–19	7–8	9–17	18 lung, 72 bone	
Status	1—NED; 1—Died	1—NED; 1—Died	1—NED; 5—Died	3—NED; 1—Died	2—Died	

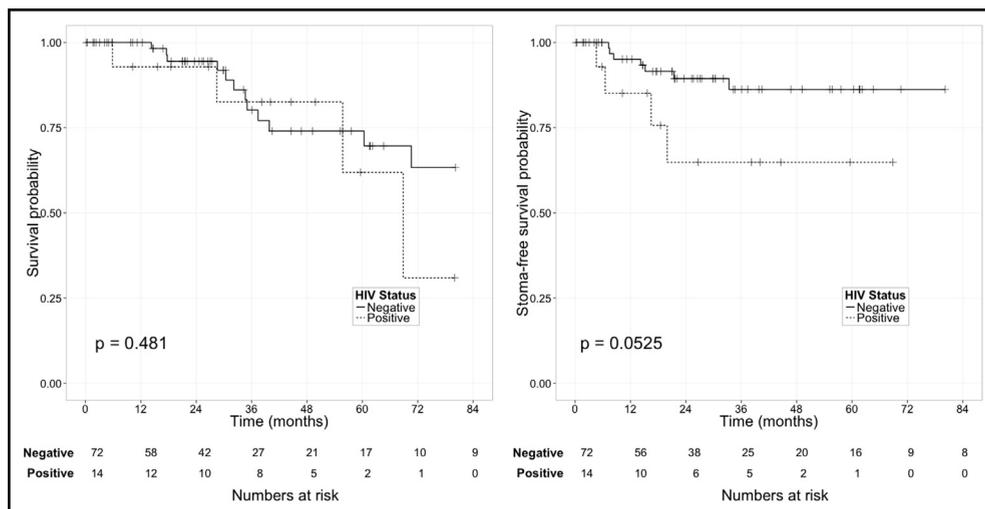
APR = abdominoperineal resection; CRT = chemoradiotherapy; HIV = human immunodeficiency virus; NED = no evidence of disease; RT = radiation therapy.

these differences were not significant, a higher percentage of HIV-positive patients had persistent disease, lower colostomy-free survival rates, and CRT tolerance issues. HIV-positive patients had similar recurrence rates and OS rates to HIV-uninfected patients.

Similar to existing reports, our study confirmed that HIV-positive patients were predominantly young men.<sup>3,16,18,20</sup> HIV-positive patients undergoing definitive CRT at our institution were diagnosed at similar stages when compared to HIV-negative patients, unlike prior studies.<sup>18,20</sup> Before excluding patients undergoing treatment other than definitive CRT in our study, we did find that HIV-positive patients were diagnosed at earlier stages, which may result from increased recognition of this population as high risk for anal squamous cell carcinoma. At our institution, which is a tertiary referral center with a specialized HIV clinic, these patients may undergo increased surveillance. Additionally, HIV-positive patients often present with HPV-related condyloma before development of anal squamous cell carcinoma,<sup>3,18,29</sup> leading to enhanced vigilance

and biopsies of anal lesions. Screening of HIV-positive patients for anal cancer precursor lesions via anal Pap smear remains controversial, as it has not yet been proven to be efficacious for preventing anal squamous cell carcinoma or anal intraepithelial neoplasia.<sup>30</sup> Thus, it is not routinely performed at our institution.

Historically, HIV-positive patients were treated differently than HIV-negative patients, with specifically modified chemotherapy protocols, because of fear of toxicity.<sup>17,19</sup> In more recent comparative studies, there is still variability in treatment approach to HIV-positive patients.<sup>3,18,20,22</sup> Current standard treatment of anal cancer is well established as MMC based by the RTOG 98-11 and ACT II trials.<sup>12,13</sup> These trials excluded HIV-positive patients. As our study included treatment before and after these trials were published, one aim of this study was to evaluate temporal practice trends at our institution. Overall, HIV-positive patients received more non-MMC-based chemotherapy; the use of 5FU/MMC-based chemotherapy in all patients increased after 2008.

**Figure 2** Overall and colostomy-free survival.

Some reports have indicated poor tolerance to and increased toxicities with CRT for treatment of anal cancer in HIV-positive, when compared to HIV-negative patients,<sup>21,23</sup> whereas others report similar treatment tolerance.<sup>22</sup> In our series, there was a trend toward higher rates of tolerance issues in HIV-positive patients, which was more pronounced and approached significance in HIV-positive patients undergoing nonstandard chemotherapy. Other studies have found significant treatment differences in patients undergoing cisplatin-based chemotherapy, which was most often substituted for MMC in the present study.<sup>3</sup> The reasoning behind the substitution approach is that cisplatin is a superior radiosensitizer, whereas MMC is known to be very myelosuppressive. It has also been suggested that tolerance to definitive therapy is improved with HAART medications,<sup>2,19</sup> and all but 2 HIV-positive patients in our study were on HAART. Further comparative studies are needed to determine toxicity and treatment tolerance to standard CRT in the HIV-positive population.<sup>31</sup> As such, the results of the AIDS Malignancy Clinical Trials Consortium (NCT00324415), testing cisplatin, fluorouracil, cetuximab, and radiation therapy in HIV-positive patients are anticipated.<sup>32</sup>

Despite the differences in CRT treatment regimens in our study, response to definitive CRT and overall outcomes were very good and did not significantly differ among the cohorts. Initial clinical response rates to CRT were high in both groups (71% and 90%), which is consistent with previous reports.<sup>18,23,33,34</sup> Many previous studies reported decreased local tumor control rates and increased recurrences in HIV-positive patients.<sup>3,18,20</sup> In our study, disease persistence was present in a higher percentage of the HIV-positive patients, although this difference was not statistically significant. Nonstandard chemotherapy treatment may have been the cause of persistent disease in this cohort. However, we did not observe increased recurrence rates in this population as we would have expected with the higher use of non-MMC-based chemotherapy regimens.

Colostomy-free and survival outcomes in HIV-positive patients with anal cancer are controversial in the literature, with some reporting no difference,<sup>18,21,22</sup> whereas others report worse colostomy-free and OS in HIV-positive patients.<sup>3,18,35</sup> Baseline health of study patients and tumor characteristics may account for this wide variation. According to the latest randomized trials, AJCC staging, in particular T stage at diagnosis, is the most important prognostic factor for progression-free and colostomy-free survival.<sup>34</sup> Our results suggest that HIV-positive patients present at similar stages and have equivalent overall and colostomy-free survival. HIV status did not worsen recurrence or OS on our multivariate analyses, a finding supported by others.<sup>35</sup> This suggests that although HIV-positive patients likely still represent a distinct subpopulation of patients with anal cancer, HIV-patients on HAART may more closely resemble HIV-negative patients, and we may continue to see improved and equivalent outcomes in the HAART era and with adoption of standard treatment regimens in these patients.

## Limitations

The main limitations of our study are its small size and retrospective design. There may be a selection bias, because of the fact that HIV positive patients with very early disease underwent local treatment only and were not included in our cohort. Furthermore, the disparity found in persistent disease and recurrence rates in the HIV-positive population with the use of nonstandard chemotherapy treatment may be simply due to the low number of patients in this cohort. To our knowledge, however, there are no studies evaluating temporal trends in chemoradiation treatment of HIV-positive patients in the HAART era.

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## Discussion

### Discussant

**Megan M. Cavanaugh, MD, (Portland, OR):** Anal canal squamous cell cancer (ASCC) is fairly rare with approximately 7,270 new cases in the United States in 2014 (4,630 in women and 2,640 in men). The number of anal cancer cases has been rising for many years. The risk of being diagnosed with anal cancer in one's lifetime is about 1 in 500, with the risk slightly higher in women than in men.

Human immunodeficiency virus (HIV) positivity is a significant risk factor for ASCC and the incidence of ASCC in the HIV positive population is 40 to 122 fold higher than the general population. ASCC is strongly linked to HPV. Approximately 95% of anal cancers are caused by HPV, most caused by HPV type 16. The HIV-induced immunosuppression likely propagates the HPV infection. The treatment of HIV with highly active antiretroviral therapy (HAART) in 1996 has been effective in decreasing malignancies associated with AIDS, but ASCC still remains prominent.

The authors of this article had a working hypothesis that there are no differences in outcomes between HIV-positive and HIV-negative patients with ASCC. The objective of their study was to evaluate the impact of HIV on the treatment and outcomes of anal cancer at a single institution in the post-HAART era as well as to evaluate temporal trends in treatment regimens.

The treatment for ASCC involves a multimodality approach with concurrent MMC, 5FU chemotherapy, and radiation therapy. Combined chemoradiotherapy (CRT) can provide some risk for HIV-positive patients with continued suppressed CD4 counts. The standard chemotherapy defined as 5FU/MMC over 5FU/cisplatin by the RTOG-9811 trial in 2008. Hence, the authors evaluated temporal trends revolving around treatment before and after 2008.

The authors performed a retrospective data analysis of patients with anal cancer treated from 2000 to 2013 at Oregon Health and Science University (OHSU). A total of 86 patients were treated with 14 HIV-positive and 72 HIV-negative. HIV-positive patients were all male (100% vs 38%,  $P < .001$ ). Twelve of the HIV-positive patients were on HAART and the remaining 2 started at the time of diagnosis.

The HIV-positive cohort was less likely to receive standard chemotherapy (36% vs 86%,  $P < .001$ ). Furthermore, there was no statistically significant difference in tolerance issues between the HIV-positive and HIV-negative cohorts.

The authors noted that the temporal trends with chemotherapy use showed significant increase in use in all patients after 2008 (83% after 2008 vs 58.3% after 2008). The use of standard chemotherapy was more evident in the HIV-negative group (96.1% after 2008 vs 61.9% before 2008,  $P < .001$ ) compared to the HIV-positive group (36.4% after 2008 vs 33.3% before 2008,  $P = 1$ ). However, we must keep in mind that the HIV-positive cohort is limited with small numbers.

The overall outcomes showed complete clinical response (CR) in 71% of the HIV-positive group vs 90% in the HIV-negative group,  $P = .08$ .

There was no significant difference between the cohorts for recurrence status or recurrence-free time.

The OS from date of treatment completion was not significantly different between the cohorts ( $P = .48$ ). The 5-year survival was 61.9% in the HIV-positive group and 74.0% for the HIV-negative group. It is interesting to note that the OS was not significantly different and this is with the HIV-positive cohort often not receiving the standard chemotherapy.

Colostomy-free survival was slightly shorter for the HIV-positive group ( $P = .053$ ).

The authors are to be commended on their article and I believe the article succeeds in pointing out the significant difference in treatment of ASCC in HIV-positive patients.

The results also do raise questions regarding the treatment of ASCC in HIV-positive patients.

1. Do you feel the toxicity of standard chemotherapy for HIV-positive patients is of significant concern that risks would outweigh the benefits and prevent its use in HIV-positive patients? Is there a lower threshold in HIV-positive patients to alter the chemotherapy regimen and not provide standard chemotherapy?
2. Can you propose an explanation for why the HIV-positive patients received more nonstandard chemotherapy but yet had overall similar survival? Do you feel this is based on the small cohort size?
3. Why are there so few HIV-positive patients at OHSU?