# Interactive CardioVascular and Thoracic Surgery

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://icvts.ctsnetjournals.org/cgi/content/full/11/4/429

Institutional report - Pulmonary

# Different morbidity after pneumonectomy: multidrug-resistant tuberculosis versus non-tuberculous mycobacterial infection

Yuji Shiraishi*, Naoya Katsuragi, Hidefumi Kita, Yoshiaki Tominaga, Miyako Hiramatsu

*Section of Chest Surgery, Fukujuji Hospital, 3-1-24 Matsuyama, Kiyose, Tokyo 204-8522, Japan*

## Abstract

To assess whether there is any difference in postoperative morbidity and mortality after pneumonectomy between patients with multidrug-resistant tuberculosis (MDR-TB) and patients with non-tuberculous mycobacterial (NTM) infections. Between January 2000 and December 2007, 61 patients with MDR-TB and 60 patients with NTM infections underwent 66 and 64 pulmonary resections, respectively. Of these, 33 patients were analyzed who underwent a pneumonectomy, including 22 patients with MDR-TB (seven right, 15 left) and 11 patients with NTM infections (seven right, four left). All bronchial stumps were covered with the *latissimus dorsi*. Patients with NTM infections were predominantly more female, older, thinner, and presented with a higher frequency of culture-positive sputum at operation than patients with MDR-TB. Operative mortality was zero. Morbidities were bronchial stump dehiscence ($n=1$) and mycobacterial empyema ($n=1$) for patients with MDR-TB, and acute respiratory failure ($n=1$), bronchial stump dehiscence ($n=5$) and mycobacterial empyema ($n=2$) for patients with NTM infections. Prevalence of bronchial stump dehiscence was significantly higher in patients with NTM infections ($P=0.010$). Five of six dehiscences occurred after right pneumonectomy. The optimal management of the bronchial stump in the setting of pneumonectomy for NTM infections needs further investigation.
© 2010 Published by European Association for Cardio-Thoracic Surgery. All rights reserved.

## 1. Introduction

Surgical resection plays an important adjunctive role in the multimodal treatment approach to multidrug-resistant tuberculosis (MDR-TB) and non-tuberculous mycobacterial (NTM) infection. Since *Mycobacterium* tuberculosis and non-tuberculous mycobacteria are species in the same mycobacterial family, similar indications for resection are used both for patients with MDR-TB and for patients with NTM infections. However, postoperative outcomes vary depending on the type of infection. Particularly, a predilection for the development of postpneumonectomy bronchopleural fistula (BPF) in patients with NTM infections has been noted [1]. This study was aimed to define the differences in postoperative morbidity and mortality after pneumonectomy for patients with MDR-TB, as compared to outcomes for patients with NTM infections.

## 2. Materials and methods

Between January 2000 and December 2007, 61 patients with MDR-TB underwent 66 pulmonary resections and 60 patients with NTM infections underwent 64 pulmonary resections. Of these 121 patients, 33 underwent pneumonectomy, including 22 patients with MDR-TB and 11 patients with NTM infections, and were analyzed in this study. Four patients undergoing completion pneumonectomy were excluded from the analysis (three with MDR-TB, one with NTM infections). The study was approved, with a waiver for patient consent, by the institutional review board on human research at Fukujuji Hospital.

There were 16 males and six females with MDR-TB at a median age of 54 years; there were three males and eight females with NTM infections at a median age of 58 years. Further patient characteristics are presented in Table 1. None of the patients was HIV-positive. In those 11 patients with NTM infections, nine patients had *Mycobacterium avium* complex disease, one patient had *Mycobacterium abscessus* disease, and one had *Mycobacterium fortuitum* disease.

Sputum smears and sputum cultures were performed upon admission or at outpatient clinic. For patients with MDR-TB, drug susceptibility testing was routinely performed on positive cultures in our laboratory [2]. Multi-drug regimens individualized based upon drug susceptibility test results were initiated in all patients. For patients with NTM infections, multi-drug regimens containing clarithromycin were initiated for patients infected with *M. avium* complex [3]. For patients infected with *M. abscessus* and with *M. fortuitum*, multi-drug regimens specialized for these organisms were initiated [4]. After giving patients chemotherapy for at least three months, we reviewed their sputum smear and culture results and radiographic appearances to examine the need for pneumonectomy. Preoperative studies

*Corresponding author. Tel.: +81-42-491-4111; fax: +81-42-492-4765.
*E-mail address:* yujishi@mvb.biglobe.ne.jp (Y. Shiraishi).

Table 1. Characteristics, pulmonary reserve, sputum status and intraoperative variables of patients in this series

| Factors | MDR-TB ($n=22$) | NTM ($n=11$) | *P*-value |
|---|---|---|---|
| Characteristic | | | |
| Sex (male/female) | 16/6 | 3/8 | 0.024 |
| Age (years)[a] | 54 (22–63) | 58 (47–69) | 0.041 |
| Body mass index[a] | 20.5 (14.4–25.8) | 16.8 (15.6–24.3) | 0.013 |
| Pulmonary reserve | | | |
| Vital capacity (% predicted)[a] | 81.2 (48.5–122.1) | 80.8 (49.5–108.1) | 0.49 |
| FEV$_1$%[a] | 75.5 (53–93.6) | 72.6 (48.3–89.4) | 0.59 |
| Perfusion to operated lung (%)[a] | 20 (4–41) | 27 (1–38) | 0.48 |
| Sputum status (positive/negative) | 8/14 | 10/1 | 0.004 |
| Intraoperative variables | | | |
| Side operated (right/left) | 7/15 | 7/4 | 0.14 |
| Operating time (min)[a] | 245 (178–442) | 252 (155–477) | 0.82 |
| Intraoperative blood loss (ml)[a] | 190 (10–1475) | 240 (75–1245) | 0.43 |

[a]Values presented as median (range).

MDR-TB, multidrug-resistant tuberculosis; NTM, non-tuberculous mycobacterial infections; FEV$_1$, forced expiratory volume in one second.

included chest X-ray, computed tomographic scan of the chest, pulmonary function tests, arterial blood gas analysis, and a quantitative perfusion scan. Emphasis was placed on ascertaining if patients had sufficient pulmonary reserve to tolerate a pneumonectomy and if they had lesions that were predominantly localized to one lung. We accepted scattered nodular lesions in the lungs on the opposite side, on the persumption that those lesions could be managed by postoperative chemotherapy.

Surgery was performed using described techniques [2, 3]. Pneumonectomy was performed either extrapleurally or intrapleurally, depending on the degree of pleural adhesions. The bronchus was divided and closed with staples in 31 patients; in two patients with NTM infections, sutured bronchial closure was used. No lymphadenectomy was performed. The bronchial stump was routinely reinforced with a *latissimus dorsi* muscle flap using interrupted 3-0 polydioxanon suture (PDS II; Ethicon, Inc, Somerville, NJ, USA). After the surgery, all but one patient were kept on chemotherapy regimens.

Operative mortality included all deaths clearly related to the operation, regardless of the postoperative interval. All bronchial stump complications and empyemas occurring during the surgical follow-up period were considered postoperative complications. Bronchial stump complications included not only BPF but also bronchial stump dehiscence without BPF.

The duration of follow-up ranged from eight to 89 months (median: 24 months) for patients with MDR-TB and from seven to 87 months (median: 41 months) for patients with NTM infections.

Categorical variables were analyzed by Fisher's exact test, and the continuous variables were analyzed by Mann–Whitney *U*-test. Statistical analyses were performed using StatView 5.0 software (SAS Institute Inc, Cary, NC, USA). A $P<0.05$ was considered statistically significant.

## 3. Results

As summarized in Table 1, patients with NTM infections tended to be female, and were older and thinner as compared to patients with MDR-TB. Prevalence of positive sputum at the time of surgery was significantly higher in patients with NTM infections than in patients with MDR-TB.

There was no operative mortality. Two complications occurred in one patient with MDR-TB, whereas eight complications occurred in five patients with NTM infections (Table 2). Acute respiratory failure occurred in a patient with *M. abscessus* disease after right pneumonectomy. The incidence of bronchial stump dehiscence was significantly higher in patients with NTM infections than in patients with MDR-TB [five of 11 (45%) vs. one of 22 (5%); $P=0.010$]. Five of six bronchial stump dehiscences (83%) occurred after right pneumonectomy, although this did not quite reach statistical significance ($P=0.062$).

For pulmonary resections other than pneumonectomy performed during the same period, bronchial stump dehiscence occurred in one of 41 resections (2%) for patients with MDR-TB, and in one of 52 resections (2%) for patients with NTM infections.

In three patients with NTM infections, bronchial stump dehiscence without empyema occurred in the relatively early postoperative phase after right pneumonectomy. One patient on a ventilator due to acute respiratory failure developed minor disruption of the hand-sewn bronchial stump two weeks postoperatively, while no increase in air was seen in the postpneumonectomy space on a chest radiograph. The patient underwent reoperative closure of the bronchus, because the stump was expected to face positive pressure ventilation for a prolonged time. Treatment was successful. The second patient developed bronchial stump dehiscence four weeks postoperatively. Increase in air space around the bronchial stump without a fall in the fluid level on a chest radiograph aroused suspi-

Table 2. Postoperative complications

| Postoperative complications | MDR-TB ($n=1$) | NTM ($n=5$) |
|---|---|---|
| Acute respiratory failure | 0 | 1 |
| Bronchial stump dehiscence | 1 | 5 (1[a]) |
| Early onset | 0 | 3 |
| Late onset | 1 | 2 (1[a]) |
| Mycobacterial empyema | 1 | 2 |
| Total | 2 | 8 |

[a]The numbers of bronchial stump dehiscence occurring on the left side are shown in parentheses.

MDR-TB, multidrug-resistant tuberculosis; NTM, non-tuberculous mycobacterial infections.

cion, though the patient was asymptomatic. Since the muscle flap prevented the stump from being disrupted any further, the dehiscence spontaneously closed without consequence. The third patient developed BPF 2.3 months postoperatively. A fall in the fluid level on a chest radiograph aroused suspicion, and the patient was asymptomatic. The fistula was successfully treated by reoperative closure of the bronchial stump.

In two patients with NTM infections, BPF with NTM empyema occurred in the late postoperative phase. One patient developed BPF six months after right pneumonectomy, and the other, nine months after left pneumonectomy. Both patients underwent an open window thoracostomy. In one patient, we found that the muscle flap had failed. One patient with MDR-TB developed bronchial stump dehiscence five months after right pneumonectomy. Lavage fluid from the bronchial stump was positive for MDR-TB. The patient underwent an open window thoracostomy. Over time, the muscle flap covering the bronchial stump was gradually eroded by the uncontrollable tuberculous infection. The patient finally developed BPF 12 months after the initial operation, resulting in tuberculous empyema.

All patients attained sputum-negative status after their surgery. Relapse occurred in one patient with MDR-TB and in three patients with NTM infections. Two late deaths without evidence of relapse occurred for patients with MDR-TB. The first death due to cerebral infarction occurred eight months postoperatively. The second death due to an unknown cause occurred 14 months postoperatively. Five late deaths due to respiratory failure occurred for patients with NTM infections. The first occurred 11 months postoperatively in the patient who developed acute respiratory failure. The second and third occurred seven and 18 months postoperatively, respectively, in the patients developing BPF with NTM empyema. The fourth occurred 29 months postoperatively in a patient with relapse, and the fifth occurred 75 months postoperatively in a patient without relapse.

## 4. Discussion

The recent emergence of MDR-TB [5] and the increased association of non-tuberculous mycobacteria with pulmonary disease [6] have revived surgical treatment as part of a multidisciplinary treatment approach to intractable mycobacterial diseases [1, 7–10]. Surgical treatment is offered to patients with limited disease for the removal of the heavy bacterial burdens in the gross lesions which hamper the efficacy of medical treatment. When patients have multiple cavities in one lung or have an entirely destroyed lung with predominantly unilateral major lesions, we may consider treating these patients by pneumonectomy. Since *Mycobacterium* tuberculosis and non-tuberculous mycobacteria appear quite similar under the microscope, one might expect that both groups of patients should have comparable postoperative outcomes after pneumonectomy. In this study, we were able to perform pneumonectomy with zero operative mortality for each group. However, we encountered a higher incidence of bronchial stump complications in patients with NTM infections than in patients with MDR-TB. This predilection for the development of postpneumonectomy BPF in patients with NTM infections was first reported by Pomerantz and associates nearly two decades ago [1].

The distinctive feature of the present study was the higher prevalence of positive sputum culture at the time of surgery in patients with NTM infections than in patients with MDR-TB. This may reflect the fact that patients with MDR-TB are more likely to respond to anti-mycobacterial chemotherapy because individualized multidrug regimens can be created based upon our drug susceptibility test results. Another explanation may be selection bias. Although we applied the same indications to both groups of patients, we have tended to perform pneumonectomy on patients with NTM infections who had suffered long-standing disease refractory to medical treatment as a last resort.

We basically closed bronchial stumps with staples, and always buttressed bronchial stumps with the *latissimus dorsi*. This management of the bronchial stump is quite effective in the prevention of bronchial stump dehiscence for patients with MDR-TB. However, it is unexpectedly less effective for patients with NTM infections, especially for those who undergo a right pneumonectomy. In contrast, we could achieve an acceptably low incidence of bronchial stump dehiscence when we performed subtotal pulmonary resections on patients with NTM infections. Mitchell and colleagues reported similar experience where nine of 11 BPFs complicating pulmonary resection for NTM disease occurred after right pneumonectomy [10]. Although right pneumonectomy itself has been a risk factor for BPF [11, 12], patients with advanced NTM disease requiring right pneumonectomy may have a distinctive vulnerability to bronchial stump complications. We speculate the following predisposing factors. As NTM disease progresses, it spreads from the main cavitary or bronchiectatic lesions transbronchially along the draining bronchus [13, 14]. Since the right main bronchus is shorter than the left main bronchus, the proximal main bronchus is more prone to be affected on the right side. Consequently, we are more likely to be compelled to divide the main bronchus at its diseased site when doing a right pneumonectomy. To make matters worse, positive sputum at the time of surgery increases the risk of bronchial stump contamination with non-tuberculous mycobacteria. The existence of the diseased bronchial wall and continued indolent mycobacterial infections at the bronchial stump may hinder wound healing.

This etiology of bronchial stump dehiscence may be different from that in other situations associated with impaired bronchial stump healing, such as pneumonectomy after high-dose radiation and concurrent chemotherapy for lung cancer, where devascularization of bronchial stump is a main predisposing factor. Bronchial stump reinforcement with omental flap rather than muscle flap may be more helpful to prevent infection-related dehiscence, as Mitchell and colleagues have proposed [10]. Their limited experience implies that, in the setting of right pneumonectomy, omental transposition is more effective than muscle transposition in the prevention of BPF. We cannot elucidate which technique of closure is more appropriate for the possibly diseased and contaminated bronchial stump, stapling or hand-sewn technique. Although we mainly used a stapling technique, we would agree with Mitchell and

colleagues, who favor hand-sewn closure in the setting of right pneumonectomy [10].

This study has several limitations. First, the number of patients enrolled is relatively small. Second, since this is a retrospective study, the characteristics of the two groups of patients are not well-matched. Nevertheless, we assume that pneumonectomy should be performed liberally for patients with MDR-TB whenever indicated. In view of the high morbidity after pneumonectomy, pulmonary resection should be considered for patients with early stage NTM disease when subtotal resection can still be performed. The optimal management of the bronchial stump in the setting of pneumonectomy for advanced NTM disease needs further investigation.

## References

[1] Pomerantz M, Madsen L, Goble M, Iseman M. Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. Ann Thorac Surg 1991;52:1108–1111.

[2] Shiraishi Y, Nakajima Y, Katsuragi N, Kurai M, Takahashi N. Resectional surgery combined with chemotherapy remains the treatment of choice for multidrug-resistant tuberculosis. J Thorac Cardiovasc Surg 2004;128: 523–528.

[3] Shiraishi Y, Nakajima Y, Takasuna K, Hanaoka T, Katsuragi N, Konno H. Surgery for Mycobacterium avium complex lung disease in the clarithromycin era. Eur J Cardiothorac Surg 2002;21:314–318.

[4] Daley CL, Griffith DE. Pulmonary disease caused by rapidly growing mycobacteria. Clin Chest Med 2002;23:623–632.

[5] Nachega JB, Chaisson RE. Tuberculosis drug resistance. A global threat. Clin Infect Dis 2003;36(Suppl 1):S24–S30.

[6] Marras TK, Daley CL. Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 2002;23:553–567.

[7] Sung S-W, Kang CH, Kim YT, Han SK, Shim Y-S, Kim JH. Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. Eur J Cardiothorac Surg 1999;16:187–193.

[8] Pomerantz BJ, Cleveland JC Jr, Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis. J Thorac Cardiovasc Surg 2001;121:448–453.

[9] Nelson KG, Griffith DE, Brown BA, Wallace RJ Jr. Results of operation in Mycobacterium avium-intracellulare lung disease. Ann Thorac Surg 1998;66:325–330.

[10] Mitchell JD, Bishop A, Cafaro A, Weyant MJ, Pomerantz M. Anatomic lung resection for nontuberculous mycobacterial disease. Ann Thorac Surg 2008;85:1887–1893.

[11] Deschamps C, Bernard A, Nichols FC III, Allen MS, Miller DL, Trastek VF, Jenkins GD, Pairolero PC. Empyema and bronchopleural fistula after pneumonectomy: factors affecting incidence. Ann Thorac Surg 2001; 72:243–247.

[12] Darling GE, Abdurahman A, Yi QL, Johnston M, Waddell TK, Pierre A, Keshavjee S, Ginsberg R. Risk of right pneumonectomy: role of bronchopleural fistula. Ann Thorac Surg 2005;79:433–437.

[13] Tanaka D, Niwatsukino H, Oyama T, Nakajo M. Progressing features of atypical mycobacterial infection in the lung on conventional and high-resolution CT (HRCT) images. Radiat Med 2001;19:237–245.

[14] Kim TS, Koh WJ, Han J, Chung MJ, Lee JH, Lee KS, Kwon OJ. Hypothesis on the evolution of cavitary lesions in nontuberculous mycobacterial pulmonary infection: thin-section CT and histopathologic correlation. Am J Roentgenol 2005;184:1247–1252.

**Different morbidity after pneumonectomy: multidrug-resistant tuberculosis versus non-tuberculous mycobacterial infection**

Yuji Shiraishi, Naoya Katsuragi, Hidefumi Kita, Yoshiaki Tominaga and Miyako Hiramatsu

**This information is current as of October 14, 2011**

| | |
|---|---|
| **Updated Information & Services** | including high-resolution figures, can be found at: http://icvts.ctsnetjournals.org/cgi/content/full/11/4/429 |
| **References** | This article cites 14 articles, 10 of which you can access for free at: http://icvts.ctsnetjournals.org/cgi/content/full/11/4/429#BIBL |
| **Subspecialty Collections** | This article, along with others on similar topics, appears in the following collection(s): **Lung - other** http://icvts.ctsnetjournals.org/cgi/collection/lung_other |
| **Permissions & Licensing** | Requests to reproducing this article in parts (figures, tables) or in its entirety should be submitted to: icvts@ejcts.ch |
| **Reprints** | For information about ordering reprints, please email: icvts@ejcts.ch |

# Interactive CardioVascular and Thoracic Surgery