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

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

Ryan Berman

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of
Master of Medicine

Johannesburg, 2020

Declaration

I, Ryan Berman declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

……

(Signature of candidate)

……day of …….2020…….in……

Abstract

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 disease in the world. With the introduction of antiretroviral therapy (ART), Acquired Immune Deficiency Syndrome (AIDS) defining malignancies (ADM's) are on the decline and non-AIDS defining malignancies (NADM's) are becoming more common with lung cancer being the commonest amongst these.

Aim: To describe a cohort of HIV-positive lung cancer patients and a cohort of HIV-negative lung cancer patients and compare the similarities and differences between the two groups.

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 commonest 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. We were unable to assess whether smoking was more common in either group or whether HIV-positive patients present at a more advanced stage than HIV-negative patients due to a paucity of data.

Acknowledgements

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Nomenclature

ADM's	AIDS Defining Malignancies
AJCC	American Joint Commission on Cancer
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CD	Cluster of Differentiation
CDC	Centre for Disease Control
CDW	Central Data Warehouse
COPD	Chronic Obstructive Pulmonary Disease
CXR	Chest X-ray
EBV	Epstein Barr Virus
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IASLC	International Association for the Study of Lung Cancer
LCNEC	Large Cell Neuroendocrine carcinoma
NADM's	Non-AIDS defining Malignancies
NCD	Non-Communicable Disease
NCR	National Cancer Registry
NHLS	National Health Laboratory Service
NIOH	National Institute for Occupational Health
NSCLC	Non-Small cell Lung Cancer
NSCLC-NOS	Non-Small cell Lung Cancer Not Otherwise Specified
PTB	Pulmonary Tuberculosis
SANHANES	South African National Health and Nutrition Examination Survey
SCC	Squamous cell Carcinoma
SCLC	Small cell Lung Cancer
VACS	Veterans Aging Cohort Study

VALSG	Veterans Administration Lung Study Group
WHO	World Health Organisation

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CHAPTER 1

Introduction and literature review

1.1 Background

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 Human Immunodeficiency Virus (HIV) associated malignancy (2, 3). The prognosis of 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 is related to treatment disparities, intolerance to chemotherapy, increased risk of treatment toxicity, or risk from AIDS and non-AIDS-related illnesses.

1.2 Literature review

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

The 2015 World Health Organisation (WHO) classification of lung tumours categorises lung cancer based on histological sub-type (7). In terms of the epithelial variants of lung tumours, the main sub-types include adenocarcinoma, squamous cell carcinoma, and neuroendocrine

tumours which comprise small and large cell carcinoma (amongst others). 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, 8, 9). In the HIV-positive population, NSCLC is reported in 84-96% of cases in which adenocarcinoma is the commonest sub-type, found in 32-50% of cases (1, 8, 10). However, some smaller studies have reported SCC as the commonest sub-type in the HIV-positive population (11, 12). However, limited power precludes these findings from being statistically significant.

HIV is a risk factor for many diseases both communicable and non-communicable (NCD) (13). NCDs in the HIV population include malignancies, cardiovascular disease, and liver disease (unrelated to chronic viral hepatitis) amongst others. The HIV Cancer Match Study estimated in 2010, that of the nearly 900 000 people living with HIV in the United States of America (USA), 7760 were diagnosed with cancer (14).

HIV associated malignancies can be separated into AIDS defining malignancies (ADMs) and Non-AIDS defining malignancies (NADMs). ADMs include Kaposi's sarcoma, sub-types of Non-Hodgkin's lymphoma (usually high grade sub-types) and invasive cervical carcinoma (1). NADMs that are increased in HIV infected individuals include anal cancer, lung cancer, Hodgkin's lymphoma and liver cancer (2, 15). It should be noted that barring lung cancer, all of these malignancies have an infectious aetiology (Human papillomavirus (HPV) for anal cancer, Epstein-Barr virus (EBV) for Hodgkin's lymphoma and Hepatitis B and C viruses for liver cancer). There has been a rise in the NADMs since the inception of antiretroviral therapy (ART) and ADMs are declining in developed countries (2, 15). One possible explanation for this is that people with HIV are living longer since the initiation of ART (16). This is supported by the 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 (15),

and this has also been demonstrated in a study from Switzerland (17). It is expected that a similar pattern will follow in South Africa, especially with the inception of the new ART guidelines (18).

A Swiss study showed a definite decrease in the incidence of ADMs between the pre-ART period, early-ART, and late-ART periods. It did not show a significant increase in the actual number of NADMs, however, due to a decrease in the number of ADMs, the NADMs were relatively proportionately more well represented (17).

In a study in Uganda, which looked at the incidence of cancer (both ADM and NADM) in relation to ART coverage, it was found that for every 10% increase in ART coverage there was a 5% decrease in the incidence of KS. However, there was a 6% increase in the incidence of NHL's (16). In a systematic review by a Brazilian group 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 (19). There is a paucity of data from the African continent comparing the change in cancer incidence between the pre-ART period and post-ART initiation period.

In terms of HIV, lung cancer is the commonest NADM encountered according to *Shiels et al* (2011) (2, 20, 21). While lung cancer is more common in the setting of HIV (1, 22), the incidence does not seem to be affected by the introduction of ART as reported by *Mani et al* (2012) (1). The prevalence of lung cancer is on the increase globally in the HIV population (14, 23-27). This is likely due to HIV-positive people living longer and thus to an age where cancer is more common (28). Some studies found that while NADMs are increasing and HIV is an independent risk for lung cancer, the incidence of lung cancer is actually on the decline in the HIV-positive population (28, 29). Additionally, it is thought that lung malignancies

occur at a relatively higher cluster of differentiation 4 (CD_{4+}) count as compared with ADMs (30) and CD_{4+} count may have no bearing on the risk of developing lung cancer (29). A study in Germany showed an average CD_{4+} cell count of 383 cells/μl in patients who developed lung cancer (30). Furthermore, a study in Italy showed no statistically significant difference in the CD_{4+} cell count of people with HIV and lung cancer receiving ART as compared with those not receiving ART with a diagnosis of lung cancer (8).Thus, ART is unlikely to affect the incidence of lung malignancies (8), however, ART use is associated with increased survival. As with other NADMs, lung cancer is found to be increasing in patients older than 50 years while remaining mostly unchanged in those below 50 years (2). This supports the hypothesis that NADMs are increasing as the HIV-positive population ages (2).

One of the reasons HIV-positive patients have a higher incidence of lung cancer compared with HIV-negative patients is their higher smoking prevalence, *Mani et al* (2012) reports a prevalence of 35-70% as compared with 20% in the general population in the USA (1). That being said, *Chaturvedi et al* (2007) showed that smoking alone cannot explain the higher incidence of lung cancer in HIV-positive patients and that other factors likely related to HIV have an effect (31). Some of the reasons postulated for this 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, 11, 32). Data reported in India found head and neck malignancies rather than lung malignancies to be the commonest NADM (33), which the authors ascribe to tobacco use (33). However, they also propose a possible link with oral HPV as the aetiology for this finding which needs to be investigated.

Lung cancer in HIV-positive patients has a male predominance similar to that in HIV-negative patients (8), however, the mean age at diagnosis is usually 10 years earlier than the

HIV-negative matched cohort (30). 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 published by *Koegelenberg et al* (2016) compared the differences between HIV infected and HIV uninfected lung cancer patients. They found that SCC was the most common histological sub-type ($p = 0.07$) found in the infected group while adenocarcinoma was the most common histological sub-type found in the uninfected group (12). The reason for this observation is unclear as the smoking prevalence was almost the same. Even though there was a slightly higher male proportion in the HIV-positive group (65% in HIV-positive and 59% in HIV-negative) this does not seem to be enough to explain why there is a slight preponderance towards SCC in the HIV-positive group. Of note, the HIV-positive cohort comprised of only 44 patients. The authors also noted that HIV infected individuals tended to be younger at diagnosis and have a poorer performance status compared with the HIV-negative group. This correlates with international findings (32).

A German study assessed the stage related survival of HIV-positive patients with lung cancer (30). They found that the overall survival of patients with stages I-IIIa was 5.18 years, while patients with stage IIIb-IV had a life expectancy of 0.81 years (30) with a median overall survival of 1.08 years (30). However, in an Italian study the median overall survival was found to be 7 months for those receiving ART (8). Patients who presented with stages I-IIIa had a higher 1-year, 2-year and 5-year survival rate than those presenting at stage IIIb and IV (30).

Helen Joseph Hospital (HJH) is a small academic hospital in Johannesburg, Gauteng, South Africa which serves as a referral centre for a number of primary and secondary level hospitals and their surrounding local clinics. There is a dedicated respiratory unit which encounters a

high burden of lung cancer and HIV infected patients and assists in diagnosis and management of these patients. Studying this group of patients allowed us to examine the relationship between lung cancer and HIV in an urban South African context.

1.3 Study Aim and Objectives

Aims:

- Describe the cohort of lung cancer patients in the respiratory clinic at Helen Joseph Hospital according to their HIV status.

Objectives

- Determine the prevalence of different histological sub-types of lung cancer in two cohorts (HIV-positive and HIV-negative).
- Determine the average age of diagnosis of lung cancer.
- Determine the proportion of lung cancer patients with a history of smoking in the two groups.
- Determine the commonest mode of presentation of cancer in the two groups.

CHAPTER 2

Methodology

2.1 Patients and data collection

Data was collected retrospectively from all patients with a histological diagnosis of bronchogenic lung cancer from 1 January 2010 to 31 December 2017 at the Helen Joseph Hospital. This was done by checking the records at the National Institute for Occupational Health (NIOH) lung database and the National Health Laboratory Service (NHLS) anatomical pathology records. These were referenced back to files at the Helen Joseph Hospital respiratory outpatient department and bronchoscopy records to collect further outstanding data as far as possible. Additional attempts at completing data were made by searching Labtrak and requesting Central Data Warehouse (CDW) assistance where missing results were not found.

Inclusion criteria required that all adult patients with histologically proven bronchogenic lung malignancies be included in the study. Adult patients include those over the age of 18; anyone below age 18 was excluded. Minimum requirements for entry into the cohort were a histological diagnosis of lung cancer and a known HIV status.

2.2 Materials and Methods

Data variables collected were captured onto a data collection sheet (see Appendix 7.1). Data collected included demographic data such as age and gender, HIV result as well as other important parameters for HIV-positive patients including CD_{4+} count, HIV viral load and whether the patient was on ART and the duration. Details pertaining to the cancer were also collected, namely, the histological sub-type, stage of presentation and presenting clinical features. Data on smoking and other occupational exposures as well as details of patient's co-morbidities were also collected.

The 2015 WHO classification of lung malignancies is the classification system used in this paper; this includes malignancies diagnosed prior to 2015. Thus, all broncho-alveolar carcinomas were classified as adenocarcinomas. All those with a histological diagnosis of non-small cell lung cancer not otherwise specified (NSCLC NOS) were grouped with large cell carcinomas. This is in concordance with the WHO classification which does not include the sub-type NSCLC NOS. Since most specimens collected were of small histological size they cannot technically be classified as large cell carcinoma, however, for ease of classification we have included NSCLC NOS specimens as large cell sub-types (34).

All non-bronchogenic lung cancers were excluded.

AIDS was defined according to the CDC definition as a CD_{4+} count of less than 200 cells/µl, or stage 3 defining illness regardless of the CD_{4+} count (35).

2.3 Data Analysis

Statistical analysis was done using Stata and Microsoft Excel. Comparative analysis between HIV-positive and HIV-negative groups, gender, and histological sub-types of lung cancer was done using the 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-squared test (larger sample sizes) and Fisher's exact test (in smaller sample sizes). Statistical significance was set at a p-value cut off of less than or equal to 0.05.

CHAPTER 3

Results

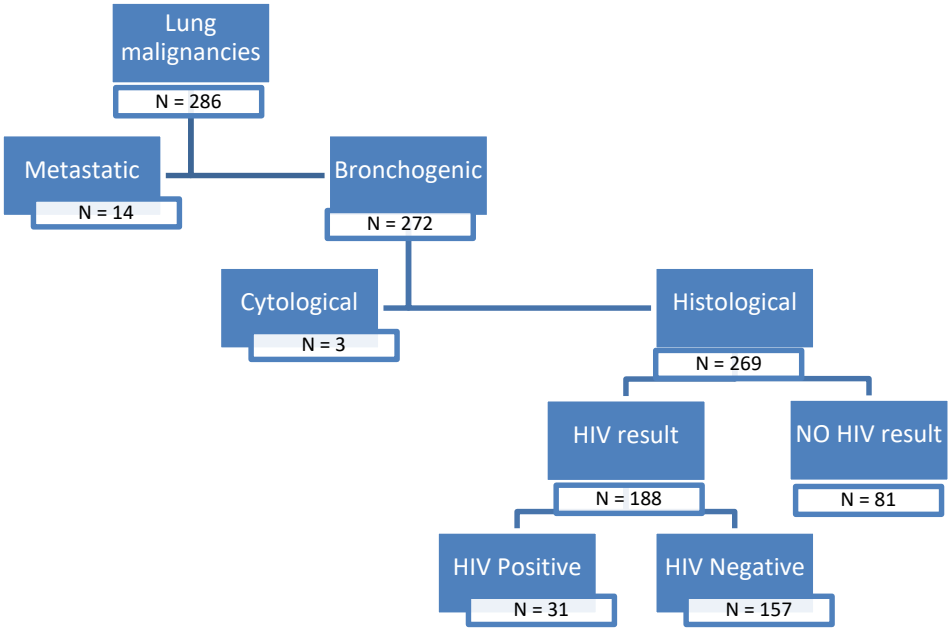

Figure 3.1 Breakdown of Lung malignancies

There were 286 patients (Figure 3.1) diagnosed with possible lung cancer at Helen Joseph Hospital between 1 January 2010 and 31 December 2017. Of those, 272 patients were diagnosed with bronchogenic carcinomas. Fourteen patients were excluded as they were diagnosed with metastatic cancer rather than primary lung cancer. Another three patients were excluded from our study as the basis of their diagnosis was on cytological specimens only, two by fine needle aspirate (FNA) and one by bronchial washings. A further 81 patients were excluded on the basis of not having an HIV result. This brought the final number of patients to 188.

The diagnosis of lung cancer has increased over time due 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 (Figure 3.2).

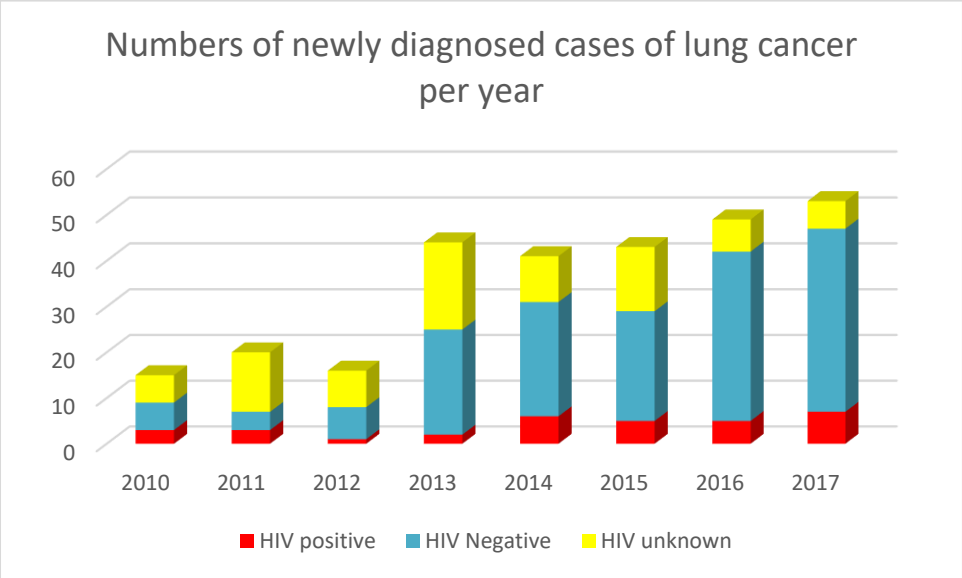

Figure 3.2 New Lung cancer cases per year

Table 3.1 Data Summary of patients

		HIV-negative (n= 157)	HIV-positive (n = 31)
Gender			
	Males	109 (69.43%)	21 (67.74%)
	Females	48 (30.57%)	10 (32.26%)
Age (years)			
	Male (Mean ± SD) (range)	61.48 ±9.10 (36 - 90)	53.57 ± 8.12 (39 - 73)
	Female (Mean ± SD) (range)	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/μL)	N/A	358 (41 - 722)
	VL - copies/mL		
	< 50		10
	50 - 1000		4
	> 1000		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%)

VL – Viral Load
NSCLC – Non-small cell lung cancer
SCLC – Small cell lung cancer

3.1 Demographics

Of the 188 patients, 157 (83.51%) were HIV-negative and 31 (16.49%) were HIV-positive. A total of 130 (69.15%) were male and 58 (30.85%) were female. There was no significant difference in the proportion of males to females when comparing the HIV-positive with HIV-negative groups ($p = 0.85$). In the HIV-negative group 109 were males (69.43%) and 48 were female (30.57%) ($p < 0.00001$) while in the HIV-positive group 21 were male (67.74%) and 10 were female (32.26%) ($p = 0.0026$).

When assessing the proportions of the different histological sub-types by gender, of the 130 males, 50 had adenocarcinoma (38.46%), 48 had SCC (36.92%), 20 had small cell lung cancer (SCLC) (15.38%), six had large cell carcinoma (4.62%) and six had other sub-types (4.62%). In the cohort of 58 females, 30 had adenocarcinoma (51.72%), 17 had SCC (29.31%), six had SCLC (10.34%), two with large cell carcinoma (3.45%) and three had other sub-types (5.17%).

When comparing the genders in the HIV-positive and HIV-negative populations, of the group of 109 HIV-negative males, 42 had adenocarcinoma (38.53%), 41 had SCC (37.61%), 17 had SCLC (15.60%), five had large cell carcinoma (4.59%) and four other sub-types (3.67%). In the group of 21 HIV-positive males, eight had adenocarcinoma (38.10%), seven had SCC (33.33%), three had SCLC (14.29%), one had large cell carcinoma (4.76%) and there were two other sub-types (9.52%). Within the female group, of the 48 HIV-negative females, 27 had adenocarcinoma (56.25%), 12 had SCC (25.00%), six had SCLC (12.50%), one had large cell carcinoma (2.08%) and there were two other sub-types (4.17%). While, of the ten HIV-positive females, three had adenocarcinoma (30%), five had SCC (50%), no patients had SCLC, one had large cell carcinoma (10%) and there was one other histological sub-type (10%).

The average age at the time of diagnosis of all patients was 60.37 years. There was no statistical difference (p = 0.41) between the genders with males having an average age of 60.2 years and females 60.74 years. There was, however, 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.

Comparing age within the different sub-types, patients with adenocarcinoma had an average age of 59.78 years while those with SCC were 63.12 years. The mean age of those with SCLC was 62.16 years. There was a significant difference found between the ages of those with SCC and adenocarcinoma (p = 0.006). There was no difference found when comparing patients with SCC to SCLC (p = 0.22) or when comparing patients with adenocarcinoma to SCLC (p = 0.26). 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 three patients) while those with SCC had an average age of 60.17 years.

3.2 Sub-types

Adenocarcinoma was the commonest histological sub-type diagnosed. This was found in 80 (42.55%) of the 188 patients, this was followed by SCC with a number of 65 (34.57%) and then SCLC with 26 (13.83%) patients. Eight (4.26%) patients were diagnosed with large cell carcinoma. Of the rarer sub-types, three patients had large cell neuroendocrine carcinomas (LCNEC). Adenosquamous carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma and sarcomatoid carcinoma were diagnosed in one patient each. Two patients had mixed tumours one of which was a mixed adenocarcinoma and SCLC and the other a mix of SCC and adenocarcinoma.

Looking at the commoner sub-types, a male predominant pattern was observed for all. Fifty (62.5%) of the 80 patients with adenocarcinoma were male and 30 (37.5%) were female ($p = 0.0007$). Of the 65 patients with SCC, 48 (73.85%) were male and 17 (26.15%) were female ($p < 0.00001$). SCLC was found in 20 (76.92%) males and six (23.08%) females ($p = 0.00005$) and of the eight patients with large cell carcinoma, six (75%) were male and two (25%) female ($p = 0.022$).

Adenocarcinoma was diagnosed in 69 of the 157 HIV-negative patients (43.95%) and 11 of the 31 HIV-positive patients (35.48%). However, there was no statistical difference between these two groups ($p = 0.38$). Within the 69 HIV-negative patients with adenocarcinoma, 42 were male (60.87%) and 27 were female (39.13%) while eight of the 11 patients in the HIV-positive group were male (72.73%) and three were female (27.27%).

SCC was found in 53 of the 157 HIV-negative patients (33.76%) and 12 of the 31 HIV-positive patients (38.71%) but there was no difference ($p = 0.60$). In the HIV-negative group, 41 of the 53 patients were male (77.36%) and only 12 were female (22.64%). Seven patients in the HIV-positive group were male (58.33%) and five were female (41.67%).

Only three of the 31 patients in the HIV-positive group had SCLC (9.68%) while 23 of the 157 patients in the HIV-negative group had SCLC (14.65%), and again no statistically significant difference was observed ($p = 0.57$). Seventeen of those in the HIV-negative group were male (73.91%) and six were female (26.09%). All three patients in the HIV-positive group were male.

Six patients in the HIV-negative group (3.82%) and two in the HIV-positive group (6.45%) had large cell carcinoma which was also not significantly different ($p = 0.62$). Five of the six

patients in the HIV-negative group were male (83.33%) with only one female (16.67%) while in the HIV-positive group there was one male and one female.

Of the rarer sub-types, in the HIV-negative group there was one patient with each of the following sub-types of lung cancer: adenosquamous, mucoepidermoid, LCNEC, adenoid cystic and sarcomatoid. Additionally, there was one patient who had a mixed tumour with part of it being SCLC and part of it showing features of adenocarcinoma. In the HIV-positive group, and there were two patients with LCNEC and one patient who had a mixed tumour with part showing features of adenocarcinoma and part SCC.

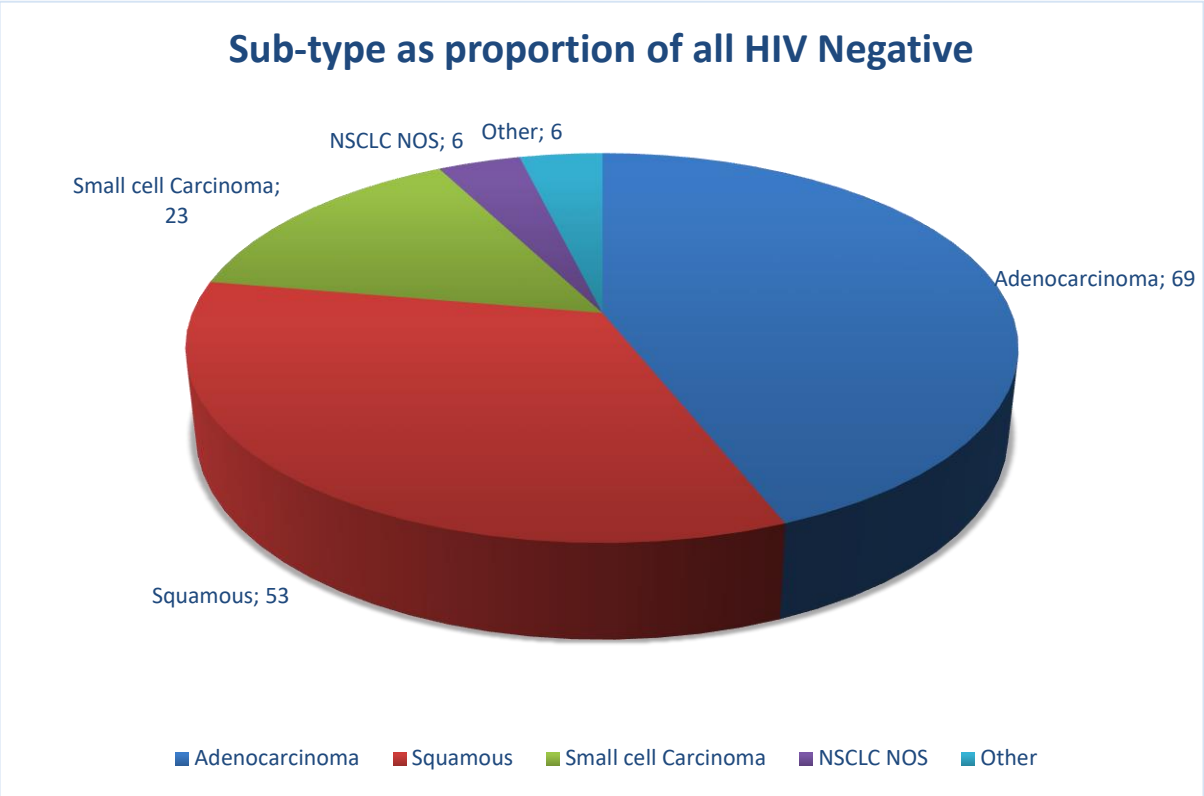

Figure 3.3 Proportions of Sub-types in HIV-negative Patients

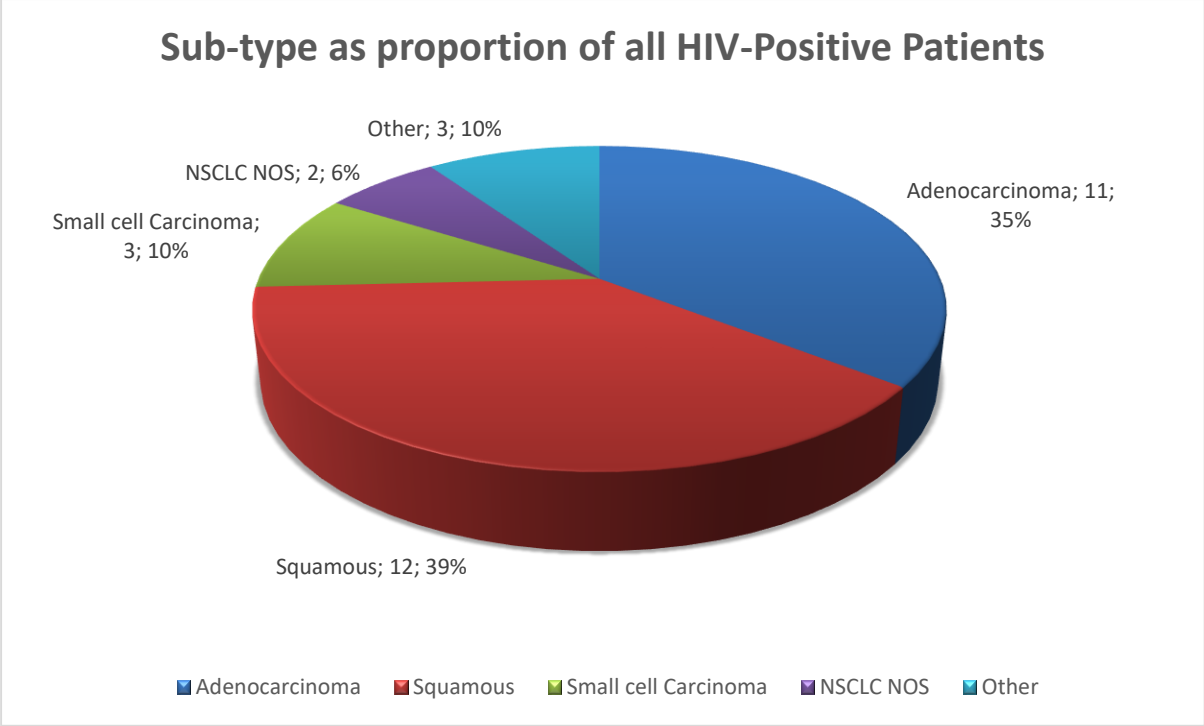

Figure 3.4 Proportions of Sub-types in HIV-positive Patients

3.3 Presenting Symptoms, Clinical Findings and Special Investigations

The commonest presenting findings that raised suspicion for lung cancer were abnormalities noted on the chest X-ray (CXR) which most but not all patients had documentation of. One-hundred and thirty-four (71.28%) of the 188 patients had a lung mass noted on CXR. Of those without a lung mass, 16 (8.51%) had a pleural effusion, 21 (11.17%) had atelectasis, six (3.19%) had bilateral infiltrates and a further six (3.19%) had pulmonary nodules without an obvious primary lung mass. Of those without any reported CXR findings, one patient had palpable supraclavicular lymphadenopathy, one had digital clubbing and one presented with seizures and was noted to have a chest wall mass which, on biopsy, proved to be lung cancer. The final two patients had unknown presentations as no history was included with the referring specimen and their files were not found.

Most patients had more than one presenting feature. As mentioned a lung mass on CXR was the commonest presenting feature being present in 134 of 188 patients, 39 of 58 females (67.24%) and 95 of 130 males (73.08%). The difference between the genders was not significant ($p = 0.41$). Fifty-one of 80 patients with adenocarcinoma (63.75%), 48 of 65 patients with SCC (73.85%), 17 of 26 patients with SCLC (65.38%) and seven of eight patients with large cell carcinoma (87.5%) had a lung mass on CXR. In the HIV-negative group, 108 of 157 patients (68.79%) had a mass on CXR as did 20 of 31 HIV-positive patients (64.52%). The difference between the HIV-positive and HIV-negative groups was not significant ($p = 0.64$).

Pleural effusions were found in 31 of the 188 patients (16.5%) and were relatively more common in females being present in 14 (24.13%) of the 58 females and 20 (15.38%) of the 130 males. The difference between the groups was not significant ($p = 0.15$). Pleural effusions were found in 18 of 80 with adenocarcinoma (22.5%), seven of 65 with SCC (10.77%), four of 26 with SCLC (15.38%), one of eight large cell carcinoma (12.5%). Twenty-four HIV-negative (15.29%) and seven HIV-positive patients (22.58%) were found to have pleural effusions, this difference was also not statistically significant ($p = 0.317$).

Forty-three patients had CXR evidence of atelectasis. Thirty (23.08%) of 130 males had this feature as did 13 (22.41%) of 58 females. When comparing the different sub-types 17 (26.15%) of 65 SCC, 17 (21.25%) of 80 adenocarcinoma, seven (26.92%) of 26 SCLC and one large cell carcinoma had atelectasis. It was found to be less common in HIV-negative patients with 32 (20.38%) patients presenting with this feature while 11 HIV-positive patients (35.48%) had this feature on CXR. This difference had no statistical significance ($p = 0.67$).

Hypercalcaemia (as defined by a serum calcium > 2.55mmol/L) was present in 29 patients (15.43%). There was no significant difference between males and females ($p = 0.4$) with 22

of 130 males (16.92%) and seven of 58 females (12.07%) having hypercalcaemia. Comparing the different sub-types, five of the 80 patients with adenocarcinoma (6.25%), 20 of 65 patients with SCC (30.77%), two of the 26 with SCLC (7.69%) and one of eight patients with large cell carcinoma (12.5%) had hypercalcaemia. There was a significantly higher number noted in those with SCC as compared with adenocarcinoma ($p = 0.0001$) and SCLC ($p = 0.02$). Assessing the difference between HIV-positive and HIV-negative groups, hypercalcemia was noted in 25 of the 157 HIV-negative patients (15.92%) and four of the 31 HIV-positive patients (12.90%) and this small difference had no statistical significance ($p = 0.67$).

Digital clubbing was observed in 40 patients (21.28%). It was more common in males being seen in 34 of the 130 males (26.15%) and only six of the 58 females (10.34%) which was significant ($p = 0.014$). Analysing the different sub-types, 19 of the 80 patients with adenocarcinoma (23.75%) had clubbing while 15 of those with SCC (23.08%) had clubbing. It is known to be quite rare in SCLC and was found in four of the 26 patients (15.38%), however, no difference between SCLC and adenocarcinoma ($p = 0.37$) or SCC was found ($p = 0.41$). Adding up all the non-small cell patients, 37 of 162 had clubbing (22.84%) but no significant difference was found between the two groups (NSCLC and SCLC) ($p = 0.39$). Statistical difference was also not found between the HIV-positive and-negative groups ($p = 0.77$) with 34 of the HIV-negative patients (21.66%) and six of those with HIV (19.35%) having digital clubbing.

Other less frequent but important findings included a hoarse voice in 12 patients (6.38%); a raised hemi-diaphragm on CXR in two patients. Malignant pericardial effusions were seen in two patients, superior vena cava (SVC) syndrome was diagnosed in 10 patients (5.32%) and Horner’s syndrome was noted in two patients.

3.4 Stage

Unfortunately due to a lack of data on staging of patients, we could not accurately define the frequencies of certain features, most notably distant metastases. In our study we found that the commonest site of distant metastases was bone, which was seen in 13 patients. Cerebral metastases were seen in 12 patients and only one of these patients had SCLC. Liver metastases were seen in four patients as were adrenal metastases present in four patients. These were mostly noted in the HIV-negative group. Twelve of the 13 patients with bone metastases, ten of the 12 with cerebral metastases and all four of those with liver and four with adrenal metastases were HIV-negative.

Patients with NSCLC were staged according to the 8th version of American Joint Commission on Cancer (AJCC) TNM staging. Of the 162 patients, 84 (51.85%) presented with stage IV disease, nine (5.56%) with stage IIIB disease and one with stage IIIA disease. The other 68 (41.96%) patients had no staging available. Looking only at the HIV-positive group 14 (50%) of the 28 patients had stage IV disease and 14 (50%) did not have a stage available, while in the HIV-negative group, 70 (52.24%) of the 134 patients had stage IV disease, nine (6.72%) had stage IIIB and one stage IIIA disease; the other 54 (40.3%) patients were not staged. Comparing males and females; 55 (50%) of the 110 males had stage IV disease, seven (6.36%) had stage IIIB and 48 (43.64%) were not staged. In the female group, 29 (58%) of the 52 females had stage IV disease, two had stage IIIB and one had stage IIIA and 20 (38.46%) had no stage.

Forty-six (57.5%) of the 80 patients with adenocarcinoma had stage IV disease and, two with stage IIIB and one with stage IIIA, 31 (38.75%) did not have staging available. Eight of the 11 HIV-positive patients were stage IV at diagnosis and the other three were unknown.

Thirty (46.15%) of the 65 patients with SCC presented with stage IV disease, seven (10.77%) with stage IIIB and 28 (43.08%) were unknown. Of the 53 HIV-negative patients, 26 (49.06%) were stage IV at presentation and seven (11.11%) stage IIIB. The other 20 (37.74%) had no staging available. In the HIV-positive group, four (33.33%) had stage IV disease and the other eight (66.67%) were unknown.

Patients with SCLC were staged according to the Veterans Administration Lung Study Group (VALSG) two-stage system. Of the 26 patients with SCLC, 14 (53.85%) had extensive stage disease, two (7.69%) had limited stage disease and ten (38.6%) were unknown. There were only three patients in the HIV-positive group of which one had extensive disease and two were unknown. Of the 23 patients in the HIV-negative group, two (8.7%) had limited disease, 13 (56.52%) had extensive disease and eight (34.78%) were unknown

There was a large amount of missing data, thus, when computing statistics on staging, those with unknown staging were excluded. This left us with a total of 94 patients, 84 of whom had stage IV disease (89.36%), nine with stage IIIB (9.57%) and one with stage IIIA (1.06%). Seventy of the 80 patients in the HIV-negative group had stage IV disease (87.5%), nine with stage IIIB (11.25%) and one with stage IIIA (1.25%). All 14 patients in the HIV-positive group had stage IV disease. Comparing males and females; 55 of the 62 males had stage IV disease (88.71%) and seven had stage IIIB (11.29%) while in the female group, 29 of the 32 females had stage IV disease (90.63%), two had stage IIIB (6.25%) and one had stage IIIA (3.125%). There was no significant difference in the amount of stage IV disease between males and females ($p = 0.77$).

When comparing the different sub-types, 46 of the 49 patients with adenocarcinoma had stage IV disease (93.88%), two had stage IIIB (4.08%) and one had stage IIIA (2.04%).

Thirty of the 37 patients with SCC presented with stage IV (81.08%) and seven with stage IIIB (18.92%).

In the patients with SCLC, 14 of the 16 had extensive disease (87.5%) and two had limited disease (12.5%).

3.5 Smoking

The smoking habits of the patients revealed that 134 of the 188 patients had a history of first hand smoking (71.27%), 14 were never-smokers (7.45%) and 40 had no smoking history documented (21.28%). Of the 130 males, 105 (80.77%) were known smokers, five (3.85%) had never smoked and 20 (15.38%) had no history available. While of the 58 females, 29 (50%) had a confirmed history of smoking, nine (15.52%) had never smoked and 20 (34.48%) had no available history. Regarding the HIV-negative population, 124 (78.98%) were known to have a history of smoke exposure, 11 (7.01%) had not smoked and 22 (14.01%) had no history available. In the HIV-positive population ten (32.26%) of the 31 patients were confirmed to have a history of smoking, three (9.68%) had never smoked and unfortunately the majority (18 of the 31, 58.06%) had no history available.

When computing statistics for smoking, the 40 patients who had no history available were excluded. Thus, for statistical purposes 134 of the 148 patients were smokers (90.54%) and 14 had never smoked (9.46%). In the HIV-negative group 124 of the 135 were smokers (91.85%) and 11 of the 135 were never smokers (8.15%). In the HIV-positive group ten of the 13 were smokers (76.92%) and three had never smoked (23.08%), however, there was no significant difference found between the groups ($p = 0.078$). There was a significant difference found when comparing smoking between the genders ($p = 0.00051$), 105 of the

110 males were smokers (95.45%) and five were never smokers (4.55%) while 29 of the 38 females were smokers (76.32%) and nine were never smokers (23.68%).

When looking at the different sub-types of lung cancer, 51 (63.75%) of the 80 patients with adenocarcinoma had a history of smoking while 13 (16.25%) had never smoked and 16 (20%) had no history available. In the SCC population, 47 (72.31%) were confirmed smokers and only one had never smoked, however, 17 (26.15%) had no available history. The sub-type with the highest proportion of smokers were those with SCLC with 23 (88.46%) of the 26 being confirmed smokers, only one non-smoker and two with no history.

When excluding those without a known history, 52 of those with adenocarcinoma were smokers (81.25%) and 12 were never-smokers (18.75%). In patients with SCC, 47 of the 48 patients were smokers (97.92%) while one was not (2.08%). In those with SCLC 23 of 24 patients had a history of smoking (95.83%) and one had never smoked (4.17%). Seven patients with large cell carcinoma were smokers and there were no patients who had never smoked. There was a significant difference found between patients with adenocarcinoma and SCC ($p = 0.0064$), however, not between those with adenocarcinoma and SCLC ($p = 0.86$). There was also no significant difference noted when comparing patients with SCC and SCLC ($p = 0.612$).

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. A number of 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 four patients were known with a pack year history less than ten (11.76%) and 32 of the known smokers did not have documentation of their pack year history (23.88%).

3.6 Comorbidities

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 six of the 188 patients (3.19%), four of whom were HIV-negative and two HIV-positive. Additionally, five other patients (2.66%), three HIV-positive and two HIV-negative, had previously suffered from PTB. The exposure to TB was thus 11 of 188 patients (5.85%).

3.7 HIV parameters

Within the group of 31 HIV-positive patients, 16 were on ART at diagnosis (51.61%), seven were not (22.58%) and eight had no history available (25.81%). Twenty-six of the patients had CD_4+ counts available, these ranged from 41 to 722 cells/μL. In the group of patients on ART, CD_4+ counts ranged from 99 to 688 cells/μL with a mean of 365 cells/μL while in those not on ART, CD_{4+} counts ranged from 169 to 722 cells/μL. The mean CD_{4+} count was 467 cells/μL but due 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 of those on ART; nine of the 16 had a VL less than 50 copies/ml (56.25%), three had VL between 50 and 1000 copies/ml (18.75%), two had viral loads greater than 1000 copies/ml (12.5%) and two had no VL charted (12.5%). Treatment success was achieved in 12 of the 16 patients (75%), treatment failure in two (12.5%). We were unable to assess whether those patients on ART have more or less advanced disease than those not on ART as all the HIV-positive patients with available staging had stage 4 disease.

CHAPTER 4

Discussion

There were 188 patients eligible for the study by fulfilling the criteria of having a histological diagnosis of lung cancer and an HIV test result. In line with the realisation that NADMs, especially lung cancer, are now becoming increasingly common in the HIV-positive population, there has been an increase in practice to check the HIV status in these patients over time. This trend is also evidenced in our study (Figure 4.1) which has seen a steady climb in patients with known HIV results. There was a higher number known in 2010 than 2011 and 2012 – a possible explanation may be that HIV was tested for other reasons at that time.

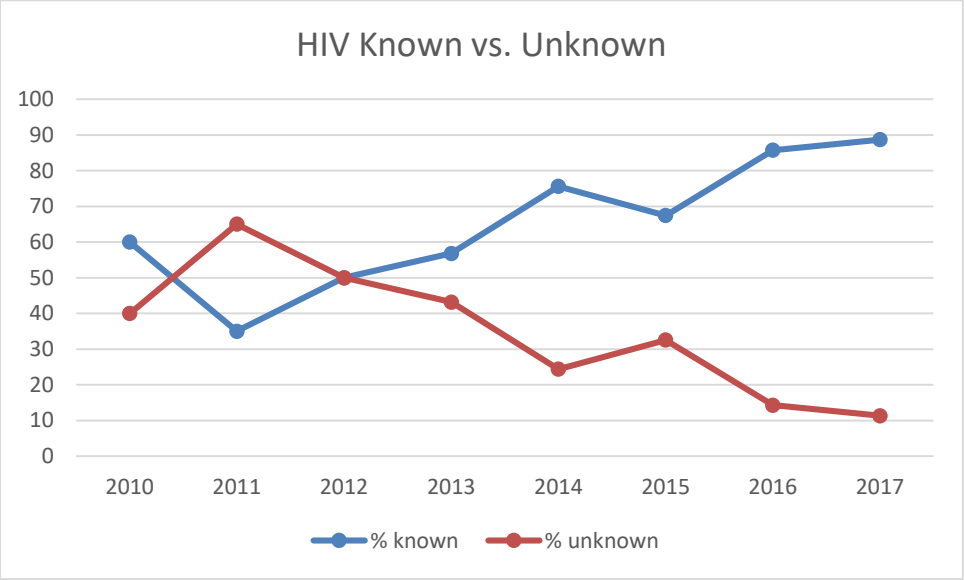

Figure 4.1 Known vs. unknown HIV status

The HIV-positive cohort accounted for 31 (16.49%) of the 188 patients, this is a higher proportion than seen in another South African study (12) where 9.38% of their lung cancer cohort was HIV-positive. The reason for such a difference ($p = 0.0096$) still needs to be investigated to as it is unlikely that absolute numbers alone can account for this increase (the other study had 469 patients).

4.1 Demographics

There is a large gender bias noted in the lung cancer population, with a far larger proportion of males as compared with females being diagnosed. This ratio of approximately two-thirds was noted in both the HIV-negative and -positive groups. This same trend was noted by *Mani et al* (2012) (1) when assessing a number of studies which looked at lung cancer in the HIV population (1). Risk-taking behaviour, including smoking, is more prevalent in males than females which is the most likely reason why there is a male predominance in the lung cancer population (36, 37). Additionally, in developed countries, both HIV and smoking are seen more frequently in males, which could be why lung cancer in the HIV population is more commonly diagnosed in men (1).

There has been a change in the smoking trends with smoking becoming more common in females. This is a phenomenon observed particularly in developed countries (38). There is a long latency period between smoking and the development of lung cancer (39) and thus, the opposite effect of a decline in smoking and the reduction of lung cancer is also expected to be true (39). 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.

The latest South African National Cancer Registry (NCR) statistics were released in 2014 in which lung cancer was found in 936 females and 1791 males (40). Thus, females comprised 34.32% and males 65.68%, a finding similar to our study, where 130 (69.15%) were male and 58 (30.85%) were female.

Regarding the ratio of male to female new cases in our study, proportions were in keeping with global findings. In 2012 there were 1.82 million new cases of which 1.24 million (~68%) were males (9).

A study by *Jemal et al* (2018) (38) looked at the trend in lung cancer by gender over a period of approximately 20 years (1995–2014), where they found a decline in the incidence of lung cancer amongst men and women. However, the decline was steeper among men and therefore a higher incidence of lung cancer was reported among women in certain age groups and races. In our study, the data collection was over a shorter time period which did not allow us to observe the marked changes that were observed in the study by *Jemal et al*. We found that for all the years, there was a male dominant pattern (around two-thirds), and there were too few numbers in the HIV-positive group (assessing each year separately) to consider the results meaningful.

In the 2014 NCR report, lung cancer made up 2.48% of all cancers in females and 4.87% of all cancers in males (40). In comparison, it made up a total of 13.5% of all new cancers (male and female combined) in the USA (41). Possible reasons for this continent disparity include lack of access to diagnostic facilities in South Africa, (outside of urban areas), late presentation of patients, clinicians empirically diagnosing TB in a high endemic area (especially in HIV-positive patients), and the frequency of HIV associated malignancies being higher in South Africa, thus, accounting for a larger proportion. Additionally, it is believed the incidence of lung cancer will rise as urbanisation becomes more popular along

with a change in lifestyle coupled with poor anti-smoking campaigns (22) and poor patient awareness of the consequences of tobacco use (37).

Lung cancer is found to be a disease of the older population. In the NCR data tables (Figure 4.2), the peak age for the diagnosis of lung cancer is from the ages of 55 – 70 years in males and females. The NCR did not have any separation based on HIV status. The younger age identified in the HIV cohort in this study of 53.94 years compared with the HIV-negative of 61.64 years has also borne out in other studies (1, 12).

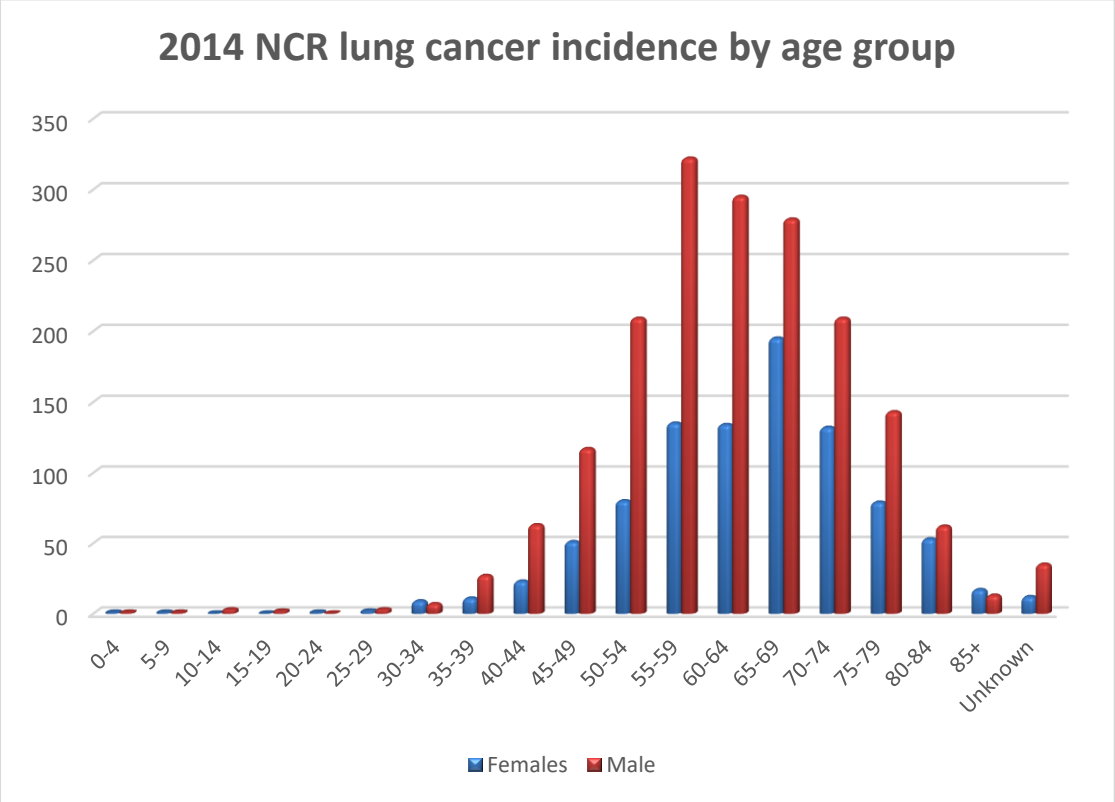

Figure 4.2 2014 NCR lung cancer incidence by age

4.2 Sub-types

In the past, the commonest sub-type of lung cancer was SCC (36). In more recent studies adenocarcinoma has been the commonest sub-type identified, followed by SCC and then large cell carcinoma (42). The figures in our study which showed adenocarcinoma was present in 80 (42.55%), SCC in 65 (34.57%) and large cell in 8 (4.26%) were similar to those seen in this study.

In a study by *Meza et al* (2015) looking at the trends of lung cancer over a 37-year period, it was noted that SCC used to be the most common cancer in males (around 50% of all lung cancers) in the early years of their study. The trend changed toward adenocarcinoma which had an initial reported incidence of around 20% in 1973 that increased to over 40% by the end of the study. At the end of the study SCC made up about 30% of all lung cancers in males (42). The incidence of SCLC stayed constant at around 20% and large cell carcinoma decreased from about 10% to 3% (42). These were not very different from the figures in our study which showed a similar proportion of adenocarcinoma and SCC but slightly less SCLC. Possible reasons for this may include less enforced anti-smoking legislation in South Africa as compared with a developed country such as the USA; less educated population; and SCC is known to have the strongest association with smoking of all the lung cancer sub-types. In terms of females, *Meza et al* (2015) noted that adenocarcinoma had always been commoner in females, although the number was less, while it now accounts for more than 50% of cases. SCC, on the other hand, accounted for around 30% in the earlier years but that had dropped to around 20% now (42). Once again, these were not very different to our findings but we observed a slightly higher amount of SCC than they did (29% vs. 20%), additionally, they reported a SCLC incidence in females similar to males (~20%) while our numbers were lower (15% and 10% for males and females respectively).

The HIV-positive population in our study had a slightly higher proportion of SCC as compared with adenocarcinoma, while the HIV-negative population demonstrated a higher proportion of adenocarcinoma. The lack of numbers in the HIV-positive group does not allow us to extrapolate this to the population at large but this same pattern was also noted in another South African study (12). However, other studies conducted in Europe showed adenocarcinoma to be the commonest sub-type in both HIV-negative and HIV-positive patients (1, 8).

A possible reason for this is related to HIV patients apparently having higher proportions of smoking, although this is not supported by *Koegelenberg et al* (2016) (12). In an article by *Mani et al* (2012), who reviewed multiple different studies of lung cancer in HIV infected people, adenocarcinoma was found to be the predominant sub-type, however, these studies were mostly conducted in developed countries (1). Additionally, in a study conducted in Italy, adenocarcinoma was also found to be the commonest sub-type (8).

Smoking is known to be the most important risk factor for developing lung cancer (9). All sub-types have an association (43), however, it is more strongly associated with SCC and SCLC and less so with adenocarcinoma (42). There have been a few reasons proposed for this including the current contents of cigarettes, which have a higher proportion of nitrosamines than previously produced cigarettes, and deeper inhalation of cigarettes which gets smoke to the peripheral airways where adenocarcinomas are more commonly located (44). In another South African study comparing HIV-positive and HIV-negative populations (12), the smoking prevalence was noted to be very high amongst both HIV-positive and HIV-negative populations (around 90%). This is comparable to what was found in other studies (1) and in the HIV-negative population of our study. We could not accurately comment on the

HIV-positive population in our study as many of them were missing details on smoking history.

4.3 Presenting Symptoms, Clinical Findings and Special Investigations

In a study by *Cadranel et al* (2006), it was quoted that the commonest feature was a mass (between 80 - 100%) on CXR (45). They also found that pleural effusions were slightly more common in the HIV-positive group, however, this difference did not reach statistical significance (45). There is limited data comparing other clinical findings in the HIV-negative and HIV-positive groups, however, it is not expected to differ greatly between the groups unless HIV-positive patients present with more advanced stage earlier in the course of their disease. Hypercalcaemia was noted to be significantly more common in those with SCC than other sub-types of lung cancer. This has also been found in other studies and is usually a sign of poor prognosis and advanced disease (46). As almost all the patients with known staging had advanced disease, it is not surprising we did not see a difference between the HIV-positive and -negative groups.

4.4 Stage

Multiple studies have found that HIV-positive patients present at a more advanced stage than HIV-negative patients (1, 8). In our study, regarding the patients with NSCLC, the HIV-positive patients, whose stage at diagnosis was known, all had metastatic disease. The HIV-negative patients were also advanced with the earliest stage diagnosed being IIIA (in one patient), a few more being diagnosed with stage IIIB but most were already metastatic at diagnosis. SCLC is known to be more aggressive with more patients expected to be found with more advanced disease (47, 48). The numbers quoted in some studies are upwards of 65% compared with 47% of NSCLC being metastatic (47, 48). We found that most patients

were at an advanced stage but were unable to differentiate between HIV-positive and -negative groups owing to the small number in the HIV-positive group.

4.5 Smoking

Smoking is the most important risk factor for lung cancer and was found to be commoner in both groups than in the general population (37). According to the International Association for the Study of Lung Cancer (IASLC) smoking is responsible for over 80% of lung cancer cases (49), while according to *Cheng et al* (9), who looked at separate countries in more depth, smoking is responsible for lung cancer in 65% of males and 25% of females in medium HDI (human development index) countries (which is where South Africa is placed) (43). In contrast, South Africa is unique because in Africa the smoking rates amongst women are low but in South Africa they are quite high, thus, accounting for a greater incidence of lung cancer among women, when compared with the rest of Africa (43).

The Human Science Research Council of South Africa released smoking data for South Africa based on the first South African National Health and Nutrition Examination Survey (SANHANES-1) (37). This 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%) as compared with 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 (49). In another study conducted in South Africa to assess the prevalence of smoking in the HIV population, it was found that 34% of HIV-positive patients were smokers (current or former) (50). Of the male participants, 52% were current smokers while only 13% of the females were current

smokers (50). These figures are higher than the general population mentioned above, thus, it is not surprising that lung cancer is more common in HIV-positive patients.

According to *Reddy et al* (2015), epidemiological data from South Africa shows a significant decrease in smoking prevalence over the last 20 years, with smoking now about half as common as it was (37). *Wong et al* (2017) found that lung cancer incidence and mortality mostly show a decreasing trend in men and an increase in women (51). This is likely due to the decline in smoking among men which is sharper than that among women (51). 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 (51).

4.6 Comorbidities

According to *Sigel et al*, COPD is an independent risk for lung cancer in HIV-positive patients (32). The prevalence of COPD is expected to be high amongst patients with lung cancer as they share a common risk factor. The number of 28 in our study is likely short of the actual number and unfortunately, a lack of documentation prevents us from confirming the actual number of those with COPD.

The link between lung cancer and pulmonary TB has been shown in a study conducted in Taiwan (52), where the incidence rate of lung cancer was 11 times higher in the group with recent PTB infection compared with those who had never had PTB. However, they did not have a separation based on HIV status and thus, we could not compare this with the two separate groups in our study.

4.7 HIV parameters

Mani et al (2012) also report that ART has no effect on lung cancer incidence and that lung cancer is no more common amongst individuals with higher as compared with lower CD_{4+} counts (1).

We also found that the HIV-positive patients in our study had relatively high CD_{4+} counts both in the group on ART and those without (mean CD_{4+} count of 365cells/μL and 467 cells/μL respectively). In other studies, the CD_{4+} count was also found to be higher, with *Bearz et al* (2014) finding a mean CD_{4+} in the ART group of 339 cells/μL and the non-ART group of 287 cells/μL (8).

One of the proposed reasons lung cancer (and other NADMs) have become more common is because patients who are on ART are no longer dying from opportunistic infections or ADMs, which occur in the setting of more advanced immune compromise (3, 31). They are living longer and thus developing NADMs. This also accounts for the moderate CD_{4+} counts seen as opposed to lower counts in the AIDS range (31). However, this issue is controversial and *Guiget et al* maintain that as the CD_{4+} drops, the risk for lung cancer increases (53). They observed that as the CD_{4+} count dropped from >500 cell/μL to 350-499 cell/μL – the risk doubled, and got worse as counts dropped further, thus suggesting a role for immune suppression (53).

4.8 Limitations of the Study & Recommendations

Data regarding ethnicity of the patients, staging and smoking was incomplete and thus we were unable to demonstrate an accurate prevalence of each of these. Data on the type of smoking (whether primary, secondary or tertiary) was also unavailable as was that 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 2 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.

CHAPTER 5

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 commonest histological sub-type of lung cancer amongst the general population, with SCC being slightly more common in the HIV-positive population, however, due to small numbers and a lack of statistical significance we cannot be certain 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 the general population, however, we were unable to determine whether smoking was more common in the HIV-positive lung cancer population due to missing data. The commonest presenting feature in both groups was a mass on CXR, atelectasis was the second commonest presentation followed by pleural effusion.

References

1. Mani D, Haigentz Jr M, Aboulafia DM. Lung Cancer in HIV Infection. Clinical Lung Cancer. 2012;13(1):6-13.
2. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. Journal of the National Cancer Institute. 2011;103(9):753-62.
3. Winstone TA, Man SFP, Hull M, Montaner JS, Sin DD. Epidemic of lung cancer in patients with HIV infection. Chest. 2013;143(2):305-14.
4. Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS. 2014;28(8):1181-91.
5. Mukansi M, Smith C, Feldman, C. A study of lung cancer in Johannesburg, South Africa: original research. Southern African Journal of Infectious Disease. 2014;29(1):43-7.
6. Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath Jr CW. Cigarette smoking and changes in the histopathology of lung cancer. Journal of the National Cancer Institute. 1997;89(21):1580-6.
7. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. Journal of Thoracic Oncology. 2015;10(9):1243-60.
8. Bearz A, Vaccher E, Martellotta F, Spina M, Talamini R, Lleshi A, et al. Lung cancer in HIV positive patients: the GICAT experience. European Review for Medical and Pharmacological Sciences. 2014;18(4):500-8.
9. Cheng T-YD, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. Journal of Thoracic Oncology. 2016;11(10):1653-71.
10. Ranjit S, Kumar S. Recent advances in cancer outcomes in HIV-positive smokers. F1000Research. 2018;7.
11. Shiels MS, Cole SR, Mehta SH, Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. Journal of Acquired Immune Deficiency Syndromes. 2010;55(4):510-5.
12. Koegelenberg CF, Van der Made T, Taljaard JJ, Irusen EM. The impact of HIV infection on the presentation of lung cancer in South Africa. South African Medical Journal. 2016;106(7):666-8.
13. Ronit A, Haissman J, Kirkegaard-Klitbo DM, Kristensen TS, Lebech AM, Benfield T, et al. Copenhagen comorbidity in HIV infection (COCOMO) study: a study protocol for a longitudinal, non-interventional assessment of non-AIDS comorbidity in HIV infection in Denmark. BMC Infectious Diseases. 2016;16(1):713.
14. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. Journal of the National Cancer Instiyute. 2015;107(4).
15. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. Curr Opin HIV AIDS. 2017;12(1):6-11.
16. Mutyaba I, Phipps W, Krantz EM, Goldman JD, Nambooze S, Orem J, et al. A Population-Level Evaluation of the Effect of Antiretroviral Therapy on Cancer Incidence in Kyadondo County, Uganda, 1999-2008. Journal of Acquired Immune Deficiency Syndromes. 2015;69(4):481-6.
17. Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. British Journal of Cancer. 2010;103(3):416-22.
18. South Africa. Department of Health. (2016). Implementation of the Universal Test and Treat Strategy for HIV Positive Patients and Differentiated Care for Stable Patients. Available from: https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf [accessed 20 December 2018]

19. Cobucci RNO, Lima PH, de Souza PC, Costa VV, de Mesquita Cornetta MdC, Fernandes JV, et al. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: a systematic review. Journal of Infection and Public Health. 2015;8(1):1-10.
20. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS. 2006;20(12):1645-54.
21. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. Clinical Infectious Diseases. 2010;51(8):957-62.
22. Sheridan J, Collins AM. Adult lung cancer in Southern Africa: epidemiology and aetiology. African Journal of Respiratory Medicine. 2013;8(2):10-12.
23. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS. 2014;28(6):881-890.
24. Monfardini S, Vaccher E, Pizzocaro G, Stellini R, Sinicco A, Sabbatani S, et al. Unusual malignant tumours in 49 patients with HIV infection. AIDS. 1989;3(7):449-52.
25. Karp J, Profeta G, Marantz PR, Karpel JP. Lung cancer in patients with immunodeficiency syndrome. Chest. 1993;103(2):410-3.
26. Rabkin CS, Yellin F. Cancer incidence in a population with a high prevalence of infection with human immunodeficiency virus type 1. Journal of the National Cancer Institute. 1994;86(22):1711-6.
27. Sridhar KS, Flores MR, Raub Jr WA, Saldana M. Lung cancer in patients with human immunodeficiency virus infection compared with historic control subjects. Chest. 1992;102(6):1704-8.
28. Thrift AP, Chiao EY. Are Non-HIV Malignancies increased in the HIV-infected population? Current Infectious Disease Reports. 2018;20(8):22.
29. Hou W, Fu J, Ge Y, Du J, Hua S. Incidence and risk of lung cancer in HIV-infected patients. Journal of Cancer Research and Clinical Oncology. 2013;139(11):1781-94.
30. Hoffmann C, Kohrs F, Sabranski M, Wolf E, Jaeger H, Wyen C, et al. HIV-associated lung cancer: survival in an unselected cohort. Scandinavian Journal of Infectious Diseases. 2013;45(10):766-72.
31. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. AIDS . 2007;21(2):207-13.
32. Sigel K, Makinson A, Thaler J. Lung cancer in persons with HIV. Current Opinion in HIV and AIDS. 2017;12(1):31-38.
33. Dhir AA, Sawant SP. Malignancies in HIV: the Indian scenario. Current Opinion in Oncology. 2008;20(5):517-21.
34. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Archives of Pathology and Laboratory Medicine. 2013;137(5):668-84.
35. Revised surveillance case definition for HIV infection--United States, 2014. MMWR Recommendations and reports : Morbidity and Mortality Weekly Report Recommedations. 2014;63(Rr-03):1-10.
36. Ridge CA, McErlean AM, Ginsberg MS, editors. Epidemiology of lung cancer. Seminars in Interventional Radiology. 2013;30(2):93-98.
37. Reddy P, Zuma K, Shisana O, Kim J, Sewpaul, R. Prevalence of tobacco use among adults in South Africa: Results from the first South African National Health and Nutrition examination survey. South African Medical Journal. 2015;105(8):648-55.
38. Jemal A, Miller KD, Ma J, Siegel RL, Fedewa SA, Islami F, et al. Higher Lung Cancer Incidence in Young Women Than Young Men in the United States. New England Journal of Medicine. 2018;378(21):1999-2009.
39. Bello B, Fadahun O, Kielkowski D, Nelson G. Trends in lung cancer mortality in South Africa: 1995-2006. BMC Public Health. 2011;11(1):209.

40. South Africa. Department of Health, National Institute of Communicable Disease. (2018). Cancer in South Africa: 2014 full report. Available from: http://www.nicd.ac.za/wp-content/uploads/2017/03/2014-NCR-tables-1.pdf [accessed 13 July 2018]
41. United States of America. National Cancer Institute. (2018). Cancer Stat Facts: Lung and Bronchus Cancer. [Online]. seer.cancer.gov. Available at: https://seer.cancer.gov/statfacts/html/lungb.html [accessed 25 August 2018]
42. Meza R, Meernik C, Jeon J, Cote ML. Lung cancer incidence trends by gender, race and histology in the United States, 1973–2010. PLoS One. 2015;10(3):e0121323.
43. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer. 2001;31(2-3):139-48.
44. Kenfield SA, Wei EK, Stampfer MJ, Rosner BA, Colditz GA. Comparison of aspects of smoking among the four histologic types of lung cancer. Tobacco Control. 2008;17(3):198-204.
45. Cadranel J, Garfield D, Lavolé A, Wislez M, Milleron B, Mayaud C. Lung cancer in HIV infected patients: facts, questions and challenges. Thorax. 2006;61(11):1000-8.
46. Takai E, Yano T, Iguchi H, Fukuyama Y, Yokohama H, Asoh H, et al. Tumor-induced hypercalcemia and parathyroid hormone-related protein in lung carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1996;78(7):1384-7.
47. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. Thorax. 2013;68(6):551-64.
48. Canada. (2013). Canadian Partnership against Cancer: Stage distribution. [Online] Systemperformance.ca. Available at: https://www.systemperformance.ca/disease-sites/lung/stage-distribution/ [accessed 15 October 2018]
49. Wasserman H, Bunn B. (2017). Lung cancer facts and statistics. [Online]. wclc2017iaslc.org. Available at: http://wclc2017.iaslc.org/wp-content/uploads/2017/09/2017-WCLC-Fact-Sheet-Lung-Cancer-Final.pdf [accessed 16 October 2018]
50. Elf JL, Variava E, Chon S, Lebina L, Motlhaoleng K, Gupte N, et al. Prevalence and correlates of smoking among people living with HIV in South Africa. Nicotine and Tobacco Research. 2018;20(9):1124-1131
51. Wong MCS, Lao XQ, Ho K-F, Goggins WB, Tse SLA. Incidence and mortality of lung cancer: global trends and association with socioeconomic status. Scientific Reports. 2017;7(1):14300.
52. Yu Y-H, Liao C-C, Hsu W-H, Chen H-J, Liao W-C, Muo C-H, et al. Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. Journal of Thoracic Oncology. 2011;6(1):32-7.
53. Guiguet M, Boué F, Cadranel J, Lang J-M, Rosenthal E, Costagliola D, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. The Lancet Oncology. 2009;10(12):1152-9.

Appendices

5.1 Data collection sheet:

Study number				
Date of diagnosis of lung cancer				
Date of birth				
Presentation of lung cancer:	Lung mass	Pleural effusion	Lymphadenopathy	
	Paraneoplastic	Other, Specify		
Histological sub-type of lung cancer:	Squamous	Adeno	Small cell	Large cell
	BAC min invasive	BAC in situ	Other, specify	
Stage at diagnosis of lung cancer				
Current stage, if known				
HIV status at diagnosis of lung cancer	Positive	Negative	Unknown	
HIV status (current):	Positive	Negative	Unknown	
When HIV diagnosed (if preceded cancer diagnosis)				
ART at diagnosis				
Date ART started				
CD4 (cells/µl) at diagnosis				
current/death CD4 (cells/µl)				
HIV-VL at diagnosis (if on ART)				
Latest VL				
when became virally suppressed (if not at diagnosis)				
Smoking history:	Yes	No	Unknown	
Pack years				
Occupational exposure				
Family history of Lung cancer				
Alive/Dead/Unknown				
Date of death (if known) or time since diagnosis				
Cause of death (if known)				
Comorbidities:	Hypertension		Pulm TB	
	Diabetes		Extrapulmonary TB	
	COPD		Other, specify	

5.2 Ethics clearance Certificate

R14/49 Dr Ryan Berman et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170625

NAME: (Principal Investigator)	Dr Ryan Berman et al
DEPARTMENT:	Internal Medicine Helen Joseph Hospital - Respiratory Division
PROJECT TITLE:	A Comparison of Lung Cancer in HIV Positive and HIV Negative Populations
DATE CONSIDERED:	30/06/2017
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S.A. van Blydenstein
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

5.3 Turnitin Originality report

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http://www.catie.ca/en/catienews/2014-09-09/french-scientists-note-change-rates-some-cancers-unrelated-aids
< 1% match (publications)
S. S. Y. Wong. "Differences in Clinical and Laboratory Diagnostic Characteristics of Penicilliosis Marneffei in Human Immunodeficiency Virus (HIV)- and Non-HIV-Infected Patients", Journal of Clinical Microbiology, 12/01/2001
< 1% match (publications)
M Bower. "British HIV Association guidelines for HIV-associated malignancies 2008", HIV Medicine, 07/2008
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Danny K Chen, Colina Yim, Keith O'Rourke, Mel Krajden, David K.H Wong, E.Jenny Heathcote. "Long-term follow-up of a randomized trial of interferon therapy for chronic hepatitis B in a predominantly homosexual male population", Journal of Hepatology, 1999
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Syed Sameer Nadvi. "Role of Cerebrospinal Fluid Shunting for Human Immunodeficiency Virus-positive Patients with Tuberculous Meningitis and Hydrocephalus :", Neurosurgery, 09/2000
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Y. Tanaka. "Increasing genetic diversity of hepatitis C virus in haemophiliacs with human immunodeficiency virus coinfection", Journal of General Virology, 09/01/2007
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Dominik Hofer. "The effect of a single mechanical treatment on the subgingival microflora in patients with HIV-associated gingivitis", Journal Of Clinical Periodontology, 3/1996
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Marc A. Judson, Steven A. Sahn. "Endobronchial Lesions in HIV-infected Individuals", Chest, 1994
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J.M. Edge, A.E. Van der Merwe, C.H. Pieper, P. Bouic. "Clinical outcome of HIV positive patients with moderate to severe burns", Burns, 2001
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Wang Jing, Rokiah Ismail. "Mucocutaneous manifestations of HIV infection: a retrospective analysis of 145 cases in a Chinese population in Malaysia", International Journal of Dermatology, 2001
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Afshin Salarieh, Chandrakant Rao, Susan RS Gottesman, Osama Alagha, Roxanne Todor, Constantine A Axiotis. "Plasma cell tumors in HIV-positive patients: Report of a case and review of the literature", Leukemia & Lymphoma, 2009
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A comparison of lung cancer in HIV positive and HIV negative populations Ryan Berman
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

Johannesburg, 2019 Abstract Background: Lung cancer is the most common cancer

worldwide and is the greatest contributor to malignancy associated deaths. HIV is an epidemic in many developing countries and South Africa carries the largest burden of disease the world. With the introduction of antiretroviral therapy (ART), AIDS defining malignancies

(ADM's) are on the decline and non-AIDS defining malignancies (NADM' s) are

becoming more common with lung cancer being the commonest amongst these. Aim: To

describe a cohort of HIV positive lung cancer patients and a cohort of

HIV negative lung cancer patients and compare the similarities and differences

between the two. Methods: A retrospective study of 188 patients with

histologically confirmed bronchogenic carcinoma was conducted. Smoking history, cancer subtype, 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 commonest subtype 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. We were unable to assess whether smoking was more common in either group or whether HIV positive patients present at a more advanced stage than HIV negative patients due to a paucity of data. i CHAPTER 1

Introduction and literature review 1.1 Background Lung malignancies are the leading

cause of malignancy related deaths globally (1, 2). Lung cancer is the most common non-

AIDS defining Human Immunodeficiency Virus (HIV) associated malignancy (3, 4). The prognosis of HIV infected persons who develop lung cancer was found to be poorer than HIV uninfected persons in several studies (4, 5). However, it is unclear if this is related to treatment disparities, intolerance to chemotherapy, increased risk of treatment toxicity, or risk from AIDS and non-AIDS-related illnesses. 1.2 Literature review In a single South African study from 1992-1998 (6) data paralleled with international findings where men have a higher

incidence of lung cancer- this is likely related to a higher smoking prevalence. In that study, squamous cell carcinoma (SCC) was found to be the most common histological sub-type

compared with international findings where adenocarcinoma is the commonest sub-type. The increase in the prevalence of adenocarcinoma in smokers has been linked to design changes in cigarettes that have promoted deeper inhalation (7). The 2015 World Health Organisation (WHO) classification of lung tumours categorises lung cancer based on histological subtype (8). In terms of the epithelial variants of lung tumours, the main subtypes include adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumours which comprise small and large cell carcinoma (amongst others). 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, 9, 10). In the HIV positive population, NSCLC is reported in 84-96% of cases in which adenocarcinoma is the commonest subtype, found in 32-50% of cases (1, 9, 11). However, some smaller studies have reported SCC as the commonest subtype in the HIV positive population(12, 13). However limited power precludes these findings from being statistically significant. Human immunodeficiency Virus (HIV) is a risk factor for many diseases both communicable and non-communicable (NCD) (14). Increased NCDs in the HIV population include malignancies, cardiovascular disease, and liver disease (unrelated to chronic viral hepatitis) amongst others. The HIV Cancer Match Study estimated in 2010, that of the nearly 900 000 people living with HIV in the United states of America (USA), 7760 had been diagnosed with cancer (15). HIV associated malignancies can be separated into Acquired Immune Deficiency Syndrome (AIDS) defining malignancies (ADMs) and Non-AIDS defining malignancies (NADMs). ADMs include Kaposi' s sarcoma, subtypes of Non-Hodgkin' s lymphoma (usually high grade sub-types) and cervical carcinoma (1). NADMs that are increased in HIV infected individuals include anal cancer, lung cancer, Hodgkin's lymphoma and liver cancer (3, 16). It should be noted that barring lung cancer, all of these malignancies have an infectious aetiology (Human papillomavirus (HPV) for anal cancer, Epstein - Barr virus (EBV) for Hodgkin's lymphoma and Hepatitis B and C viruses for liver cancer). There has been a rise in the NADMs since the inception of ART while ADMs are declining in developed countries (3, 16). One possible explanation for this is that people with HIV are living longer since the initiation of ART(17).This is supported by the increase in NADMs only being in people who are older than 40 years(3). Since 2003 the absolute number of cases of NADMs now exceeds that of ADMs 2 in the USA (16), and this has also been demonstrated in a study from Switzerland (18). It is expected that a similar pattern will follow in South Africa, especially with the inception of the new ART guidelines(19). A Swiss study showed a definite decrease in the incidence of ADMs between the pre-ART period, early-ART, and late-ART periods. It did not show a significant increase in the actual number of NADMs, however due to a decrease in the number of ADMs, the NADMs

were relatively proportionately more well represented (18). In a study in Uganda, which looked at the incidence of cancer (both ADM and NADM) in relation to ART coverage, it was found that for every 10% increase in ART coverage there was a 5% decrease in the incidence of KS. However, there was a 6% increase in the incidence of NHL's (17). There is a paucity of data from the African continent comparing the change in cancer incidence between the pre-ART period and post-ART initiation period. In a systematic review by a Brazilian group comparing the incidence of ADM's and NADMs in the pre-ART and ART periods it was found that among 600 000 patients there was an overall decrease in ADMs (20). In terms of HIV, lung cancer is the commonest NADM encountered according to Shiels et al (2011)(3, 21, 22). While lung cancer is more common in the setting of HIV (1, 23), the incidence does not seem to be affected by the introduction of ART as reported by Mani et al(2012)(1). The prevalence of lung cancer is on the increase globally in the HIV population (15, 24-28). This is likely due to HIV positive people living longer and thus to an age where cancer is more common (29). Some studies found that while NADM's are increasing and HIV is an independent risk for lung cancer, the incidence of lung cancer is actually on the decline in the HIV positive population(29, 30).Additionally, it is thought that lung malignancies occur 3 at a relatively higher CD4 count as compared to ADMs(31) and CD4 count may have no bearing on the risk of developing lung cancer(30).A study in Germany showed an average CD4 cell count of 383 cells/µl in patients who developed lung cancer(31).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 to those not receiving ART with a diagnosis of lung cancer(9).Thus, ART is unlikely to affect the incidence of lung malignancies(9), however, ART use is associated with increased survival. As with other NADMs, lung cancer is found to be increasing in patients older than 50 years while remaining mostly unchanged in those below 50 years(3). This supports the hypothesis that NADMs are increasing as the HIV positive population ages (3). One of the reasons HIV positive patients have a higher incidence of lung cancer compared with HIV negative patients is their higher smoking prevalence, with Mani et al (2012) quoting a reported prevalence of 35-70% as compared to 20% in the general population in the USA (1). That being said, Chatuverdi et al (2007) showed that smoking alone cannot explain the higher incidence of lung cancer in HIV positive patients and that other factors likely related to HIV have an effect(32). Some of the reasons postulated for this 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, 12, 33). Data reported in India found head and neck malignancies rather than lung malignancies to be the commonest NADM (34) which the authors believe may also be due to tobacco use(34). However, they propose a possible link with oral HPV as the aetiology for this finding which still needs to be investigated. Lung cancer In HIV positive patients has a male predominance similar to that in HIV negative patients(9), however the mean age at diagnosis is usually 10 years earlier than the HIV negative matched

cohort(31). HIV positive patients also tend to be diagnosed with a more advanced stage of lung cancer compared to the general HIV negative population (1). A South African study published by Koegelenberg et al (2016) compared the differences between HIV infected and HIV uninfected lung cancer patients, and found that SCC was the most common histological sub-type (p = 0.07) found in the infected group while adenocarcinoma was the most common histological sub-type found in the uninfected group (13). The reason for this observation is unclear as the smoking prevalence was roughly the same. Even though there was a slightly higher male proportion in the HIV positive group (65% in HIV positive and 59% in HIV negative) this does not seem to be enough to explain why there is a slight preponderance towards SCC in the HIV positive group. The authors also noted that HIV infected individuals tended to be younger at diagnosis and have a poorer performance status compared to the HIV negative group. This correlates with international findings (33). A German study assessed the stage related survival of HIV positive patients with lung cancer (31)found that the overall survival of patients with stages I- IIIa was 5.18 years, while patients with stage IIIb-IV had a life expectancy of 0.81 years (31)with a median overall survival of 1.08 years(31).However, in an Italian study the median overall survival was found to be 7 months for those receiving ART(9). Patients who presented with stages I-IIIa had a higher 1 year, 2 year and 5 year survival rate than those presenting at stage IIIb and IV(31). Helen Joseph Hospital (HJH) is a small academic hospital in Johannesburg, Gauteng, South Africa which serves as a referral centre for a number of primary and secondary level hospitals and their surrounding local clinics. There is a dedicated respiratory unit which sees a high burden of lung cancer and HIV infected patients and assists in diagnosis and management of such patients. Studying this group of patients allowed us to examine the relationship between lung cancer and HIV in an urban South African context. 1.3 Study Aim and Objectives Aims: o Describe the cohort of lung cancer patients in the respiratory clinic at Helen Joseph Hospital according to their HIV status.

Objectives o Determine the prevalence of different histological sub-types of lung cancer in two cohorts (HIV positive and HIV negative). o Determine the average age of diagnosis of lung cancer. o Determine the proportion of lung cancer patients with a history of smoking in o Determine the commonest mode of presentation of cancer in the two groups. CHAPTER 2 Methodology 2.1 Patients and data collection Data was collected retrospectively from all patients with a histological diagnosis of

bronchogenic lung cancer from 1 January 2010 to 31 December 2017 at the Helen Joseph Hospital. This was done by checking the records at the National Institute for Occupational Health

(NIOH) lung database and the National Health Laboratory Service (NHLS) anatomical pathology records. These were referenced back to files at the Helen Joseph Hospital respiratory outpatient department and bronchoscopy records to collect further outstanding data as far as possible. Additional attempts at completing data were made by searching Labtrak and requesting Central Data Warehouse (CDW) assistance where missing results were not found. Inclusion criteria required that all adult patients with histologically proven bronchogenic lung malignancies be included in the study. Adult patients include those over the age of 18; anyone below age 18 was excluded. Minimum requirements for entry into the cohort were a histological diagnosis of lung cancer and a HIV diagnosis. 2.2 Materials and Methods Data variables collected were captured onto a data collection sheet (see Appendix 7.1). Data collected included demographic data such as age and gender, HIV result as well as other important parameters for HIV positive

patients including CD4 count, HIV viral load and whether the patient was on ART and the duration of time. Details pertaining to the cancer were also collected namely the histological subtype, stage of presentation and presenting features. Data on smoking and other occupational exposures was also collected as well as details of patient's co-morbidities. The 2015 WHO classification of lung malignancies is the classification system used in this paper; this includes malignancies diagnosed prior to 2015. Thus, all broncho-alveolar carcinomas were classified as adenocarcinomas. All those with a histological diagnosis of non- small cell lung

cancer not otherwise specified (NSCLC NOS) were grouped with large cell carcinomas. This is in concordance with the WHO classification which does not include the subtype NSCLC NOS. Since most specimens collected were of small histological size they cannot technically be classified as large cell carcinoma, however, for ease of classification we have included NSCLC NOS specimens as large cell sub-types (35). All non-bronchogenic lung cancers were excluded. AIDS was defined according to the CDC definition as a CD4 count of

less than 200 cells/µl, or stage 3 defining illness regardless of the CD4

count(36). 2.3 Data Analysis Statistical analysis was done using Stata and Microsoft

Excel. Comparative analysis between HIV positive and HIV negative groups,

genders, and histological sub-types of lung cancer was done using the 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-squared test (larger sample sizes) and Fishers exact test (in smaller

sample sizes). Statistical significance was set at a p-value cut off of less than or equal to 0.05. CHAPTER 3 Results Lung malignancies N = 286 Metastatic N = 14 Bronchogenic N = 272 Cytological Histological N = 3 N = 269 HIV result NO HIV result N = 188 N = 81 HIV Positive HIV Negative N = 31 N = 157 Figure 3.1 Breakdown of Lung

malignancies There were 286 patients (Figure 3.1) diagnosed with possible lung cancer at

Helen Joseph Hospital between 1 January 2010 and 31 December 2017.

Of those, 272 were diagnosed with bronchogenic carcinomas. Fourteen patients were excluded as they were diagnosed with metastatic cancer rather than primary lung cancer. Another three patients were excluded from our study as the basis of their diagnosis was on cytological specimens only, two by fine needle aspirate (FNA) and one by bronchial washings. A further 81 patients were excluded on the basis of not having an HIV result. This brought the final number of patients to 188. The diagnosis of lung cancer has increased over time due 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 (Figure 3.2). Numbers of newly diagnosed cases of lung cancer per year 60 50 40 30 20 10 0 2010 2011 2012 2013 2014 2015 2016 2017 HIV positive HIV Negative HIV unknown Figure 3.2New Lung cancer cases per year Table 3.1 Data summary HIV Negative HIV Positive Gender Males 109 (69.43%) 21 (67.74%) Females 48 (30.57%) 10 (32.26%) Total 157 31 Subtypes 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%) Smoking Smoker 124 (78.98%) 10 (32.26%) Non Smoker 11 (7%) 3 (9.68%) Unknown 22 (14.01%) 18 (58.06%) Age (years) Average Age Male 61.48 53.57 Average Age Female 61.91 54.7 Average Age 61.64 53.94 HIV parameters Average CD4 (cells/ml3) N/A 358 (41 – 722) VL (copies/mL) VL <50 N/A 10 VL 50 - 1000 N/A 4 VL > 1000 N/A 4 VL unknown N/A 13 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%) CD4 = absolute CD4 count (cells/µL), VL = HIV viral load (copies/mL) 3.1 Demographics Of the 188 patients, 157 (83.51%) were HIV negative and 31 (16.49%) were HIV positive. A total of 130 (69.15%) were male and 58 (30.85%) were female. There was no

significant difference in the proportion of males to females when comparing the HIV

positive and HIV negative groups (p = 0. 85). In the HIV negative group

109 were males (69.43%) and 48 were female (30.57%) (p< 0.00001) while in the HIV

positive group 21 were male (67.74%) and 10 were female (32.26%) (p = 0.0026). When assessing the proportions of the different histological sub-types by gender, of the 130 males, 50 had adenocarcinoma (38.46%), 48 had SCC (36.92%), 20 had small cell lung

cancer (SCLC) (15. 38%), six had large cell carcinoma (4.62%) and six

had other sub-types (4.62%). In the cohort of 58 females, 30 had adenocarcinoma (51.72%), 17 had SCC (29.31%), six had SCLC (10.34%), two with large cell carcinoma (3.45%) and three had other sub-types (5.17%). When comparing the genders in the HIV positive and

HIV negative populations, of the group of 109 HIV negative males, 42 had adenocarcinoma (38.53%), 41 had SCC (37.61%), 17 had SCLC (15.60%), five had large cell carcinoma (4.59%) and four other sub-types (3.67%).In the group of 21 HIV positive males, eight had adenocarcinoma (38.10%), seven had SCC (33.33%), three had SCLC (14.29%), one had large cell carcinoma (4.76%) and there were two other sub-types (9.52%). Within the female group, of the 48 HIV negative females, 27 had adenocarcinoma (56.25%), 12 had SCC (25.00%), six had SCLC (12.50%), one had large cell carcinoma (2.08%) and there were two other sub-types (4.17%). While of the ten HIV positive females, three had adenocarcinoma (30%), five had

SCC (50%), no patients had SCLC, one had large cell carcinoma (10%)

and there was one other histological sub-type (10%). The average age at the time of

diagnosis of all patients was 60.37 years. There was no statistical difference (p = 0. 41) between the genders with males having an average age of 60 .2 years and females 60.74 years. There was a however 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. Comparing age within the different subtypes, patients with adenocarcinoma had an average age of 59.78 years while those with SCC were 63.12 years. The mean age of those with SCLC was 62.16 years. There was a significant difference found between the ages of those with SCC and adenocarcinoma (p = 0. 006). There was no difference found when comparing patients with SCC to SCLC (p = 0.22) or when comparing patients with adenocarcinoma to SCLC (p = 0.26). 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 three patients) while those with SCC had an average age of 60.17 years. 3.2 Subtypes Adenocarcinoma was the commonest histological sub-type diagnosed. This was found in 80 (42.55%) of the 188 patients, this was followed by SCC with a number of 65 (34.57%) and then SCLC with 26 (13.83%) patients. Eight (4.26%) patients were diagnosed with large cell carcinoma. Of the rarer subtypes, three patients had large cell neuroendocrine carcinomas (LCNEC). Adenosquamous carcinoma, mucoepidermoid carcinoma. Adenoid cystic carcinoma and sarcomatoid carcinoma were diagnosed in one patient each. Two patients had mixed tumours one of which was a mixed adenocarcinoma and SCLC and the other a mix of SCC and adenocarcinoma. Looking at the commoner subtypes, a male predominant pattern was observed for all. 50 (62.5%) of the 80 patients with adenocarcinoma were male and 30 (37.5%) were female (p = 0.0007). Of the 65 patients with SCC, 48 (73.85%) were male and 17 (26.15%) were female (p <0.00001). SCLC was found in 20 (76.92%) males and six (23.08%) females (p = 0.00005) and of the eight patients with large cell carcinoma, six (75%) were male and two (25%) female (p = 0.022). Adenocarcinoma was diagnosed in 69 of the 157 HIV negative patients (43.95%) and 11 of the 31 HIV positive patients (35.48%). However, there was a no statistically significant difference between these two groups (p = 0. 38). Within the 69 HIV negative patients with adenocarcinoma, 42 were male (60.87%) and 27 were female (39.13%) while eight of the 11 patients in the HIV positive group were male (72.73%) and three were female (27.27%). SCC was found in 53 of the 157 HIV negative patients (33.76%) and 12 of the 31 HIV positive patients (38.71%) but this difference was also not statistically significant (p =

0. 60). In the HIV negative group, 41 of the 53 patients were male (77.36%) and only 12 were female (22.64%). Seven patients in the HIV positive group were male (58.33%) and five were female (41.67%). Only three of the 31 patients in the HIV positive group had SCLC (9.68%) while 23 of the 157 patients in the HIV negative group had SCLC (14.65%), and again no statistically significant difference was observed (p = 0. 57). 17 of those in the HIV negative group were male (73.91%) and six were female (26.09%). All three patients in the HIV positive group were male. Six patients in the HIV negative group (3.82%) and two in the HIV positive group (6.45%) had large cell carcinoma which was also not significantly different (p = 0.62). Five of the six patients in the HIV negative group were male (83.33%) with only one female (16.67%) while in the HIV positive group there was one male and one female. 15 Of the rarer subtypes, in the HIV negative group there was one patient with each of the following subtypes of lung cancer: adenosquamous, mucoepidermoid, LCNEC, adenoid cystic and sarcomatoid. Additionally, there was one patient who had a mixed tumour with part of it being SCLC and part of it showing features of adenocarcinoma. In the HIV positive group, and there were two patients with LCNEC and one patient who had a mixed tumour with part showing features of adenocarcinoma and part SCC. SUBTYPE AS PROPORTION OF TOTAL IN HIV NEGATIVE AND HIV POSITIVE GROUPS HIV - HIV + 160 140 120 100 80 60 40 20 0 Figure 3.3 Proportions of Subtypes by HIV status 3.3 Presenting symptoms The commonest presenting findings that raised suspicion for lung cancer was pathology noted on the chest radiograph (CXR) which most but not all patients had. 134 (71.28%) of the 188 patients had a lung mass noted on CXR. Of those without a lung mass, 16 (8.51%) had a pleural effusion, 21 (11.17%) had atelectasis secondary to an endobronchial mass, six (3.19%) had bilateral infiltrates and a further six (3.19%) had pulmonary nodules without an obvious primary lung mass. Of those without any reported CXR findings, one had palpable supraclavicular nodes, one had digital clubbing and one presented with seizures and was noted to have a chest wall mass which on biopsy proved to be lung cancer. The final two patients had unknown presentations as no history was included with the referring specimen and their files were not found. Most patients had more than one presenting feature. As already mentioned a lung mass on CXR was the commonest presenting feature being present in 134 of 188 patients, 39 of 58 females (67.24%) and 95 of 130 males (73.08%) but the difference between the two genders was not significant (p = 0. 41). 51 of 80 with adenocarcinoma (63.75%), 48 of 65 with SCC (73.85%), 17 of 26 with SCLC (65.38%) and seven of eight large cell carcinoma (87.5%) had a lung mass on CXR. In the HIV negative group, 108 of 157 patients (68.79%) had a mass on CXR as did 20 of 31 HIV positive patients (64.52%). The

difference between the HIV positive and HIV negative groups was not significant (p = 0. 64). Pleural effusions were found in 31 of the 188 patients (16.5%) and were relatively more common in females being present in 14 (24.13%) of the 58 females and 20 (15.38%) of the 130 males. The difference between the groups was not significant (p = 0. 15). Pleural effusions were found in 18 of 80 with adenocarcinoma (22.5%), seven of 65 with SCC (10.77%), four of 26 with SCLC (15.38%), one of eight large cell carcinoma (12.5%). 24 HIV negative (15.29%) and seven HIV positive patients (22.58%) were found to have pleural effusions, this difference was also not statistically significant (p = 0. 317). 43 patients had CXR evidence of atelectasis. 30 (23.08%) of 130 males had this feature as did 13 (22.41%) of 58 females. When comparing the different subtypes 17 (26.15%) of 65 SCC, 17 (21.25%) of 80 adenocarcinoma, seven (26.92%) of 26 SCLC and one large cell carcinoma had atelectasis. It was found to be less common in HIV negative patients with 32 (20.38%) patients presenting with this feature while 11 HIV positive patients (35.48%) had this feature on CXR. This difference had no statistical significance (p = 0.67). Hypercalcaemia (as defined by a serum calcium >2.55mmol/L) was present in 29 patients (15.43%). There was no significant difference between males and females (p = 0. 4) with 22 of 130 males (16.92%) and seven of 58 females (12.07%) having hypercalcaemia. Comparing the different subtypes, five of the 80 patients with adenocarcinoma (6.25%), 20 of 65 patients with SCC (30.77%), two of the 26 with SCLC (7.69%) and one of eight patients with large cell carcinoma (12.5%) had hypercalcaemia. There was a significantly higher number noted in those with SCC as compared to adenocarcinoma (p = 0. 0001) and SCLC (p =0.02). Assessing the difference between HIV positive and HIV negative groups, hypercalcemia was noted in 25 of the 157 HIV negative patients (15.92%) and four of the 31 HIV positive patients (12.90%) and this small difference had no statistical significance (p = 0.67). Digital clubbing was observed in 40 patients (21.28%). It was more common in males being seen in 34 of the 130 males (26.15%) and only six of the 58 females (10.34%) which was significant (p = 0.014). Analysing the different subtypes, 19 of the 80 patients with adenocarcinoma (23.75%) had clubbing while 15 of those with SCC (23.08%) had clubbing. It is known to be quite rare in SCLC and was found in four of the 26 patients (15.38%) however no difference between SCLC and adenocarcinoma (p = 0.37) or SCC was found (p = 18 0.41). Adding up all the non-small cell patients, 37 of 162 had clubbing (22.84%) but no significant difference was found between the two groups (p = 0. 39). Statistical difference was also not found between the HIV positive and negative groups (p = 0.77) with 34 of the HIV negative patients (21.66%) and six of those with HIV (19.35%) having digital clubbing. Other less frequent but important clinical findings included recurrent laryngeal nerve palsy and a hoarse voice in 12 patients (6.38%); phrenic nerve palsy and a raised hemi-diaphragm in two patients. Malignant pericardial effusions were seen in two patients, SVC syndrome was diagnosed in 10 patients (5.32%) and Horner's syndrome was noted in two patients. 3.4 Stage Unfortunately due to a lack of data on staging of patients, we could not accurately define the frequencies of certain features, most notably distant metastases. In our study we found that the commonest site of distant metastases was bone which was seen in 13 patients. Brain metastases were seen in 12 patients and only one

of these patients had SCLC. Liver metastases were seen in four patients as were adrenal metastases present in four patients. These were mostly noted in the HIV negative group. 12 of the 13 patients with bone metastases, ten of the 12 with brain metastases and all four of those with liver and four with adrenal metastases were HIV negative.

Patients with NSCLC were staged according to the 8th version of American Joint Commission on Cancer (AJCC) TNM staging. Of the 162 patients, 84 (51.85%) presented with stage IV disease, nine (5.56%) with stage IIIB disease and one with stage IIIA disease. The other 68 (41.96%) patients had no staging available. Looking only at the HIV positive group 14 (50%) of the 28 patients had stage IV disease and 14 (50%) did not have a stage available, while in the HIV negative group, 70 (52.24%) of the 134 patients had stage IV disease, nine (6.72%) 19 had stage IIIB and one stage IIIA disease; the other 54 (40.3%) patients were not staged. Comparing males and females; 55 (50%) of the 110 males had stage IV disease, seven (6.36%) had stage IIIB and 48 (43.64%) were not staged. In the female group, 29 (58%) of the 52 females had stage IV disease, two had stage IIIB and one had stage IIIA and 20 (38.46%) had no stage. 46 (57.5%) of the 80 patients with adenocarcinoma had stage IV disease and, two with stage IIIB and one with stage IIIA, 31 (38.75%) did not have staging available. Eight of the 11 HIV positive patients were stage IV at diagnosis and the other three were unknown. 30 (46.15%) of the 65 patients with SCC, seven (10.77%) with stage IIIB and 28 (43.08%) were unknown. Of the 53 HIV negative patients, 26 (49.06%) were stage IV at presentation and seven (11.11%) stage IIIB. The other 20 (37.74%) had no staging available. In the HIV positive group, four (33.33%) had stage IV disease and the other eight (66.67%) were unknown. Patients with SCLC were staged according to the Veterans Administration Lung Study Group (VALSG) two-stage system. Of the 26 patients with SCLC, 14 (53.85%) had extensive stage disease, two (7.69%) had limited stage disease and ten (38.6%) were unknown. There were only three patients in the HIV positive group of which one had extensive disease and two were unknown. Of the 23 patients in the HIV negative group, two (8.7%) had limited disease, 13 (56.52%) had extensive disease and eight (34.78%) were unknown There was a large amount of missing data thus when computing statistics on staging, those with unknown staging were excluded. This left us with a total of 94 patients, 84 of whom had stage IV disease (89.36%), nine with stage IIIB (9.57%) and one with stage IIIA (1.06%). 70 of the 80 patients in the HIV negative group had stage IV disease (87.5%), nine with stage IIIB 20 (11.25%) and one with stage IIIA (1.25%). All 14 patients in the HIV positive group had stage IV disease. Comparing males and females; 55 of the 62 males had stage IV disease (88.71%) and seven had stage

IIIB (11.29%) while in the female group, 29 of the 32 females had stage IV disease (90.63%), two had stage IIIB (6.25%) and one had stage IIIA (3.125%). There was no significant difference in the amount of stage IV disease between males and females (p = 0. 77). When comparing the different subtypes, 46 of the 49 patients with adenocarcinoma had stage IV disease (93.88%), two had stage IIIB (4.08%) and one had stage IIIA (2.04%). 30 of the 37 patients with SCC presented with stage IV (81.08%) and seven with stage IIIB (18.92%). In the patients with SCLC, 14 of the 16 had extensive disease (87.5%) and two had limited disease (12.5%). 3.5 Smoking The smoking habits of the patients revealed that 134 of the 188 patients had a history of smoking (71.27%), 14 were never-smokers (7.45%) and 40 had no smoking history documented (21.28%). Of the 130 males, 105 (80.77%) were known smokers, five (3.85%) had never smoked and 20 (15.38%) had no history available. While of the 58 females, 29 (50%) had a confirmed history of smoking, nine (15.52%) had never smoked and 20 (34.48%) had no available history. Regarding the HIV negative population, 124 (78.98%) were known to have a history of smoke exposure, 11 (7.01%) had not smoked and 22 (14.01%) had no history available. In the HIV positive population ten (32.26%) of the 31 patients were confirmed to have a history of smoking, three (9.68%) had never smoked and unfortunately the majority (18 of the 31, 58.06%) had no history available. When computing statistics for smoking, the 40 patients who had no history available were excluded. Thus, for statistical purposes 134 of the 148 patients were smokers (90.54%) and 14 had never smoked (9.46%). In the HIV negative group 124 of the 135 were smokers (91.85%) and 11 of the 135 were never smokers (8 .15%). In the HIV positive group ten of the 13 were smokers (76.92%) and three had never smoked (23.08%) however there was no significant difference found between the groups (p = 0. 078). There was a significant difference found when comparing smoking between the genders (p = 0.00051), 105 of the 110 males were smokers (95.45%) and five were never smokers (4.55%) while 29 of the 38 females were smokers (76.32%) and nine were never smokers (23.68%). When looking at the different subtypes of lung cancer, 51 (63.75%) of the 80 patients with adenocarcinoma had a history of smoking while 13 (16.25%) had never smoked and 16 (20%) had no history available. In the SCC population, 47 (72.31%) were confirmed smokers and only one had never smoked however 17 (26.15%) had no available history. The subtype with the highest proportion of smokers were those with SCLC with 23 (88.46%) of the 26 being confirmed smokers, only one non-smoker and two with no history. When excluding those without a known history, 52 of those with adenocarcinoma were smokers (81.25%) and 12 had never smoked (18.75%). In patients with SCC, 47 of the 48 patients were smokers (97.92%) while one was not (2.08%). In those with SCLC 23 of 24 patients had a history of smoking (95.83%) and one had never smoked (4.17%). Seven patients with large cell carcinoma were smokers and there were no patients who had never smoked. There was a significant difference found between patients with adenocarcinoma and SCC (p = 0. 0064) however not between those with adenocarcinoma and SCLC (p = 0. 86). There was also no significant difference noted when comparing patients with SCC and SCLC (p = 0.612). 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. A number of ten pack years or more was arbitrarily decided on as a strong smoking history. Of the 134 smokers, 98 had a strong smoking history (73.13%), only four patients were known with a pack year history less than ten (11.76%) and 32 of the known smokers did not have documentation of their pack year history (23.88%). 3.6 Other comorbidities 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 six of the 188 patients (3.19%), four of whom were HIV negative and two HIV positive. Additionally, five other patients (2.66%), three HIV positive and two HIV negative, had previously suffered from PTB. The exposure to TB was thus 11 of 188 patients (5.85%). 3.7 HIV parameters Within the group of 31 HIV positive patients, 16 were on ART at diagnosis (51.61%), seven were not (22.58%) and eight had no history available (25.81%). 26 of the patients had CD4 counts available, these ranged from 41 to 722 cells/ µL. In the group of patients on ART, CD4 counts ranged from 99 to 688 cells/ µL with a mean of 365 cells/ µL while in those not on ART, CD4 counts ranged from 169 to 722 cells/µL. The mean CD4 count was 467 cells/µL but due 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 of those on ART; nine of the 16 had a VL less than 50 copies/ml (56.25%), three had VL between 50 and 1000 copies/ml (18.75%), two had viral loads greater than 1000 copies/ml (12.5%) and two had no VL charted (12.5%). Treatment success was achieved in 12 of the 16 patients (75%), treatment failure in two (12.5%). We were unable to assess whether those patients on ART have more or less advanced disease than those not on ART as all the HIV positive patients with available staging had stage 4 disease. CHAPTER 4 Discussion There were 188 patients eligible for the study by fulfilling the criteria of having a histological diagnosis of lung cancer and an HIV test result. In line with the realisation that NADMs, especially lung cancer, are now becoming increasingly common in the HIV positive population, there has been an overall increase in tendency to check the HIV status in these patients over time. This trend is also observable in our study (Figure 4.1) which has seen a steady climb in patients with known HIV results. There was a higher amount known in 2010 than 2011 and 2012 – a possible explanation may be that HIV was tested for other reasons in that time. HIV Known vs. Unknown 100 90 80 70 60 50 40 30 20 10 0 2010 2011 2012 2013 2014 2015 2016 2017 % known % unknown Figure 4.1Known vs. unknown HIV status The HIV positive cohort accounted for 31 (16.49%) of the 188 patients, this is a higher proportion than seen in another South African study (13) where 9.38% of their lung cancer cohort were HIV positive. The reason for such a difference (p = 0.0096) still needs to be looked into to as it is unlikely that numbers alone can account for this (the other study had 469 patients). 4.1 Demographics There is a large gender bias noted in the lung cancer population, with a far larger proportion of males as compared to females. This ratio of approximately two-thirds was noted in both the HIV negative and positive groups. This same trend was noted by Mani et al (2012)(1) when assessing a number of studies which looked at lung cancer in the HIV population(1). Risk-taking behaviour, including smoking, is more prevalent in the males than females which is the

most likely reason why there is a male predominance in the lung cancer population (37, 38).Additionally, in developed countries both HIV and smoking are seen predominantly in males which is why lung cancer in the HIV population is seen more commonly in men (1). There has been a change in the smoking trends with smoking becoming a lot more common in females than it used to be especially in developed countries (39). There is a long latency period between smoking and the development of lung cancer(40)and thus the opposite effect of a decline in smoking and the reduction of lung cancer is also expected to be true (40). The smoking rate, while improving in males, is still far higher than in females. The latency period may account for lung cancer still occurring more commonly in males despite an improvement in smoking rates. The latest South African National cancer registry (NCR) statistics were released in 2014 in which lung cancer was found in 936 females and 1791 males (41). Thus, females made up 26 34.32% and males 65.68%, a finding similar to our study, where 130 (69.15%) were male and 58 (30.85%) were female. Regarding the ratio of male to female new cases in our study, proportions were in keeping with global findings where in 2012 there were 1.82 million new cases of which 1.24 million (~68%) were males (10). A study by Jemal et al (2018)(39) looked at the trend in lung cancer by gender over a period of about 20 years (1995–2014) where they found a decline in the incidence of lung cancer among men and woman. However, the decline was steeper amongst men and therefore a higher incidence of lung cancer was reported among women in certain age groups and races. In our study, the data collection was over a shorter period which did not allow us to observe the marked changes that were observed in the Jemal study. We found that for all the years, there was a male dominant pattern mostly around two-thirds, and there were too few numbers in the HIV positive group (assessing each year as separately) to consider the results meaningful. In the 2014 NCR report, lung cancer makes up 2.48% of all cancers in females and 4.87% of all cancers in males(41).In comparison, it makes up a total of 13.5% of all new cancers (male and female combined) in the USA(42). Possible reasons for the disparity include lack of access to diagnostic facilities in south Africa (outside of urban areas), late presentation of patients, clinicians empirically diagnosing TB in a high endemic area (especially in HIV positive patients), and the amount of HIV associated malignancies being higher in South Africa thus accounting for a larger proportion. Additionally it is believed the incidence of lung cancer will rise as urbanisation becomes more popular along with a change in lifestyle coupled with poor anti-smoking campaigns (23)and poor patient awareness of the consequences of tobacco use(38). Lung cancer is found to be a disease of the older population. In the NCR data tables (Figure 4.2), the peak age for the diagnosis of lung cancer is from the ages of 55 – 70 years in males and females. The NCR did not have any separation based on HIV status. The younger age identified in the HIV cohort in this study of 53.94 years compared to the HIV negative of 61.64 years has also borne out in other studies (1, 13). 2014 NCR lung cancer incidence by age group 350 300 250 200 150 100 50 0 Females Male Figure 4.22 NCR lung cancer incidence by age 4.2 Subtypes In the past, the commonest subtype of lung cancer was SCC(37). In more recent studies adenocarcinoma has been the commonest subtype identified, followed by SCC and then large cell carcinoma (43). The figures in our study which showed adenocarcinoma was present in 80 (42.55%), SCC in 65 (34.57%) and large cell in 8 (4.26%) were similar to those seen in

this study. In a study by Meza et al (2015) who looked at the trends of lung cancer over a 37-year period, it was noted that SCC used to be the most common cancer in males (around 50% of all lung cancers) in the early years of their study but the trend changed toward adenocarcinoma which had an initial reported incidence of around 20% in 1973 that increased to over 40% now while SCC now makes up about 30% of all lung cancers in males(43). The incidence of SCLC stayed constant at around 20% and large cell carcinoma decreased from about 10% to 3% (43). These were not very different from the figures in our study which showed a similar proportion of adenocarcinoma and SCC but slightly less SCLC. Possible reasons for this may include less effective anti-smoking legislation in South Africa as compared to a developed country such as the USA, less educated population, and SCC is known to have the strongest association with smoking of all the lung cancer subtypes. In terms of females, Meza et al (2015) noted that adenocarcinoma had always been commoner in females although the number was less while it now accounts for more than 50% of cases. SCC, on the other hand, accounted for around 30% in the earlier years but that had dropped to around 20% now (43). Once again these were not very different to our findings but we observed a slightly higher amount of SCC than they did (29% vs. 20%) additionally they reported a SCLC incidence in females similar to males (~20%) while our numbers were lower (15% and 10% for males and females respectively). The HIV positive population in our study had a slightly higher proportion of SCC as compared with adenocarcinoma while the HIV negative population demonstrated a higher proportion of 29 adenocarcinoma. The lack of numbers in the HIV positive group doesn't allow us to extrapolate this to the population at large but this same pattern was also noted in another South Africa study (13). However, other studies conducted in Europe showed adenocarcinoma to be the commonest subtype in both HIV negative and HIV positive patients (1, 9). A possible reason for this is related to HIV patients apparently having higher proportions of smoking although this is not supported by Koegelenberg et al (2016)(13). In an article by Mani et al(2012),who reviewed multiple different studies of lung cancer in HIV infected people, adenocarcinoma was found to be the predominant subtype, however, these were mostly conducted in developed countries (1). Additionally, in a study conducted in Italy, adenocarcinoma was also found to be the commonest subtype(9). Smoking is known to be the most important risk factor for developing lung cancer (10). All subtypes have an association (44) however it is more strongly associated with SCC and SCLC and less so with adenocarcinoma (43).There have been a few reasons proposed for this including the current contents of cigarettes, which have a higher proportion of nitrosamines than previously produced cigarettes ,and deeper inhalation of cigarettes which gets smoke to the peripheral airways where adenocarcinomas are more commonly located (45). In another South African study comparing HIV positive and HIV negative populations (13), the smoking prevalence was noted to be very high amongst both HIV positive and HIV negative populations (around 90%).This is comparable to what was found in other studies (1) and in the HIV negative population of our study. We could not accurately comment on the HIV positive population in our study as many of them were missing details on smoking history. 4.3 Symptoms In a study by Cadranel et al(2006), it was quoted that the commonest feature was a mass (between 80 - 100%) on CXR (46).They also found that pleural effusions

were slightly more common in the HIV positive group, however, this difference did not reach statistical significance(46). There is limited data comparing other clinical findings in the HIV negative and HIV positive groups however it is not expected to differ too much between the groups unless HIV positive patients present with more advanced stage earlier in the course of their disease. Hypercalcaemia was noted to be significantly more common in those with SCC than other subtypes of lung cancer. This has also been found in other studies and is usually a sign of poor prognosis and advanced disease(47). As almost all the patients with known staging had advanced disease, it is not surprising we did not see a difference between the HIV positive and negative groups. 4.4 Stage Multiple studies have found that HIV positive patients present at a more advanced stage than HIV negative patients (1, 9). In our study, regarding the patients with NSCLC, the HIV positive patients whose stage at diagnosis was known were all already metastatic. The HIV negative patients were also advanced with the earliest stage diagnosed being IIIA (in one patient), a few more being diagnosed with stage IIIB but most were already metastatic at diagnosis. SCLC is known to be more aggressive with more patients expected to be found with more advanced disease(48, 49). The numbers quoted in some studies are upwards of 65% compared with 47% of NSCLC being metastatic (48, 49). We found that most patients were at the extensive stage but were unable to differentiate between HIV positive and negative groups owing to the small number in the HIV positive group. 4.5 Smoking

Smoking is the most important risk factor for lung cancer and was found to be commoner in both groups than in the general population (38). According to the International association for the Study of Lung Cancer (IASLC) smoking is responsible for above 80% of lung cancer cases (50), while according to Cheng et al, who looked at separate countries in more depth, smoking is responsible for lung cancer in 65% of males and 25% of females in medium HDI (human development index) countries (which is where South Africa is placed)(44). In contrast, South Africa is unique because in Africa the smoking rates amongst women are low but in South Africa they are quite high thus accounting for a greater incidence of lung cancer among women when compared with the rest of Africa (44). The Human science research council of South Africa released smoking data for South Africa based on the first South African National Health and Nutrition Examination Survey (SANHANES-1) (38). This 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%) as compared to 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 (50). In another study conducted in South Africa

to assess the prevalence of smoking in the HIV population, it was found that 34% of HIV positive patients were smokers (current or former)(51).Of the male participants, 52% were current smokers while only 13% of the females were current smokers(51). These figures are higher than the general population mentioned above thus it is not surprising that lung cancer is more common in HIV positive patients. According to Reddy et al (2015), epidemiological data from South Africa shows a significant decrease in smoking prevalence over the last 20 years with smoking now about half as common as it was (38). Wong et al (2017) found that lung cancer incidence and mortality mostly show a decreasing trend in men and an increase in women(52).This is likely due to the decline in smoking among men which is sharper than that among women(52). 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 (52). 4.6 Comorbidities According to Sigel et al, COPD is an independent risk for lung cancer in HIV positive patients(33). The prevalence of COPD is expected to be high amongst patients with lung cancer as they share a common risk factor. The number of 28 in our study is likely very short of the actual number and unfortunately a lack of documentation prevents us from confirming the actual number of those with COPD. The link between lung cancer and pulmonary TB has been shown in a study conducted in Taiwan(53) where the incidence rate of lung cancer was 11 times higher in the group with recent PTB infection compared to those who had never had PTB. However, they did not have a separation based on HIV status and thus we could not compare this to the two separate groups in our study. 4.7 HIV parameters Mani et al(2012) also report that ART has no effect on lung cancer incidence and that lung cancer is no more common amongst individuals with higher as compared to lower CD4 counts (1). 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 365cells/µL and 467 cells/µL respectively). In other studies, the CD4 count was also found to be higher with Bearz et al (2014) finding a mean CD4 in the ART group of 339 cells/µL and the non-ART group of 287 cells/µL(9). One of the proposed reasons lung cancer (and other NADMs) have become more common is because patients who are on ART are no longer dying from opportunistic infections or ADMs, which occur in the setting of more advanced immune compromise (4, 32). They are living longer and thus developing NADMs. This also accounts for the moderate CD4 counts seen as opposed to lower counts in the AIDS range (32).However, this issue is controversial and Guiget et al maintain that as the CD4 drops, the risk for lung cancer increases(54).They observed that as the CD4 count dropped from >500 cell/µL to 350- 499 cell/µL – the risk doubled, and got worse as counts dropped further, thus suggesting a role for immune suppression(54). Limitations of the study & Recommendations Data regarding staging and smoking was incomplete and thus we were unable to demonstrate the true prevalence of each of these. The data collection time was short and didn't 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 causes of death and difference in survival between the 2 groups.

Allowing only patients with a histological diagnosis meant we were unable to determine

the true prevalence of lung cancer as many patients have positive cytology and they 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 specimens as they were diagnosed either by bronchoscopy (majority) or by pleural biopsy. It would be preferable to have a prospective study with follow up so we could evaluate the survival of patients between the 2 groups and assess for mode of death (whether malignancy related or other). CHAPTER 5 Conclusion Lung cancer presents in HIV positive patients at a younger age compared to 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 commonest histological sub-type of lung cancer amongst the general population, with SCC being slightly more common in the HIV positive population however due to small numbers and a lack of statistical significance we cannot be sure 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 the general population however we were unable to determine whether it is more common in the HIV positive lung cancer population due to a lack of data. The commonest presenting feature in both groups was a mass on chest radiograph while atelectasis was the 2nd most common and then pleural effusion. 1 4 5 6 7 8 9 10 11 12 13 14 16 17 21 22 23 24 25 27 28 30 31 32 33 34 35 36 37