Pulmonary Resection for Multidrug-Resistant Tuberculosis: The Israeli Experience (1998–2011)

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ABSTRACT: **Background:** Multidrug-resistant tuberculosis (MDR-TB) presents a difficult therapeutic problem due to the failure of medical treatment. Pulmonary resection is an important adjunctive therapy for selected patients with MDR-TB.

Objectives: To assess the efficacy of pulmonary resection in the management of MDR-TB patients.

Methods: We retrospectively reviewed the charts of MDR-TB patients referred for major pulmonary resections as part of a treatment strategy. The operations were performed in the departments of thoracic surgery at Assaf Harofeh and Wolfson Medical Centers. For the period under study, 13 years (1998–2011), we analyzed patients' medical history, bacteriological, medical and surgical data, morbidity, mortality, and short-term and long-term outcome.

Results: We identified 19 pulmonary resections (8 pneumonectomies, 4 lobectomies, 1 segmentectomy, 6 wedge resections) from among 17 patients, mostly men, with a mean age of 32.9 years (range 18–61 years). Postoperative complications developed in six patients (35.3%) (broncho-pleural fistula in one, empyema in two, prolonged air leak in two, and acute renal failure in one). Only one patient (5.8%) died during the early postoperative period, three (17.6%) in the late postoperative period, and one within 2 years after the resection. Of 12 survivors, 9 were cured, 2 are still under medical treatment, and 1 is lost from follow-up because of poor compliance.

Conclusions: Pulmonary resection for MDR-TB patients is an effective adjunctive treatment with acceptable morbidity and mortality.

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KEY WORDS: multidrug-resistant tuberculosis (MDR-TB), pneumonectomy, pulmonary resection, lobectomy, tuberculosis

Multidrug-resistant tuberculosis, defined as the resistance of *Mycobacterium tuberculosis* to at least the two most powerful first-line anti-tuberculosis drugs, isoniazid and rifampicin, is a major challenge for health care authorities. Treatment with the second-line drugs is less effective and more toxic than the first-line drugs and patients require a longer period of treatment (18–24 months compared to the standard 6–9 months) [1]. MDR-TB may be newly acquired (primary MDR-TB) by contracting the infection from a patient already infected with the resistant strain, or it may evolve in a patient with a sensitive strain who was inadequately treated (secondary MDR-TB). Extensively drug-resistant tuberculosis, a subgroup of MDR-TB, now recognized to exist around the world, is defined as the resistance of *M. tuberculosis* to the most important second-line drugs (any one of the fluoroquinolones and at least one of the second-line injectable drugs) in addition to isoniazid and rifampicin and is more likely to be associated with the worst outcome. The estimated worldwide incidence of MDR-TB in 2010 was 650,000 with a prevalence of about 12 million cases of which 10% were XDR-TB [2-5]. The highest rate is found in Asia (56%) and Eastern Europe (20%). Medical treatment is usually not satisfactory, with an estimated mortality rate of 26%. Therefore, the option of pulmonary resection to remove a destroyed lung, lobe or segment may be offered to annihilate a great number of TB organisms that do not respond to chemotherapy. According to the recent literature, the outcome of patients with MDR-TB improved following pulmonary resections and the postoperative complication rate was low (5%–26%) [6-9].

Israel, a country of immigrants, has experienced mass immigration from countries highly endemic for tuberculosis, such as the Former Soviet Union and Ethiopia. About one million immigrants were absorbed in the 1990s and the incidence of new tuberculosis cases, especially MDR-TB strains, significantly increased. A recent study analyzed the outcome of MDR-TB in Israel [10] and found a relatively high mortality rate (30%). Poor prognosis factors were related to older age, hypoalbuminemia, alcohol consumption, high infectiousness, and XDR-TB. The aim of the present study was to report our surgical experience in the management of these patients.

MDR-TB = multidrug-resistant tuberculosis
XDR-TB = extensively drug-resistant tuberculosis

PATIENTS AND METHODS

The Pulmonary and Tuberculosis Department of Shmuel Harofeh Hospital in Beer Yaakov is the Israeli referral center for hospitalized tuberculosis patients and has all the required facilities for closed medical care and isolation. Since 1998, pulmonary resections have been performed in the Department of Thoracic Surgery of Assaf Harofeh Medical Center in Zerifin and in the last year also in the cardiothoracic surgery department of Wolfson Medical Center in Holon.

MDR-TB patients referred to surgery during the period September 1998 to September 2011 were identified. Room isolation with HEPA (high efficiency particulate air) filtration and use of appropriate masks (N95) by both health care workers and patients were the common methods used to prevent tuberculosis transmission in the general hospital. Data on patient history, medical course, comorbidity and outcome were retrospectively derived from the medical charts. Patients were referred to surgery based on a medical indication (hemoptysis, empyema) or on failure of the medical treatment (persistent positive acid-fast bacillus in the sputum).

All patients were initially hospitalized in the pulmonary and tuberculosis department of Shmuel Harofeh Hospital. The diagnosis of MDR-TB was made at the Referral National Tuberculosis Laboratory (Abu Kabir, Tel Aviv) which performs drug susceptibility tests for tuberculosis organisms according to standard practice (absolute concentration method with Löwenstein-Jensen medium).

Preoperative evaluation in all patients included chest radiography and computed tomography, full blood count, blood chemistry, blood coagulation tests and electrocardiogram. Pulmonary function tests and lung perfusion isotopic examination were performed in patients prepared for pneumonectomy, and arterial blood gas analysis in patients undergoing lobectomy/pneumonectomy.

SURGERY PROTOCOL

The type of operation was determined according to the extent of the disease. Using a double-lumen endotracheal tube and single-lung ventilation, surgery was performed with the patient under general anesthesia. After induction of anesthesia, a standard serratus muscle-sparing postero-lateral thoracotomy was performed. Patients with dense adhesions were selected for extrapleural dissection to keep their cavities intact. The bronchus was divided and closed with staples without reinforcement of the bronchial stump. We meticulously used electrocautery to stop all internal bleeding during surgery; after surgery warm saline with garamycin was used to irrigate the pleural cavity. Following pneumonectomy, a clamped 36 French chest tube was left in the chest cavity for 24 hours and unclamped intermittently to check hemostasis and maintain mediastinal position. Following lobectomy, two 36 French chest tubes (one straight and one curved) were used until there was no air leak and pleural excretions were less than 100–150 ml over 24 hours. After the operation, all patients were maintained on multidrug regimens, generally the same as their preoperative regimens, and on adequate analgesia using epidural catheters. Physiotherapy and early ambulation played an important role in the postoperative treatment of such patients. All the resected specimens were sent for pathological and bacteriological examination.

Operative mortality included all deaths that were clearly related to the operation and was defined as early mortality (30 day or in-hospital) or late mortality (within the first 6 months after surgery). All cases of broncho-pleural fistula or empyema that occurred after surgery were considered postoperative complications and together with a prolonged air leak were defined as major comorbidities.

Surgical follow-up was continued for a period of 1 year and more if needed, and pulmonology follow-up until completion of anti-TB treatment or at the study date, and included bacteriological response and survival.

Outcome was classified as cure if the patients completed at least 18 months of treatment with five negative cultures for the last year of treatment, failure if at least two cultures remained or became positive in the final 12 months of treatment, or if the patient interrupted the treatment for 2 or more consecutive months

The protocol of this study was approved by the Ethical Review Committee of Wolfson Medical Center and patients' confidentiality was respected.

RESULTS

We identified 17 patients, and their characteristics are described in Table 1. The majority of patients were immigrants from the former Soviet Union (15 of 17) and the remaining 2 were immigrants from Ethiopia. The patients, 14 males and 3 females, had a mean age of 32.9 years (range 18–61 years). By definition, all the patients were MDR-TB. No XDR-TB patient was identified in the cohort. The most common comorbidity was chronic pulmonary obstructive disease, but hepatitis infection and addiction to drugs or alcohol were also noted. All patients received individual anti-tuberculosis treatment according to drug susceptibility tests between 1 month and 2 years before surgery. Indication for surgery was medical treatment failure in 9/17 patients (persistent positive bacteriology), tuberculosis reactivation in 5 patients, moderate/massive hemoptysis in 2 patients and empyema in 1 patient. The patients were highly contagious (8 of 17 with positive AFB in the sputum at the time of surgery).

Preoperative diagnoses included cavitations in 10 patients (bilateral cavitations in 1 patient), destroyed lung with reduced lung volume and fibrosis in 5 patients and tuberculoma in 2

AFB = acid-fast bacillus

Table 1. Characteristics of MDR-TB patients

Patients	Gender/Age	Comorbidity	Treatment before surgery	Surgical indication	Surgical procedure	Complications	Outcome
1	M/57	NIDDM Hepatitis Smoker Alcohol abuse	N/A	Hemoptysis	Wedge resection RUL-LUL	No	Cure
2	F/29	No	6 mos	Treatment failure	RLL superior segmentectomy	No	Cure
3	M/61	Lung carcinoma COPD Alcohol abuse	1 yr	Treatment failure	LUL wedge resection	No	Death (24 mos)
4	M/43	COPD Alcohol abuse Smoker	2 yrs	Hemoptysis	RLL and LUL wedge resection	No	Late postoperative death
5	M/22	No	2 yrs	Treatment failure	RUL wedge resection	No	Under treatment
6	M/39	Smoker Hepatitis Alcohol abuse	1 yr	Treatment failure	RUL lobectomy	Air leak	Late postoperative death
7	M/25	No	In the past	Reactivation	RUL lobectomy	Air leak	Cure
8	M/32	Smoker	2 yrs	Treatment failure	LUL lobectomy	No	Under treatment
9	M/20	Smoker Hepatitis IVD	1 yr	Treatment failure	Right pneumonectomy	Right BPF with empyema	Early postoperative death
10	M/19	No	1 mo	Pneumothorax Empyema	Right pneumonectomy	Empyema	Cure
11	M/38	Smoker	1 yr	Reactivation	Right pneumonectomy	No	Cure
12	F/18	Smoker	2 yrs	Treatment failure	Left pneumonectomy	No	Cure
13	M/20	No	In the past	Reactivation	Left pneumonectomy	Acute renal failure	Late postoperative death
14	M/58	Smoker COPD	1 yr	Reactivation	Left pneumonectomy	No	Cure
15	M/30	IVD COPD Non-compliance	3 yrs	Treatment failure	Right pneumonectomy	No	Default
16	M/37	Smoker	1 yr	Treatment failure	Left pneumonectomy	No	Cure
17	F/36	Smoker	6 mos	Reactivation	LUL lobectomy	No	Cure

NIDDM = non-Insulin dependent diabetes mellitus, COPD = chronic obstructive pulmonary disease, IVD = intravenous drug abuse, RUL = right upper lobe, LUL = left upper lobe, RLL = right lower lobe, BPF = bronchopleural fistula

patients (in 1 patient bilateral tuberculoma). These 17 patients underwent 19 pulmonary resections (8 pneumonectomies, 4 lobectomies, 1 segmentectomy and 6 wedge resections). In two patients with cavitary lesions/tuberculoma on both sides, staged bilateral wedge resections were performed.

Postoperative complications developed in six patients (35.3%) (BPF in one, empyema in two, prolonged air leaks in two, and acute renal failure in one). The postoperative early mortality rate was 5.9% (one patient died due to BPF and empyema). The late postoperative mortality rate was 17.6% (three patients died: one from acute renal failure with fulminant pulmonary edema, one by suicide, and one due to general deterioration). One patient died 2 years after surgery due to other comorbidities. The two patients who suffered from a prolonged air leak were discharged with Heimlich valves until the leak disappeared at which point the tubes were removed. One patient with empyema without a BPF underwent re-thoracotomy with open-window three-rib thoracoplasty and continued with change of dressings in the pleural cavity two to three times a day at home after discharge for a period of one year.

Mean hospital stay in the surgical ward was 7.5 days. Of 12 survivors, 9 are cured, 2 continue to receive medical treatment and 1 is lost from follow-up.

BPF = bronchopleural fistula

DISCUSSION

The emergence of highly resistant *M. tuberculosis* around the world is responsible for the high rate of relapse and prolonged and expensive therapy [11]. Surgery offers an alternative adjuvant therapeutic approach, and a higher rate of cure with the combi-

nation of therapy has been reported [12-14]. The success of the surgical strategy was shown in a retrospective study published in 2004 by the National Jewish Medical and Research Center [8]. This study analyzed results of treatment and compared the outcome of 205 MDR-TB patients over a 14 year period (1984–1998) with that of an earlier period (1973–1983). Better outcome was strongly associated with the use of surgery combined with fluoroquinolone therapy. The overall cure rate improved from 56% to 75% and the death rate fell from 22% to 12%.

The primary goal of adjuvant resection surgery is to achieve sputum conversion in persistent sputum-positive patients. In addition, surgery has been proposed to be preventive and to reduce rates of recurrence, resulting in a treatment success rate of 63–96% (lower rate in resource-limited areas) [7,9,15-17]. Surgical resection can decrease the load of resistant bacilli, shorten and simplify anti-TB therapy, and promptly eliminate the source and spread of MDR-TB.

The main problem in AFB-positive patients is the significant rate of postoperative complications (5%–26%). These include respiratory failure, BPF, empyema, bleeding, wound dehiscence, prolonged air leak, thoracic residual space, chylothorax, and post-pneumonectomy syndrome. Mohsen et al. [14] reported a hospital mortality rate of 4.3% (one of 23 patients) with major complications occurring in 34.7% (8/23 patients). Wang and co-authors [18] reported an in-hospital perioperative mortality rate of 0% and morbidity of 25%, including a 16% incidence of BPF with the recommendation of routine bronchial stump reinforcement for AFB-positive patients only. They also believe that preserving the blood supply to the bronchus is crucial for the healing of the bronchial stump and therefore warn against dissection to the point of devascularization of the bronchus and specifically against using electric coagulation around the bronchus. Yaldiz et al. [19] reported an operative mortality rate of 7.6% and morbidity of 23% and concluded that despite high morbidity in the early postoperative period, surgery, in addition to medical therapy, offers cure rates higher than with medical therapy alone.

Our experience with 17 patients yielded a cure rate of 53%, with a total mortality rate of 29% (mostly late mortality) and morbidity in 5 patients (28.3%). The most devastating complication was a BPF with an empyema in a patient after right pneumonectomy which, despite aggressive surgery, was complicated by acute respiratory distress syndrome and ended in the death of the patient. We usually do not perform bronchial stump reinforcement after lobectomy/pneumonectomy and believe that this complication was connected to devascularization of the bronchial stump during dissection of severe adhesions, as mentioned earlier. With regard to the management of the bronchial stump, Deschamps et al. [20] noted that automatic stapling was more helpful than absorbable sutures in decreasing BPF. We do not use lymph node dissection during surgery because we want to preserve the vasculature around the bronchial stump and resume previous anti-TB treatment as soon as possible postoperatively.

In conclusion, our experience is satisfactory with a high cure rate and acceptable mortality and morbidity rates. We strongly recommend adjunctive surgery for the management of MDR-TB.

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References

1. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multi drug resistant tuberculosis: systematic review and meta analysis. *Lancet Infect Dis* 2009; 9: 153-61.
2. Multidrug and extensively drug resistant TB (M/XDR-TB). 2010 global report on surveillance and response. WHO/HTM/TB/2010.3.
3. Sotgiu G, Ferrara G, Matteelli A, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J* 2009; 33: 871-81.
4. Chiang CY, Yew WW. Multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009; 13: 304-11.
5. Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. *Lancet Infect Dis* 2009; 9: 19-30.
6. Törün T, Tahaoğlu K, Ozmen I, et al. The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2007; 11: 979-85.
7. Somocurcio JG, Sotomayor A, Shin S, et al. Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. *Thorax* 2007; 62: 416-21.
8. Chan ED, Laurel V, Strand MJ, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004; 169: 1103-9.
9. Yew WW, Leung CC. Management of multidrug resistant tuberculosis: update 2007. *Respirology* 2008; 13: 21-46.
10. Bendayan D, Hendler A, Polansky V, Weinberger M. Outcome of hospitalized MDR-TB patients: Israel 2000-2005. *Eur J Clin Microbiol Infect Dis* 2011; 30: 375-9.
11. Tahaoglu K, Torun T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001; 345: 170-4.
12. Sung SW, Kang CH, Kim YT, Han SK, Shim YS, Kim JH. Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. *Eur J Cardiothoracic Surg* 1999; 16: 187-93.
13. Kir A, Inci I, Torun T, Atasalihi A, Tahaoglu K. Adjuvant resectional surgery improves cure rates in multidrug-resistant tuberculosis. *J Thorac Cardiovasc Surg* 2006; 131: 693-6.
14. Mohsen T, Abou Zeid A, Haj-Yahia S. Lobectomy or pneumonectomy for multidrug-resistant pulmonary tuberculosis can be performed with acceptable morbidity and mortality: a seven-year review of a single institution's experience. *J Thorac Cardiovasc Surg* 2007; 134: 194-8.
15. Park SK, Lee CM, Heu JP, Song SD. A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2002; 6: 143-9.
16. Shiraishi Y, Nakajima Y, Katsuragi N, et al. Resectional surgery combined with chemotherapy remains the treatment of choice for multidrug-resistant tuberculosis. *J Thorac Cardiovasc Surg* 2004; 128: 523-8.
17. Takeda S, Maeda H, Hayakawa M, et al. Current surgical intervention for pulmonary tuberculosis. *Ann Thorac Surg* 2005; 79: 959-63.
18. Wang H, Lin H, Jiang G. Pulmonary resection in the treatment of multidrug-resistant tuberculosis: a retrospective study of 56 cases. *Ann Thorac Surg* 2008; 86: 1640-5.
19. Yaldiz S, Gursoy S, Ucvet A, et al. Surgery offers high cure rates in multidrug-resistant tuberculosis. *Ann Thorac Cardiovasc Surg* 2011; 17 (2): 142-7.
20. Deschamps C, Bernard A, Nichols FC, et al. Empyema and bronchopleural fistula after pneumonectomy: factors affecting incidence. *Ann Thorac Surg* 2001; 72: 243-7.