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Mukansi, Murimisi Demmy

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LUNG CANCER IN JOHANNESBURG.

Murimisi Demmy Mukansi

A Research report submitted to the Faculty of Health Sciences, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the Degree of Master of Medicine in the branch of Pulmonology.

Johannesburg 2010

DECLARATION

I declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine, It has not been submitted for any degree or examination at this or any other University.

Murimisi Demmy Mukansi

25th April 2010

DEDICATION

To Joel Magezi and Christina Vuyeleni, my first and greatest teachers, I am humbled by your ambition, sacrifices and motivation skills.

To Solani, Tinyiko and Hlekani, you are the greatest mentors of all times, many thanks for your encouragement and support.

Tintswalo and Vongani you make it all worthwhile.

PUBLICATIONS AND PRESENTATIONS

Early results of this research report were presented at the combined South African Thoracic Society and Critical Care Society of South Africa Congress in Bloemfontein, South Africa 2001 and Sun City, South Africa 2009

ABSTRACT

Lung cancer in Johannesburg

INTRODUCTION

Lung cancer remains the most common malignancy, with an estimated 1.04 million new cases each year worldwide, accounting for 12.8% of new cancer cases. Of these cases, 58% occur in the developing world. Lung cancer is the most common cancer among men, with an incidence of approximately 37.5 new cases per million. The incidence is lower in women, at 1.08 cases per million population. Lung cancer is the leading cause of morbidity and mortality in the world. There is evidence in the literature of racial and gender differences in the distribution of lung cancer. However data from South Africa is sparse.

AIM

The primary objective of this study was to investigate whether differences existed in demographic and histological features of lung cancer when comparing black versus white patients with cancer of the lung in Johannesburg

METHODS

A retrospective case record review of 817 patients presenting to the pulmonology units of the three hospitals, between January 1992 and December 1998, was undertaken. Demographic, clinical, laboratory and histological features were captured and analyzed, using the GraphPad InStat 3.10 program for Windows. The histological cell types of lung cancer were characterized using the 1981 WHO classification.

RESULTS

A total of 817 patients with lung cancer were enrolled in the study. The age group of the total sample ranged between 26-92 years with a mean±SEM of 61.0±0.04 years. There were 574 (70.3%) male patients versus 222 (27.2%) female patients. The remaining 21 (2.6%) patients had no data recorded with respect to their gender. The racial stratification of these patients in decreasing order of frequency was whites 441 (54.0%), blacks 337 (41.3%), mixed race 24 (3.0%) and Indians 15 (1.8%). The study group consisted of the 778 black and white patients. The black patients were younger (mean ±SEM, 57.3±0.5years) than the white patients (mean ±SEM, 64.0±9.9) irrespective of gender ($p < 0.001$). Overall 632 patients were smokers, either current or ex-smokers. The amount of cigarettes consumed was significantly higher in white patients compared to black

patients (mean pack years for white patients was 52.7 ± 27.1 versus 21.7± 14.3 pack years for black patients ($p < 0.001$)). This difference was irrespective of gender. The mode of diagnosis in the 778 lung cancer patients was bronchoscopy in the majority 479 (54.0%), followed by sputum cytology in 152 (18.3%) and fine needle aspiration in 105 (12.7%). Tissue biopsy was utilized to diagnose 23 (2.7%) of the lung cancers. In some cases more than a single modality of diagnosis was utilized. The radiological features of the 778 lung cancer patients varied. The majority had a mass on chest radiograph; a lung mass in 357 (46.5%) patients, a hilar mass in 166 (21.6%), and a mediastinal mass in 18 (0.3%) patients. Pleural effusions were found in 82 (10.7%), lung atelectasis in 78 (10.2%), an infiltrate in 29 (3.8%) and consolidation in 25 (3.3%).

Histological cell types of lung cancer in the 778 patients consisted of the following, in descending order of frequency; squamous cell carcinoma in 341 (43.8%), adenocarcinoma in 167 (21.5%), small cell carcinoma in 129 (16.6%) and large cell carcinoma in 68 (8.7%) of the cases. Other histological cell types accounted for 73 (9.4%) of the patients. Small cell carcinoma was overall more common amongst white patients especially males and in black patients it was exclusively in females ($p<0.0005$). However the black female patients tended to have more small cell carcinoma (40 (45.5%)), compared to the white female

patients who had more squamous cell carcinoma (54 (45.0%)) in the majority. There was a small proportion of patients considered to be operable with intent to cure -74 (9.5%). This was a poor operability rate compared to an expected operability rate of 15-20%. This rate was as distressing when divided along racial lines; 29 (8.6%) of black patients and 45 (10.2%) of white patients being considered operable.

DISCUSSION

The demographics of the study group were different. The black patients tended to be significantly younger and smoked less cigarettes compared to the white patients. There was a significantly greater number of male patients with lung cancer than female patients. This difference was irrespective of race. The ranked frequency of histological subtypes was similar in both race groups. However, the black female had more small cell carcinoma, compared to white females with a preponderance of squamous cell carcinoma. The operability of all lung cancer patients, irrespective of gender and race, was dismal at 9.5%, compared to the standard norm of 15-25% operability rate. This is worrying when one considers the fact that surgery is the means to a cure. It either suggests there is a delay in seeking medical care and/or the lack of medical resources to permit screening and early diagnosis of the malignancy.

CONCLUSIONS

This study did not demonstrate any ranked frequency differences in histological cell type distribution between black and white patients. Squamous cell carcinoma was the most common histological cell type regardless of race. Small cell carcinoma was significantly more common among white patients, especially the males while among the black patients it was exclusively found in the females. Black patients with lung cancer tended to present at an earlier age. Black females were less likely to develop lung cancer when compared with the white females. The black patients smoked fewer cigarettes than the white patients irrespective of gender. The operability of our patients, in the study, was poor in all race groups.

PREFACE

This study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand- ethics clearance protocol number: M990804

LIST OF ABBREVIATIONS

CI:	Confidence interval
CXR:	Chest radiograph
DNA:	Deoxyribonucleic acid
FNA:	Fine needle aspiration
HIV:	Human immunodeficiency virus
IARC:	International association for research on cancer
IASLC:	International association of the study of lung cancer
N:	Total number
No.	Number
NS:	Not significant
SD:	Standard deviation
SEM:	Standard error of mean
WHO:	World Health Organisation

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TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
PUBLICATIONS AND PRESENTATIONS iv
ABSTRACT v
PREFACE x
LIST OF ABBREVIATIONS xi
ACKNOWLEDGEMENTS xii
TABLE OF CONTENTS xiii
LIST OF TABLES xv
Chapter 1: LITERATURE REVIEW 1
1.1 History of lung cancer **1**
1.2 Incidence of lung cancer with emphasis on Africa and South Africa **3**
1.3 Aetiology of lung cancer **5**
1.3.1 Smoking **5**
1.3.2 Additional risk factors for lung cancer 9
1.4Classification of lung cancer histology **11**
1.5 Therapy of lung cancer **13**
1.5.1 Therapy for non-small cell lung cancer 13
1.5.2 Radiation therapy 14
1.5.3 Small cell lung carcinoma 15
1.6 Differences in the features of lung cancer in black and white patients globally **16**
Chapter 2: STUDY DETAILS 18
2.1 **Aims and objectives** 18
2.2 Hypothesis **18**
2.3 Rationale **18**
2.4 Study design and methods **19**
Chapter 3: RESULTS 20
3.1 Patient demographics 20
3.2 Mode of diagnosis 21
3.3 Radiological features 24
3.4 Histological types **25**
3.5The operability of 778 patients **26**
3.6 The comparative demographics of black and white patients **26**
3.7 The mode of diagnosis in 778 lung cancer patients **29**
3.8 The radiological features of 778 lung cancer patients **31**
3.9 The histological features of lung cancer in 778 patients stratified by race **32**
3.10 The operability of 778 lung cancer patients stratified by race **34**
Chapter 4: DISCUSSION 36
4.1 Patient demographics **36**
4.2 Mode of diagnosis **37**
4.3 Radiological features **38**
4.4 Histological types of lung cancer **38**
4.5 Operability **39**
4.6 Limitations of the study **40**
4.7 Conclusion **40**

THE FUTURE 42
REFERENCES 44

LIST OF TABLES

Table 3.1 The demographic and clinical data of lung cancer patients between 1992 - 1998.

Table 3.2 The mode of diagnosis in 778 lung cancer patients.

Table 3.3 Radiological features of lung cancer in 778 patients

Table 3.4 Histological types of lung cancer in 778 patients

Table 3.5 The operability of 778 lung cancer patients

Table 3.6a The demographics of 778 lung cancer patients stratified by race.

Table 3.6b The demographics of 778 lung cancer patients stratified by race and gender

Table 3.7 The mode of diagnosis of 778 lung cancer patients stratified by race

Table 3.8 Radiological features of lung cancer in 778 patients.

Table 3.9a Histological types of 778 lung cancer patients stratified by race.

Table 3.9b The histological types of 778 lung cancer patients stratified by race and gender.

Table 3.10 The operability of 778 lung cancer patients stratified by race

Chapter 1: LITERATURE REVIEW

1.1. History of lung cancer

The history of lung cancer starts with aetiology and dates back to 1420, when the first mines were opened in Schneeberg, Saxony (Rostoki *et al*, 1926; Selawry *et al*, 1973). Miners were known to develop "Bergsucht", called "*morbus metallicorum imprimis pulmonum*" by Theophrastus Bombastus Paracelsus of Hohenheim. It was described in the miners of Schneeberg by Agricola and others since the early sixteenth century. Pneumoconiosis, chronic bronchitis and tuberculosis were thought to be the underlying causes until 1879 when Harting and Hesse (Harting *et al*, 1879) recognized among the miners an endemic of pulmonary "Sarcoma", later classified as bronchogenic carcinoma (Selawry *et al*, 1973). This was attributed to cobalt, nickel, arsenic, the ubiquitous aspergillus and later radon, for Eve Curie had obtained most of her uranium from Schneeberg. Subsequently a high incidence of lung cancer was noted among uranium miners elsewhere.

Van Swieten described the clinical and morphological picture of lung cancer in "*Commentaria Herm*, *Boerhaave Aphorismos"*, in 1745. He called the disease "*angina scirrhosa"*. Later Morgagni noted "*ulcus cancrosum"* of the lung in *De Sedibus et Causis Morborum*, in 1761. Physicians of the early nineteenth century

recognized lung cancer as an uncommon and untreatable disease (Selawry *et al*, 1973). Diagnosis was markedly improved from 1875, when cancer cells were first described in sputum, and certainly since 1898, when Villain introduced direct bronchoscopy (Adler, 1912).

Inhalation of cigarette smoke as the most common aetiologic factor of lung cancer was first considered by Adler in 1912, after Brosch's observation of epithelial proliferation in guinea pigs exposed to "tobacco juices" in 1900 (Wynder *et al*, 1967). Epidemiological correlations between cigarette smoking and lung cancer were demonstrated by Hill and Doll, in 1950, then by Wynder and Graham, in 1951 and were widely confirmed.

Successful lobectomy for lung cancer was performed by Sauerbruch in 1908 (Wolf, 1907-1928). The first successful one-stage pneumonectomy for lung cancer is credited to Graham, in 1933 (Grahams and Singer, 1983). Radiotherapy, available since the early twentieth century, remained palliative until the supervoltage became more widely available in the early 1940s. Chemotherapy came into use in the 1940s.

1.2 Incidence of lung cancer with emphasis on Africa and South Africa

Lung cancer remains the most common malignancy, with an estimated 1.04 million new cases each year worldwide, accounting for 12.8% of new cancer cases (Bilello *et al*, 2002; Hecht, 2002). Of these cases, 58% occur in the developing world. Lung cancer is the most common cancer among men, with an incidence of approximately 37.5 new cases per million. The incidence is lower in women, at 1, 08 cases per million population. Lung cancer is the cause of 921.000 deaths each year worldwide, accounting for 17.8% of cancer related deaths. This makes lung cancer the leading cause of cancer deaths in the world (Parkin *et al*, 2005).

In South Africa, the rates are intermediate to low compared to international figures (Sitas, 1998). A previous study of lung cancer in black patients in Johannesburg undertaken in 1983, demonstrated that 62% were squamous cell, with only 11% being small cell carcinoma. In that study, the percentage of combined small and squamous cell carcinomas, however, was equal among white and black patients (C. Smith, personal communication).In Groote Schuur hospital, squamous cell cancer was the most common histological type (34% of patients).Only 11% of patients were operable (Wilcox *et al*, 1990)

Harare whites are said to have higher age standardized rates for lung cancer than whites in South Africa (36 vs. 22.3/ 100 000) (Sitas, 1998). Blacks in Harare have rates double those of South African blacks (24.6 vs. 11.7/ 100 000), suggesting underreporting in the latter (Sitas, 1998). Rates for lung carcinoma in West Africa are reported to be low (Mali 4.8; Uganda 1.5 and Gambia 1/100 000) (Sitas, 1998).

Lung cancer rates parallel smoking habit, though pack years in blacks are small in comparison to the western world. The epidemiological studies carried out in the 1960s showed that a very high incidence of the disease existed among white South Africans, and that it was on the rise (Oettle, 1964; Sitas, 1998). In comparison, the incidence among black South Africans in one study was extremely low (4.6/100 000 Johannesburg males and 1.7/100 000 in females (Oettle, 1964)). With regard to the black patients studied in Natal, a markedly higher incidence was found i.e. 24/100 000 males and 8.4/100 000 females (Schonland and Bradshaw, 1968). The postulate was that bad smoking habits in Natal contributed to a higher incidence in this group of patients. In the 1993-1995 South African cancer registry, white female lung cancer was 4th at 1 in 61, while in black females it ranked fifth at 1 in 313 (Sitas, 1998). Among the black males the lifetime risk increased from 1 in 89 to 1 in 67, while in white males the lifetime risk increased from 1 in 41 to 1 in 34 (Sitas,1998).

1.3 Aetiology of lung cancer

1.3.1 Smoking

Smoking, particularly of cigarettes, has a significant role in the aetiology of all lung cancers even though there is evidence that smoking may be a weaker cause of the more peripheral cell types (Morabia and Wynder, 1991). Because of the relationship between cell type and smoking, squamous cell is the most common type. Lung cancer incidence closely parallels tobacco use, especially for the small cell and squamous cell carcinoma histological types. There is, in fact, a linear dose-response relationship between increasing daily consumption of cigarettes and the diagnosis of squamous and small cell carcinoma (Khuder, 2001). Smoking is estimated to account for 80-90% of lung cancers, and lung cancer rates should reflect smoking rates for age, gender and ethnic groups (Alberg and Samet, 2003; Rivera, 2004). Among male smokers the lifetime risk of developing lung cancer is 17.2%, while among female smokers it is 11.6%. This risk is significantly smaller in non-smokers at 1.3 % in males and 1.4% in females (Villeneuve *et al*, 2004).

The dose of tobacco exposure in patients with lung cancer was found in one study to be associated with an increase in the various cell types, in the following

ascending order: bronchoalveolar cell, adenosquamous, adenocarcinoma, large cell, small and squamous cell (Sridar and Raub, 1992). Several factors are implicated in the change in the histological pattern; for example the decrease in nicotine content and the increase in use of filtered cigarettes may be responsible for the decrease in squamous cell carcinoma and increase in adenocarcinoma (Sridar and Raub, 1992; Hecht, 2002). Deeper inhalation and greater puff volumes allow smoke particles to reach more peripheral parts of the lung, increasing exposure to carcinogens such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a known systemic carcinogen that induces lung adenocarcinoma (Wynder and Muscat, 1995; Hecht, 2002; Alberg and Samet, 2003).

In 1998, smoking prevalence in South Africa declined to 25% overall, with 44.2% males versus 11.0% females smoking (Steyn *et al*, 2002). There was a significant increase in the use of smokeless tobacco, estimated at 45%, with African females in the majority at 13.2% (Steyn *et al*, 2002). These African women smoked lightly and started late, save for those urbanized early (Steyn *et al*, 2002). This decrease in smoking prevalence is reflected in all demographic and socio-economic groups. The most significant decreases have been recorded for males, blacks, young adults, and low-income households (Van Walbeek, 2002). External environmental smoking has the same chemicals as those inhaled

by smokers. Passive smokers have a 20-50% higher risk of lung cancer than non-exposed subjects. One study demonstrated that 28% and 19% of non-smokers were exposed to environmental tobacco smoke at home or in their workplaces, respectively (Steyn *et al*, 2002).

Epidemiological evidence for an association between cannabis and lung cancer is limited and conflicting. Cannabis smoking may have a greater potential than tobacco smoking to cause lung cancer (Aldington *et al*, 2008). Cannabis smoke is qualitatively equal to tobacco smoke, although it contains up to twice the concentration of the carcinogenic polyaromatic hydrocarbons (Hoffman *et al,* 1975; Aldington *et al,* 2008). Cannabis cigarettes are less densely packed than tobacco cigarettes, and tend to be smoked without filters (Ricket, 1982; Aldington *et al*, 2008), to a smaller butt size (Tashkin, 1991; Aldington *et al*, 2008), leading to higher concentrations of inhaled smoke. Furthermore, smokers of cannabis inhale more deeply and hold their breath for longer (Wu *et al*, 1988; Aldington *et al*, 2008), facilitating the deposition of the carcinogenic products in the lower respiratory tract. These factors are likely to be responsible for the five-fold greater absorption of carbon monoxide from a cannabis joint, compared to a cigarette of similar size despite similar carbon monoxide concentrations in smoke inhaled (Wu *et al*, 1988; Aldington *et al*, 2008).

For each joint-year of cannabis exposure, the risk of lung cancer increased by 8%, after adjusting for confounding variables, including tobacco smoke (Aldington *et al*, 2008). A major differential risk between cannabis and cigarette smoke was observed, with one joint of cannabis being similar to an equivalent of 20 cigarettes for risk of lung cancer. Smoking a joint of cannabis a day causes similar histological changes in the tracheobronchial epithelium as smoking 20-30 tobacco cigarettes a day (Roth *et al*, 1998). Key DNA repair enzymes topoisomerase II (Kogan, 2007) and rad 51 have been shown to be inhibited by cannabinoids.

The aspects of personal smoking that most influence cancer risk are: duration and intensity of smoking, depth of inhalation, smoking cessation and type of cigarette or tobacco used (Tyczynski *et al*, 2003). There are several genetic loci with association to major lung cancer, including loci chromosome 6q23-25 (Gazdar and Thun, 2007). In a small area of chromosome 15p25, there is a strong association between mutations in this region and the development of lung cancer (Hung *et al*, 2008). Additionally nicotine appears to depress the immune response to malignant growth in exposed tissues (Sopori, 2002). Mentholated cigarette may help explain the racial disparity in lung cancer distribution among blacks and whites in the American population, where the rate is higher among

blacks. The two mechanisms are, firstly, that the products of menthol combustion might directly exert a carcinogenic effect on lung tissue. Alternatively, menthol's cooling and anaesthetic properties might permit larger puffs, deeper inhalation, or longer retention in the lungs, all of which might result in increased exposure to carcinogenic elements in tobacco smoke (Brooks *et al*, 2003). Low tar cigarette may be associated with deeper inhalation and longer stay of inhaled carcinogens resulting in increased incidence of adenocarcinoma (Bennett *et al*, 2008*)*.

1.3.2 Additional risk factors for lung cancer

Occupational exposure, such as mining and industrial exposure, increases the risk of developing lung cancer (Sridar and Raub, 1992). Asbestos acts synergistically with cigarette smoking to increase the rate of lung cancer. Lung cancer incidence in smokers exposed to asbestos is 50-fold higher. Uranium exposure in miners is particularly associated with small cell carcinoma. This incidence is greatly multiplied by smoking (Saccomanno *et al*, 1976). Multiplicative interaction has also been described for tobacco and ionizing radiation and for tobacco and arsenic exposure.

Lung scarring, following pulmonary pathology such as tuberculosis and rheumatoid arthritis, is also a risk factor for development of lung carcinoma, especially adenocarcinoma (Wu et al, 1995; Mayne *et al*, 1999; Cicenas and Vincevicius, 2007). Genetic factors are also important risk factors, with reports of familial clustering and increased sibling susceptibility. Patients who are poor metabolisers of debrisoquine, an antihypertensive, by cytochrome P450, have a significantly lower risk of developing lung cancer than do rapid debrisoquine metabolisers (Alberg and Samet, 2003).

Gender differences in the distribution of histological cell types are well known. Squamous cell type is more prevalent in males, while adenocarcinoma is more prevalent in females and non-smokers (Mcduffe *et al*, 1990). Either different aetiological factors contribute to primary lung carcinoma or the gender of the host modifies the host-carcinogen interaction. Accumulating data suggest that the risk of lung cancer development is different in women compared to men. Women have a 1.2 to 1.7 fold higher odds ratio of developing lung cancer than men, at every level of cigarette smoke (Rivera and Stover, 2004). An increased susceptibility in women to the adverse effects of tobacco may be due to higher levels of DNA adducts, decreased DNA repair capacity, increased frequency of mutations in tumour suppressor genes, and hormonal differences (Rivera and

Stover, 2004). HIV infection is associated with a significantly increased incidence of primary lung cancer, especially adenocarcinoma (Parker *et al*, 1998). There is a distinct possibility that this association may be due to other cofactors not yet identified, the possible scars from repeated infection and increased prevalence of cigarette smoking in HIV infected persons (Engels *et al*, 2006).

1.4 Classification of lung cancer histology

In 1968, the World Health Organization published the first classification of lung carcinoma, which was revised in 1981. More recently, in 1999, the classification was revisited to refine the criteria. The pathology panel suggested the revision of small cell lung cancer into pure small cell cancer, small cell with large cell component and combined small cell cancer with either adenocarcinoma or squamous cell carcinoma (Brambilla *et al*, 2001; Vaporciyan *et al*, 2003). Adenocarcinoma was reclassified into 5 cell types: bronchial surface epithelial cell type, with little or no mucus, goblet cell types, Clara cell types, type II alveolar cell types and bronchial gland cell type (Brambilla *et al*, 2001; Vaporciyan *et al*, 2003) . Additionally, it was emphasized that enhancement of future histological classification may incorporate the use of monoclonal antibodies, flow cytometry, and genetic abnormalities, all of which may be

useful in predicting the malignant potential of tumours and in acting as prognostic factors.

The relative incidence of the various histological types appears to be gradually changing. The proportion of squamous carcinoma appears to be decreasing as the proportion of adenocarcinoma increases (Brambilla *et al*, 2001; Vaporciyan *et al*, 2003). In the past decades squamous carcinoma was clearly the most common type. Squamous cell carcinoma accounts for approximately 30% of all carcinomas. Adenocarcinoma account for approximately 30-45% of lung cancer and appears to be increasing proportionally. This histological type occurs more commonly in women than men. Patients with adenocarcinoma may have an associated history of chronic interstitial lung disease, such as systemic sclerosis, rheumatoid arthritis and interstitial pneumonitis, as well as tuberculosis, recurrent pulmonary infections and other necrotizing pulmonary diseases. Large cell cancer accounts for approximately 9% of lung cancers. Small cell lung carcinoma is definitely decreasing in prevalence, while there is a definite increase in others (Wingo *et al*, 1999). Neuroendocrine tumours are found in association with large cell carcinoma and justify the subtype referred to as large cell neuroendocrine carcinoma. Pulmonary neuroendocrine neoplasia includes

four major histological subtypes; small cell lung cancer, large cell neuroendocrine lung cancer, typical carcinoid and atypical carcinoid. High grade neuroendocrine lung cancer usually includes the small cell lung cancer and the large cell neuroendocrine cancer.

1.5 Therapy of lung cancer

1.5.1 Therapy for non-small cell lung carcinoma

In patients with non-small cell lung carcinoma, the most important prognostic factor is tumour stage, and this factor largely determines treatment (Mountain, 1986; Nauke et al, 1988). Surgery is the standard mode of therapy for patients with stage I-II tumours and for some patients with stage III tumours, with adjuvant or neoadjuvant radiation therapy or chemotherapy, or both, added if the tumour invades the mediastinal lymph nodes. The use of combined modality therapy in locally advanced inoperable stage III non-small cell lung cancer is an area of intense investigation. Patients with stage IV disease are treated with chemotherapy or radiation therapy or with palliative therapy alone. Patients with unresectable or inoperable non-small cell lung cancer are evaluated first for definite therapy with a combined chemoradiation therapy approach. If there are pressing symptomatic needs for palliation, such as complete major airway obstruction, haemoptysis, superior vena caval obstruction, painful bony

metastases in the weight bearing areas, or symptomatic brain metastasis, the initial treatment is radiotherapy with or without chemotherapy.

1.5.2 Radiation therapy

Patients who are inoperable are treated with radiotherapy as a potentially curative approach (Kupelian *et al*, 1995). Radiation doses in excess of 60 gray have been shown to be more effective than lower doses (improved local control, usually with a trend towards improved survival). Post-operative elective nodal irradiation for positive margins or positive lymph nodes encompasses mediastinal and ipsilateral hilar nodes with 1 to 1.5cm margin of normal tissue around the tumour region and 5cm below the carina. The dose of postoperative radiation therapy would be 2 gray per fraction and a total of 50-60 gray, depending on completeness of surgery, positivity of margins, and presence of extracapsular extension (with 60 gray delivered as a continuous course in all these latter conditions (Emami *et al*,1997)).

Radiation dose to the spinal cord is limited to 44 to 45 gray using oblique fields followed by a blast field to the target to give additional 10-20 gray to the positive margins or lymph node regions. A combination of radiation and chemotherapy

offer the best hope for long-term disease free survival in unresectable stage III non-small cell lung carcinoma (Lam and Watkins, 2007).

Endobronchial and endotracheal lesions can cause life-threatening symptoms including shortness of breath, post-obstructive pneumonitis, and haemoptysis. Endobronchial brachtherapy is used to achieve high radiation doses to these relatively accessible tumours, either as a potential curative therapy or in the palliative setting after external radiotherapy has failed. Palliative results showed symptomatic relief between 50 and 78%.

Patients with advanced lung disease should receive a two-drug regimen of chemotherapy (Ettinger, 2002). No best single regimen has been identified for non-small cell lung carcinoma. Patient with a single metastatic lesion may benefit from resection (Spira and Ettinger, 2004)

1.5.2 Small cell lung carcinoma

Less than 5% are amenable to surgery. Patients with a solitary lung nodule and no evidence of nodal involvement on mediastinal staging should undergo mediastinal node resection at time of surgery (Inoue *et al*, 2000) and receive adjuvant chemotherapy, with the addition of radiation if the mediastinum is

involved on microscopical examination of the lymph nodes (Inoue *et al*, 2000). For patients who receive a diagnosis on the basis of biopsy, management should consist of combined chemotherapy and radiotherapy without surgery. Concurrent chemotherapy and radiation therapy appear to provide better five year survival rates than sequential therapy (Lam and Watkins**,** 2007)**.**

The treatment of choice for extensive disease is chemotherapy alone, with a five year survival rate of less than 5%. Future directions for treatment are heavily weighted towards targeted therapies.

1.6 Differences in the features of lung cancer in black and white patients globally

The median age of patients in the global population with lung cancer is about 66 years, while most African studies show patients to be younger averaging 57 years. Overall black patients tend to be younger than the white patients. Black men have a higher smoking prevalence than white men in America; smoke cigarettes with a higher machine-measured tar levels, higher cotinine blood levels and higher menthol brands. However black men smoke fewer cigarettes per day and begin smoking at an older age than white populations.

When pack years are analyzed, female subjects develop lung cancer with significantly less tobacco exposure than males (41 and 59.9 pack years, respectively; p=0.032) (Rivera and Stover, 2004).

There is a geographical pattern of histological subtype distribution amongst different genders and racial classes. In Europe, squamous cell carcinoma is the predominant type of cancer except in the Netherlands, while in North America, adenocarcinoma has surpassed squamous cell carcinoma as the most common cell type of non-small lung cancer in both black and white patients (Charloux *et al*, 1997). Among men, with the exception of certain Asian populations (Chinese, Japanese), only in North America does the incidence of adenocarcinoma exceed that of squamous cell carcinoma. In women, however, adenocarcinoma is the dominant histologic subtype almost everywhere, except for Poland and England, where squamous cell carcinoma predominates, and Scotland where small cell carcinoma is the most frequent subtype (Curado *et al*, 2007). The differences in histologic profiles are strongly influenced by the evolution of the epidemic of smoking-related lung cancer over time

Chapter 2: STUDY DETAILS

2.1 Aims and Objectives

The primary objective of the study was to investigate whether differences existed in demographic and histological features of lung cancer when comparing black versus white patients with cancer of the lung in Johannesburg.

2.2 Hypothesis

Differences exist, especially in the histological subtypes of lung carcinoma at initial presentation in the different population groups of patients with lung carcinoma in Johannesburg.

2.3 Rationale

Evidence from the literature and anecdotal information from our Pulmonology units suggested that there may be disparity in demographics, clinical presentation and histological subtypes among different population groupings in South Africa. There is however sparcity of data on this issue in South Africa.

2.4 Study design and methods

A retrospective record review was undertaken of cases seen between January 1992 and December 1998. A total of 817 patients with lung cancer presenting to the pulmonology units of the Johannesburg, Hillbrow and the Helen Joseph Hospitals were reviewed. The features reviewed were, demographic data (including age, gender, race), smoking history, including quantity and pack years, histological cell type of the malignancy, radiological features on chest radiograph and operability of the patients. The endpoint was to contrast and compare white and black patients. The 1981 WHO classification of histological cell types for lung cancer was utilized to interprete the histological type of lung malignancy.

A Graphpad instat 3.10 program for Windows was utilized to analyze the data. The Mann-Whitney test was used to determine whether there were any differences in age and pack years between black and white patients. When the groups were further stratified by gender, comparisons were done using the Kruskal-Wallis test. Analyses of pack years in individual groups were undertaken using the Wilcoxon test. Contingency tables were utilized to analyze histological data, radiological features and mode of diagnoses to assess for differences.

Chapter 3: RESULTS

3.1 Patient demographics

A total of 817 patients of all race groups were diagnosed as having lung cancer in the pulmonary units during this time period. The racial classification of these patients in decreasing order of frequency were 441whites (54.0%), 337 blacks (41.3%), 24 mixed race (3.0%), and 15 Indian (1.8%). The focus of the current study is the comparative data for the black and white patients (a total of 778 patients). The age group of the total sample (817 patients), ranged between 26-92 years with a mean±SEM of 61.0±0.4 years. On gender stratification there were 574 (70.3%) male patients and 222 (27.2%) female patients. No gender data were available in 21(2.6%) of the patients.

Overall 632 (77.4%) of the patients were smokers, either current or ex-smokers. There were 32 (3.9%) nonsmokers, with the remaining 153 (18.7%) of patients lacking details of their smoking status (Table 3.1).

Table 3.1: The demographic data of lung cancer patients between 1992-1998

Parameters	Results
Umber	
Total no. of patients	817
Study sample	778
Age (years)*	
Mean ± SEM	61.0±0.4
Median	61
Range	26-92 yrs
Gender	
Male	574 (70.3%)
Female	222 (27.2%)
Unknown**	21 (2.6%)
Smoking	
Current	632 (77.4%)
Non-smoker	32 (3.9%)
Unknown	153 (18.7%)
Race	
White	441 (54.0%)
Black	337 (41.3%)
Indian	15 (1.8%)
Mixed	24 (3.0%)

* 780 patients had complete data reflecting their age
**21 patients did not have specified gender

3.2 Mode of diagnosis

The mode of diagnosis in the 778 lung cancer patients was bronchoscopy in the majority (479 (54.7%)), followed by sputum cytology in 152 (18.3%) of cases and fine needle aspiration in 105 (12.7%). Among the fine needle aspirations, 91

(11.0%) were of lung masses, 8 (1. 0%) of nodes, 4 (0.5%) of liver, and bone and skin fine needle aspirations each made up 1 case (0.1%), respectively. Tissue biopsy was utilized to diagnose 23 (2.7%) of the lung cancers. These biopsies were mainly nodal 9 (1.1%), open lung biopsy 3 (0.4%), bone marrow biopsy 3 (0.4%), skin biopsy 2 (0.2%) and liver biopsy 2 (0.2%). Brain, finger, rib and neck mass biopsies were each utilized to diagnose 1 (0.1%) of the patients. The remaining modalities of diagnosis were pleural tap in 11 (1.3%), thoracotomy in 5 (0.6%), lobectomy in 3 (0.4%) and autopsy in 1(0.1%). A significant proportion of lung cancer cases reflected no data on the modality of diagnosis (44 (5.3%)). In some cases more than one mode of investigation was utilized to make a diagnosis (Table 3.2).

Table 3.2: The mode of diagnosis in 778 lung cancer patients

Mode of diagnosis*	**Total (%)**
Bronchoscopy	479(57.7%)
Sputum cytology	152(18.3%)
F A	
Lung mass	91(11.0%)
Nodes	8(1.0%)
Liver	4(0.5%)
Bone	1(0.1%)
Skin	1(0.1%)
Biopsy	
Node	9(1.1%)
Open lung	3(0.4%)
Bone marrow	3(0.4%)
Skin	2(0.2%)
Liver	2(0.2%)
Brain	1(0.1%)
Finger	1(0.1%)
Rib	1(0.1%)
Neck mass	1(0.1%)
Pleural tap	11(1.3%)
Thoracotomy	5(0.6%)
Lobectomy	3(0.4%)
Autopsy	1(0.1%)
No modality specified	44(5.3%)
Total*	**830(100.0%)**

*There are a number of cases that were diagnosed on more than one modality

3.3 Radiological features

The radiological features of the 778 lung cancer cases were varied. The majority had a mass on chest radiograph; in 357 (46.5%) it was a lung mass, in 166 (21.6%) a hilar mass and in 18 (0.3%) a mediastinal mass. Pleural effusions were found in 82 (10.7%), lung atelectasis in 78 (10.2%), an infiltrate in 29 (3.8%) and consolidation in 25 (3.3%). Pericardial effusions and hilar lymphadenopathy were each found in 1 (0.1%) of cases. There were 4 (0.5%) cases that had a normal chest radiograph and 7 (0.9%) had a non-specific finding (Table 3.3).

Table 3.3: Radiological features of lung cancer in 778 patients

Chest Radiograph	**No. (%)**
Mass	
Lung	357(46.5%)
Hilar	166(21.6%)
Mediastinal	18 (2.3%)
Pleural effusion	82 (10.7%)
Lung atelectasis	78 (10.2%)
Infiltrate	29 (3.8%)
Consolidation	25 (3.2%)
Pericardial effusion	1 (0.1%)
Hilar nodes	1 (0.1%)
Normal	4 (0.5%)
Other*	7 (0.9%)
Total**	768 (100%)

*lung mass with atelectasis, ** no data for 10 patients

3.4 Histological types

Histological types of lung cancer in the 778 patients consisted of the following; squamous cell carcinoma in 341 (43.8%), adenocarcinoma in 167 (21.5%), small cell cancer in 129 (16.6%) and large cell carcinoma in 68 (8.7%) of the cases. Other histological types accounted for 73 (9.4%) of the patients. This category included, among others, mixed small and squamous cell carcinoma, mixed small and large cell carcinoma, mixed adenosquamous carcinoma, and intermediate and indeterminate lung cell cancer (Table 3.4).

Table 3.4: Histological types of lung cancer in 778 patients

Histology	**No. (%)**
Squamous cell	341(43.8%)
Adenocarcinoma	167(21.5%)
Small cell	129(16.6%)
Large cell	68(8.7%)
Other*	73(9.4%)
Total	778(100.0%)

*Other includes the following histological cell types;

Mixed small and squamous cell types, mixed small and large cell types, mixed adenosquamous, intermediate cell and indeterminate

3.5 The operability of the 778 patients

The clinical, radiographic and laboratory features of the 778 lung cancer patients were reviewed for possible operability. A total of 620 cases (79.7%) were considered to be inoperable, and only 74 (9.5%) were considered to be operable at presentation. The remaining 84 (10.8%) patients were of unknown operability status (Table 3.5).

Table 3.5: The operability of 778 lung cancer patients

Operability	**No. (%)**
Yes	74(9.5%)
No	620(79.7%)
Unknown	84(10.8%)
Total	**778(100%)**

3.6 The comparative demographics of the black and white patients

The study group consisted of 337 (43. 3%) black patients and 441 (56. 7%) white patients. The mean age (years) for the black patients was 57. 3±0. 5 (mean±SEM) years and for the white patients was 64.0±0.6 (mean±SEM) years. The median age for black patients was 57.0 years compared with 66.0 years for white patients ($p < 0.001$).The range for the black patients' age was from 26-86 years, a range younger than their white counterparts with age ranging from 32-92

years. The majority of white patients were smokers (364 (82.5%)) compared to 215 (63.8%) of the black patients. Among the non-smokers, black patients accounted for 20 (5.9%) of the patients versus 11 (2.5%) white patients. The mean pack years for the black smokers was 21.7±14.3 while it was higher in the white patients at 52.7±27.1 ($p < 0.001$) (Table 3.6a).

Table 3.6a: The demographics of 778 lung cancer patients stratified by race

Parameter	**Black**	**White**	**p value**
Total No. (%)	337(100.0%)	441(100.0%)	
Age(years):*			
Mean ±SD	57.3±10.3	64.0±9.9	
Mean±SEM	57.3±0.5	64.0±0.6	<0.001
Median	57.0	66.0	<0.001
Range	26-86	32-92	
Smoking**			
Yes	215(63.8%)	364(82.5%)	
No	20(5.9%)	11(2.5%)	
Pack years	21.7±14.3	52.7±27.1	<0.001

95% CI of age for white 63.1-65.0

95% CI of age for black patients 56.2-58.4

*Age data was available for 741 lung cancer patients

**Smoking data was available for 610 lung cancer patients

Among the white patients there were 269 males (36.6%) and 148 females (20.2%). Among the black patients there were 260 males (35.4%) and 57 females

(7.8%). The ages were as follows; 56.5±12.8 (mean ±SD) for black females, 57.4±9.6 (mean±SD) for black males, while the ages of the white patients were 64.3±10.2 (mean±SD) for females and 63.8±9.8 (mean±SD) for males, respectively. The median age was, for black females 56.0; for black males 58.0; for white males 64.0 and for white females 67.0. The age ranges were 30-86 years for black females, 26-81 years for black males, 35-82 years for white females and from 32-92 years for white males. The detailed smoking patterns are in the table below (Table 3.6b).

Table 3.6b: The demographics of 778 lung cancer patients stratified by race and gender

Parameter	Black Females n=57	Black Males n=272	White Females n=151	White Males n=277
Total No.	57(100.0%)	272(100.0%)	151(100.0%)	277(100.0%)
Age (years)				
Mean ±SD	56.5±12.8	57.4±9.6	64.3±10.2	63.8±9.8
Median	56.0	58.0	67.0	64.0
Range	30-86	26-81	35-82	32-92
Smoking				
Yes	24(42.1%)	191(70.2%)	127(80.9%)	236(85.2%)
No	12(21.1%)	8(2.9%)	5(3.3%)	6(2.2%)
Pack Years	22.5±11.3	21.6±14.8	53.1± 27.0	50.3±25.6

3.7 The mode of diagnosis in 778 patients with lung cancer

As noted previously the majority of the patients were diagnosed by bronchoscopy, including 199 blacks (54.3%) and 280 whites (58.5%). Sputum cytology was positive in more black patients 85 (23.2%) than white patients 67 (14.0%)($p = 0.0005$). The next mode of diagnosis was fine needle aspiration of a lung mass which was used in 42 black patients (11.4%) versus 49 white patients (10.2%). A single black patient was diagnosed with fine needle aspiration of the skin. Nodal fine needle aspiration was used in 5 white patients (1.0%) and 3 black patients (0.8%). A single white patient had a fine needle aspiration of bone for diagnosis. Liver fine needle aspiration was used in 3 white patients (0.6%) compared to a single (0.3%) black patient.

A single brain biopsy was utilized for diagnosis in a white patient and a finger biopsy was utilized for diagnosis in one black patient (0.3%). There were 3 bone marrow biopsies (0.8%) done, all on black patients. Liver biopsy was done on 2 white patients (0.4%) only. Nodal biopsies were done in 1 black patients (0.3%) compared to 8 white patients (1.7%). The pleura was biopsied in 2 black patients (0.5%) versus 5 white patients (1.0%). A single white patient had a rib biopsy. Skin biopsy was used as a mode of diagnosis in 2(0.4%) white patients only. The other modalities are detailed in the table 3.7.

Table 3.7: The mode of diagnosis of 778 lung cancer patients stratified by race

Mode of diagnosis*	**Black (%)**	**White (%)**	**P value**
Bronchoscopy	199(54.3%)	280(58.5%)	NS
Sputum cytology	85(23.2%)	67(14.0%)	0.0005
FNA			
Lung mass	42(11.4%)	49(10.2%)	NS
Skin	1(0.3%)	0(0.0%)	NS
Nodes	3(0.8%)	5(1.0%)	NS
Bone	0(0.0%)	1(0.2%)	NS
Liver	1(0.3%)	3(0.6%)	NS
Biopsy			
Brain	0(0.0%)	1(0.2%)	NS
Finger	1(0.3%)	0(0.0%)	NS
Bone Marrow	3(0.8%)	0(0.0%)	NS
Liver	0(0.0%)	2(0.4%)	NS
Node	1(0.3%)	8(1.7%)	NS
Pleura	2(0.5%)	5(1.0%)	NS
Rib	0(0.0%)	1(0.2%)	NS
Skin	0(0.0%)	2(0.4%)	NS
Open Lung	2(0.5%)	1(0.2%)	NS
Neck Mass	0(0.0%)	1(0.2%)	NS
Pleural tap	4(1.1 %)	7(1.5%)	NS
Thoracotomy	1(0.3%)	4(0.8%)	NS
Lobectomy	2(0.5%)	1(0.2%)	NS
Autopsy	0(0.0%)	1(0.2%)	NS
Unspecified	20(5.4%)	24(5.0%)	NS
Total (%)	**367(100.0%)**	**479(100.0%)**	

*More than a single modality of diagnosis was utilized in some patients

3.8 The radiological features in 778 lung cancer patients

The majority of lung cancer patients had chest masses on chest radiograph. Lung masses were documented in 130 black patients (41.5%) versus 227 white patients (49.9%). More of the white patients had a lung mass ($p<0.0001$). Hilar masses were found in 66 black patients (21.2%) compared to 100 white patients (22.0%). Mediastinal masses were found in 8 black patients (2.6%) compared to 10 white patients (2.2%). The second commonest radiological feature was pleural effusion, seen in 48 black patients (15.3%) compared with 34 white patients (7.5%). Lung atelectasis was a feature in 45 black patients (14.4%) versus 40 white patients (8.8%). There was a nonspecific lung infiltrate in 6 black patients (1.9%) compared to 23 white patients (5.1%). Consolidation was found in 10 black patients (3.2%) versus 15 white patients (3.3%). Only white patients showed evidence of hilar nodes 1 (0.2%) and a pericardial effusion 1 (0.2%). There were 4 white patients (0.9%) with normal chest radiograph (Table 3.8).

Table 3.8: Radiological features of lung cancer in 778 patients*

CXR	Black (%)	White (%)
Mass		
Lung	130(41.5%)	227(49.9%)
Hilar	66(21.2%)	100(22.0%)
Mediastinal	8(2.6%)	10(2.2%)
Pleural Effusion	48(15.3%)	34(7.5%)
Lung atelectasis	45(14.4%)	40(8.8%)
Infiltrate	6(1.9%)	23(5.1%)
Consolidation	10(3.2%)	15(3.3%)
Hilar Nodes	0(0.0%)	1(0.2%)
Pericardial Effusion	0(0.0%)	1(0.2%)
Normal	0(0.0%)	4(0.9%)
Total	**313(100.0%)**	**455(100.0%)**

* Data is available for 768 lung cancer patients

3.9 The histological types of lung cancer in 778 patients stratified by race

The histological types of lung cancer in decreasing frequency in black patients were squamous cell carcinoma in 153 (45.4%), adenocarcinoma in 72 (21.4%), small cell carcinoma in 41 (12.2%), large cell carcinoma in 38 (11.3%) and other carcinomas in 33 (9.8%).The histological types of lung cancer, in decreasing frequency, in white patients were squamous cell carcinoma in 188 (42.6%), adenocarcinoma in 95 (21.5%), small cell carcinoma in 88 (20.0%), other carcinomas in 40 (9.1%) and large cell carcinoma in 30 (6.8%) (Table 3.9a).

Small cell carcinoma was overall more common in white patients. In the white patients it was more common among the males than the females, whereas in the black patients it was found exclusively in females as demonstrated in table 3.9a and 3.9b

($p<0.005$).

Table 3.9a: Histological types of 778 lung cancer patients stratified by race

Histology	**Blacks (%) n=337**	**Whites (%) n=441**
Squamous cell	153(45.4%)	188(42.6%)
Adenocarcinoma	72(21.4%)	95(21.5%)
Small cell	41(12.2%)	88(20.0%)
Large cell	38(11.3%)	30(6.8%)
Other*	33(9.8%)	40(9.1%)
Total	**337(100.0%)**	**441(100.0%)**

*Includes the following histological subtypes: mixed small and squamous cell, mixed small and large cell, mixed adenosquamous, intermediate cell and indeterminate.

The histological types of lung cancer as stratified by gender and race are detailed below in table 3.9b

Table 3.9b: The histological types of 778 lung cancer patients stratified by race and gender*

Histology	Black males (%) n=237	Black females (%) n=88	White males (%) n=307	White females (%) n=120
Squamous cell	137(57.8%)	12(13.6%)	127(41.4%)	54(45.0%)
Adenocarcinoma	46(19.4%)	24(27.3%)	55(17.9%)	38(31.7%)
Small cell	0(0.0%)	40(45.5%)	85(27.7%)	1(0.8%)
Large cell	30(12.7%)	7(8.0%)	19(6.2%)	10(8.3%)
Other**	24(8.4%)	5(5.8%)	21(6.8%)	17(14.2%)
Total	**237(100.0%)**	**88(100.0%)**	**307(100.0%)**	**120(100.0%)**

*Lung cancer data stratified by race and gender on 752 patients

**The following histological types form the other group: mixed small and squamous cell, mixed small and large cell, mixed adenosquamous, intermediate and indeterminate cell types

3.10 The operability of 778 lung cancer patients stratified by race

With regard to operability 29 black patients (8.6%) were considered to be operable versus 45 white patients (10.2%). Overall 262 black patients (77.7%) and 358 white patients (81.2%) were considered inoperable (Table 3.10).

Table 3.10: The operability of 778 lung cancer patients stratified by race*

Operability	**Black (%) n=337**	**White (%) n=441**	**Total (%) n=778**
Yes	29(8.6%)	45(10.2%)	74(9.5%)
No	262(77.7%)	358(81.2%)	620(79.7%)
Unknown	46(13.6%)	38(8.6%)	84(10.8%)
Total	**337(100.0%)**	**441(100.0%)**	**778(100%)**

*Only 694 patients had data of operability with intent to cure.

Chapter 4: DISCUSSION

4.1 Patient demographics

In this study, 817 patients were enrolled, of whom 778 were black and white patients; the remaining population consisted of a total of 39 mixed race or Indian patients (Table 3.1). Of the study group 54.0% were white patients and 41.3% black patients.

The mean age of the study population was middle age, a fact that is reflected in worldwide data of patients with lung malignancy. The black patients were significantly younger than the white patients (Table 3.6a).

The majority of patients were male. This fact reflects the smoking pattern of the population (Van Walbeek, 2002). This trend is in keeping with the international norm. The incidence of lung cancer among men in Denmark, Finland, Germany (Saarland), Italy (Varese), the Netherlands, Switzerland and the United Kingdom has been increasing dramatically until the early 1980s, where after it has been declining (Janssen-Heijnen and Coebergh, 2003). The majority of the lung cancer patients were smokers; this confirms the causative association between lung malignancy and cigarette smoking. Black females smoked less compared to

their white counterparts. They also smoked less compared to the male patients irrespective of race. The smoking pattern of the white patients irrespective of gender was significantly more than the black patients, as reflected in pack years (Table 3.6b). In contrast, American black adults have a higher prevalence of smoking, despite a decline in the general population, a fact which has been persistent for several years (Flenaugh *et al*, 2006). A matching observation though is the fact that black patients, internationally, are light smokers.

4.2 Mode of diagnosis

The majority of patients were diagnosed using bronchoscopy (57.7%), followed secondly by sputum cytology (18.3%). This may be a reflection of expertise available within the tertiary services, and to some extent the difficult nature of the patients presenting to the pulmonology units of our institutions (Table 3.2). The Western Cape experience, as described by Abdullah and Wilcox (1998), documented the use of fine needle aspiration as the common modality of diagnosis in their tertiary institution. More of the black patients were sputum cytology positive, while the remaining modalities utilized to diagnose lung malignancy showed no racial bias (Tables 3.2 and 3.7).

4.3 Radiological features

The majority of patients had a mass on chest radiograph; these masses were either in the lungs, hilar area or mediastinal distribution (Table 3.3). There were more white patients with presence of a lung mass in the radiological features of these patients (Table 3.8)

4.4 Histological types of lung cancer

The lung cancer cell types in descending order of frequency were squamous cell, adenocarcinoma, small cell carcinoma, large cell carcinoma and the rest were mixed types (Table 3.4). This distribution is a reflection of the smoking patterns of the study population, with the majority being cigarette smokers. The rank frequency of the histological distribution did not reflect a racial disparity, an observation which is not supported by other international and local data (Table 3.9a). Black patients internationally have shown a propensity to develop adenocarcinoma, with black male smokers in the majority. Alberg *et al* (2005) noted that lung cancer was of similar prevalence among black and white American women, while to the contrary black American men had a higher occurrence when compared to American white men.

In this study white males and black females had a tendency to develop small cell carcinoma in the majority of cases, a fact unexplained by their smoking pattern. The other genders had squamous cell carcinoma as the most common cell type (Table 3.9b). In white males small cell carcinoma was the second common histologic type followed thirdly by adenocarcinoma. Adenocarcinoma was the second common tumor amongst black males and white females (Table 9b). This observation is in contrast to the international trend, where adenocarcinoma has overtaken squamous cell carcinoma among all gender groups (Alberg *et al* 2005; Belani *et al*, 2007). In the developed world, smoking related cancer was initially squamous cell carcinoma for decades followed by small cell carcinoma (Alberg et al, 2005).

4.5 Operability

Ten percent (9.5%) of the patients diagnosed with lung cancer were operable. The operability of both black patients (8.6%) and white patients (10.2%) was dismal. This observation fares badly compared to an internationally acceptable norm of 15-25% (Bolliger, 2003).Due to the high incidence of inoperability, it is anomalous that only one patient was reported radiologically to have regional lymphadenopathy. The reliability of the radiological features is doubtful.

4.6 Limitations of the study

A major limitation of this study is that it was a record of patients documented between 1992 and 1998 and that more recent changes in the demographic and histological features of lung cancer that have been demonstrated in a number of areas of the world, would not have been have been reflected in the current investigation.

The 1999 WHO/IASLC histological classification of lung and pleural tumors was not utilized in our study patients (Brambilla *et al*, 2001). There is also a recently published new TNM staging of lung cancer which was not utilized in the study (Sobin *et al*, 2009).

And the last limitation of this study is the presence of some missing data, though very little, which is a common problem in most retrospective reviews.

4.7 Conclusion

The black patients with lung cancer tended to present younger than white patients. The smoking pattern as demonstrated by pack-years was significantly different, in that black patient with lung cancer smoked less than white patients.

This study did not demonstrate ranked frequency differences in histologic cell types between black and white patients with lung cancer. This raises further questions as to the role of pre-morbid diseases, dietary history, genetic susceptibility and/ or the manufacturing and types of cigarettes smoked

THE FUTURE

This study did not show histological differences in lung cancer when comparing black and white patients, although there were differences in the age of presentation and smoking patterns. Black patients presented at a significantly younger age and had a significantly lower pack year smoking history, suggesting that there may be a difference in susceptibility of black and white patients to lung cancer in relationship to cigarette smoking. Further research to try and determine the factor(s) related to this possible increase in the susceptibility of black patients should investigate the possible role of genetic factors, the types of tobacco and/or cigarettes smoked and determine the presence of any possible pre-morbid disease states that could be promoting the development of lung cancer at an early age.

However in the first instance, it would be important to repeat this study, including patients from more recent years, to determine whether the findings and the differences seen still remain or whether changes have occurred particularly with consideration of the new classification of histology and staging.

Other questions that need to be answered are the following

- The role of occupation in determining histological cell subtypes.
- The status and role of HIV in the development of lung cancers in patients who are HIV positive with or without HAART. Furthermore the possible carcinogenic role of HIV and HAART needs to be investigated further.
- To define the role of biomass fuel in the development of lung cancer especially in black females with a negligible smoking history.
- To establish the standard of care in the screening of patients at high risk of lung cancer

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