



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

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ABSTRACT: Although surgical lung resection could improve prognosis in some patients with multidrug-resistant tuberculosis (MDR-TB), there are no reports on the optimal candidates for this surgery. The aim of the present 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 in the present study. Treatment failure was defined as greater than or equal to two of the five cultures recorded in the final 12 months of treatment being positive, any one of the final three cultures being positive, or the patient having died during treatment. The variables that affected treatment outcomes were identified through univariate and multivariate logistic regression analysis.

In total, 79 patients with MDR-TB were included in the present study. The treatment outcomes of 22 (27.8%) patients were classified as failure. A body mass index $<18.5 \text{ kg}\cdot\text{m}^{-2}$, primary resistance, resistance to ofloxacin and the presence of a cavitory lesion beyond the range of the surgical resection 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 multidrug-resistant tuberculosis patients.

KEYWORDS: Multidrug-resistant, prognosis, surgery, tuberculosis

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 hospitalisation, and results in a considerable number of mortalities [1]. According to a World Health Organization (WHO) report in 2000, 3.2% of all new tuberculosis (TB) cases are multidrug resistant (MDR). In Estonia and Latvia, MDR 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; these are less potent than first-line drugs and are not as well tolerated. Early publications on the treatment response of MDR-TB reported considerable mortality, sometimes 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 the 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 have been increasingly reported in patients with MDR-TB [5–12], there is no consensus as to which patients should undergo surgical resection. The aim of the current 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 present study were patients who had undergone surgical lung resection for the treatment of MDR-TB at Seoul National University Hospital (Seoul, Republic of Korea), a university-affiliated tertiary referral hospital, between March 1993 and December

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2004. Although the decision to perform surgical resection was made by individual physicians, the general indication for surgical resection used in the Seoul National University Hospital was MDR-TB refractory to at least 6 months of medical treatment with a main localised lesion. The medical records, microbiology results, other laboratory results, and radiographic examinations of the enrolled patients were reviewed. The protocol of the current study was approved by the Ethical Review Committee of Seoul National University Hospital.

Definitions

The type of resistance was classified according to the definitions of the WHO [15]. 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 (BMI; $\text{kg}\cdot\text{m}^{-2}$), measured just before the operation, was 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 completed treatment according to the country's protocol and had 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 was followed by a minimum of three consecutive negative cultures, taken at least 30 days apart. Treatment failure was defined as greater than or equal to two 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, a patient who died during the course of MDR-TB treatment was included in the treatment failure group.

Statistical analysis

Data are presented as median values or mean \pm SD. Chi-squared test for comparison of categorical variables and unpaired t-test for comparison of continuous variables were applied. Variables analysed include clinical characteristics (age, sex, BMI, type of resistance and drugs used), laboratory results (drug-susceptibility tests, liver-function tests, serum creatinine level and 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 a p-value <0.20 through univariate analysis. Statistical significance was determined by a p-value <0.05 .

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 seven patients and three times in one patient because of persistently positive acid-fast bacilli smear and/or *Mycobacterium 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 (fig. 1). The clinical data of 27 out 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 (range) age was 29 (19–60) yrs. The mean BMI was 21.5 and 19.8 $\text{kg}\cdot\text{m}^{-2}$ in the male and female patients, respectively. A total of 24 (30.4%) patients had other underlying diseases. None of the enrolled patients were anti-HIV antibody seropositive. The patients had received a median (range) of six (4–8) anti-TB drugs during a median (range) of 14.5 (9–112) months before the surgery. The *M. tuberculosis* isolates from these patients were resistant to a median (range) of five (2–11) drugs. Drug resistance rates among the 79 patients are summarised in table 1. At the time of operation, 77 (97.5%) patients were *M. tuberculosis* culture positive. Cavitory lesions were evident in the chest radiographs of 77 (97.5%) patients. Among them, 28 (35.4%) patients had other cavitory lesions beyond the range of the resection. These were as follows: 25 patients had cavitory lesions in the contralateral side to the resected lung and three patients had lesions ipsilateral to the resected lung. In the latter three patients, the cavities could not be completely resected because of limited lung function.

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 (55.7%) patients. Surgical complications developed in 18 (22.8%) patients (table 2). Anti-TB medications were continued for a median (range) of 18 (9–48) months after the surgery. The treatment results were as follows: cure in 57 (72.2%) patients, treatment failure in 21 (26.6%) patients, and death in one (1.2%) patient. 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,

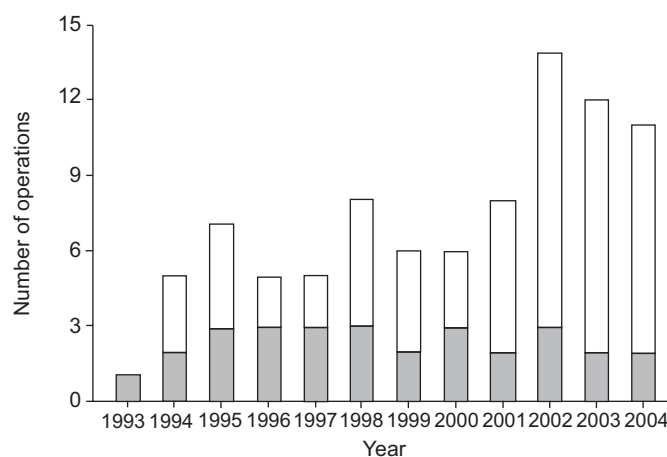


FIGURE 1. Annual numbers of lung resection surgeries in patients with multidrug-resistant tuberculosis (MDR-TB) and their results. A total of 88 operations in 79 patients with MDR-TB took place. □: successful results; ■: failure.

TABLE 1 Demographic and clinical characteristics of the 79 patients

Age yrs	29 (19–60)
Male/female n	48:31
Body mass index kg·m⁻²	
Male	21.5 (15.4–26.0)
Female	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	5 (2–11)
Resistant to neither 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	14.5 (9–112)
Persistent positive <i>Mycobacterium tuberculosis</i> culture before surgery	77 (97.5)
Number of drugs used before surgery	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	3 (3.8)
Contralateral to resected lung	25 (31.6)
Confined to one lobe	3 (3.8)
Confined to one lung	26 (32.9)
Involvement of both lungs	53 (67.1)

Data are presented as median (range) or n (%), unless otherwise indicated. COPD: chronic obstructive pulmonary disease. #: Ofloxacin was used in 21 patients, ciprofloxacin in three, levofloxacin in 44 and moxifloxacin in two.

BMI, type of resistance and 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 the variables age, sex and BMI was carried out for association with the results of surgery (table 4). BMI <18.5 kg·m⁻² ($p=0.043$), 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 the current, retrospective, cohort study, it was 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

TABLE 2 Types of surgery and results of subsequent anti-tuberculosis (TB) chemotherapy in the 79 patients with multidrug-resistant 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)
Post-operative status	
Change in the drug resistance pattern	5 out of 32 [#]
Duration of chemotherapy after surgery months	18 (9–48)
Duration of follow-up after surgery months	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

Data are presented as n (%) or median (range), unless otherwise stated. #: Pre- and post-operative drug susceptibility test results were available in 32 patients.

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 a poor prognostic factor.

Drug-resistant TB bacilli have been reported as being generally less viable than drug-sensitive bacilli both *in vitro* and *in vivo* [20], and have lower transmissibility in most cases [21, 22], although some exceptions have been reported [23, 24]. In this context, the hypothesis that transmitted bacilli with resistance to multidrugs (strains with primary resistance) are phenotypically more virulent than bacilli without definite evidence of transmissibility (strains with acquired resistance), 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 the current study should be confirmed by future studies enrolling larger numbers of patients with MDR-TB, regardless of surgical resection.

The failure rate of 27.8% seen in the current study for treatments, including surgical resection, is relatively high compared with other reports [5–12], and could be explained by several factors. First, most patients ($n=77$; 97.5%) included in the present study showed positive sputum culture for *M. tuberculosis* at the time of operation. This rate is much higher than the 50% positive sputum cultures reported among the patients in the study by POMERANTZ *et al.* [7], which showed a

TABLE 3 Individual predictors for treatment outcomes in multidrug-resistant patients who underwent surgical lung resection

	Success group	Failure group	p-value
Subjects n	57	22	
Age yrs	35 ± 14	32 ± 10	0.890
Male	36 (63.1)	12 (54.5)	0.482
BMI <18.5 kg·m ⁻²	15 (26.3)	10 (45.4)	0.101
Primary drug resistance	6 (10.5)	17 (77.3)	<0.001
<5 drugs used pre-operatively	5 (8.8)	4 (7.1)	0.238
>1 yr of pre-operative treatment	47 (82.4)	16 (72.2)	0.335
Quinolone used pre-operatively	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 >5	28 (49.1)	8 (36.4)	0.307
Multilobar involvement	54 (94.7)	22 (100)	0.273
Pre-operative positive <i>M. tuberculosis</i> culture	55 (96.5)	22 (100)	0.360
Presence of cavitory 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-pneumectomy	13 (22.8)	4 (7.1)	0.654

Data are presented as mean ± SD or n (%), unless otherwise stated. BMI: body mass index; *M. tuberculosis*: *Mycobacterium tuberculosis*.

TABLE 4 Predictors by multivariate logistic analysis for treatment failure in multidrug-resistant tuberculosis patients who underwent surgical lung resection

	Adjusted hazard ratio (95% CI)	p-value
Age [#]	1.1 (0.3–1.8)	0.878
Male	1.5 (0.7–2.9)	0.543
BMI <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 cavitory lesion beyond resection	6.4 (3.3–15.7)	<0.001

CI: confidence interval; BMI: body mass index. [#]: x+1 yrs versus x yrs.

2% failure rate. Secondly, surgical resection was used aggressively, even in patients with bilateral cavities, because no other treatment options were available. These cases increased the failure rate and showed association with unfavourable outcomes. Thirdly, because all patients with MDR-TB included in the present study had undergone surgical resection because of refractoriness to medical treatment, the results could be unfavourable when compared with 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 multidrug-resistant tuberculosis 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 body mass index, primary resistance, resistance to ofloxacin, and the presence of cavitory lesions beyond the range of the resection.

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