ANALYSIS OF BRONCHOSCOPIES PERFORMED AT CHRIS HANI BARAGWANATH HOSPITAL BETWEEN 2011–2018

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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 the branch of Internal Medicine

Johannesburg, 2021

Declaration:

I declare that this research report is my own, unaided work.

It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg.

This research report is submitted in the publishable format as recognised by the Faculty of Health Sciences.

It has not been submitted before for any degree or examination at any other University

_____A.O AJAYI_____

Signed on the 1st day of September 2020 at Johannesburg

Abstract

Background

A definitive diagnosis of respiratory disease is often elusive without tissue biopsy. Bronchoscopy is a valuable procedure to both visualise and sample endobronchial lesions and lung parenchyma.

Objectives

We describe patient demographics, indications for, and diagnosis of, patients undergoing fibreoptic bronchoscopy at Chris Hani Baragwanath Academic Hospital (CHBAH) over an 8-year period (2011-2018). We also describe associations between demographic characteristics and diagnosis.

Methods

This is a retrospective record review of patients who had undergone fibreoptic bronchoscopy at CHBAH. Demographic, clinical and histopathological data were collected.

Results

Bronchoscopy records were retrieved for 830 patients. Two thirds of patients were male; the mean (SD) age of patients was 56.2 (13.3) years. Twenty-two percent of patients who had bronchoscopy were seropositive for HIV, with a median cluster of differentiation 4 (CD4) cell count of 233 cells/mm^3 (IQR: 85-434). Bronchoscopies were performed mostly for suspected endobronchial lesions (52%) and pulmonary infiltrates (12%). Endobronchial biopsy was performed in half of patients undergoing bronchoscopy.

The most common diagnosis was primary lung malignancy, found in 39% of patients. Squamous cell carcinoma was the commonest subtype (43%) and adenocarcinoma was diagnosed in 31%. Increasing age was significantly associated with a diagnosis of malignancy [OR 95% CI, 1.05 (1.04-1.06)] $p<0.001$. Women and HIV positive patients were less likely to be diagnosed with malignancy compared to men and HIV negative patients. Our study revealed that the complication rate during bronchoscopy was 2.16%.

Conclusion

In this retrospective study, flexible bronchoscopy was found to be a useful tool aiding the diagnosis of respiratory diseases and had a low complication rate. An endobronchial lesion was detected in

44% of the patients undergoing bronchoscopy and the commonest diagnosis was primary lung cancer.

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To my lovely wife, Adetoun, for her patience, constant support, understanding and love.

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Nomenclature

BAL	Bronchoalveolar lavage
BB	Bronchial biopsy
BW	Bronchial washing
CD_4	Cluster of differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
EBB	Endobronchial biopsy
EPM	Extra-pulmonary malignancy
HIV	Human immunodeficiency virus
ILD	Interstitial lung disease
KS	Kaposi sarcoma
NHL	Non –Hodgkin Lymphoma
NHLS	National Health Laboratory Service
NSCLC	Non-small cell lung cancer
NTM	Nontuberculous mycobacterium
PLC	Primary lung cancer
RP-EBUS	Radial probe endobronchial ultrasound
SA	South Africa
SCLC	Small cell lung carcinoma
STATS SA	Statistics South Africa
TB	Tuberculosis
TBB	Transbronchial biopsy

CHAPTER 1 – PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction and Epidemiology

Respiratory disease accounts for a significant proportion of morbidity and mortality globally. It is estimated that annually, four million people die untimely from chronic respiratory disease.[1]

According to figures released by Statistics South Africa (STATS SA), tuberculosis (TB), pneumonia, influenza and chronic respiratory diseases were amongst the top ten causes of mortality among South Africans in 2016, with tuberculosis being the most common cause of death in South Africa (SA).[2]

In 2018, lung malignancy was estimated to account for 11.6% of all malignancies. Annually, up to two million people are estimated to die of lung malignancy worldwide.[3] In SA, according to the national cancer registry, 2 727 cases of lung malignancy were recorded among South African patients in 2014. Of these cases, 1 791 (66%) were recorded among men. Overall, lung malignancy constituted approximately 5% of all malignancies affecting men in that year, with an estimated lifetime risk of 1 in 80. For South African women, 936 cases of lung malignancy were reported in 2014, comprising approximately 3% of all malignancies in women reported for that year.[4]

While many diagnostic techniques are available in arriving at the correct diagnosis in the discipline of Pulmonology, the advent of bronchoscopy has revolutionised the practice of Pulmonology as it enables clinicians to visualise the respiratory tract in its diseased state while also enabling the collection of samples for histological and microbiological examination.

1.2 An Overview of Bronchoscopy

Bronchoscopy is a procedure by which a bronchoscope is inserted via the mouth or nose into the respiratory tract with the purpose of inspecting, analysing and obtaining samples that might assist in diagnosis of a variety of pulmonary conditions. Bronchoscopy may also serve a therapeutic role in a variety of other indications, such a foreign body removal.[5]

Bronchoscopy was first developed by Gustav Killian, who is regarded as the father of bronchoscopy. He was the first person to view the bronchial tree in a therapeutic attempt at foreign body removal.[5, 6] The fibreoptic bronchoscope was devised by Ikeda in 1967, with subsequent modification over the years enhancing its ease of use and its overall diagnostic performance.[5, 6, 11]

Bronchoscopy may be performed with either a rigid or flexible bronchoscope. The rigid bronchoscope comprises a straight metal tube with a bevelled distal tip that goes into the trachea. It is

particularly useful for procedures such as the removal of foreign bodies in the bronchial tree, the management of haemoptysis and dilatation or stenting of the tracheobronchial tree. It is more durable than a flexible bronchoscope.[7]

The flexible bronchoscope may also be referred to as a fibreoptic bronchoscope. The fibreoptic bronchoscope consists of the handle that contains an eyepiece, a suction button and a port to access the suction channel. In addition to the suction port, a separate port is positioned which enables the administration of local anaesthetic and oxygen.[7] A fibreoptic bronchoscope contains between 5 000 – 40 000 fibres which are aligned for image production. With time, there has been an evolution in the development of fibreoptic bronchoscopes with particular emphasis on ease of use, effectiveness and infection control. This has resulted in the development of disposable systems that do not contain fibreoptic cables, but rather consist of a distal camera which is illuminated by a light emitting diode, which transmits images onto a reusable screen. This system is cost-effective and has the advantage of reducing cross-infection among patients.[7]

Since the discovery of bronchoscopy and the subsequent widespread availability of video bronchoscopes, bronchoscopy has emerged as a cornerstone of the diagnosis of lung malignancies. However, bronchoscopy is largely ineffective at visualisation of the entire bronchial tree, as the standard bronchoscope (which measures 5.9 mm in diameter) can only see as far as one-third of the 23-generation bronchial tree. Bronchoscopy therefore misses lesions further down the bronchial tree. It is also noted that with the use of white light, subtle mucosal changes seen in squamous carcinoma *in situ* and squamous dysplasia may be missed. Mediastinal lymph nodes cannot be directly visualised using a bronchoscope.[6, 8] These drawbacks have resulted in the development of more advanced techniques that enhance the diagnostic yield of bronchoscopies. These techniques include narrow band imaging, autofluorescence bronchoscopy, endobronchial ultrasound with transbronchial biopsy and electromagnetic navigation bronchoscopy.[6] The narrow band imaging technique is effective in assessing endobronchial lesions; it has a higher sensitivity and specificity compared to standard white light bronchoscopy. Autofluorescence bronchoscopy creates a disparity between normal lung lesions and diseased bronchial tissue, which results in a greater diagnostic yield on biopsy (especially for non-visible endobronchial lesions).[6, 8]

Additional techniques include optical coherence tomography and confocal microscopy that allow for the assessment of lung lesions at cellular level. Optical coherence tomography technique allows for differentiation of benign and malignant endobronchial lesions; it elicits differences between carcinoma *in situ* and minimally invasive carcinoma.[6]

For peripheral lung lesions, the radial probe endobronchial ultrasound (RP-EBUS) technique allows for the visualisation of peripheral lung lesions and helps assess the depth of invasion of endobronchial lesions with a specificity of 100% and sensitivity of 89%. It has 94% accuracy for assessing tumour invasion.[6] Along with electromagnetic navigation bronchoscopy, virtual bronchoscopy and ultrathin bronchoscopy, these techniques have a higher diagnostic accuracy comparable with routine transbronchial biopsy.[6] With respect to mediastinal lesions, the convex probe endobronchial ultrasound-guided transbronchial aspirate has a sensitivity approaching that obtained from a mediastinoscopy with fewer complications.[6]

Other technology that has been developed include high definition bronchoscopy with real time image enhancement that is able to detect additional separate lesions in a third of patients as compared to standard bronchoscopy.[9] This technique results in a higher diagnostic yield and better accuracy in both endobronchial and peripheral lesions. This ensures timely diagnosis and reduced morbidity and mortality of patients with lung malignancies.[6, 7, 9, 10]

1.3 The Bronchoscopic Procedure

Requirements for the bronchoscopy procedure include a well-equipped bronchoscopy suite, trained personnel and appropriate resuscitation equipment.[11, 12] A patient with a suitable indication for bronchoscopy should have an appropriate history and physical examination pre-procedure, and have signed informed consent. Laboratory results should be checked, this includes a full blood count, urea and electrolytes and a coagulation profile. In most cases, the procedure is performed under conscious sedation which can be administered by a skilled assistant or an anaesthetist. An anaesthetist is required if general anaesthesia is administered. Post-procedure, a chest x-ray should be performed to exclude procedure-related complications such as a pneumothorax and monitoring should continue in the immediate period post-bronchoscopy.[11, 12]

1.4 Bronchoscopic Techniques

During bronchoscopy, a variety of methods can be used to obtain appropriate samples for laboratory examination. These include bronchial washings (BW), bronchial brushings (BB), bronchoalveolar lavage (BAL), direct bronchial biopsy, endobronchial ultrasound for visualisation of lesions followed by biopsy and transbronchial lung biopsy. Bronchoscopy is a valuable diagnostic procedure, especially when combined with cytological, microbiological and histopathological examination of samples obtained during the procedure.[11-14]

1.4.1. Bronchial washings

Bronchial washings are obtained by aspiration after the instillation of saline via the bronchoscope channel. This modality is especially important in diagnosing pulmonary infections such as pneumonia, tuberculosis (TB) and fungal infections. It is also effective in obtaining cytological specimens that aid in diagnosing lung malignancies; however, the yield is low. In non-intubated patients, the specimen obtained during BW can be contaminated by upper airway secretions.[11]

1.4.2. Bronchial brushings

This technique involves the collection of samples using a thick cytology brush which collects samples from visualised suspicious areas of the endobronchial tree. It is indicated for collection of samples for cytological examination in cases with suspected malignancies. A recognised side-effect of BB is an increase in post-procedure mucosal bleeding.[11]

1.4.3. Bronchoalveolar lavage

Bronchoalveolar lavage is a similar technique to BW, however it samples a larger part of the endobronchial tree. It is estimated that up to 1% of the lung surface is sampled during a good quality BAL procedure. [11] This procedure involves wedging the bronchoscope in a segmental bronchus, which helps isolate other segments of the airway besides the one being sampled. The specimen obtained can be sent for cytological examination, microscopy and culture and also TB polymerase chain reaction testing. In addition, BAL is of diagnostic importance in primary pulmonology conditions such as the eosinophilic pneumonias, pulmonary alveolar proteinosis, and pulmonary involvement by malignancies such as lymphangitic carcinomatosis.[11]

1.4.4 Transbronchial biopsy (TBB)

This technique ensures the collection of full thickness bronchial and alveolar parenchymal tissue for histological examination. The technique involves wedging the bronchoscope in the affected area and samples are then obtained from this area with the aid of biopsy forceps. Transbronchial biopsy can be complicated by pneumothorax. For a good diagnostic yield, four to ten biopsy specimens are required for histopathological evaluation.[11, 12]

1.4.5 Endobronchial biopsy (EBB)

This bronchoscopic technique involves obtaining samples from within the endobronchial tree for histopathological diagnosis. Recognised side-effects of this technique include haemorrhage and

pneumothorax. The yield from this technique is high as it involves visually-directed sampling of suspicious lesions.[11, 12]

1.5 Indications for Bronchoscopy

1.5.1 Diagnostic indications for bronchoscopy

Bronchoscopy may be used in order to evaluate and diagnose multiple pathological processes.[11,13] These include the evaluation of the different aetiologies of the signs and symptoms of pulmonary disease such as haemoptysis, stridor, unilateral wheezing, hoarseness and unexplained chronic cough. In the setting of suspected pulmonary infections, bronchoscopy may be employed. Indications in this setting may include pneumonia in an immunocompromised host, non-resolving pneumonia, evaluation of a cavitary lesion, ventilator-associated infections and suspected drug-resistant organisms. Diffuse lung disease such as atypical chronic interstitial lung disease, acute and subacute diffuse consolidative conditions, diffuse alveolar damage and haemorrhage, drug-induced lung disease, parenchymal nodules and masses may be diagnosed with bronchoscopy.[11, 13]

In the setting of a known or suspected malignancy, indications for bronchoscopy may include the evaluation of an endobronchial tumour, mediastinal or hilar adenopathy or mass, airway compression by invasion, as well as for the early detection of central lung malignancies.

Miscellaneous indications for bronchoscopy include airway stent evaluation, evaluation of benign airway diseases and strictures, diagnosis of tracheoesophageal fistula, lung transplant surveillance, thermal and chemical airway injury and confirmation of endotracheal tube position.[11, 13]

1.5.2 Therapeutic indications for bronchoscopy

Bronchoscopic intervention may be indicated for the relief of malignant central airway obstruction. This can be achieved via the use of laser, argon plasma coagulation, cryotherapy, brachytherapy, photodynamic therapy and electrocautery snare.[11,13]

Other treatment modalities for airway compression from extrinsic tumours include the use of self-expandable airway stents. In the setting of benign central airway obstruction, radial cuts, balloon dilatation, airway stenting and intrabronchial injections may be administered via the bronchoscope.

Treatment of fistulas including both tracheoesophageal and bronchopleural fistulas may be done via stenting and laser-induced closure in the setting of tracheoesophageal fistulas, and via airway spigots, endobronchial valves and sealants in the setting of bronchopleural fistulas.

Miscellaneous indications which may be treated with bronchoscopy include the aspiration of cysts, abscess drainage, bronchial thermoplasty and endoscopic lung volume reduction. Other miscellaneous indications include bronchoscopic intubation and the removal of mucous plugs and foreign bodies.[13]

1.6 Complications of Bronchoscopy

Due to the fact that bronchoscopy is an inherently invasive procedure, it is associated with some procedure-related risks. Such risks include laryngospasm, bronchospasm, arrhythmias, hypoxaemia and bronchial perforation. Other complications that have been identified include marked airway haemorrhage, pneumothorax, severe hypercapnia, seizures, and cardiac arrest.[11,13,14]

Bronchoscopy is relatively safe procedure. In a study conducted in Brazil in 2018, a total of 1 949 bronchoscopies were analysed. The mild adverse event rate was noted to be 7.2% overall, with a severe adverse event rate at 0.1% and 0.4% for severe bleeding and pneumothorax, respectively.[15]

1.7 Diagnostic Yield of Bronchoscopy

Multiple studies worldwide have analysed the histopathology of specimens obtained during bronchoscopy. In a study conducted in India, an assessment of histopathological results from patients with lung malignancy diagnosed on bronchoscopy was performed. This study revealed that squamous cell carcinoma was the commonest primary bronchial tumour (62.2%) followed by adenocarcinoma (26.7%). The diagnostic yield of fibreoptic bronchoscopy procedures was 100% (32/32 patients) in bronchoscopically visible tumours. Bronchial biopsy was noted to be the most sensitive (100%) in the study followed by bronchial washing (BW) (88%) and bronchoalveolar lavage (BAL) (81.3%). However, in bronchoscopically non-visible tumours, biopsy, bronchial brushings and BAL yielded diagnostic specimens in 84.6%, 76.9% and 46.1% of cases, respectively.[16]

In another study, researchers identified 110 patients with suspicious lesions on chest radiography. Bronchoscopy was performed and samples were obtained. Fifty-five percent of the lesions were malignant, and 18% were found to be inflammatory. In this series, squamous cell carcinoma was found to be the most common form of lung malignancy (35%), followed by adenocarcinoma (9%) and small cell carcinoma (7.2%). Ten percent of the samples analysed were found to be inadequate, while 2% were found to be inconclusive. In this study the authors concluded that overall diagnostic yield of bronchial biopsy was 88.2%.[17]

In an older study conducted in 2004, 90 patients with either clinical or radiographic evidence suggestive of lung malignancy had bronchoscopy performed. The histologically-confirmed diagnosis of lung malignancy was made in 72% of these patients. The researchers found that the overall diagnostic yield by all three of the available sampling techniques to be 80%. Endobronchial biopsy yielded a positive result in 76.9% of cases, bronchial brushing in 61.5% and BW in 70.76% of cases. It was concluded that for optimal yield in the diagnosis of lung malignancy, bronchoscopists should use all three diagnostic techniques, namely biopsy, brushing and washing. Histopathological results can be optimised in peripheral lesions > 4 cm in diameter by performing both washing and brushing even without fluoroscopic guidance.[18]

In a study performed to assess the efficacy of the different modalities of sample retrieval during bronchoscopy, from a total of 347 specimens obtained via BW, BAL and bronchial biopsy, 60% of cases were positive for malignancy based on cytological examination, while 72% were diagnosed on histopathological examination. The authors noted that the highest sensitivity and greatest diagnostic yield was obtained from BB as compared to BW and BAL, with the overall sensitivity of BB, BAL and BW noted as 94%, 72% and 25% respectively.[19] In the series highlighted above, squamous cell carcinoma was the most common histological variant diagnosed on both cytological and histopathological evaluation. The authors in this study also concluded that a combination of different sampling methodologies on bronchoscopy increases the diagnostic accuracy.

Much of the literature reviewed focused on the diagnosis of predominantly malignant conditions. Histopathological examination of bronchoscopy specimens can also assist in the diagnosis of non-malignant conditions. In a Brazilian study of patients whose sputum microscopy tested auramine negative for TB, bronchoscopy and histopathology of specimens obtained during the procedure revealed pulmonary TB in 127 patients (44%). Other infections including Pneumocystis pneumonia, fungal infections, or nocardiosis were diagnosed in 20 patients (7%). Non-specific chronic inflammation was demonstrated in 51 patients (18%); bronchiolitis obliterans organizing pneumonia, alveolitis, or pneumoconiosis in 14 patients (5%); lung or metastatic neoplasms in 7 patients (2%); and non-tuberculous mycobacterial (NTM) infections in 6 patients (2%). [20] For the diagnosis of TB, BAL showed a sensitivity and a specificity of 60% and 100% respectively. The authors concluded that bronchoscopy is a reliable method for the diagnosis of pulmonary TB, with low complication rates.[20]

In a study conducted in Durban, South Africa in 2014, the commonest indications for bronchoscopy were investigation of a lung mass (35.8%), non-resolving lower respiratory tract infection (15%) and

suspected TB (15%). Cytological analysis of BAL samples in the Durban series detected pathology in eight (13.1%) patients and two (3.3%) of these patients had lung cancer. Malignant (52.9%) (squamous cell carcinoma and adenocarcinoma) and benign (11.1%) (pneumonia and interstitial fibrosis) pathology were found on histology. Squamous cell carcinoma (37%) was the commonest lung cancer detected.[21] Bronchoscopy also assisted with the diagnosis of lung cancer in 20 of 43 (46.5%) patients referred with suspected lung mass. Overall the procedure complication rate in this series was 3.7%.[21]

In a study conducted in Cape Town, South Africa, bronchoscopy was considered a safe procedure with no major complications or adverse events evident in either healthy or diseased participants included in the study. Of those partaking in the post-bronchoscopy survey, 82% of participants described the procedure as tolerable, with an estimated repeatability rate of 82%. Only 14% of participants presented with minor post bronchoscopy symptoms, mainly reports of a sore throat.[22]

Studies analysing bronchoscopies are sparse in South Africa. Chris Hani Baragwanath Academic Hospital in Soweto is a large hospital serving close to 2 million people that reside in the area and its environs. Many conditions encountered in Pulmonology present a diagnostic conundrum and these conditions may require interventional pulmonology techniques in making the definitive diagnosis. A Pulmonology department within the hospital has the expertise and equipment required for fibreoptic bronchoscopy. Owing to the paucity of data surrounding the South African context, as well as the increased burden of HIV-associated infections such as TB and NTM, it would be worthwhile to analyse the indications for, and yield of, bronchoscopies in this setting.

Due to the high HIV prevalence in South Africa, it may be anticipated that infectious causes of pathology may be more prevalent in the findings as compared to that described in other countries. An evaluation of bronchoscopies performed at CHBAH has not been published. It is proposed that the findings from the local setting may have a different picture compared to the findings reported from other countries.

2. Aim of the Study

The aim of this study will be to analyse the results of bronchoscopies performed at CHBAH over an 8-year period, determining the variety of diagnoses on samples obtained during the procedure. The period 2011 – 2018 was chosen as the records were readily available and had never been analysed. The study will also aim to determine any associations between the diagnosis made and demographic variables assessed.

3. Study Objectives

- To describe the demographic characteristics of patients that have undergone fibreoptic bronchoscopy at CHBAH between 01 January 2011- 31 December 2018.
- To describe the HIV status and CD4 counts of patients undergoing bronchoscopy at CHBAH between 01 January 2011- 31 December 2018.
- To describe the indications for bronchoscopy at CHBAH between 01 January 2011- 31 December 2018.
- To describe the bronchoscopic findings during the procedure for bronchoscopy at CHBAH between 01 January 2011- 31 December 2018.
- To determine the variety and frequency of diagnoses obtained from bronchoscopy samples taken at CHBAH between 01 January 2011- 31 December 2018.
- To determine possible associations between patient demographic findings and subsequent bronchoscopic diagnosis.

4. Methods

This study will make use of the bronchoscopy register that is kept in the bronchoscopy suite within the Pulmonology department at CHBAH. The required data for analysis has been captured on a standardised bronchoscopy report which is completed for every patient that has undergone the procedure at the hospital by the Pulmonologist who performed the bronchoscopy.

The results of samples acquired during the procedure will be accessed on the online laboratory database managed by the National Health Laboratory Service (NHLS). Permission to carry out the study will be obtained from the Head of the Department of Internal Medicine and hospital management of CHBAH. Ethics approval will be sought from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

5. Data Analysis

Data will be extracted from the bronchoscopy reports and thereafter captured on Microsoft Excel. This data will be imported into Stata 15® for statistical analysis. Descriptive statistics such as the frequencies of distribution, means and standard deviations will be calculated. Frequencies will be computed for categorical variables such as gender. The total number of the various diagnoses will be tallied and described in percentages. Associations between common bronchoscopic diagnoses (cancer, chronic non-specific inflammation, infections and sarcoidosis) and age, gender and HIV

status will be explored .Univariate logistic regression models for age, gender and HIV status will be fitted with specific diagnoses. Multivariate logistic regression models will be adjusted for age, gender and HIV status. P values <0.05 will be considered statistically significant.

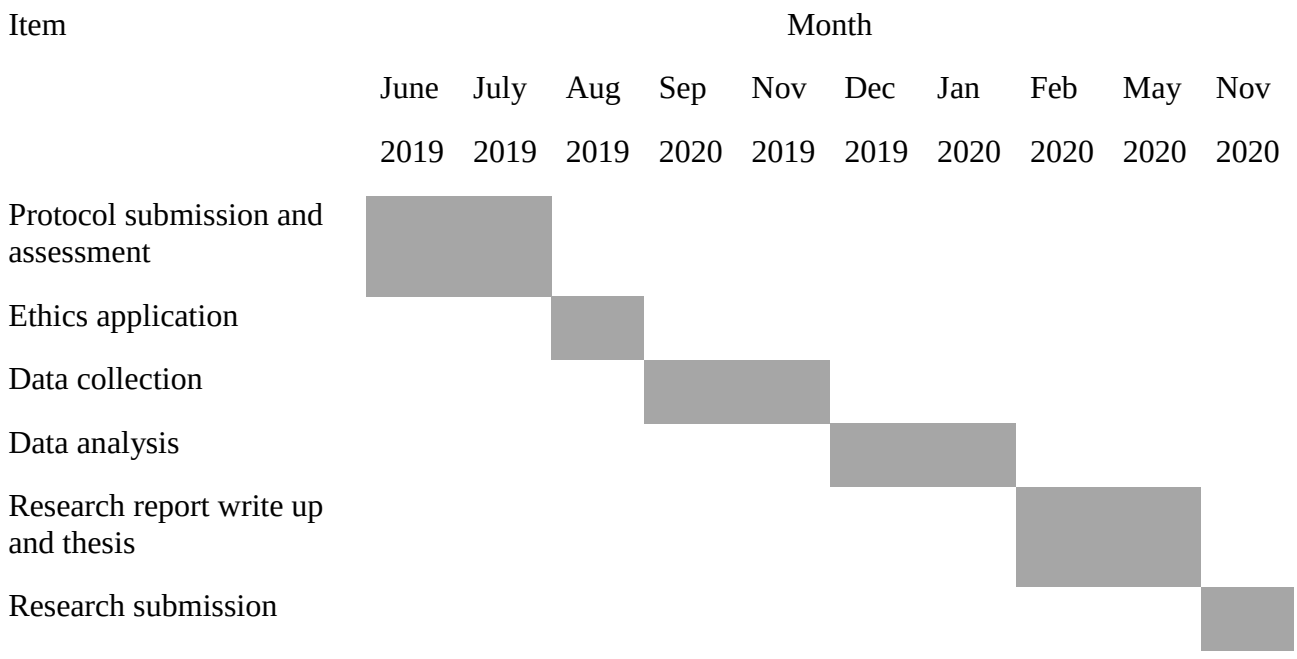
6. Ethics

This study will make use of data recorded in the bronchoscopy register and reports stored within the Pulmonology department at CHBAH. The results of specimens submitted to the NHLS will be retrieved from the NHLS TrakCare online system using unique patient identifiers such as specimen barcode numbers and hospital numbers.

Complete anonymity of the patients will be ensured by encoding patient identifiers numerically on a list that will be kept separately from study material, and stored in a locked cupboard. All study data will be recorded on a secure computer which will be password protected. Permission to access data belonging to the NHLS will be sought.

Permission to conduct the study will also be obtained from the Head of the Department of Internal Medicine at CHBAH, as well as CHBAH Management. Ethics clearance will be obtained from the Wits Human Research Ethics Committee.

7. Project outline



8. Budget and Funding

This project will be self-funded and no costs will be incurred by the hospital.

Item	Cost
Stationery	R2 500
Total	R2500

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CHAPTER 2 – SUBMISSIBLE ARTICLE

Title: Analysis of Bronchoscopies performed at Chris Hani Baragwanath Hospital between 2011-2018.

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Background

A definitive diagnosis of respiratory disease is often elusive without tissue biopsy. Bronchoscopy is a valuable procedure to both visualise and sample endobronchial lesions and lung parenchyma.

Objectives

We describe patient demographics, indications for, and diagnosis of, patients undergoing fibreoptic bronchoscopy at Chris Hani Baragwanath Academic Hospital (CHBAH) over an 8-year period (2011-2018). We also describe associations between demographic characteristics and diagnosis.

Methods

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Results

Bronchoscopy records were retrieved for 830 patients. Two thirds of patients were male; the mean (SD) age of patients was 56.1(13.3) years. 74 % of our study population had their HIV status reported in the bronchoscopy report. Twenty-two percent of this population was seropositive for HIV with a median CD4 count of 233 cells/mm^3 (IQR: 85-434). Bronchoscopies were performed mostly for suspected endobronchial lesions (52%) and pulmonary infiltrates (12%). Endobronchial biopsy was performed in half of patients undergoing bronchoscopy.

The most common diagnosis was lung malignancy, found in 39% of patients. Squamous cell carcinoma was the commonest subtype (43%) and adenocarcinoma was diagnosed in 31% of patients with primary lung malignancy. Increasing age was significantly associated with a diagnosis of malignancy [OR 95% CI, 1.05 (1.04-1.06)] $p<0.001$. Women and HIV positive patients were less likely to be diagnosed with malignancy compared to men, and HIV negative patients. An extrinsic lesion noted on bronchoscopy in 3 % of the sample population. Our study revealed that the complication rate during bronchoscopy was 2.16%

Conclusion

In this retrospective study, flexible bronchoscopy was found to be a useful tool aiding the diagnosis of respiratory diseases and had a low complication rate. An endobronchial lesion was suspected in 52 % of cases and was visualized on bronchoscopy in 44%. The most common diagnosis was primary lung cancer.

INTRODUCTION

Respiratory infections account for a significant proportion of morbidity and mortality globally. It is estimated that annually, 4 million people untimely die from chronic respiratory disease.[1] According to figures released by Statistics SA, tuberculosis, pneumonia, influenza and chronic respiratory diseases were amongst the first ten causes of mortality among South Africans in 2016 with tuberculosis being the commonest cause of death. This alarming statistic emphasises the burden of respiratory illnesses on the well-being of South Africans.[2]

In South Africa, according to the National Cancer Registry, 1791 cases of lung malignancy were recorded among South African men in 2014, constituting about 4.87 % of all malignancies affecting men in that year with an estimated lifetime risk of 1:80 for lung cancer.[3] For South African women, 936 cases of lung malignancy were reported in 2014, forming about 2.48% of all malignancies reported for that year among women. This figures highlight the significant burden of lung malignancies with its attendant morbidity and mortality.[3]

The advent of bronchoscopy has revolutionised the practice of Pulmonology as it enables clinicians to adequately visualise the respiratory tract in its diseased state while also facilitating the collection of appropriate samples for histological and microbiological examination.

Bronchoscopy has a variety of therapeutic and diagnostic indications, examples of diagnostic indications for bronchoscopy include the evaluation of signs and symptoms of pulmonary disease such as haemoptysis, stridor, hoarseness etc. Others include evaluation of suspected pulmonary infections, evaluation of suspected interstitial lung disease and evaluation of suspected pulmonary malignancies.[4, 5]

Therapeutic indications include relief of airway obstruction, treatment of extrinsic tumours, treatment of tracheoesophageal fistula and bronchopleural fistula closure with the use of airway spigots, endobronchial valves and sealants.[4, 5]

Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto is a large hospital serving close to two million people that reside in the area and its environs. A Pulmonology department within the hospital has the expertise and equipment required for fibreoptic bronchoscopy. Owing to the paucity of data surrounding the South African context, as well as the increased burden of HIV-associated infections such as tuberculosis and non-tuberculous mycobacterial disease, it would be worthwhile to analyse the indications and yield of bronchoscopies in this setting. It is proposed that the findings

from the local setting may have a different scope compared to the findings reported from other countries.

The aim of our study was to analyse the results of bronchoscopies that have been performed at CHBAH, determining the variety of diagnoses on samples obtained during the procedure. The study aimed to determine any associations between the diagnosis made and age/gender of the patients assessed.

Methodology

Study design and setting

This was a retrospective descriptive and analytical study. The study made use of the bronchoscopy reports kept at the Pulmonology department at CHBAH. The required data for this study was captured by the bronchoscopist on a standardised bronchoscopy report which is completed for every patient. Histological, cytological and microbiological results were accessed from the online laboratory database managed by the National Health Laboratory Service (NHLS). Permission to conduct the study was obtained from the Head of the Department of Medicine, the hospital management of CHBAH and the Head of the Department of Anatomical Pathology at CHBAH. Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. (M190758)

From the standardised bronchoscopy report, the following information was extracted:

- Age of patient
- Gender of patient
- HIV status and if positive, the CD_4 count of the patient, if recorded
- Indication for the bronchoscopy
- Bronchoscopy findings
- Type of specimen obtained (bronchial washings, endobronchial biopsy, transbronchial biopsy)
- Diagnosis
- Complications of the procedure

Data collection

Data collection commenced in September 2019 and was completed in November 2019. Data was extracted from the bronchoscopy reports and the NHLS online database. This was entered onto Microsoft Excel 2013® spreadsheet for statistical analysis using Stata 15®.

Statistical analysis

Frequencies and proportions were used to describe categorical variables. Patient age at presentation was normally distributed and was further described in terms of mean and standard deviation. The CD_4 count did not follow a normal distribution, and was described using the median and interquartile range. We explored associations between common bronchoscopic diagnoses (malignancy, inflammation, infections and sarcoidosis) and age, gender and HIV status. Univariate logistic regression models were used for age, gender and HIV status with specific diagnoses. Multivariate logistic regression models were adjusted for age, gender and HIV status. $P<0.05$ was deemed to be statistically significant. All analysis was done using Microsoft Excel 2013® and Stata 15®.

Results

In terms of the indication for bronchoscopy, 52% had a suspected endobronchial lesion. Bronchoscopy was performed for the evaluation of pulmonary infiltrates in 12%, cavitatory lung lesions in 3% and haemoptysis in 1%.

Suspicion for an endobronchial lesion was the commonest indication for a bronchoscopy at CHBAH; however, subcategories were identified, with mass lesions on radiological imaging responsible for more than half of these cases (55 %). Atelectasis was the reason for 29% of suspected endobronchial lesions.

Eighty-four percent of patients with suspected endobronchial lesions had this suspicion confirmed on bronchoscopy.

Table 1: Indications for bronchoscopy at CHBAH

Indication	Number	Percentage %
Suspected endobronchial lesion	433	(52.2)
Pulmonary infiltrates	100	(12.1)
Hilar/mediastinal mass/adenopathy	71	(8.6)
Investigation of pleural effusion	50	(6.0)
Non-resolving pneumonia	49	(5.9)
Cavitating lung lesion/s	29	(3.5)
Investigation of lung pathology in patients with EPM	29	(3.5)
Haemoptysis	11	(1.3)
Persistent unexplained cough	11	(1.3)
Exclusion of tracheoesophageal fistula	10	(1.2)
Previous non-diagnostic bronchoscopy	7	(0.8)
Suspected occupational lung disease	5	(0.6)
Missing data	25	(3.0)

Table 2 : Sub-categories for suspected endobronchial lesions

Indication	N	%
Mass lesion on X-ray	239	(55.1)
Atelectasis	124	(28.6)
White-out of hemithorax on X-ray	28	(6.5)
Bronchial cut-off on X-ray	26	(6.0)
Localised bronchiectasis	16	(3.7)

Table 3: Baseline demographic and clinical characteristics (n=830)

Characteristics		Mean (SD) / Median (IQR)	N (%)
Demographics			
Age (years)		56.2 (13.3)	
Gender	Male		546 (65.8)
	Female		282 (34.0)
	Unknown		2 (0.2)
Wards	Inpatient		485 (58.4)
	Outpatient		298 (35.9)
	Unknown		47 (5.7)
HIV Status	Negative		430 (51.8)
	Positive		183 (22.1)
	No result found		217 (26.1)
	CD_4 count	233 (85-434)	
Bronchoscopic test performed	Endobronchial biopsy		417 (50.2)
	No biopsy		220 (26.5)
	Transbronchial biopsy		113 (13.7)
	Both endobronchial and transbronchial biopsies		60 (7.2)
	Unknown		20 (2.3)

A total of 830 patient records were extracted from the bronchoscopy reports performed from January 2011 to December 2018. Male patients comprised 65.8%. The mean (SD) age was 56.2 (13.3) years. Outpatient bronchoscopy was performed in 36% of the study population. A total of 613 patients (74%) had a documented HIV serology result. Of these, 183 (29.9%) were seropositive with a median cluster of differentiation 4 (CD4) cell count of 233 cells/mm^3 (IQR: 85-434). About half of the study population (50.2%) had an endobronchial biopsy, Fourteen percent of the study population did not have any biopsy done and 7% of the study population had both transbronchial and endobronchial biopsy performed.

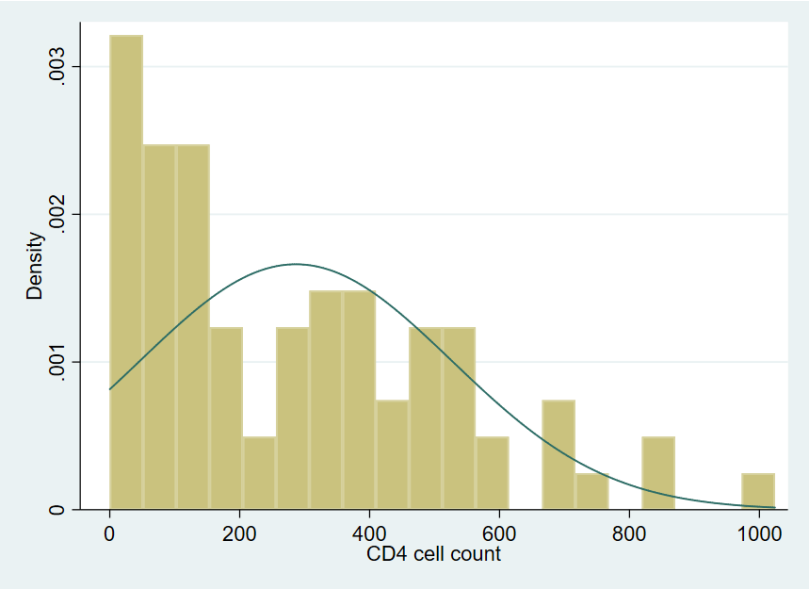

Figure 1: Distribution of CD_4 count

In terms of findings noted in the bronchoscopy report, an endobronchial lesion was found in 43.9% of the study population. Extrinsic compression was suspected in 3.1% of the study population.

Table 4: Findings at bronchoscopy (n= 830)

Findings at bronchoscopy	N	(%)
Endobronchial lesion excluded	417	(50.2)
Endobronchial lesion noted	364	(43.9)
Extrinsic compression suspected	26	(3.1)
Unknown	21	(2.5)
Endobronchial KS	2	(0.2)

Table 5: Histopathological, Microbiological and Cytological Diagnosis (n=830)

Diagnosis	N	(%)
Lung malignancy	320	(38.5)
Primary lung malignancy	240	(28.9)
Possible or probable malignancy	63	(7.6)
Secondary lung malignancy	17	(2.0)
Endobronchial lesion excluded	146	(17.6)
Normal lung biopsy/no pathological change	92	(11.1)
Non-diagnostic	73	(8.8)
Non-diagnostic - Inadequate biopsy	65	(7.8)
Non-diagnostic - biopsy not done	8	(1)
Chronic nonspecific inflammation	64	(7.7)
Infections	49	(5.9)
TB	36	(4.3)
NTM	2	(0.2)
Aspergillus	1	(0.1)
Salmonella	1	(0.1)
Missing data	24	(2.9)
Sarcoidosis	15	(1.8)
Tracheoesophageal fistula excluded	9	(1.1)
Squamous dysplasia	7	(0.8)

ILD other than sarcoidosis	6	(0.7)
Endobronchial KS excluded	5	(0.6)
Foreign body inhalation	4	(0.5)
Tracheoesophageal fistula observed	3	(0.4)
Combination	2	(0.2)
CA+TB	2	(0.2)
Hydatid disease	1	(0.1)
Organising pneumonia	1	(0.1)
Other infections	9	(1.1)

[1] *CA+TB - refers to a combination of cancer and tuberculosis*

In terms of the diagnosis obtained at bronchoscopy at CHBAH, lung malignancy was the most common diagnosis, comprising 39% of the population. Lung infections were diagnosed in 6% of the study population with TB being the most common infection diagnosed. Interstitial lung disease was diagnosed in less than 3 % of the study population.

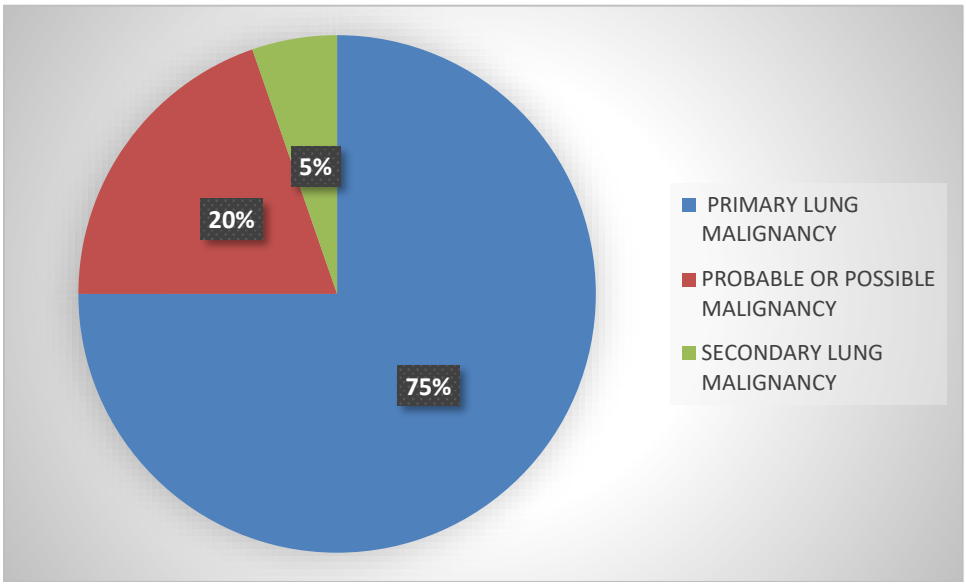

Figure 2: Types of malignancy identified.

Of all the diagnoses of malignancy made in our study, primary lung malignancy was diagnosed in 75% of such cases, with secondary lung malignancy comprising 5% of malignancies.

In terms of primary malignancy diagnoses in our study, squamous cell carcinoma was the commonest subtype diagnosed, comprising 42.5% of the total. This was followed by adenocarcinoma (31.3 %). A small proportion were a combination of two different malignancy subtypes such as the combinations of small and large cell carcinoma (< 1%) and squamous cell and neuroendocrine carcinoma (< 1%).

The diagnosis of secondary lung malignancies in our study was minimal, at fewer than 6% of all malignancy diagnoses.

Table 6: Subtypes of primary and secondary lung malignancy diagnosed

Type of malignancy	N	(%)
Primary Malignancy (n=240)		
Squamous cell carcinoma	102	(42.5)
Adenocarcinoma	75	(31.3)
Neuroendocrine carcinoma (other than small cell carcinoma)	26	(10.8)
Small cell carcinoma	9	(3.8)
Undifferentiated non-small cell carcinoma	8	(3.3)
Large cell carcinoma	5	(2.1)
Adenosquamous cell carcinoma	2	(0.8)
Combination of large cell/small cell carcinoma	1	(0.4)
Combination of squamous cell/neuroendocrine carcinoma	1	(0.4)
Other primary malignancy[1]	11	(4.6)
Non pulmonary malignancy (n=17)		
Diffuse Large B Cell NHL	9	(52.9)
Other NHL[2]	7	(41.2)
Hodgkin lymphoma	1	(5.9)

[1] Other primary malignancy includes inflammatory myofibroblastic tumours, sarcomatoid carcinoma, and muco-epidermoid carcinoma

[2] Other NHL includes all the other form of non-Hodgkin lymphoma other than diffuse large B cell non-Hodgkin lymphoma

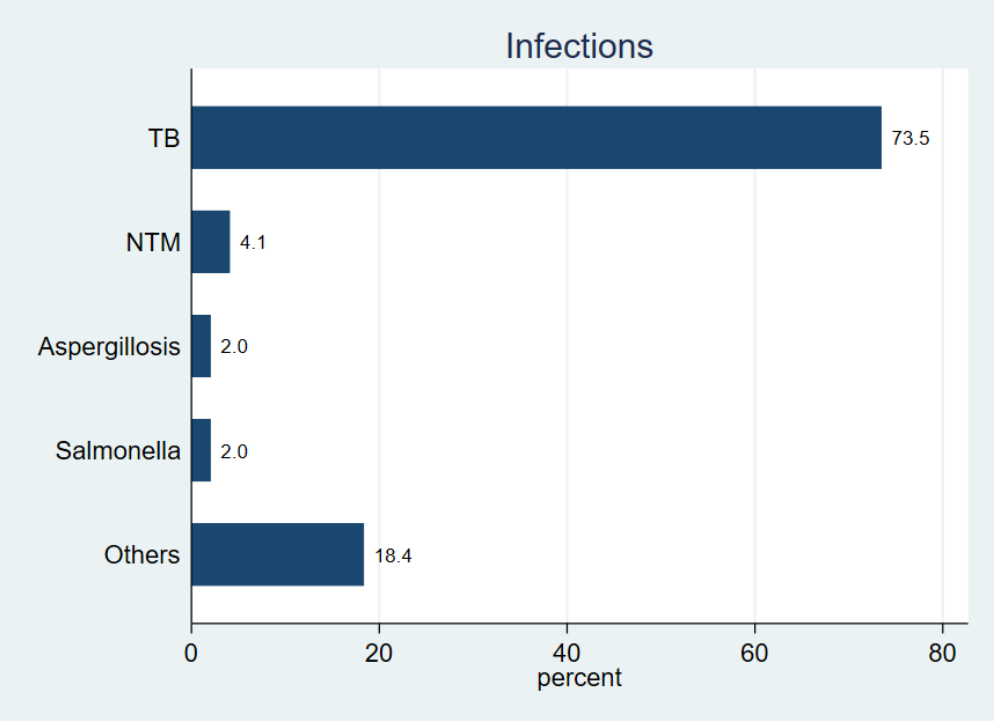

Figure 3: Types of infection diagnosed

Others include *Pneumocystis jirovecii* pneumonia (PCP), *Streptococcus bovis*, *Acinetobacter baumanii*, and *Klebsiella* spp.

Tuberculosis was the commonest infection diagnosed in our study, followed by non-tuberculous mycobacteria (NTM) in 4% of all infections diagnosed on bronchoscopy.

Table 7: Complications associated with bronchoscopy

Complication	Number	Percentage
Pneumothorax	6	(0.7)
Haemorrhage	3	(0.4)
Demised post-bronchoscopy	3	(0.4)
Significant hypoxaemia	3	(0.4)
Chest pain	1	(0.1)
Vomiting	1	(0.1)
Pulmonary oedema	1	(0.1)
No complication	812	(97.8)

Bronchoscopy is an inherently safe procedure. 97.8 % of all procedures were completed without any notable complication. The most frequent complication that was identified was pneumothorax, which occurred in less than 1% of patients, despite the absence of fluoroscopy which was not available during the period of the study.

Factors associated with specific bronchoscopic diagnoses

Malignancy

In univariate analyses, increasing age was significantly associated with a diagnosis of malignancy [OR 95% CI, 1.05 (1.04-1.06)]. There was a 5% increase in the odds of a malignancy diagnosis with each additional year of age. Women were less likely to be diagnosed with malignancy compared to men, and HIV positive patients were less likely to have a diagnosis of malignancy compared to HIV negative patients. In multivariate analyses, the association between HIV status and malignancy was no longer significant after adjusting for age and gender. The association between age and malignancy [OR 95% CI, 1.05 (1.03-1.06)] and between age and gender [OR 95% CI, 0.67 (0.51-0.96)] remained significant in multivariable analyses ($p<0.001$ and 0.026, respectively).

Chronic non-specific inflammation

There were no associations found between age and gender with chronic non-specific inflammation. HIV positive patients were more than twice as likely to receive a diagnosis of chronic non-specific inflammation as HIV negative patients. This association was statistically significant in both univariate and multivariate analysis ($p< 0.004$ and 0.009, respectively).

Infections

There were no significant associations found between gender and HIV status with infections. There was a 3% decrease in the odds of an infection with each one-year increase in age. This association persisted in multivariate analyses [OR 95% CI, 0.97 (0.95-0.99)] $p<0.005$.

Sarcoidosis

There was no association between HIV status and a diagnosis of sarcoidosis. There was a 3% decrease in the odds of a diagnosis of sarcoidosis with each one-year increase in age. This association was lost after adjusting for gender and HIV status. Women were at least 7 times more likely to be diagnosed with sarcoidosis than men and this association persisted even after adjusting for age and HIV status (OR 95% CI, 7.39 (2.04-26.77); $p<0.002$).

Discussion

The study analysed all bronchoscopies performed at CHBAH which is an academic tertiary hospital located in Johannesburg, South Africa. Literature search on this topic in the local setting revealed very few studies of similar ilk.

With regards to the socio-demographic characteristics of our study population, we found that the mean age of patients undergoing the procedure was 56.2 years, with a standard deviation of 13.3 years. This finding concurred with the findings from similar studies in Brazil, India and South Africa.[5.6,13] Making use of univariate analyses, increasing age was significantly associated with a diagnosis of malignancy (OR 95% CI, 1.05 (1.04-1.06); $p <0.001$). There was a 5% increase in the odds of a malignancy diagnosis with each additional year of age. In our study, males comprised a significant proportion of our study population (66%). This result was similar to other studies, which also noted a preponderance of males as compared to females among the study population.[5, 6, 13]

About 74 % of our study population had their HIV status reported in the bronchoscopy report. Twenty-nine percent of this population was HIV seropositive with a median CD_4 count of 233 cells/mm^3. IQR (85-434). Our study showed that HIV positive patients were less likely to be diagnosed with a malignancy, compared to HIV negative patients. In multivariate analyses, the association between HIV status and malignancy was no longer significant after adjusting for age and gender [p<0.055]. The association between age and the diagnosis of a malignancy [OR 95% CI, 1.05 (1.03-1.06)] and that between age and gender [OR, 95% CI, 0.67 (0.51-0.96)] however, remained significant in multivariate analyses (p<0.001and 0.026, respectively).

In our series, a suspected endobronchial lesion was the commonest indication for bronchoscopy (52 %). This finding differed from a Brazilian study which indicated that infection was the predominant indication for bronchoscopy in less than half of the patients reviewed. In the same Brazilian study, bronchoscopy was performed for a suspected neoplasm in 11% of the patient population.[5] A study conducted in India showed that cough was the commonest indication for bronchoscopy (90%), followed by shortness of breath (69%) and haemoptysis (40%).[6] In our series, cavitatory lung lesions and non-resolving pneumonia accounted for about 9% of the indications for bronchoscopy.

In terms of bronchoscopic findings, endobronchial lesions were noted in 44% of our study population. This was similar to the study by Kumar *et al.* in India, where the most common finding during bronchoscopy was an endobronchial lesion, which was noted in almost 60% of the study population.[6]

In our series, lung malignancy was the commonest diagnosis, comprising 39% of our series. A study done in India showed that lung malignancies constituted the most predominant finding (64%).[6] Primary lung malignancy is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with major histological subtypes listed as adenocarcinoma, squamous cell carcinoma (SCC), large cell lung carcinoma and small cell lung carcinoma.[7] Adenocarcinoma is the commonest subtype of NSCLC, accounting for between 25-30%. All over the world, recent reports indicate that squamous cell carcinoma incidence is on a downward trend, with adenocarcinoma on an upward trend [8]; however, this finding was not supported by our series. The explanation for this finding may be due to the fact that adenocarcinoma is more commonly located peripherally, therefore making them generally inaccessible to bronchoscopy.

Our study showed that SCC was the commonest histological subtype of primary lung malignancy (42%); this was followed by adenocarcinoma (31 %) and neuroendocrine tumours (11 %). The

contributions made by mixed histological subtypes such as large cell carcinoma and small cell carcinoma were negligible (0.42%), confirming the rarity of such lesions. The predominance of SCC in our study was supported by similar findings by Kumar, Gupta and Aggarwal in 2017. In their series, the incidence of SCC was 62% with adenocarcinoma at 27%.[9] Another Indian study revealed SCC to be the most common histological subtype (34.5%) with adenocarcinoma and small cell carcinoma at 9% and 7%, respectively.[10]

Bronchoscopy and subsequent cytological and microbiological evaluation of samples obtained aid in the diagnosis of respiratory infections. However, in our study, chronic non-specific inflammation, infections and organising pneumonia were diagnosed in 14% of the study population. The commonest infection diagnosed was tuberculosis (TB) (74%).

Interstitial lung disease (ILD) can also be evaluated by bronchoscopy. In our series less than 3% of patients who underwent bronchoscopy were diagnosed with ILD. Many studies reviewed failed to mention ILD as part of the diagnosis made on histological examination of bronchoscopic samples.[5, 10] Fibreoptic bronchoscopy is certainly useful in certain interstitial lung diseases such as sarcoidosis; however, in many others, surgical biopsy is indicated. In patients diagnosed with sarcoidosis on bronchoscopy, females were 7 times more likely to be diagnosed than males [OR 95% CI, 7.39 (2.04-26.77)] in our study.

Overall, bronchoscopy appears to be a relatively safe procedure. Our study revealed that the overall complication rate during bronchoscopy was 2.16%. This complication rate was comparable with other studies, which showed complication rates during bronchoscopy of between 0.08- 2%.[5, 11, 12]

From the total of 830 bronchoscopy reports evaluated, there were 3 fatalities recorded following the procedure. The recorded circumstances surrounding these deaths were (1) sudden unexpected cardiac arrest in a patient who underwent bronchoscopy whilst on mechanical ventilation (metastatic adenocarcinoma was confirmed posthumously from cytological analysis of a lymph node and pleural effusion), (2) unexplained respiratory arrest post-bronchoscopy and (3) sudden demise after transfer back to the medical ward from the bronchoscopy theatre.

A limitation of this study was that some bronchoscopy reports were missing or incomplete. However, this represented less than 2% of the study population. Secondly, the findings of this study may not be reflect the pathology seen in other hospitals as the study was conducted in a tertiary academic referral hospital.

Despite the aforementioned shortcomings, the study provides useful data from which important conclusions may be made, adds valuable information to the existing body of knowledge regarding the sociodemographic characteristics of patients undergoing bronchoscopy in a tertiary centre, the prevailing indications for this procedure, and the diagnoses obtained from performing the procedure.

Conclusion

In this retrospective study, flexible bronchoscopy was found to be a useful tool aiding the diagnosis of respiratory diseases and had a low complication rate.

An endobronchial lesion was the indication for bronchoscopy in 52% of study population and it was visualized on bronchoscopy in 44%. Squamous cell carcinoma (SCC) is the commonest form of primary lung malignancy diagnosed through fibre optic bronchoscopy, this was closely followed by adenocarcinoma. Males were noted to have had more bronchoscopies done as compared to women. Twenty-two percent of the study population was noted to be seropositive for HIV with a median CD4 count of 233 cells/mm^3 (IQR: 85-434).

There are very few studies done in South Africa that have evaluated the demographic characteristics of patients undergoing bronchoscopy, the indications for the procedure, and the diagnoses obtained from bronchoscopy. Our study helps address this deficit.

It will be worthwhile to conduct similar studies in other centres in South Africa to further determine what the indications for bronchoscopy are, and how the diagnosis obtained in different centres compares to the findings in our centre.

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CHAPTER 3 – APPENDICES

3.1 Appendix A Data collection sheet

DEMOGRAPHIC INFORMATION

Gender	Male		Female	
Age				
HIV Status	HIV Positive		CD4 Count	
	HIV Negative			
	HIV Unknown			

PROCEDURE INFORMATION

Inpatient		Outpatient					
Biopsy type	Endobronchial						
	Transbronchial only						
	Endobronchial and Transbronchial						
	No biopsy taken						
	Unknown						
Complications	Pneumothorax		Haemothorax				
	>2 scopes		>3 scopes				
Indications for Biopsy	**Clinical**	Exclusion of tracheo- or broncho-oesophageal fistula					
		Haemoptysis					
		Investigation of lung pathology in patients with extrapulmonary malignancy					
		Investigation of pleural effusion (where pleural fluid analysis unhelpful)					
		Non-resolving pneumonia					
		Persistent unexplained cough					
		Previous non-diagnostic bronchoscopy					
		Suspected endobronchial lesion					
		Suspected foreign body inhalation					
		Suspected infection					
		Suspected Kaposi sarcoma					
		Suspected occupational lung disease					
		Suspected sarcoidosis					
	Radiological	Atelectasis					
		Cavitating lung lesion/s					
		Endobronchial lesion on CT scan					
		Localised bronchiectasis					
		Mass lesion on CXR and/or CT scan					
		Miliary pattern on chest X-ray					
		Pulmonary infiltrate		Unilateral		Bilateral	
		Radiological cut-off of bronchus					

		Suspected interstitial lung disease other than sarcoidosis			
		White-out of hemithorax on chest X-ray			
	Other				

DIAGNOSIS

Malignancy	Possible/probable CA, but not proven				
	Primary lung				
	Secondary lung				
Infection	Aspergillus				
	Bilharzia				
	Cytomegalovirus				
	Cryptococcus				
	Hydatid disease				
	NTM				
	Pneumocystis carinii				
	Salmonella				
	TB				
Interstitial lung disease	Interstitial lung disease other than sarcoidosis	Definite		Possible/probable	
	Sarcoidosis				
Other	Assess bronchial tree				
	Endobronchial lesion excluded				
	Foreign body				
	Other				

OUTCOME

Biopsy not done due to high risk of bleeding		
Inadequate biopsy		
Missing data, diagnosis uncertain		
Non-diagnostic		
Therapeutic		
Combinations	CA + TB	
	ILD + TB	
	KS + MAC	
	PCP + KS	
	PCP + CMV	
	PCP + TB	
	Sarcoidosis + TB	
	TB + CMV	
	TB + KS	
	TB + CA	

3.2 Approvals

3.2.1 Appendix B Permission from CHBAH management

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 4th April 2019

TITLE OF PROJECT: An Analysis of Bronchoscopies performed at the Chris Hani Baragwanth Academic Hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr A.O Ajayi

Department: Internal Medicine

Supervisor : Dr M Venter and Prof M Wong

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 4/4/2019

Approved/~~Not Approved~~
Hospital Management
Date: 29/04/2019

3.2.2 Appendix C Permission from NHLS

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

P.O. Box 1038, Johannesburg 2000
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+27-11- 489-8479
Fax::+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : Yvonne.perner@nhls.ac.za

Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

August 20, 2019

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Adekunle Omoniyi Ajayi with his research entitled "An analysis of bronchoscopies performed at the Chris Hani Baragwanath Academic Hospital : 2011-2018".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Ajayi will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

3.2.3 Appendix D Ethics approval letter

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Adekunle Omoniyi Ajayi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190758

NAME: (Principal Investigator)	Dr Adekunle Omoniyi Ajayi
DEPARTMENT:	School of Clinical Medicine Chris Hani Baragwanath Hospital
PROJECT TITLE:	An analysis of the bronchoscopies performed at Chris Hani Baragwanath Hospital between 2011 - 2018
DATE CONSIDERED:	26/07/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/10/2019

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES