Adjuvant resectional surgery improves cure rates in multidrug-resistant tuberculosis

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Objective: Multidrug-resistant tuberculosis still continues to be a major health problem. Adjuvant surgical resection combined with antituberculous drug management is the most favorable treatment modality for patients with multidrug-resistant tuberculosis. In this article we report the results of surgical resections we performed during the years 1993 through 2005.

Methods: We performed 81 lung resections in 79 patients with multidrug-resistant tuberculosis. All these patients had at least 2 months of medical therapy before resection. Bronchial reinforcement was performed in 4 of the 81 operations. We present here the surgical results of the 81 procedures. Because 5 of 79 patients were lost to follow-up, we provide the medical treatment results on 74 of the patients.

Results: During this period, we performed 4 completion pneumonectomies, 39 pneumonectomies, 7 lobectomies with segmentectomy, 30 lobectomies, and 1 segmentectomy. Operative mortality was 2.5% (2/81). Bronchopleural fistula developed in 4 (4.9%) cases. Our overall cure rate was 94.5% (70/74). Relapse and treatment failure were 1.3% (1/74) and 1.3% (1/74), respectively. All but 5 patients are still under our follow-up.

Conclusions: Surgical resection of patients with multidrug-resistant tuberculosis combined with chemotherapy provides a favorable outcome. Our results will need to be validated more strongly by using randomized clinical trials that compare surgical resection plus chemotherapy with chemotherapy alone.

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Drug resistance is still a major problem in the treatment of tuberculosis. Resistance rates in Turkey are high because treatment approaches are often inadequate, rates of treatment completion are low, and therapy is not directly observed.¹

Surgical management of pulmonary tuberculosis emerged in the 19th century. Most interventions were collapse therapies, such as thoracoplasty, plombage, artificial pneumothorax, pneumoperitoneum, and phrenic nerve crush. The aim of these interventions was to deprive aerobic mycobacteria in lung cavities of oxygen. However, until the 1940s, the results of surgical resectional approaches were unsatisfactory. With the advent of chemotherapeutic agents and improvements in surgical techniques, anesthetics, and intensive care facilities, resectional surgical interventions became safer. However, management with multidrug agents, including rifampin [INN: rifampicin], has decreased the resectional surgery rate.² After the 1980s, epidemics of AIDS, immigration, intravenous drug abuse, deterioration in health

Abbreviations and Acronyms

BPF = bronchopleural fistula

MDR-TB = multidrug-resistant tuberculosis

care systems, delays in diagnosis, and inappropriate therapies led to an increase in tuberculosis cases and in multidrug-resistant disease.³ This led most physicians to offer resectional operations as an adjuvant treatment.⁴ In this article we update our previous experience in the surgical treatment of multidrug-resistant tuberculosis (MDR-TB).⁵

Materials and Methods

This study included 79 HIV-negative patients with MDR-TB who underwent 81 adjuvant resectional surgery procedures, each performed by the same surgeon (A.K.), between 1993 and 2005 in the Süreyyapasa Center for Chest Diseases and Thoracic Surgery, the major referral center for pulmonary diseases in Turkey. Of these patients, 17 were female and 62 were male. The mean age was 37.6 years, ranging between 16 and 65 years.

Chest radiographs revealed bilateral lesions in 27 (33.3%) cases, with a preponderance of cavities on one side. Resistance to at least isoniazid and rifampin was regarded as multidrug resistance. All the patients had been receiving antituberculosis therapy with various drugs for between 1 and 19 years. MDR-TB treatment protocols for all patients were designed by using at least 4 active drugs (average, 5 drugs; range, 4-7 drugs). In all cases one parenteral drug was used, either amikacin or kanamycin, or, if resistance was found to these, capreomycin.

The average preoperative treatment duration was 4.01 months (range, 2-8 months). Preoperative studies routinely included chest radiography, computed tomographic chest scans, pulmonary function tests, arterial blood gas analysis, and, if necessary, a quantitative perfusion scan. We performed bronchoscopic biopsies to rule out tuberculous bronchitis. None of the patients were cachectic, and all exhibited an appropriate nutritional status. Preoperatively, 13 (16%) patients had positive acid-fast bacilli in the sputum, and in 12 patients (14.8%) culture of mycobacterium tuberculosis was positive.

Two patients were operated on twice. In the first patient, who presented with bilateral lesions, we performed upper lobectomies. We operated on the second patient to perform a completion pneumonectomy because he relapsed 4 years after we performed a left lung upper lobectomy with a lower lobe superior segmentectomy. Four patients were operated on at other hospitals before admission to our hospital. Of these, one had a right upper lobectomy because of tuberculosis, and another had a right upper lobectomy for a carcinoid tumor. We performed right completion pneumonectomies on both these patients. Of the remaining 2 patients, one had had a standard thoracoplasty for cavitary tuberculosis, and we performed a left pneumonectomy. The final patient had had a left upper lobectomy because of MDR-TB but had relapsed 2 years later; in this patient we performed a left completion pneumonectomy.

Surgical resection was considered for all the patients after 2 months of medical treatment. The selection of patients for surgical intervention was made according to the criteria recommended by

TABLE 1. Types of pulmonary resection

Procedure	Right	Left	Total
Completion pneumonectomy	2	2	4
Pneumonectomy	11	28	39
Upper and middle lobectomy	2	0	2
Upper lobectomy with segmentectomy*	3	4	7
Upper lobectomy	12	11	23
Lower lobectomy	4	1	5
Segmentectomy	0	1	1
Total	34	47	81

*Upper lobectomy with resection of superior segment of the lower lobe.

Iseman and associates,⁴ which included (1) drug resistance with a high probability of failure or relapse; (2) sufficiently localized disease providing the resection of great preponderance of radiographically visible disease, leaving an adequate cardiopulmonary capacity; and (3) availability of adequate drug efficacy to provide rapid healing of the bronchial stump.

Operations were performed after achievement of general anesthesia with the use of a double-lumen endobronchial tube. After induction of anesthesia, we performed a serratus-sparing posterolateral thoracotomy. Either an intrapleural or an extrapleural dissection was performed, depending on the extent of pleural adhesions. Eighty-one pulmonary resections were performed (Table 1).

The bronchus was divided and closed with a stapler (n = 48) or sutures (n = 33). For suturing, we used Ethibond (Johnson & Johnson, New Brunswick, NJ) until 1997 and then polyglactin. In 4 stapled pneumonectomies the bronchial stump was reinforced with intercostal muscle, pericardial fat pad (n = 2), and mediastinal pleura, respectively. We used a linear cutter during lobectomies when incomplete fissures were present. After the operations, the patients were maintained on multidrug regimens, which were generally the same as their preoperative regimens.

Operative mortality included all deaths clearly related to the operations, regardless of the postoperative interval. Definitions of outcomes are based on the definitions of the World Health Organization⁶: *relapse* is recurrence of a positive smear or culture after a cure; *treatment failure* is persistence of positive smears or cultures, despite treatment for at least 18 or 24 months; *probable cure* is negative smears and cultures throughout treatment for at least 6 months; and *cure* is negative smears and cultures throughout at least 18 months of treatment (or 24 months in the absence of first-line drugs).

Results

Postoperative sputum was positive in 2 (2.5%) cases, and cultures were positive in 3 (3.7%) cases. In one patient a preoperative bronchoscopic bronchial biopsy revealed tuberculous bronchitis. In this case we postponed surgical intervention for 2 months until a repeat bronchoscopy proved negative for tuberculosis and continued medical treatment. After the repeat bronchoscopy was negative for tuberculosis, he underwent surgical intervention.

Thirty-four right-side and 47 left-side operations were performed. We performed 4 completion pneumonectomies,

TABLE 2. Postoperative major pulmonary complications

Complications	No. of patients (%)
Bronchopleural fistula with empyema	4 (4.9)
Space problem	2 (2.5)
Prolonged air leak	7 (8.6)
Atelectasis	2 (2.5)
Hemorrhage and hematoma	5 (6.2)

39 pneumonectomies, 7 lobectomies with segmentectomy, 30 lobectomies, and 1 segmentectomy. Operative mortality was 2.5% (2/81). One patient with postpneumonectomy bronchopleural fistula (BPF) died 3 months after surgical intervention of respiratory failure. The other patient died because of low cardiac output syndrome on the first day after surgical intervention.

Three left pneumonectomies and 2 right pneumonectomies required revision in the first 48 hours after intervention because of hemorrhage and hematoma. At revisions, the exact source of hemorrhage could not be detected. BPF developed in 4 (4.9%) patients, 2 of whom had had left pneumonectomies, one of whom had a right pneumonectomy, and one of whom had a right upper lobectomy with lower lobe superior segmentectomy. The rate of BPF in pneumonectomy cases was 7% (3/43). All of these patients had negative sputum results. In these cases the bronchus was divided with a stapler in 1 and with sutures in 3. In the last 43 resections, only 1 (2.3%) BPF presented. In other words, in this series in the last 7 years, only one BPF occurred. Of the 4 patients who presented with BPF, 1 patient did not accept an open window procedure and was discharged with an open tube drainage. He died in the postoperative third month because of respiratory failure. In the second case the fistula was 2 mm in diameter. The drainage and modified Clagett method resulted in a favorable outcome for this patient. In a third patient with BPF after right pneumonectomy, we performed thoracoplasty protecting the first rib. In the fourth patient BPF occurred after a lobectomy with segmentectomy, and this was treated by performing an apical limited thoracoplasty. Thirty-one patients had a total of 35 complications. Twenty patients had a major pulmonary complication (Table 2). Retreatment protocols resulted in negative cultures and smears in all patients except 1, with an average duration of 4 months (range, 1-6 months). Of the 79 patients, 5 were lost to follow-up, leaving 74. Of these, 67 (90.5%) were cured, and 3 (4.0%) were probably cured. The overall treatment success was 94.5% (70/74). Relapse occurred in 1 of 74 patients, and this patient died of massive hemoptysis 3 years after surgical intervention. Treatment failure occurred in 1 of 74 patients.

Discussion

The recent emergence of tubercle bacilli resistant to both isoniazid and rifampin, which are the most potent antituberculous drugs, is an emerging global problem.^{7,8} Surgical indications for MDR-TB are persistent cavitory disease and destroyed lung and lobe. MDR-TB and its complications are currently the main indicators for surgical intervention in pulmonary tuberculosis.⁹ The stated reasons for resection in patients with cavitory disease are the difficulty of antibiotic penetration and the large number of organisms contained within cavities. Because of this, it is important to resect all cavitory disease and destroyed lung without leaving grossly diseased lung behind.⁹

Surgical resection was considered after 2 months of treatment for all patients.¹ In these series we performed either intrapleural or extrapleural dissection, depending on the extent of pleural adhesions. We believe that local extrapleural dissection might be reserved for patients with apical or other pleural adhesions.⁵ This approach is also recommended by others.⁹

The postoperative mortality and morbidity rate for pulmonary tuberculosis is decreasing. This is largely because of proper selection of the patient, developments in anesthesia techniques, the introduction of stapling devices, and the effective postoperative use of antituberculosis agents postoperatively.¹⁰ The mortality rate of MDR-TB after resectional operations ranged from 0% to 3.3% in the most recent series.^{9,11-13} However, in the early studies the mortality rate was as high as 11%.⁴ Meanwhile, recently reported mortality rates are comparable with the mortality rate we achieved (2.4%). In our first article, which was based on the first 27 cases of our present study, the 30-day mortality rate was zero.⁵ However, in this updated series the overall mortality rate was 2.5% (2/81 cases). This increase in mortality rates between the cases presented in the first study and this one could be due to a better patient selection for surgical intervention in the earlier stages of this study.

Major complications were reported in approximately 15% and included empyema, BPF, postoperative bleeding, and respiratory failure. In previous series the BPF rate was between 25% and 40%,^{12,14-17} but in recently published studies the BPF rate was less than 6%.^{9,11-13} Some authors recommend using muscle flap to reinforce the bronchial stump and reported a low BPF incidence rate.¹⁸ Some report that nondevascularizing bronchial dissection and avoidance of electrical diathermy is important for the prevention of BPF.¹³ Although patients with positive sputum results were reported to be at high risk for BPF development,¹² we did not see any BPF in our 13 patients with positive sputum results. In this study the BPF rate was 4.9%. However, in our last 43 resections, which were performed in the last 7 years, we had only one occurrence of BPF (1/43 [2.3%] cases). We attribute this decrease to our increased surgical

experience. In addition, although we do not use bronchial stump reinforcement, our BPF rate is comparable with those of other studies that use extrathoracic muscle flaps to reinforce the bronchial stump.^{9,11} We think that handling the bronchus is the key point in the avoidance of BPF. In our study we did not routinely reinforce the bronchial stump, except in 4 cases. We think that reinforcement is not necessary because it requires excessive manipulation and unnecessary placement of sutures to the bronchus. Although BPF occurred in patients without reinforcement, the number is too small to make a healthy assessment and compare with the 4 cases with bronchial stump reinforcement. In addition, during the last 7 years, we observed only one BPF among 43 cases.

Our results show that surgical resection combined with chemotherapy in cases of MDR-TB provides a favorable outcome. Nevertheless, this result needs to be validated more strongly by randomized clinical trials that compare surgical resection plus chemotherapy with chemotherapy alone.

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