

# Outcomes of resectable pulmonary aspergilloma and the performance gap in a high tuberculosis prevalence setting: A retrospective study

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**Background.** Pulmonary aspergillomas develop in patients with underlying structural lung diseases. The mainstay of therapy is surgery. **Objectives.** To assess treatment and clinical outcomes following diagnosis of potentially resectable pulmonary aspergilloma at the Tygerberg Hospital (TBH) between January 2013 and December 2015. **Methods.** This was a retrospective analysis conducted at TBH. Patients were followed up between 6 and 29 months following diagnosis to analyse outcomes. **Results.** Fifty-nine patients presented for surgery. The mean (SD) age was 44.5 (8.8) years. Thirty-six (61.0%) were male and 13 (22.0%) were HIV-positive. A previous history of pulmonary TB was identified in 83.1% of the patients. One or both upper lobes were involved in 58 patients (98.3%) and haemoptysis was the most frequent symptom, occurring in 56 patients (94.9%). Nine patients (15.3%) were considered unfit for surgery. As of June 2016, 23 (46.0%) of the remaining 50 patients had undergone surgery and 3 (6.0%) had died before surgery was performed. The median time from multidisciplinary discussion to surgery was 190 days (interquartile range 134 - 351). Twenty patients (87.0%) underwent lobectomy and 3 (13.0%) had pneumonectomy. There was no postoperative mortality. One patient developed bleeding, persistent air leak and aspiration pneumonia postoperatively. Three patients were hospitalised for >7 days postoperatively. Following surgery, only two patients reported ongoing respiratory symptoms by day 90. **Conclusion.** Less than half of the patients accepted for lung resection at TBH underwent surgery. Waiting times were long (>1 year in 25%) and were associated with mortality. Barriers to prompt surgery are complex, but should be addressed urgently.

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*Aspergillus* is a ubiquitous fungus that causes a variety of clinical syndromes in the lung. Aspergilloma, which is the most common and best-recognised form of pulmonary involvement consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus, and tissue debris, usually developing in preformed lung cavities.<sup>[1]</sup>

The true incidence of aspergilloma is not known. In a study of 544 patients with pulmonary cavities secondary to tuberculosis (TB), 22% had radiological evidence of aspergilloma.<sup>[2]</sup> The natural history of aspergilloma is variable. In the majority of cases, the lesion remains stable; however, in ~10% of cases, it may decrease in size or resolve spontaneously without treatment.<sup>[3,4]</sup> An aspergilloma may be asymptomatic for years, although some patients experience minor haemoptysis. Severe haemoptysis may occur, with associated mortality rates between 2 and 14%.<sup>[5-10]</sup> Radiologically, an aspergilloma is classically a mobile, intracavitary mass surrounded by an air crescent, but it may also be an immobile ball, an irregular sponge-like opacity containing air spaces, or even a network of fungal strands within cavities.<sup>[11]</sup>

Medical treatment of aspergillomas with antifungal agents may be useful in preventing or treating life-threatening haemoptysis, and is considered the standard care for complex aspergilloma, also known as chronic cavitating pulmonary aspergillosis.<sup>[12]</sup> Bronchial artery

embolisation is frequently used as a temporising measure in patients with life-threatening haemoptysis; however, relapse occurs in ~50% of patients.<sup>[13,14]</sup>

Surgical resection is the definitive treatment for patients with adequate pulmonary reserve and should be considered in all patients with severe haemoptysis. It has the benefits of prevention of life-threatening haemoptysis, eradication of the pyogenic component and probable prolongation of life.<sup>[15-21]</sup> Although surgical resection is considered curative, it is not possible in every patient, for a variety of physiological and technical reasons. Such reasons may include poor physical condition, severe comorbidity, poor pulmonary reserve, extensive lung involvement or inability to localise the bleeding site. Furthermore, the thoracic surgical expertise needed to perform lung resection is often limited or unavailable in low- and middle-income countries such as South Africa (SA), where aspergillomas are most common. The purpose of our study was to retrospectively review all cases of aspergilloma accepted for surgical resection at our tertiary hospital between January 2013 and December 2015, to assess outcomes.

## Methods

Participants were retrospectively included in the study if they were: (i) at least 18 years old; (ii) diagnosed with pulmonary aspergilloma;

and (iii) presented at a multidisciplinary forum at Tygerberg Hospital (TBH) between January 2013 and December 2015 for possible lung resection based on the European Respiratory Society's guidelines.<sup>[22,23]</sup> In order to be presented for surgical resection at this forum, local protocol requires that the patient must have debilitating and/or severe and potentially life-threatening symptoms necessitating the surgery (for example, major haemoptysis or intractable pain), and in addition all patients should be deemed amenable to surgical resection by the attending pulmonologist.

Data for identified cases were collected from encounters in the chronological registers up to the end of May 2016. The hospital medical records were searched both manually and electronically for documents in hard copy and in digital format, respectively. Ethical approval for the study was obtained from the Stellenbosch University research ethics committee (ref. no. S15/07/158).

The data were captured and coded in Microsoft Office Excel 2016 (USA) before analysis using STATA 14 statistical software (StataCorp, USA). Continuous data were tested for normality using histogram plots and the Shapiro-Wilk test. For normally distributed data, means and standard deviations (SDs) were reported, while medians and interquartile ranges (IQRs) were reported for data that were not normally distributed. For categorical data, frequencies and proportions were reported.

For all estimations, 95% confidence intervals (CIs) were reported. All significance tests for comparisons were two-sided and carried out with an alpha value of 0.05. The *t*-test and Mann-Whitney *U*-test were used for comparisons between numerical data, whereas the  $\chi^2$  test and Fisher's exact test were used for categorical variables.

## Results

Between January 2013 and December 2015, 59 patients with pulmonary aspergilloma were presented to a weekly multidisciplinary forum at TBH for possible lung resection. Almost all the patients (98%) were recruited. The patients had a mean (SD) age of 44.5 (8.8) years, (range 27.4 - 66.3 years). Most patients were male (61%), and resided within the city of Cape Town municipality (52.5%) or the neighbouring Cape Winelands, a peri-urban municipality (44.1%) (Table 1). Thirteen patients (22%) were HIV-positive.

A previous history of pulmonary TB was reported in 83% of patients, and the majority (95%) of the patients presented with major haemoptysis requiring admission, while a minority (14%) reported chest pain and coughing, with or without haemoptysis. All patients presented to the forum were subjected to chest radiography, computed tomography (CT) of the chest and spirometry, and 75% underwent cardiopulmonary exercise testing as part of the work-up for possible lung resection. Seventeen percent of the patients were categorised as having simple aspergilloma on CT and the remaining as complex aspergilloma according to criteria by Belcher and Plummer.<sup>[15]</sup> Most patients (89.9%) had involvement of a single lobe, and the majority (98.3%) had involvement of the upper lobes of either lung, with approximately equal involvement of the left upper (50.9%) and right upper lobes (47.5%) (Table 1). Eleven patients reported ongoing respiratory symptoms 90 days after the multidisciplinary discussion.

Nine patients (15.3%) were found to be unfit for surgery owing to poor lung function and high surgical risk. The characteristics of these

**Table 1. Demographic characteristics**

Characteristic	n (%) <sup>*</sup>
Age (years), mean (SD)	44.5 (8.8)
Sex	
Male	36 (61.0)
Female	23 (39.0)
Residence	
City of Cape Town	31 (52.5)
Cape Winelands	26 (44.1)
Other	2 (3.4)
Symptoms	
Haemoptysis	56 (94.9)
Chest pain	8 (13.6)
Cough	4 (6.8)
Weight loss	2 (3.4)
Shortness of breath	3 (5.1)
Lobar involvement	
LUL	27 (45.8)
RUL	25 (42.4)
RUL + LUL	1 (1.7)
LUL + LLL	2 (3.4)
RUL + LLL	3 (5.1)
LLL	1 (1.7)
Type of disease	
Simple	10 (17.0)
Complex	49 (83.0)
Previous history of TB	49 (83.0)
HIV status	
Negative	41 (69.5)
Positive	13 (22.0)
Unknown	5 (8.5)
FEV1 (L/s), mean (SD)	1.83 (0.72)
Predicted % of FEV1, mean (SD)	59.3 (19.5)
DLCO (mL/min/mmHg), mean (SD)	16.1 (5.1)
Predicted % of DLCO, median (IQR)	57.1 (50.2 - 71.0)
VO <sub>2</sub> max (mL/min/kg), mean (SD), n=44	22.6 (5.8)
Surgery	
Performed	23 (39.0)
Not performed	24 (40.7)
Unfit for surgery	9 (15.3)
Died prior to surgery	3 (5.1)

DLCO = diffusion capacity for carbon monoxide; FEV1 = forced expiratory volume in the first second; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe; VO<sub>2</sub> max = maximum oxygen uptake.

<sup>\*</sup>Unless otherwise specified.

patients are summarised in Table 2. They were relatively older than patients found fit for surgery (median age 47.6 v. 44.0 years) with significantly worse lung physiology. The mean (SD) forced expiratory volume in the first second (FEV1) and the mean (SD) diffusion capacity for carbon monoxide (DLCO) of those unfit for surgery were 1.03 (0.37) L/s and 11.4 (3.6) mmol/min/mmHg, respectively, whereas those for surgically fit patients were 1.98 (0.67) L/s and 17.0 (4.9) mmol/min/mmHg, respectively. One of the patients required embolisation for recurrent haemoptysis 20 months after the discussion, while the remaining eight were lost to follow-up.

The 50 patients accepted for surgery were electively booked for the procedure with a median duration of 99 days (IQR 92 - 113) before their surgery appointment. Twenty-three of them (46%) had had surgery by June 2016. There were no significant differences in the characteristics of those who underwent surgery and those who did not (Table 3).

Surgery was delayed in the majority of cases, with the median time from presentation to surgery being 190 days (IQR 134 - 351) among those who underwent surgery. Only three patients had surgery on the appointed day. The reason for delay or lack of surgery was not identified in the majority of patients. The identified reasons for delay among those who had surgery included miscommunication (*n*=1), hospital bed shortage (*n*=1), missed appointment (*n*=1) and lack of theatre time owing to competing emergency procedures (*n*=1). Among those who did not undergo surgery, the identified reasons for delay included loss to follow-up (*n*=12), miscommunication (*n*=1), withdrawal of consent (*n*=2) and lack of transport (*n*=1). One patient developed myocarditis due to systemic lupus erythematosus and another developed active pulmonary TB. Three patients died from unknown causes before undergoing surgery. Among those who did not undergo surgery, five remained symptomatic as at June 2016.

Among those who underwent surgery, 18 (78.3%) had resection of a single lobe, 2 (8.7%) had double lobectomy and 3 (13.0%) had pneumonectomy. There was no reported postoperative mortality. One patient, however, developed bleeding, persistent air leak and aspiration pneumonia postoperatively, which required mechanical ventilation and an extended hospital stay. Three further patients were hospitalised for >7 days postoperatively. Following surgery, only two patients reported ongoing respiratory symptoms by day 90. Microscopy of specimens from 22 of the resected lung sections identified fungal elements in 17 patients (73.9%) (Table 4).

### Discussion

We found that in a selected population with symptomatic and potentially resectable aspergillomas, only 47% underwent surgery. Resection of the involved lung is regarded as the most appropriate management strategy when the diagnosis of symptomatic aspergilloma is made and the patient is suitable for operation,<sup>[24,25]</sup> with non-operative treatment having a limited role in such patients. In the context of massive haemoptysis, the risk-benefit assessment favours a surgical approach, with an observed 5-year survival of 84% of subjects receiving lung resection, compared with 41% for those who do not,<sup>[10,26]</sup> with some authors observing the development of invasive aspergillosis in 20% of non-surgically treated cases.<sup>[4]</sup> In the absence of massive haemoptysis, the indication for prophylactic surgical resection is less clear, with most authors suggesting observation of asymptomatic patients, and surgery only if symptoms develop.<sup>[27]</sup>

All our patients required surgical resection for symptomatic disease, yet the factors responsible for delays and lack of operations appeared complicated and multifactorial. On average, patients were given appointment dates at a median of 3 months after the multidisciplinary discussion, but waited twice as long for their surgery, while over a quarter of patients waited more than a year for their operation. We were unable to identify any unique predictors for the lack of surgical intervention, and there were no differences in geographical location, HIV status, respiratory physiology or the site of aspergillomas in the lung between those who underwent surgery

**Table 2. Comparison between the surgically fit and unfit patients**

Characteristic	Surgically fit (n=50), n (%) <sup>*</sup>	Surgically unfit (n=9), n (%) <sup>*</sup>	p-value
Age (years), median (IQR)	44.05 (37.00 - 49.78)	47.63 (45.95 - 53.47)	0.066
Sex, male	31 (62)	5 (56)	0.715
Residence			0.847
City of Cape Town	21 (42)	5 (56)	
Cape Winelands	27 (54)	4 (44)	
Haemoptysis	48 (96)	8 (89)	0.371
Lobe involvement			0.127
LUL	25 (50)	2 (22)	
RUL	20 (40)	5 (56)	
RUL + RLL	2 (4)	0	
LUL + LLL	0	1 (11)	
RUL + LLL	1 (2)	0	
LLL	2 (4)	1 (11)	
Type of disease, complex	40 (80)	9 (100)	0.141
HIV-positive	11 (22)	2 (22)	0.605
FEV1 (L/s), mean (SD)	1.98 (0.67)	1.03 (0.37)	0.0001
Predicted % FEV1, mean (SD)	63.3 (17.3)	37.2 (16.6)	0.0006
DLCO, mean (SD)	17.0 (4.9)	11.4 (3.6)	0.0027
Predicted % DLCO, mean (SD)	61.4 (16.1)	43.8 (9.5)	0.0014
VO <sub>2</sub> max (mL/min/kg), mean (SD)	23.4 (5.7)	17.9 (4.2)	0.0161

<sup>\*</sup>Unless otherwise specified.

and those who did not. We were therefore unable to identify any systematic patient factors that could act as barriers to surgery.

The factors responsible for delay in surgery and non-operation were probably the result of both institutional and personal factors, although in the majority of cases no reason was identified, with high rates of loss to follow-up. In our context, institutional factors such as shortage of thoracic surgical lists, and non-availability of hospital beds for elective thoracic surgical cases, play a significant role in delaying elective surgical procedures. The high rate of loss to follow-up is of concern, and it is unclear to what extent patient and clinical factors played a role. In cases where a reason for delay was identified, a wide range of reasons were given, including abatement of symptoms, miscommunication, lack of transportation to hospital, hospital bed shortage, refusal to consent, loss to follow-up, clinical worsening and lack of theatre time due to emergency procedures. Personal factors as a reason for loss to follow-up are more difficult to assess, and it is not clear to what extent patient frustration with the hospital system was responsible. When performed, surgery appeared relatively safe with no reported mortality, and was well tolerated with few complications, in keeping with multiple contemporary studies where mortality rates of <1% were reported.<sup>[17-21]</sup> Without surgery, mortality was high (5.1%) and comparable to previous studies.<sup>[6-10]</sup>

Our study population was relatively young and predominantly male. Pulmonary tuberculosis (TB) was the most common identified underlying lung disease in our study population in keeping with high incidence of the condition in the general population. TB is said to have the highest incidence among the 25 - 34 year age group, and to be twice as common in men in the Cape Town Metropolis.<sup>[28,29]</sup> Additionally, the low number of older patients in our study was likely due to selection bias, as older patients would have been less likely to be candidates for lung resection owing to greater surgical risk for a variety of reasons. Previous TB was, unsurprisingly, identified as the most likely underlying disease in our study population, owing to the extremely high background incidence of TB in our country.<sup>[30]</sup> In some studies, >50% of patients with TB developed pulmonary cavities following treatment, and 10 - 30% of these cavities are estimated to be complicated by chronic

pulmonary aspergillosis, with the cavity size significantly associated with increased risk of developing aspergillosis.<sup>[31]</sup>

The proportion of patients with HIV in our study is comparable with the ~19% prevalence of HIV in the general population of SA.<sup>[32]</sup> Remarkably, aspergillosis is unusual in patients with AIDS,<sup>[33]</sup> which contrasts with the relatively high frequency of aspergillosis in most other seriously immunocompromised patients. For example, up to 70% of patients with leukaemia have pulmonary aspergillosis after 30 days of neutropenia.<sup>[34]</sup> Nevertheless, the risk of developing TB is estimated to be between 26 and 31 times greater in people

infected with HIV, making them susceptible to the development of aspergillomas.<sup>[35,36]</sup>

Unsurprisingly, upper lobectomy was the most common surgical procedure performed. This is consistent with both the usual distribution of residual tuberculous cavities and the reported literature.<sup>[10,22,36,37]</sup>

#### Study limitations

Firstly, it was a retrospective cohort, and thus depended exclusively on existing clinical records. Therefore, a number of variables of interest were not consistently identified, and some data were not uniformly captured by all clinicians over the 3-year period. Secondly,

**Table 3. Comparison between those resected and those not resected**

Characteristic	Resected (n=23), n (%) <sup>*</sup>	Not resected (n=27), n (%) <sup>*</sup>	p-value
Age (years), median (IQR)	46.6 (40.5 - 49.8)	41.9 (32.6 - 49.8)	0.1995
Sex, male	15 (65.2)	16 (59.3)	0.665
Residence			0.383
City of Cape Town	11 (47.8)	16 (59.3)	
Cape Winelands	12 (52.2)	9 (33.3)	
Symptoms			0.908
Haemoptysis	22 (97.7)	26 (96.3)	
Chest pain	3 (13.0)	5 (18.5)	
Cough	1 (4.3)	1 (3.7)	
Weight loss	0	1 (3.7)	
Shortness of breath	0	1 (3.7)	
Lobe involvement			0.903
LUL	11(47.8)	14 (51.9)	
RUL	10 (43.5)	10 (37.0)	
LUL + LLL	1 (4.3)	1 (3.7)	
LLL	0	1 (3.7)	
RUL + LLL	1 (4.3)	1 (3.7)	
Type of disease			0.670
Simple	4 (17.4)	6 (22.2)	
Complex	19 (82.6)	21 (77.8)	
Previous history of TB	17 (73.9)	23 (85.2)	
HIV-positive	5 (21.7)	6 (22.2)	0.956
FEV1 (L/s), median (IQR)	1.86 (1.63 - 2.13)	1.88 (1.51 - 2.42)	0.7099
Predicted % FEV1, median (IQR)	56.1 (51.2 - 73.0)	65.5 (49.1 - 76.6)	0.4331
DLCO, median (IQR)	16.2 (14.4 - 20.6)	16.0 (14.8 - 18.1)	0.8269
Predicted % DLCO, mean (SD)	59.6 (55.7 - 72.3)	58.6 (51.8 - 71.4)	0.6138
VO <sub>2</sub> max (mL/min/kg), median (IQR)	23.8 (21.6 - 28.2)	22.0 (19.2 - 25.6)	0.6484

<sup>\*</sup>Unless otherwise specified.

**Table 4. Surgical outcomes for patients undergoing surgery**

Characteristic	n (%)*
Days to surgery, median (IQR)	190 (134 - 351)
Extent of resection	
Lobectomy	18 (78.3)
Bi-lobectomy	2 (8.7)
Pneumonectomy	3 (13.0)
Complications	
Extended stay	4 (17.4)
Persistent air leak	1 (4.3)
Bleeding	1 (4.3)
Pneumonia	1 (4.3)
Histology, fungal elements present	17 (73.9)

\*Unless otherwise specified.

information on patient follow-up was not routinely documented or standardised for the majority of patients, and was obtained at non-standardised intervals. Finally, selection bias on the part of the attending physicians was possible, as only cases thought likely to be operable were presented at the multidisciplinary forum. To try to minimise these biases, we included all patients presented at the forum during the defined period, and created a standardised data extraction form for use on all patients.

### Study strengths

Some of the study strengths were the 'real world' approach, i.e. not within the context of a controlled trial, which perhaps allowed a more insightful assessment of current usual practice over time. Similarly, the original data were collected by people other than the investigators, and were therefore independent of any specific hypothesis, diminishing observer bias. In addition, patients were presented in a multidisciplinary forum, which minimised the risk of errors in diagnosis.

### Conclusions

Lung resection surgery remains the mainstay of therapy for pulmonary aspergilloma, yet in our context, less than half the patients fit for surgery underwent the operation, and waiting times were long (>1 year in 25%) and were associated with mortality, highlighting the need for a patient-centred approach. Barriers to prompt surgery are complex, but should be addressed urgently.

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