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A comparison of the radiological features of lung cancer in HIV-infected and HIV-uninfected individuals in a South African hospital

Dr Andrew Nel

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

Johannesburg, 2018

DECLARATION

I, Andrew Nel, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Andrew Nel

On this 12th day of November 2018.

PUBLICATIONS AND PRESENTATIONS

This work has never been published.

It has never been presented at a congress.

ABSTRACT

INTRODUCTION:

Lung Cancer (LC) is one of the most important causes of death worldwide. With the increase in non-AIDS defining cancers, like LC, this is concerning in South Africa, with the country's high incidence of HIV.

AIM:

To correlate the CT features of LC with the histological / cytological diagnoses and compare these findings in HIV-infected and HIV-uninfected patients.

METHOD:

54 patients with lung lesions on CT, who had image-guided, biopsy-proven malignancies were retrospectively reviewed.

RESULTS:

The study population had a M:F ratio of 31:23, with 31.5% HIV-infected and a mean age of 59 years (SD±11). 85% had constitutional symptoms of LC and 59% had a smoking history. The most prevalent subtypes were squamous cell carcinoma (37%), adenocarcinoma (24.1%) and large cell carcinoma (24.1%). CT features were a mean axial lesion size anteroposterior of 67mm and transverse of 70mm, with an upper lobe predominance (76%). Other features were an irregular (70.4%), lobulated (55.6%) margin with pleural tags (61.1%) and spiculation (51.9%). Associated findings were CT significant mediastinal lymphadenopathy (77.8%), involvement of vessels or bronchi (68.5%), convergence of surrounding structures (64.8%), pleural effusion (55.6%) and secondary pulmonary lesions (51.9%). The HIV-infected patients had a mean age of 51 (SD±11) years

and a strong Tuberculosis history (60%). There was no statistical difference in the imaging features between the HIV-infected and HIV-uninfected patients.

CONCLUSION:

HIV-infected patients with LC present younger. Larger studies are needed to confirm whether this subgroup has more atypical lesions and need a different set of criteria for CT evaluation.

DEDICATION

To my wife, Elsmari, and my four children Alexander, Matthew, Heidi-Mari and Liviyah.


יְבָרֶכְךָ יְהוָה וְיִשְׁמְרֶךָ
יָאֵר יְהוָה פָּנָיו אֵלֶיךָ וִיחֻנֶּךָּ
יִשָּׂא יְהוָה פָּנָיו אֵלֶיךָ וְיָשֵׂם לְךָ שָׁלוֹם

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My family, Elsmari and our 4 children, Alexander, Matthew, Heidi-Mari and Liviyah, I want to thank for their support and motivation throughout the writing process. As well as their sacrifice of family time to enable me to complete this thesis.

Also, my supervisor, Prof Victor Mngomezulu and co-supervisor, Dr Jaishree Naidoo for their time, patience and advice. As well the staff of Tshepong Hospital Radiology Department, especially Dr Jacob Varghese and chief radiographer Alfa Williams, who supported me and helped me with the collection of my data.

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NOMENCLATURE

Malignant: Tumours that are cancerous and are made up of cells that grow out of control. Cells in these tumours can invade nearby tissues and spread to other parts of the body. These tumours may recur after attempted removal and are likely to cause death if not adequately treated (1, 2).

Benign: Benign refers to a tumour that is not cancerous, non-malignant, does not exhibit any of the malignant features mentioned above and is self-limiting (2).

Hounsfield Unit: The Hounsfield unit (HU) scale is a linear transformation of the original linear attenuation coefficient measurement into one in which the radio density of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU), while the radio density of air at STP is defined as -1000 HU (3).

Terminology related to the nodule/mass margin:

Well-defined: Refers to a sharp margin, with normal surrounding aerated lung (4). See figure A below.



Figure A Well-defined lung lesion with a sharp margin (4).

Smooth: The surface of the nodule is regular and even, with no perceptible lumps or projections (5).

Irregular: Refers to an uneven border, with either or blurred or jagged margins (5). See figure B below.

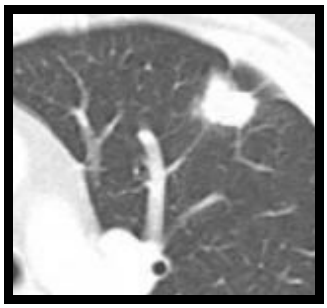


Figure B Lesion with an irregular margin, which is uneven and blurred (6).

Lobulated: Refers to an irregular nodule border, with specifically multiple rounded outpouchings or lobules (4), see figure C below.

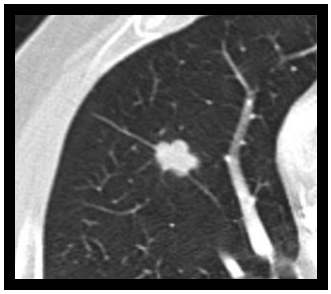


Figure C Lobulated lesion, with rounded outpouchings and lobules of the border(4).

Spiculation: The extension of malignant cells along anatomic structures in a radial manner, results in a spiculated-appearance of a lung lesion (6). See figure D below.

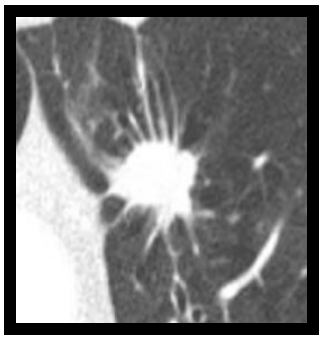


Figure D Spiculated lesion, with radial extension (6).

Pleural tag: Linear strands extending from the pleural surface to the nodule margin, due to thickening of interlobular septa (7), see figure E below.

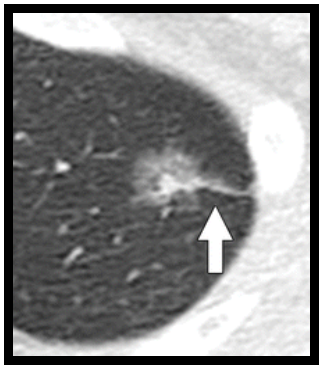


Figure E Lesion with strand extending from the pleural surface, i.e. pleural tag (7).

Terminology related to the internal features of the nodule/mass:

Homogeneous: A structure which is uniform in composition throughout, with similar components, including density and enhancement (8).

Air bronchogram: Air bronchogram refers to the phenomenon of air-filled bronchi (dark) being made visible by the opacification of surrounding alveoli (grey/white). It is almost always caused by a pathologic airspace/alveolar process, in which something other than air fills the alveoli. See figure F below (6).

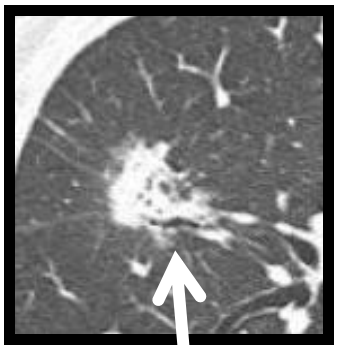


Figure F Air bronchogram, showing air-filled bronchi surrounded by opacified alveoli (6).

CT significant mediastinal lymph nodes:

In this study these were considered to be lymph nodes, of which the short axis measurement on axial views were greater than 10mm, irrespective of the post contrast enhancement pattern.

Pleural effusion: The accumulation of excess fluid in the pleural cavity. The pleural cavity is a potential space between the parietal and visceral pleura containing minimal lubricating fluid, see figure G below (9).



Figure G Excess fluid in the pleural cavity, i.e. a pleural effusion (9).

1. INTRODUCTION

1.1.Context of the study

Lung cancer (LC) was identified to be one of the most important causes of death worldwide by the World Health Organisation (WHO) (10). The Global Burden of Cancer Study (GLOBOCAN) reported that lung cancer was the leading cause of cancer-related death, accounting for 19.4% of deaths, a total of 1.6 million (11). In 2010 in South Africa, the LC rate was ranked 14th overall in men and women amongst the list of main causes of death, which translates into 6885 deaths annually (12). According to the most recent report from the South African National Cancer Registry (12) from 2013, LC was the 5th and the 8th most commonly histologically diagnosed cancer in men (1 766 cases) and women (923 cases), respectively. A study done by Winkler *et al.* (13) in 2014, attempted to use smoking prevalence data to predict the LC prevalence in South Africa in 2025. They predicted the mortality of LC in 2025 to be 3002 cases in men and 2407 cases in women per 100 000. Which is an increase from the 2010 numbers which were 2784 cases in men and 1813 cases in women, even with the stricter tobacco use laws in South Africa (13).

There has been an increase in non-AIDS-defining (non-acquired immune deficiency syndrome) cancers, amongst HIV (human immunodeficiency virus) infected persons (14), who have been found to have an especially high risk to develop LC (15, 16). According to UNAIDS (United Nations Programme on HIV and AIDS) (17), the country with the largest HIV epidemic in the world is South Africa, with 19% of the HIV-infected population of the world living in South Africa. In 2016, 7.1 million people in South Africa were living with HIV, with an adult HIV

prevalence of 18.9% (17). An early and accurate diagnoses is therefore paramount to assure the initiation of timely and effective treatment of these patients.

Five studies were found that compared the radiological findings of LC between HIV-infected and HIV-uninfected individuals (18 – 22), with a relatively small HIV-infected study population ranging from 15-30 patients.

In the past 40 years progress has been slow in terms of the treatment of LC, with only modest improvements of 4-5% in five-year survival rates for stage I-III disease and prolongation of months only for Stage IV disease (23). When early-stage surgery is combined with cytotoxic chemotherapy, the 5-year survival rate of non-small cell lung cancer (NSCLC) can be improved (23). A more detailed discussion on treatment of LC follows later.

Computed Tomography (CT) plays an important role in the imaging diagnoses of LC (24, 25). In most facilities CT remains the imaging modality of choice to stage LC, due to CTs ability to provide detailed information of the tumour and its extent. CT has its limitations, as it is not always a good predictor of extra-thoracic nodal spread. For this reason, the use of fluorodeoxyglucose positron emission tomography (FDG-PET) in combination with CT is preferred for nodal staging (24). CT furthermore helps guide decision making in terms of the appropriate method of tissue sampling for histology and plays a pivotal role in image guidance during biopsy (25).

1.2.The Research Problem

1.2.1. Primary Objective

- To describe the CT radiological features of malignant lung lesions according to the different histological/cytological diagnoses.

1.2.2. Secondary Objectives

- To describe the demographic features of patients with LC.
- To compare the CT radiological features, histological/cytological diagnoses and demography of HIV-infected and HIV-uninfected patients with malignancy.

1.3.Relevance of the study

Although many studies have been done on the CT radiological features of LC and the different histological subtypes, only 5 studies (18 – 22) were found that compared these between HIV-infected and uninfected patients. Furthermore, these studies have only had a very small HIV-infected subgroup compared to a much larger HIV-uninfected subgroup.

For this research project, we will be analysing a South African group of individuals with LC. In South Africa with its high HIV incidence, we hope to find more comparative numbers in the aforementioned subgroups to be able to determine whether there are significant differences between the two groups and therefore, whether HIV-infected individuals should be evaluated with a different set of criteria for CT.

2. LITERATURE REVIEW

2.1.Introduction

LC is abnormal cells with uncontrolled growth arising from the respiratory epithelium. These cells do not develop into normal healthy lung tissue or perform normal lung cell function. The normal function of the lung is to oxygenate the blood, but these abnormal cells proliferate into tumours that inhibit this function (1). Due to normal ageing or multiple environmental factors, as discussed later, mutations or errors in a cell's DNA occur. When a series of mutations have occurred cancer cells are formed.

In the past 40 years progress has been slow in terms of the treatment of LC with only modest improvements of 4-5% in five-year survival rates for stage I-III disease and for Stage IV, prolongation of months only (23). When early-stage surgery is combined with cytotoxic chemotherapy the 5-year survival rate of Non-small cell lung cancer (NSCLC) can be improved (23). A more detailed discussion on treatment of LC follows later.

2.2.Epidemiology of LC

According to GLOBOCAN 2012(11), LC was the most commonly diagnosed cancer, accounting for 13% (1.8 million) of cancer cases worldwide. In 2012 LC was the most common and the third most common cancer diagnosed in men and in women, respectively (10). The prevalence of LC in South Africa (SA) resembles that of the world, with LC also being one of the leading causes of cancer, and responsible for 17% of cancer-related deaths in the country (26). According to the most recent report from the South African National Cancer Registry (12) from 2013, LC was the 5th most commonly histologically diagnosed cancer in men (1 766

cases) and 8th most common in women (923 cases). The lifetime risk for LC in men was 1:76 and for women 1:205, in 2013(12). There are two main factors that influence the incidence and severity of LC and is discussed below.

2.2.1. Age

The incidence of LC is related to age, with older people having the highest incidence. Between 2013 and 2015, in the United Kingdom (UK), 4 out of 10 cases were diagnosed in individuals older than 75 years. At the age of 40 - 45 years, age-specific incidence rates rise steeply. In men, most cases of lung cancer were diagnosed between the ages of 85 to 89 years and in women, between 80 and 84 years of age (27).

In SA, age-specific incidence rates of LC show a steep rise from the age of 45 years for men, with most cases (19%) being diagnosed between the ages of 60 to 64 years. For women, a steep rise was noted from 50 - 54 years, with most cases (16%) diagnosed between the ages of 65 and 69 years (12).

2.2.2. Presenting symptoms

The diagnoses of LC is usually made in late stages of the disease, with a poor prognosis, especially in areas where a screening programme for at risk individuals is not present (28). Either the local tumour itself, local spread or distant metastases could be responsible for the symptoms. According to Latimer (28) dyspnoea and cough are the most common symptoms, with haemoptysis being the most specific. In 2005, in the UK, Hamilton *et al.* (29) found that dyspnoea, haemoptysis, loss of weight and appetite, cough, chest pain and fatigue, were

associated with LC. Dyspnoea and haemoptysis were found to be independently associated with LC, after excluding multiple variables.

2.2.3. Stage

Staging of a cancer is determined by the size and spread of the tumour. The Tumour-Node-Metastasis (TNM) staging system is used for these purposes, which is explained in more detail later. Data from the UK reported that 77% of LC cases were diagnosed at an advanced stage (Stage III or higher), and that most (55%) of the patients presented with Stage IV disease at the time of diagnoses (27).

2.3.Risk factors for LC

Major lifestyle and other risk factors are associated with LC in 89% of cases in the UK (30). It is well documented that cigarette smoking causes DNA damage (31) and thereby constitutes a significant risk factor for developing LC (1, 30, 32). Second-hand smoking, or passive smoking, is in itself also a risk factor for LC as it exposes one to the same toxins as when directly inhaling smoke (32).

Occupational exposure to asbestos, arsenic and coal in the mining industry, or the dust and fumes of nickel and chromium in the metal-working industry also increases the risk for LC (30). Other well documented (30, 32) risk factors include household radiation from the radioactive gas radon, which occurs naturally in the ground.

2.4.HIV

A literature review by Hou *et al.* (15) highlighted an increase in the risk of LC among the HIV-infected population compared to the general population. These authors (15), as well as Worm *et al.* (14) document that the introduction of highly active antiretroviral therapy (HAART) in 1996 has led to a prolonged survival of HIV-infected patients, with fewer deaths due to AIDS and AIDS-defining cancers, and more deaths related to non-AIDS-defining cancer.

Among the HIV-infected population, the most common non-AIDS-defining cancer appears to be LC (15, 18, 33). Furthermore, Sigel *et al*. (16), adjusted the LC incidence ratio rate (IRR), for age, gender, race, smoking prevalence, previous bacterial pneumonia, and COPD, and found a significant IRR of 1.7 for LC associated with HIV-infection, and therefore postulated that HIV could be an independent risk factor for LC (15, 16).

Although a direct effect of HIV on LC prognosis has not been established yet, many authors have tried to explain the reason for this phenomenon. Karp *et al.* (22) postulated that immunoregulation deficiencies could be blamed. An alteration in the first line of defence against spontaneously developing tumours, namely the activity of natural killer cells, could allow tumour cells to partially proliferate unchecked (22). This postulation is further supported by the fact that patients on immune-suppressing treatments are at increased risk to develop secondary malignancies (22). Other important factors in promoting LC in HIV-infected individuals include recurrent lung infections, the possible oncogenic role of HIV, and the HIV associated immunosuppression and decreased immune surveillance (18, 22). HIV is associated with more aggressive cancer behaviour, more advanced cancer stage, poor immune status and other opportunistic HIV-associated diseases. All of these factors add to

explain the poorer long-term LC survival rates of HIV-infected patients (14, 16). In 1993 Karp *et al.* (22) showed that the median survival for HIV-infected patients was much lower than for the control group of uninfected patients [4 weeks compared to 25.5 weeks] and in 2000 Bazot *et al.* (21) had similar findings. HIV-infected patients also present with more advanced disease, Stage IIIB or greater, in 53-100% of cases (19-22).

Numerous studies have found that HIV-infected patients with LC were younger, with a median age ranging from 38 - 48 years (18-22), compared to uninfected patients (median age ranging from 60.5 - 61 years) (19, 22). No association between CD4 cell count and LC could be found (15, 18, 20, 21). Adenocarcinoma was the most frequently found cell subtype of LC in HIV-infected individuals (30-87%) (18-22), and squamous cell cancer the second most frequent (28-30%) (18-21).

Five studies were found that compared the radiological findings of LC between HIV-infected and HIV-uninfected individuals (18-22), and these included a relatively small sample of HIV-infected patients ranging from 15-30 individuals. The mean size of the lesion in the HIV-infected population at diagnoses was found to be between 30mm (19) and 46mm (21). The tumours have been found to be more peripherally (60%-73%) situated, and have an upper lobe predominance (67-94%) (18, 19). HIV patients tend to have more pleural effusions, adenopathy and infiltrates on CT, at time of diagnoses (21, 22). The main reason for this may be due to these patients' increased risk for opportunistic infections such as tuberculosis (TB), pneumocystis jirovechii pneumonia and fungal infections (18, 19, 21). These CT changes could defer clinicians from suspecting LC in the younger population (18, 19) and appears not to be useful as a specific diagnostic criteria for LC in the HIV-infected (19). For the aforementioned

reasons it has been suggested that core biopsy of all persistent pulmonary lesions after antibiotic treatment in HIV-infected individuals should be performed to exclude possible LC (19, 21).

2.5.Management and treatment options for LC

Treatment of LC needs individualisation based upon the histological diagnoses and the stage of disease. Any combination of either surgery, chemotherapy or radiation, could be utilised in the treatment of LC (34).

Non-small cell lung cancer (NSLC) may be treated with surgery only, if the lesions are resectable and have not spread. Otherwise radiotherapy and/or a combination with chemotherapy can be used. As small cell lung cancer (SCLC) has usually metastasised by the time of diagnoses, primary surgery is not possible and it is mostly treated with chemotherapy. Radiotherapy can also be used in conjunction with chemotherapy (34).

Not all chemotherapeutic agents are equally effective to treat all subtypes of LC. Recent discoveries have changed the chemotherapeutic treatment of LC into a much more cell subtype-specific science than previously accepted, it is therefore paramount to distinguish the different histological subtypes of LC (23).

2.6.Staging

Staging of cancer is not only used to guide the management of the disease, but it also predicts the survival of the patient. Currently the 7th TNM (Tumour, nodal, metastasis)-staging system

for LC is being used. This is a system for which the use of CT is of utmost importance. Essentially the stage of the disease is determined by the tumour size, extent of nodal spread and the extent of metastasis. A summary of the staging system, compiled by UyBico *et al.* (35) can be viewed under appendix A.

Currently the International Association for the Study of Lung Cancer (IASLC) is busy reviewing the 7th TNM-staging system for LC. A subcommittee of the IASLC Staging and Prognostic Factors Committee has been tasked to develop proposals for the 8th edition TNM classification to address amongst other things, the challenge of LC patients who have more than one site of disease in their lungs. These patients were found to be difficult to classify under the current 7th TNM-staging system for LC (36). They found four patterns of disease and subsequently made specific suggestions for the application of the TNM classification rules, details of which is out of the scope of the current research project and will not be covered in this literature review.

2.7.Histological classification

Historically LC was divided into two major subtypes, namely SCLC and NSCLC. As a result of therapeutic breakthroughs, molecular revolution, and the advances in radiological, clinical, histologic and genetic aspects of LC management, the classification system was once again revised by the WHO in 2015 (37). The driving force behind the revision includes new genetic data with analyses of the alterations in LC genome. The principle of individualised genetics and medicine has changed the milieu of LC pathology and classification. The WHO (2015) LC classification now has divided the groups, with the major groups being adenocarcinoma, large

cell carcinoma, squamous cell carcinoma, neuroendocrine tumours and small cell carcinoma, with multiple changes within the subgroups of the classification, which is outside the scope of this review. These changes also have an effect on the TNM-staging of adenocarcinoma, as it is now classified as pre-invasive, minimally invasive, invasive and variants (38).

In South Africa, there is very little data about the current incidence of the different cell types of LC. The latest NCR report (2013) included no data on the incidence of the different cell types. A review by Koegelenberg *et al.* (39), suggested that squamous cell carcinoma was responsible for 50-60% of LC in South Africa in the 1980's. However, in 2011, the same author (39) conducted a study in the Western Cape at Tygerberg Hospital, which showed that adenocarcinoma has replaced squamous cell carcinoma as the most often histological diagnosed subtype. A review by Charloux *et al.* (40) in 1997, found that there was an increasing incidence of adenocarcinoma compared to squamous cell carcinoma worldwide, most likely due to changing smoking habits. A study based in Barcelona, Spain, in 2004 by Santoz-Martinez *et al.* (41), in contrast, still found squamous cell carcinoma to be the most common histological subtype, even with changing smoking habits.

2.8.CT Morphological Characteristics

CT can be used to establish a correct diagnoses of lung cancer in 66-98% of cases (25). The different histological subtypes of LC each have their own specific CT morphological features. An evaluation of the following features on CT can also be used to help differentiate between malignant and benign lung lesions. These are size, lesion borders, presence or absence of spiculation, calcifications, air bronchograms and pleural retraction. Also, arterial or venous

extension, the convergence of surrounding structures, mediastinal lymphadenopathy, pleural effusions and tumour location (25, 42, 43).

2.8.1 Malignant lung nodules

Research by Kocijančič *et al.* (25) in 2007 found that if nodules are smaller than 1 cm, the chances are almost 50% of being a benign nodule, while 97% of nodules larger than 3cm are malignant. They also reported calcification to be present in 40% of malignant lesions as well as air bronchograms in 40% of malignant lesions (25).

Dhopeswarkar *et al.* (43) reported a third of malignant lesions to have lobulated borders and spiculation to be indicative of malignancy in 90% of cases. They further found that 63% of cancers were found in the upper lobes and right lung cancers were 1.1 times more common than left (43). In summary, it does appear out of the literature that larger, spiculated lesions with calcifications and air bronchograms present in the upper lobes are more likely to be malignant.

2.8.2 Benign pulmonary nodules

Takanashi *et al.* (42) found that single pulmonary nodules, that were histologically proven to be benign, but demonstrated malignant features, were mostly due to inflammatory diseases, such as TB and pneumonia. These nodules presented mainly with ill-defined borders, but other features such as spiculation and air bronchograms were also found (42).

2.9.Biopsies

Leyden (44) first described percutaneous lung biopsy (PLB) in 1883, but image guided fine needle aspiration (FNA) of the lung was only widely accepted in the 1970's (25). The main indications for PLB are to obtain a histological diagnoses of pulmonary nodules or masses that have features suggestive of malignancy on CT and also to guide staging and help with treatment planning and initialisation (46, 47).

Authors report different diagnostic accuracy rates for CT-guided PLB. In 1985, Khouri *et al.* (47) reported an accuracy rate of 87,6% for benign lesions and 94,7% for malignant lesions. Whilst Arslan *et al.* (45), in 2002, stated an overall accuracy rate of 81,6%, of which a diagnoses was established in 88% of malignant lesions and only 34.3% of benign lesions. Kocijančič *et al.* (25), in 2007, found an overall accuracy rate of 93,2% for both benign and malignant lesions, with a 27,2% complication rate. Poulou *et al.* (48) reported an overall diagnostic yield of 96,6% for both benign and malignant lesions and a 9,7% complication rate in 2013. The complications of PLB include pneumothorax, pulmonary haemorrhage, haemoptysis, air embolism and tumor seeding (46, 48).

3. RESEARCH METHODS

3.1. Research paradigm

This study was descriptive in nature with a cross-sectional, retrospective and comparative angle. The study was based at the Tshepong hospital's radiology department in Klerksdorp, North-West province, South Africa.

3.2. Sample size and description

The study population included all patients, over a two year period (1 January 2012 to 31 December 2013), who presented to the Tshepong Hospital Radiology department, with suspicious lung lesions on CT, and who were subsequently sent for CT-guided FNA or core biopsy. The study population included all patients (that complied with the inclusion criteria), over a two year period (1 January 2012 to 31 December 2013), who presented to the Tshepong Hospital Radiology department, with suspicious lung lesions on CT, and who were subsequently sent for CT-guided FNA or core biopsy. All patients who presented to the CT department for a FNA or core biopsy of a lung lesion were identified in the CT register. These patients' hospital files were collected, and each patient was assigned a subject number to ensure anonymity. From the hospital file the demographic and clinical information and histology / cytology report were collected. If a patient's hospital file could not be traced, the demographic and clinical information was obtained through copies of the CT request form in the Radiology department's records, or from the histology / cytology report which includes some clinical history. The histology / cytology reports that could not be found in the hospital files were traced from the National Health Laboratory Service (NHLS) records. A total number of 54 patients, were included in this study.

3.2.1. Inclusion criteria

- All patients had to be 18 years and older.
- Patients should have had CT features of malignancy and were sent for CT guided FNA or core biopsy of these lung lesions.
- Patients whose biopsies or FNA's were histologically or cytologically found to be malignant.

3.2.2. Exclusion criteria

- Patients, whose original raw CT data, histology or cytology reports or clinical files could not be traced.

3.3. Data collection

3.3.1. Demographic and clinical information

Patient demographic and clinical data, as well as the histological or cytological diagnoses were captured on data capturing sheets (see attached Appendix B). This data capturing sheet consisted of the following demographic data: age, gender & HIV status. The following clinical data were included: presenting symptoms, occupational history and smoking history.

Age was collected as a continuous variable. Presenting symptoms included: dyspnoea, coughing and haemoptysis. Whether any of the presenting symptoms were present was recorded as a yes or no. If any of the following occupations were present, it was recorded as a yes or no: mining, metal industries, agricultural or other insecticide exposing industries and basic chemical industries. Most patients had undergone formal HIV testing and counselling

prior to the study, as part of their routine clinical work-up. HIV status was recorded as positive, negative or unknown. Smoking history was planned to be recorded in pack-years, however due to lack of detail in the patient file concerning pack-years, the presence of any smoking history, irrespective of duration, could only be recorded as a yes or no.

3.3.2. CT acquisition and review

All patients were scanned on the same CT scanner, a 16 slice Siemens Somaton Emotion helical CT scanner. The same scanning protocol was used for all patients. A pre-contrast phase was obtained and followed by a contrast-enhanced phase, obtained by infusion of 100ml of Omnipaque 300, administered at a rate of 3ml/sec. The scan was initiated 35seconds after the initiation of the contrast infusion. A slice thickness of 8mm was used with a reconstruction interval of 1,5mm. The raw CT data was loaded onto compact discs for repeated and safe use by the investigators. Two consultant radiologists and the principal investigator (PI) reviewed the chest CT scans. The PI underwent training by a consultant radiologist prior to reviewing the chest CTs. The radiologists used Apple computers (Cupertino, California, USA), loaded with OsiriX software (Geneva, Switzerland), which is validated for medical usage. Non-contrast as well as contrast-enhanced CT scans were reviewed for all patients, with a lung window setting (window width 1600 HU (Hounsfield Unit), window level -600 HU), and with a mediastinal window setting (window width 450 HU, window level 35HU). The CT reviewers were restricted to the axial images only.

The two consultant radiologist viewers were fully blinded to the demographic groups, clinical data, whether the lung lesions were biopsy-proven to be malignant or not and the final histological diagnoses.

The radiographic features data sheet (Appendix B) consisted of 13 specific radiographic features used to determine the malignant potential of a pulmonary lesion. The reviewers went through each chest CT individually and scored a positive (1) or negative (0) score to each of the 13 points. The radiographic features included: lesional margin (well-defined, smooth, lobulated, spiculated, pleural tag), internal features (homogeneous, presence of air bronchograms or calcification) and associated findings (pleural effusions, CT-significant mediastinal lymph nodes, convergence of surrounding structures, and involvement of vessels and bronchi). The criteria for inclusion as CT-significant mediastinal lymph nodes was a short axis diameter of more than 10mm in the axial plane, irrespective of the post contrast enhancement pattern.

The position, density, as well as maximum trans-axial size of the lesions, were also recorded by the reviewers. The position was recorded in terms of involvement of the five major lung lobes. Density was recorded in Hounsfield Units (HU) on both the non-contrast enhanced- as well as the contrast-enhanced CT scans. To ensure consistency between the three reviewers, a region of interest (ROI) with a diameter of 10mm, was drawn at the most central solid region of each lesion, to determine the density. The axial size, was recorded in mm, and the axial level where the lesion appeared to be at its largest, was used to get the maximum AP (anteroposterior) and transverse measurements, perpendicular to each other. It was recorded whether there were multiple lesions present, and in these cases the largest lesion was used to determine the radiographic features.

The data from the radiographic feature data sheet was compared to the histological / cytological diagnoses. The data was exported to a Microsoft Excel (Redmond, USA) spread

sheet for safe storage. Data of the three readers was collated by calculating the average value for measurements on Excel, and where yes or no answers were given, the answer with the two thirds majority was taken if there was any disagreement.

3.3.3. Core biopsy and FNA technique

Whether to perform core biopsy or FNA was a decision dependant on multiple factors, including size and position of the lesion, underlying lung disease and operator dependence. Needles used for core biopsy (14 to 18G[gauge]) collected a small tissue sample, which was sent in formalin for histological diagnoses. Needles used for FNA were smaller, usually 20G to 22G, and were used to collect cells which were fixed on glass slides sent for cytologic evaluation.

Patients were informed about the procedure and possible complications and informed consent obtained. Biochemical markers of patients, specifically platelets (>100), haemoglobin (>10 g/dl) & INR (International Normalised Ratio) (<1.5), were checked beforehand, and had to be within the values mentioned in brackets, before biopsy or FNA could be performed.

All the core biopsies or FNA's were performed using CT guidance on the same CT scanner (16 slice Siemens Somaton Emotion) used for the initial imaging, as mentioned above.

Positioning of the patient was determined by the patient's ability to tolerate the position, as well as the size and position of the lesion. After the patient position was established, the CT images were used to plan the access route. A local anaesthetic agent was administered at the onset of the procedure. Aseptic techniques were observed at all times.

The needle was then advanced incrementally through the chest wall, ensuring proper direction and angulation, before puncturing the pleura. The position of the needle was then confirmed with CT and if adequate, the core biopsy or FNA was performed.

A post-procedural chest radiograph was done, to rule-out any immediate complications, such as a pneumothorax, and the patients send to the ward for monitoring.

It was possible to extract data with regards to each of the demographic-, clinical-, radiological features and histological/cytological diagnoses to identify associations that might be present.

3.4. Reliability and validity

The chest CTs were reviewed by two qualified radiologists and the PI, who were given a specific set of criteria for each radiological feature of the lung lesions, to reduce inter-observer variability. Images were all viewed on the same monitor at constant ambient lighting at the same time of the day. A formalised set of radiographic features, with set definitions was made available to guide readers in their assessment of the chest CTs. Similar methods have previously been used and showed statistical significant results (42, 43).

3.5. Bias

This study population was based in a known mining area, which in itself is associated with higher incidence of LC, and there may therefore be a higher incidence of certain types of LC than in the general population. Furthermore, as the study population used for this study was

limited to a community in the North-West Province, it does not necessarily represent the total population of South Africa. Since this was a hospital based population, the HIV-infection rate was likely higher than in the general population.

All the patients included in the study had biopsy-proven malignancies, a fact that wasn't known to the 2 consultant radiologist reviewers, but however was known by the PI and could have introduced bias.

3.6. Data analysis and statistics

Descriptive analysis of the data was carried out as follows: Summaries of the percentage and frequency of categorical variables were done, and bar charts used to demonstrate these. summarised by frequency and percentage, and illustrated by means of bar charts. Depending on the normality, continuous variables were summarised as the mean and standard deviation or median and interquartile range. Histograms were used to demonstrate the distribution.

The association between the radiological morphological features of malignant lung lesions and the different histology/cytology diagnoses was determined using the Chi-squared (X^2) test. Fisher's exact test was used to determine statistical significance of the for 2 x 2 contingency tables or where the requisites for the X^2 test could not be met. Cramer's V and the phi coefficient, were respectively used to measure the strength of the associations. The following scale of interpretation was used to assess the association:

0.50 ≥	high/strong association
0.30 to 0.49	moderate association
0.10 to 0.29	weak association
0.10 ≤	little if any association

The association between categorical demographic, radiological and histological features, on the one hand, and HIV status of patients with malignancy, was also determined using the X^2 or Fisher's exact test, as described above. Continuous features were analysed using the t-test (or the non-parametric Wilcoxon rank sum test where the assumptions of the t-test were not met). Cohen's d was used to measure the effect size for parametric tests and the strength of the associations by Pearson's correlation coefficient (r-value) for the non-parametric tests. The following scale of interpretation was used:

0.80 ≥	large effect size / association
0.50 to 0.79	moderate effect size / association
0.20 to 0.49	small effect size / association
0.20 ≤	near zero effect size / association

SAS version 9.4 for Windows, was used to perform the data analysis. The 5% significance level was used ($p<0.05$).

3.7. Ethics

The Human Research Ethics Committee (HREC) at the University of the Witwatersrand, gave ethics approval. (Clearance certificate M151136 is attached as Appendix C). The CT Scans and core biopsies were performed with clinical indication, only. No additional radiographic procedures were performed. The anonymity of the participants was maintained.

Permission to collect the data was granted by the CEO of the Klerksdorp Tshepong Hospital complex, the Clinical manager of Tshepong Hospital, as well as the head of department of Radiology. These permission letters were presented to the HREC.

As this was a retrospective study, no consent from the patients was necessary to perform this study, and consent was only obtained from the relevant hospital management. No patient identifiers were accessed or used. Consent was also obtained from the two consultant radiologists that reviewed the CT scans.

3.8. Data safety

Each patient was assigned a case number that was used to identify the CT study, the demographic and clinic data and histological diagnoses, ensuring that data was collected anonymously. The key to this code was only available to the PI. The CT data was stored on compact discs that were handed over in person to the reviewers. All the hard copy data was kept in a safe by the PI. It was only removed when being reviewed for analysis. The supervisors only had access to the study data. The data was electronically encrypted to prevent access without authority.

4. RESULTS

Data was obtained from 54 patients during the time period of January 2012 to December 2013 from Tshepong Hospital in Klerksdorp, North-West Province. All of these patients had lung lesions as detected by CT and were either histologically- or cytologically-proven malignancy.

4.1. Demographics, clinical information, histological/cytological diagnoses and CT morphological features

The demographic and clinical data of the study population, the histological/cytological diagnoses and CT morphological features, which are all categorical variables, are summarised and graphically displayed using bar charts in the following tables and figures.

4.1.1. Demographic data

54 patients were included in this study. Male to Female ratio was 31:23. The ages ranged from 24 to 84 years, with a mean of 58.6 years (SD±11) and a median age of 59 years. The age distribution is shown below (Figure 4.1.). Seventeen (31.5%) of the patients were HIV-infected, of which 10 (59%) were on ARV's.

Table 4.1. Demographic characteristics of patients with lung lesions.

Variable	Category	N	%
Gender	Male	31	57.4
	Female	23	42.6
HIV status	Uninfected	33	61.1
	Infected	17	31.5
	Unknown	4	7.4
ARV status (if HIV-infected)	No	7	41.2
	Yes	10	58.8

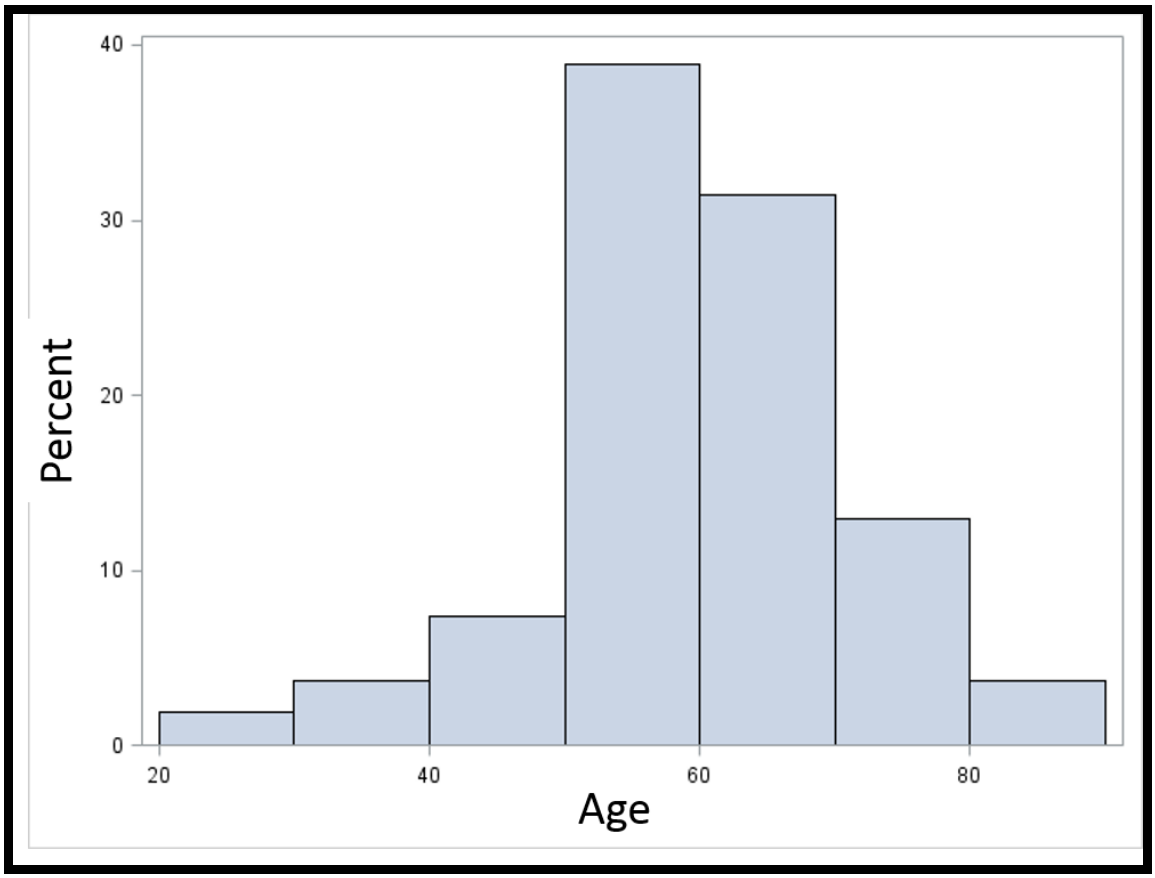


Figure 4.1. Age distribution of the study population

4.1.2. Clinical data

The most common presenting symptoms of LC (cough, dyspnoea or haemoptysis) were present in 46 (85.2%) of the patients. Eight (14.8%) had an occupational exposure history which was associated with LC. 32 (59.3%) had a smoking history and 12 (37%) a history of previous TB. The prevalence of each of the recorded clinical history factors are shown below (table 4.2.).

Table 4.2. Clinical characteristics of patients with LC.

Presenting symptoms	No	5	9.3
	Yes	46	85.2
	Unknown	3	5.6
Occupational history	No	38	70.4
	Yes	8	14.8
	Unknown	8	14.8
Smoking history	No	19	35.2
	Yes	32	59.3
	Unknown	3	5.6
TB history	No	37	68.5
	Yes	12	22.2
	Unknown	5	9.3

4.1.3. Histology and Cytology

Table 4.3. Descriptive analysis of the core biopsy and FNA findings of the study population.

Variable	Category	N	%
Biopsy type	FNA	24	44.4
	Core biopsy	30	55.6
Histological / cytological diagnoses	Large cell carcinoma	13	24.1
	Squamous cell carcinoma	20	37.0
	Adenocarcinoma	13	24.1
	Neuroendocrine tumours	4	7.4
	Malignancy present, cell type unknown	3	5.6
	Small cell carcinoma	1	1.9

Fifty six percent of the data were obtained from core biopsies; the remainder from FNA's. The most common cancers were squamous cell (37%), large cell (24%) and adenocarcinoma (24%).

4.1.4. CT morphological findings

Table 4.4. Descriptive analysis of the CT morphological findings of the study population.

Variable	Category	n	%
CT: Location	Right upper lobe (RUL)	20	37.0
	Right middle lobe (RML)	2	3.7
	Right lower lobe(RLL)	6	11.1
	Left upper lobe (LUL)	21	38.9
	Left lower lobe (LLL)	5	9.3
CT: Nodule margin	Irregular	38	70.4
	Pleural tag	33	61.1
	Lobulated	30	55.6
	Spiculated	28	51.9
	Well-defined	17	31.5
	Smooth	16	29.6
CT: Internal features	Air Bronchogram	15	27.8
	Calcification	15	27.8
	Homogeneous	10	18.5
CT: Associations	CT significant mediastinal lymph nodes	42	77.8
	Involvement of vessels/bronchi	37	68.5
	Convergence of surrounding structures	35	64.8
	Pleural effusions	30	55.6
	Multiple pulmonary lesions	28	51.9

The median AP diameter (max AP and max transverse) was 67mm (IQR 48-112mm) and 70mm (IQR 51-96mm), respectively. The distribution of the data is shown below (figure 4.2.A and B).

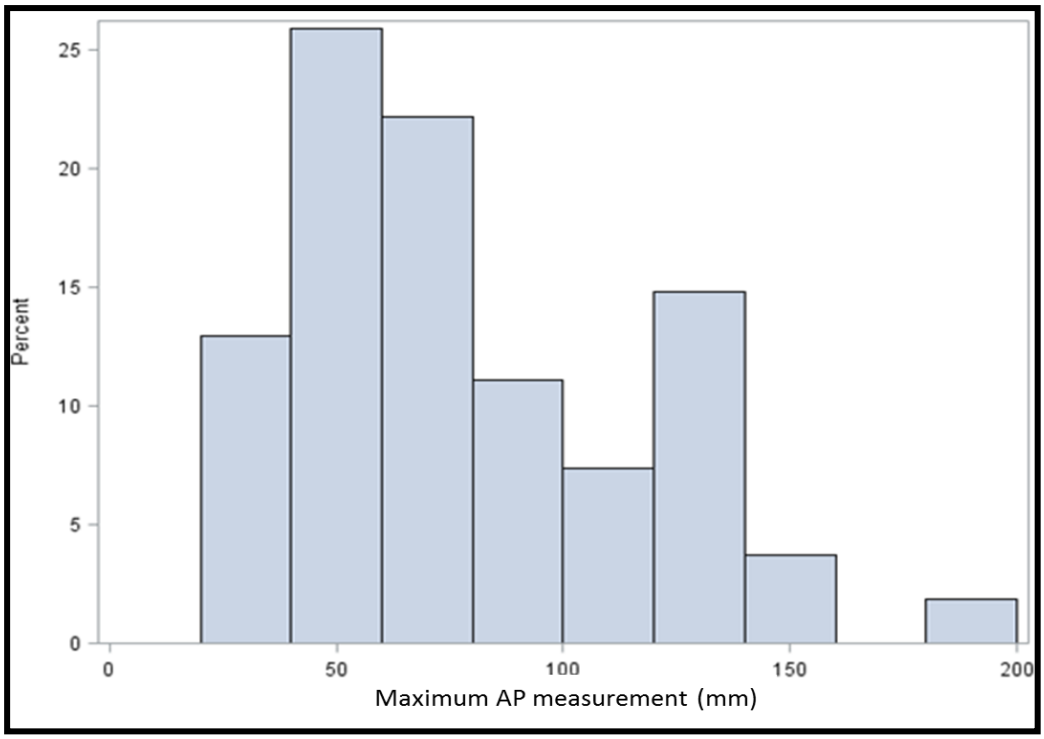


Figure 4.2.A Maximum axial AP measurement of the pulmonary lesions.

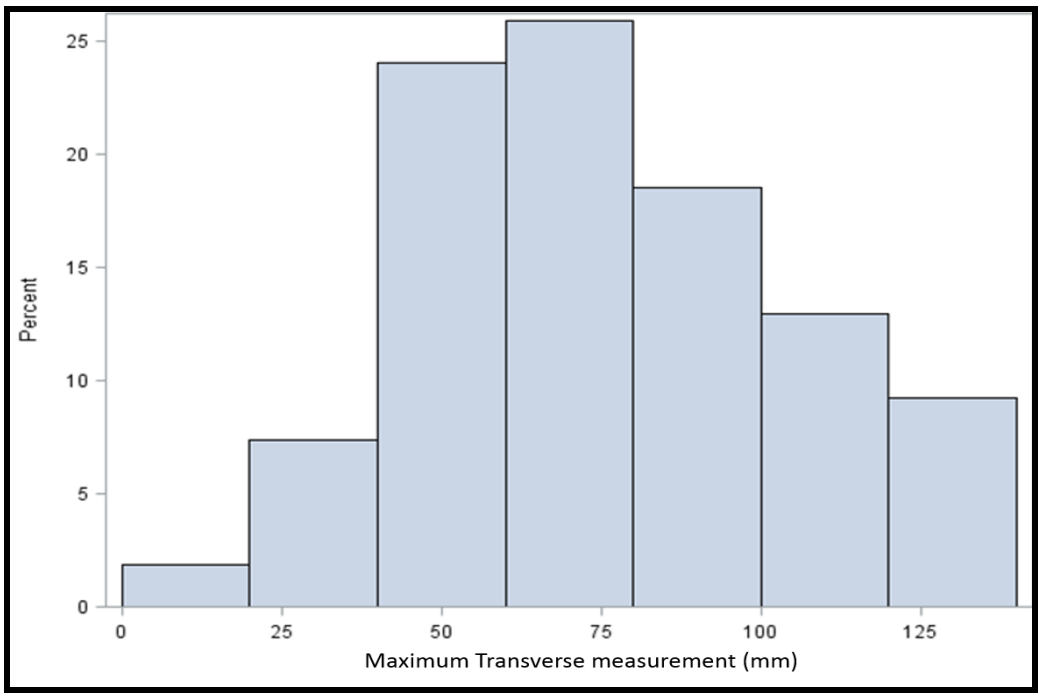


Figure 4.2.B Maximum axial transverse measurement of the pulmonary lesions.

The median density of the lesions was 30 HU (IQR 25-35) before the administration of intravenous contrast medium and 43 HU (IQR 37-56) after contrast administration. The distribution of the data is shown below (figure 4.3.A and B).

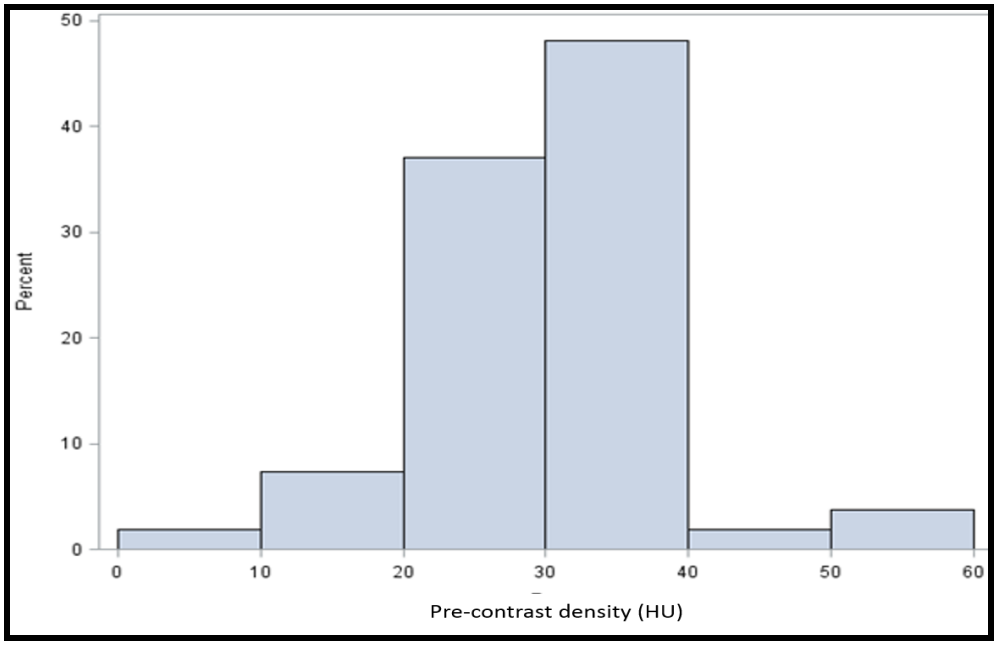


Figure 4.3.A Density of the pulmonary lesions before the administration of contrast

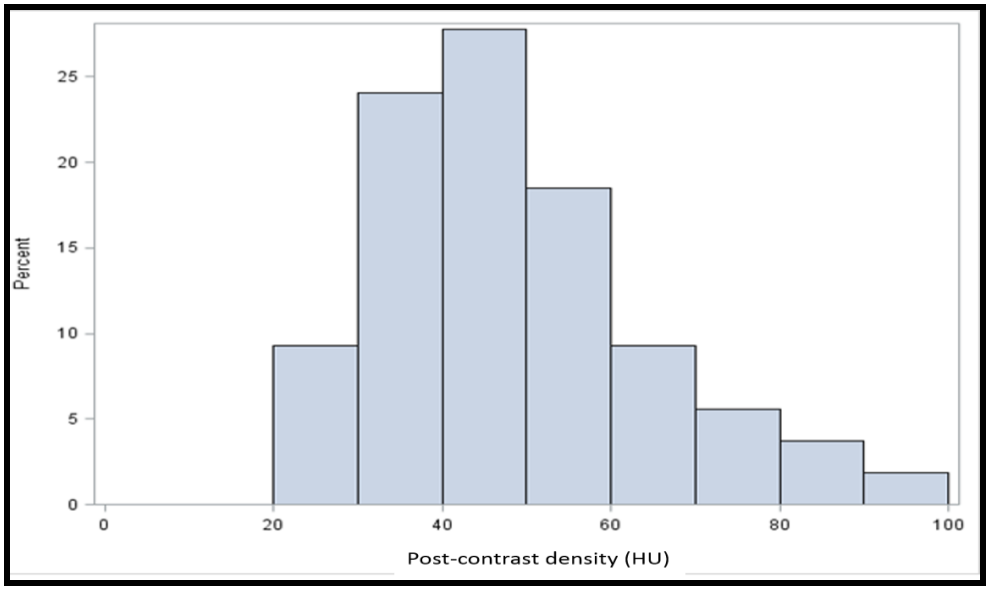


Figure 4.3.B Density of the pulmonary lesions after the administration of contrast

The most common margin features of the lesions were irregular margins (70%) and a pleural tag (61%). The most prevalent associations were the presence of CT significant mediastinal lymph nodes (77.8%) and the involvement of vessels and/or bronchi (68.5%). Since some lesions had more than one feature present for each of the above categories, the percentages for each of the above categories do not add to 100%.

4.2.Determination of associations using the Chi-square or Fisher's exact tests

4.2.1. The association between the radiological morphological features and the histological / cytological diagnoses

Only the three most common diagnoses (see histological / cytological diagnoses in Table 4.3.) were considered in this analysis since the group sizes of the other three diagnoses were too small for further analysis. The results are tabulated in table 4.5. There were no significant associations between any of the morphological features and the histological / cytological diagnoses.

Although some of the features, like the presence of a pleural tag, differed greatly between the specific LC subtypes, it was not statistically significant due to the small sample size of the study.

Table 4.5. The association between the radiological morphological features of malignant lung lesions and the histological / cytological diagnoses

Variable	Category	Overall		Histological / cytological diagnoses						p-value for between-group test
				Large cell Ca		Squamous cell Ca		Adenocarcinoma		
		n	%	n	%	N	%	N	%	
		46		13		20		13		
CT: Lesion margin	Irregular	34	73.9	11	84.6	15	75.0	8	61.5	0.40
	Pleural tag	28	60.9	5	38.5	14	70.0	9	69.2	0.15
	Lobulated	25	54.3	7	53.8	10	50.0	8	61.5	0.81
	Spiculated	22	47.8	6	46.2	10	50.0	6	46.2	0.97
	Well-defined	12	26.1	2	15.4	5	25.0	5	38.5	0.40
	Smooth	10	21.7	1	7.7	4	20.0	5	38.5	0.21
CT: Internal features	Air Bronchogram	13	28.3	4	30.8	6	30.0	3	23.1	>0.99
	Calcification	12	26.1	5	38.5	6	30.0	1	7.7	0.21
	Homogeneous	9	19.6	3	23.1	3	15.0	3	23.1	0.72

4.2.2. The association between the demographic, clinical, radiological and histological features, on the one hand, and HIV status, of patients with malignancy

Although it is standard practise for all inpatients at Tshepong hospital to undergo HIV testing, for four patients these results could not be traced. A possible reason is that Rapid HIV tests are done but are not logged on the laboratory system and if the test is negative, no further HIV related tests are done. For these 4 patients the original hospital files, where the result of the Rapid HIV test would have been documented, were lost. Their HIV status was also not documented with the other demographic and clinical data on the CT request form and histology / cytology reports, likely as they were HIV-uninfected. The four patients with unknown HIV status were excluded from the analysis.

Table 4.6. shows the tabulated results. The following significant differences between HIV-uninfected and –infected patients were found:

The mean age of the HIV-uninfected patients (63 years SD±9) was significantly higher than that of the HIV-infected patients (51 years SD±11); $p<0.0001$. The effect size was also large (Cohen's $d=1.3$).

There was a significant, strong, association between TB history and HIV status (Fisher's exact test; $p=0.0008$; phi coefficient=0.53). Ten percent (3/30) of the HIV-uninfected group had a TB history, compared to 60% (9/15) of the HIV-infected group.

Table 4.6. Comparison of the demographic and clinical features, histological / cytologocal diagnoses and CT morphological features of LC between HIV-infected and HIV-uninfected individuals.

Variable	Category	Overall		HIV status				p-value for between-group test
				Negative		Positive		
		N	%	N	%	N	%	
		50		33		17		
Gender	Male	30	60.0	19	57.6	11	64.7	0.76
	Female	20	40.0	14	42.4	6	35.3	
Presenting symptoms	No	4	8.0	4	12.1	0	0.0	0.29
	Yes	43	86.0	28	84.8	15	88.2	
	Unknown	3	6.0	1	3.0	2	11.8	
Occupational history	No	37	74.0	26	78.8	11	64.7	0.69
	Yes	8	16.0	5	15.2	3	17.6	
	Unknown	5	10.0	2	6.1	3	17.6	
Smoking history	No	18	36.0	14	42.4	4	23.5	0.21
	Yes	30	60.0	17	51.5	13	76.5	
	Unknown	2	4.0	2	6.1	0	0.0	
TB history	No	33	66.0	27	81.8	6	35.3	0.0008
	Yes	12	24.0	3	9.1	9	52.9	
	Unknown	5	10.0	3	9.1	2	11.8	
Biopsy type	FNA	22	44.0	15	45.5	7	41.2	>0.99
	Core biopsy	28	56.0	18	54.5	10	58.8	
Histological / cytological diagnoses	Large cell carcinoma	13	26.0	9	27.3	4	23.5	0.50
	Squamous cell carcinoma	18	36.0	10	30.3	8	47.1	
	Adenocarcinoma	12	24.0	9	27.3	3	17.6	
	Neuroendocrine tumours	3	6.0	3	9.1	0	0.0	
	Malignancy present, cell type unknown	3	6.0	1	3.0	2	11.8	
	Small Cell carcinoma	1	2.0	1	3.0	0	0.0	
CT: Location	RUL	18	36.0	11	33.3	7	41.2	0.76
	RML	2	4.0	2	6.1	0	0.0	0.54
	RLL	6	12.0	5	15.2	1	5.9	0.65
	LUL	19	38.0	11	33.3	8	47.1	0.37
	LLL	5	10.0	4	12.1	1	5.9	0.65
CT: Lesion margin	Irregular	35	70.0	25	75.8	10	58.8	0.33
	Pleural tag	32	64.0	21	63.6	11	64.7	>0.99
	Lobulated	26	52.0	17	51.5	9	52.9	>0.99
	Spiculated	27	54.0	21	63.6	6	35.3	0.076
	Well-defined	16	32.0	9	27.3	7	41.2	0.35
	Smooth	13	26.0	6	18.2	7	41.2	0.10
CT: Internal features	Air Bronchogram	15	30.0	8	24.2	7	41.2	0.33
	Calcification	15	30.0	9	27.3	6	35.3	0.75
	Homogeneous	9	18.0	6	18.2	3	17.6	>0.99
CT: Associations	CT significant mediastinal lymph nodes	39	78.0	25	75.8	14	82.4	0.73
	Involvement of vessels/bronchi	33	66.0	20	60.6	13	76.5	0.35
	Convergence of surrounding structures	31	62.0	21	63.6	10	58.8	0.77
	Pleural effusions	28	56.0	17	51.5	11	64.7	0.55
	Multiple pulmonary lesions	26	52.0	18	54.5	8	47.1	0.77

5. DISCUSSION

5.1. Introduction

This chapter discusses the results of the research that were presented in the previous chapter. These are viewed in conjunction with the literature review in an attempt to prove and validate the research propositions.

An analysis was done on the findings of 54 patients with CT detected lung lesions that were proven to be malignant by either core biopsy or fine needle aspiration. We looked at the study population's demographic composition, as well as each patient's clinical history, the histological / cytological subtype of the LC and the CT morphological characteristics. An analysis was also done on the association between the radiological morphological features of malignant lung lesions and the histological / cytological diagnoses. Finally, we looked at the association between the demographic, radiological and histological features, on the one hand, and HIV status of patients with malignancy on the other hand.

The major statistically significant findings were that 59% of the study population had a smoking history, an upper lobe predominance of 76% (LUL – 39%) was present and the mean age of the HIV-uninfected patients (63 years SD±9) was significantly higher than that of the HIV-infected patients (51 years SD±11), with a large effect size (Cohen's d=1.3). Also, there was a significant association between HIV status and TB History (p=0.0008;) with a positive TB history in 60% (9/15) of the HIV-infected group.

5.2.Results in context

5.2.1. Demographics

The mean age of the study population was 59 (SD±11; range 24-84 years), which compared well with data from the 2013 National Cancer Registry which found that most LC's were diagnosed in men aged between 60 to 64 years and women aged between 65 and 69 years (12). Kocijančič and co-workers (25) as well as Poulou *et al.* (48), who investigated a Greece-based study population in 2013, together with Takanashi *et al.* (42), who in 1995 studied a Japanese population, had similar findings with a median age ranging from 60.5 – 66.4 years in their respective studied populations.

In the current study, there was no significant gender predominance (57% of the patients were male) which is to a certain extent in accordance with the literature showing a wide variation in gender prevalence and a male predominance ranging from 56% to 75% (25, 42, 48).

Seventeen (31.5%) of the patients were HIV-infected, which is higher than the provincial (13.3%) (49) and national (18.9%) (17) HIV prevalence in the adult population. The reason for this difference is most likely that our population was a hospital-based population group, which tends to have a higher HIV prevalence, as HIV-infected patients are more frequently diseased and require hospital admission than the general population. The percentage of HIV-infected patients receiving ARV's (59%), was similar to the national average of 56% for adults (17).

5.2.2. Clinical history

Eighty-five percent of patients presented with at least one of the most common presenting symptoms of LC, which was either or a cough, dyspnoea or haemoptysis. This finding was in keeping with the literature, as Latimer and Hamilton *et al.* (28, 29) similarly found these not only to be the most common symptoms of LC, but also that specifically dyspnoea and haemoptysis were independently associated with LC, and haemoptysis to be the most specific symptom. Five (9.3%) of the patients presented with other symptoms, such as new onset of seizures. These patients were initially found to have brain metastases on CT of the brain and had then under gone other radiological examinations (such as chest X-ray, abdominal sonar and later a chest CT) to locate the primary cancer. Due to a lack of detail in the patient files in specifying the specific symptom/s that the patient experienced, three (5.6%) of the patients initial presenting symptoms were unknown (these patients were however included in the study, as the rest of the relevant data was available).

A positive smoking history, a well-documented risk factor (1, 30, 32, 50) for LC, was present in 59% of the patients. Unfortunately, a more quantitative smoking history in terms of pack-years could not be made as this was not documented in the patient files. Considering the diagnoses of LC, this was relevant patient history and should have been recorded and can thus be seen as a limitation of the current study.

Occupational history (i.e. mining history, metal industry, basic chemical industry, agricultural or other insecticide exposing industry) was documented in 14.8% of patients. This was an unexpectedly low percentage since the region where the study population came from is well-

known for gold mining, and the surrounding area covers one of the biggest maize farming regions in South Africa, with a suspected high exposure to insecticides. No apparent reason for this finding could be determined from the available data.

A positive TB history was present in 12 (24%) of the patients, with a significantly higher percentage in the HIV-infected (52.9%) versus the HIV-uninfected (9.1%) (P = 0.0008) subgroup. This was an expected finding, as South Africa is known as one of the countries with the highest TB prevalence in the world (ranked sixth among the 22 high burden TB countries) (51). Also it has been shown that 60% of HIV-infected patients have TB as a co-infection (49).

5.2.3. Histology and cytology

A core biopsy was used in 56% of the cases to make a definitive histological diagnoses. Six histological / cytological LC subtype groups were diagnosed. The three most prevalent cancers were squamous cell carcinoma (n=18, 36%), large cell carcinoma (n=13, 26%), and adenocarcinoma (n=12, 24%).

The above mentioned findings are in contrast to the phenomenon seen worldwide, where adenocarcinoma has surpassed squamous cell carcinoma as the most commonly diagnosed histological subtype. This was similarly found by Koegelenberg *et al.* (39) and Nanguzgambo *et al.* (52) in 2011 in the Western Cape.

In our study there was no real significant difference between the prevalence of squamous cell carcinoma (30.3%) and adenocarcinoma (27.3%) in the HIV-uninfected group, compared to the HIV-infected subgroup, where there was a significant difference

[squamous cell carcinoma (47.1%) and adenocarcinoma (17.6%)]. Our results may therefore have been influenced by the high prevalence of HIV (31.5%) in our study population, although no statistically significant conclusions could be made.

It has been postulated that the reason why adenocarcinoma has become more prevalent worldwide is due to technical- (routine use of immunohistochemistry in the diagnostic process) and smoking-related factors. The last-mentioned factors include the improved awareness of the risk of tobacco products, with a resultant lower incidence of smoking. Also, that the use of filter tips and improved tobacco blends in cigarettes have decreased the amount of tar and nicotine inhaled whilst smoking (39, 50, 52).

A positive TB history was found in 60% of the HIV-infected patients. As TB is well known for scarring of the lung parenchyma, one would expect adenocarcinoma to be much more prevalent in the HIV-infected subgroup as adenocarcinoma has been found to be the most prevalent cell type in scar carcinomas (53, 54).

The question that now needs to be asked is why squamous cell carcinoma was much more prevalent under the HIV-infected group, and not adenocarcinoma as one would suspect? The prevalence of post-TB scar tissue did not form part of this study. The smoking-related factors, mentioned above, which were postulated to have an influence on the decline in squamous cell carcinoma in Europe, might not have had the same effect in South Africa. In South Africa with a significantly poorer general population than the average European country, cheaper brand cigarettes are smoked, which do not necessarily have the ''healthier'' tobacco blend or use more advanced filter tips. Also, in poorer communities, it

is a known practice to make hand-rolled cigarettes from tobacco and newspaper. It has been postulated that HIV-infected individuals display more high-risk behaviour and engage in detrimental lifestyle activities, including a higher incidence of smoking (in our study 76.5% of HIV-infected patients had a smoking history, compared to 51.5% in the HIV-uninfected group). Could the difference in tobacco use be responsible for the continuing high prevalence of squamous cell carcinoma in HIV-infected patients, or are other factors related directly to HIV to blame?

Factors that relate directly to HIV could include recurrent lung infections, the possible oncogenic role of HIV, and the HIV associated immunosuppression and decreased immune surveillance (22). Karp *et al.* (22) postulated that immunoregulation deficiencies could be blamed, due to an alteration in the activity of natural killer cells, that then allow tumour cells to proliferate unchecked, supported by the fact that patients on immune-suppressing treatments are at increased risk to develop secondary malignancies. However, these factors would likely not predispose to the development of squamous cell carcinoma alone, but rather all subtypes of lung cancer.

Larger studies, with more detailed examination of the demographics and relevant clinical histories of HIV-infected patients with LC, need to be done, to determine causal factors more accurately.

5.2.4. CT morphological features and the association with the histological / cytological diagnoses

Most (76%) of the LC were found to be in the upper lobes, with 39% in the left upper lobe. This upper lobe predominance is a trend found throughout the literature, with Dhopeswarkar *et al.* (43) and Poulou *et al.* (48), also reporting an upper lobe predominance. They also found no significant difference between left upper lobe and right upper lobe incidence, with right upper lobe cancers being 1.1 times (43) more common.

On average, the lesions were large on presentation, with a median transverse diameter of 70mm (IQR 51-96mm, range 18-122mm) and a median AP (anteroposterior) diameter of 67mm (IQR 48-112mm, range 21-194mm) on axial views. Most of the lesions were thus classified as masses and not nodules, as they were larger than 30mm on axial views. The lesions in this study were much larger on diagnoses than those found in other studies. In a large study (1000 cases) conducted by Poulou and co-workers (48), the mean maximal diameter was found to be only 37mm, where Kocijančič *et al.* (25) found it to be even smaller at 23mm. This finding is concerning in the light of the results of Kocijančič *et al.* (25), who found that 97% of cases with lesions larger than 30mm, were malignant.

The median pre-contrast density of the lesions were 30 HU (IQR 25-35, range 7-53) and increased post-contrast to 43 HU (IQR 37-56, range 23-95), demonstrating that these lung cancers did not have significant contrast uptake.

As previously discussed, the three most prevalent LC histologic subtypes were squamous cell carcinoma (36%), large cell carcinoma (26%) and adenocarcinoma (24%). The other subtypes

totalled 14%, and due to their small prevalence, they were not considered for this analysis. Only the radiological features that stood out will be highlighted here.

An irregular margin was a very common finding in all three histological types. Takanashi *et al.* (42) similarly found an irregular margin to be a very common finding in all the histological subtypes in their study. Takanashi et al also found spiculation to be present in most squamous cell carcinomas (75%) as well as adenocarcinomas (63%), as did our study, although for both squamous cell carcinoma (50%) and adenocarcinomas (46.2%), these findings were less frequent.

Pleural tags were an especially common finding in squamous cell carcinomas (70%) and adenocarcinomas (69.2%), compared to large cell carcinomas (38.5%). Wang *et al.* (55) and Takanashi *et al.* (42) on the other hand, found pleural tags to be frequent in adenocarcinomas only.

We found air bronchograms to be an almost equally frequent finding in all 3 histological subtypes (squamous cell carcinoma (30%), adenocarcinomas (23.1%), and large cell carcinoma (30.8%), whereas Takanashi *et al.* (42), found it to be significantly more frequent in adenocarcinomas (53%). Wang (55) in their small study, also found it to be present only in adenocarcinomas.

Again, the question could be asked if the effect of HIV on tumour growth (as previously discussed in section 5.2.3.) could be responsible for potentially ‘’abnormal’’ growth of the different histological subtypes of LC and cause findings such as air bronchograms and pleural

tags to be present in almost all of the subtypes, as opposed to specific subtypes as demonstrated by other authors. Could this also be the reason why these lesions were significantly larger at the time of presentation, than those found in other studies?

Overall, calcifications were present in 26.1% of cases, and were a more frequent finding in large cell carcinoma (38.5%) and squamous cell carcinoma (30%), compared to adenocarcinomas (7.7%). A study done by Mahoney *et al.* (56) in 1990, that specifically looked at the presence of calcification in LC, found that only 6% of LC cases had calcifications present. They found a minimal difference in the frequency of calcifications between the different histologic types. This posed the question as to why nearly up to a quarter of cases in our study had calcifications. With 31.5% of our patients being HIV-infected (with an increased propensity to recurrent infections as previously stated) and a positive TB history present in 22.2% of our patients, we would like to postulate that previous recurrent lung infection and TB could be the cause for the higher rates of calcifications seen.

Our results implied that there wasn't a specific CT finding to distinguish between the different LC subtypes. The following findings did however appear as if they could be statistically significant if a much larger study population was evaluated. These are the presence of pleural tags (not commonly found in large cell carcinomas [p-value for between-group test of 0.15]), well-defined and smooth margins (more common in adenocarcinomas [between group test p-value of 0.4 and 0.21 respectively]) and calcifications (less prevalent in adenocarcinomas [between group test p-value = 0.21]). The presence of cavitation in squamous cell carcinoma is a well-documented finding (55, 57, 58) and although not evaluated for in our study, it should be added to this list as well.

CT-significant mediastinal lymph nodes, as previously defined, were found to be present in 77.8% of cases. This is another finding indicating that the study population presented at a very late stage, where metastatic disease to the mediastinal lymph nodes were already present. A large percentage (68.5%) of cases had involvement of vessels or bronchi, which could be responsible for symptoms such as haemoptysis or coughing. This derivation correlates well with our results showing that 85% of patients presented with symptoms, such as coughing or haemoptysis. Other findings such as the convergence of surrounding structures (64.8%), pleural effusions (55.6%) and multiple pulmonary lesions (51.9%) were significant and compared well with the literature who found the presence of these features to be helpful to differentiate malignant from benign lesions on CT (25, 42, 43).

5.2.5. Comparison of HIV-infected and HIV-uninfected patients with lung cancer.

A few of the differences between the HIV-infected and HIV-uninfected subgroups have already been highlighted in some of the previous sections. The most significant differences (age and TB history) will be highlighted here. As mentioned four patients' HIV status were unknown and were excluded from this analysis (n=50).

The most statistically significant difference between these groups was that the mean age of the HIV-infected patients, 51 years (SD±11) was less than the HIV-uninfected population of 63 years (SD±9), with a large effect size (Cohen's d=1.3). Other studies have similarly found that HIV-infected patients present at a younger age than the general population, and at an even younger median age than what we found. Lavolé *et al.* (59) in 2006 found a mean age of

presentation to be 45 years in the HIV-infected population. A literature review by Winstone *et al.* (60) in 2013 also found that the mean age of onset of LC was 25 to 30 years earlier in HIV-infected individuals.

There was also a significant, strong association between TB history and HIV status (p=0.0008; phi coefficient=0.53). Only 10% of the HIV-uninfected group had a TB history, compared to 60% of the HIV-infected group. This was an expected finding due to the well-known association of HIV and TB, as well as the high prevalence of both HIV and TB in South Africa (51).

A literature review by Mani *et al.* (18), reported an increased smoking history in HIV-infected patients compared to the general population, with some studies showing a positive history in 85-99% of cases. Similarly, we found a positive smoking history to be more prevalent in the HIV-infected group (76.5%) compared to the HIV-uninfected group (51.5%) (p-value =0.21). Burkhalter et al. (61) also reported a high prevalence of tobacco use (19% former smokers and two-thirds current smokers), in a cohort of HIV-infected patients with a low income. They also postulated that emotional distress, drug use and pain have an impact on HIV-infected individuals' smoking status. However, not just the increased prevalence of smoking, but also multiple other factors play a role in the increased prevalence of LC among HIV-infected groups, as mentioned earlier.

As previously discussed, contrary to literature (16, 19, 22) we did not find adenocarcinoma (17.6%) to be the most prevalent LC subtype under the HIV-infected subgroup, but rather squamous cell carcinoma (47%).

The HIV-infected subgroup's margins were more well-defined (HIV-infected 41.2%, and -uninfected 27.3%, p-value= 0.35) and smooth (HIV-infected 41.2%, and -uninfected 18.2%, p-value = 0.1), with less spiculation (HIV-infected 35.3%, and -uninfected 63.6%, p-value = 0.076) compared to the HIV-uninfected group. As mentioned in section 5.2.4. air bronchograms and calcifications were also more common among the HIV-infected subgroup. Associated findings such as the involvement of vessels or bronchi (HIV-infected 76.5%, and -uninfected 60.6%, p-value = 0.35) and the presence of pleural effusions (HIV-infected 64.7%, and -uninfected 51.5%, p-value = 0.55) were also more prevalent under the HIV-infected subgroup. As previously discussed, could the effect of HIV on tumour growth and the presence of recurrent infections be responsible for these differing morphological features? Larger, prospective studies looking at the growth patterns will have to be done, to answer this question.

5.3.Limitations of the current study

Due to the retrospective nature of the study, more specific demographic and clinical information concerning the study population couldn't be established, as these details couldn't be traced in the patient files. Clinical details such as smoking history could only be a positive or negative value and not a quantitative value such as pack-years, due to lack of available data. This was similar for occupational history and presenting symptoms.

This study was limited by the small study population, which deterred it from having more statistically significant results. Although 31.5% of the study population were HIV-infected, the number of patients weren't enough to be able to draw many statistically significant

conclusions. Similarly, although there were only three major LC histological subtypes, no definitive conclusions could be made with regards to the CT morphological features of these subtypes.

5.4. Suggestions for future research

Out of the available data, it appeared as if there could be more statistically significant differences between the HIV-infected and -uninfected subgroups. Prospective studies with larger study populations are needed to confirm if there are any significant differences, and whether HIV-infected patients with lung lesions should be evaluated with a different set of criteria to determine malignancy.

Specific points which could be confirmed with larger studies are:

- The most prevalent histological subtype of LC in the HIV-infected population.
- Why the specific cell subtype is the most prevalent in HIV-infected individuals.
- Whether there is a statistically significant difference in the CT morphological appearance of LC in the HIV-infected population compared to the HIV-uninfected population. (Such as more well-defined, smooth margins with less spiculation and the presence of calcifications and air bronchograms.)
- If a significant difference could be found in the morphological appearance, how does HIV affect the growth of LC to account for this.

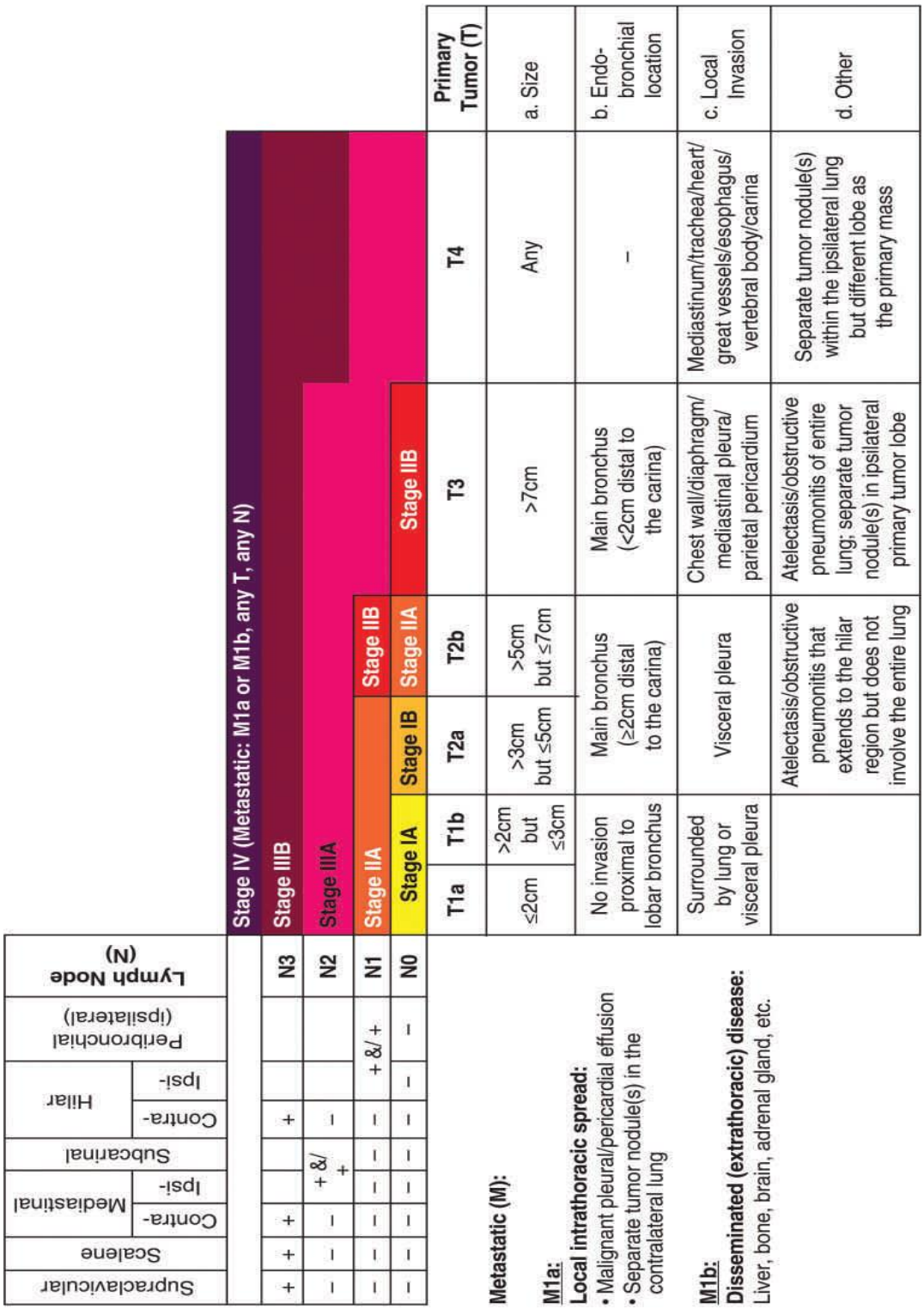
6. CONCLUSION

Many international and local studies have been done to determine the CT morphological features of LC, but only a handful investigated the effect of HIV on the radiographic features of LC. This research study makes a contribution by showing that there are differences between the CT appearances of LC in the general population compared to HIV-infected population.

Similar to other literature we found that HIV-infected patients with LC presented at a younger age, (10 years younger) than the general population. In contrast to the literature, which has found adenocarcinoma to be the more prevalent LC histological subtype, we found squamous cell carcinoma to be more prevalent, especially in the HIV-infected subgroup. Other contrasting findings, especially among the HIV-infected subgroup, were larger lesions and a higher percentage of lesions with well-defined, smooth margins with less spiculation as well as the presence of calcifications and air bronchograms, suggesting that HIV itself may have a direct impact on the growth rate and pattern of LC. This poses the question of whether HIV-infected patients with lung lesions should be evaluated with a different set of criteria than HIV-uninfected patients to detect malignancy earlier and more effectively. Larger studies need to be done to confirm these assumptions.

APPENDIX A: TNM STAGING

A summary of the 7th TNM or Tumour, nodal, metastasis-staging system for LC, compiled by UyBico *et al.* (35) follows below.



APPENDIX B: DATA COLLECTION SHEETS

Demographic and clinical data tick sheet			Case nr	
Age				
Gender	Male	Female		
HIV Status	Uninfected	Infected	Unknown	
ARV's (if HIV-infected)	No	Yes		
Presenting Symptoms (cough, dyspnoea, haemoptysis)	No	Yes		
Occupational history (mining, metal industries, agricultural or other insecticide exposing industries and basic chemical industries)	No	Yes		
Smoking History (Any)	No	Yes		
TB History	No	Yes		
Final histological / cytological diagnoses				

CT Review Tick sheet Case nr

Location

-

-

RUL	RML	RLL

LUL	LLL

Axial diameter

-

Max AP	Max Tranverse

Density (Hounsfield units)

Pre-	Post-contrast

Nodule margin

	No	Yes
Well defined		
Smooth		
Irregular		
Lobulated		
Spiculated		
Pleural tag		

Internal features

	No	Yes
Homogeneous		
Air bronchogram		
Calcification		

Associations

	No	Yes
CT significant mediastinal lymph nodes (>10mm in short axis)		
Pleural effusions		
Convergence of surrounding structures		
Involvement of vessels and bronchi		

APPENDIX C: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Andrew Nel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151136

NAME: (Principal Investigator)	Dr Andrew Nel
DEPARTMENT:	Radiology Tshepong Hospital, Klerksdorp, North West
PROJECT TITLE:	An Analysis of Biopsy Findings in Patients with Computer Tomography Detected Lung Lesions in a South African Hospital
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Victor Mngomezulu and Dr Jaishree Naidoo
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/11/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 01/12/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

7. REFERENCES

1) Lungcancer.org. 2015. Lung Cancer 101. Available: http://www.lungcancer.org/find_information/publications/163-lung_cancer_101/265-what_is_lung_cancer [Accessed on 12 August 2015]
2) National Cancer Institute. 2018. NCI Dictionary of Cancer Terms. Available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/benign-tumor [Accessed on 15 June 2018]
3) Radiopaedia.org. 2018. Hounsfield Unit. Available: https://radiopaedia.org/articles/hounsfield unit [Accessed on 24 June 2018]
4) Choromanska, A., Macura, KJ. 2012. Evaluation of solitary pulmonary nodule detected during computed tomography examination. *Polish Journal of Radiology*., 77(2):22-34.
5) Radiopaedia.org. 2018. Pulmonary Nodule. Available: https://radiopaedia.org/articles/pulmonary-nodule-1 [Accessed on 24 June 2018]
6) Radiology Assistant. 2007. Solitary pulmonary nodule: Benign versus malignant. Available: http://www.radiologyassistant.nl/en/p460f9fcd50637/solitary-pulmonary-nodule-benign-versus-malignant.html [Accessed on 24 June 2018]
7) Hsu, J.S., Han, I.T., Tsai, T.H., *et al*. 2016. Pleural Tags on CT Scans to Predict Visceral Pleural Invasion of Non-Small Cell Lung Cancer That Does Not Abut the Pleura. *Radiology*., 279(2):590-6.
8) Radiopaedia.org. 2018. Heterogeneous vs heterogenous. Available: https://radiopaedia.org/articles/heterogeneous-vs-heterogenous [Accessed on 24 June 2018]

9) Radiopaedia.org. 2018. Pleural effusion. Available: https://radiopaedia.org/articles/pleural-effusion [Accessed on 24 June 2018]

10) World Health Organisation. 2015. Cancer Fact Sheet. Available: http://www.who.int/mediacentre/factsheets/fs297/en/ [Accessed on 1 March 2015]

11) International Agency for Research on Cancer (IARC). 2012. GLOBOCAN 2012: Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Available: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx [Accessed on 30 March 2016]

12) National Institute for Occupational Health. 2013. National Cancer Registry, Cancer in South Africa, 2013, Full report. Available: http://www.nioh.ac.za/wp-content/uploads/2018/03/2013NCR.pdf [Accessed on 17 June 2018]

13) Winkler, V., Mangolo, N.J., Becher, H. 2015. Lung cancer in South Africa: a forecast to 2025 based on smoking prevalence data. BMJ Open., 5(3):e006993.

14) Worm, S.W., Bower, M., Reiss, P., *et al.* 2013. Non-AIDS defining cancers in the D:A:D Study-time trends and predictors of survival: a cohort study. *BMC Infectious Diseases*., 13:471.

15) Hou, W., Fu, J., Ge, Y., *et al*. 2013. Incidence and risk of lung cancer in HIV-infected patients. *Journal of Cancer Research and Clinical Oncology.*, 139(11):1781-94.

16) Sigel, K., Crothers, K., Dubrow, R., *et al*. 2013. Prognosis in HIV-infected patients with non-small cell lung cancer. *British Journal of Cancer*., 109(7):1974-80.

17) United Nations Programme on HIV and AIDS (UNAIDS). 2018. Country factsheets, South Africa 2016. Available: http://www.unaids.org/en/regionscountries/countries/southafrica [Accessed on 17 June]

18) Mani, D., Haigentz, M. Jr., Aboulafia, D.M. 2012. Lung cancer in HIV Infection. *Clinical Lung Cancer.*, 13(1):6-13.

19) Fishman, J.E., Schwartz, D.S., Sais, G.J., *et al*. 1995. Bronchogenic carcinoma in HIV-positive patients: findings on chest radiographs and CT scans. *American Journal of Roentgenology.*, 164(1):57-61.

20) White, C.S., Haramati, L.B., Elder, K.H., *et al*. 1995. Carcinoma of the lung in HIV-positive patients: findings on chest radiographs and CT scans. *American Journal of Roentgenology.*, 164(3):593-7.

21) Bazot, M., Cadranel, J., Khalil, A., *et al.* 2000. Computed tomographic diagnosis of bronchogenic carcinoma in HIV-infected patients. *Lung Cancer*., 28(3):203-9.

22) Karp, J., Profeta, G., Marantz, PR., *et al*. 1993. Lung cancer in patients with immunodeficiency syndrome. *Chest*., 103(2):410-3.

23) Johnson, D.H., Schiller, J.H., Bunn, P.A. 2014. Recent clinical advances in lung cancer management. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology.,* 32(10):973-82.

24) Verschakelen, J.A., De Wever, W., Bogaert, J. 2004. Role of computed tomography in lung cancer staging. *Current Opinion in Pulmonary Medicine*., 10(4):248-55.

25) Kocijančic, I., Kocijančic, K. 2007. CT-guided percutaneous transthoracic needle biopsy of lung lesions – 2-year experience at the Institute of Radiology in Ljubljana. *Radiol Oncol*., 41(3):99-106.

26) South African Medical Research Council. 2000. What are the top causes of death due to cancer in SA?. Available: http://www.mrc.ac.za/bod/faqcancer.htm [Accessed on 21 February 2016]

27) United Kingdom Cancer Research. 2014. Worldwide cancer incidence statistics. Available: http://www.cancerresearchuk.org/cancer-info/cancerstats/world/incidence/ [Accessed on 1 March 2016]

28) Latimer, K.M. 2018. Lung Cancer: Clinical Presentation and Diagnosis. *FP Essentials*., 464:23-6.

29) Hamilton, W., Peters, T.J., Round, A., *et al*. 2005. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. *Thorax*., 60(12):1059-65.

30) United Kingdom Cancer Research. 2014. Lung Cancer Risk Factors. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors [Accessed on 16 September 2015]

31) Adonis, M.I., Diaz, J., Miranda, V.R., *et al*. 2014. Biomarkers for screening of lung cancer and pre-neoplastic lesions in a high risk Chilean population. *Biological Research*., 47(1):62.

32) Karl, W. & Thomas, M. 2015. Patient information: Lung cancer risks, symptoms, and diagnosis (Beyond the Basics). Available: http://www.uptodate.com/contents/lung-cancer-risks-symptoms-and-diagnosis-beyond-the-basics [Accessed on 16 September 2015]

33) Engels, E.A., Brock, M.V., Chen, J., *et al.* 2006. Elevated incidence of lung cancer among HIV-infected individuals. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*., 24(9):1383-8.

34) United Kingdom Cancer Research. 2014. Types of treatment for lung cancer. Available: http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/treatment/which-treatment-for-lung-cancer [Accessed on 5 March 2016]

35) UyBico, S.J., Wu, C.C., Suh, R.D., *et al*. 2010. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. *Radiographics : a review publication of the Radiological Society of North America*, *Inc.*, 30(5):1163-81.

36) Detterbeck, F.C., Nicholson, A.G., Franklin, W.A., *et al*. 2016. The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer.,* 11(5):639-50.

37) International Agency for Research on Cancer. World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Geneva: WHO Press, 2015.

38) Travis, W.D., Brambilla, E., Riely, G.J. 2013. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*., 31(8):992-1001.

39) Koegelenberg, C.F., Aubeelack, K., Nanguzgambo, A.B., *et al*. 2011. Adenocarcinoma the most common cell type in patients presenting with primary lung cancer in the Western Cape. *South African Medical Journal.*, 101(5):321.

40) Charloux, A., Quoix, E., Wolkove, N., *et al*. 1997. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. *International Journal of Epidemiology*., 26(1):14-23.

41) Santos-Martinez, M.J., Curull, V., Blanco, M.L., *et al*. 2005. Lung cancer at a university hospital: epidemiological and histological characteristics of a recent and a historical series. *Archivos de Bronconeumologia*., 41(6):307-12.

42) Takanashi, N., Nobe, Y., Asoh, H., *et al*. 1995. The diagnostic accuracy of a solitary pulmonary nodule, using thin-section high resolution CT: a solitary pulmonary nodule by HRCT. *Lung Cancer.*, 13(2):105-12.

43) Dhopeshwarkar, M.R., Roberts, H.C., Paul, N.S., *et al*. 2011. Screen-detected lung cancer: a retrospective analysis of CT appearance. *Academic Radiology*., 18(10):1270-6.

44) Leyden, H. 1883. Uber infectiose pneumonie. *Dtsch Med Wochenschr*., 9:52-4.

45) Arslan, S., Yilmaz, A., Bayramgurler, B., *et al*. 2002. CT- guided transthoracic fine needle aspiration of pulmonary lesions: accuracy and complications in 294 patients. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research.*, 8(7):493-7.

46) Winokur, R.S., Pua, B.B., Sullivan, B.W., *et al*. 2013. Percutaneous lung biopsy: technique, efficacy, and complications. *Seminars in Interventional Radiology*., 30(2):121-7.

47) Khouri, N.F., Stitik, F.P., Erozan, Y.S., *et al.* 1985. Transthoracic needle aspiration biopsy of benign and malignant lung lesions. *American Journal of Roentgenology*., 144(2):281-8.

48) Poulou, L.S., Tsagouli, P., Ziakas, P.D., *et al*. 2013. Computed tomography-guided needle aspiration and biopsy of pulmonary lesions: a single-center experience in 1000 patients. *Acta Radiologica.*, 54(6):640-5.

49) Kanabus, A. 2017. Information about Tuberculosis. Available: https://www.tbfacts.org/hiv-statistics-south-africa/ [Accessed 4 July 2018]

50) Thun, M.J., Lally, C.A., Flannery, J.T., *et al.* 1997. Cigarette smoking and changes in the histopathology of lung cancer. *Journal of the National Cancer Institute.*, 89(21):1580-6.

51) Avert. 2016. HIV and AIDS in South Africa. Available: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa#footnote115_ip5ikzk [Accessed 4July 2018].

52) Nanguzgambo, A.B., Aubeelack, K., von Groote-Bidlingmaier, F., *et al*. 2011. Radiologic features, staging, and operability of primary lung cancer in the Western cape, South Africa: a 1-year retrospective study. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer.*, 6(2):343-50.

53) Kung, I.T., Lui, I.O., Loke, S.L., *et al*. 1985. Pulmonary scar cancer. A pathologic reappraisal. *The American Journal of Surgical Pathology*., 9(6):391-400.

54) Bobba, R.K., Holly, J.S., Loy, T., *et al*. 2011. Scar carcinoma of the lung: a historical perspective. *Clinical Lung Cancer.*, 12(3):148-54.

55) Wang, J.C., Sone, S., Feng, L., *et al.* 2000. Rapidly growing small peripheral lung cancers detected by screening CT: correlation between radiological appearance and pathological features. *The British Journal of Radiology.*, 73(873):930-7.

56) Mahoney, M.C., Shipley, R.T., Corcoran, H.L., *et al.* 1990. CT demonstration of calcification in carcinoma of the lung. *American Journal of Roentgenology.,* 154(2):255-8.

57) Hollings, N., Shaw, P. 2002. Diagnostic imaging of lung cancer. *European Respiratory Journal*., 19(4):722-42.

58) Pentheroudakis, G., Kostadima, L., Fountzilas, G., *et-al*. 2004. Cavitating squamous cell lung carcinoma-distinct entity or not? Analysis of radiologic, histologic, and clinical features. *Lung Cancer*., 45(3):349-55.

59) Lavolé, A., Wislez, M., Antoine, M., *et al.* 2006. Lung cancer, a new challenge in the HIV-infected population. *Lung Cancer.,* 51(1):1-11.

60) Winstone, T.A., Man, P., Hull, M., *et al. 2013.* Epidemic of Lung Cancer in Patients with HIV Infection. *Chest.,* 143(2):305–314.

61) Burkhalter, J.E., Springer, C.M., Chhabra, R., *et al*. 2005. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco*., 7(4):511-22.