Advances in Radiation Oncology (2023) **8**, 101155

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Factors Affecting Clinical Outcomes Among Patients Infected With HIV and Anal Cancer Treated With Modern Definitive Chemotherapy and Radiation Therapy

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Received 16 March 2022; accepted 9 December 2022

Abstract

Purpose: Anal cancer affects a disproportionate percentage of persons infected with human immunodeficiency virus (HIV). We analyzed a cohort of patients with HIV and anal cancer who received modern radiation therapy (RT) and concurrent chemotherapy to assess whether certain factors are associated with poor oncologic outcomes.

Patients and Methods: We performed a retrospective chart review of 75 consecutive patients with HIV infection and anal cancer who received definitive chemotherapy and RT from 2008 to 2018 at a single academic institution. Local recurrence, overall survival, changes in CD4 counts, and toxicities were investigated.

Results: Most patients were male (92%) with large representation from Black patients (77%). The median pretreatment CD4 count was 280 cells/mm^3, which was persistently lower at 6 and 12 months' posttreatment, 87 cells/mm^3 and 182 cells/mm^3, respectively ($P < .001$). Most (92%) patients received intensity modulated RT; median dose was 54 Gy (Range, 46.8-59.4 Gy). At a median follow-up 5.4 years (Range, 4.37-6.21 years), 20 (27%) patients had disease recurrence and 10 (13%) had isolated local failures. Nine patients died due to progressive disease. In multivariable analysis, clinically node negative involvement was significantly associated with better overall survival (hazard ratio, 0.39; 95% confidence interval, 0.16-1.00, $P = .049$). Acute grade 2 and 3 skin toxicities were common, at 83% and 19%, respectively. Acute grade 2 and 3 gastrointestinal toxicities were 9% and 3%, respectively. Acute grade 3 hematologic toxicity was 20%, and one grade 5 toxicity was reported. Several late grade 3 toxicities persisted: gastrointestinal (24%), skin (17%), and hematologic (6%). Two late grade 5 toxicities were noted.

Sources of support: Research reported in this publication was supported in part by the Biostatistics Shared Resource of Winship Cancer Institute of Emory University and National Institutes of Health/National Cancer Institute under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2022.101155

Conclusions: Most patients with HIV and anal cancer did not experience local recurrence; however, acute and late toxicities were common. CD4 counts at 6 and 12 months' posttreatment remained lower than pretreatment CD4 counts. Further attention to treatment of the HIV-infected population is needed.

Introduction

Anal cancer is a relatively rare cancer and accounted for approximately 0.5% of all new cancer cases diagnosed in 2021. However, rates for new cases of anal cancer have risen an average of 2.1% each year from 2009 to 2018. Death rates have increased an average of 3.2% each year during the same time frame.[1] Human papillomavirus (HPV) infection and immunosuppression, such as infection with human immunodeficiency virus (HIV), are well-known risk factors for the development of anal cancer.

HPV infection appears to persist for longer in persons living with HIV/acquired immunodeficiency syndrome (PLWHA) compared with patients uninfected with HIV; PLWHA are 7 times more likely to have persistent HPV infection, and immunosuppression from HIV could prevent HPV clearance, thus increasing the potential risk of developing anal cancer.[2] The prevalence of anal HPV infection in men with HIV is very high, with estimates of >86% in men who have sex with men (MSM); the only published prospective study estimates that the incidence of anal HPV-16 in MSM with HIV is 92%, with a clearance at 12.2% per year and a mean retention time of 36 months.[3] MSM with HIV have a particularly high incidence of anal cancer compared with the general population, women with HIV, or other men with HIV.[4-6] Individuals with HIV have a 40- to 80-fold increased risk of developing anal cancer compared with the general population and could be contributing to the overall rise of anal cancer incidence.[2]

Several prospective trials have established the standard of care treatment for localized anal cancer as definitive chemotherapy and radiation therapy (CRT); multiple attempts to decrease the acute toxicities of CRT from mitomycin (MMC) have been tested, but CRT with 5-flurouracil (5FU) and MMC continues to be the standard treatment for patients who are immunocompetent.[7,8] Toxicities have ranged as high as >20% for acute grade 3 skin and gastrointestinal (GI) toxicities for patients who are immunocompetent, often resulting in treatment breaks or delays for patients to recover from toxicities.[7-9] In a pooled analysis of Radiation Therapy Oncology Group trials 87-04 and 98-11, total treatment time of more than 53 days was correlated with lower colostomy-free survival and was significantly associated with local failure.[10] Improvements in radiation therapy (RT) technique with intensity modulated radiation therapy (IMRT) have helped decrease rates of high-grade toxicities and treatment interruptions compared with conventional 3-dimensional conformal RT.[11]

However, most prospective studies of anal cancer excluded patients with HIV infection, patients with CD4 count <200 cells/mm^3, or those with acquired immunodeficiency syndrome, even though PLWHA have a disproportionate burden of anal cancer compared with the general population. Multiple studies have reported that PLWHA experience high rates of acute grade ≥3 skin and hematologic toxicities,[12] especially compared with patients who are not infected with HIV; PWLHA frequently receive lower doses of CRT than patients who are not infected with HIV because of high-grade toxicities.[13-17] A recent meta-analysis reported that patients with localized anal cancer and HIV infection treated with CRT experienced greater risk of grade 3 to 4 skin, hematologic, and GI toxicities, as well as worse disease-free survival (DFS) and overall survival (OS) rates compared with patients who were not infected with HIV.[18]

Morbidity and mortality from anal cancer is significant among PLWHA. In contrast to the high 5-year OS rate of ~78% in the HIV-uninfected population,[7] the 5-year survival rates for PLWHA with anal cancer range from 47% to 60%.[19-21] Since the introduction of antiretroviral therapy (ART), there have been no significant improvements in survival, tumor control, or better tolerability of chemotherapy and RT in the HIV-infected population.[22] Our retrospective study evaluates the changes in pre- and post-treatment CD4 counts, acute and late toxicities from definitive treatment, and long-term oncologic outcomes in anal cancer among PLWHA treated at a single institution in a large metropolitan area.

Patients and Methods

Patients

Between 2008 and 2018, 75 consecutive patients with known HIV infection and localized anal cancer were treated with definitive CRT and reviewed under an institutional review board–approved protocol. Exclusion criteria included patients who did not have a documented HIV infection, did not initiate a definitive cancer treatment regimen, or had known metastatic disease. Cancers were staged per the seventh edition of the American Joint Committee on Cancer Staging Atlas. Clinical factors, such as age at diagnosis, tumor stage, nodal stage, race, CD4

counts, viral load, white blood counts, absolute neutrophil counts, performance status, sex, and use of ART before treatment were collected from chart review. All patients underwent computed tomography–based simulation for treatment planning. After treatment completion, patients were followed with physical examinations and surveillance imaging. Information such as RT modality, chemotherapy regimen, RT breaks, chemotherapy dose reductions/deviations, and acute toxicities were collected from chart review. The Common Terminology Criteria for Adverse Events version 5.0 was used for scoring acute and late treatment toxicity. Late toxicity was defined as occurring beyond 6 months from treatment completion. The pelvic bones were retrospectively contoured per Mell et al[23] to act as a surrogate for bone marrow dose.

Treatment

The majority of patients received IMRT, which was used exclusively in 69 patients (92%). Five patients had a combination of 3-dimensional conformal RT with IMRT boost, and 1 patient had only 3-dimensional conformal RT. Almost all patients (99%) received 5FU chemotherapy; 55% received concurrent MMC and 40% received concurrent cisplatin.

Statistical methods

Statistical analysis was conducted using SAS, Version 9.4 (SAS Institute Inc, Cary, NC), and SAS macros developed by Biostatistics Shared Resource at the Winship Cancer Institute.[24] Descriptive statistics for each variable were reported. OS was defined as months from radiation end date to date of death or last follow-up, where those alive were censored at last follow-up date. Local recurrence-free survival (LRFS) was defined as months from radiation end date to date of local recurrence, death, or last follow-up, where those who were either alive without local recurrence or who died without local recurrence were censored at last follow-up date or date of death, respectively. Distant metastasis-free survival (DMFS) was defined as months from radiation end date to date of distant metastasis, death, or last follow-up, where those who were either alive without distant metastasis or who died without distant metastasis were censored at last follow-up date or date of death, respectively. DFS was defined as time from radiation end to local recurrence, distant metastases, or last follow-up. Event-free survival (EFS) was defined as time from radiation end to any event or last follow-up. OS, LRFS, DMFS, DFS, and EFS were estimated using the Kaplan–Meier method. The association with OS, LRFS, DMFS, DFS, and EFS with patient characteristics was assessed by Cox proportional hazards models and log-rank tests. Multivariable Cox proportional hazards models were fit for select variables. Longitudinal CD4 counts were plotted as a function of time from radiation start using locally estimated scatterplot smoothing curves, with 95% confidence limits. Paired assessments of CD4 between time points were evaluated using paired t tests. Pearson correlation coefficients were generated between treatment start date and CD4 count as well as from treatment end date and CD4 count, stratifying by local recurrence. Receiver operating characteristic analysis was used to determine the utility of pelvic bone marrow volumes for various treatment doses for predicting grade 3 hematologic toxicity. Statistical significance was assessed at the .05 level, and all tests were 2-sided unless otherwise specified.

Results

Patient characteristics

The majority were male (92%), Black (78%), and had an Eastern Cooperative Oncology Group performance status 0 to 1 (97%). Median age was 47 years (Range, 31-66 years). Most (87%) patients were receiving ART before initiating CRT, and 6 patients were started on ART after definitive anal cancer treatment was initiated. The median pretreatment CD4 count was 280 cells/mm^3 (Range, 1-2211 cells/mm^3) and viral load 1.6 $\log_{10}$ copies/mL (Range, 0-5.79 $\log_{10}$ copies/mL). Only 13 (17%) had stage I cancer, whereas 21 (28%) had stage II cancers, and the majority (55%) had stage III disease. The median time from biopsy diagnosis to start of treatment was 69 days (Range, 13-356 days). Additional patient and tumor characteristics are listed in Table 1.

Treatment characteristics and deviations

Median RT dose delivered was 54 Gy (Range, 46.8-59.4 Gy) over a median of 44 elapsed days (Range, 32-160 days). RT interruptions were noted in 28 (37%) patients. The median number of elapsed treatment days for those who had RT interruptions due to acute toxicities was 52 days (Range, 47-160 days) compared with 42 days (Range, 32-50 days) in patients without RT interruptions. The median pretreatment CD4 count in the group that received MMC was 284.5 cells/mm^3 (Range, 1-2211 cells/mm^3) compared with a median of 251 cells/mm^3 (Range, 9-1823 cells/mm^3) for the cisplatin group. Chemotherapy deviation was defined as missing one or both cycles of 5FU/cisplatin or 5FU/MMC, with 14 (19%) patients experiencing chemotherapy deviations. Among those with chemotherapy deviations, the majority (71%) received one cycle of full-dose chemotherapy. Three patients received only 5FU with RT, and 1 patient received RT alone without any chemotherapy.

Table 1 Patient and treatment characteristics

Variables	N (%) = 75
Race	
Black	58 (78.4)
White	13 (17.6)
Hispanic	3 (4.1)
Missing	1
Sex	
Male	69 (92.0)
Female	6 (8.0)
Eastern Cooperative Oncology Group Performance Status	
0	17 (22.7)
1	56 (74.7)
2	2 (2.7)
Overall clinical stage	
I	13 (17.3)
II	21 (28.0)
III	41 (54.7)
T stage	
1	15 (20.0)
2	30 (40.0)
3	26 (34.7)
4	4 (5.3)
N stage	
0	34 (45.3)
1	4 (5.3)
2	14 (18.7)
3	23 (30.7)
Antiretroviral use	
No	10 (13.3)
Yes	65 (86.7)
Cisplatin	
No	43 (58.9)
Yes	30 (41.1)
Missing	2
5-Fluoruracil	
No	1 (1.3)
Yes	74 (98.7)
Concurrent mitomycin C	
No	33 (44.6)
Yes	41 (55.4)
Missing	1
Chemotherapy deviation	
No	61 (81.3)
Yes	14 (18.7)
Radiation treatment break	
No	47 (62.7)
Yes	28 (37.3)
Acute grade 2 skin toxicity	
No	12 (16.2)
Yes	62 (83.8)
Missing	1
Acute grade 2 gastrointestinal toxicity	
No	66 (90.4)
Yes	7 (9.6)
Missing	2
Acute grade 3 skin toxicity	
No	59 (80.8)
Yes	14 (19.2)
Missing	2
Acute grade 3 gastrointestinal toxicity	
No	71 (97.3)
Yes	2 (2.7)
Missing	2
Acute grade 3 hematologic toxicity	
No	58 (79.5)
Yes	15 (20.5)
Missing	2
Acute grade 5 toxicity	
No	74 (98.7)
Yes	1 (1.3)
Colostomy posttreatment	
No	68 (90.7)
Yes	7 (9.3)
Age (at start of treatment, y)	
Mean	47.40
Median	47.00
Minimum	31.00
Maximum	66.00
SD	8.38
Missing	0.00
CD4 count (pretreatment, cells/mm^3)	
Mean	368.49
Median	280.00

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Table 1 (*Continued*)

Variables	N (%) = 75
Minimum	1.00
Maximum	2211.00
SD	383.34
Missing	4.00
Viral load (pretreatment, HIV log_{10} copies/mL)	
Mean	1.91
Median	1.60
Minimum	0.00
Maximum	5.79
SD	1.79
Missing	9.00
WBC (pretreatment, K/mcL)	
Mean	7.08
Median	6.70
Minimum	2.40
Maximum	14.30
SD	3.14
Missing	0.00
Absolute neutrophil count (pretreatment, K/mcL)	
Mean	4.44
Median	3.90
Minimum	0.80
Maximum	12.78
SD	2.74
Missing	3.00
Absolute lymphocyte count (pretreatment, K/mcL)	
Mean	1.93
Median	1.80
Minimum	0.20
Maximum	6.90
SD	1.01
Missing	3.00

Abbreviations: HIV = human immunodeficiency virus; SD = standard deviation; WBC = white blood cell.

Oncologic outcomes

With a median follow-up of 5.4 years (Range, 4.37-6.21 years), 17 (23%) patients had local recurrence at a median of 50.0 months (Range, 0.7-153.3 months) from RT completion to time of local recurrence (Fig. 1). Ten (13%) patients presented with isolated local failures, 7 (9%) patients had simultaneous local recurrence and distant metastases, and 2 subjects presented with distant metastases with subsequent local recurrence 23.0 months later (Fig. 2). Five (7%) patients presented with distant metastases alone. Nine (12%) patients died due to progressive disease (Fig. 3). Although 8 (11%) patients had colostomies, only 1 received an elective diverting colostomy before definitive treatment; 4 patients received colostomies because of local recurrence, including 3 patients who had abdominoperineal resection procedures performed after their definitive chemotherapy and RT (Fig. E1). The remaining 3 patients did not have evidence of recurrence at the time of diverting ostomy placement: 2 patients opted for diverting ostomy after experiencing fecal incontinence, and 1 patient required diverting ostomy after developing colonic obstruction.

In univariate analysis, there was significant association between advanced T stage, clinical nodal involvement, chemotherapy deviation, acute and late grade 3 GI toxicity, acute and late grade 3 hematologic toxicity, late grade 5 toxicity, pretreatment white blood count, and pretreatment absolute neutrophil count with worse OS, all $P < .04$ (Table 2). With our sample size, we conducted a limited multivariable Cox regression model with 3 covariates that appeared to have large effect on univariate analysis: chemotherapy deviation, acute grade 3 GI toxicity, and N stage. With multivariate analysis, only clinical N0 stage was associated with a decreased risk of death compared with clinical node-positive disease (hazard ratio, 0.39, 95% confidence interval, 0.16-1.00, $P = .049$, Table 3). No associations were seen for those 3 covariates with LRFS, DMFS, and EFS. For LRFS, chemotherapy deviation, acute and late grade 3 GI toxicity, late grade 3 hematologic toxicity, late grade 3 skin toxicity, and older age were associated with worse outcomes ($P < .05$) on univariate analysis.

Trends in CD4 counts

The median pretreatment CD4 count was 280 cells/mm^3. However, CD4 counts dropped after treatment with median 6 months' posttreatment CD4 count at 87 cells/mm^3 ($P < .001$) and remained low at 12 months' posttreatment, at 182 cells/mm^3 ($P < .001$). A trajectory plot of available CD4 counts in relation to local recurrence after CRT is depicted in Fig. E2. We did not observe significantly significant differences in CD4 counts among patients with or without high-grade acute toxicities. The Pearson correlation coefficients for months from CD4 date to RT start date were 0.085 ($P = .1$) and −0.003 ($P = .9$) for no local recurrence and local recurrence, respectively. For months from CD4 date to RT end date, the Pearson correlation coefficients were 0.085 ($P = .1$)

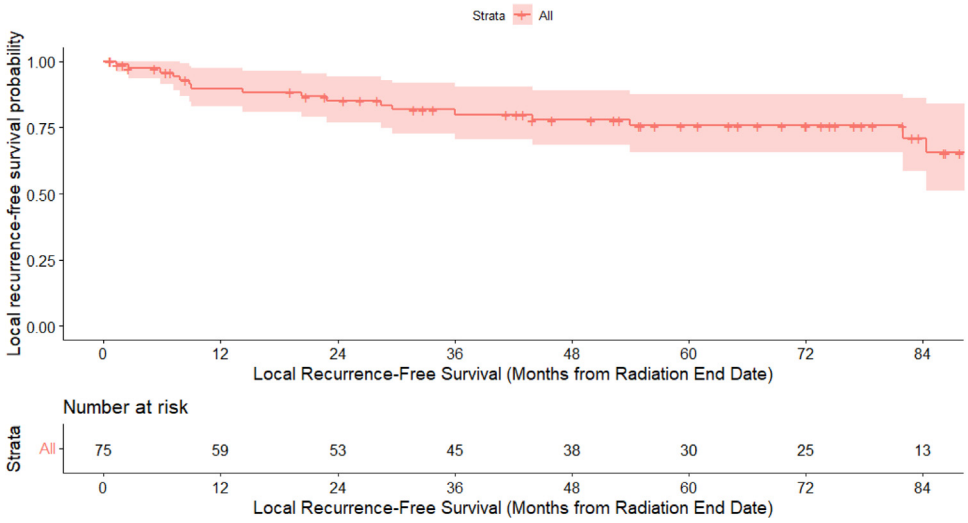

Figure 1 Local recurrence-free survival curve for 75 patients with HIV and anal cancer treated with definitive chemotherapy and radiation therapy.

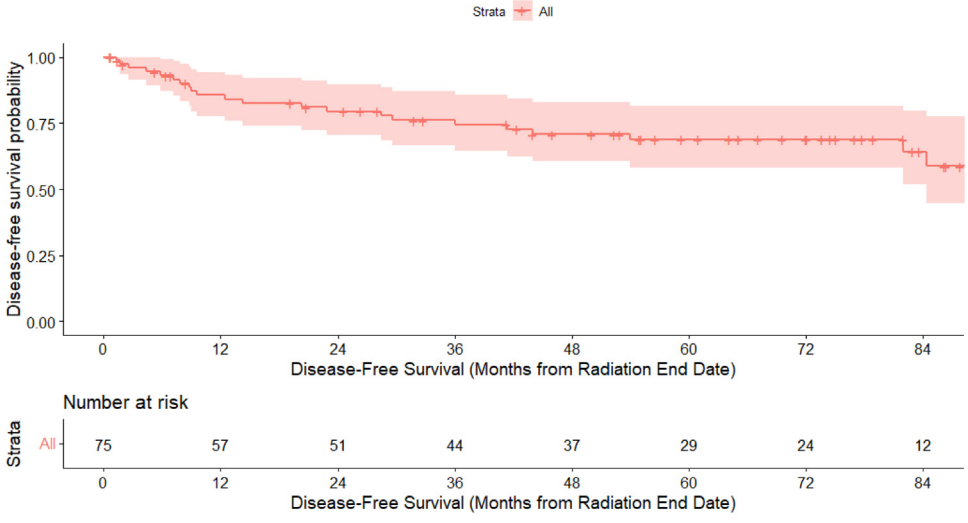

Figure 2 Disease-free survival curve for 75 patients with HIV and anal cancer treated with definitive chemotherapy and radiation therapy.

and 0.006 ($P = 1$) for no local recurrence and local recurrence, respectively.

Acute toxicities from treatment

The majority (84%) of patients experienced acute grade 2 dermatologic toxicity, and 14 (19%) had grade 3 dermatologic toxicity. GI toxicities were infrequent, with 7 (10%) experiencing grade 2 GI toxicities and 2 (3%) with grade 3 GI toxicities. Fifteen (21%) of patients experienced grade 3 hematologic toxicity. There was 1 grade 5 adverse event from sepsis.

No significant associations were seen in the receiver operating characteristic analysis comparing different bone marrow dose-to-volume relationships in predicting for grade 3 hematologic toxicities. Multiple dose levels from 5 to 50 Gy were modeled.

Late toxicities from treatment

Among the patients who experienced late toxicities from RT, GI toxicities were the most frequent (Table E1). The most common GI toxicity was grade 2 (n = 39), followed by grade 3 (n = 16). There were 2 grade 5 GI toxicities of bowel ischemia that were graded as possibly from therapy. Late grade 2 dermatologic toxicities were seen in 19 patients, and 12 patients had grade 3 dermatologic toxicity.

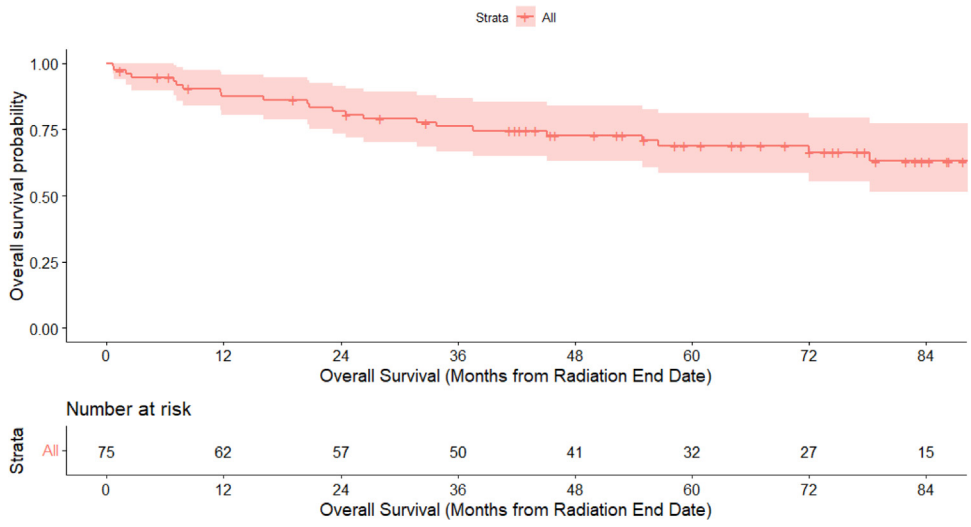

Figure 3 Overall survival curve for 75 patients with HIV and anal cancer treated with definitive chemotherapy and radiation therapy.

Table 2 Univariate overall survival analysis

		Overall survival*		
Covariate	**N**	**HR(95% CI)**	**HR *P***	**Log-rank *P***
Race				
Black	58	1.34 (0.46-3.95)	.594	.592
Other	16	—	—	
Sex				
Male	69	1.11 (0.26-4.73)	.890	.890
Female	6	—	—	
Eastern Cooperative Oncology Group Performance Status				
0	17	0.64 (0.22-1.88)	.416	.413
>0	58	—	—	
Overall clinical stage				
1	13	0.15 (0.02-1.12)	.064	.073
2	21	0.58 (0.23-1.49)	.260	
3	41	—	—	
T stage				
1	15	0.10 (0.01-0.78)	**.028**	**.013**
2	30	0.46 (0.19-1.11)	0.084	
3/4	30	—	—	
N stage				
0/1	38	0.33 (0.13-0.81)	**.016**	**.042**
2	14	0.60 (0.19-1.90)	.385	
3	23	—	—	
Cisplatin				
Yes	30	0.95 (0.40-2.26)	.900	.899

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Table 2 (*Continued*)

		Overall survival*		
Covariate	**N**	**HR(95% CI)**	**HR *P***	**Log-rank *P***
No	43	—	—	
Mitomycin C				
Yes	41	1.11 (0.48-2.57)	.811	.811
No	33	—	—	
Chemotherapy deviation				
Yes	14	2.72 (1.11-6.67)	**.029**	**.023**
No	61	—	—	
Radiation treatment break				
Yes	28	1.74 (0.77-3.95)	.185	.179
No	47	—	—	
Acute grade 2 skin toxicity				
Yes	62	1.58 (0.47-5.31)	.463	.459
No	12	—	—	
Acute grade 2 gastrointestinal toxicity				
Yes	7	2.59 (0.88-7.64)	.085	.073
No	66	—	—	
Acute grade 3 skin toxicity				
Yes	14	1.24 (0.46-3.36)	.667	.667
No	59	—	—	
Acute grade 3 gastrointestinal toxicity				
Yes	2	8.02 (1.76-36.45)	**.007**	**.001**
No	71	—	—	
Acute grade 3 hematologic toxicity				
Yes	15	2.71 (1.15-6.41)	**.023**	**.018**
No	58	—	—	
Acute grade 5 toxicity				
Yes	1	—	—	**<.001**
No	74	—	—	
Late grade 2 skin toxicity				
Yes	20	1.18 (0.44-3.14)	.746	.745
No	40	—	—	
Late grade 2 gastrointestinal toxicity				
Yes	41	0.69 (0.28-1.73)	.432	.430
No	22	—	—	
Late grade 3 skin toxicity				
Yes	12	1.58 (0.52-4.81)	.423	.419
No	50	—	—	
Late grade 3 gastrointestinal toxicity				
Yes	17	4.25 (1.72-10.51)	**.002**	**<.001**
No	45	—	—	

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Table 2 (*Continued*)

Covariate	N	Overall survival* HR(95% CI)	HR *P*	Log-rank *P*
Late grade 3 hematologic toxicity				
Yes	4	13.40 (4.10-43.79)	**<.001**	**<.001**
No	58	—	—	
Late grade 5 toxicity				
Yes	2	17.37 (3.48-86.76)	**<.001**	**<.001**
No	61	—	—	
Age (at start of treatment, y)	75	0.97 (0.92-1.02)	.219	—
CD4 count (pretreatment, cells/mm^3)	71	1.00 (1.00-1.00)	.297	—
Viral load (pretreatment, HIV $\log_{10}$ copies/mL)	66	1.05 (0.82-1.34)	.720	—
White blood count (pretreatment, K/mcL)	75	1.22 (1.07-1.38)	**.002**	—
Absolute neutrophil count (pretreatment, K/mcL)	72	1.28 (1.11-1.48)	**<.001**	—
Absolute lymphocyte count (pretreatment, K/mcL)	72	0.89 (0.59-1.36)	0.597	—

Abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; HR = hazard ratio.
*Overall survival is defined as months from radiation therapy completion.
Bolded values are stastically significant.

Table 3 Multivariable overall survival analysis

Covariate	N	Overall survival HR (95% CI)	HR *P*
Chemotherapy deviation			
Yes	14	2.55 (0.91-7.15)	.076
No	59	—	—
Acute grade 3 gastrointestinal toxicity			
Yes	2	2.65 (0.47-15.05)	.272
No	71	—	—
N stage			
0	33	0.39 (0.16-1.00)	**.049**
1-3	40	—	—

Abbreviations: CI = confidence interval; HR = hazard ratio.

Discussion

HIV infection is a well-known risk factor for the development of anal cancer. In this population of patients with HIV and anal cancer, we report that 23% experienced local recurrence, whereas a minority (7%) presented with distant metastases alone as their only site of disease progression. Thus, treatment failure at the primary site is still a major concern in PLWHA with anal cancer. In addition, a sizable portion of patients experienced acute and late toxicities from treatment. Even though most patients in our study received modern IMRT techniques, many (37%) patients required treatment breaks from RT, and 19% of patients had chemotherapy deviations. Similarly, for patients participating in the Radiation Therapy Oncology Group (RTOG) 0529 trial of dose painted-IMRT, treatment breaks were needed in 49% patients, and 16% of patients were scored as not completing both cycles of MMC and 5FU per protocol.[11] In another study, Wexler et al[16] also noted high rates of RT interruptions among patients with HIV and anal cancer, with more than two-thirds of their patients requiring RT breaks.

Among acute toxicities during CRT, we observed 19% of patients having grade 3 dermatologic toxicity, 21% having grade 3 hematologic toxicities, and 3% having grade 3 GI toxicities. Although our acute toxicities may appear lower than those reported in RTOG 0529 (23% with grade 3 dermatologic, 58% with grade 3 hematologic, and 21% with grade 3 GI toxicities), our study was retrospectively collected, unlike the prospective nature of RTOG 0529. Our observed rates of acute toxicities were similar to other reports of acute toxicities in patients with HIV treated with CRT: grade 3 skin toxicity in 25%, grade 3 diarrhea in 28%, grade 3 hematologic toxicity in 21%, and grade 4 hematologic in 48%.[16] Lymphopenia during and after CRT is common even in patients who are uninfected by HIV. A recent report noted that lymphopenia did not appear to be associated with worse OS, local control, or distant metastases in patients with anal cancer uninfected by HIV, but HIV infection was independently associated with death on multivariable analysis; however, this study notably had <5% of PLWHA in their series.[25] Our data suggest that acute grade 3 hematologic toxicity remains a frequent toxicity in patients with HIV undergoing anal cancer treatment.

Several late toxicities were still observed 6 months after RT, with the most frequent as grade 2 GI toxicities. Some patients continued to have severe GI toxicities, with 16 patients noted to have grade 3 GI toxicities. There were 2 grade 5 GI toxicities of bowel ischemia that were possibly from treatment: one at 6 months posttherapy and the other at 2 years posttreatment. Our study demonstrates that patients with HIV and anal cancer may continue to suffer from late toxicities many months to years from definitive anal cancer treatment.

Quality of life among PLWHA may be significantly affected by anal cancer treatment, but our study did not collect such data. Despite the high frequency of toxicities associated with anal cancer treatment, only a handful of studies have tracked patient-reported outcomes (PROs) during anal cancer treatment.[26-29] Some groups have noted a discrepancy between PROs compared with physician-reported toxicities, and many patients required treatment breaks (29%-45%) even with the adoption of IMRT.[27,29] Even less is known regarding how the quality of life of patients with HIV is affected during anal cancer treatment, as patients with HIV comprised a small minority of the studied populations (7.7%-19%).[30] Although our study did not collect prospective PROs, understanding the effect of PROs among PWLHA with anal cancer is needed.

ART is essential in controlling HIV infection and, as ART changes, the interaction with antineoplastic agents continues to be investigated. Significant changes in ART have improved compliance and tolerability of ART, leading to more patients with HIV living longer. However, concern has been raised about ART's association with relapse and increased toxicities with anal cancer among PLWHA. Pappou et al[31] noted that ART was associated with a greater rate of relapse in patients with HIV. Wexler et al reported that although patients with HIV taking ART had comparable oncologic outcomes with those uninfected with HIV, patients with HIV had greater rates of toxicities, with more than two-thirds of patients requiring RT interruptions due to toxicities.[16] One theory is that HIV protease inhibitors inhibit AKT signaling and increase radiation sensitivity to contribute to radiation-induced apoptosis,[18,32] thereby increasing high-grade toxicities in patients with HIV during treatment for anal cancer. Yoder et al[33] recently reported that use of protease inhibitors during CRT for anal cancer treatment did not appear to be associated with any clinical outcome or increase in nonhematologic toxicity, but observed a statistically significant association with increased hospitalizations for hematologic toxicities. Thus, it is crucial for future studies to clarify optimal treatment for patients with HIV on ART, albeit challenging because many prospective trials exclude PWLHA.

Concerns for toxicity are heightened in PWLHA with anal cancer because of its potential association of decreased local control and survival.[15,17,34] Pretreatment and posttreatment CD4 count is associated with increased acute hematologic toxicity, hospitalization for toxicity, and tumor recurrence in patients positive for HIV.[13,16,35] Bryant et al[13] reported that each 100-cells/mm^3 decrease in posttreatment CD4 count increased the risk of recurrence by 54%. Decreased CD4 count after CRT is associated with increased acute toxicity, increased tumor recurrence, and prolonged suppression of CD4 counts[13,16,35]; decreasing hematologic toxicity is important in decreasing side effects, rates of hospitalization, and risk of recurrence.[13] Prolonged suppression of CD4 counts is observed even 1-year posttreatment, exposing patients infected with HIV to cancer recurrence and opportunistic infections.[35] Although we did not observe statistically significant associations with CD4 counts with local recurrence, we may have been limited by our sample size of 75 patients.

Our study has limitations, given its retrospective nature and single-institution cohort. Although our study cohort incorporates one of the larger sample sizes of patients with HIV infection and anal cancer in the modern era, the overall number of patients may be too small to detect relationships between CD4 counts and oncologic outcomes, such as local recurrence or OS. One strength of our study is that our population contains a significant proportion of Black patients. Such a patient distribution in race is important, because the Centers for Disease Control and Prevention reported that, in 2018, Black subjects made up 42% of the 37,968 new HIV diagnoses in the United States and dependent areas.[36] More specifically, 26% of the new HIV diagnoses were among Black gay and bisexual men.[37] With the rates of anal cancer incidence and HIV infection continuing to rise, it is likely that we

will continue to see an increase in Black PWLHA diagnosed with anal cancer.

Of note, the majority of our patients were treated with IMRT. The one acute grade 5 toxicity was seen in a patient with stage III cancer who was treated with 3-dimensional fields initially. The patient did not complete treatment secondary to septic shock, which was likely related to severe desquamation in the groin from RT and pancytopenia from 5FU/MMC. However, direct comparisons between IMRT versus 3DCRT cannot be made with the limited numbers of patients treated with 3DCRT.

One strategy to improve toxicity and outcomes in PLWHA with anal cancer is focusing on anal cancer prevention. The recent findings of the randomized controlled Anal Cancer/HSIL Outcomes Research (ANCHOR) trial have been encouraging. The study was conducted in PLWHA with precursor lesions and determined that the removal of high-grade squamous intraepithelial lesions significantly reduced the chances of progression to anal cancer compared with those on active monitoring.[38] Thus, more attention toward early detection and screening in this high-risk population is warranted.

Another rising arena in anal cancer prevention is the quadrivalent HPV (qHPV) vaccine. Palefsky et al[39] reported the results of a randomized controlled trial that randomized healthy HIV-uninfected MSM to qHPV vaccine or placebo to evaluate the efficacy of qHPV vaccine in preventing anal intraepithelial neoplasia (including condyloma) and anal cancer related to HPV-6, -11, -16, or -18 infection. The vaccinated group had reduced the rates of anal intraepithelial neoplasia compared with the placebo group, and no vaccine-related serious adverse events were reported; notably, no anal cases of anal cancer was seen in this group of young men. More research on the qHPV vaccine in PWLHA may be critical in decreasing the incidence of anal cancer in the future.

Until anal cancer can be actively prevented, definitive cancer treatment for PLWHA with anal cancer needs to be further investigated. Studies that have focused on PLWHA with anal cancer have been mostly small and retrospective. Our study suggests that many patients with HIV and anal cancer can achieve good local control; however, the treatment comes at the cost of potentially severe acute and late toxicities, treatment interruptions, and persistently depressed CD4 counts. Additional attention to supportive care during treatment as well as more inclusion of PWLHA in prospective trials for anal cancer are needed.

Conclusions

Local recurrence, severe treatment toxicity, and suppressed CD4 counts continue to be problematic in patients with HIV and anal cancer despite improvements in RT techniques with IMRT. Clinical nodal involvement appears to be associated with worse OS and emphasis on early diagnosis, aggressive screening, and prevention in this high-risk population may be warranted. Further investigations including the HIV-infected population with anal cancers are urgently needed.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101155.

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