

Prognostic factors for surgical resection in patients with multidrug-resistant tuberculosis

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Short running head: Surgery in patients with MDR-TB

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Abstract

Although surgical lung resection could improve prognosis in some patients with MDR-TB, there are no reports on the optimal candidates for this surgery. The aim of this study was to elucidate the prognostic factors for surgery in patients with MDR-TB.

Patients who underwent lung resection for the treatment of MDR-TB between March 1993 and December 2004 were included. Treatment failure was defined as two or more of the five cultures recorded in the final 12 months of treatment being positive, any one of the final three cultures being positive, or having died during treatment. We identified the variables that affected treatment outcomes through univariate and multivariate logistic regression analysis.

79 patients with MDR-TB were included. The treatment outcomes of 22 patients (27.8%) were classified as failure. Body mass index lower than 18.5 kg/m² ($P = 0.04$), primary resistance ($P < 0.001$), resistance to ofloxacin ($P = 0.048$), and the presence of a cavitory lesion beyond the range of the surgical resection ($P < 0.001$) were associated with treatment failure.

Low body mass index, primary resistance, resistance to ofloxacin, and cavitory lesions beyond the range of resection are possible poor prognostic factors for surgical lung resection in MDR-TB patients.

Key words: Tuberculosis, Multidrug-Resistant, Prognosis, Surgery

Introduction

Multidrug-resistant tuberculosis (MDR-TB), resistant to at least both isoniazid and rifampicin, poses a serious threat to global health because it requires treatment for a long duration and frequent hospitalization, and results in a considerable number of mortalities [1]. According to a World Health Organization (2000) report, 3.2% of all new TB cases are MDR. In Estonia and Latvia, multidrug resistance was observed in 14% and 9% of new TB cases, respectively [2].

The treatment of MDR-TB is difficult as second-line drugs must be used, which are less potent than first-line drugs, and not as well tolerated. Early publications on the treatment response of MDR-TB reported considerable mortality, as high as 37% [3]. After the successful introduction of surgical resection of the diseased lung in patients with refractory MDR-TB [4], favourable results among patients with MDR-TB ensued [5-12]. The rates of sputum conversion or of patients who remained negative after surgical resection are as high as 80%–98% [5-12]. Recently, surgical resection along with use of new quinolones has been widely accepted to improve the results of MDR-TB treatment [13, 14].

Although surgical resection has been tried and favourable outcomes increasingly reported in patients with MDR-TB [5-12], there is no consensus on whom surgical resection should be performed on. The aim of this study was to elucidate prognostic

factors in patients with MDR-TB refractory to medical treatment who had undergone surgical resection of the diseased lung.

Methods

Inclusion criteria and data collection

The subjects included in the study were patients who had undergone surgical lung resection for the treatment of MDR-TB at Seoul National University Hospital, a university-affiliated tertiary referral hospital, between March 1993 and December 2004. Although the decision of surgical resection has been made by individual physicians, the general indication of the surgical resection used in our institution was MDR-TB refractory to at least 6 months of medical treatment with a main localized lesion. We reviewed the medical records, microbiology results, other laboratory results, and radiographic examinations of the enrolled patients. The protocol of this study was approved by the Ethical Review Committee of Seoul National University Hospital.

Definitions

We classified the type of resistance according to the definitions of the World Health Organization. MDR-TB patients without prior treatment with anti-TB drugs were classified as having primary resistance. If the patients had a history of previous anti-TB treatment, they were classified as having an acquired resistance [15]. Body mass index (kg/m^2) measured just before operation were used in the analysis. The treatment outcomes were classified in accordance with the suggested criteria of Laserson et al [16]. Cure was defined as an MDR-TB patient who has completed treatment according to the country's protocol and has been consistently culture negative (with at least five results) 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 may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart. Treatment failure was defined as two or more 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. In addition, on analysing treatment outcomes, we included in the treatment failure group a patient who died during the course of MDR-TB treatment.

Statistical analysis

Data are expressed as median values or means \pm standard deviations. The Chi-square test for comparison of categorical variables and the *t*-test for comparison of continuous variables were applied. Variables analysed include clinical characteristics (age, sex, body mass index (BMI), type of resistance, drugs used), laboratory results (drug susceptibility tests, liver function tests, serum creatinine level, lung function), and radiographic findings. To identify the predictors for the treatment failure after surgical lung resection, multivariate logistic regression models were constructed including age, sex, and any variables with *P*-value lower than 0.20 through univariate analysis. Statistical significance was determined by a *P* value less than 0.05. All statistical analyses were performed with the SPSS system for Windows® (Version 11.0).

Results

Annual number of surgeries and patient baseline characteristics

Between March 1993 and December 2004, 88 surgical lung resections were carried out at Seoul National University Hospital in 79 patients with MDR-TB refractory to medical treatment. Resections had been performed twice in 7 patients and three times in one patient because of persistently positive AFB smear and/or *M. tuberculosis* culture. In 1993, one patient with refractory MDR-TB underwent surgery. The number of surgeries increased to five in 1994 and peaked with 14 surgeries in 2002 (Figure 1). The clinical data of 27 of the 79 patients were included in an article published in 1999.[9] All patients were Korean. Among the 79 cases, 48 were male and 31 female. Their median age was 29 years (range: 19 to 60 years). The mean BMI was 21.5 kg/m² in the male patients and 19.8 kg/m² in the female patients. Twenty-four patients (30.4%) had other underlying diseases. None of the enrolled patients was anti-HIV antibody seropositive. The patients had received a median of six anti-TB drugs (range: 4 to 8) during a median 14.5 months (range: 9 to 112) before the surgery. The *M. tuberculosis* isolates from these patients were resistant to a median of five drugs (range: 2 to 11). Drug resistance rates among the 79 patients are summarized in Table 1. Seventy-seven patients (97.5%) were *M. tuberculosis* culture positive at the time of operation. Seventy-seven patients (97.5%) had cavitory lesions evident in their chest radiographs. Among them, 28 patients (35.4%) had other cavitory lesions beyond the range of the resection: cavitory lesions in contralateral side to the resected lung in 25 patients, ipsilateral to resected lung in 3 patients. In latter 3 patients, the cavities were could not be completely resected because of limited lung functions.

The results of surgical lung resection and subsequent anti-TB chemotherapy

Among the 79 patients who underwent surgical lung resection, lobectomy was the most common procedure, performed in 44 patients (55.7%). Surgical complications developed in 18 patients (22.8%; Table 2). Anti-TB medications were continued for a median of 18 months (range: 9–48 months) after the surgery. The treatment results were as follows: cure in 57 patients (72.2%), treatment failure in 21 patients (26.6%), and death in one patient (1.2%). The cause of death in the patient, in whom right pneumonectomy was performed, was respiratory failure caused by worsening TB in the left lung.

Predictors of treatment outcomes

Several variables were screened for any association with the results of treatment, including surgical lung resection. The variables evaluated included clinical characteristics (age, sex, BMI, type of resistance, drugs used), the results of microbiological tests, and the radiographic findings (Table 3). Among them, primary resistance ($P < 0.001$), resistance to ofloxacin ($P = 0.015$), and the presence of cavities beyond the range of resection were associated with treatment failure ($P < 0.001$). Multivariate logistic regression analysis involving these three variables, age, sex, and BMI was done for association with the results of surgery (Table 4). Body mass index lower than 18.5 kg/m² ($P = 0.043$), primary resistance ($P < 0.001$), resistance to

ofloxacin ($P = 0.048$), and the presence of a cavitory lesion beyond the range of the surgical resection ($P < 0.001$) were associated with treatment failure despite surgical lung resection.

Discussion

Through this retrospective cohort study, we demonstrated that lower BMI ($P = 0.043$), primary resistance ($P < 0.001$), resistance to ofloxacin ($P = 0.048$), and the presence of a cavitory lesion beyond the range of the resection ($P < 0.001$) were independently associated with poor treatment outcomes, including surgical resection for treatment of MDR-TB. A lower BMI and the presence of cavities have been reported to be associated with poor outcomes in patients with MDR-TB [17-19]. In addition, use of new quinolones along with surgical resection has been widely accepted to improve the results of MDR-TB treatment [13, 14]. However, there have been no previous reports of a primary resistance as poor prognostic factors.

Drug-resistant tuberculosis bacilli have been reported as being generally less viable than drug-sensitive bacilli in vitro and in vivo [20] and have lower transmissibility in most cases [21, 22], despite some exceptions [23, 24]. In this context, the hypothesis that transmitted bacilli with resistance to multidrugs, which means the tuberculosis bacilli in patients with primary resistance are phenotypically more virulent than bacilli in patients with acquired MDR-TB without definite evidence of transmissibility, is possible. The report of fatal outcomes from MDR-TB transmitted among family members without definite immune defects supports this hypothesis [25]. However, the observed association between primary resistance and poor prognosis in this study should be confirmed by future studies enrolling larger number of patients with MDR-TB regardless of surgical resection.

The failure rate of 27.8% seen in this study for treatments, including surgical resection, is relatively high compared to other reports [5-12], and could be explained by several factors. First, most patients (77 patients, 97.5%) included in this study showed positive sputum culture for *M. tuberculosis* at the time of operation. This rate is much higher than the 50% positive sputum cultures among the patients in the study by Pomerantz et al., which showed a 2% failure rate [7]. Second, we used surgical resection aggressively, even in patients with bilateral cavities, because they had no other available treatment options. These cases increased the failure rate and showed association with unfavourable outcomes. Third, because all patients with MDR-TB included in this study had undergone surgical resection because of refractoriness to medical treatment, the results could be unfavourable when compared to those from studies involving various indications, for example, prevention of treatment failure or relapse, or haemoptysis [8].

In conclusion, although the surgical resection of diseased lungs in patients with MDR-TB refractory to medical treatment has been accepted as a rescue therapy, clinicians should carefully select the patients for this treatment, giving consideration to possible poor prognostic factors such as a low BMI, primary resistance, resistance to ofloxacin, and the presence of cavitory lesions beyond the range of the resection.

Conflict of interest statement

We declare that we have no conflict of interest.

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Table 1. Demographic and clinical characteristics of the 79 patients.

Age (years), median (range)	29 (19–60)
Male: Female	48:31
Body mass index (kg/m ²)	
Male, median (range)	21.5 (15.4–26.0)
Female, median (range)	19.8 (16.2–25.3)
Presence of underlying diseases (%)	24 (30.4%)
Diabetes	8 (10.1%)
Cardiovascular disorders	7 (8.9%)
Chronic liver diseases	5 (6.3%)
COPD or other lung diseases	4 (5.1%)
Number of resistant drugs, median (range)	5 (2–11)
Resistant not to injectables nor ofloxacin (%)	27 (34.2%)
Resistant to injectable(%)	24 (30.4%)
Resistant to ofloxacin (%)	10 (12.6%)
Resistant to injectable and ofloxacin (%)	18 (22.8%)
Duration of chemotherapy before surgery (months), median (range)	14.5 (9–112)
Persistent positive <i>M. tuberculosis</i> culture before surgery	77 (97.5%)
Number of drugs used before surgery, median (range)	6 (4–8)
Patients receiving a regimen containing quinolones before surgery (%)	70 (88.6%)*
Radiographic characteristics	
Presence of cavity	77 (97.5%)
Presence of cavity beyond the range of resection	28 (35.4%)
- Ipsilateral to resected lung	<u>3 (3.8%)</u>
- Contralateral to resected lung	<u>25 (31.6%)</u>
Confined to one lobe	3 (3.8%)
Confined to one lung	26 (32.9%)
Involvement of both lungs	53 (67.1%)

*Ofloxacin was used in 21 patients, ciprofloxacin in 3, levofloxacin in 44, and moxifloxacin in 2.

Table 2. Types of surgery and results of subsequent anti-TB chemotherapy in the 79 patients with MDR-TB.

Type of pulmonary resection (%)

Wedge resection	7 (8.8%)
Lobectomy	44 (55.7%)
Bilobectomy	11 (13.9%)
Pneumonectomy	17 (21.6%)
Complications of surgery (%)	18 (22.8%)
Bronchopleural fistula with empyema	4 (5.1%)
Prolonged air leak	7 (8.9%)
Infection including pneumonia	5 (6.3 %)
Others	2 (2.5%)
Postoperative status	
Change in the drug resistance pattern	5/32*
Duration of chemotherapy after surgery (months), median (range)	18 (9–48)
Duration of follow up after surgery (months), median (range)	56 (9–79)
Treatment results	
Cure	57 (72.2%)
Treatment completed	0
Death	1 (1.2%)
Treatment defaulted	0
Treatment failure	21 (26.6%)
Transfer out	0

*Pre- and postoperative drug susceptibility test results were available in 32 patients.

Table 3. Individual predictors for treatment outcomes in MDR patients who underwent surgical lung resection.

	Success group (N = 57)	Failure group (N = 22)	<i>P</i> value
Age, mean \pm standard deviation (years)	35 \pm 14	32 \pm 10	0.890
Male	36 (63.1%)	12 (54.5%)	0.482
BMI lower than 18.5 kg/m ²	15 (26.3%)	10 (45.4%)	0.101
Primary drug resistance	6 (10.5%)	17 (77.3%)	<0.001
Fewer than five drugs used preoperatively	5 (8.8%)	4 (7.1%)	0.238
More than one year of preoperative treatment	47 (82.4%)	16 (72.2%)	0.335
Quinolone used preoperatively	50 (87.7%)	20 (90.9%)	0.689
Resistance to ofloxacin	4 (7.0%)	6 (27.3%)	0.015
Resistance to injectables	18 (31.6%)	6 (27.3%)	0.709
Number of resistant drugs > five	28 (49.1%)	8 (36.4%)	0.307
Multilobar involvement	54 (94.7%)	22 (100%)	0.273
Preoperative positive <i>M. tuberculosis</i> culture	55 (96.5%)	22 (100%)	0.360
Presence of cavitary lesion	55 (96.5%)	22 (100%)	0.360
Presence of cavity beyond the range of resection	11 (19.3 %)	17 (77.3%)	<0.001
Growth of <i>M. tuberculosis</i> > 200 colonies	51 (89.5%)	20 (90.9%)	0.850
Pleuro-pneumonectomy	13 (22.8%)	4 (7.1%)	0.654

Table 4. Predictors by multivariate logistic analysis for treatment failure in MDR-TB patients who underwent surgical lung resection.

	Adjusted hazard ratio (95% CI)	<i>P</i> value
Age (x + 1 years vs. x years)	1.1 (0.3-1.8)	0.878
Male sex	1.5 (0.7-2.9)	0.543
BMI lower than 18.5 kg/m ²	2.2 (1.4–5.0)	0.043
Primary resistance	7.1 (3.8–16.2)	<0.001
Resistance to ofloxacin	2.1 (0.9-4.1)	0.048
Presence of cavitary lesion beyond resection	6.4 (3.3–15.7)	<0.001

Figure 1. Annual numbers of lung resection surgeries in patients with MDR-TB and their results: 88 operations in 79 patients with MDR-TB

