Comparative Study of the Results of Anal Squamous Cell Carcinoma Treatment in HIV-positive and HIV-negative patients

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ABSTRACT

INTRODUCTION: *The treatment of anal squamous cell carcinoma (SCC) in HIV-positive patients is controversial. Although current guidelines recommend performing standard concurrent chemoradiotherapy (CRT) in patients with good immune status, some authors believe that these patients have greater toxicity and worse long-term results, so they would require a different approach. The purpose of this study was to compare the results of anal SCC treatment in HIV-positive and HIV-negative patients.*

DESIGN: *Comparative retrospective study.*

PATIENTS AND METHODS: *The records of patients treated in the Coloproctology Section, Hospital Juan A. Fernández, between January 2007 and October 2018 were retrospectively reviewed. Those of the anal canal were divided into: Group I: HIV-negative and Group II: HIV-positive patients. Demographic variables, specific risk factors, staging, CRT (drugs, toxicity, and response), curative/palliative surgical treatment, persistence/recurrence, and cancer-specific and global survival were compared.*

RESULTS: *28 patients (18 women); margin: 2, anal canal: 26 (Group I: 15, Group II: 11). Patients in Group II were mostly men who have sex with men (vs. 100% women in Group I; p<0.01), younger (45.2 ± 0.9 vs. 63.6 ± 8; p<0.01) and more smokers (82% vs. 27%; p=0.005). There was no significant difference in staging, although patients in Group II had tumors with more severe complications. The treatment was completed in 93% of Group I, vs. 64% of Group II patients; (p<0.05). Thirteen out of 14 (93%) patients in Group I, and 3/7 (43%) patients in Group II had a complete response to CRT (p<0.01). There were 3 recurrences, 2 local and 1 distant (p=NS). HIV-positive required more surgery (82% vs. 27%; p<0.01). Five patients (4 of Group II) underwent abdominoperineal resection (APR). Forty six percent of patients had permanent colostomy, with or without APR. Most of them were HIV-positive (82% vs. 27%; p=0.002). In HIV-positive patients, the RR of cancer mortality was 4 (95% CI: 1.01-16.5; p=0.02) and the RR of overall mortality was 5.45 (95% CI: 1.42-20, 8; p=0.002). These patients also had lower overall (p=0.001) and disease-free survival (p=0.01). Median follow-up: 27 (4-216) months.*

CONCLUSION: *HIV-positive patients with anal SCC were different from HIV-negative patients in that they had a lower complete response rate to CRT, and a greater need for surgical treatment. They also had a significantly lower overall and disease-free survival than HIV-negative patients.*

KEY WORDS: *Anal Squamous Cell Carcinoma; HIV-Positive; Chemoradiation Therapy; Abdominoperineal Resection; Recurrence; Survival*

INTRODUCCIÓN

Invasive anal squamous cell carcinoma (SCC) constitutes 1-2% of tumors of the digestive tract, and 2-4% of tumors of the colon, rectum, and anus in the USA.[1]

It is strongly associated with human papillomavirus (HPV) infection that is present in 80-85% of tumors.1 The population at risk for developing SCC is made up by patients with human immunodeficiency virus (HIV) infection, men who have sex with men (MSM), multiple partners, anoreceptive intercourse, patients with immunosuppression due to solid organ transplant or chronic use of corticosteroids, individuals with history of other neoplasms or high-grade intraepithelial lesions related to HPV, or genitalia warts, and smokers.[2]

Although the frequency of SCC is still higher in women, in recent decades there has been an increase of its incidence, especially in MSM and people of both genders infected with HIV .3 Among MSM the incidence of anal cancer is 35 per 100,000 inhabitants, and if in addition they are HIV-positive, increases to 75-135 per 100,000 inhabitants. It is also higher in HIV-positive women.[1] Despite that with highly active antiretroviral therapy (HAART) it is possible to achieve high CD4 counts, and virtually complete virus load suppression, 4 the incidence of anal SCC has increased during HAART era.[5,6]

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In Argentina, there are epidemiological data from five provinces, between 2008 and 2012, that show an incidence of 0.68 per 100,000 inhabitants (124 cases) in women, and of 0.57 per 100,000 inhabitants (87 cases) in men. [7]

The gold standard treatment before the 70s was abdominoperineal resection (APR). At present, concurrent chemoradiation therapy (CRT) is the treatment of choice, leaving APR for non-responders as rescue, or for patients with recurrences.[1] However, in the last three decades, treatment in HIV-positive patients has been controversial. Current guidelines recommend the standard CRT in HIV-positive patients with good immune status, since they have similar outcomes to immunocompetent patients.[8-10] However, some researchers question this indication since there are patients who experience more severe toxic effects and worse long-term results, indicating the need for a different approach. [11]

The objective of this research is to compare the results of anal SCC treatment in HIV-positive and HIV-negative patients.

MATERIAL AND METHODS

The medical records of all patients with a histopathological diagnosis of anal SSC treated at the Coloproctology Section of Hospital Juan A, Fernández, between January 2007 and October 2018 were retrospectively reviewed.

Those with non-invasive carcinomas were excluded. Tumors of anal margin and of those of anal canal were studied separately. The latter were divided into two groups. Group I: HIV-negative patients, and Group II: HIV-positive patients, which were compared regarding demographic variables, specific risk factors (Smoking, MSM, history of genital and/or anal HPV, history of SCC of the lower genital tract), staging by proctologic examination, computed tomography, and when available, high resolution nuclear magnetic resonance imaging (HR-MRI) of the pelvis. The clinical stages were performed following the AJCC 7th edition.12 Additionally, dose, duration and drugs used in CRT, toxicity, response, need for surgery with curative/palliative intention, persistence/recurrence, and specific and global survival were assessed.

Statistical analysis

Continuous variables were described with mean and standard deviation (SD), or median and interquartile range (CI 25-75%) when appropriate. Categorical variables were described with percentages. For comparison of continuous variables Student t test or Wilcoxon's test, depending on normal/non-normal distribution were used. Categorical variables were compared with Chi-square test. Survival analysis was performed with Kaplan-Meier test and Log-Rank test was used to evaluate differences between curves. A $p<0.05$ was considered statistically significant .SPSS statistical program, V18.0 was used.

RESULTS

Twenty-eight patients (18 women) with anal SCC were treated. There were 2 of anal margin and 26 of anal canal.

SCC of anal margin

The SCC located at the anal margin was diagnosed in a 42 year-old, HIV-positive, smoker, MSM, and in a 76 year-old, HIV-negative woman.

The man referred history of high-grade intraepithelial lesion of the perianal skin. Staging showed Stage I in the man and Stage II in the women. Both underwent local resection with 1 cm margin. The woman had inguinal node recurrence at 16 months, underwent lymphadenectomy, and is currently disease free at 103 months. The man presented local recurrence at 25 months, that was again excised, and a SCC of the anal canal at 50 months, with CRT about to start.

SCC of anal canal

Twenty-six patients had SCC located at the anal canal, 15 were HIV-negative (Group I) and 11 were HIV-positive (Group II). Ten of the latter had HAART treatment, with undetectable viral load in 6. The mean CD4 count was 430 cell/ m3 (62-566). Two patients in AIDS stage at the time of diagnosis had CD4 <200 cell/mm3. Median time from HIV diagnosis to anal SCC diagnosis was 9 years (1-27) in 10 patients, while in one both conditions were simultaneously diagnosed (Fig. 1). The demographic data and the risk factors are detailed in Table 1. Both groups were not homogeneous. The HIV-positive patients were mostly men, while the HIV-negative patients were all female ($p<0.01$).

Furthermore, the HIV-positive were younger (45.2 ± 0.9 vs. 63.6 ± 8; $p<0.01$). Regarding risk factors, 82% of the HIV-positive were smokers (vs. 27%, $p = 0.005$), and 89% of the men were MSM. Both groups had a comparable history of HPV or anal/genital carcinoma, although without significant difference. Most patients in both groups (60% and 54%, respectively) presented with advanced stage (EIIIA, EIIIB, EIV) (Table 2). Only 2 (4%) patients, one from each group, presented initially with distant metastases (liver). There was no significant difference regarding staging.

Response to initial chemoradiation treatment

CRT could be completed by 93% of Group I patients vs. 64% of Group II patients ($p<0.05$) (Table 3). With only

one exception, all HIV-negative patients who completed the treatment had a complete clinical response. In contrast, only 3 out of 11 HIV-positive patients had complete response (p<0.01). The 5 patients (Group I: 1, Group II: 4) with partial or absent response had advanced stages: EIIIA (2), EIIIB (2) and EIV (1) and 4 of them were tumors complicated by abscess/perianal fistula (Table 4) (Fig. 2). The only HIV-negative patient with absent response had an abscessed tumor and died 4 months after the end of CRT due to poor general condition and progression of the disease.

There were 5 patients who did not complete the CRT. Of these, in the only HIV-negative patient the cause of the treatment suspension was the occurrence of a stroke. She subsequently underwent a palliative colostomy. The remaining 4 (36%) HIV-positive patients could not start or complete chemotherapy due to bad general condition or toxicity, predominantly hematological, and only one could receive incomplete radiotherapy. Two of them underwent APR. They all died within 2 years, one for intraoperative bleeding complication and the others due to disease progression.

Recurrence after initial chemoradiation treatment

Only 2 of the patients who had an initial complete response to CRT had a local recurrence (Table 3). An HIV-negative patient (Stage II), previously treated with 5600 cGy + mitomycin + capecitabine, recurred locally at 47 months, and was rescued with APR which turned out R0. He had a new locoregional recurrence at 39 months, involving the ileum, cecum, and uterus (with an enterouterine fistula).He had palliative resection of a poorly differentiated SSC. He died by disease progression 20 months later, after surgery for intestinal obstruction.

Another HIV-positive patient (Stage II) who had been treated with 5600 cGy + 5FU + cisplatin, had a locoregional recurrence at 36 months. The rescue APR was R1 and he died 4 months after disease progression.

One HIV-negative patient (Stage II) had a lung recurrence 16 months after the completion of CRT.

Surgical treatment

Table 5 details the need for surgical treatment. The vast majority of HIV-negative patients did not require surgery (73% vs. 18%; p<0.01). The only

HIV-positive patient who did not have surgery had Stage I with complete response to CRT, and is disease free at 36 months. Five patients (4 in Group II) underwent APR for lack of complete response to CRT.

Two HIV-positive patients had failed completing treatment due to toxicity.

Of the 26 patients, 12 (46%) had a definitive colostomy,

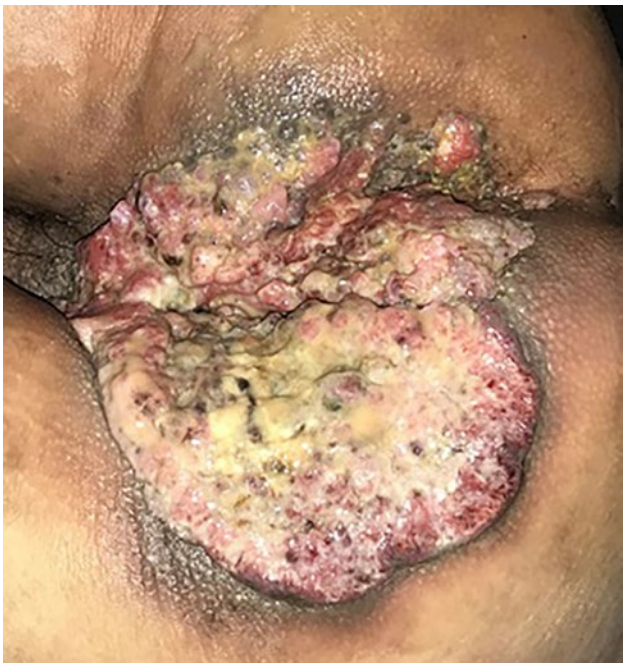

Figure 1: Initial presentation of an HIV-positive patient with anal squamous cell carcinoma. Stage IIIB (prostatic and perirectal node involvement by high resolution pelvic MRI). He had CD4 306 cells/mm3 and viral load 34,000 copies/ml.

TABLE 1: CHARACTERISTICS OF PATIENTS WITH SCC OF ANAL CANAL

	Group I (HIV-) n = 15	Group II (HIV+) n = 11
Male gender*	0	9
Mean ± SD*	63.6 ± 8	45.2 ± 0.9
MSM	0	8
Smoking*	4	9
Anal HPV	2	3
Genital HPV	2 (1 cervix and 1 vagina)	1 (vagina)
LGT cancer	1 (cervix)	1 (vagina)

*SCC = Squamous Cell Carcinoma. MSM = Men who have sex with men. HPV = Human Papillomavirus. LGT = lower genital tract. * p <0.01*

with or without APR. Most were HIV-positive (82% vs. 27%; p=0.002).

The patient with pulmonary recurrence underwent a metastasectomy. She is currently free of disease at 50 months.

Survival

The median follow-up was 27 (4-216) months. Mortality is detailed in Table 6. Specific cancer mortality was higher in HIV-positive patients (55% vs.13%), with a relative risk (RR) of 4 (95% CI: 1.01-16.5; p = 0.02). Also the RR of death from any cause was higher for these patients (5.45; 95%CI: 1.42-20.8; p = 0.002).

There was a significant difference in survival between both groups. HIV-positive patients had lower survival, both overall (p=0.001) (Fig. 3) and disease free (p=0.01) (Fig. 4).

DISCUSSION

There is very scarce bibliography with casuistic that describes experience in the treatment of SCC of the anus in centers of our country.[13-15] Stands out the paper from Hospital Bonorino Udaondo, which in 2005 showed the experience with the treatment of 108 patients (2 with carcinoma in situ), only one HIV-positive). 13 Our study, on the other hand, is the largest series presented nationwide which includes a high proportion of HIV-positive patients.

The frequency of SCC associated with HIV is increasing, and is probably related to the effectiveness of HAART treatment in preventing fatal opportunists infections, allowing for a longer life expectancy to HIV-positive patients.[16] Despite HAART is associated with improvements in immune function, patients with this treatment have persistent immune deficit and maintain the risk for HPV-related anal intraepithelial neoplasia.[17] Since our institution is a referral center for these immunocompromised patients, we had the opportunity to observe the differences that they present with respect to immunocompetent patients with regard to tolerance and response to chemoradiant and surgical treatment.

Coincidentally with most research papers,[8,9,11] the demographic analysis of the population studied in this series showed that the HIV-positive group includes mostly MSM, and they are younger and with a greater rate of smoking than its HIV-negative counterpart.

In our study we found a significant difference in the initial response to CRT between both groups, which was rarely complete in HIV-positive patients, as described by other authors.1 This could be explained because all patients who had a partial or absent response had large, complicated, and advanced stage tumors. Although the comparison of tumor complications between both groups in our series was not statistically significant, those in HIV-positive patients were more serious, being in one of them the cause of death (necrotizing fasciitis). In the work of Grew et al. 18 HIV-positive patients had a hospitalization rate for complications two times greater than in HIV-negative patients.

Wexler et al.,[19] in a multivariate analysis demonstrated that the only independent risk factor for death from cancer was tumor size.

Only 5 (19%) of our patients were unable to complete CRT, 4 were HIV-positive. In this series, the response to chemotherapy was not related to the drugs used or the number of cycles completed, since in both groups patients with total response received different combinations of drugs, obtaining a similar response when mitomycin C or cisplatin was used. In this regard, the national group with greater experience in the treatment of immunocompetent patients with SCC published very good outcomes using chemotherapy with cisplatin, 5 fluorouracil and leucovorin, and concurrent radiation therapy with 5500 cGy, which is comparable to international experiences, and one of the least expensive chemotherapy regimens.[13] However, two prospective randomized trials comparing mitomycin C with cisplatin found no superiority of this last drug with respect to the classic scheme, [20,21] and conversely, one of them showed significantly lower colostomy rates (10% vs. 19%, p = 0.02) with mitomycin C.[20]

TABLE 2: INITIAL STAGING OF TUMORS OF ANAL CANAL ACCORDING TO AJCC.[12]

	Group I (HIV-)	Group II (HIV+)
	n = 15 (%)	n = 11 (%)
T1	1	1
T2	7	2
T3	5	5
T4	2	3
N0	5	4
N1	3	2
N2	5	1
N3	2	2
Unknown	0	2
M0	13	10
M1 (liver)	1	1
Stage I	0	1 (9)
Stage II	4 (27)	1 (9)
Stage IIIA	3 (20)	3 (27)
Stage IIIB	7 (47)	3 (27)
Stage IV	1 (7)	1 (9)
Unknown	0	2 (19)

TABLE 3: DOSE, TOXICITY, RESPONSE AND RECURRENCE AFTER CHEMIORADIANT TREATMENT

	Group I (HIV-) n=15	Group II (HIV+) n=11	p
CRT completed	14 (93%)	7 (64%)	0.05
Radiotherapy dose, media ± SD	5543 cGy ± 501.6	5569 cGy ± 213.5	0.48
Radiotherapy duration: Weeks, mean ± SD	6.3 ± 2	8 ± 2.9	0.92
CT: 5FU or capecitabine			
- With mitomycin C	9	2	
- With cysplatin	5	5	
Response to complete CT			
Total	13/14	03-jul	0.01
Parcial	0	02-jul	0.08
Absent	ene-14	02-jul	0.02
Recurrence post CRT			
Local	1 (at 4 years)	1 (at 3 years)	
Distant	1 (lung)	0	

CRT = Chemoradiotherapy. CT = Chemotherapy

TABLE 4: COMPLICATIONS INHERENT TO TUMOR

	Group I (HIV-) n=15 (%)	Group II (HIV+) n=11 (%)
None*	9 (60)	5 (45)
Perianal abscess and fistula	3 (20)	4 (36)
Rectovaginal fistula	3 (20)	0
Necrotizing fasciitis	0	1 (9)
Infección por CMV	0	1 (9)

*CMV = Cytomegalovirus. * p = Not significant*

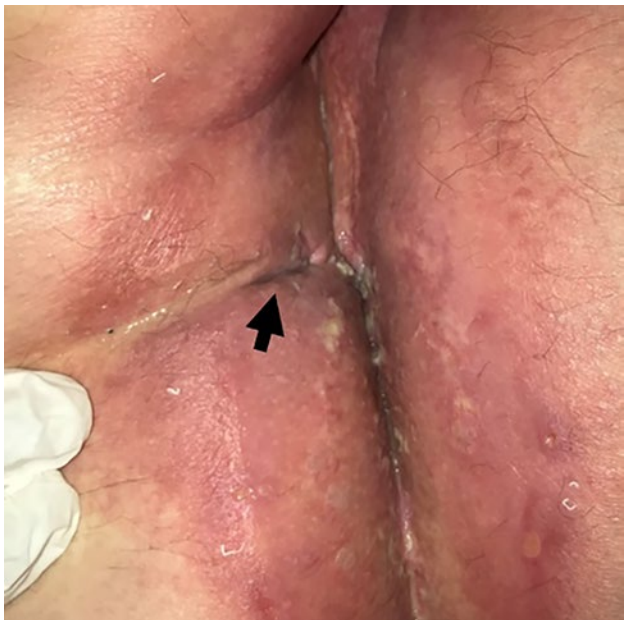

Figure 2: Squamous cell carcinoma of the anal canal abscessed and fistulized to the perianal skin (Arrow), in an HIV-positive patient with poor immune status.

TABLE 5: SURGICAL TREATMENT

	Group I (HIV-) n=15 (%)	Group II (HIV+) n=11 (%)
NO*	11 (73)	2 (18)
Pre CRT colostomy	1 (7)	3 (27,5)
Palliative colostomy	1 (7)	2 (18)
APR post complete CRT	1 (7)	2 (18)
APR post incomplete CRT	0	2 (18)
Pulmonary metastasectomy	1 (7)	0

*CRT = Chemoradiotherapy. APR = Abdominoperineal resection. * p <0.002*

TABLE 6: MORTALITY OF PATIENTS WITH ANAL SQUAMOUS CANCER

Mortality: n (%)	Group I (HIV-) n=15	Group II (HIV+) n=11
Cancer especific*	2 (13)	6 (55)
Other causes	0	2 (18)

** p=0,02*

In patients who initially responded, there was only 8% of loco-regional and 4% of distant recurrences. These figures are comparable to those of Johns Hopkins Hospital that in 93 patients (20 HIV-positive) had 8.6% local and 3.2% distant recurrences.[10] For others instead, the local recurrence

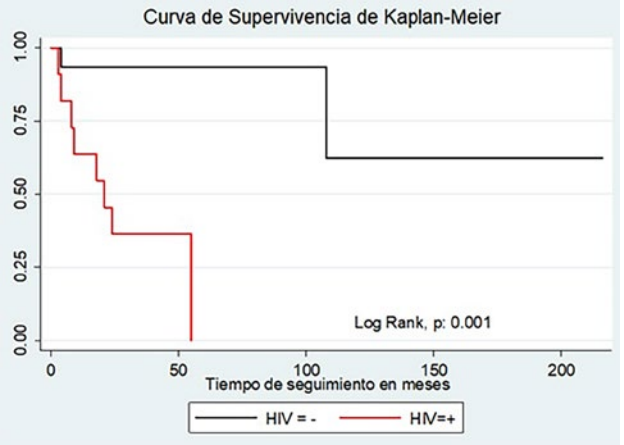

Figure 3: Overall survival curve in HIV negative and positive patients with anal squamous carcinoma.

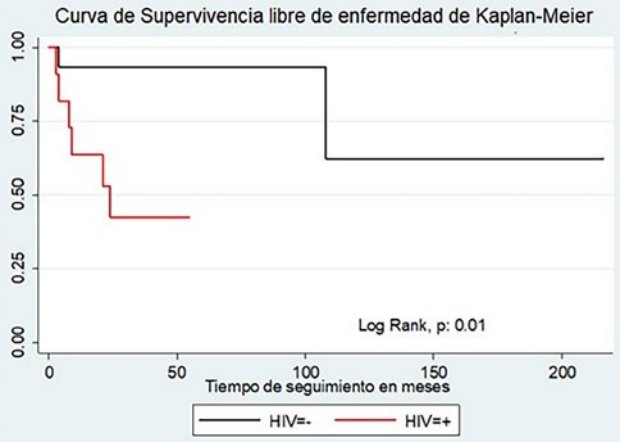

Figure 4: Disease-free survival curve in HIV negative and positive patients with anal squamous carcinoma.

rates were higher, ranging from 16 to 39%.[19,22-24]

In the series of 17 patients by Edelman et al.,[25] 53% had recurrent or persistent SCC, with 50% of them requiring rescue surgery, including a palliative procedure.

In our cases, rescue APR was necessary in 19% of patients. These cases, added to those that required colostomy prior to CRT, or for palliation, resulted in 46% of definitive ostomies. Four patients required colostomy prior to CRT, in 3 HIV-positive due to large abscessed and/or fistulized tumors, and in an HIV-negative patient with a rectovaginal fistula. None of these could be reversed. Similarly, Poynter et al.[26] could reverse only 16% of colostomies indicated for similar reasons.

Although in HIV-positive patients on HAART have been described similar oncological results than in HIV-negative patients,[9,27,28] other authors report

worse long-term outcomes for them.[11] In our series, HIV-positive patients had significantly less disease-free and overall survival than HIV negative-patients.

In accordance with our experience, it should be noted that a 2019 meta-analysis with 40 studies and 3720 pa-

tients, also demonstrated a worse overall and disease-free survival in the HIV-positive population, and a higher rate of definitive colostomies.[29] These authors speculate that one of the reasons that could explain worse results in these patients would be the lower bone marrow reserve that determines the possibility of completing chemoradiant treatment.[29] This would be the result of HIV infection, antiretroviral therapy, and/or myelosuppressive prophylactic antibiotics that would contribute to a more pronounced chemotherapy myelosuppression. However, there are no formal pharmacokinetic studies yet to prove this theory. In our series, 91% of the HIV-positive patients were on antiretroviral treatment at the time of SCC diagnosis.

Regarding tolerance to therapeutics, this research demonstrates a significant difference in the lower possibility of HIV-positive patients for completing CRT, conditioning the worst the long-term results obtained. Other authors have not observed worse long-term oncological results despite the increased acute toxicity, especially hematological, of the CRT.[8] Oehler et al.,[11] described in HIV-positive patients a 50% adherence to the radiation dose initially conceived, more weeks of treatment, lower rate of radiotherapy dose correction, and less use of mitomycin C in this group.

The risks associated with invasive SCC and its treatment makes it mandatory to increase efforts for its prevention. The investigation with anal PAP smear and high resolution anoscopy in HIV-positive patients could identify those with high-grade anal intraepithelial neoplasia at risk of progressing to invasive anal carcinoma.

CONCLUSIONS

In this study HIV-positive patients were different from HIV-negative patients for having a lower rate of complete response to CRT, and an increased need for surgical treatment.

In addition, they had an overall and disease-free survival significantly lower than HIV-negative patients.

ACKNOWLEDGMENT

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COMMENT

This article takes on a relevant topic for several aspects. First, because it originates from a reference center in this condition, created by Dr. Rene Bun, pioneer in the study of STDs in our country and Master of Coloproctology of

SACP, recently deceased. His medical and scientific work was later continued by Dr. Rita Pastore and the other authors belonging to the same service. Second, because of the size of the series. It is an important number of patients for our country, given the infrequency of the condition. The analysis from the point of view of HIV operation is also to highlight. Being a retrospective analysis, it has the bias of any work of this design, but its analysis is correct. Adding a univariate or multivariate analysis to identify associated factors, in addition to the operation of HIV to the poor prognosis of these patients could add healthcare value to identify risk subgroups.

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