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Clinical presentation and outcome of squamous cell carcinoma of the anus in HIV-infected patients in the HAART-era: a GICAT experience

F. MARTELLOTTA[1], M. BERRETTA[1], B. CACOPARDO[2], R. FISICHELLA[3], O. SCHIOPPA[1], A. ZANGHÌ[3], D. SPARTÀ[3], A. CAPPELLANI[3], R. TALAMINI[4], I. IZZI[5], A. RIDOLFO[6], A. TORRESIN[7], F. FIORICA[8], U. TIRELLI[1]

[1]Division of Medical Oncology A, National Cancer Institute, Aviano, Pordenone, Italy
[2]Division of Infectious Disease, "Garibaldi-Nesima" Hospital, School of Medicine, University of Catania, Catania, Italy
[3]Department of Surgery, School of Medicine, University of Catania, Catania, Italy
[4]Epidemiology and Biostatistic Unit, National Cancer Institute, Aviano, Pordenone, Italy
[5]Division of Infectious Disease, School of Medicine, Catholic University of the Sacred Heart, Rome, Italy
[6]Division of Infectious Disease, "Luigi Sacco" Hospital, Milan, Italy
[7]Division of Infectious Disease, "Galliera" Hospital, Genova, Italy
[8]Division of Radiotherapy, "S. Anna" Hospital, Ferrara, Italy

Abstract. – INTRODUCTION: Squamous cell carcinoma of the anus (SCCA) is a relatively uncommon cancer. In the HIV-positive patients the introduction of the highly active antiretroviral therapy (HAART) did not change the incidence of SCCA.

BACKGROUND AND OBJECTIVES: This paper describes the Italian Cooperative Group on AIDS and Tumours (GICAT) experience on HIV-positive patients with SCCA. The purposes of this retrospective study were: first to describe the clinical presentation and outcome of HIV-positive patients with SCCA, second to compare them with the ones reported in the literature.

PATIENTS AND METHODS: Between July 2000 and March 2010 we retrospectively collected epidemiological, clinical and survival data from 65 patients with SCCA in HIV infection enrolled within the GICAT.

RESULTS: Fifty-three (81.5%) patients were male. The majority of patients (40%) were homosexual Forty-three patients (66.1%) were diagnosed with HIV before 1996. Thirty-five patients (54%) had CD4-positive cells count >200/mm^3 and 28 patients (43%) had viral load >50 cp/ml at the time of SCCA diagnosis. The median time difference between HIV and SCCA diagnosis was 120 months (range 10-282 months). Sixty-one patients (96.8%) received HAART at SCCA diagnosis. Fifty-two patients (80%) had performance status (PS) 0-1 at the time of SCCA diagnosis. Twenty-seven patients (41.5%) underwent surgery with curative intent. Thirty-five patients (53.9%) were given combined modality therapy (CMT) consisting of pelvic radiotherapy with concurrent chemotherapy. No grade 3/4 haematological or extra-haematological effects were observed in our patients.

CONCLUSIONS: In summary, despite the retrospective nature of analysis, the absence of patient strict criteria of inclusion/exclusion, our data on HIV-positive patients with SCCA, compared both to general population and to small reports on HIV-positive patients present in the literature, are promising.

Key Words:
Anal cancer, HIV, HPV, Chemotherapy, Radiotherapy, HAART.

Introduction

The gastrointestinal (GI) tract is one of the most common sites of opportunistic infections or malignancies in human immunodeficiency virus (HIV)-infected patients[1]. Squamous cell carcinoma of the anus (SCCA) is a relatively uncommon cancer of the GI tract, constituting only 1.5% of all digestive system cancers[2].

Recent data describe not only a different squamous cell carcinoma of the anus (SCCA) incidence rate between HIV-positive and HIV-negative population but also increased incidence rates of SCCA among HIV-infected patients in highly active antiretroviral therapy (HAART) era compared to pre-HAART era[3]. The incidence of SCCA in men with a history of receptive anal intercourse or history of genital warts or gonorrhea,

Corresponding Author: Ferdinando Martellotta, MD; e-mail: fmartellotta@cro.it

has been estimated to be as high as 35 per 100000 person/year prior to the AIDS epidemic. In HIV-positive men the incidence rates of SCCA is about twice that of HIV-negative homosexual men[4]. Particularly, the risk of SCCA is 120 times greater in HIV-positive than in HIV-negative patients[5] and in the setting of HIV it appears to be higher for patients with lower CD4+ T cell counts[2]. In addition to the increased risk for developing SCCA, HIV infected individuals may have higher SCCA-related morbidity and mortality. In fact, the 5 year survival ranges from 47% to 60%, which is lower than the 73% 5 year disease-free survival rate reported in the general population[6]. Moreover, SCCA occurs earlier in HIV-infected persons (mean age 37 years) than in HIV-negative men or women (mean age 58 years and 65 years, respectively)[7]. Furthermore, epidemiologic studies linked cervical and anal cancers showing that women with Cervical Intraepithelial Neoplasia (CIN) or cervical cancer had a probability of developing SCCA 3 to 5 times greater than to develop other GI malignancies[3]). Also women with 10 or more sexual partners, a history of anal or genital warts, gonorrhoea, or a history of anal receptive intercourse, are more likely to have anal cancer[8] Several population-based epidemiologic studies suggest that human papilloma virus (HPV) plays an important role in the development of anal cancer similar to the role it plays in cervical cancer[2]. In fact, HPV-DNA was detected in a high percentage of women and men with anal invasive cancer but was never found in normal anal mucosa and rectal adenocarcinoma[3]. HPV infection is the most common sexually transmitted infection in the general population and approximately 75% of all sexually active persons acquired a genital HPV subtype during their lifetime[9]. There are over 80 different HPV subtypes, at least 23 of which have been shown to infect the anogenital mucosa. Specific types of HPV, such as 16 and 18 are most frequently associated with invasive anal cancer or high-grade dysplasia lesions in population-based studies[10]. The relationship between HIV and HPV is complicated. HIV likely potentates the neoplastic effects of HPV through suppression of T-cell mediated immune surveillance[2]. HIV infection does not only increase susceptibility to HPV persistence but also increases the risk of acquisition of new HPV infections and reactivation of latent infections. It seems that HIV infection favours the persistence of HPV infection through a gradual loss of control over HPV replication within infected cells during the early stage of carcinogenesis[3-8]. The impact of HAART on the natural history of SCCA remains unclear. It should be possible that successful suppression of HIV replication by HAART would be accompanied by restoration of immune response to HPV and regression of high-grade lesions. However, early data suggest that most cases of high-grade lesions do not regress after the beginning of HAART and there is a significant correlation between anal involvement and advanced clinical stage of HIV disease[11-12]. In association with HAART, an aggressive approach to the treatment of SCCA in HIV infected patients is warranted, as reported in other non-AIDS defining cancers[13-28]. In fact, patients who receive the combination chemotherapy plus HAART may achieve better response rates and higher rates of survival than those who receive antineoplastic therapy alone. Several groups have reported that with the advent of HAART, overall survival has been comparable between HIV positive and negative patients[5]. Also several clinical studies suggest that patients with CD4 cell counts greater than 200/mmc seem to have less treatment-related morbidity[4-16,29].

This paper describes the Italian Cooperative Group on AIDS and Tumours (GICAT) experience on HIV-positive patients with SCCA. The purposes of this retrospective study were: first to describe the clinical presentation and outcome of HIV-positive patients with SCCA, second to compare them with the ones reported in the literature.

Patients and Methods

Between July 2000 and March 2010 we retrospectively collected epidemiological, clinical and survival data from 65 patients with SCCA in HIV infection enrolled within the GICAT. A questionnaire was sent to the participating centres to collect the epidemiologic and clinical data (patients demographics features, clinical presentation, tumor characteristics, type of treatment, HIV exposure category, CD4+ cell count, HIV viral load, HIV stage at anal cancer diagnosis, antiretroviral therapy history, vital status, and eventual cause of death). All patients had histologically confirmed anal squamous cancer and had undergone computed tomography scans of the chest, abdomen and pelvis to assess the extent of the tumour, the status of regional lymph nodes and the presence of distant metastases. SCCA were staged according to TNM staging system developed by the American Joint Committee on Cancer (AJCC) (30). The revised

classification system for HIV infection by the Centres for Disease Control (CDC) was used for the diagnosis of AIDS[31]. Toxicity was evaluated using the toxicity scale of National Cancer Institute Common Toxicity criteria, version 2.0. Information on survival was obtained through an active follow-up based on verification of vital status of the patients and the survival analysis was measured from the date of cancer diagnosis to the date of the last follow-up. Based on the CT scans of the chest, abdomen and pelvis at baseline and every 3-6 months, tumour response was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST).

Statistical Analysis

Survival analysis was computed using the Kaplan-Meier method[32]. In all cases statistical significance was claimed for $p \leq 0.05$.

Results

On Table I, the clinical features of 65 patients with anal cancer are shown.

Fifty-three (81.5%) patients were male, and 24 patients (37%) were older than 45 years. The majority of patients (40%) were homosexual, while 25% and 27% were drug users and heterosexual,

Table I. Characteristics of 65 patients with anal cancer.

	N (%)		N (%)
Sex		**Stage**	
Male	53 (81.5)	Unknown	6 (9.23)
Female	12 (18.5)	I	26 (40.0)
Age (years)		II-III	32 (49.2)
< 40	21 (32.3)	IV	5 (8.0)
41-45	20 (30.8)	**Performance status**	
> 45	24 (30.8)	Unknown	6 (9.23)
HIV exposure category		0 + 1	52 (80.0)
Unknown	2 (3.08)	> 2	7 (11.0)
Heterosexual	18 (27.0)	**Local surgery**	
Homosexual	26 (40.0)	No	31 (47.8)
IVDU	16 (25.0)	Standard	27 (41.5)
Eterosexual/IVDU	1 (1.60)	Palliative	7 (11.0)
Homosexual/IVDU	2 (3.08)	**Therapy**	
Years of HIV diagnosis		Unknown	15 (23.0)
< 1996	43 (66.1)	Chemotherapy	7 (11.0)
> 1997	22 (33.9)	Radiotherapy	8 (12.3)
CDC classification		Chemo/radiotherapy	35 (54.0)
Unknown	2 (3.08)	**Schedule**	
A1-A3	39 (60.0)	Unknown	24 (37.0)
B1-B3	11 (17.0)	1-3 cycles	32 (49.2)
C1-C3	13 (20.0)	> 3 cycles	9 (14.0)
CD4-positive/mmc		Toxicity	
Unknown	6 (9.23)	Unknown	18 (27.7)
< 200	24 (40.0)	Yes	22 (34.0)
200-400	14 (21.5)	No	25 (38.4)
> 400	21 (32.3)	**Treatment response**	
HIV RNA cp/ml		Unknown	4 (6.15)
Unknown	13 (20.0)	CR	37 (60.0)
< 50	24 (37.0)	PR	16 (25.0)
> 50	28 (43.0)	SD	1 (1.5)
Co-infection		PD	7 (10.8)
Unknown	3 (4.62)		
Yes	31 (47.7)		
– Unknown	34 (52.3)		
– HBV	11 (17.0)		
– HCV	17 (26.1)		
– Other	3 (4.62)		
No	31 (47.7)		

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; IVDU = intravenous drug user.

respectively. Forty-three patients (66.1%) were diagnosed with HIV before 1996. Thirty-nine patients (60%) had A1-A3 CDC classification at the time of SCCA diagnosis. Thirty-five patients (54%) had CD4-positive cells count >200/mm^3 and 28 patients (43%) had viral load >50 cp/ml at the time of SCCA diagnosis. Most patients (26.1%) had HCV co-infection and 11 patients (17%) had HBV co-infection. The median time difference between HIV and SCCA diagnosis was 120 months (range 10-282 months). Sixty-one patients (96.8%) received HAART at anal cancer diagnosis. Thirty-two patients (49.2%) and 5 patients (7.7%) had clinical stage II-III and IV at diagnosis, respectively. Fifty-two patients (80%) had performance status (PS) 0-1 at the time of SCCA diagnosis. Twenty-seven patients (41.5%) underwent surgery with curative intent. Sixty-one percent of stage 1 SCCA patients benefit of local excision. Thirty-five patients (53.9%) were given combined modality therapy (CMT) consisting of pelvic radiotherapy with concurrent chemotherapy. Twenty-two patients (33.8%) had side effects during CMT. No grade 3/4 haematological or extra-haematological effects were observed in our patients. We did not find a significant correlation between low CD4-positive cells count (< 200/mm^3) and an increase in toxicity due to CMT (p = 0.6011). Among responders, 37 patients (60%) had a complete response (CR) and 16 patients (24.6%) a partial response (PR). Seven patients (10.8%) had progressive disease (PD) and 1 patient (1.5%) showed stable disease (SD). Four patients were lost to follow-up. Thirty patients (46.2%) have relapsed disease with average time of eight months (1-75). At anal cancer relapse, 23 patients (35.3%) did not receive any therapy; 12 patients (40%) underwent surgery alone; 5 patients (16.7%) received chemotherapy alone; 1 patient (3.33%) underwent radiotherapy alone; 4 patients (13.3%) received palliative surgery and 3 patients (10%) underwent radiotherapy plus chemotherapy or surgery plus radiotherapy. We did not observed any significant difference between the stage of SCCA at diagnosis (early stage vs. locally advanced and/or metastatic) and the time to relapse ($\chi^2$2 log-rank test = 2.29, p = 0.32). No significant difference occurred between the initial treatment modality (chemotherapy vs. radiotherapy vs. chemotherapy plus radiotherapy) and the time to relapse ($\chi^2$2 log-rank test = 2.48, p = 0.29). Instead we observed a significant difference between patients with CR or PR compared with patients with SD o PD and the time to relapse ($\chi^2$2 log-rank test = 7.77, p = 0.05). Figure 1 shows Kaplan-Meier survival analysis according to HIV infection. Median survival was 106 months and the probability of survival at 5 years was 51%. Twenty-six patients (40%) died: 20 patients (76.9%) for disease progression; 1 patient (3.9%) for HIV infection progression, and 5 patients (19.2%) for other complications. Figure 2 shows Kaplan-Meier survival analysis according to patient stage. Median

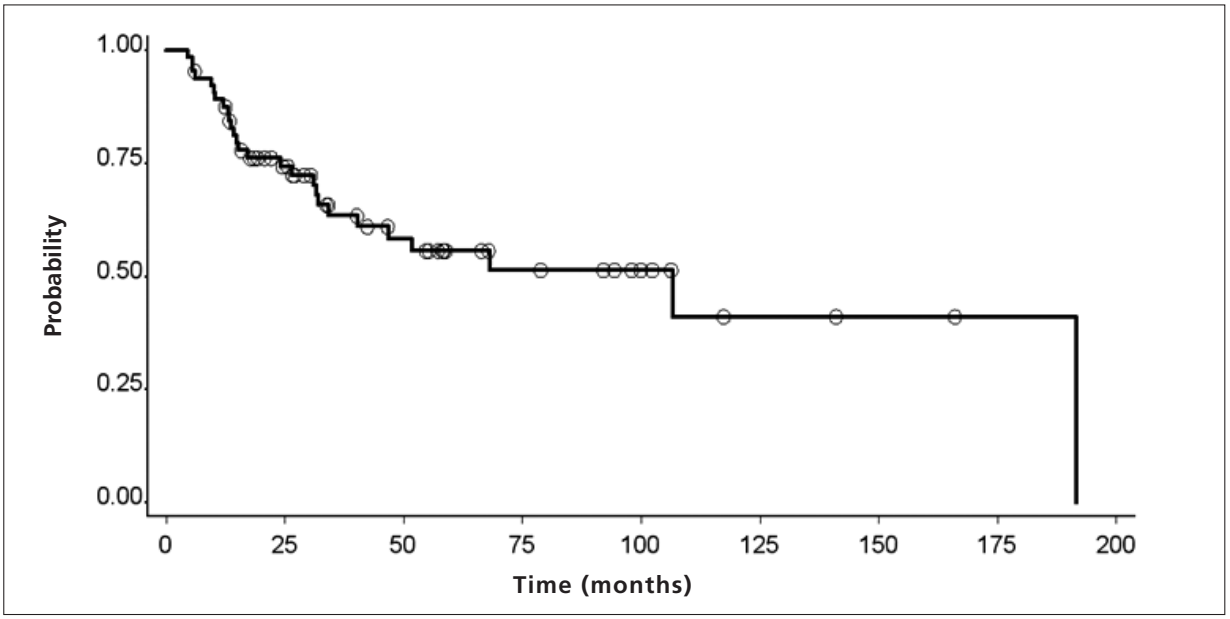

Figure 1. Overall survival of 65 patients with squamous cell carcinoma of anus.

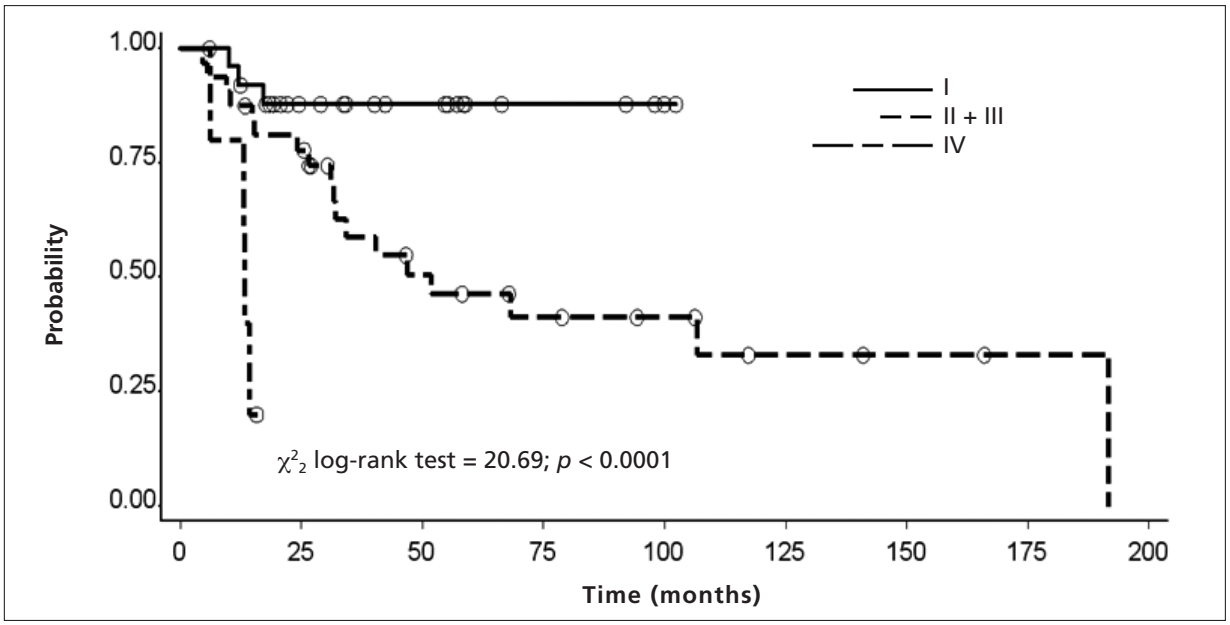

Figure 2. Survival of 65 patients with squamous cell carcinoma of the anus according to stage.

survivals were 52 months and 13 months for stage II-III and IV, respectively. Median survival was not achieved for stage I ($p \leq 0.0001$). Five-year overall survival rate by stage distribution was: stage I (88%), stage II-III (41%), stage IV (0%).

Discussion

To our knowledge, this is the largest SCCA cohort study in HIV-infected patients reported in the literature. In fact, data on SCCA in HIV-positive patients are limited and the majority of the studies are small case series. Thus the statistical power to evaluate survival differences between HIV-positive and HIV-negative persons is often inadequate. According to data in literature, we found that HIV-positive patients with SCCA were more likely to be male and were significantly younger than the general population, where the risk of SCCA is more common in females and increases with age. Probably HIV infection is likely to facilitate persistence of HPV infection of the anal region and to increase the risk of anal squamous intraepithelial lesion[7]. Moreover, in our study we observed a predominance of advanced disease at the time of diagnosis in HIV-positive patients with SCCA compared to general population where SCCA is predominantly a loco-regional disease and rarely metastatic at the time of diagnosis. This evidence is probably a result of the effect of HIV infection and immune-suppression on the natural history of anal HPV infection[3]. Furthermore, we found no correlation between low CD4-positive cells count and SCCA diagnosis, in fact, CD4-positive cells count was relatively higher (≥ 200 cell/mmc) than normal range values, in more than half of our patients. As far as survival results, we recorded a 5 year overall survival rate of 51% in our patient series. The 5 year overall survival rates by stage distribution were: stage I (88%), stage II-III (41%), stage IV (0%). Despite the retrospective nature of analysis, the absence of patient strict criteria of inclusion/exclusion, our data on HIV-positive patients with SCCA, compared both to general population and to small reports on HIV-positive patients present in the literature, are promising. We obtained these data throughout the use of best treatment modalities for stage, with CMT for more advanced stage and local surgery for earlier stages, as commonly used in general population. Historically, before the 1980s, radical surgery with abdominoperineal resection was the most frequently recommended treatment for SCCA patients. The overall five-year survival rate after radical surgery ranged between 30 and 71 percent, and loco-regional recurrence rate ranged from 18 to 45 percent[34]. In 1974, Nigro et al[35], observed complete tumour regression in some patients with anal carcinoma treated with preoperative 5-fluorouracil based

concurrent chemo-radiotherapy including either mitomycin or poriromycin, suggesting that it might be possible to cure anal cancer without surgery and permanent colostomy. Since the above mentioned report[35], surgery has been reserved to salvage therapy for non-responders or recurrent disease. A role for surgery remains also for selected patients with small, superficial tumours of the anal margin as those with lesions < 2 cm that seldom have nodal involvement and that may benefit of local excision. In this population the reported 5 year survival rate ranged between 60 and 70 percent, resulting comparable to that of patients treated with radical surgery[34]. In our population, 61% of stage 1 SCCA patients benefit of local excision. Since the report by Nigro et al, several series and prospective trials have demonstrated the feasibility and efficacy of CMT. In particular two European phase III randomised clinical trials[35,36] evaluated the benefits of CMT versus radiotherapy alone. Both these trials demonstrated a significant increase in complete remission rates, an improvement in local control, a significant decrease in local failure and need for colonstomy in the CMT arm vs. radiotherapy alone arm. For the CMT arm, were reported a 5 year survival rate of 56%[36] and 3 year survival rate of 65%[37], respectively. An American phase III trial[38] examined the importance of mitomycin-C (MMC) in the standard CMT regimen and demonstrated a significant reduced local failure rate, an improved colonstomy-free and disease free-survival rate from the addiction of the MMC compared to 5-fluorouracil-based CMT alone. The Authors reported a 4 year survival rate of 76% in the MMC arm. Interestingly, retrospective data[39] on outcomes and prognostic factors, on 19,199 SCCA patients identified from National Cancer data base (1985-2000), showed an overall 5 year survival rate of 58 percent and a survival discriminated by stage of 69.5%, 59%, 40.6% and 18.7% for stage I, II, III and IV, respectively. These data, although retrospective, are not submitted to strict patient selection criteria and prospective follow-up, as in randomized clinical trials and are not based on case-series derived from hospitals with considerable anal cancer expertise, thus reflecting true general population trends. Our results, in HIV-positive patients, are in concordance with these data, reflecting how we may obtain comparable outcomes in HIV-positive patients as in general population, through extension, to HIV-positive population, of the best treatment modalities we have at our disposal. As mentioned before, reports on HIV-positive patients with SCCA, in the literature, are usually small in number and retrospective. Nevertheless, our study corroborates the findings of these small case series. In fact, for the entire population of HIV-positive patients we studied, the median survival was 106 months and the probability of survival at 5 years was 51%. Notably, before the introduction of HAART, HIV-positive patients with SCCA, treated with CMT, had a poorer outcome than the general population. In the HAART era, the 5 year overall survival of HIV positive patients with SCCA has improved and is reported to be similar to the one of the general population. This similarity in survival may be explained by the fact that HIV-infected patients with SCCA were as likely as general population to receive treatment[6]. Stadler et al[40] found that the 2 year survival rate among 14 patients with HIV-related anal cancer was 17% in the pre-HAART era and 67% in the HAART era. Oehler-Janne et al[5] demonstrated that the 5 year survival rate among 40 HIV-positive patients with SCCA in HAART and 81 HIV-negative patients was 61% and 65% respectively[5]. The patients were treated with CMT and mainly were affected by stage II SCCA. Abramowitz et al[41] reported a non significant difference in disease-free survival (77% versus 67%) and overall survival rates (85% versus 84%), after three years of follow-up in a population of 151 patients (44 HIV-positive, 107 HIV-negative) in the HAART era. Surgery was a treatment option as in our study but good survival results reflect the clear majority of stage 1-2 SCCA patients included. Fraunholz et al[42] reported a 5 year overall survival rate of 67% among 21 HIV-positive patients treated with CMT and concomitant HAART. Finally, Blazy et al[43] reported a 100% 2 year survival rate in 9 HIV-positive patients on HAART with stage I to III SCCA. As concerns side effects, our data showed that standard CMT may be used with good efficacy and acceptable toxicity in HIV-positive patients. In fact, no grade 3/4 haematological or extra-haematological adverse events were observed. Moreover, we did not find a significant correlation between low CD4-positive cells count (< 200/mm^3) and an increase in toxicity due to CMT (p = 0.6011). These results are in contrast with some studies in the literature that focused on the poorer therapy tolerability of HIV-infected patients with SCCA compared with the general population due to unforeseeable interactions of chemotherapy with HAART. In fact, protease inhibitors and non-nucleoside reverse transcriptase

inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450 (CYP) system. The co-administration of antineoplastic drugs and HAART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs[44]. Notably, the acute toxicity represents a major clinical challenge in HIV positive patients with SCCA. Oehler-Janne reported that nearly 50% of HIV positive patients experienced acute grade 3/4 toxicity compared with 31% of HIV negative patients (particularly grade 3/4 cutaneous and hematologic toxicity)[5]. Holland et al[45] reported on 7 HIV-seropositive patients treated with CMT, although only 2 patients received mytomicin C in addition to 5-fluorouracil. All patients required treatment breaks, 3 required hospitalization and 4 required chemotherapy dose reduction. Hoffman et al[29] described 17 HIV-seropositive patients and speculated about the relationship between CD4-positive cells count and CMT related toxicity. In particular the group of 9 patients with pre-treatment CD4-positive cells count ≥ 200/mm^3 experienced a good control of the disease with acceptable toxicity, whereas the 8 patients with pre-treatment CD4 ≤ 200/mm^3 had marked dermatologic, gastrointestinal, or haematological toxicities requiring hospitalization. These data are confirmed by some Authors[46] but not by others[41,43]. In conclusion, in the HAART era the prevalence of HPV infection and the risk for SCCA is increasing and may increase even further. This evidence depends on certain factors such as history of receptive anal intercourse or recurrent genital infections and on longer life expectancy in HIV infected patients in HAART era[3-9]. On the basis of multiple epidemiologic and histopathologic correlations between anal and cervical cancer, and given the success of the PAP-smear screening programs in reducing the incidence of cervical cancer, it is likely that a similar approach for anal cancer screening is justified. Anal PAP smear screening has been proposed to screen high risk populations, including men who have sex with men and HIV-positive individuals, for anal cancer precursors. The sensitivity and the specificity of the anal PAP smear, range from 70% to 90% and from 30% to 60%, respectively[47]. The EACS 2009 guidelines propose screening with digital rectal exam and anal PAP smear with a frequency of 1 to 3 years in high risk individuals. Therefore the recommendation for routine screening with anal PAP-smear awaits evidence that screening and treatment of AIN reduces risk of progression to anal cancer[3]. Even if standard CMT is feasible and may result in similar response rates and overall survival (OS) as in HIV negative individuals, improved treatment strategies with the aim of better long-term outcomes are warranted.

In summary, despite the retrospective nature of analysis, the absence of patient strict criteria of inclusion/exclusion, our data on HIV-positive patients with SCCA, compared both to general population and to small reports on HIV-positive patients present in the literature, are promising. According to literature data we observed predominance of advanced disease at the time of diagnosis in HIV-positive patients with SCCA compared to general population. Furthermore, our data have shown a comparable outcome in HIV-infected patients as in general population. This may be explained by the fact that our patients with SCCA were subjected to standard treatment plus HAART with good efficacy and acceptable toxicity. In fact, we believe that HIV infection is a risk factor and no a discriminate factor and it is important, also in this setting of patients with SCCA, to consider the best therapeutic approaches based on cancer characteristics disease and not only on HIV status. At the same time, we believe it is important to increase screening with the anal Papanicolau (PAP) smear in this particular setting, to reduce risk of progression to SCCA.

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