Pulmonary Resection for Extensively Drug Resistant Tuberculosis in Kwazulu-Natal, South Africa

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Background. Extensively drug resistant tuberculosis (XDR-TB) has been reported in 58 countries around the world and has emerged as a major public health challenge. Our objective was to determine the impact of pulmonary resection on XDR-TB treatment outcomes in a resource-constrained setting.

Methods. We conducted a retrospective case review of 11 patients with XDR-TB who were referred for pulmonary resection between January 2007 and June 2010 at a tertiary care referral hospital in South Africa. Two pneumonectomies and three upper lobectomies were performed. Occurrence of surgical complications and TB treatment outcome were assessed.

Results. No perioperative mortality or major morbidity was noted. All patients achieved sputum conversion, with 4 regarded as “cured.” One patient defaulted on treatment, but subsequently returned and is regarded as a probable cure.

Conclusions. We describe pulmonary resection for XDR-TB management in Africa. Although the initial cohort of XDR-TB patients from Tugela Ferry demonstrated nearly complete mortality, our results demonstrate the potential of adjuvant surgical methods in XDR-TB treatment. With appropriate chemotherapy and timely adjuvant surgery, patients with XDR-TB localized to lobe or lung may achieve a “cure” with low morbidity and mortality. Consequently, this approach may be the most cost effective treatment for patients suitable for lung resection.


Extensively drug resistant tuberculosis (XDR-TB) has been reported in 58 predominantly developing countries around the world and has emerged as a major public health challenge [1]. Defined as multidrug resistant (MDR) TB, or strains of Mycobacterium tuberculosis resistant to isoniazid and rifampicin, with additional resistance to any fluoroquinolone, and at least one injectable second-line drug [2], XDR-TB reports have revealed mortality rates similar to those preceding the discovery of antibiotics [3]. Strategies to treat XDR-TB have been difficult to optimize owing to a restricted number of effective drugs, poor patient compliance, limited resources, and human immunodeficiency virus (HIV) co-infection [4]. Although treatment success rates have ranged from 34% [5] to 67% [6], the relative risk of death due to XDR-TB is 5.5 [5]. In comparison with MDR-TB, XDR-TB is associated with greater rates of treatment failure, extended hospitalization, and prolonged microbiologic conversion [7].

Improved treatment outcomes have been reported in XDR-TB patients who underwent pulmonary resection [6, 8–13]. However, few reports have come from resource-limited settings, and no study has described the surgical experience involving patients from the African continent where the TB and HIV epidemics have converged exponentially [14, 15]. We report our experience in using adjunctive pulmonary resection with individualized chemotherapy regimens for the management of XDR-TB.

Patients and Methods

King George V Hospital (KGV) is a tertiary care referral centre in KwaZulu-Natal that houses diseases of the lung and spine that are both of tuberculous and nontuberculous etiology. Medical practitioners with an interest in infectious disease treat the majority of patients with chronic pulmonary tuberculosis in sanatorium-like conditions, with traditional measures for isolation. The thoracic surgical department within the hospital has, in the last 5 years, undertaken 212 lung resections (pneumonectomy 140; lobectomy 72). Included in this cohort are a small number who underwent operative intervention for XDR and MDR-TB. A review of our experience with surgery for MDR-TB was prematurely recorded in a previous publication [16]. A retrospective review of 11 XDR-TB patients referred to KGV Hospital between January 2007 and June 2010 was conducted. During this period, 11 patients with XDR-TB were referred for pulmonary resection. Criteria for the study included patients...
with confirmed XDR-TB who underwent pulmonary resection. Data were collected on patient demographics, drug susceptibility profiles, and treatment regimens. Laboratory assessments included complete blood count, blood urea and electrolytes, albumin, and erythrocyte sedimentation rate. Preoperative diagnostic tests involved spirometry, plain chest radiography, high-resolution computed axial tomography (HRCT) scans, and, if indicated, ventilation-perfusion isotope scans.

The indications for surgery consisted of failure of a treatment regimen appropriate for XDR-TB, complications of TB sequelae such as hemoptysis or recurrent chest infections, localized disease, and adequate pulmonary reserve to tolerate resection. Open pulmonary resection was performed using established techniques as previously described [16]. Excised specimens were submitted for histology examination and microbiology culture. After surgery, the drug treatment regimen was continued for approximately 18 months, and patients were reviewed on a monthly outpatient basis at the TB clinic at KGV Hospital, a referral center that specializes in medical management of drug-resistant tuberculosis.

Treatment outcomes of cure, default, failure, and death, were designated according to the standard multidrug-resistant tuberculosis (MDR-TB) definitions [17]. Default status was defined as an interruption in treatment lasting at least 2 months in duration. Patients who demonstrated culture positivity in at least two of the five cultures in the final 12 months, culture positivity in any of the final three cultures, or based on clinical or radiographic features, were designated as treatment failures. Death was classified as resulting from any cause while on treatment. Treatment cure was considered a favorable outcome, whereas treatment failure, default, and death were considered unfavorable.

This study was approved by the Biomedical Ethics Review Committee at the University of KwaZulu-Natal.

### Results

Of the 11 XDR-TB patients referred for pulmonary resection, 6 demonstrated bilateral, extensive, cavitatory disease, and therefore did not meet the criteria for surgical intervention. Demographic features of the 5 surgical patients are presented in Table 1.

All patients demonstrated resistance to at least six drugs, and their baseline drug susceptibility profiles of the patients are presented in Table 2. Preoperative chemotherapy regimens, radiographic features, the extent of pulmonary resection undertaken, and treatment outcomes are presented in Tables 3 and 4. All patients were on an individualized chemotherapy regimen consisting of at least five drugs (median, six drugs) based on their respective drug susceptibility results. Drugs to which resistance was noted were used in regimens when no other drugs were available. Postoperative chemotherapy was continued for at least 7 months, and all patients undergoing surgery demonstrated unilateral disease. Operative procedures included pneumonectomies and upper lobectomies. There was no operative mortality, and all patients achieved culture conversion by the conclusion of the study period.

### Case Descriptions

**Patient 1.** A 36-year-old male prisoner was diagnosed with pulmonary tuberculosis in 2002. After a relapse in 2004, drug susceptibility testing confirmed MDR-TB in August 2006, followed by XDR-TB in February 2007. The patient was coinfected with HIV with an initial CD4 count of 75, managed with antiretroviral therapy, and had an undetectable viral load at the time of surgery. He was treated with a preoperative chemotherapy regimen consisting of five drugs for 4.7 months preceding surgery. Symptoms included cough and chest pain when he presented for a right upper lobectomy in April 2008. Surgery and his postoperative course were uneventful. He received 15.8 months of postoperative chemotherapy, including 6.3 months of amikacin, until he was classified as cured.

**Patient 2.** A 26-year-old woman was diagnosed with TB in 2005 and relapsed in 2006. She began a six-drug XDR-TB chemotherapy regimen for 10.8 months preceding surgery. She presented in May 2009 with bronchiectasis, cough, chest pain, and dyspnea, after which a right pneumonectomy was undertaken. The surgery and her postoperative course were uneventful, and she

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>H</th>
<th>RF</th>
<th>E</th>
<th>SP</th>
<th>KM</th>
<th>TZ</th>
<th>Z</th>
<th>ETH</th>
<th>CIP</th>
<th>OFL</th>
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<tbody>
<tr>
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<td>R</td>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
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<td>3</td>
<td>R</td>
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<td>R</td>
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<td>R</td>
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<tr>
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<td>S</td>
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<td>S</td>
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<td>S</td>
</tr>
</tbody>
</table>

CIP = ciprofloxacin; E = ethambutol; ETH = ethionamide; H = isoniazid; KM = kanamycin; OFL = ofloxacin; R = resistant; RF = rifampicin; S = sensitive; SP = streptomycin; TZ = terizidone; Z = pyrazinamide.
received 14.5 months of postoperative chemotherapy, including 13 months of capreomycin, until she was cured.

PATIENT 3. A 24-year-old nurse failed treatment after original TB diagnosis in October 2008. Drug susceptibility testing confirmed MDR-TB in February 2009, and XDR-TB in April 2009. She was maintained on a seven-drug chemotherapy regimen preceding surgery for 2.3 months before presenting with bronchiectasis, cough, and dyspnea. A right upper lobectomy was undertaken in July 2009. Her postoperative course was complicated by a right pneumothorax after the removal of a pleural drain. The pneumothorax was treated conservatively, and the patient progressively improved, with complete resolution noted on chest radiograph 1.6 months later. She received 15.4 months of postoperative chemotherapy at KGV Hospital, including 6.6 months of capreomycin, and is cured.

PATIENT 4. A 38-year-old hospital clerk was diagnosed with pulmonary TB in February 2008, and then MDR-TB in July 2008. In August 2008, drug susceptibility testing confirmed XDR-TB. She was maintained on a six-drug chemotherapy regimen for 8.1 months preceding surgery. She presented with hemoptysis, bronchiectasis, cough, and dyspnea. A right upper lobectomy was undertaken in July 2009. Her postoperative course was uneventful. She received 15.3 months of postoperative chemotherapy at KGV Hospital, including 6.6 months of capreomycin, and is still being reviewed.

PATIENT 5. A 24-year-old male student was diagnosed with TB in November 2009, failed treatment, and had confirmed XDR-TB in July 2009. Despite management with a seven-drug anti-TB regimen for 10 months, he remained culture positive, and reported persistent dyspnea. A right upper lobectomy was performed without incident in May 2010, and sputum culture obtained in June 2010 was negative. He subsequently returned to follow-up, continued 7 months of postoperative therapy, and has remained culture negative.

Comment
In this study, we describe excellent clinical and microbiologic outcomes using adjuvant pulmonary resection for XDR-TB management. All of the patients successfully achieved sputum conversion and obtained favorable treatment outcomes. This cohort did not experience any complications other than a pneumothorax, which was not directly related to the surgery. The use of pulmonary resection for XDR-TB has been previously described, but has been reported to be complicated by bronchopulmonary fistulas, empyema, postpneumonectomy syndrome, and less favorable treatment outcomes [12].

The selection of suitable surgical candidates warrants further discussion. Ideally, the patient should be nutritionally sound (as assessed by standard anthropometric tests, body mass index, and serum albumin) and in

### Table 3. Summary of Imaging Findings in Patients With Extremely Drug Resistant Tuberculosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Chest Radiograph</th>
<th>HRCT Scan</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shrunken, cavitat RUL</td>
<td>Shrunken, cavitat RUL</td>
<td>Right upper lobectomy</td>
</tr>
<tr>
<td>2</td>
<td>Tightly shrunken, bronchiectatic RLL; scattered bronchiectasis of upper and middle</td>
<td>Parenchymal RUL, occasional “tree-in-bud”; middle = bronchiectasis + “tree-in-bud” + cavity</td>
<td>Right pneumonectomy</td>
</tr>
<tr>
<td>3</td>
<td>Shrunken, bronchiectatic RUL</td>
<td>Shrunken, bronchiectatic RUL</td>
<td>Right upper lobectomy</td>
</tr>
<tr>
<td>4</td>
<td>Shrunken, cavitat LUL</td>
<td>Shrunken, cavitat LUL; cavity in apical lower</td>
<td>Left pneumonectomy</td>
</tr>
<tr>
<td>5</td>
<td>Shrunken, cavitat RUL</td>
<td>Shrunken, cavitat RUL</td>
<td>Right upper lobectomy</td>
</tr>
</tbody>
</table>

* “Tree-in-bud” pattern is the characteristic computed tomography scan appearance of numerous, small, centrilobular nodules of soft tissue attached to linear branching structures, representing obliteration of small airways, typically by caseous material in tuberculosis.

HRCT = high-resolution computed axial tomography; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe.

### Table 4. Preoperative Chemotherapy, Operative Procedures, and Treatment Outcomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Regimen</th>
<th>Duration, Months</th>
<th>Operative Procedure</th>
<th>TB outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>E, Z, ETH, TZ, OFL</td>
<td>4.7</td>
<td>Right upper lobectomy</td>
<td>Cure</td>
</tr>
<tr>
<td>2</td>
<td>E, Z, ETH, CYC, CAP, PAS</td>
<td>10.8</td>
<td>Right pneumonectomy</td>
<td>Cure</td>
</tr>
<tr>
<td>3</td>
<td>E, Z, ETH, MOX, TZ, CAP, PAS</td>
<td>2.3</td>
<td>Right upper lobectomy</td>
<td>Cure</td>
</tr>
<tr>
<td>4</td>
<td>E, Z, ETH, CYC, CAP, PAS</td>
<td>8.1</td>
<td>Left pneumonectomy</td>
<td>Probable cure</td>
</tr>
<tr>
<td>5</td>
<td>E, Z, ETH, MOX, TZ, CAP, PAS</td>
<td>10.1</td>
<td>Right upper lobectomy</td>
<td>Probable cure</td>
</tr>
</tbody>
</table>

CAP = capreomycin; CYC = cycloserine; E = ethambutol; ETH = ethionamide; MOX = moxifloxacin; OFL = ofloxacin; PAS = paraaminosalicylic acid; TB = tuberculosis; TZ = terizidone; Z = pyrazinamide.
satisfactory general condition, essentially able to withstand major thoracic surgery. A range of investigations, including biochemical measurement of acute phase reactants (C-reactive protein, erythrocyte sedimentation rate) and spirometry, were used to estimate disease activity (an erythrocyte sedimentation rate of >70 may indicate active disease) and pulmonary reserve (postoperative predicted forced expiratory volume of air in 1 s of >800 mL) [18], respectively. Radiographically, the distribution of lung disease was established by use of plain chest radiography and HRCT scan. The surgical approach to drug-resistant tuberculosis is analogous to that of malignancy, namely, the resection of all macroscopically involved lobes or lung segments and a sensitive drug regimen to treat microscopic residual disease conservatively. Radiographic and surgical pathology confirm that the microbiologic disease burden within cavitatory and bronchiectatic lung far exceeds that within nodules ($10^7$ to $10^8$ organisms versus $10^2$ to $10^4$ organisms) [19], thereby providing an opportunity for the use of pulmonary resection in tuberculosis management. Figures 1 and 2 illustrate examples of the radiographic manifestations of the XDR-TB patients involved in this study. Although these features are not pathognomonic of drug-resistant TB, they demonstrate evidence of sequelar TB (bronchiectasis and cavitation) and active parenchymal TB (“tree-in-bud” nodules). The aggressive surgical attitude should thus be tempered by an individualized, pragmatic approach incorporating nutritional status, pulmonary reserve, HRCT features, and anticipated pleural space problems in association with insufficient residual lung volume.

The principles for lung resection outlined by Naidoo and Reddi [16] for MDR-TB and inflammatory lung disease were applied to the resection in the 5 patients with XDR-TB in this study. In our view, the role of video-assisted thorascopic surgery is extremely limited for a variety of reasons in this cohort, and thoracotomy is our preference. An adherence to the simple principles of anastomotic technique, namely, a tension-free suture line, maintenance of adequate tissue blood supply, and membranous flap closure for pneumonectomy, made bronchial stump closure with absorbable interrupted sutures without a muscle pedicle feasible in all our cases.

Although the timing of surgery in XDR-TB management has not been established, Iseman and coworkers [20] recommended at least 3 months of preoperative chemotherapy. In our study, the duration on preoperative chemotherapy ranged from 2.3 to 10.8 months. The findings from our study support early surgical intervention in appropriately selected patients followed by postoperative chemotherapy to promote healing of the bronchial stump and remove residual parenchymal disease, which may be present preoperatively or as a result of contralateral contamination or “spill.” A conservative approach to surgical intervention in patients with active tuberculosis is unnecessary, and, paradoxically, persistent sputum positivity remains a strong indication for surgery to appropriately selected candidates with drug resistant TB [21].

This is the first report of its kind from Africa, which has the highest incidence of TB in the world. According to WHO data, approximately 69,000 cases of drug-resistant TB emerged in Africa 2008, with rates in some southern African countries at least five times higher than those of India and China [1]. South Africa is one of the high TB burden countries, and nearly 72% of TB patients are coinfected with HIV. Indeed, the original cohort of XDR-TB patients from Tugela Ferry were coinfected with HIV and demonstrated mortality approaching 100% [3]. Subsequent reports have confirmed the high early mor-

Fig 1. The plain chest radiograph of patient 4 is shown, demonstrating shrinkage and cavitation of the left upper lobe with the suggestion of a cavity on the left lower lobe.

Fig 2. High-resolution computed axial tomography scan confirms bronchiectasis and cavitation of the left upper lobe. In addition, the cavity in the apical segment of the left lower lobe is further illustrated. The presence of cavitary disease generally necessitates excision of the affected lobe.
tality, increased adverse events, and poor treatment outcomes experienced by HIV/XDR-TB patients [22, 23].

Patient 1 who was coinfected with HIV was successfully managed with antiretroviral therapy, achieved sputum conversion, and eventually a TB cure. In South Africa, all patients coinfected with drug-resistant strains of TB and HIV have been able to qualify for antiretroviral therapy, regardless of CD4 count, since April 2010. In addition, there is increasing coordination of TB and HIV services within correctional services. Our findings support the notion that with effective integration of HIV and TB services, disease coinfection does not necessarily imply a short, lethal, inexorable course.

According to WHO data, female TB patients in South Africa are 1.2 times more likely to exhibit drug resistant strains of *M tuberculosis* [24]. In addition, 2 of the female patients in this study were health care workers, both of whom had a previous history of pulmonary TB before being diagnosed with XDR-TB. Similar to recent reports of drug-resistant tuberculosis in South African health care workers [25, 26], XDR-TB in the health care workers of this study did not appear to be associated with HIV infection. Considering their sex and occupation (nurses are more likely to be female), nosocomial acquisition of XDR-TB is likely [27]. However, without molecular epidemiologic methods, it was not possible to determine the transmission dynamics of the infections. As health care workers are continuously exposed to patients, in addition to their families and communities, it is imperative that hospitals improve infection control measures through policies that reduce the spread of tuberculosis, especially drug-resistant strains of *M tuberculosis*.

Several limitations of our study warrant further discussion. First, as a retrospective chart review, the results are dependent upon previously recorded information, which may be influenced by incomplete data and recorder bias. Second, patients were required to meet stringent criteria before surgery could be performed, resulting in the small number of patients in this single-arm study. Furthermore, as XDR-TB was defined in 2006, prior resections may have been undertaken in patients with XDR-TB that were simply labeled MDR-TB.

In conclusion, although XDR-TB has been associated with high mortality and treatment failure rates, our results show the potential for effective adjuvant surgical methods in a group of highly selected patients with XDR-TB. Despite the discussed limitations, we are confident that appropriate pharmacologic and surgical intervention, coupled with early diagnostics and proper infection control measures, can reduce the burden of the XDR-TB. Increased communication between pulmonary physicians and thoracic surgeons may also enhance the capacity of XDR-TB management, as early surgical intervention may be appropriate for patients with persistent sputum positivity. Future studies should focus on long-term assessment of the South African cohort that has undergone surgery. In addition, prospective studies comparing chemotherapy with combined pulmonary resection and chemotherapy would provide more conclusive evidence of the efficacy of surgery in managing XDR-TB.

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References


INVITED COMMENTARY

With respect to tuberculosis (TB), Sir John Crofton, in 1959, the lead investigator of the study that confirmed combination therapy [1] as being necessary for TB, stated: “The greatest disaster that can happen to a patient with tuberculosis is that his organisms become resistant to two or more of the standard drugs. Fortunately we can prevent the emergence of drug resistance in virtually all cases if we take enough trouble to ensure that the best drug combinations are prescribed and that the patient takes them as directed” [2].

Unfortunately, the concern raised by Crofton more than 50 years ago has not been learned, and the problem of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), are becoming more prominent. TB is a slow, indolent disease for which chest roentgenograms and sputum cultures are not done daily to measure progress. It is exactly this scenario of a slow, indolent, but often progressive disease, managed by overworked physicians in short supply, in parts of the world where medical infrastructure is lacking, that MDR-TB and XDR-TB thrive and patients slip though the cracks of treatment management. XDR-TB raises the specter of a global TB epidemic, which is difficult to treat and will jeopardize gains made in the global treatment of TB.

Effective treatment for MDR-TB takes 2 years, is more toxic than standard therapy, and is at least 100 times more expensive than treatment for sensitive organisms. XDR-TB disease, however, has very little treatment options, and the scenario is obviously worse. Despite difficulties in understanding the impact of this disease in these predominantly Third World countries, there are very well documented studies on outcomes in MDR-TB and XDR-TB, particularly from South Korea. In all analyses comparing MDR-TB and XDR-TB, the results are better in less resistant patients in terms of treatment success, death, and median survival [3].

This article [4] is of only a small series with excellent results, and a reader may wonder why it is being published. There are several reasons. First, there are very few reports of surgical management of XDR-TB in the thoracic surgical literature. Second, it is quite possible that the scenario of surgical resection for XDR-TB may become more common for reasons that have been alluded to. Third, the patients are derived from an area where human immunodeficiency virus-1 (HIV-1) infection is very prevalent. About 80% of patients with active TB in the province of KwaZulu-Natal are also seropositive for HIV-1. The authors cite a cohort of patients with XDR-TB and HIV-1 from Tugela Ferry, approximately 100 miles north of Durban, where 52 of 53 patients died within 210 days of diagnosis—a frightening scenario [5].

The main lesson from this article, however, is that treatment for TB requires attention to details. It behooves us as physicians to manage these patients properly; by doing so, we may hope that the need for surgical resection will remain low.

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