PULMONARY ASPERGILLOMATA: AN ASSESSMENT OF CLINICAL OUTCOME AFTER SURGICAL RESECTION AND OF THE HOST IMMUNE RESPONSE TO ASPERGILLUS INFECTION AT CELLULAR LEVEL

by

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I. INTRODUCTION

A pulmonary aspergilloma, one of the forms of pulmonary disease caused by the ubiquitous fungus *Aspergillus species* , is a secondary fungal infection imposed on pre-existing pulmonary disease. It is commonly associated with haemoptysis, which may be life-threatening[8,9,12,17-19,30]. Colonisation of pre-existing cavities due to previous infection with *mycobacterium tuberculosis* is well described[1,2]. In South Africa, due to the high incidence of pulmonary tuberculosis[73], pulmonary aspergillomata are frequently encountered.

Whilst an aspergilloma may remain benign, and its host patient asymptomatic for many years[8,12,71], both the onset[9,18] and severity[8] of symptoms are unpredictable. Multiple publications have indicated that the optimal form of management for pulmonary aspergilloma remains contentious[4,5,8,9,14,15,17-21,23-25,40]. There appear to be three differing opinions. In the past, it has been recommended that surgery be avoided, on the basis of the attendant risks[16]. Other authors have advocated the prophylactic resection of all, even asymptomatic, simple aspergillomata in order to avoid life-threatening haemoptysis[8,19,21]. The third recommendation sees surgery as the treatment of choice for selected, symptomatic patients and stresses the value of the appropriate procedure [5,31-33,35-40].

The question as to why the danger of life-threatening haemoptysis and excessive blood loss during surgery seems to be greater in patients with aspergillomata[21,22] than post-tuberculous patients without aspergillomata, has not been satisfactorily answered.

The aims of this study are two-fold:

1. To review the outcome of patients who underwent surgical resection for pulmonary aspergillomata at a single institution and relate it to the literature.

2. To examine the histological pattern at the surface of a tuberculous cavity colonized by Aspergillus forming a classic fungal ball and those of a tuberculous cavity without colonization to determine whether there is a difference in the appearance.

II. LITERATURE REVIEW

1. BACKGROUND

The fungal genus *Aspergillus* was first described and named by Micheli in 1729[3-5], the name presumably derived from its resemblance to the *aspergillum*, the brush used to sprinkle holy water in the Catholic Church (fig.1.) The first description of human aspergillosis was reported by Bennett in Edinburgh in 1842[5-8]. Sluyter reported in 1847 on the ability of *Aspergillus* to colonise existing pulmonary cavities and to form balls consisting of fungal and necrotic material[5,7]. Virchow is credited with the original pathological description in 1856[4,5,9]. Friedreich (1856) and Fuerbringer (1876) reported the finding of the fungus growing in tuberculous cavities[3]. The characteristic radiographic appearance of a fungal ball in a pre-existing lung cavity was described by Deve in 1938[5]. Surgical intervention for Aspergillosis was first performed in 1947 by Gerstl and colleagues and the report appeared in the literature in 1948[10].

In 1952, Hinson and colleagues classified pulmonary aspergillosis based on their experience with a number of cases at the London Chest Hospital[3]. Their classification was set out as follows, in increasing order of severity:

Type I: *Saprophytic* – the Aspergillus acts as a saprophyte complicating a pre-exiting pulmonary condition

Type II: *Allergic* – sensitization to the fungus leads to an exudative reaction in the lumen of the bronchus

Type III: *Septicaemic / Pyaemic* – multiple mycotic abscesses or granulomata occur in the lungs or even elsewhere and was reported to occur more often in children than adults.

Zimmerman and colleagues and subsequently Gefter and colleagues have further sub-divided human aspergillosis into primary and secondary, as well as into invasive and semi-invasive types[12]. Kibbler and colleagues have described another entity in neutropaenic patients with previously normal lungs. They proposed the term "mycotic lung sequestrum" to describe their finding of fungal infiltration of necrotic pulmonary tissue[46].

Recently, Ikemoto[13] pointed out that the prognosis of patients with aspergillomata is dependant more on the extent of the underlying disease than on the aspergilloma itself and that the aspergilloma may remain stable for a long time. Faulkner and colleagues[14] have stated that the danger of massive bleeding in these patients may not be as great as previously feared. Karas and co-authors[15] believe that surgery should be reserved for those patients who have developed major haemoptysis, since surgery for this condition is often difficult and is not without its own attendant risks. The avoidance of surgical resection has even been recommended in the past by Varkey and Rose[16].

Rafferty et al.[17], Jewkes et al.[18], Battaglini et al.[5], Daly et al.[19], Conlan et al.[20], Kauffman[23], Kay[24], El Oakley et al.[25], and more recently Babatasi et al.[9] and Ueda et al.[31] maintain that controversy exits about how best to manage pulmonary aspergillomata. Babatasi and co-authors[9] highlight the unpredictability of the advent of eventual life-threatening haemoptysis, a point also made previously by Jewkes and co-authors[18]. Both have stated that neither the size nor the complexity of the aspergilloma, the type nor extent of the underlying pulmonary disease, nor the presence of an episode of minor haemoptysis (heralding the potential onset of a life-threatening event) could predict which patients might progress to major haemoptysis[9,18]. In the series published by Jewkes and co-authors[18], the observed 5-year survival after surgery was 84%, as opposed to 41% in non-operated patients.

Garvey and co-authors stated in 1977 that once haemoptysis has occurred, the chances of fatal haemorrhage may be as high as 30% and have, along with Daly et al[19] and Massard et al.[21], advocated the prophylactic resection of all simple pulmonary aspergillomata on the basis of the subsequent risk of major haemoptysis. Battaglini[5], Ueda[31] and Soubani[33] have not supported this view.

Results from more recently published studies have referred to the controversy in the past and have been more specific in outlining the specific selection criteria and procedures for specific types of patients to ensure optimal outcomes[32,35-40].

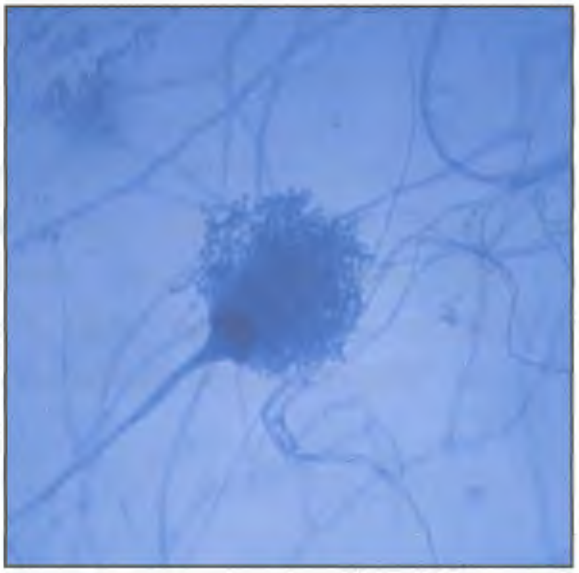


Fig. 1: Aspergillus: *Microscopic structure of an Aspergillus conidiophore (Reproduced with the kind permission of the Department of Microbiology, Groote Schuur Hospital, University of Cape Town)*

2. AETIOLOGY

Between 200 and 1000 species of *Aspergillus* have been identified[3,4] but only 19 have been reported to be potentially pathogenic, *Aspergillus fumigatus* being the most common[3]. Worldwide, *A. fumigatus* is said to be responsible for more infections than any other fungus[41]. Other species have been associated with disease in humans more rarely (*A. flavus, A. terreus, A. niger, A. nidulans*[44], *A. versicolor*[3], *A. clavatus* and *A. niveus*[33]).

A. fumigatus is ubiquitous, occurring both in- and outdoors, with its natural ecological habitat in the soil where it plays an important role in recycling environmental carbon and nitrogen[3]. Environmental studies indicate that all humans will inhale at least several hundred *A. fumigatus* conidia per day[43]. In the immunocompetent individual, this rarely has any adverse effect, since the conidia are eliminated relatively efficiently by innate immune mechanisms. Colonization is the result of an inability by the host patient to clear the inhaled spores. Subsequent germination leads to the formation of a fungus ball within the cavity[44]. *A. fumigatus* conidia have been found to outnumber other conidia in the lung at post mortem, out of relation to their ubiquity in the environment, suggesting that they possess some added survival ability in the human lung[69].

More than 90% of intracavitary fungus balls are caused by *Aspergillus fumigatus*. *Zygomycetes spp.*, *Nocardia*, *Candida*, *Mucor*, and *Fusarium* have also been implicated[5,33]. In the majority of cases, cavitation has been the result of infection with *Mycobacterium tuberculosis*[1,2,9,24,26-33,37,65,71]. Colonization of cavities with Aspergillus is possible but rare in sarcoidosis, abscess cavities, cavitating neoplasms, emphysema, bronchiectasis, congenital cysts[4], bronchial cysts, bullae, ankylosing spondylitis, pulmonary infarction[33] and, more recently, pneumatocoeles secondary to *Pneumocystis carinii* pneumonia in patients with AIDS[51,71].

3. INCIDENCES

Worldwide, *Aspergillus* is responsible for more infections than any other mould[42]. Infections caused by *Aspergillus* species, most commonly *A. fumigatus*, have traditionally been categorized into four different forms: Invasive aspergillosis, semi-invasive aspergillosis, allergic pulmonary aspergillosis and saprophytic aspergillosis (aspergilloma)[12,58]. More recently, a new manifestation of aspergillus infection affecting primarily AIDS patients, known as obstructing bronchial aspergillosis, has been described[58].

Aspergillomata have traditionally been the most common and best recognized of the aspergillus infections[33] and have been of most surgical significance[7-10,14-40]. However, increasing numbers of immune-compromised patients in the AIDS pandemic have influenced the way the *Aspergillus* infections present[71,72]. By 1992, it was estimated that the frequency of invasive aspergillosis had increased almost 14-fold in the preceding 12 years[42]. Invasive aspergillosis has surpassed candidiasis as the most frequent fungal infection detected at post mortem in European tertiary care hospitals[42].

Kibbler and co-workers described a new clinico-pathologic entity of *Aspergillus* infection among neutropaenic patients[46]. This form of fungal proliferation in infarcted, previously normal lung, while appearing similar to classic aspergillomata, had a very different pathogenesis and natural history, with consequent implications in relation to their management and outcome[47].

Invasive pulmonary aspergillosis (IPA) causes a necrotizing bronchopneumonia with invasion of lung parenchyma and vasculature and consequent thrombosis, haemorrhage and eventual dissemination[49]. The poor outcome of medical therapy alone in IPA has been documented in transplant recipients, with reported mortalities of

95-100%[48,49]. Aggressive surgical intervention has met with success in preventing dissemination, reactivation and mortality in this setting[46-50].

The category which is the subject of this thesis is the saprophytic form described as aspergilloma. Aspergilloma has been found to occur in 10-15% of patients with cavitating lung disease[1,71], it involves primarily the upper lobes, but can be multicentric

4. PATHOLOGY

4.1. Introduction

An aspergilloma grows in the lumen of a pre-formed cavity without invading the host tissues to any appreciable extent[33,45,51]. Although usually single, aspergillomata may be present in cavities in both lungs, or there may be more than one lesion in the same lung[45].

The term *mycetoma* is often applied to intracavitary fungus balls such as aspergillomas. More correctly, the term is applicable to a type of fungal granuloma characterized by the formation of multiple sinuses, usually after penetration of the soft tissues by an object, like a thorn, contaminated by a causative organism. In this sense, a mycetoma represents an infection caused by invasion of the tissues by the relevant causative organism. In contrast, an aspergilloma is an intracavitary fungus ball, which is essentially outside the tissues[45].

4.2. Morbid Anatomy

The fungal colony appears macroscopically as a grey or reddish-brown mass, although it may sometimes be white. Its consistency is sometimes firm or rubbery but may often be friable or pultaceous. Old colonies may have a gritty consistency due to the deposition of calcium salts and rarely there may be so much calcification that the ball becomes stony and may be classified as a "pneumonolith"[45]

Belcher and Pulmmer[11] classified aspergillomata into simple and complex types. According to their description, the simple type develops in isolated, thin-walled cysts lined with ciliated epithelium, with the surrounding lung being normal, while the

complex type develops in cavities formed by gross disease in the surrounding lung tissue[37].

4.3. Histological Appearance

Microscopically, an aspergilloma consists of layers of fungal mycelia, cellular debris, fibrin, inflammatory cells and a conglomerate of tangled septate hyphae[5,33], most of which are usually dead. Only the hyphae at the surface tend to be well preserved[45]. The tips of these may be coated with a large amount of hyaline eosinophilic material, probably of immune origin, giving the edge of the aspergilloma a distinctive appearance and hence the appearance which gave rise to the name[3-5].

The lining of the cavity containing the aspergilloma varies and is usually determined by the nature of the condition underlying it. The wall of an old tuberculous cavity may consist of dense, hyaline fibrous tissue, sometimes without any epithelial covering. In other cases there may be a lining of chronic inflammatory granulation tissue, usually without specific features of tuberculosis or other former disease[45].

5. PRESENTATION

5.1. Clinical Presentation

Haemoptysis has been the symptom most commonly associated with aspergilloma[8,9,12,15,18,19,20,24-26,29,30,32,37,38], with reported incidences varying between 50 and 93%[9,30,32,33,38]. In a series of aspergillomata in HIV-infected patients, haemoptysis was less prominent than in HIV-negative patients by almost a third[71]. The haemoptysis may be severe and has been reported to recur in 8-20%[17,30,38]. The reported mortality rates from haemoptysis have ranged from 2-30%[8,15,18,19]. Other symptoms reported include chronic cough, sputum production, weight loss, malaise, shortness of breath and cachexia. Weight loss, malaise and cachexia are probably more likely to be related to the underlying pulmonary disease than to the aspergilloma itself [4,5,7,17,19,57]. Fever, not commonly a symptom associated with aspergilloma, was reported as a prominent sign of aspergilloma in HIV-infected patients in the series by Adrizzo-Harris et al[71].

Bleeding is described as classically arising from the erosion of the adjoining bronchial arteries[9,18,22,24,32,38,52,53,55]. Niwa and co-authors[22] reported that vessels from the chest wall itself may also contribute, whilst Remy and co-workers demonstrated that bleeding from pulmonary artery branches, though rare, cannot be excluded[54]. Other mechanisms for the haemoptysis which have been proposed include erosion of the vascular cyst wall by motion of the fungus ball, elaboration of endotoxin by the fungus or the patient's underlying disease[32]. Extension of the mycotic process with parenchymal destruction at the periphery of the lung with invasion of the chest wall leading to erosion of the intercostals arteries has been described[47].

5.2. Radiological Presentation

The characteristic radiological appearance of an aspergilloma, first described by Deve in 1938[5,57], is usually confirmatory . The fungus ball appears as a sharply demarcated, radiopaque spheroid, resting on the wall of the dependant part of the cavity and separated from it elsewhere by a crescent of air, the classic "air crescent" sign[51,57,58]. The ball may fill the cavity completely in cases where it has developed over years. Often the ball is capable of moving within the cavity, in accordance with the patient's posture[33,51,57,58]. Certain conditions need to be differentiated from an aspergilloma, notably angioinvasive aspergillosis, hydatid cyst, tuberculosis, Rasmussen aneurysm in a tuberculous cavity, lung abscess, bronchogenic carcinoma, haematoma and *Pneumocystis carinii* pneumonia (PCP)[51,58].

Aspergillomata are often associated with thickening of the cavity wall and the adjacent pleura[51,58]. The upper lobes of the lung have been reported as the preferential location of pulmonary aspergillomas in several series[4,9,18,32,37,58].

At computerized tomography (CT), an aspergilloma is characterized by a mass with soft tissue attenuation within a lung cavity. High resolution CT may also reveal small fungal strands bridging the fungus ball and cavity wall[51,58]. CT scanning will also help to distinguish between aspergillomata and other conditions mentioned above, as well as having a higher sensitivity for detecting pathology which might not be evident on plain chest radiographs[58].

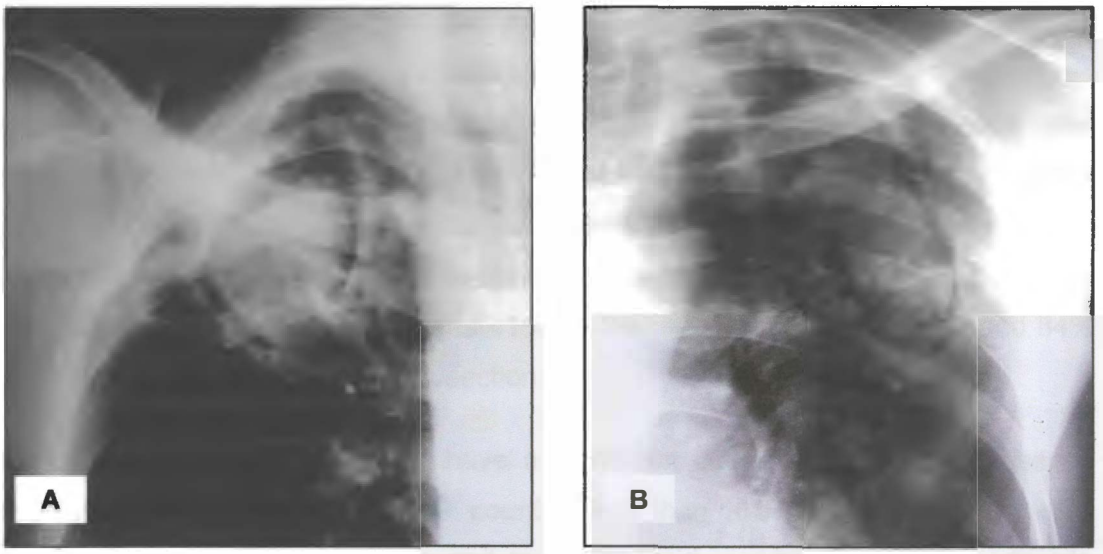


Fig. 2: Typical radiological appearance of an Aspergilloma in two different patients. (A) Demonstrates the classical "Ball in the hole" appearance in the right upper lobe of the lung, while (B) depicts a more elongated appearance of an aspergilloma in the left upper lobe.

6. THE MANAGEMENT OF ASPERGILLOMA

6.1. Background

The natural history of aspergillomata has been poorly documented[8,17,32]. Rafferty et al. suggest that the reason for this is that it is an uncommon disease and that its outcome is more often related to the underlying pulmonary pathology[17]. The rate of spontaneous resolution of aspergillomata (by expectoration of the fungus ball) in tuberculous cavities was reported as 5% over three years in a large series published in 1970 by the British Thoracic and Tuberculosis Association (BTTA)[1]. Other authors have subsequently, in smaller series, reported resolution rates varying from 0-37%[14-16]. Jewkes and colleagues reported resolution of aspergillomata in 5% of their series of medically treated patients over a period of 24 years[18]. The reported mortality associated with aspergillomata was 6% per year in the BTTA series[1] and in the series by Jewkes et al.[18] it was 31% at 5 years and 56% at 10 years. The recurrence rate of aspergillomata after resection was reported as 7%[18].

A few publications have compared surgical and non-surgical management strategies for aspergillomata[17,18,31]. Rafferty and colleagues[17] concluded in 1983 that the unsystematic approach to the disease, coupled with the attendant high mortality rates associated with both medical and surgical management, underlined the inadequate

treatment modalities at that stage. It is the opinion of these authors that the ability of surgery to improve the prognosis of the disease is based on averting fatal haemoptysis by resecting the aspergilloma before haemoptysis has occurred. Jewkes and colleagues[18] found a similar 5-year survival between surgical and medical therapy (75% vs. 65%) in patients with minor or no haemoptysis. In contrast, however, for those patients who had suffered recurrent frank haemoptysis or a single major haemorrhage, the 5-year survival was 41% for the medical treatment group and 84% for the group who had undergone resection.

HIV infection has been shown to have a significant accelerating effect on disease progression[72]. Patients with a CD4+ count of less than 100 cells per microlitre were more likely to develop symptoms and to suffer rapid disease progression, despite haemoptysis being a less prominent symptom among HIV-positive patients with aspergillomata than among their HIV-negative counterparts[71]. Progression to invasive diseaseor overlap with invasive disease, though uncommon, has been reported[71].

6.2. Surgery

6.2.1. Indications

According to Kay, surgery offers three potential benefits: control of symptoms, prevention of haemoptysis, and prolongation of life[24].

Haemoptysis has been the reason for operation in the majority of reported series[8,9,12,15,18,19,20,24-26,29,30,32,37,38]. Babatasi and colleagues[9] included 15 asymptomatic patients (18%) in their series of 84 patients. 22% of patients who had surgery in the series by Jewkes and co-workers[18] were asymptomatic. Daly and colleagues[19] and Massard and co-workers[21] share this view and advocate the surgical removal of the aspergilloma as soon as the diagnosis is made. Kabiri and colleagues[29] reported on a large series of 206 patients, 188 of whom underwent surgery "on principle". In their view, surgery should be offered to all patients with a pulmonary aspergilloma, even those who are asymptomatic, provided there is no contra-indication. Battaglini et al.[5], Ueda et al.[31] and Soubani and Chandrasekar[33] have not supported the view that asymptomatic aspergillomata should undergo surgery as a preventative measure.

Other reasons for surgical intervention have been to determine the aetiology of a pulmonary lesion, often incidentally discovered in asymptomatic patients without a

preceding history of tuberculosis[28,30]. Apart from the obvious advantage of treating symptoms and preventing potentially fatal haemoptysis, surgery might arrest further deterioration of the underlying condition[17,30].

6.2.2. Surgical Procedures and Outcomes

The initial controversy surrounding the optimal management of aspergillomata was because so many of these patients were considered medically unfit and therefore at too high a risk for major pulmonary resection[4,5,8,9,14,15,17-21,23-25,40]. Longstanding chronic infection with inflammation results in thickened, fibrotic tissue, induration of hilar structures and complete obliteration of fissures and pleural spaces, making surgical resection difficult[24]. Conlan et al. also point out that traditional trans-pleural and – fissural approaches and direct exposure of hilar structures is difficult and that the obliteration of serosal surfaces, fissures and the branches of the pulmonary artery lead to the standard surgical approaches being dangerous and prone to complications[20].

The majority of publications list lobectomy as the procedure of choice for this disease entity [4,5,9,11,18-21,26-29,30,32,37,38]. In addition to the patient's medical condition, the choice of the most appropriate procedure is determined by the ability of the remaining lung to fill the space[21,28]. The importance of assiduous surgical technique to reduce air leaks and post-operative haemorrhage, as well as to obliterate any potential post-operative space, by means of decortication, muscle plombage or supplementary thoracoplasty, has been emphasized[24,27,28]. Shiraishi et al. have reported their rationale for, and experience with, pneumonectomy for aspergilloma in a recent publication[40]. They have advocated meticulous extrapleural dissection using diathermy and argon beam coagulation of the chest wall as well as bronchial stump reinforcement using a muscle flap when performing pneumonectomy in these patients.

Jewkes et al.[18] and El Oakley et al.[25] reported disappointing outcome with cavernostomy and cavernoplasty, although several authors have published encouraging results with this less aggressive surgical procedure in high risk patients unable to withstand more extensive resection[27,30,35,37].

Reported mortalities and morbidities experienced with the surgical treatment of aspergillomata vary greatly and probably reflect a variety of factors influencing the outcome of this disease[4,5,9,18,19,20,21,26,27,29,30,32,37,38]. Table 1 summarises some of the experiences reported in the literature. Of note is the fact that most series have reported

high morbidity rates. Babatasi et al., despite a mortality of only 4%, encountered complications in over 80% of their patients[9]. Similarly, Massard and colleagues reported a 70% morbidity rate[21]. The results of Chen et al.[26], Park et al.[32] and Kim et al.[37], who reported mortality figures of 1.5%, 0.9% and 1.1% respectively, are particularly good in comparison to other series.

Table 1: *Surgical treatment of aspergilloma – selected results from the literature tabulated in the chronological order of the study period*

First Author	Time Period	No. of Patients	% TB underlying	% haemoptysis	% lobectomy	% operative mortality	% major morbidity
Daly [19]	1953-1984	53	n/s*	28	45	24.5	60.4
Jewkes [18]	1956-1980	50	28	n/s*	50	14	15
Babatasi [9]	1959-1998	84	65	66	55	4	82
Saab [4]	1960-1973	21	27	62	57	4.7	52
Chen [26]	1968-1995	67	80.6	91	73	1.5	17.9
Battaglini[5]	1972-1983	15	33	80	73	13	46.6
Massard[21]	1974-1991	63	56	21	54	8	70
Regnard[30]	1977-1997	87	70	72	42.5	5.7	56
Kim [37]	1981-1999	88	65	45	57.7	1.1	27
Conlan [20]	1982-1984	22	77	91	55	4.5	27
Kabiri [29]	1982-1998	188	n/s*	92	57	6.4	36
Csekeo [27]	1983-1995	84	31	36	62	9.5	37
Akbari [38]	1985-2003	60	45	93.3	91.6	4.3	26.1
Park [32]	1987-2000	110	89	82	74	0.9	23.6

*not specified

6.3. Medical Management Strategies

6.3.1. Anti-Fungal Therapy

6.3.1.1. Systemic Administration

Systemic administration of antifungal chemotherapeutic agents, including Itraconazole and Amphotericin B, which are still the mainstay in the treatment of invasive pulmonary aspergillosis, has largely been ineffective in treating aspergillomata[13,23,24,28,30,31,33,34,65,66]

and it is postulated that the intracavitary diffusion of the agents is inhibited by fibrosis[13,28,30]. Oral Itraconazole was administered to 16 patients by Kawamura et al.[65], only one of whom showed signs of clinical improvement. Sagawa reported a case of unsuccessful treatment of an aspergilloma with Itraconazole after 5 years, the patient eventually proceeding to removal of the fungus ball by cavernoscopy[34].

6.3.1.2. Local Installation

A variety of different antifungal agents, including Amphotericin B, Miconazole, Natamycin, Nystatin, Fluconazole, Pimaricin, Flucytosine and Ketoconazole have all been used[13]. Local instillation can be accomplished by either nebulized inhalation or the direct installation of the substance into the cavity[16]. Drug deposition during nebulizing depends on the type of nebulizer, and the drug may once again not reach the aspergilloma in sufficient quantities to be effective, hence the poor success rates achieved via this administration route[23].

Intra-cavitary installation of chemical agents has been used since 1960 and results have been more encouraging. Kaufman pointed out that it was unclear whether the efficacy of intracavitary installation was due to direct cidal activity of the agent against the *Aspergillus* or the result of local irritation and sclerosis[23], while Ikemoto pointed out that the length of time the aspergilloma is exposed to the agent might be crucial[13].

In addition, sodium iodide, potassium iodide, N-acetylcysteine and aminocaproic acid have been instilled locally, with or without Amphotericin B[23,59]. Rumbak et al.[59] obtained cessation of haemoptysis within 72 hours in all 11 of their patients in whom they instilled intracavitary potassium iodide. Yamada et al.[66] obtained clinical improvement in ten out of twelve patients to whom they administered Amphotericin B or Fluconazole.

Giron and colleagues reported their experience with the percutaneous treatment of 40 aspergillomata assessed to be inoperable[60]. Under CT guidance, a paste of Amphotericin B was injected into the aspergilloma cavity in an effort to fill the cavity and in so doing create an anaerobic environment. Six of the patients in this series were treated additionally with bronchial artery embolisation. The aspergilloma disappeared in 26 patients. Cessation of haemoptysis was achieved in all 40 patients. Complete disappearance of both the aspergilloma and the cavity was achieved in three patients. The authors stressed however that this form of treatment is palliative and still regard surgery as definitive therapy.

6.3.2. Bronchial Artery Embolization (BAE)

In a series of 104 patients published in 1977, Remy et al demonstrated the efficacy of this technique in arresting haemoptysis, but noted that it was a temporizing measure only and also noted that the method was less successful in preventing haemoptysis in patients with intracavitary aspergilloma[52]. Uflacker and co-workers[53,55] re-emphasized this and highlighted the fact the aspergillomata are *per se* a major cause for re-bleeding after BAE and do require definitive management by means of surgery provided the patient is able to tolerate it.

Following on the encouraging results of Remy and Uflacker[52-55], this form of intervention has been more widely applied, especially in patients who are not fit for major surgery[37,51], or as a temporizing measure in patients with massive haemoptysis until definitive surgical management can be performed[9,30,32,38]

7. HOST DEFENCE MECHANISMS AGAINST *A. FUMIGATUS*

7.1. Innate Immunity

Natural immunity plays an important part in the host defence against *A. fumigatus* by recognition and clearance of the organism in immunocompetent individuals. This includes three major components, viz. anatomical barriers, humoral factors and phagocytic cells and their antimicrobial products[44].

7.1.1. Anatomical barriers

Most *A. fumigatus* conidia, like the majority of airborne particles, are probably cleared from the lungs through the cilliary action of the mucous epithelium. However, clearance of *Aspergillus* conidia may be less efficient than with other saprophytic micro-organisms, since it produces certain toxic molecules which inhibit ciliary activity and may damage the epithelial tissue[44].

In humans, the role of the lung epithelium, either in the clearance of *A. fumigatus* or as a primary site of infection, is not well defined. Lung surfactant, which has to be crossed before the fungus comes into contact with the alveolar cells, also fulfils a protective role against pathogens[44].

7.1.2. Humoral components

Activation of the alternate complement pathway favours efficient binding and fungal killing by phagocytes, but more detailed studies will be required to understand the specific role of complement during the inflammatory response to *A. fumigatus* and the initiation of activation and binding of complement by each morphological form of pathogenic and saprophytic species of the aspergilli[44]. It has been demonstrated that hyphae of *A. fumigatus* do release an inhibitor of the complement system[70].

7.1.3. Phagocytic cells

Studies demonstrate a significant role for phagocytic cells in protecting against *A. fumigatus.* Since alveolar macrophages are the major resident cells of the lung alveoli, they, along with the neutrophils, which are actively recruited during inflammation, are the major cells involved in the phagocytosis of *A. fumigatus*[44]. Phagocyte dysfunction appears to be the common denominator of invasive apergillosis, generally including sub-acute cases, such as in AIDS or chronic granulomatous disease[67].

7.1.3.1. Macrophages

Alveolar macrophages mount an oxidative "burst" in response to invasion by *A. fumigatus* conidia. The spores and the hyphae demonstrate several attributes which enhance its pathogenic potential[69,70]. A diffusible substance from the spores has been identified which has the following effects on macrophages: inhibition of the respiratory burst, inhibition of phagocytosis and inhibition of chemotaxis and spreading[69]. Proteases present on the spores and hyphae have been demonstrated to have the ability to reduce cell spreading and promote detachment of cells in culture[69,70].

A. fumigatus hyphae release a number of low molecular weight toxins, which are believed to be associated with the hyphal ability to grow in tissue. In addition, the toxin is said to drastically alter, inter alia, the attachment of epithelial cells and fibroblasts, as well as inhibiting macrophage phagocytosis[70].

7.1.3.2. Neutrophils

Polymorphonuclear lymphocytes were thought to act exclusively on hyphae, as opposed to conidia, of *A. fumigatus.* However, they are also able to ingest and kill

resting or swollen conidia not previously killed by macrophages. Nevertheless, neutrophils remain responsible primarily for hyphal, not conidial, killing[44].

7.1.3.3. Platelets

In humans, platelets play a role in protection against *Aspergillus*. The importance of intravascular defences against *A. fumigatus* is usually underscored by the extensive hyphal invasion of blood vessels, leading to thrombosis and haemorrhagic infarction. Platelets attach to cell walls of the invasive hyphal form of *A. fumigatus* and become activated during this attachment. Several anti-*Aspergillus* functions, including direct cell-wall damage and enhancement of neutrophil-mediated fungicidal effects, have been associated with platelets[44].

7.2. Acquired Immunity

7.2.1. T-cell immunity

Cell-mediated immune responses and type-1 / type-2 cytokine dysregulation has been studied extensively in human mycoses. A type-1 response, which is usually associated with a strong cellular immune response and increased levels of IL-2, gamma interferon and IL-12, favours resistance to mycotic disease. A type-2 response is usually associated with a minimal cellular response and an increase in antibody production, with the associated production of IL-4, IL-5 and IL-10. This pattern of reactivity can be associated with pathological findings as well. Nevertheless, until recently, few studies have focused on acquired immunity to *Aspergillus* infections[44].

Studies of T-cell immunity in humans are lacking, and the putative role of these cells is suggested only by the increased incidence of Invasive Aspergillosis seen in human immunodeficiency virus-infected patients, in whom the decreased numbers and the dysfunction of $CD4^+$ T lymphocytes is well known[44].

Although animal studies have shown a central role for T-lymphocytes in protection, the effector cells and mechanisms responsible for this protective immunity remain unclear. In addition, the role of antibodies in protective immunity has not been properly investigated[44].

Dendritic cells play an important role in the initiation of primary T-cell responses to foreign antigens Henderson and colleagues[68] have reported that infection with *M. tuberculosis* results in the direct activation and maturation of these dendritic cells, thereby facilitating migration to the lymph nodes and enhanced presentation of antigens to T-cells.

More information concerning the mechanisms of the host immune response to mycobacterial infection is coming to light. Evidence from a large collaborative study, including South African investigators from the University of Cape Town, has been published to suggest that a complex immunological process at the luminal surface of tuberculous cavities may result in the failure of T-cell-macrophage interaction and a subsequent permissive environment for bacillary growth. Growth was inhibited in the peri-necrotic zone of tuberculous granulomata[41].

III. MATERIALS AND METHODS

This review is divided into two sections: Section A comprises a clinical audit of all patients who underwent surgical resection for pulmonary aspergillomata in the Christiaan Barnard Division of Cardiothoracic Surgery at the University of Cape Town during the eleven-and-a-half-year period from May 1994 to November 2005.

Section B consists of a histological investigation into the cavity surface of 5 typical cavities containing aspergillomata to assess the microscopic appearance, compared with a control group of tuberculous cavities without aspergilloma. The objective of this was to attempt to gain some insight into why the danger of life-threatening haemoptysis and excessive blood loss during surgery seems to be greater in patients with aspergilloma[21,22] than post-tuberculous patients without aspergillomata.

SECTION A

Details were obtained from an interrogation of patients' clinical records. The following parameters were analyzed:

- patient age
- gender
- presenting symptom(s): major / minor haemoptysis
- pre-operative pulmonary functions (FEV1/FVC)
- pre-operative diagnosis on chest X-ray and / or CT-scan
- presence of pulmonary tuberculosis:
    - previously treated?
    - active at surgery?
- nutritional status: body mass index
- Presence of HIV infection
- indications for surgery

- surgical procedure
- procedure status: elective, urgent or emergency
- length of post-operative hospital stay
- morbidity
- mortality

For the purposes of description in this work, massive haemoptysis is defined as an episode of haemoptysis producing more than 600ml of fresh blood during any single 24-hour period in the time preceding surgical intervention.

The standard approach at our institution has been to admit patients with major haemoptysis to hospital, institute an aggressive medical treatment regimen and to observe the patients' response to this management strategy. This protocol comprises general resuscitative measures, including intravenous rehydration, transfusion of red blood cells if required, anti – TB chemotherapy, antibiotic therapy with Penicillin, Gentamycin and Metronidazole, anti-tussive therapy with Codeine and sedation using oral Morphine with or without additional oral Diazepam. The objective of this is to allow the haemoptysis to settle and to resuscitate the patient adequately, after which one would have time to fully investigate and assess their need and suitability for major pulmonary resection. This review includes only the patients who underwent surgery for confirmed pulmonary aspergillomata and does not include all haemoptysis admissions during the period mentioned.

Resection was decided upon according to the algorithm set out in figure 3. In cases with borderline lung functions, the predicted postoperative FEV_1 ($ppoFEV_1$) was calculated according to the following formula:

$$ppoFEV_1 = \text{pre-operative } FEV_1 \times (1 - \text{fraction of total perfusion for the resected lung})$$

where the $ppoFEV_1$ is expressed as a percentage of the predicted FEV_1[74]. A $ppoFEV_1$ of less than 30% of the predicted FEV_1 served as our cut-off figure for elective cases, as we have shown in a previous study at our institution that surgery in inflammatory disease with a $ppoFEV_1$ between 20-40% of the predicted FEV_1 is feasible and can be performed with an acceptable outcome.

The surgical procedure was classified according to the type of resection performed.

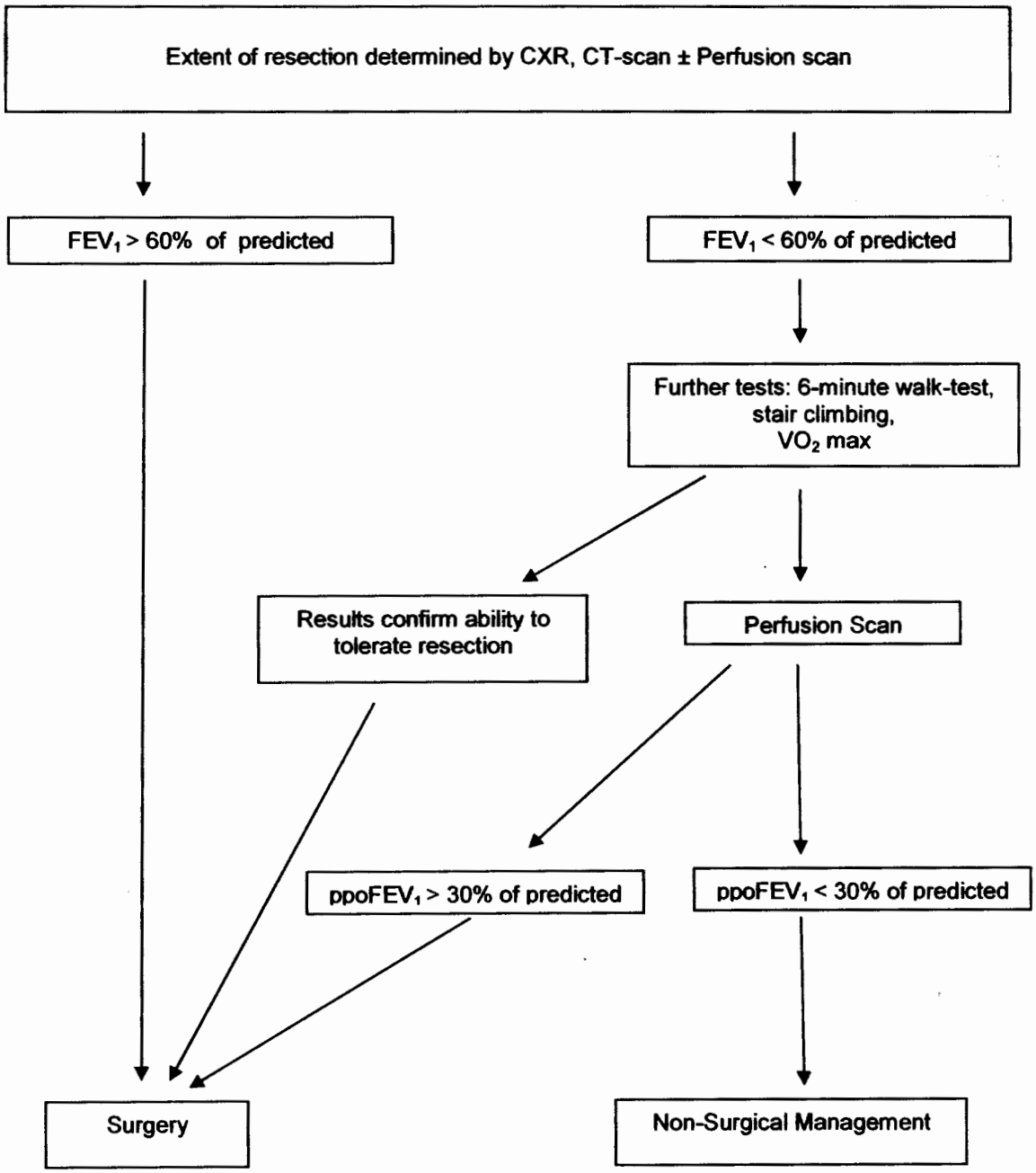


Figure 3: Algorithm outlining the system according to which suitability of patients for surgery was assessed.

The urgency of the procedure was classified as follows: if the procedure was performed as a life-saving measure, without cessation of potentially life-threatening haemoptysis between hospital admission and surgery, the procedure was labelled as an emergency. Patients who were admitted with active haemoptysis, but who settled on conservative treatment, yet who still underwent surgery during the same hospital admission, were labelled as urgent. Those patients admitted electively for surgery, without an active episode of haemoptysis during the surgical admission, were labelled elective.

The nutritional status of the patients was judged according to the body mass index (BMI) and was classed as follows: good (>25); normal (20–25); undernourished (15-20); cachectic (<15).

The indications for surgical intervention in patients with radiological evidence of aspergilloma were as follows:

- Active, unremitting, major haemoptysis
- Previous major haemoptysis with a surgically accessible identifiable cause
- Ongoing minor haemoptysis with a surgically accessible identifiable cause
- Tuberculous lung destruction with a history of repeat reactivation and with the incidental finding of an aspergilloma / aspergillomata

Morbidities comprised the following:

- Major post-operative haemorrhage necessitating re-exploration
- Persistent air leaks (> 5 days) with incomplete expansion of remaining lung after lobectomy or segmental – or wedge resection
- Stump break-down with bronchopleural fistula (BPF)
- Empyema with and without air leak
- Prolonged ventilation (>72 h)
- Other (pneumonia, end-organ failure other than respiratory, sepsis)

A multivariate analysis was performed using the Epi Info™ Version 3.3 statistical calculation software to identify risk factors for the development of major morbidities. Risk factors investigated were the following:

- Presence of active TB at the time of surgery
- Poor nutritional status (BMI < 20)
- Urgent / Emergency Surgery
- Major Haemoptysis
- Pneumonectomy

Mortality was defined as any patient who did not leave hospital alive after undergoing surgery for aspergilloma or death within 30 days of surgery.

SECTION B

This section involved histological examination of the cavity surface of 5 representative specimens of typical aspergilloma cavities to assess the extent of the host's inflammatory response to the fungus infection. These were then compared to the cavity surfaces of 5 patients with cavities due to previous infection with Mycobacterium tuberculosis without secondary fungal infection.

Histologic sections were investigated with the permission of the Department of Anatomical Pathology, University of Cape Town. Intra-operative samples were placed in 10% formalin in Phosphate-buffered Saline (PBS) at room temperature and transferred from the operating room to the laboratories of the Department of Pathology. After embedding in paraffin wax, 3µm sections were cut and stained with Haematoxylin and Eosinophylin, and Grocotts for fungal staining. Ten patients with proven tuberculous cavities were histologically analyzed, 5 of which had a super-imposed Aspergillus infection. For each of the 10 patients, 10 sections were assessed.

A scoring system was used which assessed the presence of the following:

- fungal mycelia
- vascularisation of the cavity wall
- epithelial covering of the cavity wall
- presence of tuberculous granulomata
- presence Langerhans cells
- haemorrhagic areas.

The histological analysis was included into the study in order to determine whether the super-infection with Aspergillus results in a different histological appearance. Particular emphasis was placed on the cavity wall vascularisation in view of the fact that bleeding constitutes a feared complication of Aspergillomata.

The initial selection and investigation of histology was done by the author, under the supervision of a specialist pathologist. In the final histological analysis, scoring and photography, the author was extensively aided by a senior cardiothoracic surgeon with extensive experience in the field of histology. The latter surgeon was blinded with respect to which group of patients the slides belonged to.

IV. RESULTS

SECTION A

During the eleven-and-a-half year period from May 1994 to November 2005, 54 patients underwent surgical resection for what were all post-operatively confirmed aspergillomata. There were 35 males and 19 females. The mean age of the patients was 42.6 years (range 28 – 65). The overall mean length of post-operative hospital stay was 12.8 days (range 6 - 51). The Raw Data of the clinical audit are summarized in Appendix I.

In 46 of 54 patients (85.2%), there was a previous history of tuberculosis (TB) and these patients were all sputum negative at the time of surgery. In 2 other patients, there was a strong clinical suspicion of TB without pre-operative proof. The operative specimens yielded proof of active TB infection, one on histological findings and one on culture. One other patient presented as a non-tuberculous mycobacterium (previously referred to as mycobacterium other than tuberculosis, or MOTT), which had been treated on four previous occasions, and it was felt that the destroyed left lung was the nidus for the recurrent infections. Pre-operative CT scanning demonstrated the presence of an aspergilloma in the left upper lobe. Another patient presented with known pulmonary sarcoidosis and ongoing minor haemoptysis, without any evidence of TB. In the remaining four patients (7.4%), no proof of TB could be established clinically, radiologically or on laboratory investigations pre- and post-operatively.

The diagnosis of aspergilloma was made on pre-operative plain chest X-ray alone in 30 of 54 patients (55.6%). In 11 additional patients (20.4%), there was the suspicion on chest X-ray but the definitive diagnosis was confirmed on CT scan, whilst the diagnosis was only made after CT scan of the chest in a further 9 (16.6%) patients. 4 patients (7.4%) underwent resection of TB destroyed lungs and no aspergilloma was seen on pre-operative chest X-ray. None of these patients underwent CT scans of the chest and the diagnosis of aspergilloma was only established once histological examination of the resected lungs had been completed.

Lung function und nutritional status was only 94.4% complete, with the necessary information missing from the folders of three patients. Of the remaining 51 patients, 18 had lung function test results of less than 60% of their predicted values. Three of these eighteen patients underwent

emergency surgery for active, unremitting haemoptysis. The remaining 15 patients were assessed according to the algorithm depicted in the materials and methods chapter. Eleven of these 15 patients underwent perfusion scans. Eight of these eleven patients underwent pneumonectomy, while the remaining three underwent lobectomy. The remaining 3 tolerated their effort tolerance tests and underwent surgery without perfusion scans. These 3 patients underwent segmental resections.

The lowest recorded ppoFEV_1 was in a patient who had initially undergone an uncomplicated left pneumonectomy and subsequently re-presented with significant haemoptysis from an aspergilloma in the right upper lobe. Surgery was initially not considered as a treatment option due to his very poor respiratory reserve (FEV_1 = 840ml; predicted 2240ml), and percutaneous radiological intervention with embolization was attempted. However, his haemoptysis continued unabated and he subsequently underwent an emergency right upper lobectomy and thoracoplasty. Although having a very stormy intra- and post-operative course, complicated by respiratory failure and prolonged ventilation, he survived to eventual hospital discharge after 51 days and was noted to be well at follow up, having re-attained his pre-operative functional status. His FEV_1 at 6 months follow-up was recorded as 710ml.

The majority of the patients in this study were undernourished, with 29 (53.7%) having a BMI of < 20. There were two patients who were classed as cachectic (BMI < 15). The average BMI was 19.7 (range 13.7 – 28.4). The patient with the highest BMI had Klinefelter's syndrome and presented with an episode of major haemoptysis. The lowest BMI of 13.7 was recorded in the patient mentioned earlier with a previous pneumonectomy and ongoing, life-threatening haemoptysis on whom emergency left upper lobe resection had to be performed. The distribution of the BMI values is presented in figure 2.

The indication for surgery in 51 of the 54 patients in this review (94.4%) was haemoptysis. Four patients presented with active, massive haemoptysis and underwent emergency surgery. In 19 patients (35.2%) there was a history of at least one episode of massive haemoptysis (>600ml/24 hours), although their haemoptysis was not active at the time of surgery. Moderate to minor haemoptysis (<600ml/24hous) was the main presenting symptom in a further 28 (51.2%) patients. In the remaining three patients (5.6%), the symptoms were those of an ongoing productive cough without haemoptysis. One of these was a patient with the diagnosis of non-tuberculous mycobacterium (previously referred to as mycobacterium other than tuberculosis, or MOTT), whilst the other two had presented with a chronic cough and lungs destroyed by

tuberculosis (TB) and the diagnosis of aspergilloma was made on histological examination post-operatively.

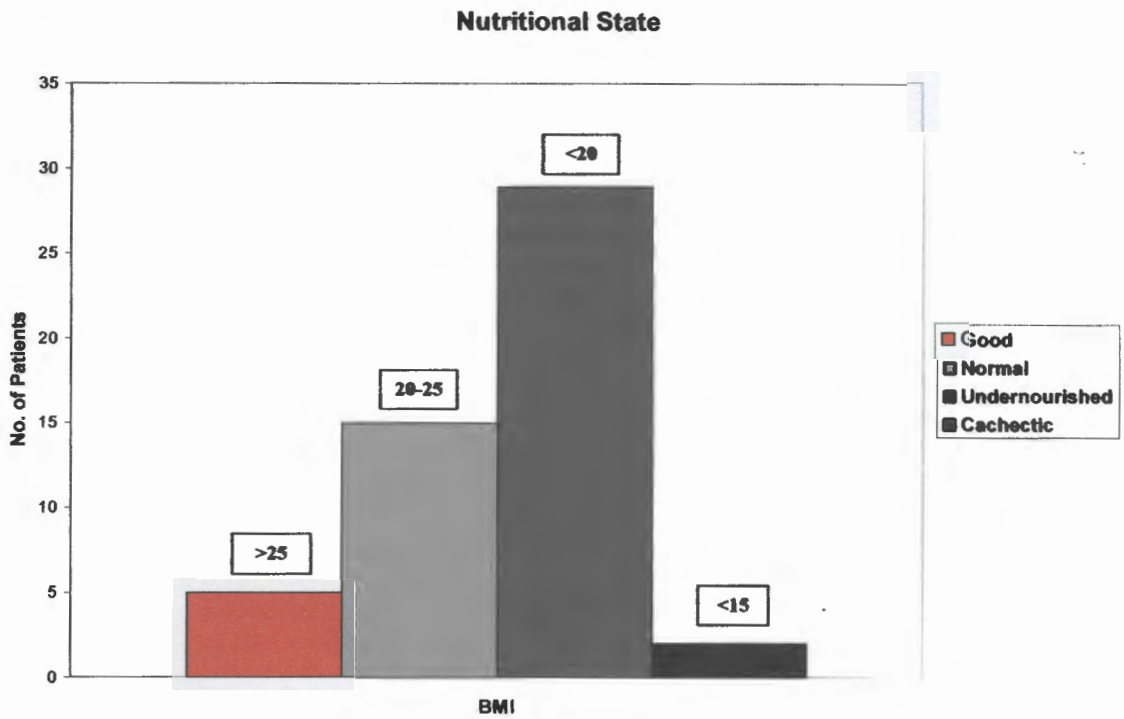


Figure 4: BMI distribution

Of the 54 patients, 4 (7.4%) underwent emergency surgical intervention for unrelenting, life-threatening major haemoptysis. One of these patients underwent an emergency right upper lobectomy and thoracoplasty, after having previously undergone a left pneumonectomy, and has been discussed in more detail previously. Of the remaining three, two underwent emergency left upper lobectomy and one underwent left pneumonectomy. All four of these patients survived.

Fifteen of the 54 patients (27.8%) were operated upon urgently, i.e. during the same hospital admission as the one for the initial haemoptysis. The average length of hospitalisation for these 15 patients was 21.7 days (range 15 – 41), while their average length of post-operative stay was 11.1 days (range 6 – 29).

The remaining 35 operations (64.8%) were performed electively in patients who had been investigated and had been assessed to be fit for major pulmonary resection. The average post-operative hospital stay in this group was 12.2 days (range 6 – 51).

A total of 54 lung resections were performed during the study period and 3 of the patients subsequently underwent thoracoplasty. Resections were grouped as follows:

- Lobectomies: 27
  - Upper: 22
  - Lower: 2
  - Middle: 1
  - Bi-lobectomy: 2
- Pneumonectomies: 20
  - 14 left
  - 6 right
- Segmental resections: 6
- Wedge resections: 1
- Thoracoplasties: 3 (1 concomitant and 2 subsequent)

The overall mortality was 3.7% (2 patients). One patient had pre-existing chronic renal impairment and underwent elective surgery for a radiologically confirmed Aspergilloma with a previous bout of massive haemoptysis. Although his surgery as such was uneventful, his post-operative course was complicated by acute on chronic renal failure requiring dialysis, and a severe bleeding diathesis. He developed an uncontrollable upper gastro-intestinal haemorrhage and demised on the tenth post-operative day.

The second patient had respiratory failure post-operatively and required prolonged ventilation due to ARDS, despite having met the pulmonary function requirements for resection. He was successfully weaned from ventilatory support and was discharged from the Intensive Care Unit in stable condition on day 10, but suffered a respiratory arrest on the ward and demised on the twelfth post-operative day.

Morbidities were encountered in 13 of 54 patients (24.1%), with several patients developing more than one complication. The morbidities are broken down into the six major components mentioned in the materials and methods section in the table below.

Morbiditiy	Incidence
Empyema	8
Haemorrhage requiring re-operation	6
Persistent air-leak (> 5 days)	4
Stump Breakdown	3
Prolonged Ventilation (>72h)	2
Pneumonia	2

The total incidence of empyema was 14.8% (8 of 54 patients). In 4 of these 8 patients, broncho-pleural fistulae were encountered. A further 3 had undergone re-exploration for ongoing post-operative haemorrhage and had subsequently developed an empyema. Of these 8 patients, 5 were managed by intercostal tube drainage and 3 required an open drainage stoma (Eloesser flap), 2 of whom eventually required thoracoplasty as the definitive therapy.

6 of the 54 patients operated upon (11.1%) had to undergo re-operation within the first 24 hours following the first procedure for bleeding. One of these patients had to undergo a second re-operation for ongoing haemorrhage. This patient's further course was uncomplicated and no further adverse events were encountered. Two of these were patients who underwent urgent surgery while the remaining three had undergone elective surgery. Three of the remaining patients who underwent re-operation for bleeding went on to develop an empyema and required Eloesser flaps for drainage.

Three patients developed a stump breakdown with a subsequent bronchopleural fistula and empyema.. Two of the empyemas were managed by intercostal tube drainage alone as the stump healed and soft tube drainage into a stoma bag was well tolerated. The remaining patient required

open thoracostomy (Eloesser flap) for permanent drainage. This patient was found to have active TB on the operative specimen. However, the resection margins of the bronchus were reported to show no evidence of active TB.

Two other patients developed pneumonia in the non-operated lung. In one it did not affect his eventual outcome, while the second pneumonia was recorded in one of the two patients who demised and has already been discussed.

Surprisingly, no significant post-operative space problems were encountered in this series. This is a well-described problem after lobectomy for aspergiloma[19,21,28,30]. One patient in the series, who had undergone a previous pneumonectomy, re-presented with ongoing, life-threatening haemoptysis and an aspergilloma in the upper lobe of his right lung. Bronchial artery embolisation failed to arrest the haemoptysis and he underwent an emergency right upper lobectomy and osteoplastic thoracoplasty in anticipation of a residual space problem.

A multivariate analysis of risk factors for the development of the major morbidities listed above failed to identify any specific risk factors in the cohort of patients studied. The results of the calculations are tabulated below.

	Odds Ratio	95%	C.I.	Coeff.	S. E.	Z-Statistic	P-Value
Active TB	6.9673	0.4500	107.8705	1.9412	1.3978	1.3887	0.1649
BMI < 20	1.3679	0.3623	5.1648	0.3133	0.6779	0.4622	0.6440
Emergency Surgery	0.3101	0.0158	6.0911	-1.1709	1.5193	-0.7707	0.4409
Non-elective Surgery$	1.1823	0.2948	4.7417	0.1675	0.7086	0.2364	0.8131
Major Haemoptysis	1.3494	0.3768	4.8318	0.2997	0.6508	0.4604	0.6452
Pneumonectomy	0.9490	0.2718	3.3134	-0.0523	0.6379	-0.0820	0.9346
CONSTANT	*	*	*	-1.2935	0.6158	-2.1007	0.0357

$ = Combination of urgent and emergency surgery

Table2: *Statistical calculations of multivariate analysis of risk factors for the development of major morbidity.*

SECTION B

All ten specimens showed the following features:

- High vessel density in the cavity walls which tended to be denser in patients with super-imposed Aspergillus infection.
- High vessel density was particularly pronounced in areas which were not epithelialised
- Marked arterial wall hyperplasia, particularly in medium-sized arteries where most of the lumen was almost completely obliterated
- Approximately 30% of the surface of the cavities was lined by a respiratory epithelium with varying degrees of dysplasia.
- Tuberculous tissue response was present in all cavities.
- Approximately 30% of the surface of the cavities showed a dysplastic squamous cell epithelium with a broad spectrum of intermittent stages including single cuboid linings
- Tuberculous granulomata were found in the majority of samples, typically exhibiting caseous central necrosis often surrounded by lymphocyte-rich epitheloid cells with scanty Langerhas giant cells
- The Aspergilloma mycelia were mostly preserved but not always detectable. Typically, they loosely bordered on the cavernous surface, whether it was epithelialised or not.
- There was never any deeper tissue penetration of hyphae observed.

One of the most pronounced features in all specimens was arterial hyperplasia. This arterial hyperplasia was particularly pronounced in medium sized arteries and very often reached a degree whereby most of the lumen was almost completely obliterated.

In summary, the histological picture of all 10 patients was dominated by typical tissue changes attributable to tuberculosis. Additional histological features as a result of the super-infection with Aspergillus were mild and may still be interpreted with a normal range of variation rather than a true trend.

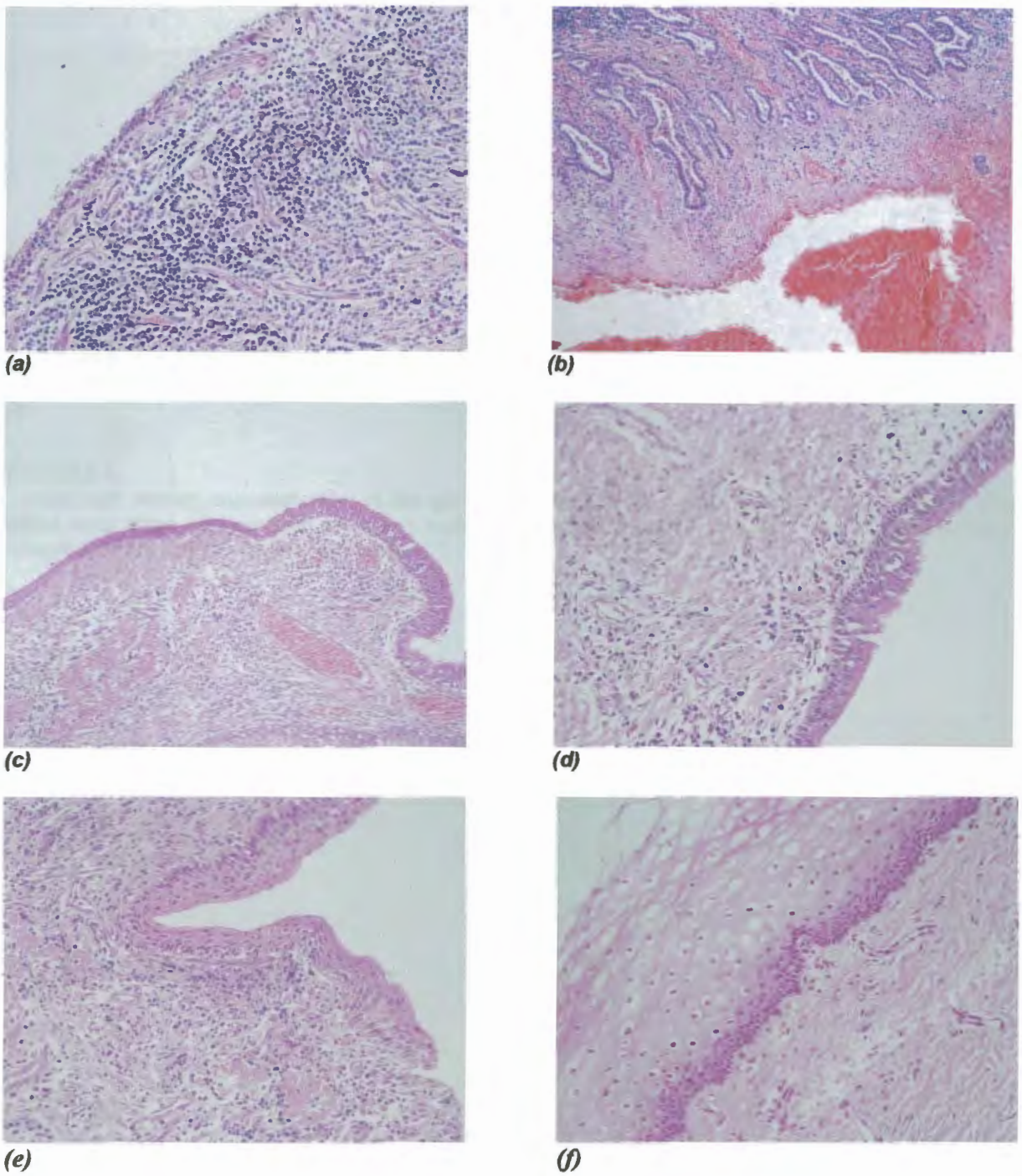
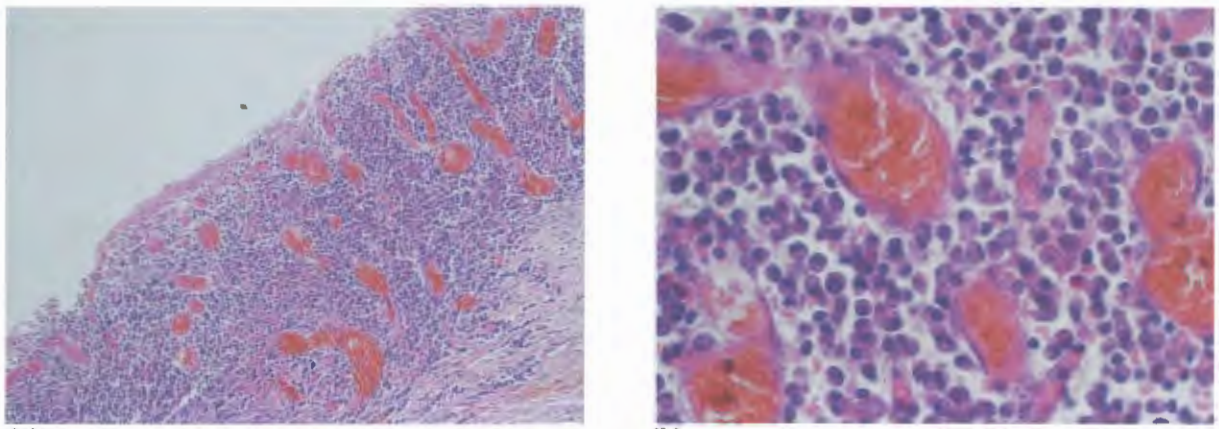
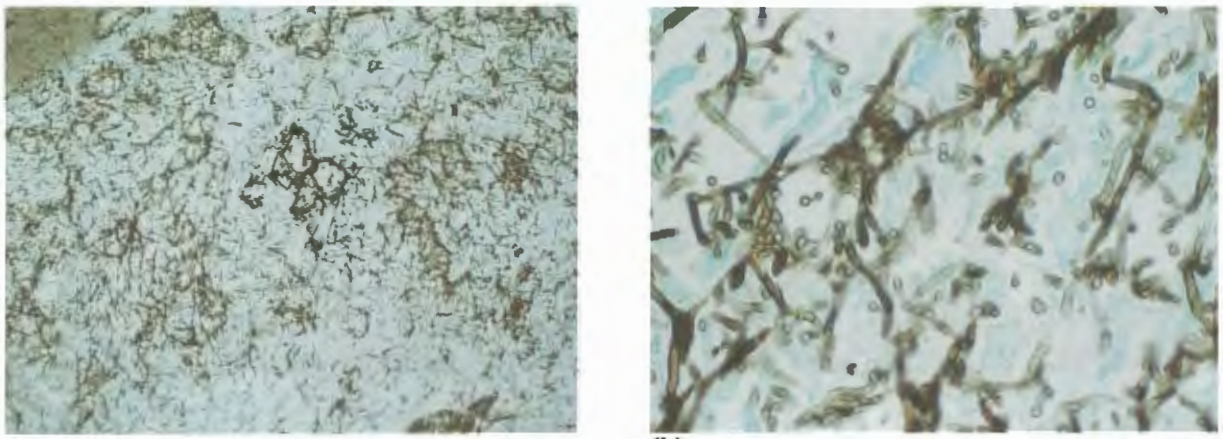


FIGURE 5
Shows the various surfaces of the cavities. Some areas were not epithelialised and just covered by blood, fibrin and cell-rich granulation tissue [Fig.(1a), (1b)]. Other areas showed typical respiratory epithelium [Fig (1c), (1d)] whereby the respiratory epithelium often ebbed out into a single layer cuboid lining [Fig (1c)]. Approximately one third of all cavities was covered by squamous cell dysplasia which did not necessarily need to be a continuation of the respiratory epithelium but often existed in an otherwise non-epithelialised cavity [Fig (1e)]. Rarely, the squamous cell lining even showed a tendency towards keratinising on the surface [Fig (1f)].



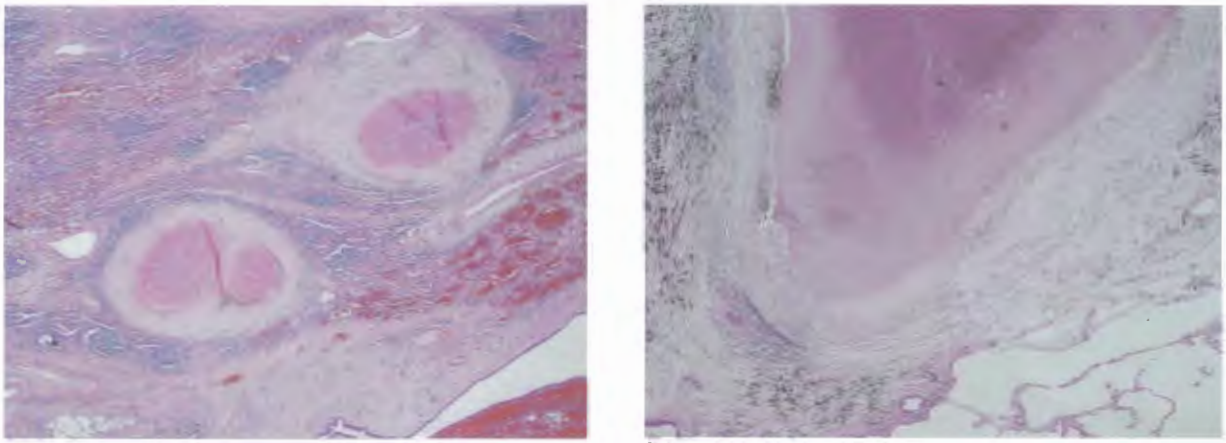
(a) *(b)*

FIGURE 6
Typical high density vascularisation of the granulation tissue in non-epithelialised of the cavity. These areas were often only covered by a thin layer of fibrin and otherwise showed densely packed blood vessels surrounded by mononuclear cells.



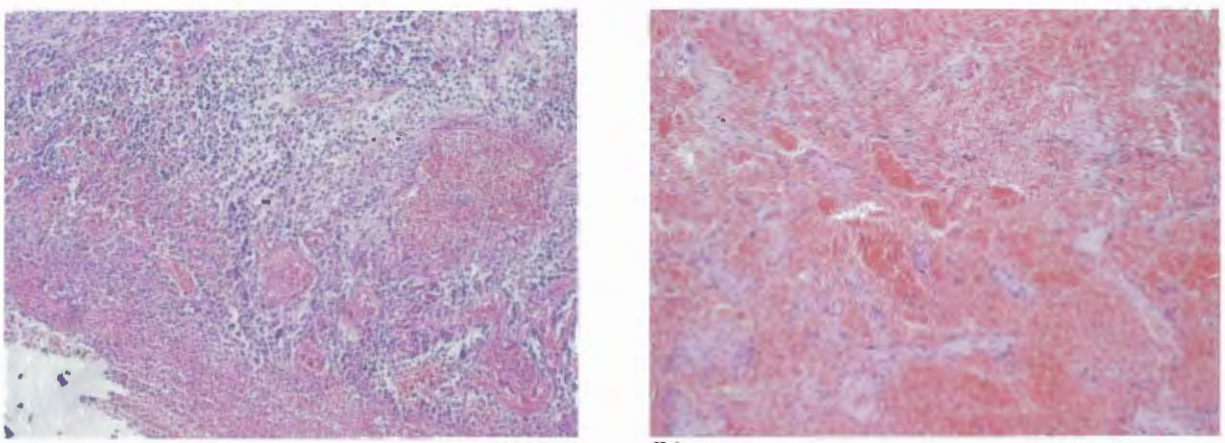
(a) *(b)*

FIGURE 7
Typical Aspergillus – in low and high magnification (Grocott's stain).



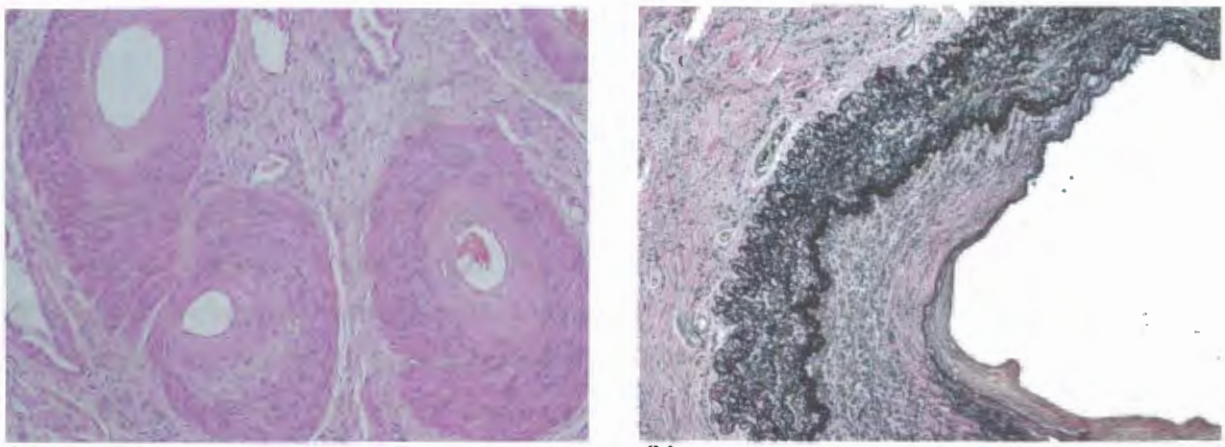
(a) *(b)*

FIGURE 8
Typical tuberculous caseous granulomata with a central necrotising area and the lymphocyte-rich surrounding demarcation. Both magnifications are too low for showing the epitheloid cell layer in between.



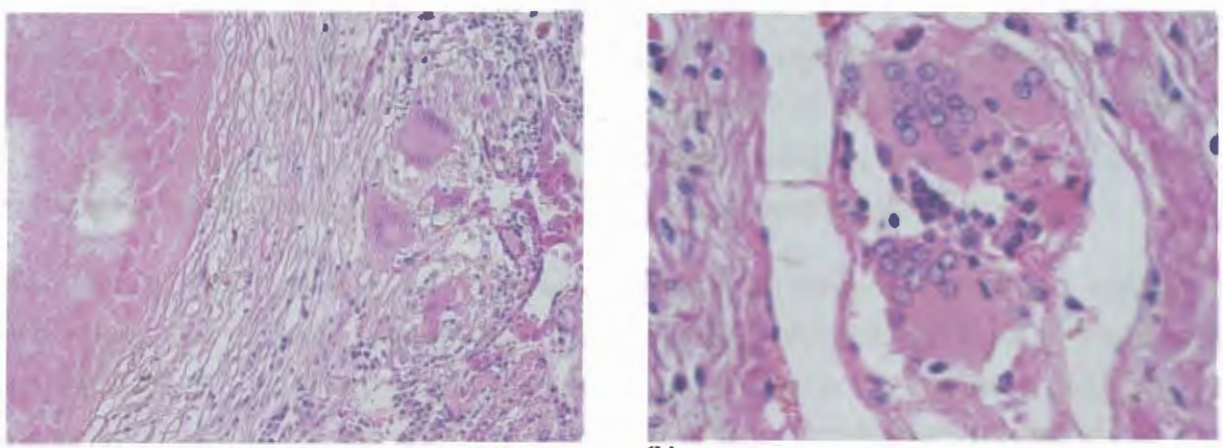
(a) *(b)*

FIGURE 9
Typical haemorrhagic boundary areas between the cavernous space, the granulomata and the surrounding area of lung tissue.



(a) *(b)*

FIGURE 10
Hyperplastic medium sized arteries either embedded or in the vicinity of the granulomata and cavity. One can typically see a slightly hyperplastic media and a cell-poor layer of intimal hyperplasia. On the right side is a Van Gieson Elastin staining which clearly shows the demarcation between the internal elastic lamellae and the hyperplastic half-moon shaped intimal hyperplasia.



(a) *(b)*

FIGURE 11
Typical Langerhans cells in the area of the epitheloid outside layer of a caseous tuberculus granuloma.

V. DISCUSSION

Fungal disease of the lung is predominantly treated medically. The role of surgery in pulmonary fungal diease is either diagnostic, as in the case of indeterminate solitary pulmonary nodules, e.g. in patients undergoing treatment for leukaemia, or alternatively it may be curative, as in appropriately selected patients with pulmonary aspergilloma. Two other indications for curative surgical intervention in pulmonary fungal disease include fungal broncholiths causing bronchial obstruction, and localised invasive pulmonary aspergillosis (IPA). The immunocompromised portion of all populations is growing, due to the influence of increased organ transplantation, and the increasing incidence of HIV-related disease. The prevalence of malignancy and related oncology has probably played an even bigger role than organ transplants in the emergence of this phenomenon[76]. This has resulted in an increased incidence of IPA. The challenge of treating IPA has resulted in the growing recognition of surgery as the most appropriate method of treatment in some patients [42,46,48-50].

This study focuses solely on the saprophytic form of Aspergillus infection of the lung, which occurs in patients with underlying cavitatory disease mainly due to previous infection with *Mycobacterium tuberculosis*. This is a problem more commonly encountered in South Africa than in the developed world. The incidence of TB in South Africa is among the highest in the world. The reported prevalence in SA for all forms of TB was 458 per 100 000, with an incidence of 536 per 100 000 of the population in 2003[73]. In all probability, the real figures are higher, despite the fact that TB is a notifiable disease. Pulmonary TB accounts for the vast majority of these cases.

This study had two objectives. The first was to describe an eleven-and-a-half-year experience with surgery in pulmonary Aspergillomata at Groote Schuur Hospital and to relate it to current opinion regarding the treatment of pulmonary aspergillomata in the published literature. The second was to examine the histological pattern at the surface of a tuberculous cavity colonized by Aspergillus forming a classic fungal ball and those of a tuberculous cavity without colonization to determine whether there is a difference in the appearance. With the insights gained from this, the author attempted to create a practical approach to treatment decision making in patients with symptomatic and asymptomatic aspergillomata.

The preferred method of treatment of aspergillomata has been the subject of ongoing debate[4,5,8,9,14,15,17-21,23-25,40]. However, based on their clinical and radiological presentation, four groups of patients can be identified, which provides a practical approach to management decisions. This concept incorporates the algorithm described in chapter III of this dissertation and combines and modifies a previously suggested grouping from El Oakley and co-authors[25] with that of Belcher and Plummer[11] as follows:

- Group 1a:- Asymptomatic patients with simple aspergillomata who are fit for surgery.
- Group 1b:- Asymptomatic patients with complex aspergillomata who are fit for surgery.
- Group 2:- Asymptomatic patients with simple or complex aspergillomata who are unfit for surgery.
- Group 3:- Symptomatic patients (e.g. haemoptysis) with simple or complex Aspergillomata who are fit for surgery
- Group 4:- Symptomatic patients (e.g. haemoptysis) with simple or complex aspergillomata who are unfit for surgery.

Little controversy exits as to the indications for surgery in fit patients with symptomatic aspergillomata (patients in Group 3). Similarly, the contra-indications for surgery in unfit patients who are predicted to have insufficient physiological reserves to survive lung resection are clear[5,31-33,35-40]. These are the patients found in groups 2 and 4.

However, controversy does exist in offering lung resection surgery to fit, asymptomatic patients whose aspergillomata are uncomplicated (Group 1a and b). Some authors advocate prophylactic resections in order to avoid complications, particularly life-threatening haemoptysis[8,19,21,29], whilst others do not[16]. Separating simple from complex disease[11] recognises the importance of the extent of underlying lung disease in determining the likely extent of lung resection required and the eventual prognosis.

Randomised controlled trials (RCT's) remain the standard by which clinical practice is measured in an evidence-based medical community. Unlike the administration of drugs, which may be blinded and exactly reproducible, surgery differs from patient to patient and from surgeon to surgeon[62]. Lee and co-workers investigated 50 major general thoracic surgical procedures and

came to the conclusion that only 7 of these had the backing of RCT's[63]. As there are no randomised controlled trials comparing treatment options in the various groups, the clinician has to make therapeutic decisions based on historical data, own experience and the natural course of the disease. The decision to proceed to surgery must be balanced by the presence or the absence of symptoms, the natural history of the disease, the extent of the surrounding lung disease, the patient's general physical state and the potential risks of surgery. In asymptomatic disease (Group 1), the clinician therefore has to weigh the relative risk of complications occurring in untreated disease, against the relative risk of morbidity and mortality of lung resection.

Haemoptysis during the natural history of aspergilloma occurs in 50 – 90% of patients, of whom as many as 30% can be expected to die as a result[8,15,18,19]. Although patients with asymptomatic uncomplicated disease represent as many as 20%[9,18,30] of some series, no mortality has been reported specifically in this group. The overall mortality after surgery has been reported to be between 0.9 – 34%[19,21,25]. It is reasonable to argue, therefore, that if the mortality associated with lung resection is lower than that associated with the natural course of the disease, surgery must be considered a reasonable treatment option in asymptomatic disease. Babatasi and co-authors[9] emphasize the potential value of an aggressive surgical approach, even in asymptomatic patients, and list 4 possible benefits: preventing haemoptysis, preventing the pyogenic element, limiting symptoms by avoiding growth increase of the aspergilloma and prolonging life. Other authors[9,12,21] also insisted that all patients who did not present a prohibitive surgical risk, even if asymptomatic, should undergo surgical resection to avoid potential fatal haemoptysis.

No asymptomatic patients were operated on in the present series, probably because only symptomatic patients were referred. Jewkes and colleagues have emphasized the fact that neither the size nor the complexity of the lesions, nor the presence of a warning minor haemoptysis can predict those patients who will progress to life threatening haemoptysis[18]. The sudden onset of massive haemoptysis poses both diagnostic and therapeutic problems[56], and mitigates in favour of preventative measures by performing surgery on asymptomatic aspergillomata[8,19,21,29,30]. The aggressive approach espoused by these authors is made more attractive in that it offers the additional potential advantages of avoiding further haemoptysis, recurrent infections, ongoing cough and reactivation.

Patients in this series were generally followed up for a period of about one month, after which they were discharged, unless complications were encountered. Failure to follow up patients for longer than this may reasonably be regarded as a limitation in the interpretation of the medium- to long-term outcome. However, this must be weighed against the lack of data regarding the long-term outcome of non-operated patients with this disease.

Patients in group 4 pose a particular problem. They are unfit for surgery and have aspergillomata complicated by life threatening or lesser but persistent haemoptysis. This group requires therapeutic measures alternative to lung resection, such as percutaneous installation of Amphotericin B paste into the cavity[60]. It is well established that intra-cavity Amphotericin B solution yields poor results in eradication of the fungus[13,16,23]. Other alternatives of treatment in Group 4 patients are cavernostomy and myoplasty as combined or staged procedures in these physiologically unfit patients[18, 34-36].

Multivariate analysis of several risk factors for the development of major morbidity or mortality failed to reveal any single factor to be significantly associated with morbidity or mortality in this series. This was an unexpected finding which contradicts clinical expectations, and is explained in part by the small numbers of patients available for subgroup analysis, and in part by the accuracy of data recording, which is an acknowledged potential flaw in retrospective descriptive research of this nature. Despite the fact that the majority of patients (54%) in this study were undernourished, with a BMI of < 20, and 2 patients were cachectic, with BMI < 15, multivariate analysis failed to reflect a statistically significant relationship between low BMI and morbidity or mortality, even though this relationship is clinically important.

However, the incidence of major morbidity (24%), mortality (4 %), and the lobectomy rate (50%) as recorded in this series, is similar to data published in the literature. Mortality rates in published literature vary from as low as 0.9% overall mortality[32], to 34%[19] in complex aspergillomata.

Pneumonectomy has been historically associated with a high complication rate due to post operative empyema, bronchial stump dehiscence and post-pneumonectomy respiratory failure. Massard and co-workers reported a mortality rate for pneumonectomy for aspergilloma of 16% (n=1/6) [21]. The present series revealed a pneumonectomy rate of 37% without mortality, which was similar to another South African paper published by Conlan et al in which the pneumonectomy rate was 41%[20]. However, 6 of the 20 patients (30%) who underwent pneumonectomy in this series, developed complications.

The most common complication in this series was post-operative empyema, with an incidence of 14.8% (8/54), four of whom had an associated broncho-pleural fistula. Two of the patients in this series had active TB confirmed from operative specimens, one of whom developed stump breakdown and empyema. Massard et al.[21] reported a high incidence of empyema after pneumonectomy (4/5 patients) but none after lobectomy with a low overall incidence of 5%. Similarly, Babatasi[9] and co-workers reported a low incidence of empyema, but in a group of patients with mostly localized disease. This emphasises the increased effect on morbidity exerted by extensive underlying lung disease. Factors which may have contributed to the development of empyema include intra-operative spillage, a long bronchial stump and re-exploration for bleeding. Indeed, 3 of the 6 patients requiring re-exploration for bleeding in this series developed an empyema.

The issue of excessive blood loss during a difficult resection has also been highlighted[1,3,29,38]. Although the volume of blood loss during each procedure was not specifically recorded nor reviewed for the present series, it is noteworthy that the incidence of re-exploration for major ongoing haemorrhage necessitating re-exploration was 11.1%, which was the second most common complication. Quite apart from the immediate problems directly associated with ongoing haemorrhage, such as haemodynamic instability and shock, medium- to longer-term sequelae may be encountered. These include massive transfusion requirements with their attendant complications (infection risks, pulmonary complications, increased cost) and the increased risk of secondary wound infection and empyema as a result of repeated surgical intervention.

No significant post-operative space problems were encountered in this series, which is a well-described problem after lobectomy for aspergilomata[19,21,28,30]. One patient in the series, who had undergone a previous pneumonectomy, re-presented with ongoing, life-threatening haemoptysis and an aspergilloma in the upper lobe of his right lung. Bronchial artery embolisation failed to arrest the haemoptysis and he underwent an emergency right upper lobectomy and limited thoracoplasty in anticipation of a residual space problem.

The histological findings in the 10 cases examined and found to be very similar in all respects, must be interpreted against the small sample. However, it is important to note that no invasion of the fungus beyond the cavity surface was identified in any of the specimens with Aspergillus super-infection, which is in keeping with the findings of Soubani[33] and Franquet[51].The possible

differences between cavities in patients with haemoptysis or not, remain a possible avenue for future research; in particular the role of the dendritic cells needs to be examined.

VI. CONCLUSION

Based on the results of this analysis and the evidence from the literature, the author concludes the following:

- Surgical resection is the preferred method of treatment for pulmonary aspergillomata in fit, symptomatic patients.
- Surgery is recommended in fit, asymptomatic patients.
- Patients can be grouped into categories based on their presentation and underlying lung function for the purpose of developing a practical approach to clinical decision-making
- Pneumonectomy requires careful evaluation according to the suggested algorithm, but can be performed with a low mortality rate.
- For patients deemed unfit for the required surgical resection, alternative, less invasive procedures, such as wedge resection, cavernostomy, embolisation or the local instillation of fungicidal paste should be considered on an individual basis.
- Further histological investigation in combination with immunological staining should be pursued.

REFERENCES

1. British Thoracic and Tuberculosis Association. Aspergilloma and residual tuberculosis cavities – the results of a resurvey. Tubercle 1970; 51: 227-45
2. Johnston ID. Mycobacterium xenopi infection and aspergilloma. Tubercle 1988; 69: 139-44
3. Hinson KF, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis; a review and a report of eight new cases. Thorax. 1952 Dec;7(4):317-33.
4. Saab SB, Almond C. Surgical aspects of pulmonary aspergillosis. J Thorac Cardiovasc Surg. 1974 Sep; 68(3):455-60
5. Bataglini JW, Murray GF, Keagy BA, et al. Surgical management of pulmonary aspergiloma. Ann Thorac Surg 1985; 39(6): 512-6
6. Bennett JH. On the parasitic vegetable structures found growing in living animals. Trans Roy Soc Edinburgh (1842)15:277-279
7. Kilman JW, Ahn C, Andrews NC, et al. Surgery for pulmonary aspergillosis. J Thorac Cardiovasc Surg. 1969 May;57(5):642-7
8. Garvey J, Crastnopol P, Weisz D, et al. The surgical treatment of pulmonary aspergillomas. J Thorac Cardiovasc Surg. 1977 Oct;74(4):542-7.
9. Babatasi G, Masetti M, Chapelier A, et al. Surgical treatment of pulmonary aspergilloma: Current outcome. J Thorac Cardiovasc Surg 2000; 119: 906-12
10. Gerstl B, Weidman WH, Newman AV. Pulmonary Aspergillosis. Report on two cases. Ann Intern Med 1948; 28: 662-71(Abstract)
11. Belcher JR, Plummer NS. Surgery in bronchopulmonary aspergillosis. Br J Dis Chest 1960;54: 335-41 (Abstract)
12. Shirakusa T, Ueda H, Saito T, et al. Surgical treatment of pulmonary aspergilloma and *Aspergillus* empyema. Ann Thorac Surgery 1989; 48: 779-82
13. Ikemoto H. Medical treatment of pulmonary aspergilloma. Intern Med. 2000 Mar; 39(3):191-2.
14. Faulkner SL, Vernon R, Brown PP, et al. Haemoptysis and pulmonary aspergilloma: Operative versus non-operative treatment. Ann Thorac Surg 1978; 25: 389-92
15. Karas A, Hankins JR, Attar S, et al. Pulmonary aspergilloma: an analysis of 41 patients. Ann Thorac Surg 1976; 22: 1-7
16. Varkey B, Rose HD. Pulmonary aspergilloma: a rational approach to treatment. Am J Med 1976; 61: 626-31
17. Rafferty P, Biggs B, Crompton G, et al. What happens to patients with pulmonary aspergilloma? Analysis of 23 cases. Thorax. 1983 Aug; 38(8):579-83.
18. Jewkes J, Kay PH, Paneth M, et al. Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. Thorax 1983; 38: 579-83
19. Daly RC, Pairolero PC, Piehler JM, et al. Pulmonary aspergilloma: results of surgical treatment. J Thorac Cardiovasc Surg 1986; 92: 981-8
20. Conlan AA, Abramor E, Moyes DG. Pulmonary aspergilloma - indications for surgical intervention. An analysis of 22 cases. S Afr Med J. 1987 Mar 7;71(5):285-8.
21. Massard G, Roeslin N, Wihlm JM, et al. Pleuro-pulmonary aspergilloma: Clinical spectrum and results of surgical treatment. Ann Thorac Surg 1992; 54: 542-7
22. Niwa H, Yamakawa Y, Fukai I, et al. Subclavian artery branch ligation reduces hemorrhage during resection of pulmonary aspergilloma. Ann Thorac Surg 1995; 59: 1234-5

23. Kauffman C. Quandary about the treatment of aspergillomas persists. Lancet 1996; 347: 1640
24. Kay PH. Surgical management of pulmonary aspergilloma. Thorax 1997; 52: 753-4
25. El Oaley R, Petrou M, Goldstraw P. Indications and outcomes of surgery for pulmonary aspergilloma. Thorax 1997; 52: 813-5
26. Chen J, Chang Y, Luh S, et al. Surgical treatment for pulmonary aspergilloma: a 28-year experience. Thorax 1997; 52: 810-3
27. Csekeo A, Agocs L, Egervary M, et al. Surgery for pulmonary aspergillosis. Eur J Cardiothorac Surg 1997; 12: 876-9
28. Chatzimicalis A, Massard G, Kessler R, et al. Bronchopulmonary aspergilloma: a reappraisal. Ann Thorac Surg 1998; 65: 927-9
29. Kabiri H, Lahlou K, Achir A, et al. Les aspergillomes pulmonaires: resultants du traitement chirurgical. A propos d'une serie de 206 cas. Cirurgie 1999; 124: 655-60 (Abstract)
30. Regnard J-F, Icard P, Nicolosi M, et al. Aspergilloma, a series of 89 surgical cases. Ann Thorac Surg 2000; 69: 898-903
31. Ueda H, Okabayashi K, Ondo K, et al. Analysis of various treatments for pulmonary aspergillomas. Surg Today. 2001;31(9):768-73.
32. Park CK, Jheon S. Results of surgical treatment for pulmonary aspergilloma. Eur J Cardiothorac Surg 2002;21: 918-23
33. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. Chest 2002; 121: 1988-99
34. Sagawa M, Sakuma T, Isobe T, et al. Cavernoscopic removal of a fungus ball for pulmonary complex aspergilloma. Ann Thorac Surg 2004; 78: 1846-8)
35. Gebitekin C, Byram AS, Akin S. Complex pulmonary aspergilloma treated with single stage cavernostomy and myoplasty. Europ J Cardiothor Surg 2005; 27: 737-40
36. Kurul IC, Demircan S, Yazici U, et al. Surgical management of pulmonary aspergilloma. Asian Cardiovasc Thorac Ann. 2004 Dec;12(4):320-3 (Abstract)
37. Kim YT, Kang MC, Sung SW, et al. Good long-term outcomes after surgical treatment of simple and complex pulmonary aspergilloma. Ann Thorac Surg 2005; 79: 294-8
38. Akbari JG, Varma PK, Neema PK, et al. Clinical profile and outcome for pulmonary aspergilloma: a single centre experience. Ann Thorac Surg 2005; 80: 1067-72
39. Metin M, Sayar A, Turna A, et al. Emergency surgery for massive haemoptysis. Acta Chir Belg. 2005 Nov;105(6):639-43. (Abstract)
40. Shiraishi Y, Katsuragi N, Nakajima Y et al. Pneumonectomy for complex aspergilloma : is it still dangerous ? Europ J Cardiothor Surg 2006; 29: 9-13
41. Kaplan G, Post FA, Moreira AL, et al. Mycobacterium tuberculosis growth at the cavity surface: a microenvironment with failed immunity. Infect Immun 2003; 71 (12): 7099-7108
42. The Institute for Genomic Research: The Aspergillus fumigatus Genome Project Internet Website
43. Chiller TM, Stevens DA. Treatment strategies for *Aspergillus* infections. Drug Resistance Update 2000; 3: 89-97
44. Latge JP. Aspergillus fumigatus and aspergillosis. Clin Microbiol Rev. 1999 Apr;12(2):310-50.
45. Corrin B. Pathology of the lungs 1st Ed. Churchill Livingstone, 2000.
46. Kibbler CC, Milkins SR, Bhamra A, et al. Apparent pulmonary mycetoma following invasive aspergillosis in neutropenic patients. Thorax. 1988 Feb;43(2):108-12

47. Young VK, Maghur, HA, Luke, DA, et al. Operation for catitating invavsive pulmonary aspergillosis in immunocompromised patients. Ann Thorac Surg 1992;53: 621-4

48. Robinson LA, Reed EC, Galbraith TA, et al. Pulmonary resection for invasive *Aspergillus* infections in immunocompromised patients. J Thorac Cardiovasc Surg. 1995; 109(6): 1182-97

49. Salerno CT, Ouyang DW, Pederson TS, et al. Surgical therapy for pulmonary aspergillosis in immunocompromised patients. Ann Thorac Surg 1998; 65: 1415-9

50. Habicht JM, Reichenberger M, Gratwohl A, et al. Surgical aspects of resection for suspected invasive pulmonary fungal infection in neutropenic patients. Ann Thorac Surg 1999; 68: 321-5

51. Franquet T, Muller NL, Gimenez A, et al. Spectrum of Pulmonary Apergillosis: Histologic, clinical and radiologic findings. Radiographics 2001; 21: 825-37

52. Remy J, Arnaud A, Fardou H, et al. Treatment of haemoptysis by embolization of bronchial arteries. Radiology 1977; 122: 33-37

53. Uflacker R, Kaemmerer A, Neves C, et al. Management of massive haemoptysis by bronchial artery embolization. Radiology 1983; 146: 627-34

54. Remy J, Lemaitre L, Lafitte J, et al. Massive haemoptysis of pulmonary arterial origin: diagnosis nad treatment. AJR 1984; 143: 963-9

55. Uflacker R, Kaemmerer A, Picon P, et al. Bronchial artery embolization in the management of hemoptysis: technical aspects and long-tern results. Radiology 1985; 157: 637-44

56. Abal AT, Nair PC Cherian J. Haemoptysis: aetiology, evaluation and outcome – a prospective study in a third-world country. Respir Med 2001; 95: 548-52

57. Roberts CM, Citron KM, Strickland B. Intrathoracic aspergilloma: Role of CT in diagnosis and treatment. Radiology 1987; 165: 123-8

58. Gotway MB, Dawn SK, Caoili EM, et al. The radiologic spectrum of pulmonary aspergillus infections. J Comput Assist Tomogr 2002; 26(2): 159-73

59. Rumbak M, Kohler G, Eastridge C, et al. Topical treatment of life-threatening haemoptysis from aspegillomas. Thorax 1996; 51: 253-5

60. Giron J, Poey C, Fajadet P, et al. CT-guided percutaneous treatment of inoperable pulmonary aspergillomas: a study of 40 cases. European Journal of Radiology1998; 28: 235-42

61. Yamada H, Kohno S, Koga H, et al. Topical treatment of aspergilloma by antifungals. Relationship between duration of the disease and efficacy of therapy. Chest 1993; 103: 1421-5

62. Swart MJ, Joubert G. Should I change to OPCAB? Cardiovascular Journal of South Africa 2005; 16(3):166-70

63. Lee JS, Urchel DM, Urchel, JD. Is general thoracic surgical practice evidence based? Ann Thorac Surg 2000; 70: 429-31 (Abstract)

64. Currie DC, Prendergast CM, Pearson MC. Audit of bronchial artery embolisation in a specialist respiratory centre. Qual Health Care. 1992 Jun;1(2):94-7 (Abstract)

65. Kawamura S, Maesaki S, Tomono K, et al. Clinical evaluation of 61 patients with pulmonary aspergilloma. Intern Med 2000; 39: 209-12

66. Yamada H, Kohno S, Koga H, et al. Topical treatment of pulmonary aspergilloma by antifungals: relationship between duration of the disease and efficacy of therapy. Chest 1993; 103(5): 1421-5

67. Denning DW, Riniotis K, Dobrashian R, et al. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: Case series, proposed nomenclature change, and review. Clin Infect Dis 2003; 37(Suppl 3): S265-80

68. Henderson RA, Watkins SC, Flynn JL. Activation of human dendritic cells following infection with Mycobacterium tuberculosis. J Immunol 1997; 159: 635-43

69. Slight J, Nicholson WJ, Mitchell CG, et al. Inhibition of the alveolar macrophage oxidative burst by a diffusible component from the surface of the spores of the fungus Aspergillus fumigatus. Thorax 1996; 51(4):389-96

70. Mitchell CG, Slight J, Donaldson K. Diffusible component from the spore surface of the fungus Aspergillus fumigatus which inhibits the macrophage oxidative burst is distinct from gliotoxin and other hyphal toxins. Thorax 1997; 52(9):796-801

71. Addrizzo-Harris DJ, Harkin TJ, McGuinness G, et al. Pulmonary aspergilloma and AIDS. A comparison of HIV-infected and HIV-negative individuals. Chest. 1997;111(3):612-8

72. Greenberg AK, Knapp J, Rom WN, et al. Clinical presentation of pulmonary mycetoma in HIV-infected patients. Chest. 2002;122(3):886-92.

73. Global tuberculosis control: surveillance, planning, financing. WHO report 2005. Geneva, World Health Organization.

74. Beckles MA, Spiro SG, Colice GL, et al. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest 2003; 123: 105S-114S

75. Bolliger CT, Guckel C, Engel H et al. Prediction of functional reserves after lung resection: comparison between quantitative computed tomography, scintigraphy and anatomy. Respiration 2002; 69(6): 482-9

76. Al Kattan K, et al. Surgery pr pulmonary aspergilloma in post-tuberculous vs. immuno-compromised patients. Eur J Cardiothorac Surg 2001: 20; 728-33

APPENDIX 1

Raw Data

ID#	Age	Gender	Elect / Emerg	Procedure	Re-op. for bleed	Post-op. Hosp stay	Mortality (Cause)	Morbidity: Major / Minor (Specifiy)
1	43	F	Urgent	Left Pneumonectomy	No	7	No	None
2	49	M	Elective	Left Upper Lobectomy	Yes	19	No	Yes: Major (Bleeding)
3	40	M	Elective	Right Middle Lobectomy	No	6	No	None
4	49	F	Elective	Segmental Resection	No	8	No	None
5	32	M	Elective	Right Lower Lobectomy	No	14	No	None
6	53	F	Urgent	Right Upper Lobectomy	No	12	No	None
7	28	M	Elective	Segmental Resection	No	6	No	None
8	36	M	Elective	Right Upper Lobectomy	Yes	18	No	Yes: Major (Bleeding)
9	39	M	Elective	Right Upper Lobectomy	No	28	No	Yes: Major (Prolonged air leak)
10	42	M	Urgent	Left Pneumonectomy	No	10	No	None
11	45	M	Emergent	Left Upper Lobectomy	Yes	22	No	Yes: Major (BPF; Empyema)
12	47	M	Elective	Right Lower and Right Middle Lobectomy	No	11	No	None
13	29	F	Elective	Left Lower Lobectomy	No	9	No	None
14	50	M	Elective	Right Upper Lobectomy; Thoracoplasty	No	20	No	Yes: Major (Stump breakdown -> BPF; Empyema)
15	37	M	Elective	Segmental Resection	No	12	No	None
16	32	M	Elective	Left Pneumonectomy	No	8	No	None
		M	Emergent	Combined Lung and Chest Wall Resection	No	41	No	Yes: Major (Prolonged ventilation)
17	35	F	Elective	Left Upper Lobectomy	No	6	No	None
18	44	F	Elective	Segmental Resection	No	7	No	None
19	31	M	Elective	Right Upper Lobectomy	No	10	No	None
20	28	M	Elective	Right Upper Lobectomy	No	8	No	None
21	40	M	Elective	Left Upper Lobectomy	No	14	No	None
22	48	M	Elective	Left Pneumonectomy	Yes	51	No	Yes: Major (Bleeding; Empyema; Eloesser flap)
23	34	M	Elective	Right Pneumonectomy	No	11	No	None
24	47	F	Elective	Left Pneumonectomy	No	11	No	None
25	38	F	Elective	Left Upper Lobectomy	No	16	No	Yes: Major (Prolonged air leak)
26	37	M	Elective	Right Upper Lobectomy	No	5	No	None
27	30	M	Urgent	Right Upper Lobectomy	No	6	No	None
28	52	M	Elective	Left Upper Lobectomy	No	10	GIT Haemorrhage	
29	44	M	Urgent	Right Pneumonectomy	No	29	No	Yes: Major (Empyema)
		M	Elective	Thoracoplasty	No	8	No	None
30	56	M	Urgent	Right Upper Lobectomy	No	10	No	None
31	56	M	Urgent	Segmental Resection	No	7	No	None
32	65	M	Urgent	Left Upper Lobectomy	No	10	Respiratory failure	Yes: Major (Air leak ->demise)
33	42	M	Elective	Left Pneumonectomy	No	11	No	None
34	30	F	Elective	Left Upper Lobectomy	No	10	No	None
35	45	M	Urgent	Left Pneumonectomy	Yes	19	No	Yes: Major (Bleeding)
36	37	F	Elective	Left Pneumonectomy	No	8	No	None
37	47	M	Urgent	Right Pneumonectomy	No	10	No	None
38	33	F	Elective	Right Upper Lobectomy	No	8	No	None
39	48	F	Elective	Right Upper Lobectomy	No	14	No	None
40	46	F	Elective	Right Pneumonectomy	No	9	No	None
41	40	F	Emergent	Left Pneumonectomy	No	11	No	None
42	29	F	Elective	Left Pneumonectomy	No	10	No	None
43	44	M	Elective	Left Upper Lobectomy	No	8	No	None
44	44	F	Elective	Left Pneumonectomy	Yes	28	No	Yes: Major (Bleeding; Empyema)

ID#	Age	Gender	Elect / Emerg	Procedure	Re-op. for bleed	Post-op. Hosp stay	Mortality (Cause)	Morbidity: Major / Minor (Specify)
45	44	M	Emergent	Left Upper Lobectomy	No	6	No	None
46	38	M	Urgent	Left Pneumonectomy	No	10	No	None
47	51	M	Elective	Left Pneumonectomy	No	12	No	None
48	57	M	Urgent	Right Upper and Right Middle Lobectomy	No	28	No	Yes: Major (Empyema)
49	44	M	Urgent	Right Upper Lobectomy	No	8	No	None
50	47	M	Elective	Wedge Resection Lung	No	6	No	None
51	45	F	Elective	Right Pneumonectomy	No	7	No	Yes: Major (Stump breakdown -> BPF; Empyema)
52	40	F	Elective	Left Pneumonectomy	No	11	No	None
53	41	M	Elective	Right Pneumonectomy	No	12	No	Yes: Major (Stump breakdown -> BPF; Empyema)
54	49	M	Elective	Segmental Resection	No	23	No	Yes: Major (Prolonged air leak)

ID#	Secondary Procedure	FEV1/FVC	Symptoms	CXR/CT Findings	PTB	Nutritional Status (BMI)
1	No	1940/2140	Minor Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Normal (22.1)
2	Yes (Re-op. for bleeding)	2480/3940	Minor Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Good (28.0)
3	No	2430/3120	Minor Haemoptysis	Aspergilloma RML (CT)	Previously Rx PTB	Normal (23.2)
4	No	1990/3460	Minor Haemoptysis	Aspergilloma LLL (CT conf.)	NO previous PTB	Undernourished (19.8)
5	No	1750/2670	Minor Haemoptysis	Aspergilloma RLL (CT conf.)	Previously Rx PTB	Undernourished (17.7)
6	No	960/1790	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (17.8)
7	No	3250/5150	Minor Haemoptysis	Aspergilloma LUL (CT)	Sarcoid (NO previous PTB)	
8	Yes (Re-op. for bleeding x 2)	2890/4130	Minor Haemoptysis	Aspergilloma RUL (CT)	Previously Rx PTB	Normal (21.2)
9	No	3800/4760	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Good (26.5)
10	No	2070/3600	Minor Haemoptysis	Aspergilloma LLL	Previously Rx PTB	Undernourished (17.1)
11	Yes (Re-op. for bleeding)	640/1700	Massive Haemoptysis (Active)	Aspergilloma LUL (CT)	Previously Rx PTB	Emaciated (13.7)
12	No	1630/1800	Massive Haemoptisis	Aspergilloma RLL (CT conf.)	Previously Rx PTB	Undernourished (16.9)
13	No	1820/2420	NO Haemoptysis	Aspergilloma LLL	Previously Rx PTB	Normal (22.2)
14	Yes (Elflap -> Thoracopl)	1620/2270	Minor Haemoptysis	Aspergilloma RUL (CT conf.)	On histology!!	Undernourished (18.9)
15	No	2060/2710	Minor Haemoptysis	Bilateral UL Asperg.	Previously Rx PTB	Normal (24.3)
16	No	1820/2460	Minor Haemoptysis	Aspergilloma LUL (CT)	Previously Rx PTB	Undernourished (18.2)
	No	840/1470	Massive Haemoptysis (Active)	Aspergilloma RUL (CT)	Previously Rx PTB	Undernourished (16.9)
17	No	1750/2070	Massive Haemoptisis	Aspergilloma LUL (CT conf.)	NO previous PTB	Good (25.4)
18	No	1120/1740	Minor Haemoptysis	Aspergilloma LUL (CT conf.)	Previously Rx PTB	Undernourished (17.2)
19	No	2920/3670	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (18.1)
20	No	1990/2600	Massive Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Normal (21.7)
21	No	3790/4430	Massive Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Normal (22.4)
22	Yes (Re-op. bleed; El flap)	1970/3120	Minor Haemoptysis	Aspergilloma LUL (CT conf.)	Previously Rx PTB	Undernourished (17.3)
23	No	2500/3300	Massive Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (19)
24	No	2820/3470	Minor Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Normal (22.8)
25	No	1780/3030	Minor Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Normal (22.1)
26	No	2770/3600	Massive Haemoptysis	Aspergilloma RUL (CT conf.)	Previously Rx PTB	Normal (24.0)
27	No	3240/4050	NO Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (18.1)
28	No	2200/3200	Massive Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Undernourished (18.7)
29	Yes (Eloesser flap)	1060/2260	Massive Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Good (28.4) Klinefelter sdm.
	No					
30	No	990/2700	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Emaciated (14.4)
31	No	1130/1930	Massive Haemoptysis	Aspergilloma LUL (CT)	Previously Rx PTB	Undernourished (17.1)
32	No	1760/3050	Massive Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Undernourished (17.9)
33	No	2710/4000	Minor Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Undernourished (18.7)
34	No	2980/4010	Minor Haemoptysis	Aspergilloma LUL (CT conf.)	Previously Rx PTB	Undernourished (19.4)
35	Yes (Re-op. for bleeding)	1200/2000	Massive Haemoptysis	Destr. LL; NO Asperg.	Previously Rx PTB	
36	No	1910/2350	Minor Haemoptysis	Destr. LL; NO Asperg.	Previously Rx PTB	Normal (20.2)
37	No	1570/3390	Massive Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Normal (20.8)
38	No	2780/3000	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Good (25.7)
39	No	1300/1400	Massive Haemoptysis (Active)	Aspergilloma RUL	Previously Rx PTB	Undernourished (15.6)
40	No	1660/1860	Minor Haemoptysis	Aspergilloma RUL	MDR TB fully Rx	Normal (22.1)
41	No	1240/2050	Massive Haemoptysis	Destr. LL c Asp. / Asp. RUL	Previously Rx PTB	Undernourished (18.3)
42	No	1280/1710	NO Haemoptysis	Destr. LL c Aspergilloma LUL	MOTT (inactive)	Undernourished (18.2)
43	No	1880/4220	Massive Haemoptysis	Aspergilloma LUL	Previously Rx PTB	Normal (22.3)
44	Yes (Re-op. bleed; El flap)	1100/2070	Minor Haemoptysis	Destr. LL c Aspergilloma LUL	Active PTB (post-op. cultures)	Undernourished (17.1)

ID#	Secondary Procedure	FEV1/FVC	Symptoms	CXR/CT Findings	PTB	Nutritional Status (BMI)
45	No		Massive Haemoptysis (Active)	Aspergilloma LUL	Clinically supected	Undernourished (17.7)
46	No	1060/1710	Minor Haemoptysis	Destr. LL; **NO** Asperg.	Previously Rx PTB	Undernourished (19.1)
47	No	2180/3670	Minor Haemoptysis	Aspergilloma LUL (CT conf.)	Previously Rx PTB	Undernourished (18.6)
48	No	1590/2600	Minor Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (18.7)
49	No	1440/2130	Massive Haemoptysis	Aspergilloma RUL	Previously Rx PTB	Undernourished (17.4)
50	No	1190/3190	Massive Haemoptysis	Aspergilloma apex LLL	**NO** previous PTB	Normal (23.6)
51	Yes (Bronch; closed pl drain)	1000/2530	Massive Haemoptysis	Aspergilloma RUL (CT conf.)	Previously Rx PTB	Undernourished (19.1)
52	No	1300/2170	Massive Haemoptysis	Destr. LL; **NO** Asperg.	Previously Rx PTB	Undernourished (18.8)
53	Yes (Bronch; closed pl drain)		Massive Haemoptysis	Aspergilloma RUL (CT)	Previously Rx PTB	Undernourished (17.4)
54	No	1970/3210	Minor Haemoptysis	Aspergilloma LUL (CT)	Previously Rx PTB	