

Difference in toxicity between HIV-positive and HIV-negative patients with squamous-cell cancer of the anal canal treated with concomitant radio-chemotherapy

Camila Casadiego-Peña¹, Marcelo Torres-Minacapilli¹, Manuel Najera², Pedro Ferrer², Enrique Chajon³, Hugo Marsiglia^{1,2}

¹International Master in Advanced Radiotherapy, International Atomic Energy Agency (IAEA)-Fundacion Arturo Lopez Perez (FALP)-Los Andes University, Santiago, Chile; ²Instituto Oncologico Fundacion Arturo Lopez Perez (FALP), Santiago, Chile; ³Centre Eugene Marquis, Rennes, France *Contributions:* (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: C Casadiego-Peña, M Torres-Minacapilli, M Najera; (V) Data analysis and interpretation: C Casadiego-Peña, M Najera, P Ferrer; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Camila Casadiego-Peña. Ricardo Matte Perez 483, 7500873 Providencia RM, Chile. Email: cami1204@hotmail.com.

Background: The incidence of squamous cell carcinoma of the anal canal has been increasing over the last 30 years. HIV has been found to be a risk factor for the development of this disease; radio-chemotherapy (RTCT) may also be more toxic than in HIV-negative patients. The study aims at assessing whether there are any differences in terms of toxicity between HIV-positive and HIV-negative patients treated with concomitant RTCT.

Methods: Search in MEDLINE, EMBASE, CENTRAL (via Cochrane Library-Wiley), DARE, LILACS bibliographic databases. Experimental and analytical observational studies with at least two comparative arms were included: squamous-cell (SC) anal-canal cancer (ACC) treated with RTCT in HIV-positive *vs.* HIV-negative patients.

Results: Fifteen publications, 14 retrospective studies and 1 systematic review, were found. All radiotherapy (RT) techniques and all chemotherapeutic agents used to manage this disease were included. No differences were found in terms of duration (P=0.67) and dose (P=0.53) of RT, while CT results were contradictory. Acute and hematological toxicities were significantly higher in HIV-positive patients, while gastrointestinal, dermatological and chronic toxicities did not significantly differ between the two groups. Given the high heterogeneity of the studies, no objective comparison could be made between studies that included antiretrovirals and those that did not.

Conclusions: HIV-positive patients may be at higher risk for acute and hematological toxicity than HIV-negative patients. A precise conclusion cannot be drawn on the use of antiretrovirals, given the high heterogeneity of data.

Keywords: HIV; anal canal cancer (ACC); radio-chemotherapy (RTCT)

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Introduction

The incidence of anal canal cancer (ACC) has been increasing over the last three decades. According to the 2018 GLOBOCAN study (1), around 48,541 new cases are diagnosed worldwide, with 19,129 deaths and a 5-year

prevalence of 127,599 cases. The etiopathological behavior of ACC is more similar to that of malignant tumors of the genital tract than to tumors of the gastrointestinal tract (2). About 85% to 90% of ACCs are squamous cell carcinomas. Patients positive for HIV have been described to be at higher risk of developing this disease (3,4).

The number of HIV-infected patients with squamouscell (SC) ACC has been increasing, mostly among younger patients (mean age at presentation: 40 years), and with a predominance among the male population (4).

The current standard of treatment for patients with ACC is radio-chemotherapy (RTCT), while surgery plays a role as salvage treatment when this first line of curative management fails (5-12). Although HIV positivity is an exclusion criterion for randomized clinical trials in patients with ACC, some series including HIV-positive patients treated with radiotherapy (RT) alone or in combination with chemotherapy (CT) report similar oncological results for HIV-negative and HIV-positive patients, with locoregional control rates of 65% or more. However, other series report lower rates of local control and sphincter preservation for HIV-positive patients despite early-stage diseases and good initial tumor responses (13-20). Regarding treatment toxicity in HIV-positive patients, some series report more severe side effects (13,15,20).

The current recommendation is that HIV-positive patients should be treated similarly to HIV-negative patients, taking into account the complications that patients with HIV/AIDS can present and the consequent possible need for treatment modification (21,22).

This systematic review aims at evaluating the available literature describing observed toxicities, their impact in treatment compliance and published data on quality of life for HIV-positive and HIV-negative patients, treated with RTCT for non-relapsing SC-ACC stages T1-T4N0/+ M0.

Methods

Information search

We carried out a systematic literature review following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (23). In order to identify relevant studies, a systematic search was conducted in electronic databases (MEDLINE, EMBASE, COCHRANE, DARE, LILACS). Syntaxes were adapted for each database through the use of controlled terms (MeSH, EMTREE and DeCS), free language terms and Boolean and proximity operators. No restrictions by language, publication date or type of design were applied. References from selected studies were evaluated and experts in the field were consulted, as additional search sources. Special collections of the *International Journal of Radiation Oncology, Biology & Physics*, Radiotherapy & Oncology, and Lancet Oncology were also reviewed.

Study selection

Titles and summaries were independently reviewed by two authors who also independently verified inclusion and exclusion criteria; inconsistencies were resolved by a third author. Selection criteria were: (I) experimental or analytical observational studies on patients diagnosed with SC ACC treated with RTCT; (II) two comparison arms of HIVpositive *vs.* HIV-negative patients; (III) any RT techniques, regardless of volumes, doses and fractionations; (IV) any CT drugs. Studies including metastatic disease were excluded from our review as were single-arm studies not comparing HIV-positive *vs.* HIV-negative patients.

Qualification, extraction and synthesis of information

Bias risk assessment was performed according to the type of design. Randomized studies were evaluated by Cochrane Collaboration criteria and non-randomized studies were evaluated using the Scottish Intercollegiate Guidelines Network (SIGN) tool (23,24). Information was extracted in a format previously designed for independent review by an author and subsequent review by a second author. Information was extracted related to the defined variables.

A summary estimator of primary outcomes was generated to estimate heterogeneity by I2 statistic, using the Review Manager program, version 5.3 (Cochrane Collaboration). Publication bias was assessed by performing a funnel plot using the Egger test.

To obtain data missing in the published articles, the authors were contacted by email. When this was not possible, the data were analyzed omitting the missing information. The data included in the analysis were those reported by intention-to-treat analysis.

Results

Study description

As a result of the search process, 527 references were found. Of them, 14 retrospective studies and one systematic review complied with our inclusion and exclusion criteria (15,19,25-37). Of the 1,395 patients included in the retrospective studies reviewed, 372 were HIV-positive and





1,023 HIV-negative. *Figure 1* shows the study selection process.

Table 1 describes the characteristics of the selected studies. The studies compared HIV-positive *vs.* HIVnegative patients with SC ACC managed with RTCT. The main outcome was toxicity and the secondary one was quality of life. Since no quality of life study comparing the two arms was found at the time of the search, only differences in terms of toxicities between HIV-positive versus HIV-negative patients were analyzed.

Bias risk of selected studies

Since all the studies were retrospective, they were evaluated according to SIGN criteria. Overall, a high risk of confusion and detection biases was found. Furthermore, since they were all retrospective studies, it was not possible to evaluate performance and attrition biases. *Table 2* shows the results of the qualification.

In order to avoid publication bias, gray literature and reports cited in clinical trials were reviewed; no new publications or records were found (38,39). Egger test and funnel plot graph

Table I Studies	included in the review		
Author	Patients' characteristics	Radiotherapy	Chemotherapy
Holland, 1994 (25)	73 patients: 55 HIV negative, 11 undetermined but at high- risk for HIV and 7 HIV-positive	Mean dose: 53.8 Gy	5 FU alone or combined with MMC
	Antiretroviral use not reported		Doses not reported
Kim, 2001 (33)	73 patients: 13 HIV+ and 60 HIV–	50–54 Gy	5 FU (1,000 mg/m ^{2} as a continuous infusion during the first four days of radiation therapy and again at its completion) + MMC (10 mg/m ^{2} as a bolus injection on day 1 of chemotherapy)
	Antiretroviral use not reported		
Vatra, 2002 (29)	44 patients: 20 HIV+ and 24 HIV-	Up to 65 Gy	5 FU alone (1,200–1,400 $$ mg/d) or combined with either MMC (bolus 15 mg/m²) or DDP (4 mg/m²)
	Antiretroviral use not reported		
Oehler-Jänne, 2006 (30)	91 patients: 10 HIV+ (antiretroviral use) and 81 HIV–	45 Gy 3D CRT, 1.8 Gy per fraction + EBRT or BT boost (total dose 59.4 Gy).	5 FU (continuous infusion during the first five days of radiotherapy at a dose of 750 mg/m^2 or over four days at 1,000 mg/m^2) + MMC (bolus on day one of radiotherapy (15 mg/m^2) or twice
			during week 1 and 5 (10 mg/m ²)
Oehler-Jänne, 2008 (15)	121 patients: 40 HIV+ (antiretroviral use) and 81 HIV–	3D CRT or BT boost for a total dose of 59.4 Gy (Zurich), 60 Gy (Paris), 58 Gy (Geneva) or 52 Gy (Montreal)	5 FU (continuous infusion during the first five days of radiotherapy at a dose of 750 mg/m ² or over four days at 1,000 mg/m ²) + MMC (bolus on day one of radiotherapy (15 mg/m ²) or twice during week 1 and 5 (10 mg/m ²) or DDP (on week 1 and 4 or 5 at a dose of 40 mg/m ² /d (Zurich) or 25 mg/m ² /d over 4 days (Paris)
Abramowitz 2009 (36)	151 patients: 107 HIV– and 44 HIV+ (antiretroviral use)	45 Gy Pelvic RT box technique + EBRT or BT boost for a total dose of 60 to 65 Gy	5-FU + cisplatin (doses not reported)
Hogg, 2009 (34)	87 patients: 21 patients HIV+ (antiretroviral use) and 66 patients HIV–	Not specified	5-FU + MMC (doses not reported)
Hammad 2011 (19)	45 patients: 13 HIV+ (antiretroviral use) and 42 HIV–	45–59 Gy HIV+ and 45–63 cGy HIV–	5-FU (750 to 1,000 mg/m ² /d) + MMC (10 mg/m ²) for 4 to 5 days on weeks 1 and 5 of radiation
Fraunholz 2011 (26)	70 patients: 25 HIV+ (antiretroviral use) and 45 HIV–	3D CRT	5-FU (1,000 mg/m ² /d as 4-day continuous infusion in the first and fifth week of RT) + MMC (10 mg/m ²) was administered as intravenous bolus on day 1 of each cycle
		50–60.4 in HIV+ and 45–60 in HIV– patients	
Munoz- Bongrand 2011 (31)	46 patients: 20 HIV+ (antiretroviral use) and 26 HIV–	Four fields: total dose 60 y 70 Gy with either EBRT or BT	5-FU (1,000 mg/m ² /day 5 from day 1 to day 3) as a continuous infusion), DDP (50 mg/m ² /day on days 1 and 2, infusedin 1 h)

Table 1 Studies included in the review

Table 1 (continued)

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Author	Patients' characteristics	Radiotherapy	Chemotherapy
White 2017 (28)	258 patients: 53 HIV+ (antiretroviral use in 70% of them) and 205 HIV-	30 Gy Pelvic RT box technique + EBRT or BT boost up to 54 Gy	5-FU (1,000 mg/m ² /d on days 1 to 4 and 29 to 32) + MMC (10 mg/m ² given on day 1 \pm day 29)
		After 2007: IMRT (RTOG 0529)	
Grew 2015 (35)	108 patients: 69 HIV– and 39 HIV+ (antiretroviral use)	3D CRT or IMRT; total dose 5,400 cGy	5-FU (1,000 mg/m²/d on days 1 to 4 and 29 to 32) + MMC (10 mg/m² on days 1 and 29)
Martin 2016 (27)	142 patients: 42 HIV+ and 100 HIV- (antiretroviral use)	3D CRT and IMRT 50.4 (34.2–60) Gy—91 patients (64%) had additional EBRT boost 5.4–10.8 Gy	5-FU (1,000 mg/m ² /d or 800 mg/m ² /d) as 4- or 5-day continuous infusion + MMC (10 mg/m ² on day 1 of each cycle)
Wieghard 2016 (32)	86 patients: 14 HIV+ and 72 HIV– (antiretroviral use)	IMRT: 45 to 54 Gy as a total dose	5-FU + MMC or DDP. As recommended by current guidelines

5-FU, 5-fluorouracil; MMC, mitomycin-C; IMRT, intensity modulated radiation therapy.

Table 2 Biases of observational studies

Author, year	Selection	Detection	Confusion	Selective report
Holland 1994 (25)	Unknown	Low	High	Low
Kim 2001 (33)	Unknown	Low	High	Low
Vatra 2002 (29)	Unknown	High	Unknown	High
Oehler-Jänne 2006 (30)	Unknown	High	Unknown	Low
Oehler-Jänne 2008 (15)	Unknown	High	Unknown	Low
Abramowitz 2009 (36)	Unknown	Low	High	Low
Hogg 2009 (34)	Unknown	Low	High	Low
Hammad 2011 (19)	Unknown	Low	High	Low
Fraunholz 2011 (26)	Unknown	Low	High	Low
Munoz-Bongrand 2011 (31)	Unknown	High	Unknown	High
White 2014 (27)	Unknown	High	Unknown	Low
Grew 2015 (35)	Unknown	Low	High	Low
Martin 2016 (27)	Unknown	High	Unknown	Low
Wieghard 2016 (32)	Unknown	High	Unknown	Low

were also performed, finding no publication bias.

RTCT-related toxicity

Regarding RT, a study showed no significant differences in the duration of irradiation between HIV-positive and negative patients (P=0.67) (36). Three studies showed that there were no differences in terms of the dose received in both HIV-positive and HIV-negative patients. Of these, one showed that there were no significant differences in terms of total dose (P=0.91), another showed that there were no significant differences in the total RT dose to the pelvis (P=0.53) or in the boost dose (P=0.53) and another showed that there were no significant differences in radiation dose to electively treated lymph nodes or tumors, without calculating statistical significance (26,35,36).

Regarding RT technique, three studies used the box technique, three studies administered conformational RT and one study applied intensity modulated radiation therapy (IMRT); of the remaining studies, one switched from the box technique to IMRT after 2007, and two other studies used both conformational RT and IMRT, while four studies did not specify the RT technique used (15,19,25-37). Five studies used brachytherapy as boost (15,28,30,31,36).

Regarding the drugs used, eight studies administered 5-fluorouracil (5-FU) and mitomycin-C (MMC), two studies used 5-FU plus cisplatin (CDDP), two studies used 5-FU in combination with either MMC or CDDP, one study used 5-FU either alone or combined with MMC, and one study used 5-FU alone or combined with either MMC or CDDP (15,19,25-37).

One study showed that there was no significant difference in CT dose reduction between HIV-positive and HIVnegative patients (P=0.74) (36). However, another study showed that the full dose of 5-FU/MMC was administered to 72% of HIV-positive patients compared to 91% of HIVnegative patients (P=0.04). CT had to be stopped after the second cycle due to hematological toxicity and/or infections in 4 HIV-positive patients (16%), and the CT dose reduced after the second cycle in 3 HIV-positive patients (12%), while in HIV-negative patients a CT-dose reduction after the second cycle was necessary in only 4 cases (9%) (26). One study showed significantly lower tolerance to MMC (P≤0.001) in HIV-positive patients, while another showed no differences in the administration of MMC in both groups (32,35).

One study reported lower, non-significant compliance in HIV-positive patients, due to a higher toxicity rate in this population, particularly in patients with low CD4 counts or severe thrombocytopenia before or during treatment (30). Another study reported no statistically significant differences in compliance between the two groups but did not report the statistical magnitude (35).

Hospitalization, treatment interruption and duration

Four studies reported the need for hospitalization, three of them by study arm, showing a significantly higher rate of hospitalization in HIV-positive patients compared to HIV-negative patients (25,28,34,35). Grew reported a hospitalization rate of 33% vs. 15% (P=0.024) in HIVpositive vs. HIV-negative patients respectively (35); a second article reported a hospitalization rate of 48% and 41% in HIV-positive vs. HIV-negative patients respectively, which was not significant (P=0.62) (34); a third study reported a 43% vs. 7% hospitalization rate in HIV-positive vs. HIV-negative patients, without reporting statistical significance (25). Finally, one study reported overall hospitalization in 18% of patients, without differentiating between the two groups (28).

Treatment interruption was also reported in five studies (25), of which, one reported an overall 30% rate in RT pause (mean interruption 7 days) (28), three studies showed that pauses were longer in HIV-positive patients (25,31,34), and one study showed that they were longer in HIV-negative patients (26). Of the three studies that showed longer interruptions in HIV-positive patients, one reported that 34 patients required treatment pauses for more than five days, 43% HIV-positive and 38% HIVnegative patients (P=0.80, not significant) (34); in another study, all HIV-positive patients required pausing treatment vs. 55% of HIV-negative patients, no statistical significance was reported (25); the third study reported a complete stop of the RTCT treatment at 45 Gy in 2 HIV-infected patients due to local infections and in 1 patient not infected with HIV due to perianal necrosis (31). This same study showed that 26 patients (11 infected and 15 not infected with HIV) received prolonged RTCT treatment (31). The study that reported a higher interruption rate in HIV-negative patients showed that temporary (>3 days) interruption of RT was necessary in 8% of HIV-positive patients and in 11% of HIV-negative patients, without reporting any statistical significance (26).

Regarding treatment duration, one study showed that due to the acute toxicity of RTCT there was an increase in the duration of treatment in HIV-infected patients compared to uninfected patients (P=0.027) while another paper showed that RTCT duration did not significantly differ between the cohorts (median 96.5 days, IQR 73.0 to 118.8 for the HIV-positive cohort and 88.5 days, IQR 73.0 to 118.8, for the HIV-negative cohort, P =0.57 (31,32).

Acute toxicity

Overall acute toxicity was evaluated in five studies (15,28,30,31,34) where statistically significant differences were reported between HIV-positive and HIV-negative patients (P=0.001) with a low heterogeneity (*Figure 2*). However, when reviewing the publications, two showed that acute toxicity was higher in HIV-positive patients; one

Study or Subgroup	VIH neg Events	Total	VIH pos Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year		Odds M-H, Rand	Ratio om, 95% C	a.	
Kim 2001	10	33	8	10	6.6%	0.11 [0.02, 0.61]	2001					
Oehler 2006	24	81	6	10	10.4%	0.28 [0.07, 1.09]	2006			ł		
Oehler 2008	25	81	19	40	28.1%	0.49 [0.23, 1.08]	2008			ŧ		
Hogg 2009	48	66	17	21	12.7%	0.63 [0.19, 2.12]	2009			 		
White 2014	85	205	28	53	42.2%	0.63 (0.34, 1.16)	2014			t		
Total (95% CI)		466		134	100.0%	0.48 [0.31, 0.76]			•			
Total events	192		78									
Heterogeneity: Tau ² = 0.03; Chi ² = 4.44, df = 4 (P = 0.35); I ² = 10%								0.01	01		10	100
Test for overall effect:	Z = 3.19 (F	P = 0.00	11)					0.01	VIH neg	VIH pos	10	100

Figure 2 Acute toxicity.



Figure 3 Hematological toxicity.

of them registered a non-significant difference of 81% vs.73%, and the other showed that although the frequency of grade 3–4 acute 3toxicities doubled in seropositive individuals (60% vs. 30%) this difference was not significant (30,34). Two studies divided acute toxicity into hematological and non-hematological toxicity (dermatitis, diarrhea) and did not report any statistically significant grade 3-4 events among HIV-positive or HIV-negative patients (P=0.43) (25,28).

Hematological toxicity was reported in 5 studies, four of which showed no statistically significant differences between the two arms (15,25,28,33).

A paper did show statistically significant results, finding that HIV-positive patients experienced a significantly lower mean white blood cell nadir than HIV-negative patients (2.15 versus 3.05 thousand cells/ μ L; P=0.004); however, there were no significant differences in neutrophils, platelets or hemoglobin (35).

CT-induced grade 3–4 hematological toxicity was higher in HIV-positive (33%) compared to HIV-negative patients who received MMC (12%; P=0.08); two of the four HIVpositive patients with severe hematological adverse effects had CD4 >200 cells/µL; no severe hematological toxicity was observed in HIV-positive patients who received cisplatin (15). Another study that also assessed CT-induced hematologic toxicity showed that 50% of HIV-positive patients receiving antiretrovirals who were treated with MMC CT developed acute grade-3 thrombocytopenia, compared with 0% of HIV-negative patients (P=0.05) (30). It should be noted that two of the patients had a CD4 count >200 cells/ μ L, suggesting adequate compliance with antiretroviral treatment (30).

Four studies reported similar risks of hematological toxicity; we assessed whether HIV-positivity posed a higher risk, finding a statistically significant (P=0.009) higher risk for hematological toxicity in HIV-positive patients, despite highly heterogeneous data (*Figure 3*) (15,26,28,33).

Four studies reported no statistically significant differences in grade 3–4 skin toxicities between HIV-positive and – negative patients (15,19,27,35), while two studies reported that acute grade 3–4 dermatitis was more frequent among HIV-positive patients without reporting statistical data (26,33). The meta-analysis results showed that the risk of grade 3–4 skin toxicity among HIV-positive patients was not significantly different compared to HIV-negative patients (*Figure 4*). Severe skin toxicity induced by RT was observed in 35% of HIV-positive and 17% of HIV-negative patients (P=0.04) (15,19,26,27,33,35).

Five studies did not report any significant differences in gastrointestinal toxicity between the two arms (15,19,25,27,35), while one showed that HIV-positive patients had a higher risk of diarrhea (4% versus 16%)

	VIH neg		VIH pos			Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	lom, 95% C	1	
Kim 2001	5	60	5	13	16.0%	0.15 [0.03, 0.62]	2001	_	•			
Oehler 2008	12	81	16	40	18.5%	0.26 [0.11, 0.63]	2008					
Hammad 2010	13	23	3	13	15.6%	4.33 [0.94, 20.03]	2010					
Fraunholz 2011	18	45	24	25	13.0%	0.03 [0.00, 0.22]	2011	← ••				
Grew 2015	25	69	6	39	18.0%	3.13 [1.15, 8.48]	2015				-	
Martin 2016	38	100	13	42	18.9%	1.37 [0.63, 2.95]	2016		-	-		
Total (95% CI)		378		172	100.0%	0.59 [0.17, 2.06]			-	-		
Total events	111		67									
Heterogeneity: Tau ² =	Heterogeneity: Tau ² = 2.01; Chi ² = 35.44, df = 5 (P < 0.00001); I ² = 86%							h 01		<u> </u>	10	100
Test for overall effect	Z = 0.83 (F	P = 0.41)					0.01	VIH neg	VIH pos	10	100

Figure 4 G3-4 skin toxicity.

	VIH neg		VIH pos			Odds Ratio		0	dds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, R	andom, 95% C	I	
Holland 1994	26	55	3	17	22.8%	4.18 [1.08, 16.21]	1994				
Oehler 2008	5	81	4	40	22.7%	0.59 [0.15, 2.34]	2008		•		
Hammad 2010	3	23	2	13	18.5%	0.82 [0.12, 5.71]	2010				
Grew 2015	1	69	1	39	13.2%	0.56 [0.03, 9.19]	2015		•	-	
Martin 2016	3	100	9	42	22.8%	0.11 [0.03, 0.44]	2016				
Total (95% CI)		328		151	100.0%	0.67 [0.17, 2.62]					
Total events	38		19								
Heterogeneity: Tau ² =	= 13.67	7, df = 4 (F	P = 0.00	(8); I ^z = 71	%		0.01 0.1		10	100	
Test for overall effect.	Z = 0.57 (F	= 0.57)					VIH neg	VIH pos	10	100

Figure 5 Diarrhea.

without reporting the significance of the finding and another study showed that acute gastrointestinal toxicity was higher in HIV-positive patients than in HIV-negative patients (48% and 24%, respectively; P=0.04) (26,34).

The need for colostomy was reported in two studies that showed no difference between the two arms (26,34). The risk of developing diarrhea was evaluated in five studies (15,19,25,27,35), with no statistically significant differences between HIV-positive and HIV-negative patients (*Figure 5*).

None of the studies documenting higher toxicity for HIV-positive patients specified what the CD4 count was for the patients who tolerated the treatment poorly, nor did they report whether medical follow-up with CD4 count was performed. The studies that reported use of antiretrovirals did not specify whether a change in drugs was necessary for patients presenting opportunistic infections due to the RTCT treatment (15,19,25-36).

Late and chronic toxicity

Overall, four studies reported the risk of chronic toxicity, finding no statistically significant differences in the risk of developing chronic toxicity between HIV-positive and HIV-negative patients (15,28,34,38) (*Figure 6*).

Two studies reported a higher rate of toxicity to the abdomino-pelvic area in HIV positive patients. Vatra *et al.* reported 40% abdomino-pelvic toxicities in HIV-positive *vs.* 12% in HIV-negative (P=0.04) while Fraunholz *et al.* reported a higher risk of serious late gastrointestinal toxicities (diarrhea, perforation, enteritis, infection) in HIV-positive patients (11% *vs.* 4.4%) (26,29).

Furthermore, one study reported that anal stenosis was the main cause of late toxicity in the HIV-positive group (34). Another study found that a late grade-4 large perineal ulcer was more frequent in patients with HIV, while another study reported higher gastrointestinal toxicity in HIV-negative patients, and the authors suggested that this was possibly because they received higher RT doses (33,34).

Antiretrovirals use

Of all the studies, only three did not report the use of antiretrovirals in HIV-positive patients (25,29,33). Although an equitable comparison cannot be made, since most studies used antiretrovirals, the three studies that did not report antiretroviral use registered higher toxicity rates among HIV-positive patients, while in the studies that used



Figure 6 Chronic toxicity.

antiretrovirals, most of the toxicities evaluated did not yield any statistically significant differences.

Additionally, it was evaluated whether RTCT-induced toxicity in patients with ACC was related to overall survival. This data was reported in 6 studies. Kim et al. (33) reported non-significant overall survival of 3.1 years in HIV+ patients versus 5.3 years in uninfected patients (P=0.06); Hammad et al. (19) reported median overall survival of 33.5 months for HIV+ patients, with a 58% rate in 24 months (90% CI, 34-82%) versus 71.8 months, with a 77% rates in 24 months for HIV-negative patients (90% CI, 65-90%), Holland et al. (25) showed a 71% 4-year overall survival rate in uninfected patients versus a 29% 2-year survival rate in HIV-positive patients, but did not report statistical data; Vatra et al. (29) documented a 40% 3-year survival rate for HIV-positive vs. 21% for HIV-negative patients (data available for 10/20 infected patients and for 22/24 of HIVnegative patients), median survival for HIV+ patients was 18 months (range, 10-43 months), which was significantly shorter (P<0.01) than the 28-month (range, 18-172 month) median survival observed in the HIV-group. Abramowitz et al. (36) did not find any statistical differences between the two groups (P=0.92) while White et al. (28) reported a trend toward worse 3-year overall survival in the HIV-positive group at univariate analysis (72% vs. 84%; P=0.06).

None of these studies reported whether survival was negatively influenced by treatment-related toxicity, however, four studies assessed the possible impact of CD4 counts on overall survival. Vatra *et al.* (29) found that HIV+ patients with CD4 counts <250/mm³ at diagnosis survived an average of 9 months; two studies found no differences in overall survival between patients with CD4 counts < or >200 (P=0.57) (34) and HR: 1.34 (0.32–5.96; P=0.67) (28), while a forth study showed no impact of CD4 counts on overall survival, without reporting CD4 range or statistical values (31).

Discussion

This review compiles the evidence published until June 2019 on the different toxicities from RTCT treatment in HIV-positive compared to HIV-negative patients with SC ACC. It is important to take into account that all RT techniques and CT agents used for the disease were included. All studies were retrospective; a systematic review published in 2018 was also found (15,19,25-37). We planned to assess whether there were any differences in quality of life between these two groups of patients, however, no studies were found that evaluated this item, which was therefore excluded from the results.

Regarding treatment toxicity in HIV-positive patients, some series report more severe side effects, particularly to the perineal skin, anorectal mucosa and hematological system, especially with RT doses over 30 Gy (13,15,40). Two factors that can predict the increase in acute toxicity to normal tissues have been found: a Cluster of Differentiation 4 (CD4) count <200/µL at the start of treatment, and the presence of acquired immune deficiency syndrome (AIDS), although these are not always associated with poor tolerance (25,41). Small observational studies have assessed the relationship between low CD4 count and treatment tolerance. One series found that patients with <200 cells/µL were more often hospitalized for myelosuppression, diarrhea or moist desquamation, and colostomy for treatment-related complications or persistent/recurrent disease, while three other series where patients received modern antiretroviral therapy found no significant relationship between CD4 count and treatment-related toxicity, even when CD4 was <200 to 300 cells/µL (42).

RTCT studies in patients with ACC including patients with CD4 counts >300 cells/mm³ show similar results between HIV-positive and -negative patients (43,44). Another therapeutic option that has been assessed is the use of a immunomodulators for HIV+ patients. Some studies including subjects with CD4 counts >200 cells/mm³ and others with counts >300 cells/mm³, have shown promising results: some studies are still ongoing (45-47). To date, there are no randomized clinical studies including HIV+ patients with ACC treated with RTCT.

The role of modern antiretrovirals in the improvement of treatment tolerance and cancer outcomes for HIV-positive patients with ACC is contradictory (15,19,20,23-29,48-50). It is important to remember that when antiretrovirals are administered concomitant to antineoplastic drugs, the risk for cross-toxicity must be taken into account, as well as the possible pharmacokinetics and pharmacodynamics of these drugs, since a drug accumulation can occur, as well as possible toxicity or decreased efficacy of one or both drug groups. This, however, should not be considered an obstacle to standard-dose treatment; it should only be taken as a warning for a strict surveillance of this subset of patients so as to avoid adverse reactions (21).

This review found that hematological and acute toxicities are significantly higher in HIV positive patients; however, several studies reported other events occurring more frequently, although without any statistical significance, in HIV positive patients, such as reduced treatment compliance, higher hospitalization and interruption rates. One of the possible reasons that can explain this, and that some authors mentioned, is the low number of HIV-positive patients compared to HIV-negative ones in the reviewed studies (372 *vs.* 1,023). However, with the use of more effective antiretrovirals, the performance status of HIVpositive patients has improved, potentially contributing to a significant decrease in toxicity rates.

When comparing studies that used antiretrovirals and those that did not, it was found that the three studies that did not use antiretrovirals showed higher toxicity rates for HIV-positive patients, while the studies where antiretroviral drugs were used reported mostly non-significant toxicity differences between the two groups, suggesting that antiretrovirals may play an important role in the reduction of toxicity (15,19,25-36). It was not possible to establish whether the RT technique used or the drugs used for CT played a role in toxicity, given the high heterogeneity of data.

Regarding overall survival, none of the studies that reported this outcome document that it was affected by toxicities during the course of treatment (19,25,28,29,33,36). However, some studies analyzed if overall survival was impacted by CD4 count in HIV-positive patients, finding conflicting results (28,29,31,34).

One of the limitations of our analysis is that all the evaluated studies were retrospective. There was also a large difference between the number of HIV-positive and HIVnegative patients.

When comparing the results of this systematic review with a recently published one, which analyzes whether there are any differences in terms of cancer outcomes between HIV-positive and HIV-negative patients, we found that in terms of dermatological and gastrointestinal toxicity, our results are consistent with those found by Camandaroba *et al.* Hematologic toxicity, on the other hand, cannot be compared because in our review we report it as a whole, while the other systematic review evaluates it depending on the cellularity affected (37).

Current guidelines recommend that HIV-positive patients should be treated the same way as HIV-negative ones, encouraging the use of antiretrovirals to diminish the side-effects caused by lower CD4 counts. However, a strict surveillance is necessary during treatment in order to detect any toxicity, as well as to carefully assess any possible drug interaction between antiretrovirals and antineoplastic agents (21,22).

In conclusion, the available literature comparing treatment-related toxicity between HIV-positive and HIVnegative patients treated by concurrent chemo-radiation for an ACC is scarce and disparate. Available data suggest that HIV-positive patients may be at higher risk of developing hematological toxicity than HIV-negative patients; they also show a higher trend of non-compliance with the treatment, treatment interruptions and need of hospitalization. Regarding the impact of antiretrovirals, a precise conclusion cannot be drawn given the high heterogeneity of the data analyzed. However, a beneficial effect might exist reflecting the importance of a better control of the HIV infection.

We hope randomized clinical trials for ACC in the future will include HIV-positive patients treated with RTCT, so as to clarify all doubts on oncological outcomes and treatments tolerance in this population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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