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Original Article

Outcomes of Men With HIV and Germ Cell Cancer: Results From an International Collaborative Study

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BACKGROUND: Previous studies have shown that men with HIV and germ cell cancer (HIV-GCC) have inferior overall survival (OS) in comparison with their HIV-negative counterparts. However, little information is available on treatments and outcomes of HIV-GCC in the era of combination antiretroviral therapy (cART). **METHODS:** This study examined men living with HIV who were 18 years old or older and had a diagnosis of histologically proven germ cell cancer (GCC). The primary outcomes were OS and progression-free survival (PFS). **RESULTS:** Data for 89 men with a total of 92 HIV-GCCs (2 synchronous GCCs and 1 metachronous bilateral GCC) were analyzed; among them were 64 seminomas (70%) and 28 nonseminomas (30%). The median age was 36 years, the median CD4 T-cell count at GCC diagnosis was 420 cells/μL, and 77% of the patients on cART had an HIV RNA load < 500 copies/mL. Stage I disease was found in 44 of 79 gonadal GCCs (56%). Among 45 cases with primary disseminated GCC, 78%, 18%, and 4% were assigned to the good-, intermediate-, and poor-prognosis groups, respectively, of the International Germ Cell Cancer Collaborative Group. Relapses occurred in 14 patients. Overall, 12 of 89 patients (13%) died. The causes of death were refractory GCC (n = 5), an AIDS-defining illness (n = 3), and other causes (n = 4). After a median follow-up of 6.5 years, the 5- and 10-year PFS rates were 81% and 73%, respectively, and the 5- and 10-year OS rates were 91% and 85%, respectively. **CONCLUSIONS:** The 5- and 10-year PFS and OS rates of men with HIV-GCC were similar to those reported for men with HIV-negative GCC. Patients with HIV-GCC should be managed identically to HIV-negative patients. ***Cancer* 2022;128:260-268**.
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LAY SUMMARY:

- Men living with HIV are at increased risk for germ cell cancer (GCC).
- Previous studies have shown that the survival of men with HIV-associated germ cell cancer (HIV-GCC) is poorer than the survival of their HIV-negative counterparts.
- This study examined the characteristics, treatments, and outcomes of 89 men with HIV-GCC in the era of effective combination antiretroviral therapies.
- The long-term outcomes of men with HIV-GCC were similar to those reported for men with HIV-negative GCC.
- Patients with HIV-GCC should be managed identically to HIV-negative patients.

KEYWORDS: AIDS, germ cell cancer, HIV, HIV-related germ cell cancer, nonseminoma, seminoma.

INTRODUCTION

Testicular germ cell cancer (GCC) is the most common cancer diagnosis in men aged 15 to 35 years, and the incidence has risen in recent decades.[1] Today, a cure is achievable in approximately 95% of all patients and in 80% of those who have metastatic disease. The incidence of GCC is slightly elevated in men living with HIV. The standardized incidence ratios for HIV-associated germ cell cancer (HIV-GCC) range from 0.7 to 3.1.[2-4] Notably, the risk of GCC appears to be unrelated to the $CD4^+$ T-cell count and the duration of HIV/AIDS.[2,5]

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Before the introduction of effective combination antiretroviral therapy (cART), the survival of men with HIV-GCC was poorer than that of their HIV-negative counterparts.[6-9] This was mainly due to infectious complications and to the lower dose intensity of the chemotherapy applied.[8,9] A matched case-control study comparing HIV-infected and HIV-uninfected men with GCC showed that men with HIV-GCC had similar cancer-free survival but inferior overall survival (OS) in comparison with their HIV-negative counterparts.[10] However, very little information is available on the outcomes of HIV-GCC since the introduction of cART.[11]

The objective of this multi-institutional study was to analyze the characteristics, treatments, and outcomes of HIV-GCC in the cART era.

MATERIALS AND METHODS

Centers collaborating within the Global Germ Cell Cancer Collaborative Group and within the German Testicular Cancer Study Group and institutions specializing in HIV/AIDS were contacted to share their data for men with HIV-GCC. Detailed information was collected anonymously via structured questionnaires. The following items were included: patient characteristics regarding both HIV/AIDS and GCC, treatment of HIV infection, primary and any further treatment of GCC, responses to antineoplastic treatments, course of the $CD4^+$ T-cell count and HIV viral load during and after cancer treatment, treatment of relapse, and outcomes. Data were anonymized locally, transferred, and entered into a database at the Red Cross Hospital in Munich, Germany.

The study was approved by the ethics committee of Ludwig Maximilian University (Munich, Germany) and by each participating institution. The study was performed in accordance with the Declaration of Helsinki. Toxicity was rated according to the Common Toxicity Criteria.

Eligibility and Staging

The inclusion criteria for the study were as follows: male sex; being 18 years old or older; histology-confirmed GCC; primary GCC diagnosis after January 1, 1996; and proven infection with HIV (enzyme-linked immunosorbent assay and Western blotting) at the time of the GCC diagnosis.

Patients were excluded if their HIV infection was diagnosed more than 2 months after the diagnosis of GCC. A simultaneous diagnosis of both GCC and HIV infection was assumed if an HIV infection was diagnosed within the 2 months after the diagnosis of GCC.

The GCC stage was reported according to the International Union Against Cancer classification.[12] For allocation into risk categories, the prognostic classification of the International Germ Cell Cancer Collaborative Group (IGCCCG) was used.[13] The HIV infection status was classified according to the 1993 Centers for Disease Control and Prevention (CDC) criteria.[14]

Definitions of Response

Complete response: The complete disappearance of all clinical, radiographic, and biochemical evidence of disease (normal α-fetoprotein and human chorionic gonadotropin) for a minimum of 4 weeks.

No evidence of disease: The complete disappearance of all biochemical evidence of disease with complete surgical resection of all residual radiographic masses that, if pathologically positive for malignant residual GCC, show margins microscopically free of disease. Patients must be free of disease for a minimum of 4 weeks.

Partial response with negative tumor markers (PRm–): The complete disappearance of all biochemical evidence of disease in patients without a surgical procedure for a residual radiographic mass. There is no biochemical recurrence or progression of radiographic masses for a minimum of 4 weeks.

Stable disease: Patients who do not have a response sufficient to qualify as PRm– or a complete response but do not meet criteria for progressive disease.

Progressive disease: Rising tumor markers above the limit of normal over a period of 3 weeks or an increase in the tumor volume unless this is caused by a mature teratoma that is completely resectable.

Relapse: Recurrent GCC after a complete response, no evidence of disease, or PRm–.

Statistics

The primary outcomes were OS and progression-free survival (PFS). Secondary outcomes included GCC-free survival, characteristics of GCC and HIV infection, treatment, and causes of death. Associations between categorical characteristics were assessed with the χ^2 test. The Mann-Whitney *U* test was used to compare continuous variables between the 2 groups. PFS was calculated from the date of diagnosis to the time of progression, relapse, or death. OS was measured from the date of diagnosis to the last follow-up or to death from any cause. Cancer-free survival was calculated from the date of diagnosis to the last follow-up or death by GCC. Censoring was performed at the date of last

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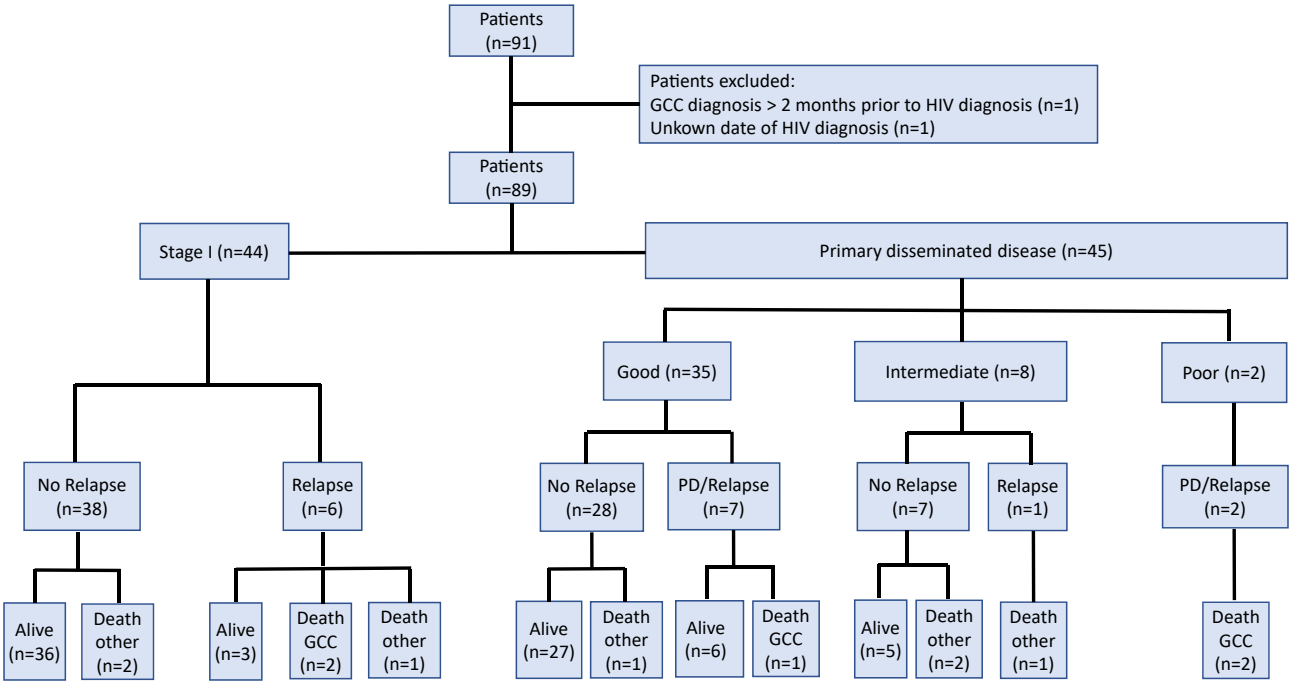

Figure 1. Patient flow diagram. GCC indicates germ cell cancer; PD, progressive disease.

contact. The probability of PFS, OS, and disease-free survival (DFS) was determined by the Kaplan-Meier method, and differences between subgroups of patients were assessed with the log-rank test. Univariable Cox proportional hazards models were used to explore the prognostic value of each covariable. Statistical analyses, including descriptive statistics such as frequencies, means, medians, ranges, interquartile ranges, minima, and maxima, were performed with R statistical software (version 3.5.2). All *P* values were 2-sided. *P* values of .05 or less were considered statistically significant.

RESULTS

Patient Population

Data for 91 patients from 23 institutions and 6 countries were registered. Two patients were excluded because the time of the HIV diagnosis was unknown (n = 1) or the diagnosis of GCC was made more than 2 months before the HIV diagnosis (n = 1). Thus, 89 patients were included in the study. A patient flow diagram is provided in Figure 1.

Two patients had a synchronous GCC, and 1 had a metachronous bilateral GCC; this resulted in a total of 92 HIV-GCCs diagnosed from January 1996 to July 2018. There were 64 seminomas (70%) and 28 nonseminomas (30%). Ten of the 89 cases (11%) were primary extragonadal GCC. Stage I disease was found in 44 of 79 gonadal GCCs (56%). Among the 46 cases with primary disseminated GCC, 78%, 17%, and 4% were assigned to the IGCCCG good-, intermediate-, and poor-prognosis groups, respectively. The median time from the first positive HIV test to the GCC diagnosis was 5 years (range, 0-29 years), the median $CD4^+$ T-cell count at GCC diagnosis was 420 cells/μL (range, 3-1503 cells/μL), and 83% of the patients were on cART. Patient characteristics are outlined in Table 1.

Treatment

All of the 44 stage I cases underwent orchiectomy, with 22 (50%) being followed by active surveillance and 11 (25%) receiving adjuvant chemotherapy or radiotherapy (Supporting Table 1). Among 45 patients, there were 46 stage II/III GCCs (1 metachronous bilateral case was included); 39 (85%) received cisplatin-based chemotherapy, 6 (13%) received radiotherapy for stage IIA/B seminoma, and 1 patient with stage IIA nonseminoma underwent primary retroperitoneal lymph node dissection (RPLND). The types and numbers of cycles of primary chemotherapy are shown in Table 2.

A dose reduction of the first-line chemotherapy was necessary in 3 of 39 patients (8%) because of myelotoxicity (n = 2) or both myelotoxicity and cholangitis (n = 1).

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TABLE 1. Patient Characteristics (n = 89)

Characteristic	No.	%
Age at GCC diagnosis, median (range), y	36 (22-52)	
GCC		
Unilateral	86	
Bilateral synchronous	2	
Bilateral metachronous	1	
S	64	70
NS	28	30
Gonadal	79	89
Extragonadal	10	11
Retroperitoneal	7	70
Mediastinal	3	30
ECOG performance status (n = 74)		
0	50	68
1	22	30
2	1	1
3	1	1
UICC stage I	44	49
S	32	73
NS	12	27
Mediastinal	3	
S	2	
NS	1	
IGCCCG prognostic group (n = 46)[a]		
Good[b]	36	78
S	28	78
NS	8	22
Intermediate[c]	8	17
S	2	25
NS	6	75
Poor	2	4
AFP in metastatic NS by IGCCCG prognostic group, median (range), ng/mL		
Good	124 (0-337)	
Intermediate	45 (7.5-1159)	
Poor	13387 (7-26767)	
β-HCG in metastatic NS by IGCCCG prognostic group, median (range), IU/L		
Good	46 (5.4-363)	
Intermediate	598 (1-1278)	
Poor	750 (154-1347)	
LDH in metastatic NS by IGCCCG prognostic group, median (range), U/L		
Good	227 (0-250)	
Intermediate	1056 (570-3297)	
Poor	1074 (1010-1138)	
CDC (n = 69)		
A	43	62
B	13	19
C	13	19
Absolute CD4 T cells, median (range), /μL	420 (3-1503)	
Prior or current cART (n = 80)	66	83
HIV RNA < 50 copies/mL (n = 67)	38	57
HIV RNA < 500 copies/mL (n = 67)	39	58
HIV RNA < 500 copies/mL + cART (n = 51)	39	76
Years from first positive HIV test to GCC diagnosis, median (range)	5.0 (0-29)	

Abbreviations: AFP, α-fetoprotein; β-HCG, β-human chorionic gonadotropin; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; ECOG, Eastern Cooperative Oncology Group; GCC, germ cell cancer; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; NS, nonseminoma; S, seminoma; UICC, Union for International Cancer Control.
[a]A case of metachronous bilateral GCC was counted twice.
[b]Including 5 cases of primary retroperitoneal S.
[c]Including 1 case of primary retroperitoneal NS and 1 case of retroperitoneal S.

TABLE 2. Primary Chemotherapy for Advanced-Stage Germ Cell Cancer (n = 39)

Prognostic Group	Seminoma	Nonseminoma
Good	22	7
	17 (3× PEB)	5 (3× PEB)
	3 (4× PEB)	1 (4× VIP)
	1 (2× PEB)[a]	1 (4× TIP)[b]
	1 (1× PEB → RT at 36 Gy)[c]	
Intermediate	2	6
	2 (4× PEB)	6 (4× PEB)
Poor	0	2
		1 (4× PEB)
		1 (3× POMB/ACE)

Abbreviations: PEB, cisplatin, etoposide, and bleomycin; POMB/ACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin, cyclophosphamide, and etoposide; RT, radiotherapy; TIP, paclitaxel, ifosfamide, and cisplatin; VIP, etoposide, ifosfamide, and cisplatin.
[a]Termination after 2× PEB because of neutropenic sepsis and complete remission.
[b]Case of metachronous bilateral nonseminoma.
[c]Switch to radiotherapy because of neutropenic sepsis after 1 cycle of PEB.

The administration of chemotherapy was delayed in 4 of 39 patients (10%) because of myelotoxicity with or without neutropenic infections (n = 3) or bleomycin-associated dyspnea (n = 1). Furthermore, chemotherapy was terminated early in 3 patients (8%) because of neutropenic sepsis after 1 or 2 cycles of cisplatin, etoposide, and bleomycin (PEB) in good-prognosis seminoma (n = 2) or because of neutropenic fever and deterioration in the general state of a patient with primary mediastinal nonseminoma (PMNS) after 3 cycles of cisplatin, vincristine, methotrexate, bleomycin, actinomycin, cyclophosphamide, and etoposide (POMB/ACE) chemotherapy.

Residual tumor resection after first-line chemotherapy was performed in 11 of 39 patients (28%; 7 nonseminomas and 4 seminomas). Nine of those patients underwent RPLND, 1 underwent both RPLND and resection of lung metastases, and the patient with PMNS underwent resection of the mediastinal mass and lung metastases. Histopathological examinations revealed necrosis in 8 cases (73%) and both necrosis and teratoma in 2 cases (18%). A viable tumor was found in the patient with PMNS (9%).

Antiretroviral Therapy and CD4 T-Cell Counts

Data on cART were available for 80 patients. After orchiectomy, 67 patients (84%) were on cART, and the regimen was modified in 14 of 32 cases (44%) at the start of chemotherapy. The HIV viral load was below 500 copies/mL in 39 of 51 patients (76%) on cART for whom data on HIV RNA were available (Table 1).

The $CD4^+$ T-cell count was well documented for 27 patients under chemotherapy and for 14 patients under

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radiotherapy. There was no significant difference in the median $CD4^+$ T-cell counts before chemotherapy (median, 454 cells/μL; range, 150-1270 cells/μL) and thereafter (median, 441 cells/μL; range, 168-903 cells/μL). CD4 T cells increased in 18 patients (67%), 16 of whom were on cART, and they declined in 9 (33%), 4 of whom were on cART.

Under radiotherapy, $CD4^+$ T cells decreased from 480 cells/μL (range, 3-1503 cells/μL) to 223 cells/μL (range, 15-578 cells/μL).

Disease Control and Survival

The response to primary treatment was evaluated in 45 of the 46 patients with advanced-stage GCC. The remission status remained undetermined in 1 patient who died of a traffic accident shortly after the end of chemotherapy. A complete response, PRm–, stable disease, and progressive disease were noted in 39 (87%), 3 (7%), 1 (2%), and 2 (4%), respectively.

Relapses or primary refractory disease occurred in 15 patients (Table 3). There were 6 relapses from stage I and 9 from primary disseminated GCC, which corresponded to relapse rates of 32% (14 of 44) and 20% (9 of 46), respectively. The median time from the GCC diagnosis to relapse in patients without early progression was 10 months (range, 3-107 months). There were no significant differences in the $CD4^+$ T-cell counts at GCC diagnosis and at the end of primary treatment between patients with and without relapse (420 vs 429 cells/μL and 370 vs 409 cells/μL, respectively). Among the 6 patients who relapsed from stage I GCC, 5 received chemotherapy, and 1 underwent radiotherapy for retroperitoneal relapse of seminoma. Salvage chemotherapy was given to 8 of 9 patients who relapsed from primary disseminated GCC (Table 3). Notably, 3 patients who underwent high-dose chemotherapy and autologous stem cell transplantation as second salvage chemotherapy did not experience any unexpected toxicity.

Treatment resulted in ongoing complete remission in 4 cases, whereas 2 patients experienced further relapses or progressive disease and died of GCC. After salvage chemotherapy in patients with primary disseminated GCC, 6 patients remained in ongoing complete remission, and 2 experienced refractory GCC (Table 3).

In the entire cohort, 12 patients (13%) died (Table 4). The causes of death were refractory GCC (n = 5 [including a patient with late relapse at 8.9 years]), an AIDS-defining illness (n = 3), and sepsis 12.8 and 8.9 years after the diagnosis of GCC (n = 2). Another patient died of rectal cancer as a second primary malignancy 10 years after the GCC diagnosis (Table 4).

After a median follow-up of 6.5 years (range, 0.3-20.9 years), the 5- and 10-year PFS rates were 81% (95% confidence interval [CI], 0.730-0.899) and 73% (95% CI, 0.622-0.854), respectively (Fig. 2A). The OS rates of the entire cohort at 5 and 10 years were 91% (95% CI, 0.850-0.977) and 85% (95% CI, 0.760-0.957), respectively (Fig. 2B), and the 5- and 10-year DFS rates were 95% (95% CI, 0.903-0.999) and 95% (95% CI, 0.903-0.999), respectively, without significant differences among the good-, intermediate-, and poor-prognosis groups (Fig. 2C).

According to a univariate analysis, patients with seminoma had a significantly lower risk for progression or death than those with nonseminoma (hazard ratio [HR], 0.38; 95% CI, 0.15-0.94; $P = .023$), and chemotherapy dose reductions resulted in significantly shorter PFS (HR, 4.03; 95% CI, 1.03-14.70; $P = .045$; Supporting Table 2). A performance status higher than 1 (HR, 12.91; 95% CI, 1.43-117.00; $P = .023$) and IGCCCG poor risk (HR, 21.20; 95% CI, 1.58-285.32; $P = .021$) were significantly associated with inferior OS, whereas other variables such as CDC stage, $CD4^+$ T-cell counts, age, and chemotherapy dose reductions had no significant impact on OS. A multivariate analysis was not performed because of an insufficient number of events.

DISCUSSION

There are some important findings from this large cohort study of men with HIV-GCC. First, long-term outcomes of HIV-GCC no longer appear to be related to HIV infection. The 91% OS rate at 5 years is markedly better than the previously reported 2-year OS rates of 81% and 62%.[9,10] Notably, both previous studies were much smaller and included patients mostly from the pre-cART era, and each reported a 20% death rate from HIV/AIDS. By contrast, only 3 of 89 patients (3%) died of HIV-related causes in the current study. Effective cART with a preserved or reconstituted immune system at the GCC diagnosis and thereafter may have greatly contributed to the better outcomes in our study. In fact, the median $CD4^+$ T-cell count at the diagnosis of GCC was 420 cells/μL in the current study (vs 261, 325, and 315 cells/μL in previous studies[7,9,11]), and it remained stable even during chemotherapy; this indicated the effectiveness of cART. This is noteworthy in light of the marked decline in the $CD4^+$ T-cell count during chemotherapy reported in previous studies of HIV-GCC[8,9,11] as well as HIV-associated malignant lymphoma.[15-17]

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TABLE 3. Characteristics and Outcomes of Patients With Progressive Disease or Relapse

No.	Pathology	Stage/IGCCCG	Primary Treatment	Response	TTR, mo	IGCCCG at Relapse	Treatment	Result	Outcome
1	S	I	AS	—	49	Good	RT at 30 Gy	CR	Death from sepsis
2	S	I	RT	—	9	Good	3× PEB + RPLND[a] Various regimens, including HD-CE	CR, 3 further relapses	Death from GCC
3	NS	I	AS	—	6	Good	3× PEB + surgery	CR	Alive without evidence of disease
4	NS	I	AS	—	5	Good	4× PEB	CR	Alive without evidence of disease
5	NS	I	AS	—	107	Poor	2× PEB, 5× TIP	PD	Death from GCC
6	S	I	AS	—	17	Good	4× PEB + surgery	CR	Alive without evidence of disease
7	NS	IIA Good	RPLND	NED	5	—	1× PEB, 2× VIP	CR	Alive without evidence of disease
8	S	IIA Good	RT	CR	29	—	4× PEB + RT mediastinum	CR	Alive without evidence of disease
9	S	IIB Good	3× PEB	CR	11	—	4× VIP, 3× HD-CE	CR	Alive without evidence of disease
10	S	IIC Good	4× PEB	PD	0	—	4× TIP, 2× HD-CE	CR	Alive without evidence of disease
11	S	IIC Good	3× PEB	PD	0	—	2× TIP	PD	Death from GCC
12	S	IIIB Good	3× PEB	NED	13	—	1× TIP, 3× VIP	CR	Alive without evidence of disease
13	NS	IIIB Intermediate	4× PEB	PRm–	8	—	3× TIP	CR	Death from cryptococcosis
14	NS	IIIC Poor	4× PEB	PRm–	0	—	4× Carbo + surgery	PD	Death from GCC
15	NS	Mediastinal Poor	3× POMB/ACE + surgery	SD	3	—	None	PD	Death from GCC

Abbreviations: AS, active surveillance; Carbo, carboplatin; CR, complete remission; GCC, germ cell cancer; HD-CE, high-dose carboplatin/etoposide; IGCCCG, International Germ Cell Cancer Collaborative Group; NED, no evidence of disease; NS, nonseminoma; PD, progressive disease; PEB, cisplatin, etoposide, and bleomycin; POMB/ACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin, cyclophosphamide, and etoposide; PRm–, partial response with negative tumor markers; RPLND, retroperitoneal lymph node dissection; RT, radiotherapy; S, seminoma; SD, stable disease; TIP, paclitaxel, ifosfamide, and cisplatin; TTR, time to relapse; VIP, etoposide, ifosfamide, and cisplatin.

[a]NS at relapse.

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TABLE 4. Deceased Patients

No	Pathology	UICC	IGCCCG	Primary Treatment	Relapse/Progression	Cause of Death	Time, y[a]
1	S	I	—	AS	Yes	Sepsis from cholangitis, liver failure	12.8
2	S	I	—	RT	Yes	GCC	3.2
3	NS	I	—	AS	Yes	GCC	10.2[b]
4	S	IIC	Good	3× PEB	Yes	GCC	0.7
5	NS	IIIB	Intermediate	4× PEB	Yes	Cryptococcosis	4.9
6	NS	IIIC	Poor	4× PEB	Yes	GCC	1.1
7	NS	Mediastinal	Poor	3× POMB/ACE + surgery	Yes	GCC	0.6
8	S/NS[c]	IIB	Good	3× PEB	No	Traffic accident	0.3
9	NS	IIIB	Intermediate	4× PEB + surgery	No	AIDS[d]	9.1
10	NS	IIIB	Intermediate	4× PEB + surgery	No	Rectal cancer	10.0
11	S	I	—	AS	No	Pneumonia/sepsis	8.9
12	S	I	—	AS	No	Kaposi sarcoma	0.6

Abbreviations: AS, active surveillance; GCC, germ cell cancer; IGCCCG, International Germ Cell Cancer Collaborative Group; NS, nonseminoma; PEB, cisplatin, etoposide, and bleomycin; POMB/ACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin, cyclophosphamide, and etoposide; RT, radiotherapy (30 Gy); S, seminoma; UICC, Union for International Cancer Control.
Patients with relapse/progression are arranged downward in the same order used in Table 3.
[a]From GCC diagnosis.
[b]Late relapse at 8.9 years.
[c]Synchronous bilateral GCC.
[d]Not further specified.

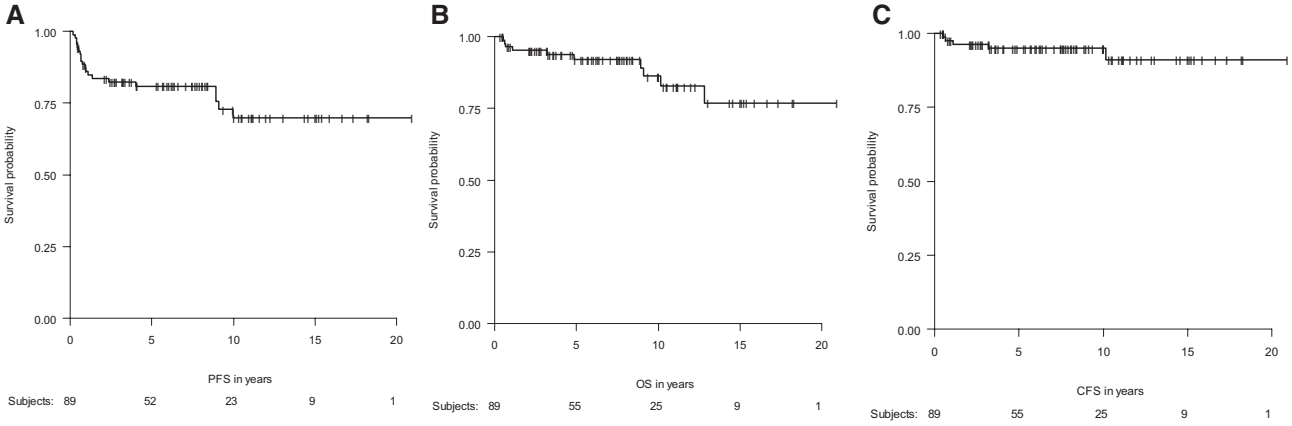

Figure 2. (A) Progression-free survival (PFS), (B) overall survival (OS), and (C) cancer-free survival (CFS).

The only available comparative study investigating the impact of cART on the outcomes of HIV-GCC compared 22 patients diagnosed with GCC before the introduction of cART in 1996 with 13 diagnosed after this date.[10] The 5-year actuarial survival was 88% for patients in the cART era, which was slightly below the 91% 5-year OS rate reported in the current study. However, the current study is much larger and thus provides more reliable data on the beneficial effects of cART in HIV-GCC.

Second, the antineoplastic treatments administered largely represent the standard of care.[18,19] The 7% dose reduction rate and the 10% rate of delay in the administration of first-line chemotherapy compare favorably with data from a previous study in which the planned schedule of chemotherapy delivery was not respected in 42% of the patients.[9] However, unexpected severe toxicity during chemotherapy was also observed in the current study, with 2 patients with stage IIA/B seminoma experiencing severe sepsis during the first and second cycles of PEB. As a result, chemotherapy was terminated early after 2 cycles in the first patient and was switched to radiotherapy after 1 cycle in the second patient, with both patients remaining disease-free at the last follow-up.

Third, the 95% DFS rates at 5 and 10 years and the 5-year OS rate of 91% were in line with the 5-year relative survival rates of 94% and 89% reported for HIV-negative men with testis cancer in Europe diagnosed from 1995 to

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1999 and from 2000 to 2007, respectively.[20,21] However, the 5-year OS rate seems slightly below survival rates reported in a population-based study from Denmark, in which the 5-year probability for nonseminomatous GCC with a good prognosis was 95%.[22]

Two of the 44 patients with stage I GCC (4.5%) died of recurrent disease; this number is slightly higher than that reported for HIV-negative patients, although this may merely be due to small patient numbers.[23-26] In light of the decrease in $CD4^+$ T cells during radiotherapy, which was also observed in previous studies,[8,10] active surveillance appears to be the best approach for stage I seminoma. On the other hand, for stage I nonseminoma, either active surveillance or a risk-adapted approach with 1 cycle of adjuvant PEB for high-risk patients seems appropriate.[18,19]

The proportions of patients assigned to the IGCCCG good-prognosis group (78%) and the IGCCCG intermediate-prognosis group (17%) were similar to recent data from 2 cohort studies in HIV-negative GCC, in which 69% and 78% had good-risk GCC and 19% and 17% had intermediate-risk GCC.[27,28] The low proportion of poor-risk patients observed in the current study (4% vs 19% and 9% in HIV-negative GCC, respectively) might be explained by the continuous health care monitoring of men living with HIV/AIDS, which prevents them from being diagnosed with late-stage GCC.

Response rates to both primary and salvage chemotherapy were in the expected range, and this emphasizes that men with HIV-GCC should be treated identically to HIV-negative patients.[2,5]

The IGCCCG classification was recently re-evaluated in a database from a large international consortium.[29,30] Survival probabilities were shown to have significantly improved in both seminoma and nonseminoma. Another important finding was that the original IGCCCG classification still distinguished 2 and 3 prognostic groups among patients with metastatic seminoma and nonseminoma, respectively. However, in seminoma, lactate dehydrogenase at a cutoff 2.5 times the upper limit of normal was identified as a new adverse prognostic variable among otherwise good-prognosis patients,[29] whereas a new cutoff of lactate dehydrogenase at 2.5 times the upper limit of normal, increasing age, and the presence of lung metastases were identified as additional adverse prognostic markers in metastatic nonseminoma.[30] With respect to our cohort of men with HIV-GCC, differences in survival between groups were not calculated on the basis of the IGCCCG update criteria because of the low number of patients in each group. However, the updated IGCCCG classification should also be applied to men with HIV-GCC in the future.

Nonseminomatous pathology and chemotherapy dose reductions were associated with inferior PFS but not OS, and this indicated that patients underwent effective salvage therapy. Furthermore, a poor performance status and IGCCCG poor risk predicted inferior survival, whereas HIV characteristics such as the CDC stage, $CD4^+$ T-cell counts, and HIV viral load did not. This again emphasizes that the prognosis of HIV-GCC is mainly determined by the GCC stage and risk category rather than HIV-related immunosuppression.

The retrospective, uncontrolled design is a limitation of the current study. However, because of the relative rarity of HIV-GCC, a large prospective study is unlikely to be conclusive.

In conclusion, the 5- and 10-year PFS and OS rates of men with HIV-GCC are similar to those reported for HIV-negative GCC. Patients with HIV-GCC should remain on cART and be managed identically to HIV-negative patients.

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CONFLICT OF INTEREST DISCLOSURES

Marcus Ulrich Hentrich has served on advisory boards for Amgen, Janssen, BMS, Sanofi, AbbVie, Hexal, and Jazz Pharmaceuticals; has served on speaker bureaus for Amgen, Janssen, Sanofi, Takeda, and BMS; and has received travel grants from Amgen, Janssen, Takeda, Celgene, and Sanofi. Mark Bower reports lecture honoraria from EUSA, ViiV, Merck, and Gilead. Gedske Daugaard has served on boards for Astellas, Bayer, Bristol, Janssen, and Sanofi. Albrecht Stoehr has served on advisory boards for ViiV, MSD, Gilead, and AbbVie and has received travel grants from AbbVie, Janssen, and Gilead. Julia Heinzelbecker has served on the speaker bureau for Roche and has received travel grants from Ipsen, Pfizer, and Bayer. Klaus-Peter Dieckmann declares an ownership interest in and has served on advisory boards for miRdetect GmbH. Andrea Necchi declares that an immediate family member is employed by and holds ownership interests in Bayer; he has served as an consultant for Immunomedics, MSD, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen, Incyte, Seattle Genetics/Astellas, BMS, Rainer Therapeutics, GlaxoSmithKline, and Ferring; he has received travel grants from Roche, MSD, AstraZeneca, Janssen, and Rainer Therapeutics; he has received honoraria from Roche, Merck, AstraZeneca, Janssen, Foundation Medicine, and BMS; and he has received research funding from MSD, AstraZeneca, and Ipsen. Pablo Maroto Rey has served as a consultant for Bayer, Ipsen, Janssen, Astellas Oncology, BMS, Novartis, Pfizer, and Roche; has received research funding from Bayer and Roche; and has received travel grants from Ipsen, Janssen, and Pfizer. Jürgen Kurt Rockstroh has received honoraria from Gilead, Janssen, Merck, and ViiV Healthcare. Margarida Brito reports participation on boards for Roche and Novartis. Christian Hoffmann has served as a consultant for EUSA Pharma, Gilead, Hexal, Hormosan, Janssen, ViiV Healthcare, and MSD Brazil; has served on speaker bureaus for EUSA Pharma, Gilead, Hexal, Hormosan, Janssen, ViiV Healthcare, and MSD Brazil; has received research funding from EUSA Pharma, Gilead, Janssen, ViiV Healthcare, and MSD Brazil; and has received travel grants from EUSA Pharma, Gilead, Hexal, Hormosan, Janssen, ViiV Healthcare, and MSD Brazil. The other authors made no disclosures.

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AUTHOR CONTRIBUTIONS

Marcus Ulrich Hentrich: Design and conception of the study, essential study material and patients, collection and assembly of the data, analysis of the data, and drafting of the manuscript. **Mark Bower:** Essential study material and patients. **Gedske Daugaard:** Essential study material and patients. **Annette Dieing:** Essential study material and patients. **Markus Bickel:** Essential study material and patients. **Massimiliano Berretta:** Essential study material and patients. **Florian Lesmeister:** Design and conception of the study, essential study material and patients, collection and assembly of the data, analysis of the data, and statistical analysis. **Vindi Jurinovic:** Analysis of the data and statistical analysis. **Albrecht Stoehr:** Essential study material and patients. **Julia Heinzelbecker:** Essential study material and patients. **Ivanka Krznaric:** Essential study material and patients. **Klaus-Peter Dieckmann:** Essential study material and patients. **Andrea Necchi:** Essential study material and patients. **Pablo Maroto Rey:** Essential study material and patients. **Jürgen Kurt Rockstroh:** Essential study material and patients. **Margarida Brito:** Essential study material and patients. **David Pfister:** Essential study material and patients. **Christian Hoffmann:** Design and conception of the study, essential study material and patients, and analysis of the data. All the authors have interpreted, critically appraised, and given final approval of the manuscript.

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