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# Institutional report - Thoracic general

## Experience with pulmonary resection for extensively drug-resistant tuberculosis<sup>☆</sup>

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### Abstract

Extensively drug-resistant tuberculosis is becoming a global threat. It is a relatively new phenomenon, and its optimal management remains undetermined. We report our experience in using pulmonary resection for treating patients with this disease. Records were reviewed of 54 consecutive patients undergoing a pulmonary resection for multidrug-resistant tuberculosis at Fukujuji Hospital between 2000 and 2006. These patients were identified using the definition approved by the World Health Organization Global Task Force on extensively drug-resistant tuberculosis in October 2006. Five (9%) patients (3 men and 2 women) aged 31–60 years met the definition. None of the patients was HIV-positive. Although the best available multidrug regimens were initiated, no patient could achieve sputum conversion. Adjuvant resectional surgery was considered because the patients had localized disease. Procedures performed included pneumonectomy (2) and upper lobectomy (3). There was no operative mortality or morbidity. All patients attained sputum-negative status after the operation, and they were maintained on multidrug regimens for 12–25 months postoperatively. All patients remained free from disease at the time of follow-up. Pulmonary resection under cover of state-of-the-art chemotherapy is safe and effective for patients with localized extensively drug-resistant tuberculosis.

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**Keywords:** Extensively drug-resistant tuberculosis; Pneumonectomy; Lobectomy; Multidrug regimens

### 1. Introduction

Extensively drug-resistant tuberculosis (XDR-TB), a very serious form of drug-resistant tuberculosis, is becoming a global threat [1, 2]. Actually, XDR-TB has been observed worldwide [3]. Patients with XDR-TB have very poor prognosis. Extremely high mortality in patients co-infected with 'possible' XDR-TB and HIV has been reported from South Africa [4]. Moreover, the presence of extensive drug resistance is an independent poor prognostic factor even in non-HIV-infected patients with multidrug-resistant tuberculosis (MDR-TB) [5]. Because XDR-TB is still a relatively new phenomenon, the optimal management of this disease remains undetermined. Although a previously reported series regarding surgical treatment of MDR-TB probably included a certain number of patients with XDR-TB [6–10], reports on treatment outcomes of resectional surgery exclusively for XDR-TB are scarce. We report our experience in using pulmonary resection for treating patients with XDR-TB.

### 2. Materials and methods

This study was approved by the institutional review board on human research at Fukujuji Hospital. Between January

2000 and December 2006, 54 patients underwent a pulmonary resection for MDR-TB at Fukujuji Hospital, which is affiliated with the Japan Anti-Tuberculosis Association. To identify patients with XDR-TB, we used the definition approved by the World Health Organization Global Task Force on XDR-TB in October 2006 [11]. Thus, XDR-TB is tuberculosis having resistance to at least isoniazid and rifampicin, which is the definition of MDR-TB; resistance to any fluoroquinolone; and resistance to at least one of the three following injectable drugs used in anti-tuberculosis treatment: capreomycin, kanamycin, and amikacin. Drug susceptibility testing for levofloxacin is the only available susceptibility testing for fluoroquinolones in our laboratory. Capreomycin and amikacin are no longer used for the treatment of tuberculosis in Japan. Therefore, in this study, patients with XDR-TB were the MDR-TB patients whose isolates had acquired additional resistance to both levofloxacin and kanamycin.

Of the 54 patients, five patients (9%) met the definition and were the subjects of this study. There were three men and two women (Table 1), including two foreign-born. Age at the time of surgery ranged from 31–60 years (median: 44 years). None of the patients was HIV-positive. All patients had received chemotherapy for tuberculosis at the referral hospitals, which failed, and were transferred to our hospital to seek specialized care for highly drug-resistant tuberculosis. Sputum smears and sputum cultures

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Table 1  
Results of drug susceptibility testing

Patient	Sex	Age (years)	INH	RFP	LVFX	KM	SM	EMB	PZA	CS	ETH	EVM	PAS
1	F	31	R	R	R	R	R	R	R	S	S	S	R
2	M	36	R	R	R	R	R	R	R	S	R	S	S
3	M	60	R	R	R	R	R	R	R	S	R	R	R
4	M	57	R	R	R	R	R	R	S	S	R	S	R
5	F	44	R	R	R	R	R	R	R	S	S	R	S

INH, isoniazid; RFP, rifampicin; LVFX, levofloxacin; KM, kanamycin; SM, streptomycin; EMB, ethambutol; PZA, pyrazinamide; CS, cycloserine; ETH, ethionamide; EVM, enviomycin; PAS, para-aminosalicylic acid; F, female; M, male; R, resistant; S, sensitive.

were obtained upon admission. Drug susceptibility testing was performed on positive cultures in our laboratory.

The results of drug susceptibility testing are shown in Table 1. Isolates were resistant to isoniazid, rifampicin, levofloxacin, kanamycin, and to another four or six drugs. Although few effective drugs were left, multidrug regimens employing three to five drugs were initiated in all patients (Table 2). Drugs included in the regimens were chosen based upon drug susceptibility testing results. The drugs to which the isolates were resistant were included in the regimens when there were no other available drugs. Despite the fact that all the isolates were resistant to levofloxacin, we tried to use alternative fluoroquinolones such as gatifloxacin and sparfloxacin to improve the efficacy of less potent chemotherapy. Other drugs employed included kanamycin, pyrazinamide, cycloserine, enviomycin, ethionamide, para-aminosalicylic acid, and sultamicillin tosilate.

Adjuvant resectional surgery was considered, because the five patients did not achieve sputum conversion in response to the best available multidrug regimens and had lesions predominantly localized to one lung. Preoperative studies included a chest roentgenogram, computed tomographic scan of the chest, pulmonary function tests, arterial blood gas analysis, and a quantitative perfusion scan. Scattered nodular lesions on the contralateral side were accepted; indeed only two patients had their tuberculosis limited entirely to one side with the opposite side totally intact.

Surgery was performed using the technique previously reported [12]. In patients having dense adhesions, we preferred extrapleural dissection to keep their cavities intact. During the course of extrapleural dissection, we used electrocautery and bipolar scissors (PowerStar Bipolar Scissors; Ethicon Inc, Somerville, NJ) to reduce blood loss. The pleural cavity was irrigated with at least 10 l of saline and povidone iodine, and the chest was then drained of fluid.

Table 2  
Preoperative chemotherapy, operative procedures, and intraoperative valuables

Patient	Preoperative chemotherapy	Operative procedure	Bronchial stump coverage	Operating time (min)	Bleeding (ml)
1	SPFX, PZA, CS, ETH, EVM	Left pneumonectomy	Latissimus dorsi	310	415
2	GFLX, CS, EVM, PAS	Left upper lobectomy	Latissimus dorsi	453	240
3	GFLX, PZA, CS	Right upper lobectomy	Latissimus dorsi	245	315
4	GFLX, PZA, EVM	Right pneumonectomy	Latissimus dorsi	267	180
5	KM, CS, ETH, PAS, SBTPC	Right upper lobectomy	Intercostal muscle	120	20

SPFX, sparfloxacin; PZA, pyrazinamide; CS, cycloserine; ETH, ethionamide; EVM, enviomycin; GFLX, gatifloxacin; PAS, para-aminosalicylic acid; KM, kanamycin; SBTPC, sultamicillin tosilate.

After surgery, all patients were maintained on multidrug regimens, generally the same as their preoperative ones. Follow-up data were obtained from outpatient or hospital charts, or by direct contact with patients or relatives. Post surgical follow-up was completed on 31 March 2008. Duration of follow-up ranged from 31–66 months (median: 38 months). Operative mortality included all deaths clearly related to the operation, regardless of the postoperative interval. All cases of bronchopleural fistula or empyema occurring subsequent to the date of surgery were considered postoperative complications.

### 3. Results

Procedures performed included pneumonectomy (2) and upper lobectomy (3) (Table 2). The bronchus was divided and closed with staples, and the bronchial stump was reinforced with a muscle flap in all resections. The muscle used was the latissimus dorsi in four resections and the intercostal muscle in one. Operating time ranged from 120–453 min (median: 267 min). Median intraoperative blood loss was 240 ml (range: 20–415 ml). Despite careful dissection, a small amount of the contents of cavities was spilled into the operative field in two patients. In all patients, cultures from their resected specimens were positive for tuberculosis.

There was no operative mortality. We encountered neither bronchopleural fistula nor empyema in any patient. All patients attained sputum-negative status after the operation, and returned to their normal daily activities. Duration of postoperative chemotherapy ranged from 12–25 months (median: 19 months). All five survivors remained free from disease at the time of follow-up.

### 4. Discussion

Chest physicians and thoracic surgeons have been struggling with MDR-TB since the 1990s and are now facing XDR-

TB. Since XDR-TB is a very serious form of MDR-TB, this disease has possibly been present in the world for many years. However, it was not until 2006 that a report from South Africa about a surprisingly high mortality in patients with ‘possible’ XDR-TB drew global attention to XDR-TB [4]. The World Health Organization established the definition of XDR-TB in the same year [3, 11], and the significant impact of the presence of XDR-TB on a global battle against tuberculosis has been accepted widely. XDR-TB is now defined as ‘tuberculosis showing resistance to at least rifampicin and isoniazid, which is the definition of MDR-TB, in addition to any fluoroquinolone, and to at least one of the three following injectable drugs used in anti-tuberculosis treatment: capreomycin, kanamycin and amikacin [11]’.

The extremely high mortality reported from South Africa was observed in patients co-infected with ‘possible’ XDR-TB and HIV [4]. In addition, the presence of extensive drug resistance is an independent poor prognostic factor in non-HIV-infected patients with MDR-TB [5]. Resistance to fluoroquinolones and injectable drugs allows us fewer effective drugs for XDR-TB than for ordinary MDR-TB, and makes the medical treatment regimens for XDR-TB less potent. Therefore, to reduce bacterial burden by resecting cavitory lesions or destroyed lobes may play an important adjunctive role in the management of XDR-TB. However, pulmonary resection for XDR-TB may carry the same risk as surgery for tuberculosis in the pre-antibiotic era when pulmonary resection was being performed without adequate coverage with effective anti-tuberculosis drugs.

In the year 2000, our hospital was certified as one of the key centers for treating MDR-TB in Japan [12]. This certification has brought an increasing number of referrals for treatment of patients with MDR-TB. Our MDR-TB surgical series has become one of the largest cohorts in Japan. This retrospective review of 54 consecutive patients undergoing pulmonary resection for MDR-TB from 2000 to 2006 sorted out five patients with XDR-TB. Since the concept of XDR-TB is relatively new, we did not realize at the time of surgery that these patients had XDR-TB. We used to regard these patients as extremely drug-resistant tuberculosis patients.

It was difficult to create effective multidrug regimens for these XDR-TB patients, because their isolates were resistant to at least isoniazid, rifampicin, streptomycin, ethambutol, levofloxacin, and kanamycin. We were forced to employ alternative fluoroquinolones, such as gatifloxacin [13] and sparfloxacin [14], and other second-line drugs to create multidrug regimens. Investigators in South Korea even used isoniazid and rifampicin, to which the isolates were resistant on drug susceptibility testing, to create multidrug regimens [5]. As we previously reported, patients should have been treated with multidrug regimens for at least three months before resectional surgery is considered for them [12]. Although none of the patients had their sputum converted from negative to positive preoperatively in this study, we believe that preoperative chemotherapy might play a significant role in decreasing the bacterial burden prior to the surgery. This is important to reduce the incidence of bronchopleural fistula as pointed out by Iseman and associates, who proposed ‘sufficient drug activity

to diminish the mycobacterial burden enough to facilitate probable healing of the bronchial stump’ [15]. In addition to multidrug regimens, we used a muscle flap to cover the bronchial stump to reduce the incidence of bronchopleural fistula. We prefer the latissimus dorsi because it is a large muscle and also can be used to reduce the post-resectional space.

In this study, resectional surgery combined with state-of-the-art multidrug regimens achieved high cure rates in patients with XDR-TB. This successful outcome may be due in part to the fact that we have been performing pulmonary resection restrictively for patients who must have sufficient pulmonary reserve to tolerate pulmonary resection and have lesions predominantly localized to one lung [12]. We have obeyed this rule for selecting eligible patients for surgical treatment strictly, or we should have experienced a high failure rate. Kim and co-workers have pointed out that cavitory lesions beyond the range of resection is one of the possible poor prognostic factors for surgical resection in MDR-TB patients [7]. In order to achieve favorable outcomes, it is crucial that we choose the type of resection that can remove all gross lesions like cavities or destroyed lobes. Moreover, although the scattered nodular lesions that were left at the time of surgery carry few bacterial burdens, patients should be kept on multidrug regimens for at least one year postoperatively to keep these lesions stabilized.

There are some limitations to the wide application of our findings. First, our study was a single arm study with a small number of patients. Second, the patients enrolled in this study had already been very highly selected. Third, this report comes from an institute with broad experience in surgical treatment of drug-resistant tuberculosis. Nevertheless, to the best of our knowledge, this study is the first published series dealing with outcomes of pulmonary resection exclusively for XDR-TB. In conclusion, pulmonary resection under cover of state-of-the-art chemotherapy is safe and effective for patients with localized XDR-TB. All efforts to create the best available multidrug regimens and adherence to rigorous patient selection criteria for surgical therapy are the keys to success in the management of this dreadful form of tuberculosis.

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