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Critical Review

Prostate Cancer Outcomes in Patients Living With HIV/AIDS Treated With Radiation Therapy: A Systematic Review

Tina Vaziri, BS,[a] Yuan J. Rao, MD,[a] Michael Whalen, MD,[b] Jeffrey Bethony, PhD,[c] Jianqin Lin, MD,[d] and Sharad Goyal, MD[a,*]

[a]Departments of Radiation Oncology, George Washington University School of Medicine and Health Sciences, Washington, DC; [b]Departments of Urology, George Washington University School of Medicine and Health Sciences, Washington, DC; [c]Departments of Microbiology, Immunology, and Tropical Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC; [d]Departments of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC

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Abstract

Purpose: A consensus has not been reached regarding the treatment and outcomes of prostate cancer (PCa) in people living with HIV/AIDS (PLWHA). This systematic review aims to summarize the evidence on the management of PCa with radiation therapy (RT) in PLWHA diagnosed with PCa.

Methods and Materials: Searches were conducted in the PubMed, Cochrane Library, and Scopus databases during September 2021 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Articles reporting on outcomes of PLWHA treated for PCa with definitive RT were sought for inclusion.

Results: A total of 9 studies with 187 patients with HIV who received diagnoses of PCa met inclusion criteria. The duration of HIV infection to PCa diagnosis ranged from 8.5 to 18.6 years with 69% to 100% of patients on highly active antiretroviral therapy at the time of diagnosis. Patients' prostate-specific antigen levels ranged from 8 to 82 ng/mL. The majority of patients (59%) were treated with external beam RT, followed by brachytherapy (20.5%). The 4- or 5-year biochemical failure–free rate was reported to be between 87% and 97% in 3 studies, and 2 studies reported an 84% to 97% 5-year cancer-specific survival. Using Common Terminology Criteria for Adverse Events criteria, 3 studies reported toxicities and grade 3 toxicity was observed in only 2 patients.

Conclusions: RT is efficacious and well tolerated in PLWHA as supported by the comparable biochemical control, clinical outcome, and mortality to the general population as well as by the mild reports of radiotoxicity. There is mixed evidence regarding the effect of RT on CD4 count and viral load, and further studies are needed to better understand this relationship. These findings support the use of definitive RT in PLWHA with PCa.

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*Corresponding author: Sharad Goyal, MD; E-mail: shgoyal@mfa.gwu.edu

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Introduction

The development of highly active antiretroviral therapy (HAART) has dramatically altered the disease progression of people living with HIV/AIDS (PLWHA). Historically, AIDS-defining cancers (ADC), such as Kaposi sarcoma and non-Hodgkin lymphoma, were leading causes of morbidity and mortality in PLWHA.[1] However, as the life expectancy secondary to HIV complications has improved in the post-HAART era, non-AIDS-defining cancers (NADCs) have become a growing concern for these patients.[2] These NADCs include but are not limited to prostate, breast, anal, lung, head and neck, and Hodgkin lymphoma. Epidemiologic data from the HIV/AIDs Cancer Match Study has shown that while the incidence of ADCs has declined 3-fold from the period of 1995 to 2005, the incidence of NADCs has conversely risen by 3-fold.[3] In the United States, NADCs comprised 31.4% of all diagnosed cancers in PLWHA from 1991 to 1995 and have increased to 58.0% with HAART development.[4]

Prostate cancer (PCa) is the second most diagnosed cancer in men worldwide and the most diagnosed non-skin malignancy in the United States.[5] Its incidence increases with age, and it is more prevalent in the Black population.[6] The true incidence of PCa in PLWHA is unknown as contrasting studies have concluded elevated, lowered, or even similar risk compared with the general population.[7-9] It has been proposed that previous reports of the lower incidence of PCa in PLWHA can be attributed to discrepancies in prostate-specific antigen (PSA) screening in this patient group.[10]

Advances in surgery, radiation therapy (RT), and chemotherapy have significantly improved the way in which PCa is managed. Despite this, there is a paucity of data describing management and outcomes of PCa in PLWHA. This is of importance as it must be considered whether the pathogenesis of PCa in PLWHA may be influenced by the immune status of patients as well as by the effects of HAART on cancer treatment. Some studies suggest that PCa is more aggressive in PLWHA. For instance, it has been shown that patients do not respond well to androgen deprivation therapy (ADT) as a consequence of the hypogonadal state observed with HIV infection.[11] Other possible mechanisms for altered PCa progression include impaired immune cell surveillance and suppression of cell-mediated immunity.

Currently, PLWHA have the same standard of care treatment options available to them as the general population. These options include surgery, RT, or active surveillance for localized, nonmetastatic disease. Findings from the recent ProtecT Trial showed low PCa-specific mortality irrespective of these management approaches and lower incidences of disease progression with RT or surgery.[12] Among these approaches, RT has the potential to cause genitourinary (GU) and gastrointestinal (GI) toxicity. Further, as RT is known to cause a mild decline in multiple blood cell parameters, including CD4 count, it is unclear if RT could have an additive effect in patients with HIV infection. Historically, PLWHA may have been excluded from participation in many National Cancer Institute −sponsored clinical trials, limiting the generalizability of any conclusions to this patient population. Thus, the purpose of this systematic review is to evaluate the clinical outcomes and toxicity of PLWHA diagnosed with PCa treated with definitive RT.

Methods and Materials

A literature review was performed that included all the elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive literature search of PubMed, Scopus, and Cochrane Library databases was performed during September 2021 with no limit put on the date of publication. The search string contained combinations of title/abstract keywords and medical subject heading (MeSH) terms that are synonyms of human immunodeficiency virus, prostate cancer, and radiation therapy. The full search strategy for these databases is presented in Appendix E1. Eligible studies included randomized control trials, retrospective cohort studies, prospective cohort studies, case-control studies, and review articles presenting new data. References in these publications were examined for other relevant studies. The titles and abstracts of the potentially relevant publications (n = 341) were examined to include only English-language studies that reported outcomes of PCa treated with RT in PLWHA. Among 30 manuscripts that were initially identified for a full review, 9 were selected for inclusion (Table 1). The remaining 21 articles were not included because of the following exclusion criteria: (1) including only patients undergoing prostatectomy, (2) case reports, (3) participating number of patients <5, and (4) paucity of details on clinical outcomes or toxicities.

Qualified studies were then cross referenced until the search strategy was exhausted. Articles included were published between 2005 and 2021 and consisted of retrospective studies with the exception of 1 review article, which also presented previously unpublished data. Information regarding the clinicopathologic characteristics of patients' PCa, treatment plans, oncological outcomes, and HIV parameters were obtained from the included studies. The results were reviewed by a multidisciplinary team composed of medical, surgical, and radiation oncologists. Critical issues were identified and key findings from the current literature are summarized in this report. The article selection process is summarized in Fig. 1.

Table 1 Study and patient characteristics

Study	Country	Cohort size, n		Study period	Average at PCa Dx (range)		Race		Outcomes measured
		HIV+	HIV−		HIV+	HIV−	HIV+	HIV−	
Levinson et al 2005 [21]	United States	10	NA	NR	54 (41-69)	NA	Black (n = 6, 60%)	NA	Change in PSA post treatment
							White (n = 2, 20%)		
							His (n = 2, 20%)		
Ng et al 2008 [19]	United States	14	NA	2000-2006	61 (49-71)	NA	NR	NA	Change in PSA post treatment, FACT-G quality of life, mortality, change in HIV parameters, toxicities
Pantanowitz et al 2008 [20]	United States	17	NA	1996-2006	59 (46-76)	NA	Black (n = 3, 18%)	NA	Biochemical recurrence, mortality
							White (n = 8, 47%)		
							His (n = 2, 12%)		
							Haitian (n = 1, 6%)		
							Un (n = 3, 18%)		
Wosnitzer et al 2010 [18]	United States	11*	NA	NR	NR	NA	NR	NA	Biochemical recurrence
Kahn et al 2012 [17†]	United States	13	26	1999-2009	55 (44-74)	60 (50-73)	Black (n = 10, 77%)	Black (n = 20, 77%)	BFF survival, mortality, change in HIV parameters, toxicities
							White (n = 3, 23%)	White (n = 6, 23%)	
Schreiber et al 2014 [16†]	United States	15	NA	2003-2010	65	NA	Black (n = 12, 80%)	NA	BFF survival, mortality, change in HIV parameters, toxicities
							White (n = 1, 7%)		
							His (n = 2, 13%)		
Ong et al 2015 [14]	Australia	12	NA	2000-2015	62.7 (46-79)	NA	NR	NA	BFF survival, mortality
Reidel et al 2015 [15†]	United States	49	1496	2000-2011	60.7	64	Black (92%)	Black (45%)	Differences in PCa staging between HIV+ and HIV−, mortality
							White (8%)	White (52%)	
								NR (3%)	
Ruden et al 2021 [13†]	United States	46	137	2000-2016	57.2	58.2	Black (n = 41, 89%)	Black (n = 122, 89%)	BFF survival, castration-resistance survival, PCa-specific mortality, overall mortality
							White (n = 3, 7%)	White (n = 8, 6%)	
							His (n = 2, 4%)	His (n = 7, 5%)	

Abbreviations: BFF = biochemical failure–free; FACT-G = Functional Assessment of Cancer Therapy–General; His = Hispanic; NA = not applicable; NR = not reported; PCa = prostate cancer; PSA = prostate-specific antigen; Un = unknown.

* Seven of the 11 patients included in the cohort received radiation therapy.

† The median is reported instead of the mean for average.

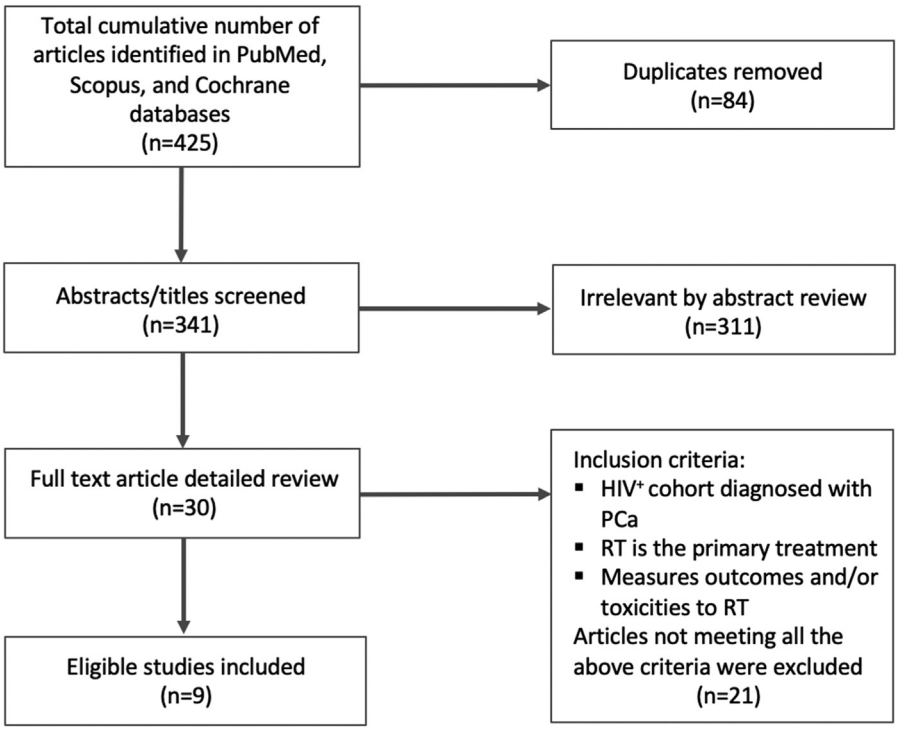

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram representing the approach to identification, screening, eligibility, and inclusion of articles.

Results

Patient demographics and characteristics of HIV infection

Tables 1 and 2 summarize the patient demographics and the characteristics of HIV infection, respectively. A total of 187 HIV-positive patients were included in 9 studies.[13-21] Three articles, which notably have been published in the past 10 years, included a control arm with a total of 1659 HIV-negative patients.[13,15,17] A matched cohort analysis for patient age, race, and tumor stage was performed in 2 of these 3 studies.[13,17]

Patient race was reported for 149 patients in 6 of the 9 studies: 118 Black (79%), 21 White (14%), 8 Hispanic (5%), and 2 unknown (1.3%).[13,15,16,17,20,21] Of the 3 studies with a control group, Kahn et al and Ruden et al had matched controls.[13,17] Meanwhile, Reidel et al included 1496 patients with PCa from the general population, which had a greater frequency of White patients (52%) and a lower frequency of Black patients (45%) compared with patients with HIV.[15]

As reported in 7 studies, the average duration between HIV infection and PCa diagnosis ranged from 8.5 to 18.6 years.[13,14,15,16,18,20,21] The majority of patients were on HAART at the time of PCa diagnosis (range, 69%-100%) and the average CD4 count ranged from 336 to 523 cells/mm^3. Viral load at the time of PCa diagnosis showed great variability among patients within the same study and between studies, with a range from undetectable to greater than 100,000 copies/mL. As expected, individual patient data from these studies showed that those who were not receiving HAART had a lower CD4 count and higher viral load compared with those that were receiving HAART.

Prostate cancer characteristics and therapy

The characteristics of PCa at the time of diagnosis and therapy type are summarized in Table 3. Average patient age at the time of PCa diagnosis ranged from 54 to 65 years. Seven studies reported patient PSA levels, with averages ranging from 8 to 82 ng/mL, while the remaining 2 studies reported that the majority of their patients had PSA levels <10 ng/mL. Gleason staging was provided in 8 studies and most patients had a score of 6 or 7 (range, 2-10). Of the studies that reported the individual clinical T stages of each patient: 69% of patients were T1, 27.4% of patients were T2, 2.4% of patients were T3, and 1.2% of patients were T4. Interestingly, Reidel et al reported that HIV-positive patients were more likely to present with advanced-stage PCa as they found the incidence of stage III-IV to be 36% in HIV-positive patients versus 14% in the general population ($P < .001$).[15]

The type of RT patients received was identified in 127 patients from 8 studies.[14-21] Of these, 75 (59%) were

Table 2 Characteristics of HIV infection

Study	% Receiving HAART	Average duration (y) of HIV infection (range)	Average CD4 T-cell count/mm^3 (range)	Average viral load, RNA copies/mL (range)
Levinson et al 2005 [21]	90	8.75 (0.5-19)	417 (76-1070)	UD (n = 5, 50%)
				141.67 (50-106,000)*
Ng et al 2008 [19]	79	NR	523 (200-946)	UD (n = 9, 64%)
				(UD-27,000)
Pantanowitz et al 2008 [20]	82	8.5 (2-20)†	336 (24-759)	17,319 (0 to >100,000)
Wosnitzer et al 2010 [18]	100	EBRT: 18.6 (14-22)	EBRT: 437 (76-1070)	EBRT: 255 (25-501)
		BT: 10.8 (6-17)	BT: 1417 (454-4117)	BT: 12.5 (UD-50)
Kahn et al 2012 [17]	69	NR	412.3 (50-1002)	UD (n = 5, 38%)
				(UD-20,718)
Schreiber et al 2014 [16]	87	9.8 (1-21)	464.2 (138-994)	UD (n = 11, 73%)
Ong et al 2015 [14]	100	11.9	485 (235-1116)‡	UD (67%)
Reidel et al 2015 [15‡]	82	10.5	391 (IQR, 301-634)	≤400 (n = 37, 76%)
Ruden et al 2021 [13‡]	91	8.63	400.5 (IQR, 254-581)	40 (IQR, 40-124)

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; HAART = highly active antiretroviral therapy; IQR = interquartile range; NR = not reported; UD = undetectable.

* The viral load of the 1 patient not on HAART was 106,000 copies/mL.

† The average is reported for 13 of 17 patients, as 2 patients received diagnoses with HIV 1 and 3 years after prostate cancer diagnosis, and the duration of HIV infection is unknown for 2 patients.

‡ The median is reported instead of the mean for average.

Table 3 Prostate cancer characteristics and treatment details

Study	Pretreatment average or % PSA, ng/mL (range)	Mean Gleason score, n or % (range)	AJCC prostate stage or anatomic stage		Therapy type, n or %	
			HIV+	HIV−	HIV+	HIV−
Levinson et al 2005 [21]	9.2 (4.5-19.9)	6; GS 5 (20%) GS 6 (60%) GS 7 (20%)	T1c (70%) T2a (20%) T2b (10%)	NA	BT (20%) EBRT (30%) RP (10%) CS (10%) ADT (10%) WW (20%)	NA
Ng et al 2008 [19]	14.3 (0-77)	6.5; GS 6 (57%) GS 7 (36%) GS 8 (7%)	T1c (43%) T2b (36%) T2c (21%)	NA	EBRT (14%) BT (29%) EBRT + BT (57%)	NA
Pantanowitz et al 2008 [20]*	30 (4.5-77)	6.8 (6-8)	pT1c (41%) pT2 (12%) pT3 (6%) NR (41%)	NA	EBRT + ADT (41%) BT (18%) RP (18%) 2 ADT (12%) WW (6%)	NA
Wosnitzer et al 2010 [18]	ERBT: 8 BT: 10	NR	T1c (82%) T2a (9%) T2b (9%)	NA	ERBT (27%) BT (36%) RP (36%)	NA
Kahn et al 2012 [17]	<10 (85%) 10-20 (15%) >20 (0%)	GS <7 (46%) GS 7 (46%) GS >7 (8%)	T1c (77%) T2a (15%) T2c (8%)	T1c (77%) T2a (19%) T2c (4%)	EBRT (100%) 3D-CRT (54%) IMRT (46%)	EBRT (100%) 3D-CRT (54%) IMRT (46%)
Schreiber et al 2014 [16]	<10 (73%) 10.1-20 (20%) >20 (7%)	GS 2-6 (20%) GS 7 (47%) GS 8-10 (33%)	T1c (80%) T2a (7%) T2b (7%) T3b (7%)	NA	EBRT (100%) 3D-CRT (n = 7) IMRT (n = 8) Adj ADT (n = 5)	NA
Ong et al 2015 [14†]	11.1 (3.9-269)	GS 6 (33%) GS 7 (33%) GS 8 (8%) GS 9 (25%)	T1c (58%) T2a (8%) T2c (17%) T4 (17%)	NA	EBRT (42%) BT (8%) EBRT + ADT (8%) CS + ADT + EBRT (8%) RP (17%) AS (17%)	NA
Reidel et al 2015 [15]	82 (2.5-1830)	7 (5-10)	I (14%) II (49%) III (18%) IV (18%) T1-2 (n = 34, 70%) T3-4 (n = 15, 30%)	I (5%) II (68%) III (7%) IV (7%) Unknown (13%) T stage NR	EBRT (51%) BT (25%) Orchiectomy (4%) RP (22%) Chemo (12%) WW (10%)	NR
Ruden et al 2021 [13†]	HIV+ 10.5 (IQR, 3.9-24.5) HIV− 10.6 (IQR, 6.4-22.5)	GS 6 (53%) GS 7 (30%) GS 8-10 (10%)	T1c (47.6%) T2 (40%) T3 (4.8%) T4 (7.1%)	T1c (55.9%) T2 (38.2%) T3 (3.7%) T4 (2.2%)	RT (56.5%) ADT (4.3%) RP (17.4%) AS (8.7%) None (13%)	RT (38.7%) ADT (16.7%) RP (27%) AS (13.9%) None (3.7%)

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; Adj = adjuvant; ADT = androgen deprivation therapy; AS = active surveillance; BT = brachytherapy; Chemo = chemotherapy; CS = cryosurgery; EBRT = external beam radiation therapy; GS = Gleason score; IMRT = intensity modulated radiation therapy; IQR = interquartile range; NA = not applicable; NR = not reported; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; WW = watchful waiting.

* Staging provided for 10 of 17 patients. For therapy type, 1 patient was untreated and died of dementia and 1 patient's therapy is not accounted for.

† The median is reported instead of the mean for average.

treated with external beam RT (EBRT) alone, 26 (20.5%) were treated with brachytherapy (BT) alone, and 8 (14%) were treated with a combination of EBRT + BT. For patients who received EBRT alone, the dosage delivered ranged from 72 to 81 Gy. For those treated with BT alone, 4 patients and 1 patient received 120 Gy using ^{103}Pd and 145 Gy using ^{125}I, respectively (data not shown).[14,19] Using χ^2 analysis, Ruden et al found that PLWHA with localized disease were more likely to receive definitive RT (59.5% vs 44.8%) or withhold therapy (13.5% vs 4.3%), and less likely to receive surgery (16.2% vs 30.2%) than the matched cohort ($P = .04$).[13]

Outcomes

The effect of HIV on RT treatment outcome for PCa was assessed by measurement of follow-up PSA levels, biochemical failure (BCF) rates, and/or mortality and is summarized in Table 4. Since 2006, the definition of BCF has shifted from the American Society for Radiation Oncology criteria to the Phoenix criteria, which defines BCF as a rise in 2 ng/mL or more above the nadir PSA.[22] Thus, included studies after 2006 used the Phoenix definition when reporting BCF outcomes. Three studies commented on follow-up PSA levels and found that 91% showed declining or stable PSA levels status post-RT treatment.[19-21] The 4- or 5-year biochemical failure–free (BFF) rate was reported to be between 87% and 97% in 3 studies with a combined rate of 94.2%.[13,16,17] This was comparable to the 89% and 85% BFF rate found in the HIV-negative control group in the study by Kahn et al and Ruden et al, respectively.[13,17] Ong et al performed the longest duration of assessment of BCF and found that 1 patient who was treated with EBRT developed recurrence at 7 years after completion of therapy.[14]

Mortality was reported in 7 studies. In the studies that contained a cohort of <40 HIV-positive patients, no PCa-specific deaths were reported.[14,16,17,19,20] The remaining 2 studies found the 5-year cancer-specific survival to be between 74% and 97%.[13,15] Further, Ruden et al found no difference between the 5-year cancer-specific survival of HIV-positive patients and HIV-negative patients.[13] However, through Kaplan-Meier analysis, these authors as well as Reidel et al found the 5-year overall survival rate to be worse for HIV-positive patients (Table 4).[13,15]

The effects of RT on CD4 count and viral load in PLWHA with PCa are reported in 3 studies with varying results. While Ng et al found a mean increase from 523 to 577 cells/mm^3, Kahn et al and Schreiber et al observed a decline in CD4 count in the majority of their patients (Table 5).[16,17,19] However, both groups also noted that all or a majority of their patients showed subsequent improvement in CD4 levels over time after completion of RT.[16,17] Kahn et al did not comment on the time course of CD4 recovery, and Schreiber et al reported recovery at the time of most recent CD4 count, which ranged from 25 to 103 months. Both authors reported that there were no cases of opportunistic infections as a consequence of the temporary increase in immunosuppression. The studies did not specify differences in the change in CD4 count and viral load for those treated with RT alone versus those placed on ADT; however, it appears that only 1 HIV-positive patient in the study by Kahn et al received ADT.[17]

Toxicities

There is limited published data on the toxicities/adverse events of RT treatment of PCa in PLWHA. Of the 9 included studies, 3 reported GU and GI toxicities, which are summarized in Table 5.[16,17,19] All studies used the Common Terminology Criteria for Adverse Events version 3.0, a comprehensive grading system for reporting the acute and late effects of cancer treatments.

Kahn et al found that HIV-positive patients had better tolerance to RT compared with the matched-controls as both reports of acute and chronic GI and GU toxicities were higher in the control groups ($P < .001$).[17] The remaining 2 studies did not include control groups; however, both reported mild to moderate toxicities.[16,19] Schreiber et al found that GU toxicity was predominantly limited to less than or equal to grade 2 and both acute and chronic GI toxicity was infrequently reported.[16] Two patients reported grade 3 toxicity, 1 of which had a history of urethral stricture and developed recurrence requiring dilations, and 1 patient that developed rectal bleeding requiring argon plasma coagulation. Ng et al had a small cohort of 15 patients, of which 43% reported acute grade 2 GU/GI toxicities, and 14% reported chronic grade 2 GU/GI toxicities (19). No patients reported grade 3 or higher GU or GI toxicities. This study also found that 50% of patients reported erectile dysfunction at their most recent follow-up, which declined to 31% by the time of last follow-up with a median follow-up time of 26 months. Finally, the authors also assessed quality of life after RT using the Functional Assessment of Cancer Therapy–General (FACT-G) survey, a 27-item questionnaire that considers physical, social, emotional, and functional well-being. The mean scores were 83, 80, and 74 for patients of subsets BT, BT + EBRT, and EBRT, respectively, with a total mean score of 80.1.[19]

Discussion

The treatment of cancer in PLWHA is challenging as standards of care are concluded from data of clinical trials that typically exclude HIV-positive patients. To address this knowledge gap, a number of studies have assessed outcomes of these patients compared with the standard recommended treatment for various NADCs. Herein, we

Table 4 Prostate cancer outcomes and mortality

Study	Median follow-up duration (y), (range)	PCa outcomes	Mortality
Levinson et al 2005 [21*]	2.3 (1.4-3)	PSA < baseline (n = 8, 100%); PSA <1.5 ng/mL (n = 4, 50%); stable PSA with WW (n = 2, 100%)	NR
Ng et al 2008 [19]	2.17 (0.67-6.1)	PSA ≤1.1 ng/mL (n = 13, 93%); PSA increased (n = 1)[†]; mean FACT-G score, 80.1; BT, 83; BT + EBRT, 80; EBRT, 74 (range, 48-104)	PCa-specific (n = 0); heart failure (n = 1), 15 mo post-RT
Pantanowitz et al 2008 [20]	NR	Undetectable PSA and no tumor recurrence (n = 17, 100%)	PCa-specific (n = 0); urosepsis (n = 1); HIV encephalopathy (n = 1); cirrhosis (n = 1); unknown (n = 2)
Wosnitzer et al 2010 [18]	EBRT: 5 BT: 6.25 RP: 1.54	EBRT: stable PSA (mean, 1.36 ng/mL) and no recurrence (n = 3, 100%); BT: PSA <0.1 ng/mL (n = 2, 50%), lost to follow-up (n = 1)	NR
Kahn et al 2012 [17]	3.25 (0.25-9.17)	No difference in 4-y BFF survival between HIV+ (87%) and HIV− patients (89%) (P = .94)	HIV+ total deaths (n = 0); HIV− total deaths (n = 2) from PCa-nonspecific causes
Schreiber et al 2014 [16]	4.08 (2.08-8.58)	5-y BFF survival (92.3%); BCR 28 and 63 mo posttreatment (n = 2)	PCa-specific (n = 0); cholangiocarcinoma (n = 1), 35 mo post-RT
Ong et al 2015 [14]	3.83 (0.75-8.58)	EBRT: BCR 7 y post-RT (n = 1, 20%) BT: 5-y BFF survival (n = 1, 100%)	PCa-specific (n = 0); anal cancer (n = 1); ischemic heart disease (n = 2)
Reidel et al 2015 [15]	HIV+: 2.7 (IQR, 1.4-3.9) HIV−: NR	NR	HIV+ total deaths (n = 13, 27%); 5-y PCa-specific survival (74%); HIV− total deaths (n = 342, 22%); worse overall mortality in HIV+ patients (P = .006)
Ruden et al 2021 [13]	3.9 (IQR, 2.1-5.6)	No difference in 5-y BFF survival between HIV+ (97%) and HIV− patients (85%) (HR, 0.89; P = .84)	No difference in PCa-specific mortality (HR, 2.99; P = .83); worse risk of mortality in HIV+ patients (HR, 2.89; P = .04)

Abbreviations: BCR = biochemical recurrence; BFF = biochemical failure–free; BT = brachytherapy; EBRT = external beam radiation therapy; FACT-G = Functional Assessment of Cancer Therapy–General; HR = hazard ratio; IQR = interquartile range; NR = not reported; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; WW = watchful waiting.

* The mean is reported instead of the median for follow-up duration.

† Patient with increased PSA posttreatment was found to have metastasis.

summarized the results of such studies that evaluated the outcomes and toxicities in PLWHA with PCa treated with definitive RT. Our review ultimately included 187 HIV-positive patients from 9 studies. No overt disparity in oncologic outcomes for RT in PLWHA was seen, as the BFF survival rate (87%-92.3%), mirrored published historical data (85.7% in HIV-negative patients with intermediate-risk PCa).[23] Further, PCa-specific survival rates

Table 5 effect on HIV parameters and toxicities

Study	Effect on CD4 count	Effect on viral load	Genitourinary		Gastrointestinal	
			Acute	Chronic	Acute	Chronic
Ng et al 2008 [19]	Stable (n = 13, 93%); declined (n = 1, 7%)	Stable (n = 12, 86%); increased (n = 2, 14%)	Grade 2 (n = 6, 43%)	Grade 2 (n = 2, 14%)	Grade 2 (n = 6, 43%); diarrhea (n = 5, 36%)	Grade 2 (n = 2, 14%)
Kahn et al 2012 [17]	Declined (n = 11, 85%); mean decline, 193 cells/mm^3 (range, 42-498); all had recovery of CD4 count	Increased (n = 7, 54%); declined (n = 5, 38%); UD (n = 3, 23%)	Greater in HIV− patients ($P < .001$); no acute toxicity in 46% HIV+ versus 4% HIV−; grade 3 toxicity in 0% HIV+ versus 4% HIV− patients	Greater in HIV− patients ($P < .001$); no chronic toxicity in 62% HIV+ versus 30% HIV− patients	Greater in HIV− ($P = .003$); no acute toxicity in 46% HIV+ versus 30% HIV−; no acute grade 3 in HIV+ or HIV− patients	Greater in HIV− patients ($P < .001$); no chronic toxicity in 75% HIV+ versus 58% HIV; grade 3 toxicity in 0% HIV+ versus 15% HIV− patients
Schreiber et al 2014 [16]	Declined (n = 8, 89%)*; most had recovery of CD4 count	NR	Grade 1 (n = 4, 27%) Grade 2 (n = 5, 33%) Grade 3 (n = 1, 7%)	Grade 2 (n = 2, 13%) Grade 3 (n = 1, 7%)	Grade 1 (n = 4, 27%)	Grade 3 (n = 1, 7%)

Abbreviation: NR = not reported.

* CD4 count was measured throughout radiation therapy treatment in 9 of the 15 patients. Toxicity grading performed using the Common Terminology Criteria for Adverse Events version 3.0 grading system for genitourinary and gastrointestinal complications.

tend to be favorable in low and intermediate-risk PCa and are comparable to those seen here in PLWHA.[24]

While majority of the authors found that the oncological outcomes of RT in HIV-positive patients are similar to that of the HIV-negative general population, Reidel et al reported higher overall mortality in their cohort of HIV-positive patients. The authors also found that a higher proportion of their patients presented with advanced stage disease (III/IV), which could account for this discrepancy. Indeed, when stratifying HIV-positive patients based on staging, those with stage III/IV disease had worse overall mortality compared stage I/II.[15] As this systematic review comprised overwhelmingly of stage I/II disease, the findings of Reidel et al highlight the limitation of the other studies and this review to evaluate outcomes of HIV-positive with advanced stage disease. Thus, we are unable to conclude that the outcomes of RT in HIV-positive patients are similar to that of HIV-negative patients in this case. Later-stage PCa can require chemotherapy, which may worsen immunosuppression or interact with HIV medication contributing to worse overall mortality. Further studies would be useful to carefully examine outcomes of PLWHA diagnosed with advanced stage PCa.

While this review focuses on the use of RT in HIV-positive patients with PCa, a few published studies have evaluated the outcomes after surgery and have concluded radical prostatectomy (RP) to be a safe therapeutic option with similar postoperative related complications to that of HIV-negative patients.[25,26] A retrospective cohort study by Murphy et al found that HIV-positive patients received significantly less RP and more RT compared with HIV-negative patients.[27] Although both RT and RP are considered appropriate therapeutic options, the discrepancy in the use of RP in HIV-positive patients raises curiosity regarding the underlying factors contributing to differences in this treatment pattern.

Concerns regarding the use of RT in PLWHA include radiosensitivity and the development of worse radiotoxicity. A prior study found the expected acute grade 2 rectal toxicity to be 4.5% and acute grade 2 urinary symptoms to be 28% when using intensity modulated RT in the general population.[28] Further, the likelihood of developing chronic grade 2 GU toxicity after RT has been shown to be around 15% in multiple studies.[28,29] Given this, RT is well tolerated in PLWHA as the rates of chronic grade 2 GI and GU toxicities were comparable to those expected in the general population. Furthermore, there were only a couple reports of grade 3 or higher toxicities in these patients.

Only Ng et al explored the functional consequences of RT therapy for PCa in PLWHA with the FACT-G survey and found patients to have a mean score of 80.1 with scores of 83, 80, and 74 for patients of subsets BT, BT +EBRT, and EBRT, respectively. This is comparable to the published rates between 66% and 85% from previous studies that used the same survey in patients with PCa

treated with BT, BT+EBRT, or EBRT alone.[30-32] Furthermore, Ng et al and these studies found that the overall quality of life was lower in patients treated with EBRT alone compared with treatment with BT alone. While Ng et al did not stratify toxicity data based on treatment modality, previous studies have reported greater rates of GU toxicities with BT, which may account for the reports of lower quality of life in comparison to EBRT.[33,34]

The data regarding the effects of RT for PCa on CD4 T-cell count and viral load are limited and were not observed independently of ADT. The studies in this review that reported on this measure had conflicting results with findings of both an increase and decrease in CD4 count. The declines in CD4 count post-RT were also reported to have recovered throughout follow-up in majority of the patients, although the time frame of recovery remains unclear. Calkins et al recently found that in a study of patients with HIV and a cancer diagnosis, chemotherapy and/or RT resulted in a decline in CD4 count of 203 cells/μL, with every 100 cells/μL, decrease resulting in a 27% increase in mortality.[35] However, as patients with PCa were not routinely treated with first-line chemotherapy during the era of the included studies, admittedly this scenario is not entirely applicable. Given these inconclusive findings and the possible effect of worse mortality with declining CD4 count, it is imperative that further studies explore the relationship between CD4 count and RT treatment of PCa in PLWHA. It is also imperative to account/control for the receipt of concomitant ADT.

There are several limitations of our systematic review. First, our search strategy may have missed relevant articles; however, the systematic approach and review by 2 independent reviewers minimized this risk. Second, direct comparison of data was difficult because of the heterogeneity of study designs, settings, and populations across the relevant articles. In addition, the retrospective nature of the relevant articles has inherent limitations, including selection bias and heterogeneity in the reporting of treatment response and adverse events. Finally, a formal meta-analysis was not performed given the heterogeneity in reported outcomes and small sample size of HIV-positive cases. Therefore, the study was largely observational. Nevertheless, these findings are encouraging and as the life expectancy of PLWHA extends with the use of HAART, there is a demand for larger studies evaluating long-term outcomes of PCa in those treated with RT.

Conclusion

The studies reported in this review support the tolerance and efficacy of definitive RT treatment for PCa in PLWHA. Future studies should evaluate the correlation between the safety and efficacy of RT and CD4 cell count, HIV load, PCa treatment selection, and oncologic outcomes for PLWHA. As the National Cancer Institute's Cancer Therapy Evaluation Program has recently expanded eligibility for enrollment in clinical trials to include HIV-infected patients on effective antiretroviral therapy with undetectable viral load within 6 months, we are hopeful that such studies will soon be more readily achievable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101074.

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