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CLINICAL INVESTIGATION

Efficacy and Toxicity of (Chemo)Radiation Therapy in HIV+ Patients with Squamous Cell Anal Cancer, a Subgroup Analysis of the National Multicenter Cohort FFCD-ANABASE

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Purpose: The influence of human immunodeficiency virus (HIV) infection on clinical outcomes in patients receiving (chemo) radiation therapy (RT) for squamous cell carcinoma of the anus (SCCA) is debated. The objective of this study was to compare efficacy and safety according to HIV status in patients with SCCA treated with C/RT.

Methods and Materials: Between January 2015 and April 2020, 488 patients with a known HIV status (17.6% HIV+) were treated with radiation therapy for SCCA and included in the FFCD-ANABASE multicentric prospective cohort. Clinical outcomes including overall survival (OS), locoregional recurrence-free survival, colostomy-free survival, response rate at 4 to 6 months, cancer-specific survival, relapse-free survival, and severe acute and late toxicity were compared between HIV+ and HIV− patients.

Results: The median follow-up was 35.8 months. HIV+ patients were younger ($P < .01$) and predominantly male ($P < .01$). Intensity modulated radiation therapy was performed in 80.7% of patients, and 80.9% received concurrent chemotherapy. A higher proportion of HIV+ patients received induction chemotherapy compared with HIV- patients. No statistically significant difference in overall treatment time or severe acute and late toxicities was found between HIV+ and HIV- patients. In

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univariate analyses, OS (HR = 2.1 [CI 95% 1.2;3.5], $P = .007$), locoregional recurrence-free survival (HR = 1.7 [1.1;2.7], $P = .02$), and colostomy-free survival (HR = 1.7 [1.1;2.6], $P = .01$) were significantly shorter in HIV+ patients than in HIV- patients. Response rate, cancer-specific survival, and relapse-free survival were not significantly different. The recurrence site was significantly different according to HIV status.

In the multivariate analysis, prognostic factors for OS were a World Health Organization performance status of ≥1 for the whole population, as well as HIV+ status for the subgroup of women.

Conclusions: HIV+ patients treated with chemo-RT for SCCA have poorer clinical outcomes, especially women. No difference was found in toxicity according to HIV status with intensity modulated radiation therapy technique.

Introduction

In 2023, squamous cell carcinoma of the anus (SCCA) remains a rare malignancy, although its incidence is increasing. It represents 3.0% of gastrointestinal cancers and less than 0.5% of all cancers in the USA.[1] In the Global Cancer Observatory (GLOBOCAN) study, the number of new SCCA cases per year was 50,865 worldwide, with 19,293 deaths per year.[2] SCCA is strongly associated with human papillomavirus (HPV) infection, where the risk of persistent infection is increased through numerous sexual partners, ano-receptive intercourse, and coinfection with human immunodeficiency virus (HIV).[3] For patients living with HIV, the SCCA incidence is higher than that in the rest of the population and is not reduced by the use of highly active antiretroviral therapy (HAART).[4] The use of HAART, by improving survival, may prolong the duration of HPV infection, which could explain the increased risk of SCCA. Indeed, patients living with HIV for at least 15 years are 12 times more likely to develop SCCA than those who have been infected for less than 5 years.[5]

First-line treatment of localized and locally advanced SCCA is based on radiation therapy or chemoradiation therapy, depending on the tumor stage.[6] Several cohorts of HIV+ patients treated for SCCA have been reported in the literature, but conclusions about clinical outcomes and treatment toxicity differ. Most of these cohorts were retrospective and employed 3-dimensional conformal radiation therapy (3DCRT). Some observed decreased overall survival (OS)[7,8] or worse tolerance,[9-12] while others described similar outcomes.[13-17] CD4 count appears to be predictive of treatment-related adverse events in some cohorts[18,19] but not in others.[8,20,21] Concomitant use of antiretrovirals, which may be radiosensitizing, could contribute to increased toxicity.[22-24]

Advances in radiation therapy techniques with the use of intensity modulated radiation therapy (IMRT) allow better sparing of healthy tissues, thus improving tolerance, which may reduce differences in clinical outcomes between HIV+ and HIV− patients,[17,25] as well as improved antiretrovirals.

The aim of the present multicenter study was to compare clinical outcomes and tolerance according to HIV status in patients with SCCA treated with modern (chemo)radiation therapy (C/RT).

Methods and Materials

Patients and study design

The FFCD-ANABASE cohort is a prospective multicentric observational study conducted by the Fédération Francophone de Cancérologie digestive (FFCD) in 60 French centers.[26] Patients were eligible if they had a histologically proven SCCA. To be included, they had to be over 18 years old and treated after January 1, 2015, for a newly diagnosed SCCA or a relapse. Patients who for psychological, social, familial, or geographic reasons could not be followed up regularly were excluded. For this subpopulation analysis, we included only patients with newly diagnosed SCCA, without distant metastases, who were treated with C/RT. We excluded patients whose HIV status was unknown.

Treatment

Patients were treated according to the French recommendations of the Thésaurus National de Cancérologie Digestive,[27] mainly with chemoradiation therapy (CRT), except for some patients with T1-2N0M0 tumors or patients with a low CD4 count, who received exclusive radiation therapy.

Radiation therapy was delivered by IMRT in most centers (static, rotational, or tomotherapy) or by 3DCRT. Total dose to gross tumor, prophylactic dose to lymph node regions, fractionation, and treatment breaks were recorded.

Chemotherapy regimens varied from one center to another. Standard chemotherapy consisted of 2 cycles of mitomycin C (MMC) and 5-fluorouracil (5FU) or capecitabine during weeks 1 and 5 of the treatment. Other regimens were used, such as 5FU-cisplatin, 5FU alone, capecitabine alone, MMC alone, MMC-cisplatin, or 5FU-MMC-panitumumab, for patients included in the FFCD 0904 phase 2 trial.[28] Doses and adjustments were not collected.

This study was approved by an ethics committee (CCTIRS-15.698) and the Commission National de l'Informatique et des Libertés (authorization number 915622). All patients received written information and provided verbal informed consent.

Outcomes and follow-up

The main objective was to compare OS between HIV+ and HIV− patients. We also evaluated the response rate at

4 to 6 months (RR), locoregional recurrence-free survival (LRFS), relapse-free survival (RFS), colostomy-free survival (CFS), cancer-specific survival (CSS), and severe acute and late toxicities. Predictive factors of these outcomes were evaluated.

RR was assessed by clinical and radiologic examination (magnetic resonance imaging [MRI] and/or positron emission tomography [PET] scan) between 4 and 6 months after the end of treatment. OS, CSS, LRFS, RFS, and CFS were calculated from the treatment start (chemotherapy or radiation therapy) to the time of event or death or last follow-up date.[26]

Grade 3 or higher toxicities were collected and scored using the National Cancer Institute Common Toxicity Criteria, version 4.0.

Statistical analysis

The quantitative variables were described by the usual descriptive statistics: mean, standard deviation, median, interquartile range, minimum, and maximum. They could also be categorized according to known cut-offs found in medical literature. The qualitative variables were described using numbers and percentages. Comparisons according to HIV status were performed by a Student or Wilcoxon test (according to the distribution of the variables) for quantitative variables, and by a χ^2 test or Fisher exact test for qualitative variables. Confidence intervals (CIs) were 95% 2-sided intervals. OS, CSS, RFS, LRFS, and CFS were plotted using the Kaplan-Meier estimator.[29] Survival rates at different times were calculated, and their 95% CIs were also estimated. Numbers of events were described according to HIV status. The standard error was estimated using the Greenwood formula, and the log-log transformation was used to compute CIs. Comparisons according to HIV status were performed on an exploratory basis using the log-rank test.[30] Univariate and multivariate analyses were conducted using the Cox model to determine prognostic factors of OS, LRFS, RFS, CFS, and CSS. Multivariate analyses included variables with $P < .15$ in the univariate analysis. We applied in a univariate Cox model the inverse of probability of treatment weighting method using a propensity score with age, gender, smoking status, and body mass index. Because of the strong interaction between HIV status and gender, we performed additional univariate and multivariate analyses in subgroups of women and men separately. Median follow-up was calculated using the reverse Kaplan-Meier method. Statistical analyses were conducted using SAS software version 9.4.

Results

Baseline demographic and clinical characteristics

Among 1015 patients with localized SCCA treated with radiation from 60 centers between January 2015 and April 2020, 488 patients with a known HIV status were included in our analysis (86 HIV+ patients and 402 HIV− patients; Fig. 1).

Baseline characteristics according to HIV status are shown in Table 1. HIV+ patients were significantly younger ($P < .001$), more likely to be male ($P < .001$), and more likely to have a history of condyloma or precancerous lesions ($P < .001$). There were significantly more smokers in the HIV+ group ($P = .011$), but alcohol consumption did not differ significantly between the 2 groups.

The majority of HIV+ patients were on HIV treatment (97.6%) and had controlled disease (median CD4 count was 458/mm^3, and 8 patients had a CD4 count of <200/mm^3). HIV+ patients were treated with an association of nucleoside analog reverse-transcriptase inhibitors (NRTI) and integrase inhibitor (31.3%), NRTI and protease inhibitor (17.5%), a combination of NRTIs (11.3%), or NRTI and nonnucleoside analog reverse transcriptase inhibitor (11.3%).

The morphologic baseline evaluation was based on a computed tomography (CT) scan (57.4%), MRI (74.8%), PET CT (79.3%), and endo-anal ultrasound (30.7%). The most frequent tumor location was the anal canal (73.8% in HIV+ patients vs 81.9% in HIV− patients), followed by the anal margin (17.9% vs 9.8%) and the lower rectum (7.1% vs 7.8%). Tumor size, with a median of 40 mm in both groups, T stage (58.6% of T1-2, 41.4% of T3-4), and N stage (50% of lymph node involvement) were not statistically different between the 2 populations. A diverting colostomy was performed before starting treatment in 5.8% of HIV+ patients and 5.0% of HIV− patients.

Treatment characteristics and compliance

Treatment characteristics for HIV+ and HIV− patients are presented in Table 2. Radiation therapy technique did not differ significantly between the 2 groups: IMRT was used in 84.7% of HIV+ patients and 81.1% of HIV− patients, and brachytherapy boost was realized in 8.2% of HIV-positive patients and 7.9% of HIV− patients. The median duration of radiation therapy was similar (53 days in HIV+ population vs 51 days in HIV−, $P = .27$), as was the tumor dose. Median total dose to the gross tumor volume was 61.2 Gy (range, 20-64 Gy) for HIV+ patients and 60 Gy (range, 18-68.4 Gy) for HIV− patients ($P = .32$). Median elective dose to lymph node regions, if performed, was 45 Gy in both groups (range, 14.0-56.0 Gy in HIV+ patients and 20.0-49.5 Gy in HIV− patients). HIV+ patients did not have more treatment breaks than HIV− patients ($P = .097$). The majority of patients received concurrent chemotherapy (77.9% in HIV+ patients vs 81.6% in HIV− patients, $P = .43$). The most commonly used chemotherapy regimens were MMC-5FU or MMC-capecitabine (81.1% in HIV+ patients and 85.5% in HIV− patients), followed by 5FU-cisplatin (5.8% and 3.5%). Twelve HIV+ patients received an induction

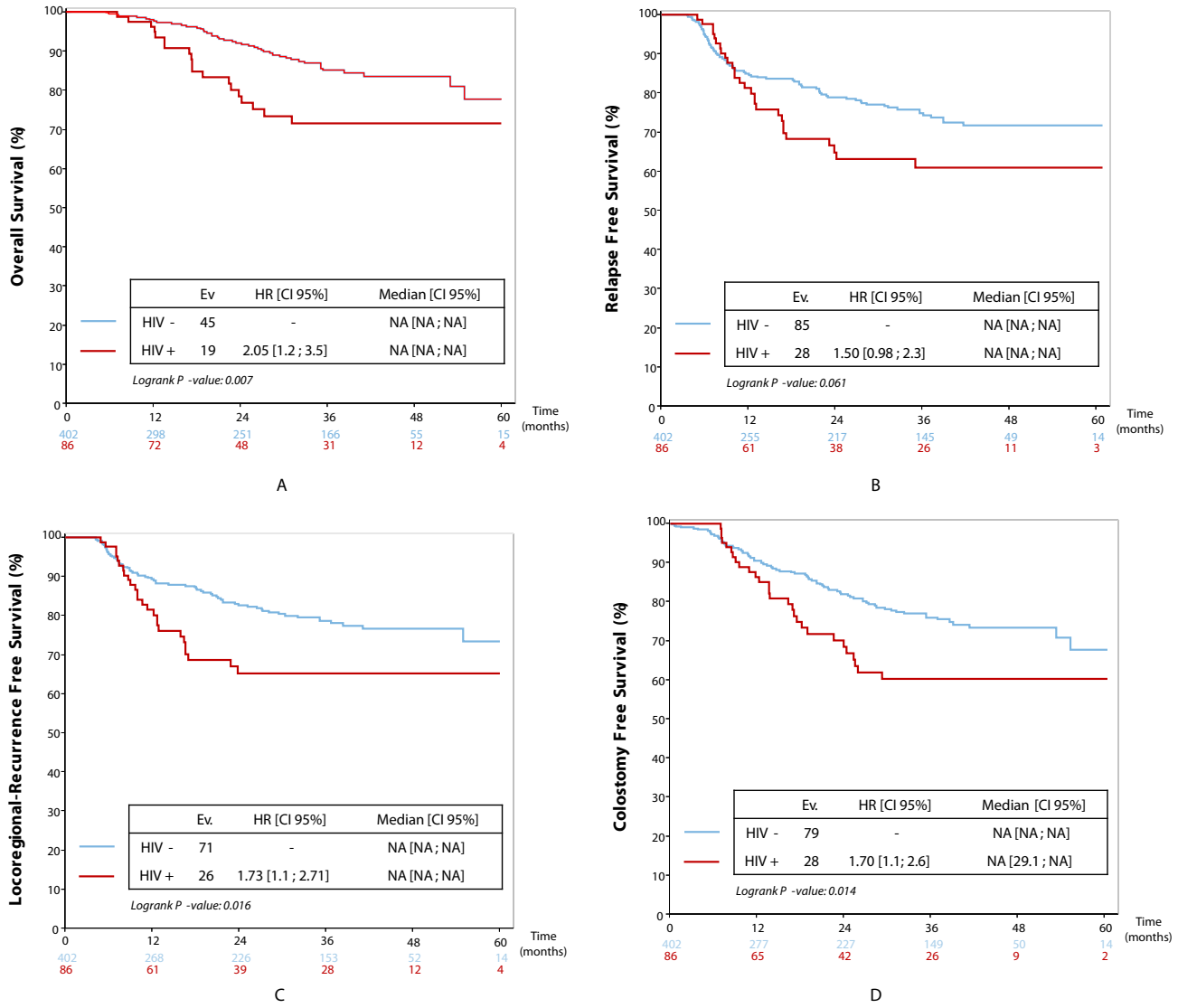

Fig. 1. Clinical outcomes according to HIV status: Overall survival (A), Relapse Free survival (B), Locoregional Recurrence Free survival (LRFS) (C), Colostomy Free survival (D). *Abbreviations:* NR = not reached; NE = could not be estimated; Ev = event; HR = Hazard ratio; CI = Confidence interval.

chemotherapy versus 22 HIV− patients (14.0% vs 5.5%, $P = .005$), mostly with 5FU-cisplatin or 5FU-carboplatin.

Acute and late toxicities (Table 2)

Severe acute toxicity due to C/RT did not differ significantly between the 2 groups. In our population, 47.7% of HIV+ patients experienced at least 1 toxicity of grade 3 or higher versus 45.0% of HIV− patients ($P = .65$). Mucocutaneous toxicity was the most frequent radiation-induced toxicity of grade ≥3, with radioepithelitis, anitis, and vulvitis (31.4% in HIV+ patients vs 31.1% in HIV− patients), followed by digestive toxicity (pain, enteritis, nausea, vomiting, diarrhea, rectal obstruction, fistula, and perforation) (12.8% in HIV+ vs 14.9% in HIV−), hematological toxicity (leucopenia, anemia, and thrombopenia) (10.5% in HIV+ vs 8.0% in HIV−), and urinary toxicity (dysuria, cystitis, fistula, and hematuria) (5.8% in HIV-positive vs 1.5% HIV−). One HIV+ patient died of postoperative complications (Table 3). Severe acute toxicity was not related to CD4 count or smoking status ($P = .38$).

The proportion of patients with late toxicity of grade 3 or higher was low and comparable in HIV+ and HIV− patients (4.7% vs 2.7%, $P = .35$).

Clinical outcomes

The median follow-up was 35.8 months (95% CI [34.5; 37.2]) for the entire cohort (37.2 months for HIV+ patients and 35.8 for HIV− patients). RR at 4 to 6 months was significantly lower in HIV+ patients (Table 3). Among HIV+ patients, 70.2% had a complete response (CR), 15.5% had a partial response (PR), 6.0% were stable, and 8.3% had a progression, versus 77.2%, 13.4%, 1.3%, and 8.1%, respectively,

Table 1 Baseline characteristics according to HIV status

		Overall population (N = 488)	HIV-positive (N = 86)	HIV-negative (N = 402)	*P* value
Patient characteristics					
Age, median (min; max) (y) n = 488		62.00 (32; 94)	56.00 (32; 92)	64.00 (35; 94)	**<.001**
Gender n = 488	Male	160 (32.8%)	66 (76.7%)	94 (23.4%)	**<.001**
	Female	328 (67.2%)	20 (23.3%)	308 (76.6%)	
WHO PS n = 476	0	314 (66.0%)	48 (57.1%)	266 (67.9%)	.234
	1	144 (30.3%)	34 (40.5%)	110 (28.0%)	
	≥2	18 (3.7%)	2 (2.4%)	16 (4.1%)	
BMI (kg/m^2) n = 480	Median (min; max)	23.8 (13.2; 45.6)	23.1 (15.2; 37.3)	24.0 (13.2; 45.6)	.069
Condyloma n = 400	Yes (%)	61 (15.3%)	36 (50.7%)	25 (8.6%)	**<.001**
AIN (1, 2, or 3) n = 367	Yes (%)	76 (20.4%)	27 (42.9%)	49 (15.8%)	**<.001**
Smoking status n = 435	Yes (%) Including current (%)	222 (51.0%) 125 (58.7%)	51 (63.8%) 32 (64%)	171 (48.2%) 93 (57.1%)	**.01**
Neutrophils count (G/L) n = 408	Median (min; max)	4.01 (0.79; 14.68)	3.89 (0.79; 12.8)	4.03 (1.0; 14.7)	.30
Tumor characteristics					
P16 (if achieved) n = 482	Positive	258 (93.1%)	45 (95.7%)	213 (92.6%)	.86
Tumor size (cm) n = 467	Median (min; max)	4.00 (0.2; 15.0)	4.00 (0.7; 15.0)	4.00 (0.2; 13)	.67
T stage n = 488	T1	70 (14.3%)	17 (19.8%)	53 (13.2%)	.32
	T2	216 (44.3%)	32 (37.2%)	184 (45.8%)	
	T3	131 (26.9%)	23 (26.7%)	108 (26.9%)	
	T4	71 (14.5%)	14 (16.3%)	57 (14.2%)	
N stage n = 487	N0	243 (49.9%)	45 (52.9%)	198 (49.3%)	.54
	N≥1	244 (50.1%)	40 (47.1%)	204 (50.7%)	
AJCC stage n = 487	I	53 (10.9%)	13 (15.3%)	40 (10.0%)	.66
	IIA	134 (27.5%)	22 (25.9%)	112 (27.9%)	
	IIB	39 (8.0%)	7 (8.2%)	32 (8.0%)	
	IIIA	98 (20.1%)	13 (15.3%)	85 (21.1%)	
	IIIB	17 (3.5%)	3 (3.5%)	14 (3.5%)	
	IIIC	146 (29.9%)	27 (31.8%)	146 (29.9%)	
Radiation therapy characteristics					
RT regimen n = 482	3DCRT	88 (18.3%)	13 (15.3%)	75 (18.9%)	.238
	Static IMRT	108 (22.4%)	15 (17.6%)	93 (23.4%)	
	Rotational IMRT	232 (48.1%)	43 (50.6%)	189 (47.6%)	
	Tomotherapy	54 (11.2%)	14 (16.5%)	40 (10.1%)	

(*Continued*)

Table 1 (*Continued*)

		Overall population (N = 488)	HIV-positive (N = 86)	HIV-negative (N = 402)	*P* value
Brachytherapy Boost n = 478	Yes	38 (7.9%)	7 (8.2%)	31 (7.9%)	.915
RT duration n = 486	Median (min; max), days	51.00 (6;150)	53.00 (35;134)	51.00 (6;150)	.266
Total dose to the tumor n = 481	Median (min; max), Gy	60.00 (18;68.4)	61.20 (20;65)	60.00 (18;68.4)	.324
Radiation therapy treatment break n = 483	Yes	165 (34.2%)	36 (41.9%)	129 (32.5%)	.097
	Planned	90 (55.6%)	21 (58.3%)	69 (54.8%)	
Chemotherapy					
Induction chemotherapy n = 488	Yes	34 (7.0%)	12 (14.0%)	22 (5.5%)	**.005**
Concurrent chemotherapy n = 488	Yes	395 (80.9%)	67 (77.9%)	328 (81.6%)	.430
Type of concurrent chemotherapy n = 395/395	MMC +/- 5FU or capecitabine +/- other	364 (92.2%)	59 (88.1%)	305 (93.0%)	.516
	5FU-Cisplatin	13 (3.3%)	4 (6.0%)	9 (2.7%)	
	Capecitabine	13 (3.3%)	3 (4.5%)	10 (3.0%)	
	Other	5 (1.2%)	1 (1.4%)	4 (1.3%)	

Abbreviations: HIV = human immunodeficiency virus; N = number of patients; n = number of patients with data available; WHO PS = World Health Organization performance status; BMI = body mass index; AIN = anal intraepithelial neoplasia; AJCC = American Joint Committee on Cancer; RT = radiation therapy; 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; MMC = mitomycin C; 5FU = 5-fluorouracil.

among HIV− patients (χ^2 = 0.0471). At 3 years, the OS, CSS, RFS, LRFS, and CFS rates were respectively 71.6%, 83.6%, 61.5%, 65.3%, and 60.4% for HIV+ patients, versus 85.1%, 90.8%, 74.7%, 78.6%, and 76.2% for HIV− patients (Table 2). OS was significantly lower in HIV+ patients (Fig. 1; HR, 2.05; 95% CI [1.20; 3.5], *P* = .007). The propensity score-adjusted hazard ratio by inverse of probability of treatment weighting analysis also showed statistically significant lower OS for HIV+ patients compared with HIV− patients (HR, 1.25; 95% CI [1.08; 1.45], *P* = .003) and lower RFS (HR, 1.25; 95% CI [1.07; 1.47], *P* = .005) and CFS (HR, 1.20; 95% CI [1.02; 1.41], *P* = .03).

OS according to gender and HIV status is shown in Figure 2. OS was significantly lower in HIV+ women than in HIV− women (HR, 5.06; 95% CI [1.92; 13.28]) and in men (HIV+ or HIV−) compared with HIV− women (HR,

Table 2 Acute and late toxicities

		HIV-positive N = 86 n (%)	HIV-negative N = 402 n (%)	*P* value
Acute toxicity G≥3	**All**	**41 (47.7)**	**181 (45.0)**	**.65**
	Mucocutaneous	27 (31.4)	125 (31.1)	
	Digestive	11 (12.8)	60 (14.9)	
	Hematological	9 (10.5)	35 (8.7)	
	Urinary	5 (5.8)	6 (1.5)	
	Others	4 (4.7)	25 (6.2)	
Late toxicity G≥3	**All**	**4 (4.7)**	**11 (2.7)**	**.35**

Table 3 Clinical outcomes according to human immunodeficiency virus (HIV) status: 4- to 6-month response rate, site of recurrence, and cause of death according to HIV status

4-6 Month response rate				
	Total N = 479	**HIV+ N = 84**	**HIV− N = 395**	***P* value**
Complete response	364 (76.0%)	59 (70.2%)	305 (77.2%)	**X^2: .0471**
Partial response	66 (13.8%)	13 (15.5%)	53 (13.4%)	
Stability	10 (2.1%)	5 (6.0%)	5 (1.3%)	
Progression	39 (8.1%)	7 (8.3%)	32 (8.1%)	
Site of recurrence				
	Total N = 98	**HIV+ N = 24**	**HIV− N = 74**	***P* value**
Local	34 (34.7%)	10 (41.7%)	24 (32.4%)	**χ^2: .0015**
Locoregional	22 (22.4%)	12 (50.0%)	10 (13.5%)	
Metastatic	32 (32.7%)	2 (8.3%)	30 (40.5%)	
Local + metastatic	1 (1.0%)	0 (0.0%)	1 (1.4%)	
Locoregional + metastatic	8 (8.2%)	0 (0.0%)	8 (10.8%)	
Unknown	1 (1.0%)	0 (0.0%)	1 (1.4%)	
Cause of death				
	Total N = 64	**HIV+ N = 19**	**HIV− N = 45**	
Cancer progression	36 (56.3%)	9 (47.4%)	27 (60.0%)	
Other cancer	4 (6.2%)	1 (5.3%)	3 (6.7%)	
Other cause	14 (21.9%)	4 (21.0%)	10 (22.2%)	
Toxicity of the treatment	1 (1.6%)	1 (5.3%)	0 (0.0)	
Not specified	9 (14.0%)	4 (21.0%)	5 (11.1%)	

2.35; 95% CI [1.23; 4.50] for HIV+ men; HR = 2.43; 95% CI [1.34; 4.39] for HIV− men; $P = .0003$). The most common cause of death was cancer progression in both groups (47.4% for HIV+ patients and 60.0% for HIV− patients) (Table 3). There was a trend but no significant difference in CSS (HR, 1.72; CI 95% [0.83; 3.54], $P = .14$) and RFS (HR, 1.50; 95% CI [0.98; 2.30], $P = .061$). The site of recurrence was significantly different according to HIV status ($P = .002$), with more metastatic relapse in HIV− patients (8.3% of relapses in HIV+ patients vs 40.5% of relapses in HIV− patients) (Table 3). Locoregional RFS was significantly worse in HIV+ patients (HR, 1.73; 95% CI [1.10; 2.71], $P = .016$) as was CFS (HR, 1.70; 95% CI; [1.11; 2.62], $P = .014$). After completing C/RT, 20.9% of HIV+ patients and 14.7% of HIV− patients underwent surgery ($P = .15$). Surgery was performed for a relapse, or for functional or diagnostic purposes. Abdominoperineal excision was conducted in 14.0% of HIV+ patients and 8.7% of HIV− patients ($P = .13$) and colostomy, in 17.4% and 11.2% of HIV+ and − patients, respectively ($P = .68$).

Univariate and multivariate analysis of prognostic factors (Table 4)

Prognostic factors were investigated with univariate and multivariate analysis (Table 4). HIV status was associated with poorer OS ($P = .009$), LRFS ($P = .017$), and CFS ($P = .016$) in the univariate analysis but not the multivariate analysis of the whole population. In the female subgroup, HIV status was significantly associated with poorer OS ($P = .006$), RFS ($P = .007$), and CFS ($P = .036$) in MV analysis. WHO performance status of 0 (versus ≥1) and T1-T2 stages (versus T3-T4 stages) were related to improved OS, RFS, LRFS, and CFS in the univariate and multivariate analysis (except T stage for OS). CR after treatment (versus PR or stable disease) was predictive of improved outcomes. Age, excisional biopsy, treatment break, radiation therapy dose, radiation therapy type (3DCRT or IMRT), radiation therapy duration, time from diagnosis to the first treatment, CD4 rate, and HIV viral load were not associated with any endpoint in the univariate analysis. In the male subgroup, we found no significant prognostic factor in the multivariate analysis.

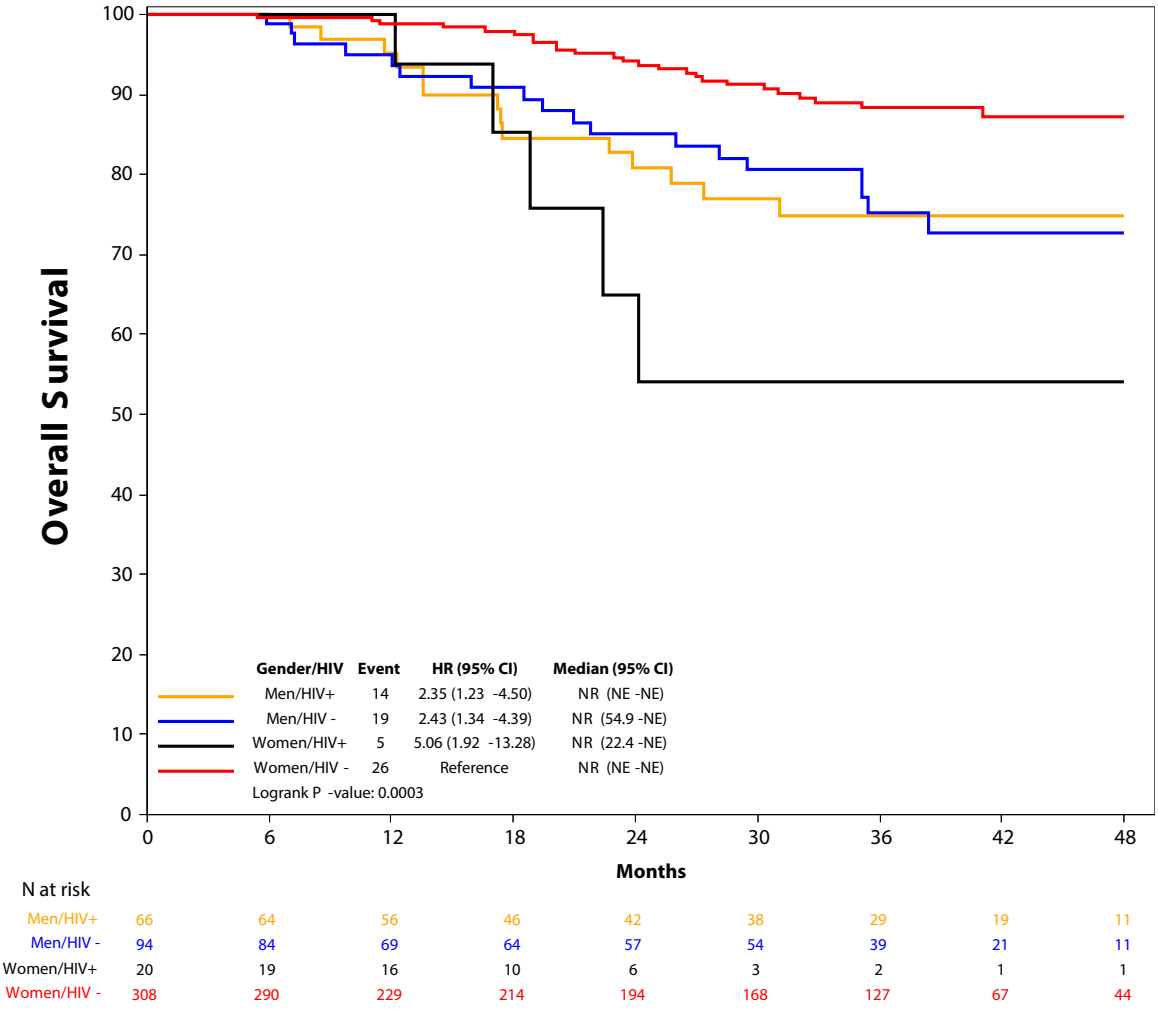

Fig. 2. Overall survival according to gender and HIV status. *Abbreviations:* NR = not reached; NE = could not be estimated; HR = Hazard ratio; CI = Confidence interval.

Discussion

This analysis of the FFCD-ANABASE cohort included 488 patients with SCCA who received C/RT. Toxicities were independent of HIV status. OS was statistically significantly reduced in HIV+ patients, as were LRFS and CFS. CSS and RFS did not differ significantly with HIV status, although there was a trend for RFS ($P = .06$). The CR rate was significantly lower in HIV+ patients (70.2% vs 77.2% in HIV− patients, $\chi^2 = 0.047$). Although the association between HIV status and OS, LRSS, and CFS was not confirmed in MV analyses in the whole population, it was an independent prognostic factor in the female subgroup.

Tolerance did not differ according to HIV status in our cohort, which is consistent with data from the most recent cohorts using modern radiation therapy techniques.[16,17,31,32] Most patients received IMRT, which was not the case for most of the cohorts published before 2017, whose treatment was mainly based on 2D or 3DCRT.[7,9,11,13,14,18,20,21] CD4 rate was not associated with toxicity, but only 8 patients (9.3% of HIV patients) had a lymphopenia <200/mm^3. Thus, with IMRT, overall treatment time and acute and late toxicity do not appear to be increased in HIV+ patients.

Tumor characteristics (T stage, N stage, and p16 expression) and neutrophil count at diagnosis were well balanced in both populations.[6,33-36] Treatment characteristics, including radiation doses delivered to gross tumor, radiation therapy duration, and proportion of patients receiving concurrent chemotherapy with MMC, were not statistically different. However, there were more men in the HIV+ population, and male gender is known to be a negative prognostic factor, although causal factors have not been identified.[33,34,37,38] The large predominance of men among HIV+ patients may have contributed to the poorer prognosis of HIV+ patients. Both male gender and HIV status were significantly associated with survival in the univariate analysis, but not in the multivariate analysis of the overall population. Because of this strong interaction between gender and HIV status, which may alter the results of the multivariate analyses, we conducted univariate and multivariate analyses in the male and female subgroups separately. We did not find any correlation

Table 4 Univariate and multivariate analysis of prognostic factors (hazard ratio, CI 95%, *P* value)

	Overall survival		Relapse-free survival		Locoregional recurrence-free survival		Colostomy-free survival	
	UV	MV	UV	MV	UV	MV	UV	MV
Gender (male vs female)	2.09 [1.28; 3.41] *P* = .003	-	1.52 [1.05; 2.21] *P* = .028	-	1.87 [1.26; 2.79] *P* = .002	-	1.75 [1.19; 2.55] *P* = .004	-
HIV status (positive vs negative)	2.05 [1.2; 3.51] *P* = .009	-	-	-	1.73 [1.1; 2.71] *P* = .017	-	1.7 [1.11; 2.62] *P* = .016	-
WHO PS (0 vs ≥1)	0.33 [0.2; 0.54] *P* < .001	0.37 [0.20; 0.67] *P* = .001	0.46 [0.31; 0.66] *P* < .001	0.45 [0.28; 0.75] *P* = .001	0.41 [27; 0.72] *P* < .001	0.42 [0.25; 71] *P* = .001	0.47 [0.32; 0.69] *P* < .001	0.53 [0.33; 0.86] *P* = .010
T stage (1-2 vs 3-4)	0.44 [0.27; 0.73] *P* = .001	-	0.42 [0.29; 0.61] *P* < .001	0.53 [0.32; 0.89] *P* = .016	0.46 [0.27; 0.61] *P* < .001	0.55 [0.32; 0.97] *P* = .037	0.37 [0.25; 0.54] *P* < .001	0.40 [0.23; 0.68] *P* < .001
N stage (N- vs N+)	0.56 [0.34; 0.93] *P* = .024	-	0.50 [0.34; 0.74] *P* < .001	-	0.60 [0.4; 0.9] *P* = .014	-	0.51 [0.35; 0.76] *P* = .001	-
Neutrophils count (≥ 5 G/L vs <5 G/L)	2.00 [1.18;3.39] *P* = .010	-	1.76 [1.15; 2.71] *P* = .009	-	1.87 [1.19; 2.95] *P* = .006	-	1.60 [1.03; 2.47] *P* = .035	-
Induction CT (yes vs no)	2.58 [1.35; 4.95] *P* = .004	-	2.22 [1.31; 3.76] *P* = .003	-	2.45 [1.41; 4.25] *P* = .001	-	2.15 [1.27; 3.71] *P* = .006	-
CT type (MMC-5FU/Cap vs other)	0.51 [0.27; 0.97] *P* = .040	-	0.51 [0.31; 0.84] *P* = .008	-	0.52 [0.3; 0.89] *P* = .017	-	0.54 [0.33; 0.9] *P* = .018	-
Brachytherapy boost (yes vs no)	-	-	-	-	-	-	0.31 [0.1; 0.96] *P* = .043	-
Time from diagnosis to RT	1.29 [1.12; 1.5] *P* = .001	-	-	-	-	-	1.16 [1.01; 1.33] *P* = .033	-

Abbreviations: UV = univariate analysis; MV = multivariate analysis; HIV = human immunodeficiency virus; WHO PS = World Health Organization performance status; CT = chemotherapy; MMC = mitomycin C; 5FU = 5-fluorouracil; RT = radiation therapy.

between HIV status and OS in the male subgroup, nor between HIV status and other factors (including WHO performance status). Male gender may be such a strong poor-prognosis factor that it might hide other factors such as HIV status. By contrast, we found that OS was strongly associated with HIV status and WHO performance status in the female subgroup. This observation is highly significant but is based on a low number of patients and a low number of events (deaths) and must therefore be confirmed by other cohorts. In the recent cohort published by the German Cancer Consortium - Radiation Oncology Group (DKTK-ROG), HIV status was not associated with OS in the whole population in a univariate analysis but was associated with OS in cT1-2 patients in a multivariate analysis.[39]

A higher proportion of HIV+ patients received induction chemotherapy, compared with HIV− patients. Induction chemotherapy, by delaying the initiation of radiation therapy and prolonging overall treatment time, may decrease local control and CFS.[40] These results suggest the importance of not delaying the initiation of radiation therapy, as doing so may have a negative effect on survival.[41] However, patients who received induction chemotherapy had more advanced tumors, which were associated with worse outcomes in the univariate and multivariate analyses.

Location of recurrence varied significantly according to HIV status. Recurrence was most frequently local or locoregional in HIV+ patients (91.7% of recurrences in HIV+ patients), whereas it was more often distant in HIV− patients (52.7% of recurrences in HIV− patients). Abramowitz et al also observed more metastatic relapses in HIV− patients, but the difference was not statistically significant (7% of relapses in HIV+ patients vs 35% of relapses in HIV− patients, $P = .06$).[14] The predominance of local recurrence in HIV+ patients could suggest a degree of radioresistance. Its mechanism remains unknown, but it could be partly explained by the role of the local immune response, with the tumor infiltration by lymphocytes, which is known to be a prognostic factor.[42] Indeed, a low tumor infiltrating lymphocyte score was associated with poorer disease-free survival, CSS, and OS,[42] and a low intratumoral CD3+ T-cell density and a low (or high, compared with moderate) CD4+ T-cell count were associated with OS in another study.[43] We could hypothesize that poorer local immune response might be seen in HIV+ individuals, which could explain the higher rate of local recurrence.

The different HPV genotype implicated according to HIV status[44] may also be involved.

The 3-year OS rate of 72% in HIV+ patients versus 85% in HIV− patients is very similar to that described by White et al in 2017 (72% vs 84%), for which the difference was not significant, probably owing to a lack of power ($P = .06$).[16] In other series, a significantly shorter OS in HIV-positive patients was reported.[7,8,45] However, some recognized prognostic factors were not balanced between HIV+ and − populations: in some studies, lymph node involvement was more common in HIV+ patients, with a lower use of concurrent chemotherapy,[45] or a significantly longer treatment duration than in HIV− patients.[7]

The FFCD-ANABASE cohort is a multicenter cohort, with data collected prospectively over a short period of 6 years. With 86 patients with HIV, it is one of the largest cohorts published, apart from the analysis of the Veterans Affairs database.[46,47] The most recent analysis of the Veterans Affairs database, including 219 HIV+ patients, did not compare HIV+ and − patients, but rather HIV+ patients with or without protease inhibitor medication.

Treatment was delivered according to the French guidelines and habits of the centers, and its modalities were therefore heterogeneous, but representative of French practice. For example, 7% of patients received induction chemotherapy, and a treatment break was planned from the start in 18% of patients.

Among the 1015 patients included in the main analysis of the ANABASE cohort, HIV status was only available for 488 patients (48%), despite several updates of the data. HIV serology may not have been performed systematically, especially in patients with very localized tumors, for whom concurrent chemotherapy was not indicated, or in elderly women. Patients with an unknown HIV status were excluded and were not considered HIV− patients to avoid biasing the results. We found no significant difference in specific survival, but the cause of death was unknown in some cases (21.0% in HIV+ patients vs 11.1% in HIV− patients, $P = .4$), which may bias this result.

Some data were not included in the case report form, such as the chemotherapy doses. Therefore, it was not possible to exclude a difference in chemotherapy doses between HIV+ and HIV− patients, who could have minimized a possible difference in treatment tolerance. Nevertheless, the rate of concurrent chemotherapy as well as the dose of radiation therapy delivered did not differ significantly between the 2 populations.

The evolution of the CD4 count after treatment was not described, whereas it appears in the literature to be a predictive factor of tumor recurrence and survival.[41,48] Thus, control of HIV and restoration of the immune system with a CD4 count >150/mm^3 after treatment appear to be important predictive factors of RFS, which highlights the important role of immunity in tumor control and the importance of close multidisciplinary oncological and infectious follow-up. Introduction of immunotherapy concomitantly or adjuvant to the CRT could be interesting, to enhance antitumor activity. A randomized phase 2 trial testing the addition of durvalumab to CRT in patients with locally advanced SCCA is currently open for enrollment.[49] There are encouraging results with immunotherapy in metastatic patients progressing after the first line of treatment, and immunotherapy seems to have a favorable benefit-risk balance in HIV+ patients, as well in HIV− patients.[50-52]

The high rate of local recurrence in HIV+ patients compared with that in HIV− patients could justify the exploration of a dose escalation strategy in these patients, which seems to be feasible with IMRT in the absence of observed increased toxicity.

Conclusion

In the FFCD-ANABASE cohort, HIV+ patients treated with C/RT for localized SCCA had poorer clinical outcomes, especially HIV+ women compared with HIV− women. Indeed, OMS performance status and HIV status were independent prognostic factors for OS, RFS, and CFS in the female subgroup. No difference was found in toxicity according to HIV status with IMRT technique.

This study suggests that HIV+ patients should be treated the same way as HIV− patients. Furthers trials are needed to understand these differences and improve outcomes in these patients, in which HIV+ patients must be included.

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