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HIV-Associated Lung Cancer in the Era of Highly Active Antiretroviral Therapy (HAART)

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Abstract

Background—Lung cancer is the leading cause of death among non-acquired immunodeficiency syndrome (AIDS) defining malignancies. Since highly active anti-retroviral therapy (HAART) has improved survival for human immunodeficiency virus (HIV) patients, we evaluated lung cancer outcomes in the HAART era.

Methods—HIV-positive patients diagnosed with lung cancer in our institution during the HAART era (1995-2008) were analyzed. Patient charts were reviewed for clinical and laboratory data. CD4 count at diagnosis was treated as a continuous variable and subcategorized into distinct variables with 3 cut-off points (50, 200, & 500 μl). Pearson's correlation coefficients were estimated for each covariate studied. Survival was determined by the Kaplan-Meier method.

Results—Out of 80 patients, 73 had non-small cell lung cancer. Baseline characteristics were: median age-52 yrs; male-80%; African American-84%; injection drug use-25%; smokers-100%; and prior exposure to antiretroviral agents-55%. Mean CD4 count and viral load were 304 μL and 82,420 copies/ml, respectively at cancer diagnosis. The latency between diagnosis of HIV and lung cancer was significantly shorter in women (4.1 yrs vs. 7.7 yrs, P=0.02) and 71% of the patients received anti-cancer therapy. The 1- and 3-year survival rates were 31% and 4% overall. Grade 3/4 toxicities occurred in 60% with chemo-radiation vs. 36% with chemotherapy. Cancer-related survival was better for patients with CD4 count >200 (P=0.0298) and >500 (P=0.0076).

Conclusions—The latency from diagnosis of HIV to lung cancer was significantly shorter for women. Although outcomes for lung cancer patients with HIV remain poor, high CD4 count is associated with an improved lung cancer-related survival.

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Keywords

lung cancer; HIV; survival; anti-retroviral therapy; HAART

Introduction

The availability of highly antiretroviral therapy (HAART) since 1996 has improved AIDS-related outcomes, transforming HIV from a rapidly lethal disease to a chronic illness [1]. While the incidence of HIV has reached a plateau, an estimated one million people in the United States have been infected as of 2006 and the numbers continue to rise [2]. As a result, non-AIDS-related contributing to the morbidity and mortality of HIV-infected patients [3]. Thirty percent of HIV-infected patients will develop cancer by the age of 60 in the post-HAART era [4]. The marked decline in AIDS-defining cancers (ADCs) that has accompanied the use of HAART has resulted in an increase in the proportion of non-AIDS-defining cancers (NADCs). The largest study to examine cancer incidence revealed that lung cancer represented 20% of the 563 NADCs diagnosed from 1996 to 2002 [5]. Malignancies now account for a third of all HIV-related deaths, of which lung cancer is the leading cause of non-AIDS-defining cancer mortality [6, 7].

HIV patients are 2-4 times more likely to develop lung cancer than the general population [5, 8, 9]. Although smoking remains an independent risk factor for lung cancer, it alone does not account for the increased incidence found in this population [10, 11]. In fact, organ transplant recipients on immunosuppressive agents have a lung cancer incidence rate comparable to that of HIV-infected patients, thus implicating a role for immunosuppression [12]. This is further substantiated by the association between the development of lung cancer and AIDS [5, 8]. However, single data point estimation of CD4 counts does not appear to be directly correlated to lung cancer incidence, a fact which may be attributed to the inherent variability of CD4 counts [5, 10]. Rather, the population range of CD4 levels, which correlates more accurately with the degree of immuosuppression seems to have an association [13]. A recent study has suggested that malignancy rates approach that of the general population in HIV patients with CD4 counts >500 [14]. Additional evidence has also implied that declining CD4 counts are associated with higher lung cancer risk and advanced stage disease at diagnosis [13, 15]. While antiretroviral therapy (ARV) and its associated viral load suppression have not been shown to clearly impact lung cancer incidence, it may have an indirect effect by improving CD4 counts [9, 11, 13, 16].

HIV patients often present with advanced stage lung cancer at a younger age and have an inferior overall survival when compared to non-HIV patients with lung cancer [15]. While HAART has improved HIV-related outcomes, our understanding of its effect on the risk and clinical behavior of lung cancer is still evolving [15]. The current literature in the modern HAART era is sparse with regards to information about lung cancer, optimal treatment, and outcomes in HIV-infected patients. We therefore conducted a retrospective review of lung cancer in HIV positive patients treated at our institution to further characterize the clinical aspects of this population.

Methods

Patient Population

All HIV patients diagnosed with lung cancer from January 1995 to October 2008 were identified via ICD-9 codes and tumor registry at the Atlanta Veteran's Administration (VA) and Grady Memorial Hospital. HIV and primary lung cancer histology was confirmed in 80 patients. Individual patient charts and lab systems were reviewed for clinical data,

specifically age, gender, race, sexual orientation, IV drug use history, smoking exposure, the date of HIV and cancer diagnosis, antiretroviral therapy (ARV) exposure, history of opportunistic infections, performance status, tumor pathology, AJCC 6th edition TNM cancer stage at diagnosis, cancer treatment with associated complications, CD4 lymphocyte count, and HIV viral load at cancer diagnosis. Patient vital records were obtained from chart review and social security index. The protocol for this study was approved by the Institutional Review Board at Emory University.

Statistical Analysis

Pearson's correlation coefficients were estimated for each covariate studied: age at HIV diagnosis, age at cancer diagnosis, latency (time from HIV to cancer diagnosis), smoking, CD4 count at cancer diagnosis, **cancer stage,** and whether a patient received definitive treatment. CD4 count at diagnosis was treated as a continuous variable and also subcategorized into discrete variables using 3 different cutoff points (50, 200, & 500 μl). The Kaplan-Meier method was used for cancer-related survival analysis using either the date of death or the date of data censorship (12/29/2009) if patients were still alive at the time of this analysis.

Results

Patient Characteristics

Eighty patients with HIV and primary lung cancer were identified for analysis within the Atlanta Veteran's Administration (n=21) and Grady Memorial (n=59) hospitals. Table 1 shows the patient characteristics for the cohort. The majority of patients in this cohort were males (80%) and African American (84%) with a median age of 52 years (range 28-73). About one-third of patients (n=23) were either homosexual or bisexual. Seventy-one percent (n=54) used recreational drugs including marijuana and 25% (n=19) were intravenous drug users. Excessive alcohol consumption was noted in 61% (n=49) of the study cohort. Twenty-one patients had detailed histories and consumed >4 alcohol containing drinks/day; while the remaining 28 patients had a diagnosis of alcohol abuse, but detailed histories were not readily available. All 77 patients with documented smoking histories were smokers with an averageof 37 pack-years (range 10-100). Twenty patients were co-infected with hepatitis C and 8 with hepatitis B. In terms of other infectious comorbidities, past medical histories were significant for zoster (n=16), latent tuberulosis (n=15), disseminated mycobacterium (n=8), clostridium difficile colitis (n=5), and tuberculosis (n=5). Twenty-seven patients were clinically diagnosed with recurrent bacterial pneumonias and 21 with pneumocystis jiroveci pneumonia. Patients were twice as likely to present with right-sided cancers than left-sided cancers and more than half of the primary tumors were located in the upper lobes. Seventy-three patients had non-small cell lung cancer (NSCLC) of which 38% (n=30) was adenocarcinoma, 29% (n=23) squamous cell, and 25% (n=20) NSCLC unspecified. Most patients presented with advanced stage disease (74% stage IIIB/IV vs. 20% stage I/II), however neither CD4 count nor a prior history of AIDS was associated with advanced stage disease. Almost half of the patients with stage IV disease presented with multiple nodules. Of the 7 patients with small cell lung cancer (SCLC), 5 patients presented with extensive stage disease.

Mean latency from diagnosis of HIV to lung cancer was 7 years (range 0-18) and was significantly shorter in women (4.1 yrs vs. 7.7 yrs, P=0.02). Eight patients were diagnosed with HIV at the time of their cancer diagnosis, while the rest of the cohort had a diagnosis of HIV that preceded their cancer diagnosis. Patients who were diagnosed with HIV at a younger age were more likely to have a longer latency ($\rho=-0.47$, $p<0.0001$). Table 2 shows the HIV-related characteristics of the patients in this cohort. At the time of cancer diagnosis,

the mean CD4 count and viral load were 304 μL (range 3-1361) and 82,420 copies/ml (range <50 to >750,000), respectively. Smoking correlated with a higher CD4 count (ρ=0.27, p=0.02). Fifty-nine patients (74%) had a previous diagnosis of AIDS, yet only 44 (55%) had prior exposure to antiretroviral agents while 12 (15%) others were initiated on ARVs after being diagnosed with lung cancer. Exposure to anti-retrovirals ranged from 1 to 12 regimens over a patient's lifetime which often involved modifications to 1 or 2 drugs within a regimen. Overall, patients received a median of 2 regimens **with a maximum of 6 drugs at any given time**. ARV therapy mainly consisted of a nucleotide reverse transcriptase inhibitors (NRTI) alone or in combination with non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI). Only 2 patients were treated with a combination that included either an integrase or fusion inhibitor. The most common ARV regimens that a patient received included NRTI/NRTI/PI (n=24), NRTI/PI/PI (n=22), NRTI/NRTI (n=20), NRTI (n=15), NRTI/NRTI/NNRTI (n=13), or NRTI/NNRTI/PI/PI (n=7). Seventeen patients (27%) had an undetectable HIV viral load at the time of cancer diagnosis.

Lung Cancer Treatment

Lung cancer treatment-related parameters among the cohort are summarized in Table 3. Thirty-one of the 50 (62%) evaluable patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Fifty-three (71%) patients received some form of anti-cancer therapy. Among those treated, 11 (21%) underwent surgical resection, 15 (28%) received combined modality therapy with chemotherapy and radiotherapy, 14 (26%) received chemotherapy alone, and 13 (25%) received palliative radiation only. Of those patients who were surgically resected, 1 had a wedge resection, 3 had right-sided pneumonectomy, and 7 had lobectomy. Poor performance status (n=2) and acute infection (n=2) prevented some patients from receiving treatment beyond palliative radiation alone, while others were not treated further either because they refused chemotherapy (n=2) or for reasons not clearly documented (n=7). Five patients declined all forms of anti-cancer therapy and 17 (22%) patients were ineligible for treatment secondary to either poor performance status (n=2), death prior to initiation of treatment (n=8), or for reasons not clearly documented (n=7). A greater proportion (76%) of treatment ineligible patients had a CD4 count ≤200 compared to those who were definitively treated (30%). Receiving cancer-directed therapy was significantly associated with ARV use (p=0.002) and a higher CD4 count (p=0.02) irrespective of a prior history of AIDS or CD4 count nadir (Table 4). Treated patients had a mean CD4 count of 349 vs. 183 in the untreated patients. Grade 3 or 4 toxicities occurred in 1/11 (9%) patients undergoing surgical resection, 9/15 (60%) receiving chemo-radiation, and 5/14 (36%) receiving chemotherapy alone. One lobectomy was complicated by lung atelectasis, respiratory failure, and sepsis resulting in end stage renal disease. The most common complications included treatment delays secondary to neutropenia (n=5), fever due to neutropenia (n=5), infections unrelated to neutropenia (n=4), radiation-related esophagitis (n=6), and acute renal failure (n=4). One patient died due to sepsis, acute renal failure, and respiratory failure following a dose of paclitaxel. Detailed treatment information is presented in Table 5. Patients with a previous history of AIDS were more likely to experience treatment-related complications when compared to those who merely had a CD4 count ≤ 200. Five patients with NSCLC and 3 patients with SCLC received second-line chemotherapy after progression. Only 1 patient received third-line chemotherapy for SCLC.

Lung Cancer-Related Outcomes

The 1- and 3-year survival rates were 31% and 4% overall; 25% and 0% for patients with stage IIIB/IV disease; and 53% and 8% for all treated patients, respectively. Overall, median survival of the whole cohort was 6.1 months. Median survival for patients with advanced stage (IIIB/IV) **NSCLC** was 4 months, which was significantly worse than for those who

presented at earlier stages (p=0.0013). Patients with stage I had better survival rates compared to those with other stages (Figure 1). In a multivariate analysis after adjusting for gender, race, age, latency, CD4 count, and smoking pack-years; early stage disease (p=0.03) and treatment vs. palliative radiation or no treatment **(p=0.0004)** were associated with overall survival **for patients with NSCLC** (Table 6). CD4 count nadir, history of AIDS, ARV use, and histology did not affect overall survival. Lung cancer survival was significantly better for those patients with a CD4 count >200 (p=0.0298, Figure 2) and >500 (p=0.0076, Figure 3), but not for those stratified by a CD4 count of 50 (Figure 4). When CD4 count was separated in quartiles (<50, 51-200, 201-500, >500), those with a CD4 count >500 had a improved survival (Figure 5). However, CD4 count in the multivariate analysis was not a significant predictor of survival when adjusted for cancer stage. Patients who were treated with surgery or chemo-radiation had a significantly better survival compared to those who received palliative radiation or no treatment at all (p<0.0001, Figure **6**).

Discussion

In this large case series, we describe HIV patients with primary lung cancer in the post-HAART era. Consistent with other case series [15, 17-23], patients in this cohort were predominantly younger male smokers (median age 52, 80% males, and all smokers) many of whom presented with adenocarcinoma (38%) and advanced stage disease (74% stage IIIB/IV). While immunosuppressed patients have a higher risk of developing lung cancer [5, 8, 12, 13], HIV-infected patients who develop lung cancer are often characterized as having moderate immunosuppression. Although the majority of these patients (74%) had a previous diagnosis of AIDS, the mean CD4 count was 304 μL at the time of cancer diagnosis. Several studies have failed to demonstrate a direct correlation between absolute CD4 count and lung cancer risk, which may be partially attributed to CD4 count variability [5, 10, 11, 15, 17, 24-28]. In this study, we demonstrated that smoking is associated with a higher CD4 count as reported in other studies [29], supporting smoking as one of many factors that affect the absolute CD4 count.

Gender is another factor that may affect lung cancer risk. In the general population, women are more susceptible to the effects of smoking and to developing lung cancer with emerging evidence suggesting that estrogen may play a role [30-36]. Females in our cohort had a significantly shorter latency from HIV to lung cancer diagnosis than males (4.1 yrs vs. 7.7 yrs, P=0.02) implicating that HIV-positive females may also be at greater risk for developing lung cancer. The Women's Interagency HIV Study (WIHS) supports the idea that women are at an increased risk for lung cancer irrespective of HIV status [37]. However, the retrospective nature of our study and its inherent biases could explain the difference seen in latency, especially if females either had a delay in HIV diagnosis or presented earlier with lung cancer.

Patients diagnosed with HIV at a younger age had a longer latency from HIV to lung cancer diagnosis. While this may imply that HIV positivity is a risk factor for lung cancer, the fact that 27% of the cohort had an undetectable viral load at cancer diagnosis suggests that this is likely a function of age rather than HIV infection itself. Ultimately, the duration of HIV positivity did not impact cancer-related survival. However, analysis of the cohort revealed that **cancer stage,** CD4 count, and treatment all affected overall survival. As in the general population, advanced cancer stages are associated with a poorer prognosis. Though patients with stage I disease clearly demonstrated an improved survival compared to stage IIIB/IV patients, small patient numbers may explain the unexpectedly low survival of patients with stage II lung cancer. Yet, overall outcomes were poor, with a 1-year survival of 25% and median survival of 4 months for patients with stage IIIB/IV disease. Although the 6.1-month median survival for all patients is comparable to that in other reported case studies, it is

considerably worse than the expected 10-12 month median survival of lung cancer patients with the most advanced stage (IIIB/IV) in the general population [38, 39].

CD4 count and cancer-directed treatment may account for some of the discrepancy in overall lung cancer survival seen between HIV patients in this cohort and the general population. A high CD4 count (>200/500 μL) in this cohort was associated with an improved lung cancer-related survival. However, when survival was analyzed in CD4 quartiles (<50, 51-200, 201-500, >500), it appears that a favorable outcome was observed only in patients with a CD4 count >500 μL, though the number of patients are small in each subset. Once adjusted for stage in the multivariate analysis, CD4 count was no longer a significant predictor of survival which suggests that cancer stage is a stornger predictor of outcome than CD4 count. Furthermore, patients who were treated had a significantly higher CD4 count (349 μL) than those who were not treated (183 μL). Brock et al. demonstrated a similar correlation between CD4 count and survival [15]. Therefore, it appears that patients with a lower CD4 count were more likely to be deemed ineligible for definitive cancer-directed therapy due to the presence of either other comorbidities or a poor performance status. In our series, poor performance status or other comorbidities prevented 28 (37%) patients from being offered definitive therapy. **Receiving** definitive treatment had a greater impact on survival **(p=0.0004)** in the multivariate analysis compared to those who only received palliative radiation or supportive care. Since systemic chemotherapy is associated with myelosuppression, it is conceivable that HIV-positive patients could be at higher risk for opportunistic infections during chemotherapy. This concern has often led to the use of suboptimal treatment regimens in this patient population. Furthermore, treatment data are limited to smaller case studies and the optimal treatment of lung cancer in HIV-positive patients is yet to be determined. Of those treated with chemotherapy or chemo-radiation about a third (9/29) developed an infection and one resulted in death. However, our data suggest that eligible patients benefit in terms of an improved survival from definitive treatment with manageable toxicities. A prior history of AIDS appeared to be more predictive of a treatment complication than merely having a CD4 count <200 alone. However, patient numbers were small, making definitive conclusions difficult to assess.

Lung cancer is the most fatal non-AIDS defining malignancy and frequently presents at an incurable stage [40]. While a CD4 count <500 is associated with a worse prognosis, it may only reflect the fact that treatment options are limited by associated co-morbid illness or a poor performance status. Future interventions need to focus on smoking prevention, early initiation of ARVs (CD4 count <500) and higher index of suspicion of lung cancer in patients with suggestive symptoms. It will also be important to evaluate the prevalence of certain molecular abnormalities such as epidermal growth factor receptor mutation, ALK translocation, K-ras and p53 mutations. This will allow for development of molecularly targeted therapeutic approaches for patients with HIV-related lung cancer. Prospective studies with commonly used therapeutic regimens are needed to further understand tolerability and efficacy outcomes. In summary, our study supports the use of stage-appropriate standard therapeutic options for lung cancer in HIV-positive patients with a good performance status who do not have significant comorbidities.

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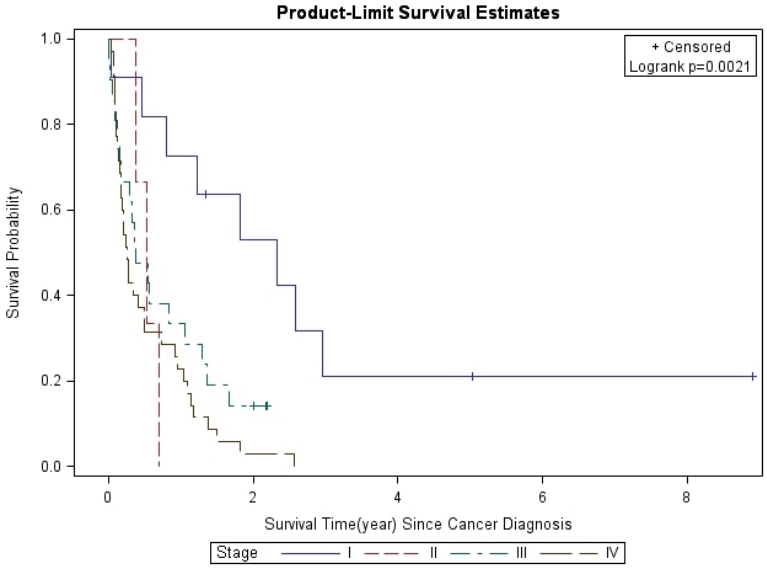

Figure 1. Lung Cancer Survival Based on Stage

Lung cancer survival was analyzed by the Kaplan-Meier method for different stages (I-IV) of NSCLC at diagnosis.

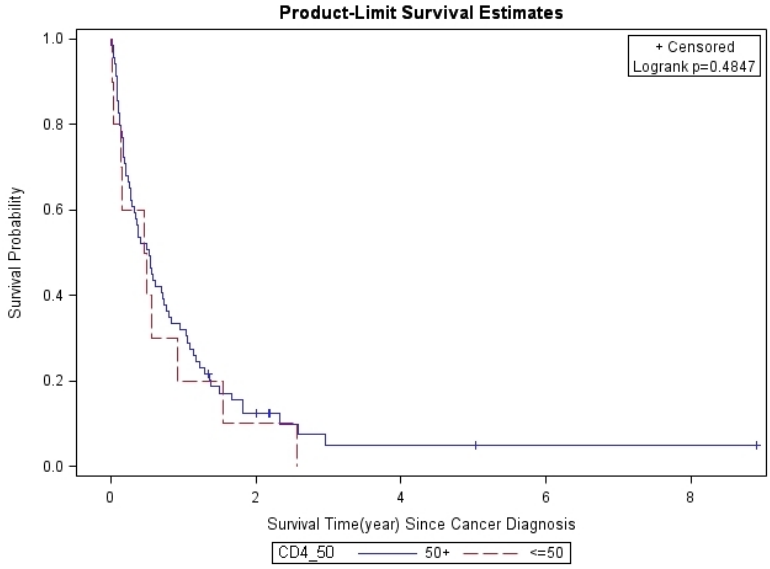

Figure 2. CD4 Count at Cancer Diagnosis (≤50 vs. 50+)

Lung cancer survival was stratified by CD4 count at cancer diagnosis, and analyzed by the Kaplan-Meier method.

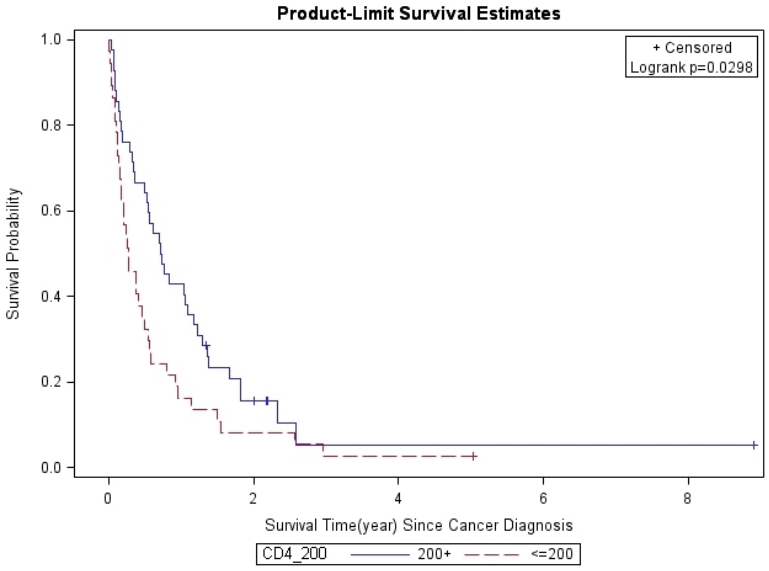

Figure 3. CD4 Count at Cancer Diagnosis (≤200 vs. 200+)

Lung cancer survival was stratified by CD4 count at cancer diagnosis, and analyzed by the Kaplan-Meier method.

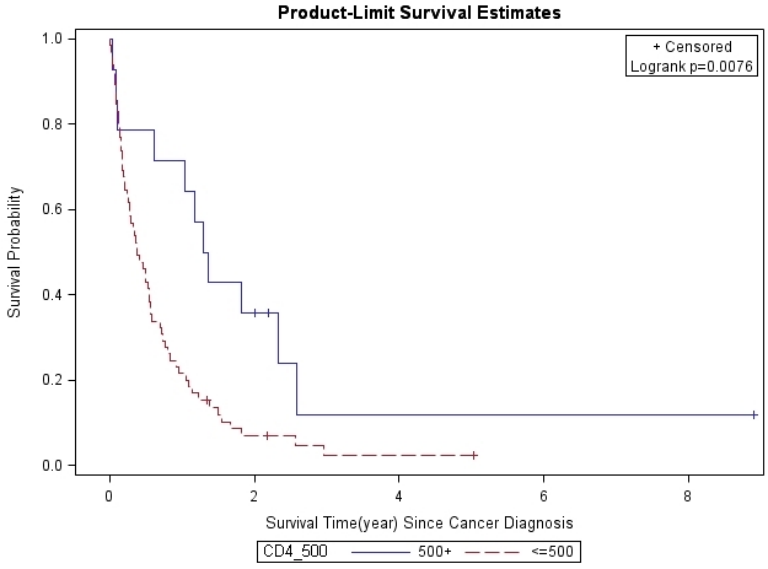

Figure 4. CD4 Count at Cancer Diagnosis (≤500 vs. 500+)

Lung cancer survival was stratified by CD4 count at cancer diagnosis, and analyzed by the Kaplan-Meier method.

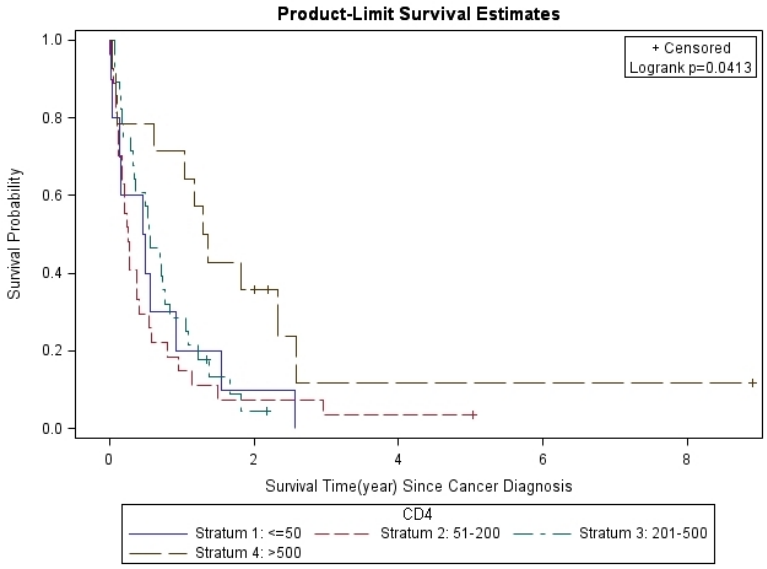

Figure 5. Lung Cancer Survival Based on CD4 Count

Lung cancer survival was stratified by CD4 count (<50, 51-200, 201-500, >500) at cancer diagnosis and analyzed by the Kaplan-Meier method.

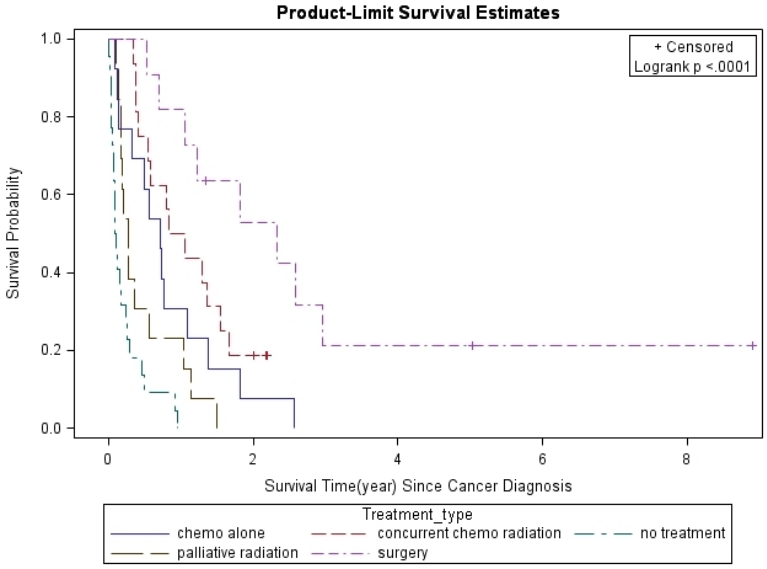

Figure 6. Lung Cancer Survival Based on Treatment Modality

Lung cancer survival was analyzed by the Kaplan-Meier method for different treatment modalities.

Table 1

Patient Characteristics

Patient Characteristics	Results N (%)
Median Age/Range (years), N=80	52/28-73
Males, N=80	64 (80)
African Americans, N=80	67 (84)
Smoking, Mean pack-years/Range, N=77	37/10-100
Sexual Orientation, N=69	
Heterosexual	46 (67)
Men who have sex with Men	13 (19)
Bisexual	10 (14)
Intravenous Drug Use, N=76	19 (25)
Substance abuse (any), N=76	54 (71)
Alcohol abuse, N=80	49 (61)
Mean Latency of HIV to Lung Ca Diagnosis/ Range (years), N=80	7/0-18
Histology, N=80	
Small Cell Lung Cancer	7 (9)
Non-small Cell Lung Cancer	73 (91)
Adenocarcinoma	30 (38)
Squamous	23 (29)
NSCLC NOS	20 (25)
Stage at Diagnosis	
SCLC, N=7	
Limited	2 (28)
Extensive	5 (71)
NSCLC, N=70	
IA	3 (4)
IB	8 (11)
IIA	0
IIB	3 (4)
IIIA	3 (4)
IIIB	18 (25)
IV	35 (49)

N=number of patients with available data. Ca=Cancer, NSCLC=Non-small cell lung cancer, NOS=Not otherwise specified, SCLC=Small cell lung cancer

Table 2

HIV Related Factors

Patient Characteristics	Results N (%)
Mean CD4 at CA diagnosis/Range (μL), N=79	304/3-1361
Mean VL at CA diagnosis/Range (copies/ml), N=61	82,420/<50- >750,000
Viral Load (VL) undetectable	17 (27)
Viral Load ≥ 200,000	7 (11)
AIDS diagnosed prior to CA diagnosis, N=80	59 (74)
Antiretroviral use, N=80	
Initiated prior to CA diagnosis	44 (55)
Initiated after CA diagnosis	12 (15)
None	24 (30)

N=number of patients with available data. CA=Cancer, VL=Viral load.

Table 3

Lung Cancer Treatment

Patient Characteristics	Result N (%)
ECOG performance status, N=50	
0-1	31 (62)
≥2	19 (38)
Treatment, N=75	53 (71)
Surgery	11 (21)
Concurrent chemo-radiation	15(28)
Chemotherapy alone	14 (26)
Radiation alone	13 (25)
WBXRT only	5 (9)
No Treatment, N=75	22 (29)
Ineligible for Treatment	17 (77)
Declined Treatment	5 (23)
CD4 <200 in Treated Patients, N=75	12/40 (30)
Surgery	2/11 (20)
Concurrent chemo-radiation	6/15 (40)
Chemotherapy alone	4/14 (29)
Treatment Ineligible, N=75	17 (23)
CD4 <200	13 (76)
Treatment complication, N=75	14/40 (35)
Surgery	1/11 (9)
CD4 ≤200	0/2
Prior diagnosis of AIDS	1
Concurrent chemo-radiation	9/15 (60)
CD4 ≤200	3/6
Prior diagnosis of AIDS	7
Chemotherapy alone	5/14 (36)
CD4 ≤200	3/4
Prior diagnosis of AIDS	5

N=number of patients with available data. WBXRT=Whole brain radiation.

Table 4

Factors Affecting Cancer Directed Therapy

	Cancer Directed Therapy		p-value
	Yes	**No**	
Antiretroviral use (ARV) Yes No	43 (81%) 10 (19%)	10 (45%) 12 (55%)	0.002
AIDS Onset prior to Cancer Diagnosis Yes No	39 (74%) 14 (26%)	18 (82%) 4 (18)	0.56
CD4 Count Mean (standard error)	348.8 (40.4)	183.4 (51.7)	0.02
CD4 Count Nadir ≤ 200 >200	43 (83%) 9 (17%)	18 (82%) 4 (18)	0.93

Table 5

First-line Treatment and Treatment-related Complications for Individual Patients

Treatment (dose mg/m2)		Treatment Complications
Limited Stage Small Cell Lung		
1	Cisplatin/VP16 × 2 c	Fever with neutropenia
Extensive Stage Small Cell Lung		
2	Cisplatin(60)/VP16(75) × 1 c	Decline in PS
3	Cisplatin(75)/ VP16(100) × 3 c	ARF, clostridium difficile
	Cisplatin(60)/ VP16(120)× 1 c->(75)/(100) ×1 c->(75)/(80) × 2 c +XRT(30Gy)	Pericarditis, Prolonged neutropenia
4	Cisplatin(75)/ VP16(100) × 4 c	Prolonged neutropenia
Stage II Non-small Cell Lung Cancer		
5	Cisplatin(50)/VP16(50) × 2 c + XRT	Pseudomonas bacteremia
6	Cisplatin + XRT	
Stage III Non-small Cell Lung Cancer		
7	Carboplatin(AUC 6)/Paclitaxel(175)× 2 c +XRT(37Gy)->1	
8	Carboplatin (AUC 1.5)/Paclitaxel(50) × 5 wkly c +XRT->1 c	Prolonged neutropenia
9	Cisplatin(50)/VP16(100)× 2 c +XRT(34Gy)	
10	Cisplatin(50)/VP16(50) × 1 c->Carboplatin(AUC 2)× 3 wkly c + XRT(66Gy)	Fever with neutropenia, ARF, decline in PS, pneumonia
11	Cisplatin(50)/VP16(50) × 2 c + XRT(66Gy)	
12	Cisplatin(75)/ (100)× 1->XRT(61 Gy)	Myelosuppression, ARF
13	Carboplatin/Paclitaxel × 4 c + XRT	Esophagitis requiring gastric tube
14	Carboplatin/Paclitaxel × 6 wkly c + XRT(66Gy)-> 3 c	Esophagitis, dehydration, pneumonia
15	Carboplatin(AUC 5)/Paclitaxel(135)× 1 c	Neutropenia, hypotension
16	Cisplatin ×4 wkly c + XRT	Esophagitis
17	Carboplatin(AUC 5)/Paclitaxel(175)× 2 c + XRT(66 Gy)-> 2 c	Syncope, esophagitis
Stage IV Non-small Cell Lung Cancer		
18	Carboplatin/Paclitaxel × 4 c	
19	Cisplatin(30) wkly c +XRT(37.5 Gy)->Paclitaxel × 1 c	Esophagitis, ITP/hemoptysis, aspergillosis/VRE sepsis, ARF, respiratory failure and death
20	Carboplatin(AUC 6)/Paclitaxel(200) × 2 c	Esophagitis
21	Carboplatin(Auc 2)/Paclitaxel(45)×7 wkly c + XRT(57 Gy)	Prolonged neutropenia, esophagitis
22	Carboplatin/Paclitaxel × 4 c	
23	Carboplatin/Paclitaxel × 1 c	
24	Carboplatin/Paclitaxel × 5 c	
25	Carboplatin(AUC 5)/Paclitaxel(175)× 4 c	Zoster, symptomatic anemia
26	Carboplatin/Paclitaxel × 4 c	

VP16=Etoposide, c=cycles, PS=performance status, ARF=acute renal failure, ITP=immune thrombocytopenia, VRE=vancomycin resistant enterococcus

Table 6

Multivariate Analysis of Cancer-Related Overall Survival and Prognostic Factors

Variable	Categorical variables	Hazard Ratio (95% CI)	p-value
Age at Cancer Diagnosis		0.993 (0.959, 1.029)	0.7079
Smoking (pack-year)		1.015 (0.997, 1.032)	0.0949
Latency		0.998 (0.941, 1.058)	0.9413
CD4 at Cancer Diagnosis		0.999 (0.998, 0.99999)	0.1571
Gender:	Female	1.064 (0.521, 2.174)	0.8646
	Male	Reference	
Race	African American	1.054 (0.420, 2.643)	0.9114
	White	Reference	
Stage	I	0.227 (0.079, 0.652)	0.03
	II	1.436 (0.359, 5.745)	
	III	1.012 (0.492, 2.081)	
	IV	Reference	
Treatment	No treatment or Palliative radiation	4.169 (1.893, 9.181)	0.0004
	Treated	Reference	