Characteristics of AIDS-related and non-AIDS-related cancers in an Italian cohort of HIV patients in the period 1996-2018

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Background

HIV-infected patients have a higher risk of developing malignancies than general population, especially virus-associated cancers. The advent of the combined antiretroviral therapy (cART) led to a strong reduction of the incidence of AIDS-defining cancers (ADCs) and raised life expectancy among people living with HIV (PLWH). At the same time, new issues have emerged: chronic degenerative diseases and non-AIDS-defining cancers (NADCs) have increased. Currently, malignant neoplasms are the leading cause of death for PLWH in Western countries. For this reason, in recent years, international guidelines for the management of PLWH have highlighted the importance of oncological screening interventions, both those shared with the general population and those specific for PLWH. The aim of this study was to define from an epidemiological and prognostic point of view the neoplastic pathology in PLWH.

Material and Methods

This retrospective, observational cohort study has been carried out at the Infectious Diseases Department of Padova, Italy. We enrolled PLWH with a cancer diagnosis occurred between January 1996 and March 2018 who met the following inclusion criteria: 1) Age over 18 years. 2) Diagnosis of primitive malignant neoplasia concomitant or subsequent to the diagnosis of HIV. 3) Histological, cytological or radiological diagnosis of primary malignant tumor according to diagnostic criteria of each cancer (metastases without evidence of primary tumor, in situ carcinomas and tumor recurrences were excluded). 4) At least two follow-up visits after the diagnosis of cancer. The clinical and immuno-virological characteristics and survival rates were analysed comparing two periods of observation (1996-2006 versus 2007-2018). Then, we evaluated the incidence trend for the period 1996-2018, of overall cancers and distinct in ADCs and NADCs, . Finally, we performed survival analysis with the Kaplan-Meier method, first for the entire population and then distinguished by type of tumor and observation period.

Results

188 patient were enrolled, for a total of 204 cancer diagnosis; 15 patients had two or more tumors in the observation period. Second and third diagnosis of cancer in the same subject were excluded in order to avoid bias in the survival analysis; therefore, statistical analysis was performed on 188 patients with 188 different cancers. They were equally distributed in the two observation periods (94 cases in each period), with median age at the diagnosis of malignancies of 46.5 years (IQR 38.75-54). The 18% of patients were female and 9% of foreign nationality; these percentages didn't change significantly between the two observation periods. 103 patients had an ADC and 85 patients had a NADC, respectively 67 and 27 in the period 1996-2006 and 36 and 58 in the period 2007-2018. The most frequent neoplasms were NHL (27.7%), KS (27.1%) and hepatocellular carcinoma (8.5%), as shown in table 1.

Table I. Types of neoplasia distinct in ADCs and NADCs and divided by the period of observation.

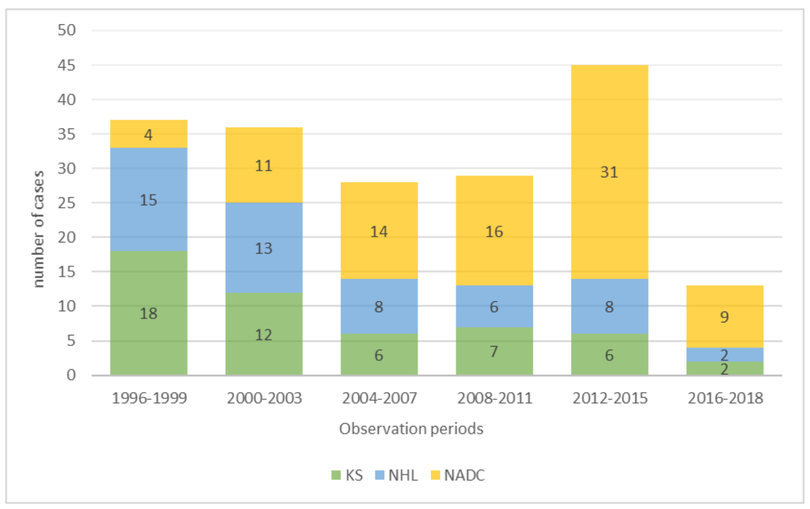
Cancer type		Whole cohort (n=188)	1996-2006 (n=94)	2007-2018 (n=94)	P-value
ADCs (%)		*103 (54,8)*	*67 (71,3)*	*36 (38,3)*	*<0,001*
NADCs (%)		*85 (45,2)*	*27 (28,7)*	*58 (61,7)*	
ADCs	NHL (%)	52 (27,7)	35 (37,2)	17 (18,1)	0,003
	KS (%)	51 (27,1)	32 (34,0)	19 (20,2)	
NADCs	Hepatocarcinoma (%)	16 (8,5)	3 (3,2)	13 (13,8)	
	Anal cancer (%)	8 (4,3)	4 (4,3)	4 (4,3)	
	Non-melanoma skin tumors (%)	8 (4,3)	2 (2,1)	6 (6,4)	
	Lung cancer (%)	8 (4,3)	4 (4,3)	4 (4,3)	
	Brest cancer (%)	7 (3,7)	3 (3,2)	4 (4,3)	
	Prostate cancer (%)	4 (2,1)	0 (0,0)	4 (4,3)	
	Cholangiocarcinoma (%)	4 (2,1)	3 (3,2)	1 (1,1)	
	Others[1] (%)	30 (16,0)	8 (8,5)	22 (23,4)	

[1] ≤ 3 cases (3 Colon cancers, 3 Hodgkin lymphoma, 3 larynx cancers, 3 tonsil cancer, 3 multiple myelomas, 2 Stomach cancers, 2 tongue cancers, 2 melanomas, 2 oropharynx cancers, 1 testis cancer, 1 thyroid cancer, 1 bladder cancer, 1 vulva cancer, 1 ovary cancer, 1 kidney cancer, 1 undifferentiated carcinoma).

Comparing the two periods of observation, we noticed a statistically significant difference (p <0.001) in the distribution by age group at the time of cancer diagnosis, passing from a median age of 41 years (IQR 36-49) in the first period to 49 years (IQR 45-56) in the second period. In 23 years of observation there was a significant reduction in the incidence of ADC, in particular of KS, and a parallel significant growth in NADC, which increased from 10.8% on the total number of cancers diagnosed in 1996-1999 to 69.2% of tumors in 2016-2018 (Fig. 1).

Comparing the two periods of observation (1996-2006 vs. 2007-2018), there were no significant differences in the T CD4 + lymphocyte values (<200 CD4/mL 71.6% vs 66.7%) and HIV viral load (> 5 log10 cp/mL 41.8% vs 54.3%) at the diagnosis of ADC, which predominantly arouse in a context of immunosuppression and high viral load (table 2). We observed a high percentage of patients whose ADCs were diagnosed in coincidence with HIV infection, not significantly different in the two observation periods (47.8% vs 47.2%), as shown in table 3.

Figure 1. Number of tumor cases, distinguished by type of neoplasia (KS, NHL and NADC) and by observation period.



Regarding NADCs, patients with undetectable viral load and CD4 + lymphocytes T cells> 500 cells/µL at tumor detection were 18.5% and 7.4% respectively in the first observation period and 70.7% and 44.8% in the second period, with a statistically significant difference (table 2). The median age at the NADC finding increased significantly from 42 years to 50.5 years (table 3).

Table 2. Immuno-virological parameters distinguished by ADC and NADC and by observation period.

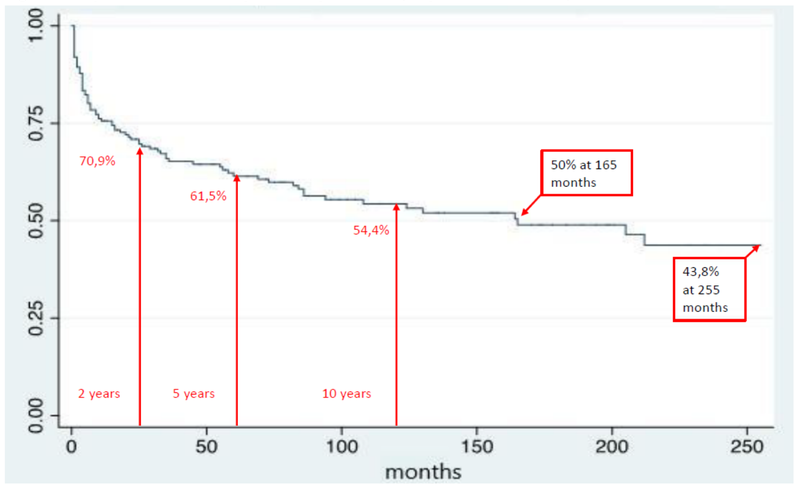
Variables	Categories	ADCs			NADCs		
		1996-2006 (n=67)	2007-2018 (n=36)	p-value	1996-2006 (n=27)	2007-2018 (n=58)	p-value
Lymphocytes CD4+/µL (%)[1]	< 200	48 (71,6)	22 (66,7)	0,358	15 (55,6)	12 (20,7)	0,001
	200-500	15 (22,4)	8 (24,2)		10 (37,0)	20 (34,5)	
	> 500	4 (6,0)	5 (15,2)		2 (7,4)	26 (44,8)	
Log10 copies HIV-RNA/mL (%)[1]	< 3	13 (19,4)	9 (25,7)	0,322	11 (40,7)	47 (81,0)	0,002
	3-3,9	5 (7,5)	3 (8,6)		6 (22,2)	5 (8,6)	
	4-4,9	21 (31,3)	5 (14,3)		6 (22,2)	4 (6,9)	
	≥ 5	28 (41,8)	18 (54,3)		4 (14,8)	2 (3,5)	
Copies HIV-RNA/mL (%)[1]	≤ 40	5 (7,5)	5 (14,3)	0,261	5 (18,5)	41 (70,7)	<0,001
	>40	62 (92,5)	30 (85,7)		22 (81,5)	17 (29,3)	
Median CD4+ cells/µL (IQR)[1]		110 (37-205)	129 (60-265)	0,291	190 (120-280)	480 (282-712)	<0,001
Median CD4+ cells/µL (IQR)[2]		90 (30-195)	100 (48-196)	0,918	100 (60-180)	160 (90-280)	0,248
Median CD4+ cells/µL (IQR)[3]		260 (80-550)	526 (200-760)	0,013	180 (105-314)	406 (263-686)	<0,001
Median log10 copies HIV-RNA/mL (IQR)[1]		4,81 (3,79-5,35)	5,04 (2,90-5,42)	0,987	3,66 (3,87-4,56)	0 (0-1,77)	<0,001

Table 3. Characteristics of tumors at diagnosis, for ADCs and NADCs and for the period of observation.

Variables	Categories	ADCs			NADCs		
		1996-2006 (n=67)	2007-2018 (n=36)	p-value	1996-2006 (n=27)	2007-2018 (n=58)	P-value
Coincidence between diagnosis of cancer and HIV (%)	no	35 (52,2)	19 (52,8)	1,00	27 (100)	57 (98,3)	1,00
	yes	32 (47,8)	17 (47,2)		0 (0,0)	1 (1,7)	
Median time between HIV and cancer diagnosis in months (IQR)		5 (0-70)	9 (0-80)	0,894	158 (90-199)	230 (132-289)	0,001
Median age at the diagnosis of cancer (IQR)		40 (35,5-48)	45,5 (40-51)	0,067	42 (36,5-52,5)	50,5 (47-61)	0,001

Survival analysis of the entire population is shown in figure 2 and divided for cancer type in figure 3. Survival differed significantly with the type of tumor: KS was associated with an excellent survival (85.4% at 10 years), while NHL and HCC were associated with an increased risk of mortality, with similar survival in the first two years of follow-up (52.8% and 52.1% respectively) and a significant increase in mortality for HCC from the second to the fifth year of follow-up.

Figure 2. Kaplan-Meier survival probability over time, expressed in months, over the whole cohort.



In addition, highest CD4 nadir values, taking cART at the time of tumor diagnosis and, obviously, the complete remission of cancer correlate all with a better survival (table 4). In multivariate analysis, the CD4 value at nadir and the diagnosis of KS were found to reduce mortality, while the diagnosis of hepatocellular carcinoma was found to increase the risk of mortality by about 3 and a half times (table 5).

Table 4. Role of eight binary covariates in modifying the risk of death. Kaplan-Meier method.

Variable	Risk	P- value
HCC	Increased	<0.001
NHL	Decreased	0.003
KS	Increased	<0.001
Period of observation	-	Not significant
Opportunistic infection	-	Not significant
Complete remission of cancer	Decreased	<0.001
In AIDS at time of cancer diagnosis	-	Not significant
In cART at time of cancer diagnosis	Decreased	<0.001

Figure 3. Effect on the probability of survival over time (months) of the three most common types of cancer and the remaining types considered together. Kaplan-Meier method.

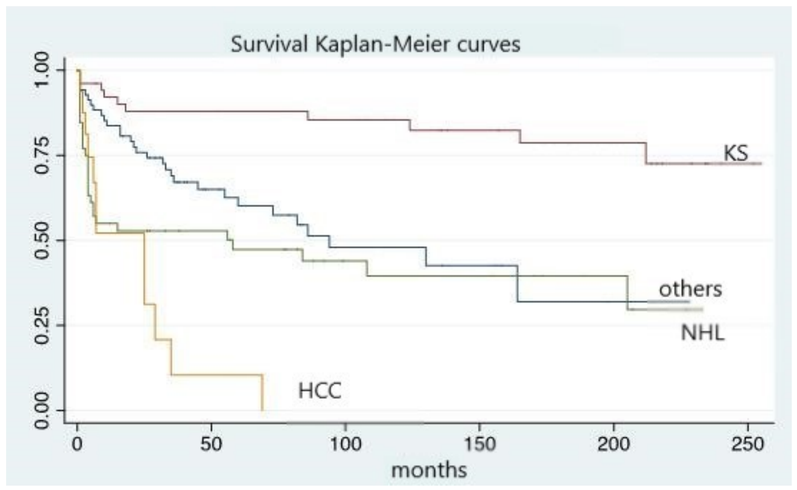


Table 5. Cox multivariate model. The Hazard ratio is a coefficient that multiplies the basic risk, expressing the effect exerted by the covariate.

Covariates	Haz. Ratio	Std. Err.	z	P	Conf. Interval 95%
CD4 nadir	0.4954	0.1253	-2.78	0.006	0.3017 - 0.8134
HCC	3.6431	1.5064	3.13	0.002	1.6199 - 8.1931
HNL	1.6607	0.7148	1.18	0.239	0.7144 - 3.8607
KS	0.2860	0.1463	-2.45	0.014	0.1050 - 0.7795
IO	1.3830	0.5159	0.87	0.385	0.6657 - 2.8733
In AIDS at diagnosis	0.8695	0.4252	-0.29	0.775	0.3335 - 2.2672
In cART at diagnosis	1.3630	0.4147	1.02	0.309	0.7508 - 2.4746
Period 2007-2018	0.6451	0.1887	-1.50	0.134	0.3636 - 1.1446

Conclusions

In our series, according to the literature data, the neoplastic disease still represents a major cause of morbidity and mortality. The study showed a significant reduction in the diagnosis of ADCs from the first to the second observation period. ADCs, however, continue to occur primarily in a context of severe immunosuppression and high viral load. Even in the second period, a considerable proportion of ADCs occurs in patients not in antiretroviral treatment, who become aware of their seropositivity simultaneously with the diagnosis of cancer (late presenters). On the other hand, we have highlighted a significant increase in NADCs over time. These tumors are not strictly related to the state of immunosuppression, in fact the risk of onset persists despite immune reconstitution and optimal control of HIV viremia, probably because the risk is linked to the aging of PLWH, to the chronic inflammation and to the immunosenescence. Finally, the survival of patients with HIV infection and malignancy is predominantly influenced by the type of cancer diagnosed. Being in cART at the time of the diagnosis of neoplasia has been shown to reduce the risk of mortality, as well as a high value of CD4+ lymphocytes at nadir.

In this regard, it is important to raise awareness about the risk of HIV infection, favouring timely diagnosis of the disease, to allow an early start of the cART. Moreover, in PLWH it is essential to maintain a strict surveillance to intervene on potential risk factors, to diagnose early the neoplastic pathology and thus to guarantee the most appropriate therapeutic approach, as well as the continuity of care. All this with the ultimate goal of improving the duration and quality of life of patients with HIV-infection.

References

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