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Pulmonary resection in the treatment of 43 patients with well-localized, cavitary pulmonary multidrug-resistant tuberculosis in Shanghai

Boxiong Xie[†], Yang Yang[†], Wenxin He, Dong Xie and Gening Jiang*

Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

* Corresponding author. Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, No. 507 Zhengmin Road, 200083 Shanghai, China. Tel: +86-21-65115006; fax: +86-21-65111298; e-mail: jgn1121@163.com (G. Jiang).

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Abstract

OBJECTIVES: Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis resistant to at least isoniazid and rifampicin *in vitro*, poses a significant challenge to the control of TB worldwide. Despite global efforts to control tuberculosis, it remains the leading cause of death from an infectious agent. Although modern tuberculosis treatment relies on chemotherapy, surgery is accepted as adjuvant treatment for multidrug-resistant tuberculosis.

METHODS: In a retrospective cohort study, 43 MDR-TB patients (28 males and 15 females: mean age 45.3 years) who underwent pulmonary resection between January 1993 and December 2011 were reviewed. Every patient with well-localized, cavitary lesions showed sputum-positive preoperatively. Individually tailored treatment regimens were selected at a once-weekly staff conference following review of the patient's case history and drug susceptibility results. The variables that affected treatment outcomes were identified through multivariate regression analysis.

RESULTS: There was no surgical mortality. Forty (93.0%) patients demonstrated sputum conversion and/or remained negative after surgery. Each patient had completed treatment, and during a mean of 81 follow-up months (range 18–214 months), 1 patient relapsed. This patient was cured after another course of treatment. Operative procedures included 30 (69.8%) lobectomies, 2 (4.7%) bilobectomies, 8 (18.6%) pneumonectomies and 3 (6.98%) lobectomies plus segmentectomy. There were no operation-related deaths, and there were five major postoperative complications (11.6%). Overall, 40 of 43 (93.0%) MDR-TB patients remained free of TB following surgery. The duration of chemotherapy before surgery had correlation with postoperative outcome ($P = 0.001$).

CONCLUSIONS: The proper selection of the patients and early decision for surgical intervention can achieve a high success rate of pulmonary MDR-TB with well-localized pulmonary cavities.

Keywords: Surgery • Tuberculosis • Multidrug resistant • Pulmonary cavity

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), defined as bacillary resistant to at least isoniazid and rifampicin *in vitro*, poses a significant challenge to the control of TB worldwide. According to the World Health Organization (WHO), in 2008, there were an estimated 8.9–9.9 million (about 141 per 100 000 population) incident cases of TB, and 1.55–2.32 million deaths from TB [1]. The total TB resistant rate is 20.0%, among these, the multidrug-resistant rate was 5.3% and TB incidence still increased by 1% per year. Despite global efforts to control TB, it remains the leading worldwide cause of death from an infectious agent [2–4]. China is one of the 22 TB high-burden countries with the number of patients ranking second in the world, after India, which ranks first. In Shanghai, TB remains a major public health problem. Six thousand eight hundred and eighty-one (30/1 000 000) newly diagnosed TB cases were reported in 2010 by the Shanghai Municipal Health Bureau. Although modern TB treatment relies on chemotherapy, timely resectional surgery has a distinct adjunctive role in the management of MDR-TB in selected patients [5]. Cavitation on the chest radiographs and computed tomography (CT) has been found to be common among persons afflicted with MDR-TB, particularly when occurring in multiples [6]. Moreover, there is no consensus regarding which patients should undergo surgical resection. The aim of the current study was to elucidate the indications and the role of pulmonary resection in the treatment of patients with well-localized, cavitary pulmonary MDR-TB. We here report our experience with this treatment approach.

[†]These authors contributed equally to this work.

PATIENTS AND METHODS

This was a prospective case study. All patients were treated in the Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, China. The hospital is an 825-bed facility that serves as a TB-only treatment centre for the TB patients in Shanghai. Approximately 98% of hospitalized patients have pulmonary disease, and about 4000 TB cases were treated by the centre annually, of whom 10.2% were MDR-TB patients. Some of these patients had previously been treated at other hospitals and were subsequently referred to the centre for further management. All drug susceptibility tests were performed in the centre's mycobacteriology laboratory.

From January 1993 to December 2011, there were 43 consecutive patients undergoing pulmonary resection for the treatment of MDR-TB with well-localized, pulmonary cavities. In the same period, 22 213 general thoracic procedures were performed and 11.7% of these were pulmonary TB. The Shanghai Scientific Committee approved and provided financial aid to formulate the protocol of the current project. A team of surgeons and nurses trained in the management of MDR-TB monitored the patients' progress during and after hospitalization. Consultation with specialists was available as needed. Treatment was monitored for all patients using monthly sputum smears, cultures and chest radiographs during treatment and twice yearly thereafter.

Cure was defined as the completion of treatment and at least five consecutive negative cultures from samples collected during the final 12 months of treatment. If only one positive culture was reported during that time, and there was no concomitant clinical evidence of deterioration, a patient could still be considered cured, provided that this positive culture was followed by a minimum of three consecutive negative cultures, taken at least 30 days apart. Treatment failure was defined as greater than or equal to two of the five cultures recorded in the final 12 months being positive, or any one of the final three cultures being positive, as recently suggested. Relapse was defined as the recurrence of positive smear or culture after the achievement of a cure.

Patient records were reviewed for the following information: age, sex, concomitant disease(s), prior treatment history and medication received, results of acid-fast smear and culture of sputum, drug susceptibility results, other laboratory results, continuous months of chemotherapy before surgery, operation procedure and complications as well as final outcome. Chest radiographies were read by 5–9 of our group. Human immunodeficiency virus (HIV) infection was routinely tested for the latter two-thirds of this group. Based on the negative results and the follow-up history, it was felt that the possibility of HIV infection among these MDR-TB patients was very low.

Among the 43 cases, 28 (65.1%) were male. Their mean age was 45.3 (17–69) years. The patients had received a median (range) of 5.2 (3–9) anti-TB drugs during a median (range) of 11.3 (3–102) months before the surgery. The *Mycobacterium tuberculosis* isolates from these patients were resistant to a median (range) of 5 (2–11) drugs. Their demographic and clinical characteristics are summarized in Table 1. At the time of operation, all patients were *M. tuberculosis* culture positive and had more than one cavitary lesion in the chest radiographs. Major preoperative clinical manifestations included coughing in 26 patients, chest pain in 3, expectoration in 12, haemoptysis in 14, chest distress in 5, weight loss in 31 and fever in 8.

Preoperative examinations included full blood analysis, biochemistry, arterial blood gas analysis, electrocardiogram, spirometry, acid-fast sputum smear, culture and drug sensitivity testing, chest roentgenogram and CT as well as fiberoptic bronchoscopy.

There are seven strict selection criteria for adjunctive surgery in this study.

Table 1: Demographic and clinical characteristics of the 43 patients

	Average	% of 43	Minimum–maximum
Age	45.3		17–69
Male	28	65.1	
Female	15	34.9	
Presence of underlying diseases (%)	12	27.9	
Diabetes	4	9.3	
Cardiovascular disorders	4	9.3	
Chronic liver diseases	3	7.0	
COPD or other lung diseases	2	4.7	
Side			
Right/left	24	55.8	
Left	19	44.2	
Family history			
Deaths because of pulmonary tuberculosis	4	9.3	
Symptom			
Cough	26	60.5	
Chest pain	3	7.0	
Expectoration	12	27.9	
Haemoptysis	14	32.6	
Chest distress	5	11.6	
Systemic symptoms			
Weight lost	31	72.1	
Fever	8	18.6	
Radiographic characteristics			
Presence of cavity	43	100.0	
Presence of cavity beyond the range of resection	2	4.7	
Confined to one lobe	30	69.8	
Confined to one lung and beyond one lobe	13	30.2	
Single cavity	36	83.7	
Two or more cavity	7	16.3	
Operative procedures			
Lobectomies	30	69.8	
Bilobectomies	2	4.7	
Pneumonectomies	8	18.6	
Lobectomy plus segmentectomy procedures	3	7.0	
Drug-resistant			
Number of resistant drugs	5		2–11
Duration of chemotherapy before surgery (months)	11.6		3–102
Persistent positive			
Mycobacterium tuberculosis culture before surgery	43	100.0	

COPD: chronic obstructive pulmonary disease.

(i) Drugs tolerated include at least isoniazid and rifampin, as revealed by *in vitro* susceptibility testing. The disease is so severe or extensive that there is a high probability of failure or relapse with medical therapy alone.
(ii) Persistent positive sputum smear and existence of cavity after anti-tuberculous chemotherapy for at least a 3-month period (WHO).
(iii) Disease is confined to one lung or even in one lobe with a well-localized, pulmonary cavity that can be recognized by imaging.
(iv) Disease can be resected with the expectation of adequate cardiopulmonary reserve post-surgery.
(v) Repeated haemoptysis or progression of disease despite second-line therapy.

(vi) Treatment regimen had been composed of at least four effective drugs to diminish the mycobacterial burden.
(vii) Need to exclude endobronchial TB by bronchoscopy preoperation.

For all cases included in the study, we conducted drug susceptibility testing for first-line drugs on admission, using BACTEC MGIT 960 and the proportion method. On the basis of the following drugs and concentrations (final concentration in MGIT tubes): isoniazid 0.1 µg/ml, rifampicin 1.0 µg/ml, ethambutol 5.0 µg/ml and streptomycin 1.0 µg/ml, resistance was indicated by >100 growth units and susceptibility was determined by <100 growth units. Treatment was directly observed during the hospitalization period, and drugs were self-administered after discharge.

Surgical resection was performed by a posterolateral or axillary thoracotomy under general anaesthesia. Double-lumen endobronchial intubation was routinely used. Extrapleural dissection was performed whenever there were firm adhesions. If pleural contamination did occur, the chest cavity was thoroughly washed with 0.25% neomycin solution plus 1:20 iodophor solution and saline. Anti-TB medications were continued for a median (range) of 12 (9–24) months after the surgery.

To identify the risk factors for an unfavourable outcome after surgery, we divided the 43 patients into two groups. The success group ($n = 35$) consisted of those patients who showed negative sputum smears and cultures without further therapy after surgery. The unfavourable group ($n = 8$) included those who showed positive sputum smear results postoperatively, or had further treatment for major postoperative complications. We applied multivariate regression analysis to assess the effects of different factors on the outcome after surgery. Probability values of <0.05 were considered significant.

RESULTS

Various complications were observed in 10 (23.3%) patients, and there were five major postoperative complications, including 2 patients with postoperative intrathoracic bleeding necessitating re-exploration, 2 with bronchopulmonary fistula (BPF) + empyemas, and 1 chronic tuberculous empyema occurred without fistula. The patients with BPF + empyemas were treated by closed drainage, and medical treatment was administered together with careful pleural irrigation using 0.25% neomycin solution and metronidazole solution alternatively twice a day until the patients were stable. The other 5 patients, comprised 2 patients with prolonged pulmonary air leak, 1 with recurrent laryngeal nerve damage, 1 with respiratory failure requiring mechanical ventilation for 19 days and 1 with supraventricular arrhythmia. There were no surgery-related deaths (Table 2).

Table 2: Postoperative complications in 10 (27.8%) patients

Complications	*N*	%
Intrathoracic bleeding necessitating re-exploration	2	5.56
Bronchopulmonary fistula + empyema	2	5.56
Chronic tuberculous empyema without fistula	1	2.78
Prolonged air leak	2	5.56
Recurrent laryngeal nerve damage	1	2.78
Respiratory failure requiring mechanical ventilation	1	2.78
Supraventricular arrhythmia	1	2.78

Sputum negativity was achieved in all but 3 (93.0%) patients. One patient achieved sputum negativity in the eighth postoperative month. Forty-three patients were followed up for a median period of 81 (range 18–214) months. One relapse was observed throughout the follow-up period due to taking anti-TB drugs irregularly after operation, but this patient recovered after re-medication.

Patients were followed up postoperatively at the outpatient Department of Shanghai Pulmonary Hospital. Patients underwent sputum examination monthly until two consecutive negative smears were obtained, then every other month for 6 months, and every 6 months thereafter. Patients underwent chest roentgenogram each month for 3 consecutive months, once at 6 months and every 6 months thereafter. As of December 2009, follow-up ranged from 18 to 214 months, and no patient has been lost to follow-up.

We applied multivariate regression analysis to assess the effects of different factors on the outcome after surgery, which showed that only the duration of chemotherapy before surgery had a correlation with postoperative effects ($P = 0.001$); the unfavourable group had longer preoperative therapy.

COMMENT

The incidence of MDR–TB has increased considerably all over the world [7]. It still continues to be a serious health and economic problem, particularly in developing countries. The WHO has expressed deep concern that a worldwide epidemic of MDR–TB appears imminent [8]. Due to the high mobility of the floating population, the diagnosis of those with TB suspicious symptoms is very difficult, and only 20% of TB patients can be treated in Shanghai. In addition to prevalence, China still faces the rapid growth of MDR-TB. According to a national baseline survey of drug-resistant TB, the MDR rate of the new TB patients is 8.32%, and the XDR rate is 0.68%. The MDR rate of TB patients in China is 6.8%, which is a serious situation compared with other countries.

Cavitation is the most typical manifestation of MDR-TB (40–80%). TB cavity is due to the large population of tubercle bacillus, which damages local lung tissue, after which caseous necrosis occurs. The lesion deliquesces and perforates the bronchus, necrotic material is coughed from the bronchial and air enters to form the cavity.

The main treatment for TB is medical. More than 90% of TB cases can be treated by new chemotherapeutics. However, medical treatment alone fails in 20–40% of the MDR–TB patients [7]. Facing the challenge of MDR-TB, surgical intervention for the treatment of pulmonary TB, having been relegated to the distant background for decades, may now play a role once again. For selected pulmonary MDR-TB patients with localized disease, the combination of pulmonary resection and second-line anti-TB agents has been previously reported to achieve a very favourable outcome [5]. Surgery for MDR-TB can be considered as a neoadjuvant procedure to remove a major, focal burden of tubercle bacilli contained within necrotic and non-viable lung tissue. Incomplete resection of tuberculous lesions, particularly cavities, but also nodules, bullae, microcavities or fibrotic areas, is one of the risk factors for disease relapse [9].

The timing of surgery is crucial for postoperative mortality, morbidity and the chance of cure. In patients with well-localized MDR-TB, cavitary pulmonary TB can progress extensively and may result in deterioration of lung function. The best time for surgery is the period with the least number of bacilli. This occurs ∼3 months after the start of a new regimen. Lalloo *et al.* [10] also pointed out that timely surgical intervention was necessary in order to prevent the spread of MDR-TB and to protect the remaining normal lung. For the same reason, we advocate that if a diagnosis of MDR-TB is established, no highly effective anti-TB agents are available, and symptoms are progressive, lung resection should be considered to prevent further damage to the lungs [11].

For patients with cavitary, we hypothesized from the literature [12, 13], well-localized TB that is radiographically confined to the portion of lung that is removed, microscopic populations of organisms remaining in the lung(s) after surgical resection might be very few. Our results demonstrate that postoperative drug therapies including these and other first-line agents can successfully inhibit the growth of any residual infection in such carefully selected MDR-TB patients and lead to durable cure. The duration of postoperative chemotherapy should be based on MDR-TB-sensitive drugs to determine individual programmes, and the course should not be <18–24 months.

Surgical complications for TB patients will continue to represent a challenge to practicing thoracic surgeons. As for the morbidity in our study, major complications developed in 5 (11.6%) patients, which was similar to the report by Reed *et al.* [14], and a higher incidence of total complications ranging from 20 to 46% was reported [14, 15]. Complications of surgical resection mainly include respiratory failure, bronchopleural fistula, lung and other infections, empyema, wound bleeding and/or breakdown as well as recurrent laryngeal nerve palsy. Therefore, ventilation/perfusion scan, pulmonary function tests and CT of the chest are important investigations for preoperative assessment.

Postoperative BPF is a cause of significant morbidity and potential mortality in patients with TB. The incidence of this complication ranges from 0 to 16.7% [4, 5].

The management of the bronchial stump is still controversial to a certain extent. Bronchial stump reinforcement is aimed at preventing stump breakdown and bronchopleural fistula formation, with or without space infections [10]. Studies have shown that a vascularized pedicled muscle, pleura or pericardial flap is most frequently used for bronchial stump reinforcement in order to reduce the incidence of BPF [7, 16, 17]. Van Leuven *et al.* [18] did not advocate routine bronchial stump reinforcement except for sputum-positive patients. They also believed that preserving blood supply to the bronchus was crucial to the healing of the bronchial stump, and as such warned against dissection to the point of devascularization of the bronchus and specifically against using electric coagulation around the bronchus. Meanwhile, the possible residual dead space should be eliminated to avoid local infection. If the treatment for bronchial stump was not satisfactory, the inhalation of anti-TB drugs, capreomycin, etc., might be used in the perioperative period in order to prevent the emergence of fistulae.

Closure of the bronchial stump, either by stapler or manually, is still controversial. We preferred to reinforce the bronchial stump with live tissues after pneumonectomy in all cases. All bronchi were closed manually.

On the other hand, endobronchial TB is one of the significant risks leading to postoperative BPF and empyema. For this reason, it is also important to exclude endobronchial TB by preoperative bronchoscopy for MDR-TB patients. Many scholars have put forward a similar view. Park *et al.* [19] retrospectively studied lung resection for MDR-TB and found that endobronchial TB was a risk factor for developing post-pneumonectomy BPF. On the basis of the above hypothesis, frozen section pathology should be performed on the resected bronchial stump to make sure that no *M. tuberculosis* remains in it. Therefore, if the endobronchial TB bronchial segment cannot be removed completely, then surgery is not a good choice, as lung cancer surgery requires a negative residual bronchial stump. At the same time, we recommend the removal of apparently affected peri-bronchial lymph nodes to reduce the chance of empyema and BPF, because *M. tuberculosis* in the regional lymph may retain some activity and could cause relapse of disease when conditions are favourable. On the contrary, we do not disrupt seemingly normal lymph nodes because we want to preserve the vasculature around the bronchial stump.

Although surgery is controversial for sputum-positive cases, recent studies advocate surgical resection if the patient has a cavitary lesion or destroyed lung or lobe. The reasons for resection in patients with cavitary lesions are the difficulty of antibiotic penetration and the number of organisms contained within the cavity, which may be as high as 10^7–10^9 organisms per cavity [7]. For these reasons, it is important to resect all cavitary lesions and destroyed lungs and lobes, leaving no grossly diseased parenchyma behind. Moreover, MDR-TB patients usually have very dense adhesions [16]. Hence, we preferred extrapleural dissection in all patients to prevent contamination of thorax through rupture of the cavity.

However, factors affecting treatment success among MDR-TB patients are still under investigation. In-hospital perioperative mortality in our study was 0%, with a 5.56% incidence of BPF. We consider that postoperative individualized chemotherapy is mandatory for MDR-TB patients even after the removal of the most grossly involved lesions, to ensure long-term cure [20].

Through our analysis, only the duration of chemotherapy before surgery had a correlation with postoperative effects ($P = 0.001$). Average preoperative antibiotic use of the successful group lasted 7.3 months, while the time of the unfavourable group was 28 months. As such, we believe that the longer the use of preoperative antibiotics lasted, the greater the negative impact on the results of operations. It may be attributed to fact that the long-term application of antibiotics enhanced the resistance of TB, and the long-unhealed disease also increased the damaged lung tissue of patients, which are detrimental to surgical outcomes.

The success rate is relatively high compared with other reports [17, 19, 21] and could be explained by several factors. First, most patients ($n = 32$; 74.4%) included in the present study had lobectomy. Secondly, all patients were selected strictly, the disease was confined to one lung or even in one lobe with well-localized pulmonary cavity and the preoperative use of bronchoscopy ruled out endobronchial TB. Thirdly, the results could be favourable when compared with those from studies involving various indications, for example, tuberculous empyema or bilateral cavities, or those with massive haemorrhage.

Of course, this study still has shortcomings such as the small sample size, large span of study time and the fact that some patients were transferred from other hospitals, due to which they did not have a unified standard premedication, which made it difficult to obtain more instructive clinical conclusions. We hope that further future research will be improved to enhance the clinical treatment of multidrug-resistant TB.

Conflict of interest: none declared.

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