

A comparison of lung cancer in HIV-positive and HIV-negative populations

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Background. Lung cancer is the most common cancer worldwide and is the greatest contributor to malignancy-associated deaths. Human immunodeficiency virus (HIV) is an epidemic in many developing countries and South Africa carries the largest burden of this disease in the world. With the introduction of antiretroviral therapy (ART), acquired immune deficiency syndrome (AIDS)-defining malignancies (ADMs) are on the decline and non-AIDS-defining malignancies (NADMs) are becoming more common, with lung cancer being the most common among these.

Objective. To describe and compare a cohort of HIV-positive lung cancer patients and a cohort of HIV-negative lung cancer patients.

Methods. A retrospective study of 188 patients with histologically confirmed bronchogenic carcinoma was conducted. Smoking history, cancer sub-type, cancer stage, HIV parameters and demographic data were collected.

Results. There were 31 (16.94%) HIV-positive patients. They presented at a younger age (53.94 years) than the HIV-negative group (61.64 years) ($p=0.0001$). Adenocarcinoma was the most common sub-type in the HIV-negative cohort while squamous cell carcinoma was slightly more common in the HIV-positive cohort. Both groups predominantly presented with locally advanced or metastatic disease.

Conclusion. HIV-positive patients present at a younger age than HIV-negative patients and both groups show a male-predominant pattern.

Keywords. HIV; lung cancer; malignancy; South Africa

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Lung malignancies are the leading cause of malignancy-related deaths globally.^[1] Lung cancer is the most common non-acquired immune deficiency syndrome (AIDS)-defining malignancy.^[2,3] The prognosis of human immunodeficiency virus (HIV)-infected persons who develop lung cancer was found to be poorer than HIV-uninfected persons in several studies.^[3,4] However, it is unclear if this finding is related to treatment disparities, intolerance to chemotherapy, increased risk of treatment toxicity, or risk from AIDS and non-AIDS-related illnesses.

In a South African (SA) study from 1992 - 1998,^[5] data parallel international findings, where men have a higher incidence of lung cancer; this is probably related to a historically higher smoking prevalence. In the same study, squamous cell carcinoma (SCC) was found to be the most common histological sub-type compared with international findings, where adenocarcinoma was the most common. The increase in the prevalence of adenocarcinoma in smokers has been linked to design changes in cigarettes that have promoted deeper inhalation.^[6]

In the global general population, the most common type of lung cancer found is non-small-cell lung cancer (NSCLC), adenocarcinoma sub-type (16.86% - 63.98% of NSCLC).^[1,7,8] In the HIV-positive population, NSCLC is reported in 84 - 96% of cases in which adenocarcinoma is the most common sub-type, found in 32 - 50% of cases.^[1,7,9] However, some smaller studies have reported SCC as the most common sub-type in the HIV-positive population.^[10,11]

HIV-associated malignancies can be separated into AIDS-defining malignancies (ADMs) and non-AIDS-defining malignancies (NADMs). ADMs include Kaposi's sarcoma, high-grade sub-types of non-Hodgkin's lymphoma and invasive cervical carcinoma.^[1] NADMs that are more prevalent in HIV-infected individuals include anal cancer, lung cancer, Hodgkin's lymphoma and liver cancer.^[2,12] There has been a rise in NADMs since the inception of antiretroviral therapy (ART), while ADMs are declining in developed countries.^[2,12] One possible explanation for this trend is that people with HIV are living longer since the initiation of ART.^[13] This suggestion is supported by an increase in NADMs in people who are older than 40 years.^[2] Since 2003, the absolute number of cases of NADMs now exceeds that of ADMs in the USA.^[12,14] It is expected that a similar pattern will follow in SA, especially with ART now being started without the need for a specific cluster of differentiation 4 (CD4+) count.^[15]

When comparing the incidence of ADMs and NADMs in the pre-ART and ART periods, it was found that among 600 000 patients, there was an overall decrease in ADMs.^[16]

It is thought that lung malignancies occur at a relatively higher CD4+ count as compared with ADMs.^[17] A study in Germany showed an average CD4+ cell count of 383 cells/ μ L in patients who developed lung cancer.^[17] Furthermore, a study in Italy showed no statistically significant difference in the CD4+ cell count of people with HIV and lung cancer receiving ART as compared with those not receiving ART with a diagnosis of lung cancer.^[7]

The prevalence of smoking is higher in the HIV-positive population, which could potentially contribute to the higher incidence of lung cancer. Mani *et al.*^[11] report a prevalence of 35 - 70% as compared with 20% in the general population in the USA. Chaturvedi *et al.*^[18] showed that smoking alone cannot explain the higher incidence of lung cancer in HIV-positive patients and that other factors have an effect. Some considerations include the oncogenic role of HIV itself, recurrent lower respiratory tract infections, local inflammation of the lung, systemic inflammation and a possible role of immunosuppression.^[1,10,19]

Lung cancer in HIV-positive patients has a male predominance similar to that in HIV-negative patients;^[7] however, the mean age at diagnosis is usually 10 years earlier than the HIV-negative matched cohort.^[17] HIV-positive patients also tend to be diagnosed with a more advanced stage of lung cancer compared with the general HIV-negative population.^[1]

A South African study from 2016 showed the most common subtypes of lung cancer were SCC in HIV-positive patients and adenocarcinoma in HIV-negative patients.^[11] The researchers also found HIV-positive patients were younger and had a worse performance status, which correlates with international findings.^[19]

A German study assessed the stage-related survival of HIV-positive patients with lung cancer.^[17] It found that the overall survival of patients with stages I - IIIa was 5.18 years, while patients with stages IIIb - IV had a life expectancy of 0.81 years^[17] with a median overall survival of 1.08 years.^[17] An Italian study found the median overall survival was 7 months for those receiving ART.^[7]

Methods

Patients and data collection

Data were collected retrospectively from all patients with a histological diagnosis of bronchogenic lung cancer from 1 January 2010 - 31 December 2017 at the Helen Joseph Hospital, using records at the National Institute for Occupational Health (NIOH) lung database and the National Health Laboratory Service (NHLS) anatomical pathology records, Helen Joseph Hospital respiratory outpatient department and bronchoscopy records.

Inclusion criteria required patients to be 18 years or older, have a histological diagnosis of lung cancer and a known HIV status.

The 2015 WHO classification of lung malignancies is the classification system used in the present paper. All those with a histological diagnosis of non-small-cell lung cancer not otherwise specified (NSCLC NOS) were grouped with large-cell carcinomas. This was done for ease of classification as most specimens collected were of small histological size and could not technically be classified as large-cell carcinoma.^[20]

All non-bronchogenic lung cancers were excluded.

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved this study (ref. no. M170625).

Data analysis

Statistical analysis was done using Stata (StataCorp., USA) and Excel (Microsoft Corp., USA). Comparative analysis between HIV-positive and HIV-negative groups, gender, and histological sub-types of lung cancer was done using Student's *t*-test (normally distributed data) and Wilcoxon rank sum test (non-normally distributed data) for continuous

variables. Comparisons between two categorical variables were done using the chi-square test (larger sample sizes) and Fisher's exact test (in smaller sample sizes). Statistical significance was set at a $p \leq 0.05$.

Results

There were 272 patients diagnosed with possible lung cancer between 1 January 2010 and 31 December 2017. This number was reduced to 188, as we excluded 3 owing to cytology omissions and 81 owing to lack of a HIV result.

Of the 188 patients, 157 (83.51%) were HIV negative and 31 (16.49%) were HIV positive. There was no significant difference in the proportion of males to females when comparing the HIV-positive with HIV-negative groups ($p=0.85$) (Table 1). The average age at diagnosis was 60.37 years. There was a statistically significant difference between the ages of the HIV-negative and HIV-positive populations ($p=0.0001$), with the average age of the HIV-negative group being 61.64 years and the HIV-positive group being 53.94 years. The younger age at presentation in HIV-positive patients was noted mostly in those with adenocarcinoma, who had an average age of 50.09 years and SCLC, with an average age of 45.33 years (of note, there were only 3 patients) while those with SCC had an average age of 60.17 years.

Ninety-four patients had a known stage. Seventy of the 80 patients in the HIV-negative group had stage IV disease (87.5%), 9 with stage IIIB (11.25%) and 1 with stage IIIA (1.25%). All 14 patients in the HIV-positive group had stage IV disease. In the patients with SCLC, 14 of the 16 had extensive disease (87.5%) and 2 had limited disease (12.5%).

Forty patients had no history available on smoking and were excluded. There were 134 smokers (90.54%) and 14 never-smokers (9.46%). In the HIV-negative group, 124 of the 135 were smokers (91.85%). In the HIV-positive group, 10 of the 13 were smokers (76.92%). A significant difference was found when comparing smoking between the genders ($p=0.00051$): 105 of the 110 males were smokers (95.45%) while 29 of the 38 females were smokers (76.32%).

There is no defined pack-year history that causes lung cancer; however, the longer the duration and the greater the exposure, the greater the risk of developing lung cancer. Ten pack-years or more was arbitrarily decided on as a significant smoking history. Of the 134 smokers, 98 had a significant smoking history (73.13%), only 4 patients were known with a pack-year history <10 (11.76%) and 32 of the known smokers did not have documentation of their pack-year history (23.88%).

Chronic obstructive pulmonary disease (COPD) was documented in 28 (14.89%) patients in the study.

Active pulmonary tuberculosis (PTB) was found in addition to lung cancer in 6 of the 188 patients (3.19%), 4 of whom were HIV negative and 2 HIV positive. Additionally, 5 other patients (2.66%) – 3 HIV positive and 2 HIV negative – had previously suffered from PTB. The exposure to TB was therefore 11 of 188 patients (5.85%).

Within the group of 31 HIV-positive patients, 16 were on ART at diagnosis (51.61%), 7 were not (22.58%) and 8 had no history available (25.81%). Twenty-six of the patients had CD4+ counts available, which ranged from 41 to 722 cells/ μ L. In the group of patients on ART, CD4+ counts ranged from 99 to 688 cells/ μ L with a mean of 365 cells/ μ L, while in those not on ART, CD4+ counts ranged from

Table 1. Data summary of patients

| Patient data | HIV-negative (N=157), (n%) | HIV-positive (N=31), n (%) |
|--------------------------------|----------------------------|----------------------------|
| Gender | | |
| Male | 109 (69.43) | 21 (67.74) |
| Female | 48 (30.57) | 10 (32.26) |
| Age (years), mean (SD) (range) | | |
| Male | 61.48 (9.10) (36 - 90) | 53.57 (8.12) (39 - 73) |
| Female | 61.91 (10.07) (30 - 84) | 54.7 (13.83) (28 - 73) |
| Average age | 61.64 | 53.94 |
| Smoking | | |
| Smoker | 124 (78.98) | 10 (32.26) |
| Non-smoker | 11 (7) | 3 (9.68) |
| Unknown | 22 (14.01) | 18 (58.06) |
| HIV parameters | | |
| Average CD4 (cells/ μ L) | N/A | 358 (41 - 722) |
| VL, copies/mL | | |
| <50 | | 10 |
| 50 - 1 000 | | 4 |
| >1 000 | | 4 |
| Unknown | | 13 |
| Sub-types | | |
| Adenocarcinoma | 69 (43.95) | 11 (35.48) |
| Squamous | 53 (33.76) | 12 (38.71) |
| Small cell | 23 (14.56) | 3 (9.68) |
| Large cell | 6 (3.82) | 2 (6.45) |
| Other | 6 (3.82) | 3 (9.68) |
| Stage – NSCLC | | |
| 1 | 0 | 0 |
| 2 | 0 | 0 |
| 3A | 1 (0.75) | 0 |
| 3B | 9 (6.72) | 0 |
| 4 | 70 (52.24) | 14 (50) |
| Unknown | 54 (40.3) | 14 (50) |
| Stage – SCLC | | |
| Limited | 2 (8.7) | 0 |
| Extensive | 13 (56.52) | 1 (33.3) |
| Unknown | 8 (34.78) | 2 (66.6) |

SD = standard deviation; VL = viral load; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer.

169 to 722 cells/ μ L. The mean CD4+ count was 467 cells/ μ L but owing to the low numbers, no statistical difference was observed ($p=0.46$) between those on ART and those not on ART. When considering viral loads (VLs) of those on ART, 9 of the 16 had a VL <50 copies/mL (56.25%), 3 had a VL between 50 and 1 000 copies/mL (18.75%), 2 had VLs >1 000 copies/mL (12.5%) and 2 had no VL charted (12.5%). Treatment success was achieved in 12 of the 16 patients (75%), and treatment failure in 2 (12.5%). We were unable to assess whether those patients on ART had more or less advanced disease than those not on ART as all the HIV-positive patients with available staging had stage 4 disease.

Discussion

The diagnosis of lung cancer has increased over time owing to increased awareness and clinical suspicion as well as access to

more specialised centres where bronchoscopy and specialists are available. The number is, however, still believed to be short of the actual expected number.

We found a large gender bias in the lung cancer population, with a far larger proportion of males than females being diagnosed. This ratio of approximately two-thirds was noted in both the HIV-negative and -positive groups. This same trend was observed in a study which looked at lung cancer in the HIV population^[1] and in the South African National Cancer Registry (NCR) statistics from 2014.^[25] Risk-taking behaviour, including smoking, is more prevalent among males than females, which is the most likely reason why there is a male predominance in the lung cancer population.^[21,22]

There has been a change in smoking trends, with smoking becoming more common in females. This is a phenomenon observed particularly in developed countries.^[23] There is a long latency period

between smoking and the development of lung cancer^[24] and therefore the opposite effect of a decline in smoking and the reduction of lung cancer is also expected to be true.^[24] The smoking rate, while declining globally in males, is still far higher than in females. The latency period may account for lung cancer still occurring more commonly in males despite a decline in smoking rates.

A study by Jemal *et al.*,^[23] looked at the trend in lung cancer by gender over a period of ~20 years (1995 - 2014), where they found a decline in the incidence of lung cancer among men and women. The decline was steeper among men and therefore a higher incidence of lung cancer was reported among women in certain age groups and races.

The younger age identified in the HIV cohort in the present study of 53.94 years compared with the HIV-negative tally of 61.64 years and has also been borne out in other studies.^[1,11]

Multiple studies have found that HIV-positive patients present at a more advanced stage than HIV-negative patients.^[1,7] SCLC is known to be more aggressive, with more patients expected to be found with more advanced disease.^[27,28] The numbers quoted in some studies were upwards of 65% compared with 47% of NSCLC being metastatic.^[27,28] We found that most patients were at an advanced stage but we were unable to differentiate between HIV-positive and -negative groups owing to the small number in the HIV-positive group.

According to Cheng *et al.*,^[8] smoking is responsible for lung cancer in 65% of males and 25% of females in medium human development index (HDI) countries, which is where SA is placed.^[26] In contrast, SA is unique because the smoking rates among women in Africa are low but in SA they are quite high, so accounting for a greater incidence of lung cancer among women, when compared with the rest of Africa.^[26]

The Human Sciences Research Council of SA released smoking data for South Africa based on the first South African National Health and Nutrition Examination Survey (SANHANES-1).^[22] This survey showed that 17.6% of South Africans smoked cigarettes and this number grew to 20.1% when including other tobacco products in addition to cigarettes. Smoking was also noted to be far more prevalent in males (29.2%) than among females (7.3%). The smoking prevalence is far greater in the lung cancer population, where upwards of 80% are smokers while others may be exposed to second-hand smoke.^[29] In a study assessing the prevalence of smoking in the HIV-positive population, 52% of males and only 13% of females were current smokers.^[30]

Epidemiological data from SA show a significant decrease in smoking prevalence over the last 20 years, with smoking now about half as common as it was.^[22] Wong *et al.*,^[31] found that lung cancer incidence and mortality mostly show a decreasing trend in men and an increase in women. This is probably due to the decline in smoking among men which is steeper than that among women. They also found a higher incidence of lung cancer associated with higher HDI countries and attribute this to increased exposure to tobacco and pollution, as these countries are more industrialised.^[31]

Mani *et al.*,^[1] also report that ART has no effect on lung cancer incidence and that lung cancer is no more common among individuals with higher as compared with lower CD4+ counts.

We also found that the HIV-positive patients in our study had relatively high CD4+ counts both in the group on ART and those without (mean CD4+ count of 365 cells/ μ L and 467 cells/ μ L, respectively).

That HIV-positive patients are living longer also accounts for the moderate CD4+ counts seen as opposed to lower counts in the AIDS range.^[18] This issue is controversial and Guiguet *et al.*,^[32] maintain that as the CD4+ drops, the risk for lung cancer increases. They observed that as the CD4+ count dropped from >500 cell/ μ L to 350 - 499 cell/ μ L, risk doubled and became worse as counts dropped further, thus suggesting a role for immune suppression.^[32]

Study limitations and recommendations

Data regarding ethnicity of patients, staging and smoking were incomplete and therefore we were unable to demonstrate an accurate prevalence of each of these factors. Data on the type of smoking (whether primary, secondary or tertiary) were also unavailable as were those on other tobacco exposure (e.g. pipe smoke). The data collection time was limited and did not allow us to show change in certain trends observed in other studies, such as the relative increase in female smoking. Lack of documentation and follow-up meant we were unable to ascertain occupational and mining history, causes of death and difference in survival between the two groups. Allowing only patients with a histological diagnosis meant we were unable to determine the true prevalence of lung cancer, as patients having a cytological diagnosis only were excluded. Our classification of large-cell carcinoma by the accurate definition was not correct, as the WHO classification does not cater for the diagnosis of NSCLC NOS and, in order to diagnose large-cell carcinoma, a large or excisional specimen is required, which we did not have for any of our patients, as they were diagnosed either by bronchoscopy (majority) or by pleural biopsy.

It would be preferable to have a prospective study with adequate follow-up of patients so we could evaluate the survival of patients between the two groups.

Conclusion

Lung cancer presents in HIV-positive patients at a younger age compared with HIV-negative patients. It is often diagnosed late, both in HIV-positive and -negative patients, with most patients presenting with locally advanced or metastatic disease (stage IIIB or IV). Lung cancer is more common in males. Adenocarcinoma was found to be the most common histological sub-type of lung cancer among the general population, with SCC being slightly more common in the HIV-positive population; however, owing to small numbers and a lack of statistical significance, we cannot be certain that this is accurate or representative of the general HIV-positive population. As expected, the prevalence of smoking in the lung cancer population is much higher than in the general population. However, we were unable to determine whether smoking was more common in the HIV-positive lung cancer population owing to missing data.

Declaration. Approval for the study was received from the university's Human Research Ethics Committee (Medical), M170625. Owing to the retrospective nature of the work, informed consent was not sought from individuals, but hospital ethics approval was given. All authors give consent to the publication of this manuscript. Anonymised supporting data will be made available upon request, and are available on an Excel spreadsheet.

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Author contributions. RB: conception, design of the work, data collection and sample collection, interpretation of data, drafted the work, substantively revised it, approved the submitted version, and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, were appropriately investigated, resolved, and the resolution documented in the literature. SAVB and AKG: conception, design of the work, substantively revised it, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, were appropriately investigated, resolved, and the resolution documented in the literature.

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