GENERAL THORACIC SURGERY

PULMONARY RESECTION FOR MULTI-DRUG RESISTANT TUBERCULOSIS

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Objectives: *Mycobacterium tuberculosis* continues to be a major cause of morbidity and mortality throughout the world. Complacency by the medical profession and by patients has caused a new strain of *Mycobacterium tuberculosis* to emerge that is highly resistant to current antibiotics. The possibility of a new worldwide epidemic of drug-resistant *Mycobacterium tuberculosis* is of concern. Optimal therapy for patients infected with multi-drug resistant tuberculosis often requires surgical intervention to eradicate the infection. We report on our experience with pulmonary resection for multi-drug resistant tuberculosis.

Methods: During a 17-year period, 172 patients underwent 180 pulmonary resections. All patients had multi-drug resistant tuberculosis and had a minimum of 3 months of medical therapy before surgery. Muscle flaps were frequently used to avoid residual space and bronchial stump problems.

Results: During the study period, 98 lobectomies and 82 pneumonectomies were performed. Eight patients underwent multiple procedures. Operative mortality was 3.3% (6/180). Three patients died of respiratory failure, 2 patients died of a cerebrovascular accident, and 1 patient had a myocardial infarction. Late mortality was 6.8% (11/166). Significant morbidity was 12% (20/166). One half (91) of the patients had positive sputum at the time of surgery. After the operation, the sputum remained positive in only 4 (2%) patients. Mean length of follow-up was 7.6 years (range 4-204 months).

Conclusions: Surgery remains an important adjunct to medical therapy for the treatment of multi-drug resistant *Mycobacterium tuberculosis*. In the setting of localized disease, persistent sputum positivity, or patient intolerance of medical therapy, pulmonary resection should be undertaken. Pulmonary resection for multi-drug resistant tuberculosis can be performed with acceptable operative morbidity and mortality. (J Thorac Cardiovasc Surg 2001;121:448-53)

Pulmonary infection with *Mycobacterium tuberculosis* (MTB) continues to be a major cause of morbidity and mortality throughout the world. The increase in MTB infection has prompted the World Health

Organization to declare MTB a global emergency.¹ In 1995 MTB resulted in more deaths than any other infectious disease.¹ Currently, it is estimated that almost one third of the world's population is infected with MTB.² Numerous projects have been implemented throughout the world in an attempt to slow the spread of MTB. The result of such projects has been to slow the rate of infection and improve the cure rate in certain countries. However, another result of MTB therapy has been the emergence of multi-drug resistant MTB (MDR-TB). To be classified as MDR-TB, the tuberculosis bacillus must be resistant to both isoniazid and rifampin. Emergence of MTB strains resistant to the primary antibiotics has largely been due to physician and patient complacency,

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Fig 1. Computed tomographic scan demonstrating left upper lobe cavity.

Fig 2. Chest radiograph demonstrating total left lung destruction.

which raises the concern of a new worldwide epidemic of MDR-TB. When characterized by lung destruction or persistent cavitary disease, MDR-TB is difficult to treat with medical therapy alone.

Surgery for pulmonary MTB infection was an important form of therapy until the introduction of effective antibiotics in the 1960s. Since that time, surgery has largely been supplanted by medical therapy. With the emergence of MDR-TB, surgery is again becoming a necessary treatment modality. Indications for surgery in patients infected with MDR-TB include highly resistant MTB with localized disease, persistent cavitary disease, continued sputum positivity, MDR-TB with destroyed lobe or lung, massive hemoptysis, bronchopleural fistula, and bronchial stenosis. We report our series of 172 patients undergoing 180 pulmonary resections for MDR-TB infection.

Patients and methods

We retrospectively reviewed the hospital records of patients who underwent pulmonary resection for MDR-TB. Between August 1983 and April 2000, 172 patients with pulmonary tuberculosis resistant to isoniazid and rifampin underwent 180 pulmonary resections. All operations were performed by the senior author (M.P.). In most patients, the infection was resistant to 6 or more antibiotics. Racial distribution is listed in Table I. The group comprised 114 male and 66 female patients and the average age was 39 years.

All patients had received individualized multiple-drug chemotherapy, as determined by drug susceptibility studies. Timing of the operation is essential and dictated by the degree

Table I. MDR-TB racial distribution

White	67
Asian	42
African American	30
Hispanic	24
Other	17
Total	180

of resistance and the mycobacterial counts. Those patients in whom the organism is resistant to almost all antibiotics are usually operated on within 1 to 2 months after initiation of the best available therapy. Patients in whom the organism is sensitive to some of the primary antibiotics, as well as other antibiotics, usually have therapy for at least 3 months. By this time the sputum is either negative for acid-fast organisms or the mycobacterial count is as low as it will get. It is critical to operate before the mycobacterial count begins to rise. The chemotherapy regimen was continued postoperatively for a maximum of 2 years after conversion of the sputum and culture to negative. Preoperative evaluation included chest radiography, computed tomography with contrast medium, ventilation/perfusion scans, pulmonary function tests, bronchoscopy, and right heart catheterization when there was a question of pulmonary hypertension. In addition, all patients underwent a nutritional evaluation and received appropriate supplementation.

At the time of the operation, approximately 50% of the patients had sputum positive for MTB. A total of 170 patients were operated on for MDR-TB with localized disease usually complicated by cavity formation (Fig 1) or destroyed lung (Fig 2). Often bronchopleural fistulas were present preopera-

Table II. *Pneumonectomies performed for MDR-TB*

	<i>Left</i>	<i>Right</i>
Pneumonectomy	15	4
Pneumonectomy + muscle flap	34	12
Pneumonectomy + muscle flap + Eloesser	1	0
Completion pneumonectomy	2	1
Completion pneumonectomy + muscle flap	7	5
Completion pneumonectomy + omentum	1	0
Total	60	22

Table III. *Lobectomies performed for MDR-TB*

<i>Operation</i>	<i>No.</i>
Right upper lobectomy*	47
Right upper and middle lobectomy†	8
Right lower lobectomy	4
Left upper lobectomy‡	28
Left lower lobectomy	6
Segmental resections	5
Total	98

*Sixteen lobectomies with muscle flaps.

†Two bilobectomies with muscle flaps.

‡Fourteen lobectomies with muscle flaps.

tively. Only 1 patient was operated on for bronchial stenosis and only 1 patient had massive hemoptysis, which had stopped before the operation.

Surgical resection was performed with the patient under general anesthesia. A double-lumen endobronchial tube or an endotracheal tube with a bronchial blocker was used. A combination of single-dose narcotic intrathecal analgesia (Duramorph; Elkins-Sinn, Inc, Cherry Hill, NJ), epidural analgesia, patient-controlled analgesia, and rib blocks with local anesthesia were used for postoperative pain control. In addition, intravenous ketorolac (Merck & Company, Whitehouse Station, NJ) has been used for up to 3 days after surgery. Operations performed are listed in Tables II and III. After the initial 8 patients, all patients with positive sputum at the time of the operation underwent placement of a muscle flap to buttress the bronchial stump. The technique of muscle flap construction used was initially described by Pairolero, Arnold, and Piehler.³ The serratus anterior muscle was initially used, but the latissimus dorsi muscle is now our muscle of choice. The latissimus dorsi is dissected from the chest wall, with the vascular supply left intact. A portion of either the third or fourth rib is resected, through which the muscle is passed into the thoracic cavity. The muscle is then placed over the bronchial stump and secured with suture. A total of 91 muscle flaps were used. The indications for use of a muscle flap are (1) positive sputum at the time of surgery, (2) pre-existing bronchopleural fistula, (3) polymicrobial contamination of the thoracic cavity, and (4) anticipated space problems after lobectomy. Muscle flaps were not used after lower lobec-

tomies or segmental resections. One patient underwent a completion pneumonectomy with placement of an omental flap to cover the bronchial stump. The indication for an omental flap in this patient was a previous thoracotomy with inadequate viable muscle to cover the bronchial stump. Eight patients underwent multiple surgical procedures (Table IV). Six of these operations were performed in a staged fashion and were done 4 to 6 weeks apart. Two patients who underwent a right upper lobectomy had a completion pneumonectomy after recurrent disease. The majority of resections were done extrapleurally because of obliteration of the pleural space largely due to the involvement of parietal pleura in the cavity wall.

Results

Follow-up was complete in all patients. The average period of follow-up was 7.7 years (range 4 months–17 years). There were 6 early deaths (30-day mortality 3.3%). Postpneumonectomy pulmonary edema, bronchopleural fistula with respiratory failure, and myocardial infarction each accounted for 1 death. Cerebral vascular accidents accounted for 2 early deaths, 1 of which occurred in a patient who had had renal transplantation. There were a total of 11 late deaths. Four patients died of late respiratory failure and 3 patients of recurrent MDR-TB. One patient each died of a self-induced drug overdose, myocardial infarction, and renal failure. One death was due to an unknown cause. Late mortality was 6.8%. Twenty patients had postoperative complications (Table V). Six patients had respiratory failure necessitating prolonged ventilator assistance, 5 had a bronchopleural fistula, all of whom had positive sputum at the time of the operation, and 3 had wound infections. Three patients required 4 or more units of packed red blood cells for postoperative bleeding, and 2 patients had recurrent laryngeal nerve injury. Intrathoracic bowel herniation occurred in the 1 patient in whom an omental flap was used. This hernia was repaired 6 months after the initial operation without subsequent adverse complications.

Table IV. Multiple operations

<i>First operation</i>	<i>Second operation</i>	<i>No.</i>
Right upper lobectomy + muscle	Left upper lobectomy + muscle	4
Left pneumonectomy + muscle	Right upper lobectomy + muscle	2
Right upper lobectomy	Completion pneumonectomy + muscle	2
Total		8

Discussion

The incidence of MDR-TB has risen considerably throughout the world. Largely as a result of the complacency of physicians and patients, as well as the high rate of infection in developing countries, strains of MTB resistant to conventional antimicrobial agents have emerged. Tuberculosis, once thought to be easily controlled, continues to be a major cause of morbidity and mortality. The World Health Organization has expressed deep concern that a worldwide epidemic of MDR-TB appears imminent.^{2,4,5} Clearly, newer chemotherapeutic agents will be necessary to combat this increasing incidence of MDR-TB. However, surgical resection will likely remain a crucial adjunct to medical therapy in addressing this epidemic.

The economic impact of tuberculosis is far reaching. With almost one third of the world's population (1.3 billion persons) infected with tuberculosis, proper treatment presents a challenge in developing countries. Even more discouraging is that in developing countries, 90% of persons infected with tuberculosis are younger than the age of 50.¹ Unfortunately, this group represents the primary wage earners in these countries. It is necessary to identify patients early who may benefit from surgery to limit the economic impact of this disease. Furthermore, the cost of treating drug-sensitive tuberculosis may range from \$2,000 to \$15,000. This pales in comparison with the treatment of MDR-TB, which may approach \$200,000 (Iseman M: Personal communication, 2000).

In the 21st century, absolute indications for surgical treatment of MDR-TB are persistent cavitary disease and lung or lobar destruction. Currently, MDR-TB and its associated complications are the primary indications for pulmonary tuberculosis surgery in the United States. The reasons for resection in patients with cavitary disease are the difficulty of antibiotic penetration and the high number of organisms contained within the cavity, 10^7 to 10^9 organisms per cavity.⁶ For these reasons, it is important to resect all cavitary disease and destroyed lung, leaving no grossly diseased lung behind.

Table V. Complications of MDR-TB

	<i>No.</i>
Respiratory failure	6
Bronchopleural fistula	5
Wound infection	3
Postoperative hemorrhage	3
Recurrent nerve injury	2
Intrathoracic bowel herniation	1
Total	20

The operative mortality in our series is consistent with that for lobectomies and pneumonectomies for patients with cancer. This is surprising given that our cohort of patients underwent more difficult procedures with a relatively higher incidence of comorbid risk factors. The low late mortality is due in part to the aggressive medical therapy and prolonged follow-up by our medical colleagues. In most cases, postoperative antibiotic therapy is continued for 2 years after conversion of the sputum smear and culture to negative.

Anatomically, this experience reveals several intriguing observations. Left lung destruction was found in more than 70% of the patients who underwent a pneumonectomy. The predilection for left lung destruction in patients with pulmonary tuberculosis has been reported by others.^{7,8} The reason for this is not clear. It is possible that the anatomic differences between the left and right main stem bronchi and the location of the lobar bronchi may account for this discrepancy. When there is isolated infection without total lung destruction, the right upper lobe is the most common site of infection.

Malnutrition remains a major problem in this group of patients. All but 2 of the 172 patients were at or below their ideal body weight. We use aggressive preoperative enteral and parenteral supplementation in an attempt to obtain a positive nitrogen balance and increase the serum albumin level to 3 g/dL or greater. These goals are difficult to achieve in a number of patients because of the severity of their illness.

We were surprised to find that only 3 patients in our series died of recurrent MDR-TB. We believe this low

mortality is due in large part to the prolonged postoperative use of appropriate antibiotics. In addition, optimal timing of surgical intervention remains difficult to determine. We would advocate that positive sputum be converted to negative sputum and that pulmonary mechanics be maximized with aggressive preoperative pulmonary rehabilitation. The presence of the senior author (M.P.) in weekly multidisciplinary mycobacterial rounds was essential. A certain number of patients required intervention before these goals could be obtained, because their disease was pursuing a virulent, aggressive course. The combination of surgery along with the continuation of directly observed antituberculosis therapy is very effective for the treatment of MDR-TB.

To our knowledge, this is the largest series of patients operated on for MDR-TB. We have demonstrated that although patients with MDR-TB are often quite ill, with little functional reserve, they can be operated on with a reasonably low operative mortality (3.3%) and with acceptable morbidity. In our experience, the use of muscle flaps has decreased the incidence of bronchial stump dehiscence and residual space problems with little associated morbidity. Given the increasing global epidemic of MDR-TB, it is likely that thoracic surgeons in the 21st century will occupy an integral role in the optimal treatment of MDR-TB. The experience and judgment of the surgeon, combined with dedicated pulmonologists, infectious disease physicians, and perioperative support, undoubtedly will contribute to the low morbidity and mortality in this difficult group of patients.

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Discussion

Dr John R. Benfield (*Los Angeles, Calif*). My congratulations to Marvin Pomerantz for the outstanding results and to Ben Pomerantz for a fine report of this largest of all reported series of patients in whom MDR-TB was treated with operations that are among the most technically challenging in surgery.

John Alexander of the University of Michigan is remembered for his classic book about collapse therapy for the treatment of tuberculosis, a mode of treatment that was ending as I was entering thoracic surgery. During the subsequent 40 years of my practice, I saw the number of thoracic surgeons with personal experience in the surgery of tuberculosis dwindle to almost naught. Today's presentation tells us that MDR-TB is a persistent and growing problem and that modern thoracic surgeons are needed to solve the problem. It is remarkable that all except 4 of 91 patients, who had positive sputum at the time of their operations, achieved negative sputum as a result of resections of destroyed lung and obliteration of pleural space. The basic principles remain unchanged: best available drug therapy, followed by resection of residual active foci of disease, accompanied by obliteration of abnormal pleural spaces, followed by best available drug therapy.

Even the best results demand analysis with the question of whether and how one might have done better. Therefore, I wish to focus on the 11 patients (6.8%) who died in the late postoperative period and the 3 patients who died of respiratory failure during the postoperative period. Retrospectively, could anything have been done to avoid these deaths? Were at least some of these patients sufficiently dysfunctional preoperatively to justify resurrection of collapse therapy such as a thoracoplasty or a muscle flap without pulmonary resection? In my own experience of treating patients with far-advanced MDR-TB, often from Southeast Asia or the former Soviet Union, at intervals of 12 to 24 months I would encounter a patient for whom a modern version of collapse therapy was the best available treatment. What has been the experience of the National Jewish Hospital/University of Colorado group with collapse therapy in recent years?

Dr Pomerantz. We have not used collapse therapy at all for the treatment of tuberculosis, but we do use it for the treatment of other pulmonary diseases. With the excellent results we achieve with primary resection and the association of progressive respiratory failure with thoracoplasty, we believe that we have better results doing a primary resection. Just to touch on the 3 late respiratory deaths, pulmonary hypertension developed in 1 of those patients after lobectomy, and we

are not exactly sure why. The other 2 patients had pneumonectomy on one side and old tuberculosis on the opposite side, which had caused a lot of scarring, and they had progressive pulmonary fibrosis.

Dr Benfield. This report clearly supports the liberal prophylactic use of muscle flaps to cover bronchial closure sites and to obliterate pleural spaces. I cannot recall a single occasion of regret that I had used a muscle flap, and each of us can remember times when we wished we had used one. In the manuscript I noted that muscle flaps were routinely used to cover upper lobe and main stem bronchial closures, but they were not routinely used after lower lobectomies. Of course, this is because of the expectation that the diaphragm can rise and that space problems are less frequent after lower lobectomies than after upper lobe resections. Nonetheless, I suspect that there were instances of using muscle flaps or some modification of collapse therapy in conjunction with lower lobectomies. Would you please comment about this point?

Dr Pomerantz. We performed only 10 lower lobectomies. We did not encounter any space problems in these patients. We did, however, try to cover the bronchial stump with either pleura or a pericardial fat pad.

Dr James B. D. Mark (*Stanford, Calif*). I would like to congratulate Dr Pomerantz the elder for his persistent work in treating this difficult disease over an extended period and Dr Pomerantz the younger for a very fine presentation. Those of you in this room who have not had experience with this operation, and I suspect that represents the great majority, have no idea about the technical problems that one may face or the blood, sweat, and tears involved in taking care of these patients in the operating room. The greatest challenge in this group, I think, is operating under a thoracoplasty. You mentioned that you did not do any collapse procedures, but were you faced with operating under a previous thoracoplasty? Would you comment on any special technical problems that you encountered?

Dr Pomerantz. One patient did have a previous thoracoplasty, and the extrapleural dissection was challenging enough by itself. We did not really encounter any specific

technical problems other than the usual problems associated with an extrapleural dissection in that 1 patient.

Dr Mark. I remember in the old days when we were doing these types of operations, we used to yearn for a nice clean cancer case.

Dr Pomerantz. That is right.

Dr Steven Guyton (*Seattle, Wash*). Dr Pomerantz, you had 5 bronchopleural fistulas. Did they occur in the presence of a muscle flap, or were they lower lobe fistulas?

Dr Pomerantz. I believe all of them were without muscle flaps and were in patients with positive sputum. I do not remember the specifics, but more than half of our patients did get muscle flaps.

Dr Arthur Thomas (*San Francisco, Calif*). I congratulate you for a very important paper on the largest series of patients of this type, comprising more patients than any of the rest of us have seen. I would like to hear a little detail about your technique of closing bronchial stumps. Are these stapled? Are they hand sewn? If they are hand sewn, what suture material did you use?

Dr Pomerantz. We generally use a staple closure for the bronchial stump. If the bronchial stump is too short, we sew it closed by hand, usually with Prolene sutures.

Dr Quentin Stiles (*Palos Verdes Estates, Calif*). Dr Pomerantz, your paper reminds me of the old days, and I am talking about the really old days, even before the formation of the Samson Thoracic Surgical Association. The point that really struck me was your statement that 2 billion persons are affected by tuberculosis. You must be talking about people with positive skin tests. Two billion is one third of the population of the whole universe.

Dr Pomerantz. Yes, that is right. Those are the individuals who test positive for purified protein derivative, and about 10% of them actually harbor the active infectious disease. There are more than 3 million deaths annually from tuberculosis. It is estimated that 100,000 persons in Russia have MDR-TB. This disease is a huge global problem. A primary reason for the problem is the global economic issues in developing countries, which seem to be the predominant harborers of this disease.