SURGERY FOR PULMONARY TUBERCULOSIS, A COMPARISON BETWEEN ACTIVE AND SEQUELAR DISEASE WITH IMPLICATIONS FOR MANAGEMENT.

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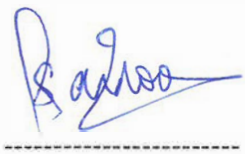
DECLARATION

I certify that this thesis is my own unaided work. It has not been submitted previously to this or any other university.



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DEDICATION

To Cheryl, unwavering in her support and understanding as well as Deevashan for lighting up my life.

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ABSTRACT

Introduction and objective

Pulmonary tuberculosis poses a major public health threat. Reports indicating a higher morbidity with surgery in active disease have resulted in a reluctance to operate. This study examines the results of lung resection in two groups of patients, one with active pulmonary tuberculosis, defined on microbiological and pathological grounds, and the second with sequelar disease. The hypothesis that surgery should be avoided in patients with active disease, in view of the perceived increased risk of complications, is tested.

Materials and methods

A retrospective review of the outcomes for patients operated on for active and sequelar tuberculosis was undertaken. One hundred and sixty three patients underwent anatomical lung resection for pulmonary tuberculosis between 1998 and 2004. There were 106 patients with active tuberculosis (group 1). Disease activity was determined by radiographic, microbiological and pathological assessment. The sequelar group (group 2) consisted of patients with no evidence of disease activity.

Indications for surgery included multidrug resistant tuberculosis (group 1 = 27, group 2 = 2), haemoptysis (group 1 = 44, group 2 = 32), bronchiectasis (group 1 = 27, group 2 = 23) and diagnostic dilemma in 8 patients in group 1. Statistical analysis was performed using SPSS 11.5® and EpiCalc 2000®.

Results

A total of 85 pneumonectomies (group 1 = 59, group 2 = 26) and 76 lobectomies (group 1 = 47, group 2 = 29) were performed. The overall morbidity was 22.7% (9.4% in the active group and 22.8% in the sequelar group). There was no significant difference in morbidity

between the groups [p = 0.081 RR 0.63 CI 0.36 – 1.11] despite a trend to a higher morbidity in the sequelar group. There was also no correlation between the indication for surgery and morbidity (p = 0.719), although patients with sequelar disease and haemoptysis did appear to be at risk for complications [p = 0.043, RR 1.61, CI 1.06 – 2.45]. The incidence of bronchopleural fistulae was 0.9% in group 1 and 1.8% in group 2. Post-pneumonectomy empyema occurred in 5.7% in group 1 and 5.3% in group 2. There were 3 deaths. HIV status did impact on overall morbidity [p = 0.041, RR 1.88, CI 1.05 – 3.36] despite the small numbers. There was no correlation between complications and HIV status in the individual groups.

Conclusion

Specific management guidelines cannot be advocated in view of the limited number of patients in this study; however there are trends that should be noted.

Surgery may be undertaken in the face of active disease with results comparable to sequelar disease, this is emphasised by the results in the challenging MDR group. Haemoptysis, often requiring surgery in the acute setting, may also be managed in the setting of disease activity with the understanding that surgical results are comparable to that of sequelar disease. In addition to this, it is suggested that further study is required on the impact of HIV on thoracic surgical interventions.

Introduction

1.1 History

The surgical discipline of Thoracic Surgery owes much of its early development to *Mycobacterium tuberculosis.* (MTB) On review, there are three periods over which the surgical management of tuberculosis has evolved [1].

The first period extended from the eighteenth to the early nineteenth century when drainage of tuberculous cavities was first reported in 1726. In 1844, Hastings and Stork opened a cavity through the chest wall with success. Further efforts met with limited success and surgery fell out of favour. Koch isolated the tubercle bacillus in 1882, helping facilitate the development of appropriate drug therapy [1,2].

The surgical armamentarium expanded in the second half of the nineteenth century and the early twentieth century with the introduction of "collapse therapy" using a therapeutic pneumothorax pioneered by Forlanini. This procedure aimed to collapse the infected lung, allowing the lung to "rest", thereby facilitating healing. It was also believed that disease spread to uninvolved lung would be limited. Surgical options to achieve collapse included phrenicectomy, extrapleural plombage with insertion of foreign material such as methyl-methacralate balls, thoracoplasty and the creation of an artificial pneumothorax. Alternatives included apical pleural adhesiolysis via thoracoscopy.

The limitations of thoracotomy with thoracoplasty were cosmetic and functional with impairment of limb girdle movement. There was a concomitant increase in the popularity of sanatoria for isolation of patients with tuberculosis

The first limited resection was undertaken by Tuffier in 1891 [1,2]. Pulmonary resection was undertaken reluctantly in view of the high morbidity. It was during this period, in 1895, that radiographic evaluation became available helping define the pathology and disease extent, and in planning surgical intervention.

The latter half of twentieth century saw a surge in the number of pulmonary resections for tuberculosis being undertaken. This coincided with the development of effective chemotherapeutic options in the 1960's, prior to which, patients had little chance of cure and were confined to sanatoria in the hope of healing themselves.

The first lobectomy was attributed to Freedlander in1935 [1]. Surgical resection became more attractive as a management strategy with further improvements in anaesthetic and surgical technique producing better results. The key principles were optimal pre-operative preparation including nutritional supplementation and physiotherapy.

The success of medical therapy, with effective cure rates of over 90%, resulted in surgery being relegated to limited indications ie. Haemoptysis and the management of complications post treatment. Medical success was short-lived as patient non-compliance over the prolonged treatment period, the emergence of the Human Immunodeficiency Virus (HIV) and the persistence of social issues i.e. malnutrition, poverty and overcrowding, surrounding the disease led to the emergence of multi-drug resistant tuberculosis (MDR TB), defined as resistance to at least rifampicin and isoniazid [3,4,5].

MDR TB has helped redefine the role of surgery for tuberculosis as a valuable adjunct with operative assisted cure rates of over 90% [3,4,5].

1.2 Pathology

Mycobacterium tuberculosis is one of more than 30 members of the genus *Mycobacterium.* It is a facultative aerobic, acid-fast bacillus transmitted via the respiratory route. The presence of the organism produces an infection with or without clinically significant disease dependant largely on the immune response generated.

Inhalation of the organisms is followed by macrophage phagocytosis. The organism may then be destroyed or continue multiplying. Multiplication results in the destruction of the macrophage and release of a large number of the bacilli. This bacteraemia may result in no symptoms or produce a "flu-like" illness.

The bacteraemia continues for 2-10 weeks until a cell mediated immune response and a delayed hypersensitivity reaction limit multiplication and allows healing.

This hypersensitivity reaction produces caseous necrosis and granuloma formation, which in turn, may produce fibrosis resulting in lung damage.

The disease may progress primarily or remain quiescent with later reactivation. The usual risk of disease progression is 5-10% in the patient's lifetime, co-infection with HIV increases this to 5-10% per year [6,7].

Progressive pulmonary tuberculosis, in unsensitized patients, may present as an acute bacterial pneumonia with consolidation distributed mainly in the lower and middle lobes. This distribution is determined by the airborne transmission of the organism. Hilar lymphadenopathy and pleural effusions may also occur.

In patients sensitized to the organism, disease reactivation results in a distribution that favours the apex of the upper lobe and the superior segment of the lower lobe as a result of the increased oxygen tension and reduced lymphatic drainage in these regions. The tissue response to reactivation disease produces fibrosis that walls of the focus and cavitation. Lymphadenopathy is generally uncommon[7].

The cavities that form may be colonized by either fungal elements eg. *Aspergillus fumigatus*, producing aspergillomas, or bacterial organisms. Persistence of the cavities despite medical "cure" may occur resulting in significant haemoptysis requiring emergency surgery. The haemoptysis may be related to an aspergilloma, erosion of a pulmonary artery branch traversing the cavity, rupture of a Rasmussen aneurysm or bronchial artery erosion.

Miliary disease may also involve the lung when a collection of the bacilli enters the blood stream or the lymphatic vessels.

1.3 Overview and literature review

Pulmonary tuberculosis poses a major threat to public health in South Africa. It has been reported that there is one TB related death every 40 minutes with 180 000 new cases annually, two thousand of which are MDR TB, co-infection with HIV in 60% of adults having dormant TB infections [8,9].

Worldwide, there is a new tuberculosis infection every second with one third of the world's population being infected with the bacillus. In keeping with this, Furak reported that surgical intervention for TB has been increasing annually as well by 5-6% [10].

The indications for surgery in pulmonary tuberculosis include [1,2,3,5]:

i) multi-drug resistant tuberculosis

ii) complications of tuberculosis, including haemoptysis and bronchiectasis

iii) complications of surgical treatment including post-resectional infections

iv) diagnostic dilemma where tumour cannot be excluded

The key issue in planning surgery is the control of disease activity prior to intervention in an effort to reduce complications [11]. Active tuberculosis, indicated by sputum smear positivity or a positive histology demonstrating acid fast bacilli and/or necrotizing granulomatous inflammation, has been considered a relative contraindication to surgery [11,12].

The reasons behind the avoidance of surgery in the presence of disease activity are based on the historically reported morbidity. Mouroux reported a morbidity of 12.5% and mortality of 5.5% in a group of 11 patients with active disease [13]. Reed and Rizzi have reported complication rates of 17% to 30% respectively [14,15]. Furak reported a morbidity rate of 22.9% in patients with active disease with an overall morbidity of 45.8% [10]. Morbidity rates of 30% in MDR patients who were sputum positive have also been reported [3].

Surgical resection, limited to non-anatomical wedge resection and lobectomy, for active tuberculosis results in a morbidity of 14% [12]. The overall cure rate for these patients is 64.8%.

It is evident that lung resection for inflammatory lung disease is not considered an innocuous procedure [10,13,16,17,18,19]. The technical complications as well as anticipated post-operative complications including bleeding, air leaks, post-pneumonectomy empyemas (PPE) and bronchopleural fistulae (BPF) have prompted Reed to suggest that surgery be avoided in these patients [15].

In consideration of the above-mentioned facts, patients are managed medically, if possible, until sputum negative and then operated on electively.

The minimum duration of medical therapy prior to surgical intervention is dependant on the indications for surgery.

Iseman, supported by Pomerantz, has concluded that a minimum of 3 months of appropriate therapy is required in the MDR group [3]. Patients with the sequelar forms of the disease are managed with a full course of anti-tuberculous therapy prior to surgery.

The primary indications for surgery in active disease include MDR TB, where surgery is considered for persistent sputum positivity, and in those presenting with massive haemoptysis where surgery is undertaken emergently.

1.3.1 MDR TB

Surgery for MDR TB is recognized as a valuable adjunct to the medical therapy of these patients in retrospective studies [3,20-27]. There are currently no prospective trials comparing medical therapy alone against surgery combined with medical therapy.

Medical therapy alone is disappointing with reported cure rates of 50%, of greater concern is that 50% of these patients will develop disease recurrence [3].

Surgery is offered mainly for failure of medical therapy. It is believed that the fibrous tissue around cavities forms a "firewall" protecting the organism from the drugs. Cavities have been shown to house 10^7 - 10^9 organisms and removal of this tissue allows for better drug

tissue penetration [20]. Nodules also harbour significant numbers of the organisms and should ideally not be left behind in surgery for MDR TB.

Surgery is offered after a minimum of 3 months of appropriate culture directed therapy. Goble showed that sputum conversion was usually achieved between 1 to 8 months of medical therapy with a median of 2 months [3]. Pomerantz added that surgery might be undertaken following 2 months of treatment in patients with high profile drug resistance [26].

The indications for surgery include localised disease in persistently sputum positive patients, disease recurrence and high profile drug resistance to at-least 4 drugs. Patients with bilateral disease were originally excluded from surgery. Sung [21] and Shiraishi [27]et al have reported the use of surgery in patients with bilateral disease, with good results, where the disease left behind was in the form of nodules, minor cavities or fibrosis. The proviso however is that the contra lateral disease must be parenchymal and amenable to medical therapy or localized enough to facilitate later surgery should cure not be achieved. Takeda [23] also undertook staged bilateral resections on the condition that the patient's pulmonary function was adequate.

Surgery is associated with complication rates of 17.4% - 30% [20-27]. It is largely because of experience in this group of patients that the use of a muscle flap for bronchial reinforcement has been advocated to prevent the development of a BPF.

Pomerantz advocated the use of muscle flaps in the following circumstances:

1. sputum positivity pre-operatively
2. the presence of a BPF prior to surgery
3. polymicrobial space contamination

4. anticipated space problems following lobectomy

A further risk factor is the presence of endobronchial tuberculosis [5].

The current literature does not support the theory that all sputum positive patients with MDR TB require muscle flap reinforcement of the bronchial stump.

Van Leuven [20], Naidoo [22], Sung [23], Park [24] and Takeda [27] have reported studies where muscle flaps were not routinely used, even in sputum positive patients.

The incidence of bronchopleural fistulae in these reports ranges from 0 – 6% [20,22-24,27]. This is encouraging when one considers that original reports documented an incidence of 30% in sputum positive patients [3].

The reduction in this complication is difficult to explain, as there are differences in surgical technique in the new reports with variations in the technique of bronchial stump closure. There are no comparative trials looking at suture versus staple closure in this cohort of patients. In our unit, stapling devices are not used due to financial constraints. It is not considered a superior technique.

In the local experience, surgery is associated with cure rates of over 90% with acceptable morbidity (17.4%) and no mortality [22].

The current feeling is that a more aggressive strategy involving earlier surgery should be considered [21,22,23]. The incidence of surgical intervention has been increasing with the current recourse to surgery being around 83% [25]. The earlier use of surgery, combined with appropriate medical therapy, is based on the high cure rates achieved. This may avoid a progression to extensive bilateral disease precluding surgery.

Disease-free survival of more than 80% after 36 months has been demonstrated [20].

The duration of post-operative treatment varies. Eighteen months of appropriate treatment is generally used following radical resection and 24months if residual infiltrative lesions are present. Van Leuven [20] suggested an approach regarding the duration of drug therapy dependant on surgical resection and sensitivities.

Operations undertaken for MDR TB have supported the theory that surgery may be undertaken in patients with active disease, as most of these patients are sputum positive disease at the time of surgery. The results in this group of patients support the hypothesis of this study.

1.3.2 Haemoptysis

Ten to fifteen percent of patients with tuberculosis develop life-threatening haemoptysis [28].

The difficulty in the management of these patients is that they may present as an emergency with or without previous TB therapy.

Minor haemoptysis may be managed conservatively with patients being allowed to complete a course of antituberculous medication prior to consideration for surgery.

Massive haemoptysis, defined as a single bout of more than 250ml or at least 600ml over 24 hours, is associated with a mortality of between 30-50% with medical therapy alone [28]. With this concern, definitive management at the time of admission is essential, including surgery if suitable. [28,29,30].

The risk of recurrent bleeding once stabilized is as high as 36.4% with a mortality of 45% of these patients dying from asphyxiation or haemorrhage [28]. The main cause of death is hypoxia and asphyxiation compounded by pre-existing pulmonary disease.

Knott-Craig [28], Conlan [29]and Blyth [30]have described the management of this condition from a South African perspective. The initial strategy includes stabilization and medical therapy consisting of intravenous antibiotics, antituberculous therapy and opioid sedation. [Figure. 1] Detailed evaluation of disease extent is determined with high-resolution computerized tomography (HRCT) scan of the thorax [31]. General clinical condition and effort tolerance are then used to assess patient suitability for resection.

The commonest source of bleeding is the systemic bronchial artery. In view of this, our current protocol includes bronchial artery embolisation for patients not suitable for lung resection [Figure. 2 and 3]. This strategy is also adopted as a temporizing measure for patients where active disease is present. Success rates of 85% in the short term have been reported with a drop to 58% in the long term [32]. Ice-cold saline lavage has also been used as a temporizing measure in both surgical and non-surgical patients. As such, it allows surgery to be undertaken electively with a reduced operative mortality [33].

The reluctance to offer surgery in these patients is based on the presence of active disease, the inevitable poor pulmonary reserve due to spill over of blood into contra lateral normal lung and the difficulty in bronchoscopically localizing the source of the bleeding in some patients.

Early elective surgery in this group, with a mortality of 7%, is preferred to emergency surgery with mortality rates of 22 - 42.9% [28,29,30].

The dilemma is the timing of surgery. Knott-Craig [29] has advocated a brief period of medical stabilization of around 5 – 10 days prior to surgery. Delaying surgery may increase the risk of recurrent bleeding and increase mortality whereas surgery prior to stabilization may also result in significant mortality and morbidity.

The question also arises as to whether surgery in the face of relatively untreated active disease is advisable. If so, surgery could be offered to patients early after admission and medical stabilization.

1.3.3 Diagnostic dilemma

Tuberculosis has been known to mimic bronchial carcinoma and in this situation, the latter must be excluded [Figure. 4]. The suspicion of a tumour has been shown to be an indication for surgery in 77% of cases where tuberculosis was subsequently proven [34]. In situations where a malignancy is difficult to exclude, patients are usually treated for tuberculosis for a trial period (6 weeks) and the response, or lack thereof, noted.

The cause for concern in this group is that lung cancer has been shown to be associated with TB in 33% of cases, although this has not been borne out locally [22].

Ishida [34] showed that 66% of tuberculomas have the radiographic criteria for malignancy thus making tissue diagnosis mandatory.

The diagnostic strategy includes the submission of sputum for cytology and microbiology, bronchoalveolar lavage specimens and fine needle aspiration biopsy, either via the transthoracic route or through a fibreoptic bronchoscope [35]. This procedure has a diagnostic

yield of over 90% for malignancy and approximately 12% for a specific benign diagnosis, thus limiting its value for the latter [36].

It is clear that a negative result for malignancy does not exclude a tumour unless a specific benign diagnosis is established. This leads to the next line of invasive investigations for tissue diagnosis either via video assisted thorascopy (VATS) or open thoracotomy with the aid of frozen section.

Furak [10] explored 34% of patients where tuberculosis was eventually diagnosed and Rizzi [14] operated on 24.2% of patients with diagnostic dilemma. Extensive pulmonary resection is rarely required although Keagy [35] reported on 9 patients where pneumonectomy was necessary to exclude malignancy. In this study, major pulmonary resections were performed in 24% of patients without confirmation of a bronchial carcinoma. The reasons for this included the central location of the mass and its proximity to blood vessels. It must be noted that it is not ideal to undertake major resection with only a suspicion of bronchial carcinoma in view of a mortality rate of 11.4% for pneumonectomy and a more reasonable rate of 2.05% for lobectomy [35].

1.3.4 Bronchiectasis

The rationale for lung resection in patients with the so-called destroyed lung is to:

a. reduce complications such as haemoptysis

b. improve patient quality of life by reducing recurrent infections

c. remove any organisms present and the lung that harbours them [37]

Surgery is generally undertaken in these patients following a course of anti-TB medication. The anatomical extent of the disease is documented radiographically by means of HRCT and surgery is planned once active infective processes have resolved.

1.3.5. Morbidity

Surgery for active tuberculosis has been reported as part of larger series looking at surgery for inflammatory lung disease [37]. The consensus is that surgery in these patients is not an innocuous procedure and should be avoided because of the prohibitive morbidity and mortality. The complications causing the most concern include bronchopleural fistulae (BPF) and post-pneumonectomy empyema (PPE).

1.3.5.1. Bronchopleural fistulae

Bronchopleural fistulae may :

1. indicate technical deficiencies in bronchial stump closure
2. be a precursor to or indicate the presence of intrapleural sepsis
3. require surgical re-intervention that may include a mutilating thoracoplasty

The incidence of this complication varies in the literature from 4 – 32%. Pomerantz has reported the higher incidence in sputum positive patients with MDR TB [3].
There have been numerous reports attempting to determine the risk factors for the development of a BPF. Tae Kim [4] reported that old age and sputum positivity were risks on univariate and multivariate analysis with a low pre-operative forced expired volume in 1 second (FEV 1) increasing the risk on multivariate analysis. Endobronchial TB at the stump has also been found to be a risk factor for the development of this complication.

The technical issues relating to the prevention of this complication have been dealt with in the literature and include:

1. meticulous suture technique incorporating a tension free suture line

2. preservation of the vascular supply by minimising bronchial stump skeletonisation and devascularisation.

Deschamps [38] has also evaluated stapling devices in a study including patients undergoing surgery for malignancy. The BPF risk was higher with hand sutured bronchial closure, benign inflammatory lung disease, right-sided resections and low pre-operative FEV 1.

The traditional method of closing the bronchial stump involves interrupted non-absorbable sutures. Pomerantz [5] found that there was no difference in the incidence of bronchial stump disruption with either staple or suture closure. Blyth [34] demonstrated a BPF rate of 1.9% using the hand-sewn technique with either absorbable or non-absorbable sutures, comparable with alternative strategies. Vicryl ® (Johnson & Johnson) has been recommended as the current suture material of choice for bronchial stump closure by Shields [36].

Reinforcing the bronchial stump with a muscle flap, be it intercostal muscle or lattisimus dorsi, has also been advocated, mainly in the MDR patient. Massard [16] advocated the routine use of this technique after reporting a 12% incidence of bronchopleural fistulae and 32% risk of postpneumonectomy empyema with no muscle flap reinforcement. Sputum positivity and the presence of endobronchial TB are said to warrant this intervention, however local experience with MDR TB does not support the routine use of the muscle flap[22].

1.3.5.2. Post-pneumonectomy empyema

The post-pneumonectomy empyema occurs in 13-45% of cases and has significant implications for surgeon and patient [37]. It commits the patient to a prolonged period of

drainage and sterilisation of the pleural space and may require further surgical intervention for definitive management, either in the form of open drainage or thoracomyoplasty.

It occurs more commonly on the left and the so-called *left bronchus syndrome* coined by Ashour [39] attempts to offer an explanation. It is believed that the more horizontal plane of the left main bronchus, the decreased peribronchial space and the fact that the bronchus is 15% narrower than the right main bronchus all contribute to the increased incidence of left sided disease. It is for this reason that a left pneumonectomy is the commonest resection performed. The other risk factors include:

1. polymicrobial space contamination during surgery
2. resection through an empyema [37,42]
3. active disease
4. violation of parenchymal cavities
5. increased intra-operative blood loss
6. re-opening for bleeding
7. increased patient age
8. low pre-operative FEV 1,

which increase the incidence of post-pneumonectomy empyema [6,32]. Blyth reported a 22% incidence of this complication in a cohort of patients with active disease [35].

1.3.6 HIV

A confounding variable that has not been addressed in the literature is the impact of HIV on the surgical management of patients with TB. There are no large reports dealing with this issue and it is hoped that this review will highlight the need for more research. The

importance of the CD 4 count lies in the postulate that the level may correlate with outcome following surgery.

Notwithstanding the worldwide distribution of pulmonary tuberculosis, to date there are no large reports on anatomical pulmonary resection in patients with active disease and HIV. The anxiety about surgical intervention in older reports regarding surgery for TB must be viewed with circumspection, as advances in both surgical and anaesthetic technique must be considered.

1.4 Aims and hypothesis

1.4.1 Aims

1. Determine if lung resection for pulmonary tuberculosis could be undertaken in patients with active disease with results in keeping with or better than reports in the literature.
2. Compare the results in the active group, in a descriptive study, with a similar cohort of patients with sequelar pulmonary tuberculosis to determine if the morbidity and mortality were equivalent.

1.4.2 Definitions

1. Active pulmonary tuberculosis was defined by the presence of
    a. Post-operative histology and microbiology results where active tuberculosis was demonstrated by the presence of caseating, necrotizing granulomatous inflammation with or without acid-fast bacilli.
    b. Any of the following
        i. History of inflammatory lung disease
        ii. Positive pre-operative sputum culture result if available
        iii. Chest radiographic and HRCT features of active pulmonary tuberculosis ie. nodules, interstitial infiltrates, mediastinal lymphadenopathy with central breakdown
2. Sequelar disease was defined by the presence of
    a. Post-operative histology with no caseous granulomatous inflammation. The presence of fibrosis and necrotizing granulomatous inflammation alone was discussed with the pathologists and was used to indicate sequelar disease.

b. Any of the following

i. History of inflammatory lung disease

ii. Negative sputum culture results pre-operatively were not always available. If this was the case, the other defining factors were used in distinguishing sequelar disease.

iii. Radiographic features suggesting old/burnt out disease

1.4.3 Objectives

1. Identify sequential patients, with inflammatory lung disease, with similar clinical presenting features.
2. Separate these patients into cohorts based on the presence or absence of active tuberculosis.
3. Evaluate the cohorts in terms of the pre-operative treatment, indications for surgery, surgical intervention and post-operative complications including :
    i) post resectional empyema
    ii) bronchopleural fistula
    iii) prolonged air leak
    iv) persistent space problems
    v) bleeding
4. Identify factors that may contribute to the morbidity following surgery i.e.
    i) the presence of HIV co-infection
    ii) indications for surgery
    iii) duration of pre-operative treatment
    iv) histological disease activity

5. Evaluate the follow-up looking for differences between the active and sequelar cohorts.

The hypothesis that surgery may be undertaken in patients with active tuberculosis with a morbidity and mortality equivalent to a similar cohort with sequelar disease was tested.

2. Materials and methods

A clinical retrospective analytical non-randomised cohort study was undertaken to review all lung resections for inflammatory lung disease in our unit over a 7year period from 1998 to 2004.

Records of sequential patients from the Department of Cardiothoracic Surgery at Wentworth Hospital and subsequently at Inkosi Albert Luthuli Central Hospital as well as King George V hospital were reviewed. Ethical approval was obtained from the Faculty of Medicine Ethics Committee at the University Of Kwa-Zulu Natal.

Patient inclusion was dependant on the following:

1. Active and sequelar tuberculosis as previously defined
2. Medical history of previous or current therapy for tuberculosis in the sequelar group
3. Anti-tuberculous therapy was not a prerequisite for inclusion in the active group
4. Suitability for pulmonary resection based on general condition and radiographic disease distribution
5. Anatomical pulmonary resection with the minimum being a lobectomy
6. Patients were excluded if pre-operative testing confirmed the presence of malignant lung disease

Patient evaluation included the documentation of demographic data with a detailed review of the past medical history. Suitability for pulmonary resection was based partially on the New York Heart Association disability grading system. In addition to this, pulmonary function testing was undertaken, excepting those patients presenting with massive haemoptysis where it was felt that this might precipitate bleeding. Resting arterial blood gases were obtained in this situation.

Plain chest radiographs and HRCT were undertaken to assess the anatomical extent of the disease and plan surgery. Plain chest radiographs tended to underestimate the disease extent. HRCT has been reported to be effective in diagnosing tuberculosis in up to 91% of cases [32]. Extensive bilateral disease precluded surgery. Resection was considered in patients with localized bilateral disease that were amenable to staged resections, mainly in the MDR group. Localization of the source of bleeding in patients with bilateral disease dictated the site of resection.

Testing for HIV was undertaken with informed consent. There was no access to antiretroviral medication during this review and it was the Cardiothoracic Surgery unit policy not to operate electively on HIV positive patients with a CD4 count less than 400cells/mm^3. In those found to be HIV positive, CD4 counts were determined prior to surgery unless the procedure was undertaken as an emergency. Emergency surgery was undertaken independent of the test.

Informed consent for lung resection was obtained in all patients.

The indications for resection included the following:

2.1 Multi-drug resistant tuberculosis (MDR TB)

a. This was defined as resistance to at-least rifampicin and isoniazid.
b. Surgery in this group was only undertaken after a minimum of 3 months of therapy guided by sputum culture and sensitivity results. There were no standardized protocols for the medical therapy which included at least 3 new drugs, of which 2 were bacteriocidal. Regimens are variable and not

standardized, many including 4-5 oral drugs combined with an aminoglycoside and / or capreomycin continued for a period of 6-24 months. The exact strategy was determined by resistance patterns, local experience and physician choice. Drugs were administered daily or 5 times weekly. A flouroquinolone was included in all patients.

c. Indications for surgery included localised disease in persistently sputum positive patients, disease recurrence and high profile drug resistance to at-least 4 drugs.

d. Patients were subsequently followed up at the MDR clinic at King George V Hospital, receiving an 18 month post-operative course of appropriate drug therapy

2.2 Bronchiectasis with recurrent infections

a. Completion of a course of anti-tuberculous therapy, consisting of rifampicin, isoniazid, pyrazinamide and ethambutol for the initial 2 months followed by rifamipicin and isoniazid for a further 4 months prior to surgery was essential

b. Admission was followed by rigid bronchoscopy looking for evidence of active suppuration. Infections were managed by culture directed antibiotics and physiotherapy

c. Repeat bronchoscopy was undertaken after a period of medical therapy and surgery was planned only when the acute infection was controlled.

d. In certain circumstances, it was not possible to completely clear the secretions. Surgery was then performed using bronchial isolation techniques to minimize contralateral contamination. These will be discussed later.

2.3 Emergencies, exclusively haemoptysis

a. This group included massive haemoptysis, defined as a single bout of more than 250ml or a cumulative amount of more than 600ml over 24 hours, a volume less than the above being regarded as minor.

b. The local strategy for management is illustrated in figure. 1

c. Anti-tuberculous therapy, intravenous broad-spectrum antibiotics and opioid sedation were part of the initial management of patients with massive haemoptysis.

d. Minor haemoptysis allowed time for assessment for surgery, which was performed electively following a minimum of 3 months of anti-tuberculous therapy.

e. Non-surgical patients were offered bronchial artery embolisation (BAE), an interventional strategy performed by the radiologists.

f. The unit policy occasionally dictated instillation of ice-cold saline [33] into the airways as a last resort for patients with non-surgical disease.

g. The presence of extensive bilateral disease on HRCT precluded surgery.

h. Staged resections were undertaken electively for localized bilateral disease.

2.4 Diagnostic dilemmas

a. The usual radiographic picture was that of an isolated pulmonary nodule or a suspicious opacity with non-specific symptoms.

b. Investigations included plain chest radiograph, with comparison to previous films, HRCT and sputum examination for microbiology and cytology.

c. Bronchoscopy, either by means of a rigid or flexible instrument was undertaken to obtain further specimens for microbiology and cytology.

d. Failure of the above mentioned tests necessitated transthoracic fine needle aspiration biopsy.

e. The unit policy was to undertake exploratory thoracotomy where fine needle aspiration was unhelpful as video-assisted thoracoscopic facilities were not available. In the early part of this review, the Dept of Anatomical Pathology was geographically separate from the Cardiothoracic Unit and frozen section was difficult. In view of this, anatomical resection was performed. It was felt that it was better to treat the more sinister condition.

f. The current location of our department makes frozen section more accessible and has eliminated major pulmonary resections for tuberculosis in the case of a diagnostic dilemma.

2.5 Surgery

Surgery was performed under general anaesthesia, with the use of epidural analgesia dependant on the experience of the anesthetist. When not inserted, intercostal rib blocks were used and the post-operative analgesia was provided by parenteral opioids combined with non-steroidal anti-inflammatory agents.

Bronchial isolation was essential to reduce contralateral contamination by secretions. Techniques included the use of a double lumen endotracheal tube or bronchus blockers (embolectomy catheters or Foley ® urinary catheters) in younger patients. In rare instances, prone positioning was required as described by Sellors Brown.

A second-generation cephalosporin (cefuroxime) provided antibiotic prophylaxis with surgery being performed under cover of anti-tuberculous medication.

Standard posterolateral thoracotomy incisions were used; the dissection was usually within the pleural plane. The extrapleural route[28,41] was reserved for localized, densely adherent areas depending on surgical preference and expertise. This plane was avoided in view of the increased risk of bleeding.

The bronchial stump was managed according to the following principles:

1. limited dissection, minimal skeletonisation to maintain vascularity
2. interrupted absorbable sutures were commonly used for closure non-absorbable sutures being dependant on the surgeon's preference
3. stapling devices were never used due to the prohibitive financial cost
4. generally, no attempt was made to use muscle flap reinforcement and the bronchial stump was kept short to reduce infective complications.

The pleural space was drained by means of a single underwater seal drain following pneumonectomy and 2 drains were used for lesser resections. The post-pneumonectomy space was drained for 24 hours with the drain being clamped and released intermittently for 5 minutes every hour. Drainage was continued depending on the residual air leak in the patients undergoing lesser resections.

Ambulation was commenced on day 1 and discharge usually effected within 7 – 10 days if complication free. Anti-tuberculous medication was continued for 6 months in all patients with active disease except for the MDR group where the post-operative course was over 18 months.

The following outcomes were assessed in both groups:

1. Sputum conversion where pre-operative sputum status was available
2. Development of major complications ie.
    i. Bronchopleural fistulae – major airway communication with pleural space indicated by air leak from the drains and the bronchoscopic evidence of a fistula
    ii. Post-resectional empyema – infection in the residual pleural space defined by the presence of frank pus or culture positive pleural fluid. This was usually accompanied by the systemic signs of sepsis.
    iii. Residual space problems – radiographic evidence, plain radiograph and HRCT, of a space with incomplete re-expansion of the residual lung. There were no symptoms with this complication. Concomitant space infections were included in the post-resectional empyema group
    iv. Prolonged air leak – drainage for more than 7 days
    v. Post-operative bleeding with more than 150ml/hr for more than 3 hours.
3. Mortality

These outcomes were used as they represent the commonest complications following lung resection. As mentioned in the introduction, inflammatory lung disease is a risk factor for them and surgery for active tuberculosis is suggested to be associated with a higher risk than with sequelar disease.

Follow up was at the Thoracic Clinic and the MDR patients were reviewed at a separate clinic run by the physicians.

2.6 Statistical analysis

Statistical analysis was undertaken in consultation with a statistician from the Medical Research Council. Patients were separated into groups depending on the presence of active disease. The HIV positive group of patients was also analysed.

It was expected that a statistical difference would be detected between the active and sequelar forms of the disease if 377 patients are included in Group 1 and 188 in Group 2, provided the difference was as large as 11%, i.e. 5% morbidity in the Group 2 and 16% in Group 1. In the course of collecting the data, it became clear that the numbers were insufficient for this purpose and it was suggested that the study concentrate more on clinical significance and trends.

Relative risks and 95% confidence intervals were determined to compare the incidence of the morbidity between the exposure groups using EpiCalc 2000, Version 1.02 [40]. Confounding variables, including Human Immunodeficiency Syndrome (HIV) status, pre-operative TB therapy and sputum status were controlled for using Poisson regression. The statistical analysis was undertaken with SPSS 11.5 ®. Statistical significance was defined by a p value < 0.05

3. Results

One hundred and sixty three patients underwent lung resection. One hundred and six fell into the active group (Group 1) and 57 patients had sequelar disease (Group 2). There were 105 males and 58 females with a mean age of 33.5years (range 2 – 69yrs). The further results have been divided into the two groups.

3.1 Active tuberculosis (n = 106)

There were 67 males and 39 females in this group, with a mean age of 33.3yrs (range 2 – 69yrs)

3.1.1 Multi-drug resistant tuberculosis (n = 27)

The MDR group had all received a minimum of 3 months of appropriate therapy based on drug sensitivities. Surgery was offered in this group for localized cavitatory disease (n = 12), multiple recurrences (n = 4) and persistent sputum positivity (n = 11).

Radiographic confirmation of the disease extent was undertaken with HRCT and in 2 patients with multiple recurrences; there was contralateral limited parenchymal disease.

The commonest resection was a left pneumonectomy. (Table 1)

Two patients required re-thoracotomy for bleeding in the immediate post-operative period with a further 2 developing post-pneumonectomy empyemas (7.4%). A bronchopleural fistula developed in a single patient (3.7%) resulting in an overall major morbidity rate of 18.5% (Table 3). Minor complications developed in 2 patients, one developing minor skin wound sepsis and the second developing a pneumonia managed with oral antibiotics. The overall morbidity was 25.9%.

Six patients in this group were HIV positive, all with CD4 counts over 400cells/mm^3.

In this sub-group, a single patient developed a post-pneumonectomy empyema with the wound sepsis and pneumonia occurring in 2 other patients resulting in 50% morbidity.

Two patients were found to be sputum positive at the end of 18 months of therapy. They had been in the group with multiple recurrences and had developed contralateral disease precluding further surgery. Surgery produced a cure rate of 92.6%.

3.1.2 Haemoptysis (n = 44)

The mean duration of pre-operative anti-TB therapy in the group with haemoptysis was 43.7days (range of 2days to 6months). Four patients were sputum positive in this group. Bronchial artery embolisation was undertaken in 9 patients, including the four patients that were sputum positive pre-operatively. This allowed for the "elective" planning of resection in 4 patients during the same admission.

A single patient developed massive haemoptysis following BAE mandating emergent surgery.

The complications included minor wound sepsis in 2 patients, atelectasis of the remaining lung in a patient undergoing an upper lobectomy and post-operative pneumonia in a further 2 patients, one of whom was sputum positive. The overall morbidity rate was 11.4%. There was no major morbidity.

There were 2 patients that demised in the post-operative period resulting in a mortality rate of 4.5%. The first patient died on day 3 post-operatively from an unknown cause; his family refused consent for a post-mortem to be performed. The second patient was HIV positive; his presumptive cause of death was a pulmonary embolus.

Post-operative therapy was continued for 6 months. Seven patients were HIV positive, with CD4 counts ranging from 350 – 666cells/mm^3.

Follow up was achieved in 36 patients over a period ranging from 1 – 8months. (Mean of 2.1months)

3.1.3 Bronchiectasis (n = 27)

Surgery was indicated in these patients with recurrent chest infections and radiographic evidence of bronchiectasis. This included patients with previous empyema where the underlying lung was destroyed.

Five patients were found to be sputum positive on pre-operative assessment and received a further 3 months of therapy prior to surgery.

The resections undertaken are listed in Table 1. Two patients were HIV positive in this group with CD4 counts over 400cells/mm^3. There were no complications in the HIV positive patients.

Morbidity occurred in 18.5% of patients:

i) PPE in three patients (11.1%) requiring prolonged drainage with subsequent sterilization of the pleural space

ii) post-operative pneumonia in a single patient

iii) failure of residual lung re-expansion in a further patient resulting in a persistent pleural space. This had resolved on follow up.

3.1.4 Diagnostic dilemma (n = 8)

The evaluation and management of patients where malignancy could not be excluded involved a trial of anti-TB therapy. The mean duration of this trial period was 42.5days.

Pre-operative needle aspiration had been undertaken unsuccessfully in all patients. Exploration was based on the radiographic features that favoured malignancy. In one patient, in light of the clinical suspicion of malignancy rather than inflammatory lung disease, a pneumonectomy was undertaken. This is not the standard practice. In view of the difficulties already mentioned regarding the initial availability of frozen section, it was felt that the patient was better served by the operation performed.

It was unfortunate that a PPE developed in this patient with a resultant morbidity rate of 12.5% ($p = 0.563$). There was no evidence of a BPF and the PPE was managed by drainage and sterilization. There were no operative or early post-operative deaths.

3.2 Sequelar disease (n = 57)

There were 38 males and 19 females with a mean age of 31.9yrs (range 3 – 61yrs).

3.2.1 Multidrug resistant tuberculosis (n = 2)

There were only 2 patients in this cohort with no complications or mortality.

3.2.2 Haemoptysis (n = 32)

Twenty-four of these patients had received treatment prior to surgery over a period ranging from 10 to 365days (mean 94.5days). Thirteen patients had undergone bronchial artery embolisation prior to surgery.

There were 12 patients that were HIV positive in this group with CD 4 counts ranging from 9 – 1102cells/mm^3.

The following complications occurred:

i) post pneumonectomy empyema in 2 patients, both of whom had received treatment prior to surgery in addition to a previous course of medication.

ii) bronchopleural fistula in a single patient requiring prolonged drainage, no further surgical intervention was required

iii) ventilation in two patients immediately post-operatively following emergency surgery. They were both extubated within 48hours.

iv) minor wound sepsis in a single patient

v) pneumonia requiring oral antibiotics in a single patient

vi) persistent pleural space in 6 patients which remained, albeit without symptoms, in 3 patients on follow up

The overall morbidity was 40.6% with a major morbidity rate of 15.6%. There were no deaths in this group. The commonest resection was a lobectomy (Table 2).

3.2.3 Bronchiectasis (n = 23)

There were nineteen patients in this group that were operated on whilst receiving anti-TB medication. The remaining patients had all received a course before admission. There were 2 patients that were HIV positive.

The following complications developed:

i) post pneumonectomy empyema in a single patient (4.3%) that was managed by open drainage

ii) post-operative pneumonia in one patient

iii) persistent pleural space in a further patient

The morbidity rate was 13%. There was a single death in this group from causes unknown. No post-mortem was performed.

3.3 Analysis

The overall major morbidity in the study was 13.8%. There was no statistically significant difference between the morbidity in the active and sequelar groups (9.4% and 22.8%, p = 0.081, RR 0.63 with CI 0.36 – 1.11). The morbidity, somewhat surprisingly, was higher in the group with sequelar disease.

The commonest complication in both groups was that of a post-pneumonectomy empyema occurring in 5.7% and 5.3% of patients with active and sequelar disease respectively (p = 0.734, RR 1.25 with CI 0.34 – 4.67). Bronchopleural fistulae occurred in 0.9% of patients in group 1 and 1.8% in group 2 (p = 0.067, RR 0.77 with CI 0.19 – 3.08).

These results are comparable to the reports in the literature.

There was no correlation between the indications for surgery and morbidity (p = 0.719). This held true for both groups, although the sequelar group of patients with haemoptysis experienced more complications (40.6% vs. 11.4%) than the active group. This was statistically significant (p = 0.02, RR 1.61 with CI 1.06 – 2.45), suggesting an increased risk for complications in patients with haemoptysis and sequelar disease.

There was no significant difference in the age ranges between the active and sequelar groups with haemoptysis (33.7yr and 39yr). There were more males in the sequelar group with haemoptysis but this did not reach statistical significance (p 0.53). Males were more at risk of developing complications though with a RR of 1.83 with CI 0.51 – 6.57. In keeping with the urgent nature of the surgical intervention, the active group had received much less anti-tuberculous therapy than the sequelar group (50.9days and 94.5days). Surgery was undertaken as emergency in these patients but there was no difference in the ratio of emergency surgery in either active or sequelar group.

It is possible that the higher number of HIV positive patients in the sequelar group with haemoptysis may have had some influence on this result (12/32 vs 7/44). HIV positivity did suggest a greater risk for complications in the sequelar group with a RR of 1.94 with CI 0.85 – 4.43. The numbers in this group, were however to small to allow proper comparison.

Twenty five percent of the sputum positive patients developed complications. This figure is obviously limited by the fact that some patients may have undergone surgery as an emergency with no pre-operative sputum being submitted. Once again, there was no statistical correlation, using Fischer's exact test, between sputum status and the risk of complications (p = 0.118, RR 1.79 with CI 0.71 – 4.51), but the trend indicated that sputum positivity was a risk for complications in the patients with histologically active disease. The obvious limitation is the fact that this study is underpowered.

There was also no correlation between morbidity and the anatomical extent of the resection in either group 1 (p = 0.850) or 2 (p = 0.451).

Pretreatment with anti-tuberculous drugs was also considered. Only 135 patients had received pre-operative treatment. The duration in both groups ranged from 0 -515 days with a mean of 79.1days. Unfortunately this resulted in a skewed graph as the majority of patients had received < 100 days of treatment prior to surgery. (Graph 1) The mean duration of treatment was 106.9days in group 2 compared to 58.7days in group 1 ($p = 0.024$). (Graph 2) In the patients with complications, it was interesting to note that the Group 2 patients had received twice as much pretreatment (60days vs. 30days) than the Group 1 patients. Pretreatment must not be confused with prior anti-TB medication which was defined as any previous treatment irrespective of the time period separating it from the surgical intervention. In group 1, 23.6% of patients had received prior therapy, compared to 28.1% in group 2. There was no correlation between prior treatment and the risk of developing post-operative complications in either group.

3.4 HIV status

The positive HIV status of 30 patients was also considered in the analysis. The overall morbidity in this cohort was 36.7% (Table 4). There were complications in 26.6% of HIV positive patients in group 1 compared to 46.7% in group 2. The morbidity in the HIV negative patients in group 1 was 17.6%.

The addition of being HIV positive did not increase the risk of complications in patients with active disease significantly ($p = 0.450$, RR 1.52 with CI 0.59 – 3.92). The relative risk of 1.52 suggests that HIV positivity may be a risk for complications in patients with active disease. This cannot be stated conclusively as the numbers are inadequate. Within group 2, the difference in morbidity, 46.7% in HIV positive patients vs. 23.8% in HIV negative patients ($p = 0.093$, RR 1.96 with CI 0.91 – 4.21) was also not statistically significant.

HIV status overall was a risk factor for morbidity (p = 0.041, RR 1.88 with CI 1.05 – 3.36). HIV positivity increased the risk of complications in all patients operated on by a factor of 1.88. There was no correlation between HIV status and the risk of developing a PPE or BPF (p = 0.893 and p = 0.246 respectively).

It was not possible to compare patients according to indications for surgery due to the small number of HIV positive patients, nor was it possible to correlate morbidity with CD4 count in view of the small numbers and the fact that the CD4 count distribution was skewed with almost all the counts over 400cell/mm^3 (Graph 3). This was expected in view of the unit policy. Interestingly, the range of CD4 counts were much greater in patients with complications with more people having lower counts (Graph 4). The mean counts were similar however.

Multivariate analysis showed that the only variable that reached statistical significance for complications was gender in the sequelar group (Table 5). Males were more at risk for developing complications (p = 0.036).

Follow up remains a problem, it is inferred that our patients are well in view of the fact that we are the only Thoracic Surgical service in the province and all our patients are returned if they complicate. Follow up was available in 135 patients (94 in group 1 and 41 in group 2). The duration of follow up ranged from 1 – 18months. The mean duration was 2.7months in group 1 and 2.4months in group 2.

4. Discussion

Thoracic surgery owes much of its development to pulmonary tuberculosis [1,2]. The original difficulties reported, with regards to the operative complications have largely been eradicated due to developments in both surgical and anaesthetic technique.

4.1 MDR TB

Surgical intervention has traditionally followed a full course of appropriate medical therapy. Recent work on MDR patients has sparked interest in the possibility of earlier surgery. Surgery in this group of patients has been considered earlier and in patients that are sputum positive with active disease. The results in this study are comparable with the literature with an acceptable morbidity and mortality and a cure rate of over 90% [21,23]. The MDR group may therefore be considered one of the prototypes for surgical intervention in the face of active disease. In terms of the controversies:

1. Bronchial stump closure with muscle flap reinforcement needs further study although the available literature and the results from the local experience suggest that routine reinforcement is not necessary [20 - 25]. In this review, there were insufficient patients where the stump was reinforced with muscle to allow for statistical comparison. Further limitations include the low number of sputum positive patients together with the absence of endobronchial tuberculosis, a recognized risk factor [15], which may account for the low BPF rate.

   Pomerantz [5], Van Leuven [20]and Shiraishi [21]are advocates of routine muscle reinforcement of the bronchial stump. In a report by Takeda et al [23], 26 sputum positive patients with MDR TB underwent surgery with no muscle flap reinforcement of the bronchial stump. Their incidence of bronchopleural

fistulae was zero. The BPF rate of 3.7% is reasonable in patients with active disease. No statistical correlation could be made to patients with sequelar disease in view of the numbers.

2. It was also not possible to compare suture versus staple closure. The cost limitations in the local unit prevent this. Further study is required to evaluate these techniques.

The role of surgery as an adjunct to the medical management in MDR TB is now well established [3,6,12,14]. The results in this study confirm the reports in the literature. The management of the bronchial stump without muscle flap reinforcement resulted in a low incidence of bronchopleural fistulae in the study groups, although larger numbers are needed to draw conclusions. Whilst it is not possible to state conclusively that the method of stump closure used in this study was the sole reason for the low complication rate, it is suggestive and warrants further investigation. It was not possible to assess other variables such as pre-operative sputum status in view of the lack of adequate numbers.

It is the current contention that surgery should be considered earlier in these patients in an attempt to eradicate disease activity [24]. The rationale is that the disease is controlled prior to the development of extensive bilateral disease.

4.2 Haemoptysis

Patients with haemoptysis, by virtue of the urgent nature of the intervention, may also undergo surgery in the face of active disease. The results in this review, with morbidities of 11.4% in group 1 and 40.6% in group 2 correlate with reports in the literature of between 30 – 50% [28]. One must bear in mind however that this was in the setting of emergency surgery. The trend towards a higher morbidity in the sequelar group is noted; and using the Fischer's exact test is significant.

It is difficult to explain why surgery in patients with sequelar disease and haemoptysis is a risk for morbidity.

Evaluating the patient profile did show that there were more males in the sequelar group relative to females (24 males and 8 females). This did not reach statistical significance. There was also no correlation with the number of HIV positive patients and the risk of complications in the sequelar group. These patients had completed a course of anti-TB medication and surgery was generally elective. The fibrotic healing reaction induced by medical treatment may make surgery hazardous but not more so than in the active group where there would be vascular adhesions induced by the presence of active inflammation. Patients in both groups underwent surgery in the emergency setting with no difference between groups. There are no reports in the literature comparing surgery for haemoptysis between cohorts of patients with active and sequelar disease.

The results also tend to support the contention that surgery may be undertaken in the face of active disease with acceptable results.

In consideration of the higher operative mortality with emergency surgery for active haemoptysis, it is suggested, that semi-elective surgery on a patient rendered stable is a reasonable alternative. There was no correlation between surgery for active disease with haemoptysis and an increased morbidity in this review. In effect, once patients are admitted and stabilized, surgery, if anatomically and physiologically feasible, should be planned on the next elective list. This supports the work of Knott-Craig [28] and Conlan [29]. The previous strategy of delaying surgery in these patients if active disease is suspected needs to be revised in view of the results in this review.

4.3 Morbidity

The incidence of bronchopleural fistulae and post-resectional space infections in the active group, 0.9% and 5.7%, are lower than most of those reported in the literature. Comparatively, 1.8% of patients in group 2 developed bronchopleural fistulae and 5.3% developed post-resectional infections. Whilst there was no statistical significance between the active and sequelar groups, the trend was to a higher morbidity in the sequelar group (28.1%) than in the active group (17%), despite the longer mean duration of medical pretreatment. The absence of a statistical difference was expected to a large extent in view of the numbers and the study being underpowered. Once again it is difficult to explain this as the opposite was expected. There was no significant difference in either patient profile with the only risk in the sequelar group on multivariate analysis being gender with males more at risk for complications.

The low incidence of bronchopleural fistulae is despite the fact, as already mentioned, that muscle flap reinforcement of the bronchial stump is not routine. There are limitations that preclude one drawing conclusions from this but it does warrant further investigation. Stapling devices and sputum results were not available in all patients. The technique of interrupted suture bronchial closure, with preservation of the blood supply, is a recognized technique that warrants comparative study with other methods, preferably in a prospective randomized manner.

The absence of endobronchial tuberculosis in the resected specimens may also explain the low incidence of these complications.

The key principles in the history of surgery for TB have been the promotion of healing of the bronchial stump and the avoidance of pleuropneumonic sepsis [1,2].

4.4 HIV status

The impact of HIV on Thoracic Surgery has yet to evaluated locally. There were only a small number of HIV positive patients in this review with a further major limitation being the lack of access to antiretroviral medication. This led to deferment of surgery in patients with CD 4 counts under 400cells/mm^3. The departmental policy is being re-evaluated as the availability of these drugs should allow surgery on patients with lower counts and with easy access to antiretrovirals, it will be possible to commence medication prior to surgery, and continuing post-operatively.

It was expected that the HIV status would correlate with increased morbidity, this was true overall ($p = 0.041$) with HIV positive patients being almost twice as likely to develop complications compared to HIV negative patients [RR 1.96]. In specific groups however, there was no correlation with morbidity. Being HIV positive and having active disease was not a risk factor for morbidity despite a high relative risk [RR 1.52]. There was also no correlation between HIV positivity and the development of either a PPE or BPF. The small numbers of HIV positive patients in the subgroups could explain this. The relative risks suggest a higher risk of these complications.

The role of the thoracic surgeon in HIV positive patients has not been fully addressed. To date there are no reviews addressing this problem and surgery in these patients is largely dictated by the circumstances i.e. emergencies or unusual disease manifestations.

5. Conclusion

Surgery for tuberculosis has come full circle; originally one of the pillars of patient management; to being relegated to adjunctive treatment to medical therapy. Whilst the results obtained do not demonstrate statistical significance, trends are evident.

This study has demonstrated that surgery may be undertaken in the face of active disease with acceptable morbidity (9.4%). The reported range for morbidity in this group is 12.5 – 30% [3,10,13,14,15]. The lack of a statistical difference between the active and sequelar group, due mainly to the numbers in the study, would suggest that surgery may be undertaken effectively.

Lung resection in selected MDR patients produces high cure rates of over 95% with acceptable morbidity and mortality.

The results, morbidity of 11.4%, in the patient group with haemoptysis suggest that immediate medical stabilization with in-patient surgery is a valid management strategy. Urgent surgery may be undertaken rather than submitting patients to further medical therapy in order to obtain disease quiescence prior to surgery.

In additions, this study highlights the need for further research on;

a. the impact of HIV on thoracic surgery
b. the strategy for management of the bronchial stump in patients with active disease

The key principles to bear in mind, as with any surgical decision include careful patient selection and preparation, meticulous surgical technique and appropriate post-operative surgical care.

6. Limitations

The major limitations in the study are;

1. The study is retrospective from a review of patient records from departmental archives. Complications other than the major ones were all subjectively reported thus producing a skewed picture with regards to the minor complications.
2. The numbers in the cohorts are small and thus the study is underpowered limiting statistical significance and conclusions that one may draw from them. Trends may however may be determined and the areas of further study may be determined
3. The results in the HIV positive group are also skewed by the lack of access to antiretroviral results and the departmental policy that precluded elective surgery on patients with CD4 counts below 400cells/mm^3.

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7. Tables, graphs and figures

RESECTIONS	MDR TB (n = 27)	Haemoptysis (n = 44)	Bronchiectasis (n = 27)	Diagnostic dilemma (n =8)
Right upper lobectomy	1	9	0	6
Right lower lobectomy	1	1	0	0
Right pneumonectomy	6	10	11	1
Left upper lobectomy	5	8	4	0
Left lower lobectomy	2	2	1	1
Left pneumonectomy	11	9	11	0
Upper and middle lobectomy	1	3	0	0
Middle and lower lobectomy	0	2	0	0

Table 1. Resections distributed according to indications for surgery in the active group

RESECTIONS	MDR TB (n = 2)	Haemoptysis (n = 32)	Bronchiectasis (n = 23)
Right upper lobectomy		9	1
Right lower lobectomy		1	0
Right pneumonectomy		7	6
Left upper lobectomy		9	3
Left lower lobectomy		0	1
Left pneumonectomy		6	7
Middle lobectomy	0	0	2
Middle and lower lobectomy	0	0	2
Upper and middle lobectomy	0	0	1

Table 2. . Resections distributed according to indications for surgery in the sequelar group.

	ACTIVE DISEASE (n = 106)	SEQUELAR DISEASE (n = 57)
Bleeding – rethoracotomy	2	0
Post-pneumonectomy empyema	6	3
Bronchopleural fistula	1	1
Space complications	1	7
Ventilation	0	2
TOTAL	10 (9.4%)	13 (22.8%)

Table 3. Complications following surgery

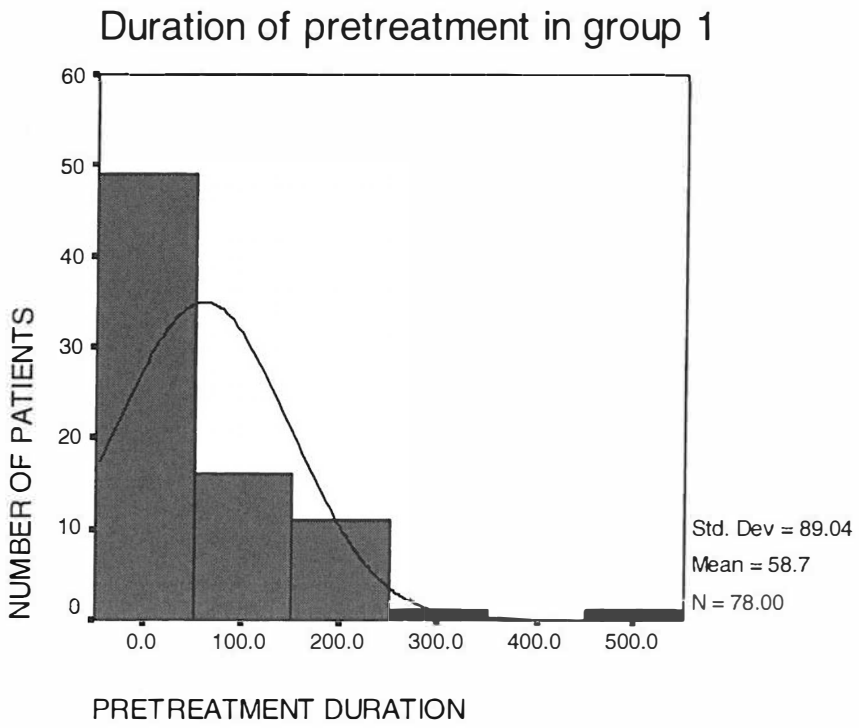
COMPLICATIONS	ACTIVE DISEASE (n = 2)	SEQUELAR DISEASE (n = 5)
Bronchopleural fistulae	1	0
Post-pneumonectomy empyema	1	1
Space problems	0	2
Ventilation	0	2

Table 4. Morbidity in the HIV positive patients correlated with disease activity

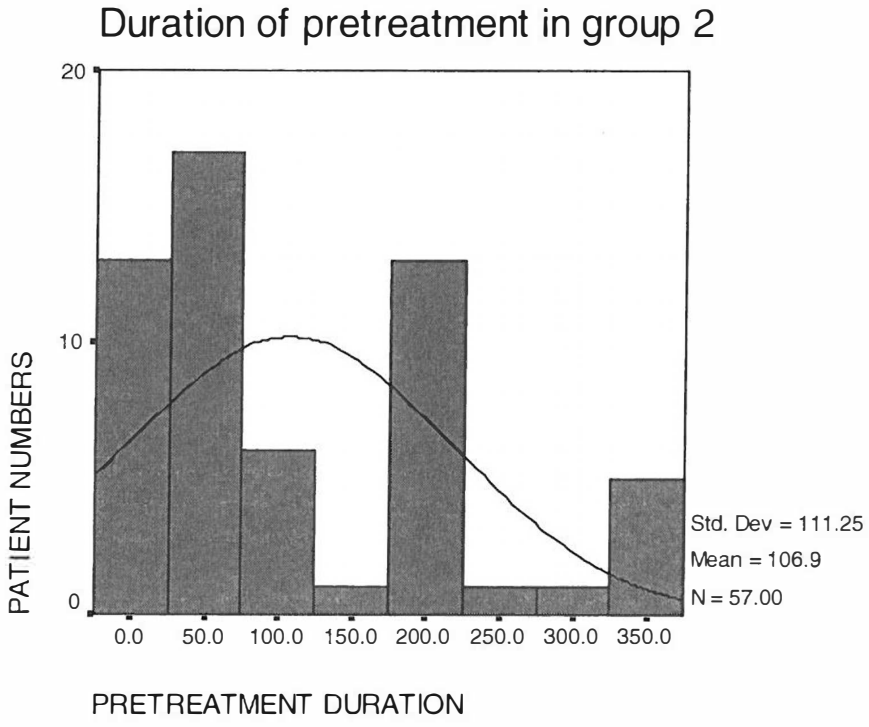
	ACTIVE DISEASE	SEQUELAR DISEASE
	p value	*p* value
Age	.09	.283
Sputum positivity	.582	.703
Indication for surgery	.670	.408
Lung resection	.948	.531
HIV status	.075	.273
Gender	.321	.036

Statistical significance with $p < 0.05$

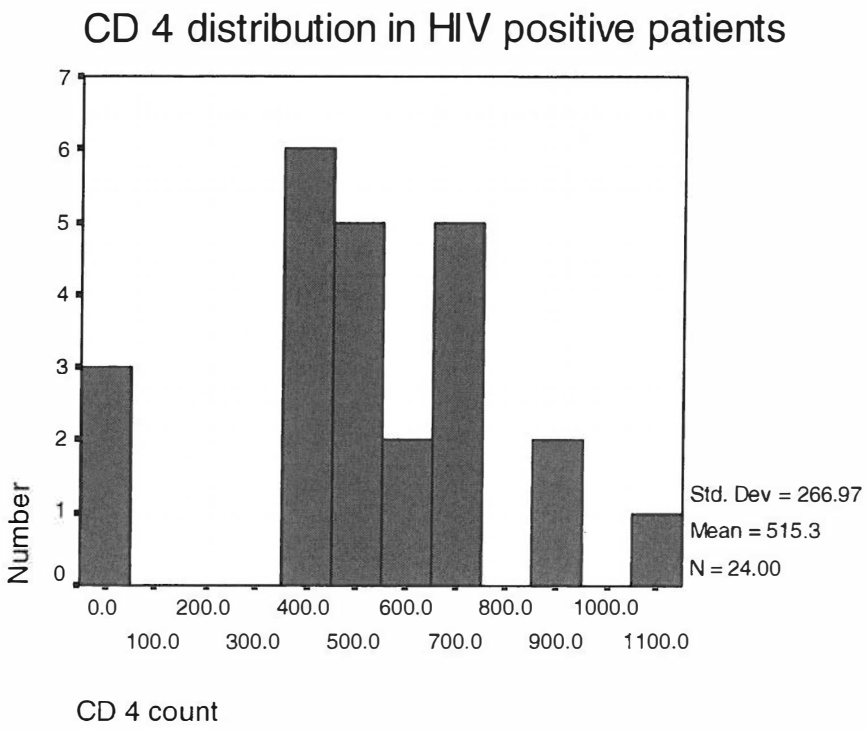
Table 5. Multivariate analysis of risk factors for major complications.



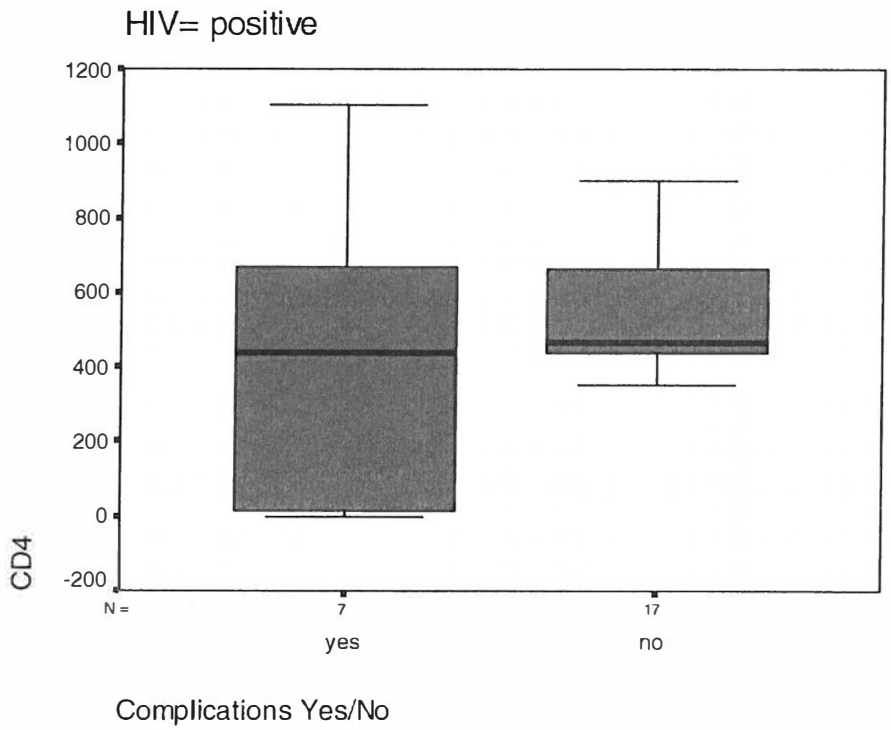
Graph 1. Duration of pre-treatment in patients with active disease



Graph 4. Duration of pre-treatment in patients with sequelar disease



Graph 3. Distribution of CD4 counts in the HIV positive patients in both group 1 and group 2



Graph 4. Distribution of CD4 counts in all patients with complications

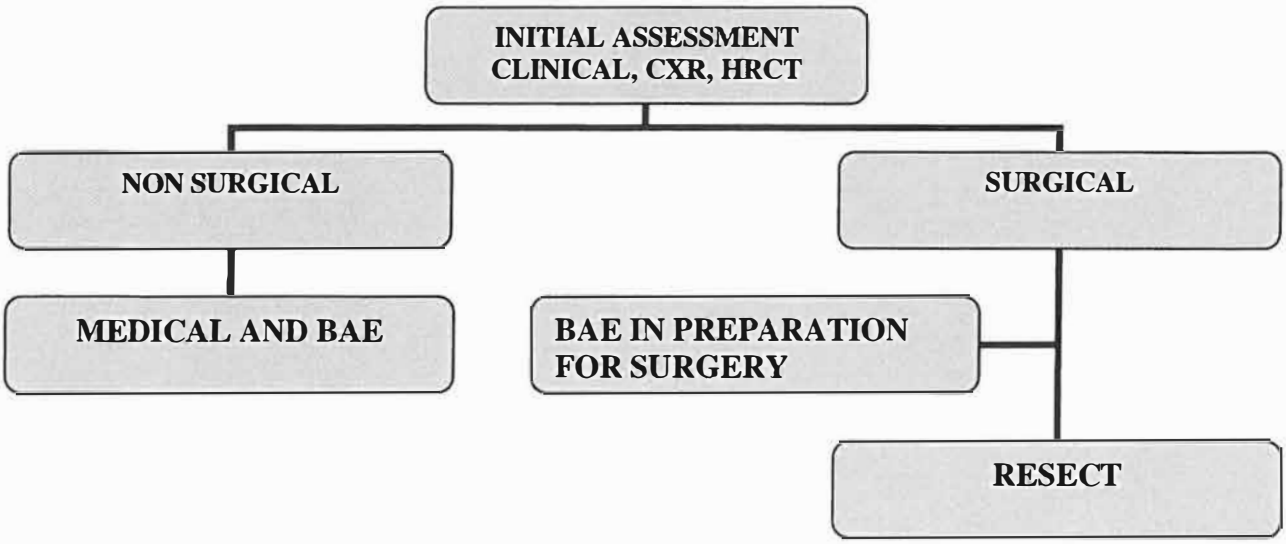


Figure 1. Algorithm for management of patients with haemoptysis (adopted from Blyth [30])
BAE – Bronchial artery embolisation

Figure 2. Injection into pathological right bronchial artery demonstrating abnormal vessels with neovascularisation

Figure 3. Post bronchial artery embolisation demonstrating no filling of the abnormal vessels

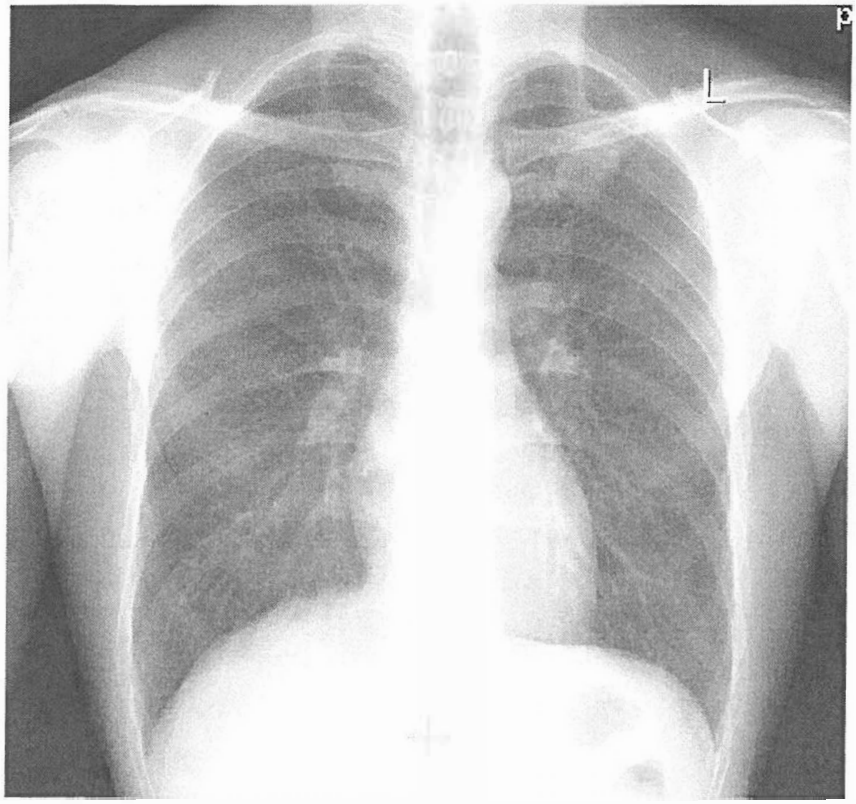


Figure 4. Chest radiograph demonstrating an opacity in the left upper lobe where a malignancy could not be excluded, histology demonstrated caseous necrosis consistent with tuberculosis.

8. Appendix

1. MTB – mycobacterium tuberculosis
2. HIV – Human Immunodeficiency Virus
3. MDR TB – multi-drug resistant tuberculosis
4. TB – tuberculosis
5. PPE – post-pneumonectomy empyema
6. BPF – bronchopleural fistula
7. VATS – video-assisted thoracoscopic surgery
8. FEV 1 – forced expiratory velocity in one second
9. HRCT – high resolution computerised tomography
10. CD4 – cluster of differentiation 4