Title

Factors Impacting Differential Outcomes in the Definitive Radiation Treatment of Anal Cancer Between HIV-Positive and HIV-Negative Patients.

Journal

The oncologist, 25(9)

ISSN

1083-7159

Authors

Susko, Matthew
Wang, Chia-Ching Jackie
Lazar, Ann A
et al.

Publication Date

2020-09-01

DOI

10.1634/theoncologist.2019-0824

Peer reviewed

The Oncologist®

Gastrointestinal Cancer

Factors Impacting Differential Outcomes in the Definitive Radiation Treatment of Anal Cancer Between HIV-Positive and HIV-Negative Patients

Matthew Susko,[a,b] Chia-Ching Jackie Wang,[c,d] Ann A. Lazar,[a] Stephanie Kim,[d] Angela Laffan,[b] Mary Feng,[a,b] Andrew Ko,[b,c] Alan P. Venook,[b,c] Chloe E. Atreya,[b,c] Katherine Van Loon,[b,c] Mekhail Anwar[a,b]

[a]Department of Radiation Oncology, [b]Helen Diller Family Comprehensive Cancer Center, and [c]Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, California, USA; [d]Zuckerberg San Francisco General Hospital, San Francisco, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Anal cancer • HIV-positive • Radiation therapy

Abstract

Background. Anal squamous cell carcinoma (ASCC) is uncommon, yet seen more frequently in the setting of the human immunodeficiency virus (HIV). Chemoradiotherapy is the definitive modality of treatment for patients with ASCC; this study examines factors impacting clinical outcomes in a large cohort of HIV-positive and HIV-negative patients.

Methods. A retrospective review was conducted of patients treated for nonmetastatic ASCC at a single institution between 2005 and 2018. Freedom from local recurrence (FFLR), freedom from distant metastasis, and overall survival (OS) were calculated using the Kaplan-Meier method, and univariate and multivariate analysis were performed using the Cox proportional hazards model.

Results. During the study period, 111 patients initiated definitive treatment for ASCC. Median age of the entire cohort was 56.7 years (interquartile range, 51.5–63.5), with 52 patients (46.8%) being HIV-positive. At median follow-up of 28.0 months, the 2- and 5-year FFLR were 78.2% (95% confidence interval [CI], 70.4–87.0) and 74.6% (95% CI, 65.8–84.5), respectively. Multivariate analysis revealed time from diagnosis to treatment initiation (median, 8 weeks; hazard ratio, 1.06; 95% CI, 1.03–1.10) to be significantly associated with worse FFLR and OS. HIV-positive patients had a trend toward worse FFLR (log-ranked p = .06). For HIV-positive patients with post-treatment CD4 less than 150 cells per mm^3, there was significantly worse OS (log-ranked p = .015).

Conclusion. A trend toward worse FFLR was seen in HIV-positive patients, despite similar baseline disease characteristics as HIV-negative patients. Worse FFLR and OS was significantly associated with increased time from diagnosis to treatment initiation. Poorer OS was seen in HIV-positive patients with a post-treatment CD4 count less than 150 cells per mm^3. ***The Oncologist*** 2020;25:772–779

Implications for Practice: Human immunodeficiency virus (HIV)-positive patients with anal squamous cell carcinoma can represent a difficult clinical scenario. Definitive radiation with concurrent chemotherapy is highly effective but can result in significant toxicity and a decrease in CD4 count that could predispose to HIV-related complications. As HIV-positive patients have largely been excluded from prospective clinical trials, this study seeks to provide greater understanding of their outcomes with radiation therapy, potential predictors of worse local control and overall survival, and those most at risk after completion of treatment.

Introduction

Anal squamous cell carcinoma (ASCC) is an relatively uncommon malignancy, with approximately 8,200 new patients diagnosed each year in the U.S. [1]. During the 1990s to 2010s, there was an increasing incidence of ASCC noted predominantly in patients positive for human immunodeficiency virus (HIV); however, contemporary trends note an increasing rate in standard risk patient populations [2, 3]. A large contribution to this epidemiological shift has been

Correspondence: Mekhail Anwar, M.D., Ph.D., 1825 4th St., Department of Radiation Oncology, San Francisco, CA 94158, USA. Telephone: 415–502–7222; e-mail: mekhail.anwar@ucsf.edu Received October 29, 2019; accepted for publication April 10, 2020; published Online First on June 4, 2020. http://dx.doi.org/10.1634/theoncologist.2019-0824

associated with sexual behavior, human papilloma virus prevalence, and continued improvement in survival among HIV-positive patients because of increasing use of antiretroviral therapy (ART) [4, 5].

In HIV-positive patients, the risk of developing ASCC is 40–80-fold higher compared with the general population [4]. Additionally, worse colostomy-free survival and higher recurrence rates have been associated with lower post-treatment CD4 counts [6, 7]. Impaired immunity plays a role in both the development of ASCC and increased rate of recurrent disease after treatment completion in HIV-positive individuals. This may be compounded by the impact of socioeconomic factors in the HIV-positive population, which correlate with poorer prognosis [8].

In patients diagnosed with localized disease, the standard of care remains definitive treatment with radiation therapy and concurrent mitomycin-C (MMC) and 5-florouracil (5-FU), also known as the Nigro regimen [9–12]. This regimen results in a local control rate of 60%–70% but may cause significant life-threatening toxicities related to treatment [13, 14]. Alternative chemotherapy regimens have been investigated, but none have been found to be more effective than the Nigro regimen [14–17]. Additionally, trials investigating ASCC treatments typically exclude HIV-positive patients, making it difficult to assess the optimal treatment for this population.

Understanding the factors that affect treatment and outcomes for patients with ASCC is critical for providing patients the maximal chance of achieving a cure while also limiting severe dose-limiting toxicities. Studies have shown that extended total treatment time and treatment breaks can negatively impact the efficacy of chemoradiotherapy [18–20]. A key goal of the current study is to better understand which factors most significantly affect ASCC outcomes in HIV-positive patients. To further elucidate opportunities for improvement of care and outcomes, we aimed to evaluate predictors of clinical outcomes of ASCC treatment among both HIV-positive and HIV-negative patients.

Materials and Methods

Patients

All patients with biopsy-proven ASCC who received definitive treatment at a single institution between January 1, 2005, and May 1, 2018, were retrospectively reviewed. Prior to initiation of treatment, all patients underwent staging with contrast-enhanced positron emission tomography (PET)-computed tomography (CT), or CT studies, to exclude the presence of distant metastases. Only patients with localized or locally advanced disease who were treated with definitive radiation therapy, with or without chemotherapy, were included in this analysis. Baseline patient characteristics including age, gender, disease staging, and HIV status were abstracted from the medical record. All patients without a known diagnosis of HIV underwent HIV testing prior to initiation of therapy. For HIV-positive patients, use of ART as well as baseline and post-treatment CD4 counts and viral loads (VL) were collected for analysis. Over this time period, there were no absolute institutional cutoffs based on CD4 count that resulted in specified changes to oncologic treatment for these patients.

Treatment and Follow-Up

All patients were seen in consultation by a medical oncologist and radiation oncologist after initial pathologic diagnosis. Decisions regarding treatment, including specific chemotherapy and radiation therapy regimens, were decided by our multidisciplinary care team. Prior to initiation of radiation therapy, a CT simulation for planning and delineations of gross tumor volume, tissues harboring microscopic disease, and neighboring organs at risk was performed. Over the study period, both three-dimensional conformal radiation therapy and intensity modulated radiation therapy plans were used. While on treatment, patients were seen at least on a weekly basis to assess treatment response, acute toxicities, and ongoing medical needs. It was at the discretion of the providers to determine the need for treatment breaks, modifications to the treatment regimen, or any other alterations to the treatment plan.

The choice for chemotherapy regimen was at the discretion of the treating providers, with standard dosing based upon our institutional protocol: infusional 1000 5-FU mg/m^2 per day on days 1–4 and 29–32 and 10 mg/m^2 MMC via infusion on days 1 and 29. Prior to the second cycle of chemotherapy patients were assessed for the need for dose reductions of either agent based on the accumulated toxicity (hematologic, mucosal, gastrointestinal, etc.). Reductions of chemotherapy from the standard protocol were abstracted from the medical record.

Elapsed treatment time was evaluated retrospectively and was calculated from the calendar date of the first fraction of radiation to the calendar date of the final fraction, inclusive of nontreatment days for weekends and treatment breaks. Date of diagnosis was defined as the date of biopsy-proven invasive malignancy or the date of the diagnostic staging study, if the biopsy date was not available on chart review. Time to initiation of treatment was calculated as the time elapsed from date of diagnosis to the date of the first fraction of radiation. Radiation intensity was calculated retrospectively as the total prescribed dose over the elapsed treatment time in days [18]. The median value of these variables served as a categorical stratification for further analysis of local recurrence and overall survival. Evaluation for recurrence was based on post-treatment diagnostic imaging, including PET-CT, as well as clinical exam with anoscopy. Patients considered to have recurrent disease by these methods were censored at the earliest date of abnormality being found on these exams.

Statistical Analysis

Statistical analysis was performed with the assistance of the departmental statistician (A.A.L.). Categorical variables were compared using the χ^2 or Fisher's exact test. Survival characteristics were calculated from the date of final radiation treatment until censoring at the time of an event, or the last clinical or imaging follow-up. Freedom from local recurrence (FFLR) was defined as the time from last radiation treatment to locally recurrent disease or last follow-up; freedom from distant metastasis (FFDM) was defined as the time from last radiation treatment to distant recurrence of disease or last

follow-up, and overall survival (OS) was the time from last radiation treatment to date of death or last follow-up. Survival analysis was performed using the Kaplan-Meier method, with the log-rank test for significance at a p value of .05. Variables known to be associated with outcomes including, age, gender, T-stage, N-stage, HIV status, time from diagnosis to treatment, and treatment duration were prespecified for use in analysis. Numerical variables including CD4 count, time from diagnosis to treatment, and treatment duration were planned for dichotomized at approximate median values for evaluation of differential outcomes. Additional subgroup analysis was planned for patients receiving the Nigro regimen. Univariate Cox proportional hazards model was performed to assess which factors were associated with FFLR and OS. Multivariable Cox proportional hazards model assessed variables simultaneously that were previously tested in the univariate model. Hazard ratios and associated confidence intervals were presented to assess the magnitude of the association and its uncertainty. Two-sided p values less than .05 were considered statistically significant. All statistical analyses were performed using R Studio (Rstudio).

Results

During the study period, 111 patients initiated definitive treatment for ASCC at a single institution. The median age was 57 years; 76 (68.5%) of the patients were men and 35 (31.5%) were women. Of the 111 patients, the median follow-up was 28.0 months (interquartile range [IQR], 10.7–65.5), with additional patient characteristics available on Table 1. Fifty-two patients (46.8%) were known to be HIV-positive at the time of treatment, with a significant difference in age between HIV-positive and HIV-negative patients (54 vs. 63 years; $p < .001$). HIV-positive patients were predominantly male (95% vs. 44%; $p < .001$). Nearly all HIV-positive patients (50 patients, 96%) were already on ART at the time of ASCC diagnosis, and two (4%) either refused or did not require initiation of ART. Median CD4 count in HIV-positive patients prior to initiation of treatment was 382 (IQR, 242–577) cells per mm^3, with most patients having an undetectable VL (range, 0–127,627 IU/mL). Median post-treatment CD4 value was 137 (IQR, 89–242) cells per mm^3, with the majority of patients (82%) having an undetectable VL (range, 0–118,866 IU/mL). Post-treatment CD4 count was obtained at a median of 2 months (IQR, 1–6). Over the course of treatment, this reflected a median of a 67.0% (IQR, 49.5–77.0) drop in CD4 counts among patients in this cohort.

Of the entire cohort, 110 patients were treated with definitive chemoradiotherapy, with 1 patient being treated with radiation therapy alone due to multiple comorbid conditions including HIV and hepatitis B and C. Combination 5-FU/MMC was used for 104 patients, three received weekly 5-FU/cisplatin, and three received an alternative regimen with either capecitabine or 5-FU alone. Of the patients receiving the Nigro regimen 42 (40.4%) required dose reduction of their second cycle of chemotherapy (day 29) of MMC, 5-FU, or both. In total, 17 of those patients were HIV-positive and 25 HIV-negative. Of patients requiring dose reduction, the median reduction for MMC was 50% (IQR, 25%–50%) and for 5-FU was 25% (IQR, 20%–50%). The median radiation dose to the primary tumor was 5580 cGy (IQR, 5400–5800) with treatments being delivered in a median of 30 fractions (IQR, 28–31). Further description of the treatment characteristics can be found in Table 2.

Table 1. Patient characteristics

Characteristics	HIV+	HIV-	p value
Total patients (n = 111)	52	59	
Median age	54	62.7	<.001
Median BMI	26.2	24.4	.15
Gender			
Male	50	26	<.001
Female	2	33	
T-Stage			.85
T1	13	13	
T2	26	31	
T3	12	12	
T4	1	3	
N-Stage			
Negative	34	29	.19
Positive	18	30	
HAART			
Yes	50		
No	2		
Median pretreatment CD4, cell per mm^3	382		
Median pretreatment viral load, cells per *IU*	0 (undetected)		

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

The median time from initial diagnosis to initiation of definitive treatment was 7.8 (IQR, 5.9–10.0) weeks, with HIV-negative patients taking a median of 7.6 weeks to initiate treatment versus 8.7 weeks for HIV-positive patients (p = .21). A total of 108 patients completed their course of definitive radiation therapy, with one HIV-positive patient and two HIV-negative patients who did not complete the prescribed course and refusing further treatment at a mean dose of 4320 cGy. Chemotherapy dose reductions were not significantly different for HIV-positive patients overall (p = .45), for MMC (p = .25), or for 5-FU (p = .07). The median number of elapsed calendar days for completion of radiation therapy was 50 (IQR, 44 – 56), with no statistically significant difference between HIV-positive and HIV-negative patients (p = .84). Radiation intensity was calculated for each patient with a median value of 110.2 cGy/day (IQR, 99.3– 124.4).

During the follow-up period, there were 23 local failures with an overall 2-year and 5-year FFLR of 78.2% (95% confidence interval [CI], 70.4–87.0) and 74.6% (95% CI, 65.8–84.5), respectively. In the overall cohort, the 2-year FFLR for HIV-positive patients was 71.3% (95% CI, 58.7–86.7), compared with 83.5% (95% CI, 74.2–94.0) for HIV-negative patients, which trended toward significance (p = .057) and is displayed in Figure 1. When evaluating patients receiving the Nigro regimen, a significant difference was found between HIV-positive and HIV-negative patients with 2-year FFLR of

Table 2. Treatment characteristics

Characteristics	HIV+	HIV-	*p* value
Chemotherapy			.06
5-FU/MMC	47	57	
5-FU/cisplatin	3	0	
Other	1	2	
None	1	0	
Median radiation dose (IQR), cGy	5,580 (5400–5,580)	5,580 (5400–5,600)	.87
Median radiation fractions (IQR)	30 (28–31)	30 (28–31)	.70
Median diagnosis to RT start time (IQR), wk	8.7 (6.7–12.2)	7.6 (5.6–9.7)	.21
Median RT duration (IQR), d	50 (43–57)	50 (44–55)	.84
RT intensity	108.0 (98.7–124.7)	111.6 (99.6–124.2)	.77
Diagnosis to RT start ≥8 wk			.31
Yes	28	25	
No	24	34	
RT duration ≥50 d			
Yes	28	32	.99
No	24	27	
RT intensity ≥110 cGy/d			.3
Yes	23	33	
No	29	26	

Abbreviations: 5-FU, 5-florouracil; HIV-, human immunodeficiency virus negative; HIV+, human immunodeficiency virus positive; IQR, interquartile range; MMC, mitomycin-C; RT, radiotherapy.

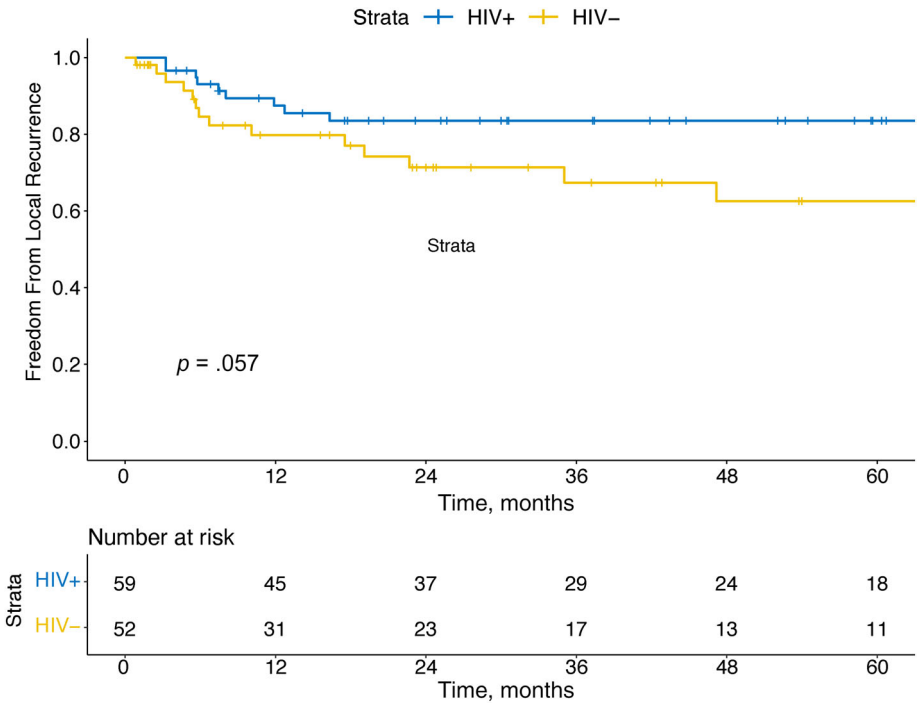

Figure 1. Freedom from local recurrence stratified by HIV status with log-ranked *p* value.
Abbreviations: HIV-, human immunodeficiency virus-negative; HIV+, human immunodeficiency virus-positive.

67.8% (95% CI, 54.1–84.9) and 86.4% (95% CI, 77.5–96.3), respectively (p = .01). For patients who required >50 days to complete radiation therapy, the 2-year FFLR was significantly lower at 70.3% (95% CI, 59.3–83.2), compared with 89.4% (95% CI, 79.9–99.9) for those taking <50 days (p = .029), as shown in Figure 2.

On univariate analysis, increased time from diagnosis to treatment initiation, elapsed radiation therapy duration, and advanced stage were all significantly associated with local recurrence ($p \leq .001$). The results of the univariate and multivariate analyses are reported in Table 3. When compared on multivariate analysis, each factor remained significant, with

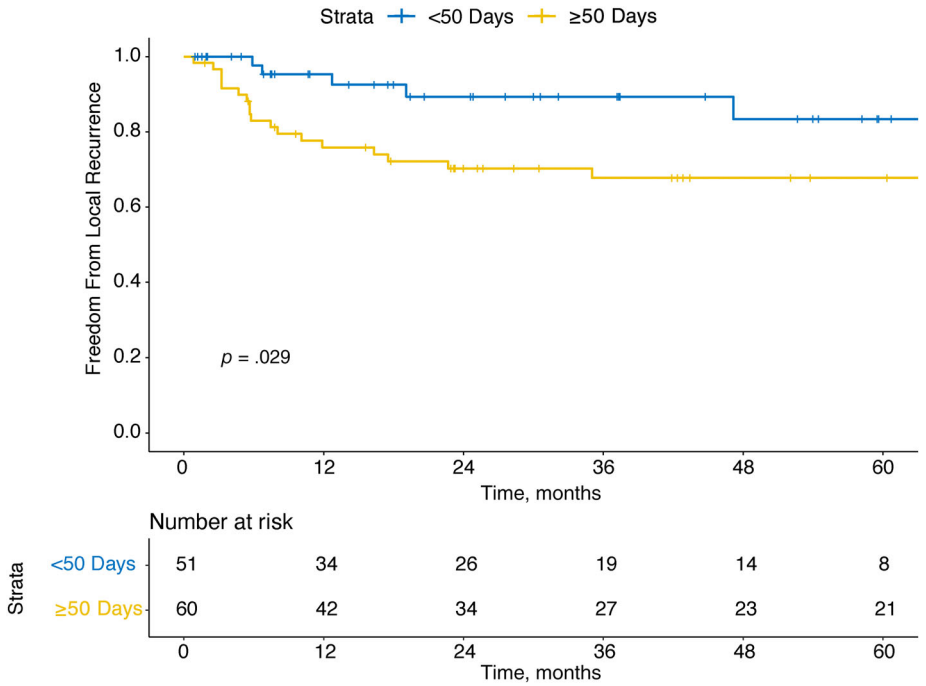

Figure 2. Freedom from local recurrence stratified by elapsed treatment duration with log-ranked *p* value.

Table 3. Univariant and multivariate analysis for factors affecting freedom from local recurrence

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age	0.998 (0.958–1.040)	.92		
Gender (M to F)	2.659 (0.904–7.820)	.076		
HIV status (HIV- to HIV+)	2.207 (0.955–5.100)	.0641	1.69 (0.701–4.073)	.242
T-Stage	4.431 (1.932–10.160)	<.001	4.373 (1.826–10.47)	<.001
N-Stage	1.945 (0.850–4.450)	.115		
Diagnosis to RT initiation, wk	1.05 (1.024–1.077)	<.001	1.063 (1.032–1.095)	<.001
RT duration, d	1.052 (1.022–1.083)	<.001	1.042 (1.013–1.078)	.005

Abbreviations: CI, confidence interval; F, female; HIV-, human immunodeficiency virus negative; HIV+, human immunodeficiency virus positive; HR, hazard ratio; M, male; RT, radiotherapy.

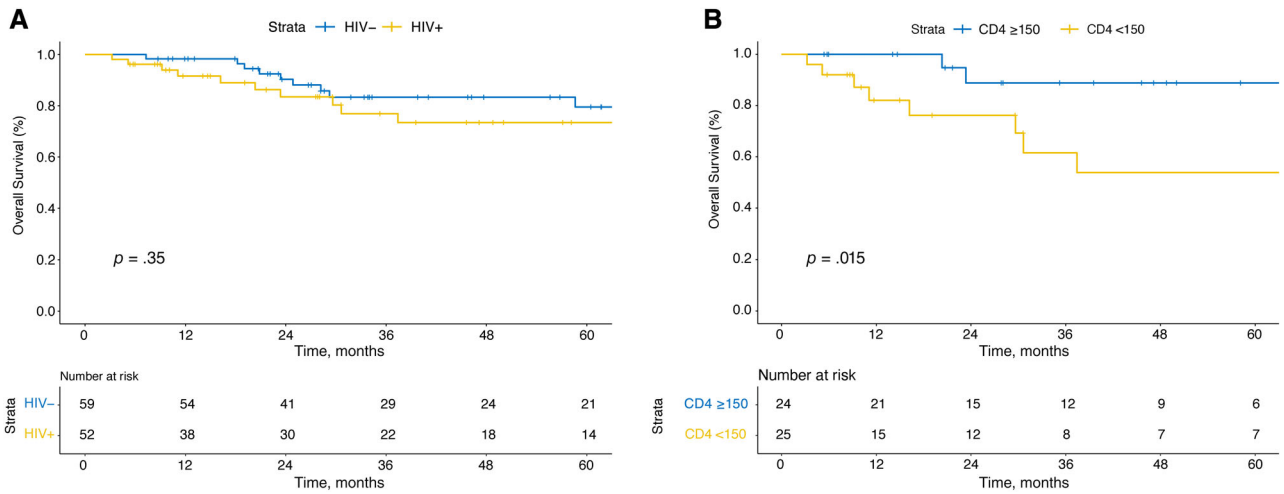

Figure 3. Overall survival by HIV status and CD4 count. **(A):** Overall survival by HIV status with log-ranked *p* value. **(B):** Overall survival by stratified post-treatment CD4 count in HIV+ patients.
Abbreviations: HIV-, human immunodeficiency virus-negative; HIV+, human immunodeficiency virus-positive.

Table 4. Univariate and multivariate analysis for factors affecting overall survival

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age	1.020 (0.975–1.0660)	.391		
Gender (M to F)	1.691 (0.619–4.6220)	.306		
HIV status (HIV- to HIV+)	1.502 (0.666–3.5380)	.353	1.457 (0.598–3.551)	.407
T-Stage	1.939 (0.774–4.8590)	.158	1.856 (0.705–4.884)	.21
N-Stage	2.259 (0.943–5.4080)	.067	2.420 (0.972–6.026)	.058
Diagnosis to RT Initiation	1.02 (1.001–1.0400)	.043	1.024 (1.003–1.045)	.027
RT Duration	1.016 (0.984–1.0650)	.5		

Abbreviations: CI, confidence interval; F, female; HIV-, human immunodeficiency virus negative; HIV+, human immunodeficiency virus positive; HR, hazard ratio; M, male; RT, radiotherapy.

hazard ratios (HRs) of 1.06 (95% CI, 1.03–1.10), 1.04 (95% CI, 1.01–1.08), and 4.37 (95% CI, 1.83–10.47), respectively.

In this cohort, there were 10 distant failures, 5 of which occurred in patients who also manifested a local failure. The overall 2-year FFDM for HIV-positive patients was 91.8% (95% CI, 83.3–100) and for HIV-negative patients (p = .44) was 89.1% (95% CI, 81.2–97.8). On subgroup analysis, there were no significant differences in FFDM for HIV-positive and HIV-negative patients treated according to the Nigro regimen (p = .68). Failures were managed with abdominoperineal resection in eight patients, systemic therapy alone in nine patients, and symptom directed care or radiation therapy in nine patients.

The 2-year OS and 5-year OS for the entire cohort were 87.3% (95% CI, 80.7–94.3) and 76.8% (95% CI, 67.8–87.0), respectively. Of the 21 deaths in this cohort, 14 (67%) were attributed to ASCC, 4 (19%) were attributed to HIV or other infection, and 3 (14%) were attributed to other malignancies or chronic health conditions. When stratified by HIV status, the 2-year OS and 5-year OS were 90.3% (95% CI, 82.5–98.8) and 79.5% (95% CI, 68.0–93.1) for HIV-negative patients and 83.5% (95% CI, 72.8–95.7) and 73.4% (95% CI, 60.2–89.6) for HIV-positive patients (see Fig. 3). There was no significant association between HIV status and OS (p = .35). Univariate analysis demonstrated a significant association of increased time from diagnosis to treatment initiation with OS (p = .043) with an HR of 1.02 (95% CI, 1.00–1.04). Univariate and multivariate analysis are shown on Table 4, with only time from diagnosis to treatment initiation being significantly associated with OS with HR 1.02 (95% CI, 1.00 – 1.05).

Notably, among HIV-positive patients, there was a significant (p = .015) association with decreased OS and post-treatment CD4 count of <150 cells per mm^3 and a nonsignificant (p = .1) association with risk for local recurrence, by log-ranked test. In this set of patients, the 2- and 5-year OS were both 88.8% (95% CI, 75.3–100) for patients with post-treatment CD4 count greater than 150 cells per mm^3, whereas in patients with counts lower than 150 cells per mm^3, the OS were 76.2% (95% CI, 59.6–97.3) and 53.9% (95% CI, 33.8–85.8), respectively, as demonstrated in Figure 3. Similarly, HIV-positive patients who had a post-treatment CD4 count drop of 67% or greater had significantly worse OS (p = .049) and can be found in supplemental online Figure 1, with an exploratory analysis of the effect HIV status on the T and N stage survival outcomes of patients. No significant association was detected between pretreatment CD4 count and either FFLR or OS.

Discussion

This study demonstrates that elapsed radiation treatment time and the time from diagnosis to treatment initiation were associated with worse local control, and the latter also had a significant effect on OS. Although baseline and treatment characteristics were similar to that of HIV-negative patients, HIV-positive patients trended toward worse FFLR. In the cohort of HIV-positive patients, post-treatment CD4 was an important prognostic marker, with patients <150 cells per mm^3 having significantly worse OS.

As the largest single institution study of HIV-positive patients with ASCC, this study allows for comparison in outcomes to HIV-negative patients treated during the same time period. Similar to prior reports, HIV-positive patients were found to be younger in age and more predominantly male than HIV-negative patients [21–23]. Even with these demographic differences, HIV-positive patients were found to have similar T and N stage as HIV-negative patients, with the majority having early stage disease. Regardless of the similarity of the baseline characteristics, multiple prior investigations have recognized worse FFLR and OS for HIV-positive patients treated definitively for ASCC [6, 7]. In this series, HIV-positive patients tended to have a FFLR more similar to HIV-negative patients with one higher T-stage (i.e., FFLR for HIV-positive/T1 being similar to HIV-negative/T2).

A key factor associated with poorer outcomes for HIV-positive patients was their post-treatment CD4: post-treatment CD4 counts lower 150 cells per mm^3 were significantly associated with worse OS. Similarly, a drop in CD4 count of >67% was also associated with poorer OS. In a prior study of 40 HIV-positive patients, 5-year local control was significantly (p = .008) worse at 38%, when compared with HIV-negative patients at 87% [22]. Overall, the outcomes for HIV-positive patients in this study demonstrated a trend toward worse FFLR, although notably, HIV-positive patients did not experience worse OS when compared with HIV-negative patients. Additionally, HIV-positive patients in this cohort did not have significant differences in the elapsed treatment time, time from diagnosis to treatment initiation, or tumor stage, which were found to be most significantly associated with local recurrence. Likely, HIV status alone

does not drive worse outcomes in and of itself; however, further investigation needs to be undertaken on which HIV-positive patients are at greatest risk of failure.

Demonstration of worse FFLR in HIV-positive patients with low CD4 counts after treatment is not without precedence. A recent database analysis of 142 HIV-positive patients found that post-treatment CD4 count, and not pretreatment, was associated with a 54% increased risk of recurrence for every 100 cells per mm^3 decrease [7]. Similarly, the current study found that post-treatment CD4 count less than 150 cells per mm^3 resulted in a significantly worse OS among HIV-positive patients (p = .015), whereas pretreatment CD4 count was not significantly associated. Unfortunately, as pretreatment CD4 count is not predictive of outcomes, it is difficult to identify a priori which patient will fall below that threshold and be at greater risk of poor outcome. As the median decline in CD4 count was 67.0% in this series, it can be reasonably assumed that patients with a CD4 less than approximately 450 cells per mm^3 would be at greatest risk for local recurrence. Additionally, if patients have a relative drop of greater than 67% in CD4 count, this may herald the need for improved treatment options and further investigation of to identify patients at high risk of CD4 decline.

Consistent with prolonged treatment breaks being associated with poorer outcomes in ASCC, longer treatment duration had poorer FFLR for all patients. Numerous analyses have been performed to understand the effect of treatment length on outcomes in patients with ASCC, but many have shown mixed results [18–20, 24]. Similar to the present study, a retrospective analysis of two large prospective randomized trials found total treatment time to be significantly associated with local control [18]. One key difference in the prior analysis is the use of a delayed boost, depending on pathologic response, likely increased the total treatment time and potentially biased toward radioresistant tumors. Even with this, the cutoff of ≤53 days was significant for improved local control, similar the <50 days found in this study. Likely, this indicates that elapsed radiation treatment times greater than 7 weeks, regardless of cause, should be concerning for worse outcomes. Although the cause of extended treatments is likely multifactorial in nature, HIV status was not significantly associated with increased elapsed treatment days, as both HIV-positive and HIV-negative patients took a median of 50 days to complete radiation therapy.

The rationale behind the potential detrimental effect of a protracted course of radiation is one of the fundamental aspects of radiation biology. Extended delays between fractions of radiation can result in increased tumor cell repopulation at the latter stages of treatment [25–28]. This has been shown to be clinically important in other mucosal malignancies, and is the rationale for alternative fractionation regimens aimed at improving local control [29–31]. Although little evidence exists for the use of hyperfractionation, or other alternative schedules for treatment of ASCC, its effect may be abrogated by the use of concurrent chemotherapy as has been seen in oropharyngeal cancer [32]. Regardless, the need for enhanced supportive care for patients undergoing combined modality treatment is apparent, and can play a significant role in the outcomes.

This study also found that time from diagnosis to treatment initiation was associated with worse FFLR and overall survival. Delays to treatment completion have previously been associated with worse outcomes in head and neck malignancies; however, this is the first report of this association in ASCC [33, 34]. Although likely multifactorial in nature, with elements related to delayed referral for treatment or other social factors, we found that HIV-positive patients had a nonsignificant 1-week increase in time from diagnosis to treatment initiation.

The limitations of this work are inherent to its retrospective nature and the heterogeneous population treated over the time period of this study. For this reason, collection of specific toxicity data was limited, and the choice was made to represent this by the need for chemotherapy dose reduction. HIV-negative patients were not routinely tested for CD4, counts limiting the ability to evaluate the potential for treatment-related effects in this population compared with HIV-positive patients. Additionally, data on the vital status and date of death for patients was largely available; however, because of privacy concerns, specific causes of death potentially related to HIV were not accessible. This has the potential to add source of bias to the data; however, given the rarity of the disease, these data serve as a bench mark for future treatment outcomes of HIV-positive patients with ASCC. Further understanding of this is most feasible at high volumes centers with the capacity to undertake prospective analyses on patient reported outcomes, psychosocial interventions, and enhanced allied provider support.

Conclusion

The treatment of ASCC in HIV-positive patients is complex and requires excellent diagnostic and supportive care. Although no pretreatment variables were predictive of worse outcomes for HIV-positive patients, there was a trend toward worse FFLR in the overall cohort, even among patients treated on the Nigro regimen; however, this did not translate to a difference in OS. Post-treatment CD4 count of <150 cells per mm^3 in HIV-positive patients was associated with worse OS, likely reflecting a cohort of patients in need of enhanced post-treatment surveillance and support. Even with this difference, the outcomes of HIV-positive patients treated with radiation therapy for ASCC were favorable, with a FFLR of >70% at 2 years.

Author Contributions

Conception/design: Matthew S. Susko, Chia-Ching Jackie Wang, Ann A. Lazar, Stephanie Kim, Angela Laffan, Mary Feng, Andrew Ko, Alan P. Venook, Chloe E. Atreya, Katherine Van Loon, Mekhail Anwar
Provision of study material or patients: Matthew S. Susko, Chia-Ching Jackie Wang, Ann A. Lazar, Stephanie Kim, Angela Laffan, Mary Feng, Andrew Ko, Alan P. Venook, Chloe E. Atreya, Katherine Van Loon, Mekhail Anwar
Collection and/or assembly of data: Matthew S. Susko, Chia-Ching Jackie Wang, Stephanie Kim, Mekhail Anwar
Data analysis and interpretation: Matthew S. Susko, Ann A. Lazar, Mekhail Anwar
Manuscript writing: Matthew S. Susko, Ann A. Lazar, Mekhail Anwar
Final approval of manuscript: Matthew Susko, Chia-Ching Jackie Wang, Ann A. Lazar, Stephanie Kim, Angela Laffan, Mary Feng, Andrew Ko, Alan P. Venook, Chloe E. Atreya, Katherine Van Loon, Mekhail Anwar

Disclosures

Chia-Ching Jackie Wang: Bristol-Myers Squibb (RF); **Angela Laffan:** Lexicon, Tachici Sandofi (C/A); **Andrew Ko:** Celgene, Roche/Genentech, Astellas, Bristol-Myers Squibb, Abgenomics, Apexigen,

Merrimack, Halozyme, AstraZeneca, Merck, TwoPoreGuys (RF-all paid to my institution) Gilead (C/A one-time), Gritstone, ARMO, Celgene (SAB-one time), Erytech, Imugene, SynCore (Other-Data Safety Monitoring Board); **Chloe E. Atreya:** Bristol-Meyers Squibb, Novartis, Merck, Guardant Health, Kura Oncology (RF), Array Biopharma, Pionyr Immunotherapeutics (SAB). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

2. Johnson LG, Madeleine MM, Newcomer LM et al. Anal cancer incidence and survival: The Surveillance, Epidemiology, and End Results experience, 1973-2000. Cancer 2004;101:281–288.

3. Shiels MS, Pfeiffer RM, Chaturvedi AK et al. Impact of the HIV epidemic on the incidence rates of anal cancer in the United States. J Natl Cancer Inst 2012;104:1591–1598.

4. Dandapani S V, Eaton M, Thomas CR Jr et al. HIV- positive anal cancer: An update for the clinician. J Gastrointest Oncol 2010;1:34-44.

5. Melbye M, Rabkin C, Frisch M et al. Changing patterns of anal cancer incidence in the united states, 1940-1989. Am J Epidemiol 1994;139: 772–780.

6. Grew D, Bitterman D, Leichman C et al. Significantly worse colostomy-free survival in human immunodeficiency virus-positive patients after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 2014;90:S398–S399.

7. Bryant AK, Mudgway R, Huynh-Le MP et al. Effect of CD4 count on treatment toxicity and tumor recurrence in human immunodeficiency virus-positive patients with anal cancer. Int J Radiat Oncol Biol Phys. 2018;100:478-485.

8. Lin D, Gold HT, Schreiber D et al. Impact of socioeconomic status on survival for patients with anal cancer. Cancer 2018;124:1791–1797.

9. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet 1996;348:1049–1054.

10. Bartelink H, Roelofsen F, Eschwege F et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the EORTC. J Clin Oncol 1997;15:2040–2049.

11. Flam M, John M, Pajak TF et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: Results of a phase III randomized intergroup study. J Clin Oncol 1996;14:2527–2539.

12. Nigro ND, Seydel HG, Considine B et al. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 1983;51:1826–1829.

13. Kachnic L, Winter K, Myerson R et al. RTOG 0529: A phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-c for reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol 2009;75:S5.

14. Ajani JA, Winter KA, Gunderson LL et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. JAMA 2008;299:1914–1921.

15. James RD, Glynne-Jones R, Meadows HM et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): A randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol 2013;14:516–524.

16. Gunderson LL, Winter KA, Ajani JA et al. Long-term update of US GI intergroup RTOG 98-11 Phase III trial for anal carcinoma: Survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012; 30:4344–4351.

17. James R, Wan S, Glynne-Jones R et al. A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II). J Clin Oncol 2009;27:LBA4009a.

18. Ben-Josef E, Moughan J, Ajani JA et al. Impact of overall treatment time on survival and local control in patients with anal cancer: A pooled data analysis of radiation therapy oncology group trials 87-04 and 98-11. J Clin Oncol 2010;28:5061–5066.

19. Allal AS, Mermillod B, Roth AD et al. The impact of treatment factors on local control in T2-T3 anal carcinomas treated by radiotherapy with or without chemotherapy. Cancer 1997;79: 2329–2335.

20. Graf R, Wust P, Hildebrandt B et al. Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. Oncology 2003;65:14–22.

21. Hammad N, Philip PA, Shields AF et al. A retrospective review of squamous cell carcinoma of the anal canal in HIV-positive and HIV-negative patients. J Clin Oncol 2009;27:e15586.

22. Oehler-Jänne C, Huguet F, Provencher S et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: A multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol 2008;26:2550–2557.

23. Kinsella TJ, Kinsella MT, Reynolds H et al. Comparable tumor responses and acute/late normal tissue toxicities with standard combined modality treatment for anal squamous cell carcinomas in HIV+ and HIV– patients. Int J Radiat Oncol 2005;63:S16.

24. Weber DC, Kurtz JM, Allal AS. The impact of gap duration on local control in anal canal carcinoma treated by split-course radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys 2001;50:675–680.

25. Kim JJ, Tannock IF. Repopulation of cancer cells during therapy: An important cause of treatment failure. Nat Rev Cancer 2005;5:516–525.

26. Sham E, Durand RE. Repopulation characteristics and cell kinetic parameters resulting from multifraction irradiation of xenograft tumors in SCID mice. Int J Radiat Oncol Biol Phys 1999;43:617–622.

27. Denekamp J. Changes in the rate of repopulation during multifraction irradiation of mouse skin. Br J Radiol 1973;46:381–387.

28. Skladowski K, Law MG, Maciejewski B et al. Planned and unplanned gaps in radiotherapy: the importance of gap position and gap duration. Radiother Oncol 1994;30:109–120.

29. Maciejewski B, Preuss-Bayer G, Trott KR. The influence of the number of fractions and of overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int J Radiat Oncol Biol Phys. 1983;9: 321–328.

30. Overgaard J, Hansen HS, Specht L et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. Lancet 2003;362:933–940.

31. Fu KK, Pajak TF, Trotti A et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.

32. Ang K, Pajak T, Wheeler R et al. A phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas (RTOG 0129): Report of efficacy and toxicity. Int J Radiat Oncol 2010;77:1–2.

33. Ang KK, Trotti A, Brown BW et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–578.

34. Murphy CT, Galloway TJ, Handorf EA et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. J Clin Oncol 2016;34:169–178.

See http://www.TheOncologist.com for supplemental material available online.