Pulmonary nodules in patients with drug-resistant tuberculosis who have undergone adjuvant lung resection in a high-HIV-burden setting

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Introduction. Radiological findings of drug-resistant tuberculosis (DR-TB) have been described; however, results were focused on HIV-negative patients.
Objectives. To describe the radiological distribution of pulmonary nodules in patients who have undergone lung resection. Furthermore, the study establishes the association between perioperative nodules and sputum culture conversion in HIV-positive and -negative patients.
Methods. A retrospective review was conducted of clinical and radiological records of adult patients who had undergone lung resections for DR-TB, between 1 January 2011 and 31 December 2013, at a hospital in Durban, South Africa.
Results. Lung resections were undertaken in 47 patients with drug-resistant tuberculosis (DR-TB.) Among patient infections, 74.5% were multidrug-resistant TB (MDR-TB) and 25.5% were extensively drug-resistant TB (XDR-TB). The prevalence of HIV was 54.3% in patients with MDR-TB and 66.7% in XDR-TB. Pre-operative radiological studies showed a similar distribution of pulmonary nodules in HIV-positive and -negative patients. Positive pre-operative sputum cultures were noted in 34% of patients, but were not associated with pulmonary nodules on pre-operative radiological evaluation (p=0.81). At 1 month postoperatively, 81.3% of patients with a positive pre-operative sputum culture converted to negative sputum culture. The cumulative culture conversion rate was 87.5% at 2 months post-operatively. Using composite sputum culture outcomes, a good outcome was defined as consistently negative postoperative sputum cultures. There was no association between poor outcomes and the presence of nodules, either pre-operatively (p=0.73) or postoperatively (p=0.52), irrespective of HIV status.
Conclusion. The presence of pulmonary nodules on pre-operative images was not associated with perioperative positive sputum results or poor outcomes. The clinical significance of residual pulmonary nodules in DR-TB, following lung resection, remains uncertain.

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The epidemic of drug-resistant tuberculosis (DR-TB) remains a global challenge. Even though the incidence and mortality of tuberculosis (TB) has decreased worldwide, the overall prevalence of multidrug-resistant tuberculosis (MDR-TB) is increasing alarmingly, especially in sub-Saharan Africa. This global distribution and low cure rates with medical therapy has resulted in renewed interest in adjuvant surgical therapy, especially in XDR-TB. The role of adjuvant surgery in these patients is still being refined, but has been beneficial in patients with severe radiological disease symptoms, and those with delayed microbiological response to medical therapy.[1,2] Indications for lung resection have remained largely unchanged since they were developed by Iseman *et al*.[2,3] in 1990. In medical therapy, drugs do not adequately penetrate lung cavities and pulmonary nodules – focal areas of TB. Adjuvant surgery is gainfully directed at sources of ongoing lung disease where pharmacological therapy is suboptimal, but the physiological cost of lung resection may be significant. In addition, resection is usually limited to areas of severe cavitation. Due to their distribution and multitude, pulmonary nodules are not usually amenable to surgical resection.

Pulmonary nodules may, however represent active TB infection with a lower mycobacterial burden than cavities. It stands to reason that these high-disease-burden nodules should be resected with the intention of decreasing the bacillary load, yet sometimes, resecting these may not be feasible. The aim of surgery in patients with DR-TB is to excise pulmonary cavities with the intention of reducing the bacteriological burden of disease and potentiating cure. Patients with scattered nodules or bilateral reticular infiltrates have been selected, with the premise that surgery would be a 'debulking' procedure and that remaining lesions could be cleared with pharmacological therapy.[4] Nodules are sometimes left unresected when it is not feasible, e.g. when nodules are surrounded by otherwise normal lung tissue, or when there is inadequate pulmonary reserve to justify additional lung resection outside of the cavitary lobe. To our knowledge, no studies have investigated the microbiological profiles of resected nodules, or the significance of nodules on the postoperative chest radiographs in DR-TB patients. This study describes the presence of pulmonary nodules in patients with DR-TB who have undergone adjuvant lung resection surgery. This study evaluated the relationship between perioperative pulmonary nodules and the intermediate treatment outcome of culture conversion.

Methods

A retrospective review of adult patients with DR-TB was done between 1 January 2011 and 31 December 2013. Data were extracted from inpatient, outpatient and surgical records. Radiological images were accessed via a picture-archiving and communication system. Alternatively, plain films were used when electronic records were not available.

Adjuvant lung resection was performed if disease was localised to one lung (absolute criterion) and if any of the following were present: persistently positive sputum smear or culture despite optimal antituberculous chemotherapy; extensive isolate drug-resistance pattern with a high probability of failure or relapse; severe cavitary disease; two or more relapses while on treatment; intolerance to medical therapy; haemoptysis; or bronchiectasis.

The extent of lung resection was guided by radiological (chest X-ray (CXR) and computed tomography (CT) chest scans) investigations. The presence of cavities in the lobes identified for resection was considered mandatory. Nodules were resected only when feasible. Lobes that contained nodules alone were not resected.

After surgery, all patients were maintained on their pre-operative DR-TB regimens based on the resistance profile of the last positive sputum culture. After recovery, patients were followed up at a postoperative clinic initially at 6 weeks after surgery, and then monthly for 6 months.

CT scans were done pre-operatively, and chest radiographs were done both pre- and postoperatively. Postoperative chest radiographs were performed 6 weeks after surgery. Chest radiographs and CT scans were blind-reviewed in a random order, and independently, by two thoracic surgeons blinded to case details. Images were reported for the presence, pattern and distribution of cavitary disease and pulmonary nodules. Discrepant findings were resolved by consensus or through the opinion of a third reviewer.

For the chest radiographic analyses, each lung was divided according to its lobar anatomy using posterior-anterior and lateral views. The observers assessed the extent and presence of lung parenchymal abnormalities with particular attention to cavities and presence of nodules.

Data analyses was undertaken using SPSS software (SPSS 23.0, IBM Corp., USA). For all statistical comparisons, a 5% level of significance was used ($p<0.05$); correspondingly, 95% confidence intervals were used to describe effect size. All data were assessed for normality, and non-parametric tests were used where necessary. Median values and interquartile ranges (IQRs) were used for data not amenable to parametric description. A two-tailed χ^2 test was used to assess the association between categorical variables of interest.

The study was conducted under the oversight of the Biomedical Research Ethics Committee at the Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa (SA) (ref. no. BE511/14).

Results

The median (IQR) age of patients was 31 (26 - 41) years and the majority (68%) of patients were female. The prevalence of HIV in this study was 57.4%, with the majority of these infections occurring in women (21/27, 77.8%) (Table 1).

Lung resection was performed in 47 patients with DR-TB infection. MDR-TB constituted 74.5% of the cases, while the remainder were XDR-TB infections. The prevalence of HIV was 54.3% in the MDR-TB cohort and 66.7% in the XDR-TB cohort.

All of the HIV-positive patients were either already on antiretroviral therapy (ART) and had achieved a supressed viral load (85.2%), or were not yet on ART as their CD4 counts were above the threshold for initiation (14.8%) at the time of the study.

All of the patients studied were on appropriate drug-resistant treatment prior to surgery, according to national treatment guidelines and each patient's individual resistance profile at the time of surgery. Specific information on the number of effective drugs in each regimen that was used is unknown. At the time of surgery, 38% of patients had been on treatment for more than 24 months; there was no difference in the duration of medical therapy between patients with and without HIV infection (p=0.427).

Pre-operative chest radiography performed a week before surgery indicated that the upper lobes were the most common site of pulmonary nodules, with 49.8% occurring in either the right or left upper lobe (RUL; LUL). The rest of the lobar distribution pattern were middle lobe (RML) 17%, left lower lobe (LLL) 12.8%, and right lower lobe (RLL) 6.4% (Table 1). The distribution of pulmonary nodules on CXR was similar for both HIV-positive and -negative individuals.

Pre-operative, high-resolution computed tomography (HRCT) scans, performed 2 months pre-surgery, also revealed pulmonary nodules predominantly in the upper lobes (61.3%), with 25.8% of nodules in the LLL, 22.6% in the RML, and 12.9% in the RLL. The distribution of pulmonary nodules on HRCT was similar for HIV-positive and -negative patients. Despite medical therapy during the pre-operative evaluation, 34% patients were sputum culture positive, only two of whom had had less than 12 months of treatment. There was no association between pre-operative sputum culture status and HIV infection.

The majority of patients (66%) in this study were sputum negative at the time of surgery. There was no association between pre-operative sputum culture status and the finding of pulmonary nodules on pre-operative radiological evaluation (p=0.81).

The most commonly performed surgical procedure was a left pneumonectomy (48.9%), with no difference in the distribution of sites of resection between HIV-positive and -negative patients. Right upper lobectomies were performed in 25.5% of patients.

At the first postoperative assessment (6 weeks after surgery), both radiographs and sputum analyses were evaluated. A total of 81.3% of patients with a positive pre-operative sputum culture had converted to sputum culture-negative; cumulative culture conversion rates were 87.5% at 2 months. Similar culture conversion rates were achieved in HIV-positive and -negative patients (88.9% v. 85.7%; p=0.853).

Table 1. A comparison of HIV-positive and -negative patients with drug-resistant tuberculosis (DR-TB) who had undergone adjuvant lung resection

	Total DR-TB (*n*=47)	HIV-positive (*n*=27)	HIV-negative (*n*=20)	*p*-value
Age (years), median (IQR)	31 (26 - 41)	30 (23 - 44)	31.5 (28.25 - 35.75)	0.628
Females, *n* (%)	32 (68.1)	21 (77.8)	11 (55)	0.098
Drug-resistant profile				0.454
Patients with MDR-TB, *n* (%)	35 (74.5)	19 (70.4)	16 (80)	
Patients with XDR-TB, *n* (%)	12 (25.5)	8 (29.6)	4 (20)	
Duration of treatment prior to surgery, *n* (%)				0.427
0 - 12 months	6 (12.8)	4 (14.8)	2 (10)	
13 - 18 months	12 (25.5)	9 (33.3)	3 (15)	
19 - 24 months	11 (23.4)	5 (18.5)	6 (30)	
>24 months	18 (38.3)	9 (33.3)	9 (45)	
Pre-operative location of nodules on CXR, *n* (%) (*n*=47)				
RUL	14 (29.8)	8 (29.6)	6 (30)	0.978
RML	8 (17)	3 (11.1)	5 (25)	0.210
RLL	3 (6.4)	1 (3.7)	2 (10)	0.383
LUL	9 (19.1)	5 (18.5)	4 (20)	0.898
LLL	6 (12.8)	2 (7.4)	4 (20)	0.201
Pre-operative location of nodules on CT scan, *n* (%) (*n*=31)				
RUL	12 (38.7)	7 (25.9)	5 (25)	0.733
RML	7 (22.6)	2 (7.4)	5 (25)	0.105
RLL	4 (12.9)	2 (7.4)	2 (10)	0.674
LUL	7 (22.6)	4 (14.8)	3 (15)	0.736
LLL	8 (25.8)	4 (14.8)	4 (20)	0.573
Pre-operative sputum culture of *M. tb*, *n* (%)				
Positive (DR)	16 (34)	9 (33.3)	7 (35)	0.905
Not on ART (CD4 >200)	4 (8.5)	4 (14.8)	n/a	
Patients on ART, *n* (%)	23 (48.9)	23 (85.2)	n/a	
Patients with undetectable HIV viral load, *n* (%)	23 (48.9)	23 (85.2)	n/a	
Site of resection, *n* (%)				0.719
Left pneumonectomy	23 (48.9)	14 (51.9)	9 (45)	
Right pneumonectomy	6 (12.8)	3 (11.1)	3 (15)	
RUL	12 (25.5)	6 (22.2)	6 (30)	
RML	0 (0)	0 (0)	0 (0)	
RLL	2 (4.3)	2 (7.4)	0 (0)	
LUL	4 (8.5)	2 (7.4)	2 (10)	
LLL	0 (0)	0 (0)	0 (0)	
Cumulative sputum culture conversion following surgery, *n* (%)				
At month 1 (first post-op assessment)	13 (81.3)	8 (88.9)	5 (71.4)	0.389
At month 2	14 (87.5)	8 (88.9)	6 (85.7)	0.853
Relapse	2 (12.5)	1 (11.1)	1 (14.3)	0.853
Persistent positive sputum culture	2 (12.5)	1 (11.1)	1 (14.3)	0.853
Postoperative location of nodules on CXR, *n* (%) (*n*=35)				
RUL	8 (17)	5 (18.5)	3 (15)	0.535
RML	5 (10.6)	2 (7.4)	3 (15)	0.356
RLL	5 (10.6)	3 (11.1)	2 (10)	0.644
LUL	0 (0)	0 (0)	0 (0)	-
LLL	3 (6.4)	2 (7.4)	1 (5)	0.613

IQR = interquartile range; *M. tb* = *Mycobacterium tuberculosis*; n/a = not applicable; ART = antiretroviral therapy; XDR = extensively drug-resistant; CXR = chest X-ray; CT = computed tomography; RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe.

At the end of the study, three sputum culture relapses were noted in patients with pre-operative positive sputum cultures. Only one of these relapses remained culture-positive at the end of the 6-month postsurgical follow-up period. In total, three patients had a positive sputum culture during the surgical treatment follow-up period: two with persistently positive sputum cultures, and one patient with microbiological relapse in the postoperative period.

Pulmonary nodules on the postoperative chest radiograph were either new or nodules that were not resected during the lung resection (Table 2). Of the 47 patients in the study, 28 had pulmonary nodules on the pre-operative chest radiograph. These nodules were resected in six patients, while spontaneous clearance of nodules occurred in the unresected lungs of an additional seven patients following surgery. Three patients developed new nodules following surgery, while residual nodules accounted for 83.3% (15/18) of all nodules seen on the postoperative evaluation. There was no association between the finding of nodules postoperatively and pre-operative sputum culture status (p=0.44). Since most patients were managed by left pneumonectomy, there were fewer left-sided residual nodules. No residual nodules were noted in the LUL, and three patients were noted to have residual nodules in the LLL. It was noted that most postoperative nodules were located in the right lung, with a distribution pattern that showed RUL (n=8), RML (n=5) and RLL (n=5) nodules. Findings were similar in patients with and without HIV infection.

A positive outcome was defined as persistently negative sputum cultures following surgery. This composite sputum culture outcome could not be defined upon inspection. There was no association between this composite sputum culture outcome and the presence of nodules, either pre-operatively (p=0.73) or postoperatively (p=0.52). In addition, neither HIV status (p=0.7) nor the site of resection (p=0.37) were associated with a poor sputum culture outcome.

Discussion

According to the World Health Organization in 2015, there were an estimated 10.4 million new TB cases worldwide, with 11% of patients HIV-positive.[5] TB, and especially DR-TB, remains a global health challenge, with high treatment costs. Due to the global burden of disease and the low cure rates of DR-TB with medical therapy alone (especially XDR-TB), there is renewed interest in adjuvant surgical therapy.

Previous studies have analysed the outcomes of adjuvant lung resection in patients with DR-TB and HIV co-infection. The perioperative radiological distribution of disease and the significance of the unresected pulmonary nodules have not been previously investigated.[6] Cha *et al.*[7] found that the predominant radiological features in HIV-negative XDR-TB patients were cavities and nodules. This study aimed to determine if the perioperative presence of pulmonary nodules had any clinical or microbiological significance.

In this study, patients were mostly young, with more than half of the patients living with HIV. The prevalence of HIV in this study was 57.4%, with the majority of these infections occurring in women, which was similar to findings in a previous study by Lomtazde *et al.*[8] A study of XDR-TB in SA found that 73% of the cohort was HIV co-infected, and 61% received combined ART, with a reported treatment success rate of 22%.[9]

All patients in this study had severe cavitary disease, which served as the primary indication for surgery in this cohort. Resection was considered for patients with cavitary disease owing to the difficulty of antibiotics penetrating the cavity and the high number of organisms that are contained within the cavity.[10] Cavitary disease (100%) and nodules (28/47 = 59.6%) were the predominant radiological features found on radiological examination. The most frequent radiographic abnormalities in the study by Cha *et al.*[7] in patients with XDR-TB were nodules (100%), reticulonodular densities (73%) and cavities (47%). The same study showed no significant differences in imaging findings between patients with XDR-TB and MDR-TB.

Compared with previous studies of adjuvant surgery for DR-TB, this study revealed similar chest radiographic findings and a similar duration of therapy perioperatively.[11] The upper lobes were the predominant radiographic location of nodules, with 49.8% of all nodules occurring here. Similar distribution patterns were observed in other studies.[7] The distribution of pulmonary nodules on chest radiographs was also similar for both HIV-positive and -negative individuals. Badie *et al.*[12] compared the radiological appearance of pulmonary TB in groups of patients with and without HIV infection. In that study, HIV-positive patients, compared with HIV-negative patients, had more atypical features, evidenced by consolidation and military nodules with bilateral lung involvement, diffuse involvement, and middle- and lower-zone predominance(as opposed to upper lobe). The same study by Badie *et al.*[12] found CXR findings were less characteristic in HIV-positive patients compared with HIV-negative patients.

Pre-operative HRCT findings were similar to CXR findings in relation to the distribution of disease. Distribution of pulmonary nodules on HRCT was similar for HIV-positive and -negative patients.

Table 2. The number of surgically treated patients with pulmonary nodules by anatomical site (*N*=40)

Anatomical site	Preoperative, *n*	Postoperative, *n*	Resected, *n*	Cleared, non-resected, *n*	New, *n*
RUL	14	8	2	6	2
RML	8	5	1	2	0
RLL	3	5	1	0	3
LUL	9	0	4	5	0
LLL	6	3	3	1	1
Multiple sites*	28	18	6	7	3

RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe.
* Figures are lower than the column totals as some patients had nodules in more than one lobe.

As the patients in this study were required to have a suppressed HIV viral load on ART or a CD4 cell count of greater than 200 cells/µL, it is possible that this group of patients with HIV do not reflect the clinical, radiological or microbiological profiles of patients with advanced or untreated HIV. Geng *et al*.[13] found the most important determinant of radiologic patterns of parenchymal abnormalities to be immunological status based on HIV infection, rather than the TB drug-resistance pattern. Fishman *et al*.[14] found that cavitation was less frequent in patients with MDR-TB with advanced HIV, compared with HIV-negative or -positive immunocompetent patients.

We found that the majority of patients in this study were sputum culture negative at the time of surgery. This is in keeping with the emerging role of adjuvant surgery in reducing the risk of relapse in these patients, who were likely selected on the basis of their increased risk for relapse. There was no association between pre-operative sputum culture status and the presence of pulmonary nodules on pre-operative radiological evaluation. Our findings differed from those of other studies where the presence of pulmonary nodules was a reliable marker of active disease, and was the most frequent finding in sputum positive patients, whereas traction bronchiectasis and atelectasis were more frequent in the sputum negative patients.[15] Nonetheless, there is a paucity of data on the microbiological or histological profile of pulmonary nodules, and this remains an important area for future research. It was difficult to determine if the presence of nodules represented old fibrotic disease, or if they were indeed active lesions from the current DR-TB infection. The use of metabolic imaging, such as a positron emission tomography-computed tomography (PET-CT), would have been beneficial to discriminate between these possibilities, but was unfortunately impractical in our setting.[16]

Most patients with positive pre-operative sputum cultures had converted to sputum culture negative within a month of surgery, and at 2 months, cumulative culture conversion rates were 87.5%. These outcomes were similar to those of other studies of adjuvant lung surgery for DR-TB in low-TB/HIV-burden settings.[3,11] In appropriately selected patients who received early adjuvant lung resection surgery, Xie *et al*.[17] showed that high conversion rates can be achieved. The finding of higher conversion rates in surgically treated patients may be confounded by the strict inclusion criteria for surgery, and the overlap between criteria for fitness for surgery and predictors of treatment success. Indeed, it is possible that patients who are surgical candidates are likely to be in better general condition than those excluded from such interventions, therefore creating a bias for the true effectiveness of the surgery. It is unclear whether surgically treated patients are systematically different to patients within the general DR-TB cohort. However, this seems unlikely based on the comparison of baseline covariates such as median CD4 cell counts in patients managed with medical therapy alone. A study by O'Donnell *et al*.[18] that evaluated the non-surgical treatment of XDR-TB in patients with HIV infection in SA, found a median CD4 count of 200.5 cells/µL In that cohort, only 20% experienced sputum culture conversion, while 42% of patients died. The patients in our cohort had a similar degree of immunological suppression, with superior clinical outcomes.

It remains clear that there is a significant association between surgical intervention and successful outcome when compared with non-surgical treatment alone.[19] Similar culture conversion rates were achieved in patients with and without HIV infection (88.9% v. 85.7%; p=0.853). Brust *et al*.[20] similarly found that MDR-TB/HIV co-infected patients can achieve culture conversion outcomes similar to those reported in HIV-negative cohorts, albeit lower rates than those achieved in patients treated with adjuvant surgical lung resection.

Despite the negative intermediate treatment outcome based on sputum culture status, two out of the three patients with poor outcomes in this study went on to culture convert within 6 months of surgery. It is important to note that both had pulmonary nodules that remained postoperatively. Indeed, the majority of patients who were culture negative at the time of surgery, and those who achieved satisfactory outcomes post-surgery, had residual nodules on postoperative imaging. It is unlikely that pulmonary nodules should serve as entities of surgical interest in adjuvant surgery for DR-TB.

Although this was a retrospective study of a small cohort of patients with DR-TB, it serves as one of the largest described cohorts of surgically treated patients with DR-TB. We did not evaluate excised nodules microbiologically or histologically. This remains a future area of interest. Residual nodules following lung surgery were not evaluated further. The use of 2-deoxy-2-(18F)fluoro-D-glucose (FDG)-PET scans to determine activity of these nodules may be useful going forward. FDG-PET may play a role in the diagnosis of active TB infection in settings where conventional microbiological methods are unavailable and holds particular promise for monitoring response to therapy, particularly in MDR-TB and extra-pulmonary TB.[16] The next priority should be to determine the impact of residual pulmonary nodules on final treatment outcomes, and on the risk for disease relapse.

Limitations

Although this is currently the largest study of the impact of pulmonary nodules in patients with DR-TB treated by adjuvant lung resection, we recognise several noteworthy limitations. The retrospective design of this study meant that all patient data originated from programmatic medical records, and that imaging was neither protocoled, nor standardised. Nonetheless, a unit protocol existed to ensure the timing of images during the postoperative period, and all images were performed at a single radiology service with standard operating procedures for all radiological examinations. Similarly, sputum culture assessments were not performed under research conditions, but were conducted under programmatic conditions within an accredited medical laboratory. Studies of surgery for DR-TB all invariably suffer unavoidably from selection bias, as only those patients with appropriate cardiopulmonary reserve and adequate nutritional status are selected for surgery. It may be that patients undergoing resectional lung surgery are more likely to have a better pre-operative functional baseline and physiological status, and therefore experience superior treatment outcomes, regardless of any surgical intervention, than those declined for surgery based on pre-operative workup. However, studies in medically treated patients with similar baseline characteristics as patients in this study have demonstrated poorer outcomes.[9] This study evaluated only intermediate outcome using sputum culture status during a 6-month post-surgical follow-up period. Larger scale, longitudinal studies with longer follow-up, evaluating the clinical significance of pulmonary nodules on final treatment outcomes, are crucial to informing the role of adjuvant lung surgery in the treatment of DR-TB.

Conclusion

There is a paucity of evidence of the clinical significance of pulmonary nodules and cavities in DR-TB. Adjuvant surgery is emerging as a potential modality for improving treatment outcomes in these vulnerable patients. This study found no association between the presence of residual pulmonary nodules and the intermediate treatment outcome of culture conversion. It also demonstrated similarly good outcomes for HIV-positive and -negative patients. As the role of adjuvant surgery becomes more clearly defined, it will be of greater importance to determine the necessary extent of such an invasive strategy. The targeting of pulmonary nodules, for example, needs to be investigated further. However, present evidence supports the current practice of preserving non-cavitary lungs that contain pulmonary nodules

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