



# Clinico-bacteriological analysis for video-assisted thoracoscopic biopsy of non-tuberculous mycobacteria

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**Background:** The prevalence of non-tuberculous mycobacteria (NTM) has been increasing in recent years, and thus the number of related surgeries. In recent studies, a few recent studies reported that NTM patients require preoperative treatment. In addition, some cases are found to be granuloma suspected to be NTM (gsNTM) after surgery. We conducted a clinico-bacteriological examination of resected NTM and gsNTM cases we managed.

**Methods:** Between 2003 and 2017, 82 patients with NTM and gsNTM underwent video-assisted thoracoscopic (VATS) biopsy at our institution. The objectives of surgery, perioperative treatment, progression of NTM and gsNTM, and bacteriological data were analyzed.

**Results:** We enrolled 42 men and 40 women with a median age of 65 years. The bacteriological findings were *Mycobacterium avium* in 38 cases, *M. intracellulare* in 6 cases, *M. kansasii* in 3 cases, and gsNTM in 35 cases. The objectives of surgery were the diagnosis in 77 cases, and resistance to treatment in 6 cases. We performed postoperative treatment in 8 cases. There was no surgery-related (30-day mortality) death or complication.

**Conclusions:** We analyzed surgical outcome for pulmonary NTM infections. We need to reconsider the surgical procedure for single pulmonary NTM lesion and whether adjuvant chemotherapy is necessary for NTM treatment.

**Keywords:** Non-tuberculous mycobacteria (NTM); resection of pulmonary infection; video-assisted thoracoscopic surgery (VATS)

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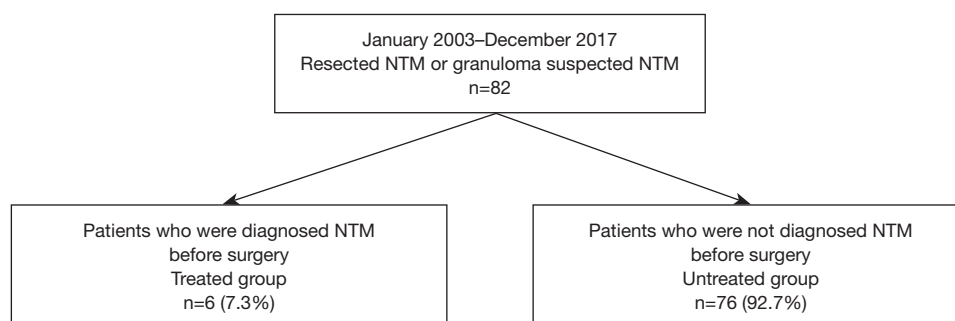
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## Introduction

Human infections due to *Mycobacterium* have been mainly attributable to *Mycobacterium tuberculosis* (TB) (1). However, species of mycobacterium other than *Mycobacterium avium* (*M. leprae*) that cause clinical disease have been identified, such as non-tuberculous mycobacteria (NTM). Similar to TB, NTM infections can occur throughout the body. However, pulmonary infections, lymphadenitis, skin, and

soft tissue infections are the most commonly described (2). The prevalence of NTM has been increasing in recent years, and thus the number of related surgeries. The estimated incidence of pulmonary NTM disease in Japan has increased from 1.5 per 100,000 in 1985 to 3.52 in 1997 (3). However, the effectiveness of surgery for NTM remains unclear. According to the 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) statement on NTM, the primary treatment involves



**Figure 1** Flow chart of patients analyzed in this study.

a multidrug treatment regimen (4). Moreover, surgery for NTM is performed for patients in whom pulmonary nodules are resistant to antimycobacterial therapy. However, pulmonary nodules suspected to be lung cancer are commonly treated surgically to reveal NTM. We also observe cases of granuloma that are suspected to be NTM; however, no bacteria are detected.

This study aimed to clarify the clinical outcomes of the therapeutic resection and video-assisted thoracoscopic (VATS) biopsy for NTM or granuloma suspected to be NTM (gsNTM).

## Methods

Between January 2003 and December 2017, 82 patients (83 surgeries) underwent therapeutic resection and VATS biopsy for NTM in the Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. A retrospective chart review was performed for the clinical records. This study was performed after obtaining approval from the institutional review board. Most pulmonary nodules were suspected to be lung cancer but were subsequently revealed to be NTM or gsNTM. Patients suspected of NTM underwent bronchoscopy and confirmed their diagnosis on bronchoalveolar lavage. All the patients with proven NTM infections (diagnosed from bronchoalveolar lavage) were given preoperative treatment with antimycobacterial therapy, including various combinations of clarithromycin, ethambutol, and rifampicin (3) (*Figure 1*). We defined gsNTM as granuloma and histiocytes or macrophages were observed in the resected nodules and no bacteria were detected in Ziel-Neelsen stain. We retrospectively reviewed the clinical and bacterial findings, preoperative and postoperative antimycobacterial therapy, surgical procedure, pathological findings, and NTM progression.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the Institutional Review Board of Komagome Hospital. The duration of NTM progression following resection was calculated from the date of the surgical procedures and analyzed with the Kaplan-Meier method. Potential prognostic factors of progression-free survival were analyzed with the log-rank method and the Cox proportional hazards model. P values <0.05 were considered significant. We used EZR Version 1.35 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for statistical analyses.

## Results

The median age of the 82 patients was 65 years (25–85 years), and 40 were men. The median duration of postoperative follow-up was 31 months (interquartile range, 1–162 months). *Table 1* shows the patient characteristics of the subjects in both groups. Indication for surgery was resistance for antimycobacterial therapy in 6 cases (preoperative treated group) and the diagnosis of pulmonary nodules in 76 cases (preoperative untreated group). Thirty-six subjects were smokers, and the median smoking index was 420 [2–1,220]. The median size of the nodules was 0.9 cm (0.2–5.5 cm) in the preoperative treated group and 1.5 cm (0.1–5.2 cm) in the untreated group; multiple surgeries were performed in only 1 case in the preoperative untreated group. In the untreated group, localized nodules were confirmed in 71 cases. The bacteriological findings were *M. avium* in 5 cases and *M. intracellulare* in 1 case in the preoperative treated group; the findings indicated *M. avium* in 33 cases, *M. intracellulare* in 5 cases, *M. kansasii* in 3 cases, and gsNTM in 35 cases in the untreated group. In the preoperative CT findings, there were 3 nodules exhibiting

**Table 1** Characteristics of the patients who underwent pulmonary resection for NTM

Characteristics	Preoperative treated group (N=6)	Preoperative untreated group (N=76)	P value
Range of age [median], years	44–70 [63]	25–85 [65]	0.691
Gender			1.000
Male	3	39	
Female	3	37	
Smoking			0.693
Yes	2	34	
No	4	42	
Range of Brinkmann Index (median)	0–400 (0)	0–1,220 (0)	0.349
Range of the size of nodule (median), cm	0.2–5.5 (0.9)	0.1–5.2 (1.5)	0.993
Multiple surgeries			1.000
Yes	0	1	
No	6	75	
Multiple nodules			1.000
Yes	0	5	
No	6	71	
Pathological findings			0.108
<i>M. avium</i>	5	33	
<i>M. intracellulare</i>	1	5	
<i>M. kansasii</i>	0	3	
No definite diagnosis of species	0	35	
Preoperative CT findings			1.000
Nodules exhibiting GGO	0	3	
Solid nodule	6	73	

NTM, non-tuberculous mycobacteria; GGO, ground-glass opacity.

ground-glass opacity in the preoperative untreated group and the remaining were solid nodules. The surgical data are summarized in *Table 2*. The surgical procedures were lobectomy in 3 cases and segmentectomy in 3 cases in the preoperative treated group, while they were wedge resection in 64 cases (65 surgeries), lobectomy in 7 cases, segmentectomy in 3 cases, and mediastinal lymph node biopsy in 2 cases in the preoperative untreated group.

We performed lobectomy or segmentectomy in all the cases in the preoperatively treated group. We performed postoperative treatment in 8 cases and only surgery in 74 cases. NTM progression was observed in 7 cases, and 2 patients died due to causes other than lung disease; the cause of death was colorectal cancer in 1 case and interstitial

pneumonia in 1 case.

*Table 3* shows the characteristics of the patients in the preoperative treated group. In all the cases, they were treated with clarithromycin, ethambutol, and rifampicin. Only in 1 case, we could not continue treatment because of complications. However, in the other 5 cases, we could continue preoperative treatment for >2 months. In these cases, NTM progression was confirmed in 1 case because we did not perform post-operative treatment at the request of the patient.

*Table 4* shows the characteristics of the 7 patients with postoperative progression of NTM; 1 patient was in the treated group and 6 were in the untreated group. Residual diseases were confirmed in 3 patients; 2 of whom underwent

**Table 2** Surgical details of pulmonary resection for NTM

Variables	Preoperative treated group (N=6)	Preoperative untreated group (N=76)	P value
Surgical procedure			0.018
Wedge resection	0	64	
Lobectomy	3	7	
Segmentectomy	3	3	
Mediastinal lymph node biopsy	0	2	
Postoperative therapy			0.011
Yes	3	5	
No	3	71	
Recurrence or progression of NTM			0.421
Yes	1	6	
No	5	70	
30-day all-cause postoperative mortality and complications	0	0	1.000
Death during the observation period	0	2	1.000

NTM, non-tuberculous mycobacteria.

**Table 3** Characteristics of the patients who received preoperative treatment

Cases	Preoperative treatment content	Duration of preoperative treatment (days)	Complications for preoperative treatment	Medical past history	Residual disease	Postoperative treatment	Recurrence or progression of NTM
1	CRE	1,081	None	Colorectal cancer	None	None	Yes
2	CRE	134	None	DM	None	Yes	None
3	CRE	167	None	Colorectal cancer	None	None	None
4	CRE	211	None	None	None	Yes	None
5	CRE	142	None	CML	None	Yes	None
6	CRE	41	Yes	None	None	None	None

CRE, clarithromycin + rifampicin + ethambutol; NTM, non-tuberculous mycobacteria; DM, diabetes mellitus; CML, chronic myeloid leukemia.

postoperative therapy, and the other refused postoperative therapy. Patients who were not treated with postoperative therapy and showed a progression of NTM were all performed chemotherapy because of other diseases.

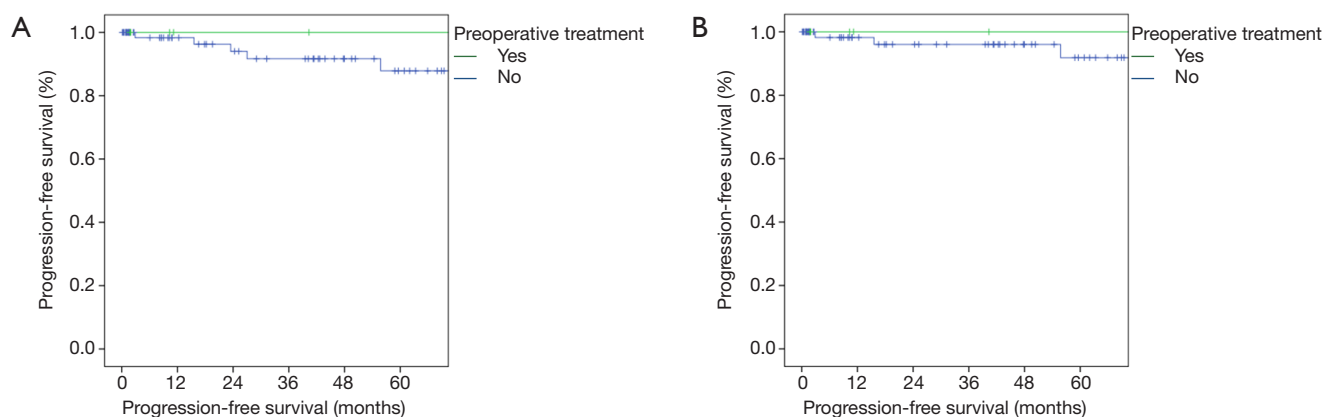
Univariate analyses of the variables of sex, age, smoking index, tumor size, pathological findings, surgery procedures (wedge resection or not), and induction therapies for surgery were performed for NTM progression. No prognostic factor was revealed. The 5-year progression-

free rate was 100% in the treated group and 87.8% in the untreated group (*Figure 2A*). In the untreated group, wedge resection in 64 cases (65 surgeries), lobectomy in 7 cases, segmentectomy in 3 cases, and mediastinal lymph node biopsy in 2 cases were performed. The 5-year progression-free rate was 100% in the treated group and 91.9% in the untreated group without residual disease (*Figure 2B*). The differences between the two groups were not statistically significant.

**Table 4** Characteristics of the patients with postoperative progression or recurrence of NTM

Cases	Preoperative treatment	Preoperative treatment content	Duration of preoperative treatment (days)	Medical history	Residual disease	Duration from surgery to progression or recurrence of NTM	Treatment content for progression or recurrence of NTM
1	None	–	–	None	Yes	4,555	LVFX
2	None	–	–	None	None	1,673	CRE
3	None	–	–	SJS	Yes	810	CRE
4	Yes	CRE	211	None	None	87	CRE
5	None	–	–	RA	None	467	CRE
6	None	–	–	None	Yes	704	GRNX
7	None	–	–	BC	None	2,908	CRE

CRE, clarithromycin + rifampicin + ethambutol; NTM, non-tuberculous mycobacteria; SJS, Sjogren syndrome; RA, rheumatoid arthritis; BC, breast cancer; LVFX, levofloxacin; GRNX, garenoxacin.

**Figure 2** Progression-free survival curves of preoperative treated and untreated patients with pulmonary resection (A) and complete resection (B) for NTM.

## Discussion

This study evaluated the outcomes in 82 patients who underwent VATS biopsy for NTM lung disease. The treatment of NTM lung disease is challenging with medication alone; however, the introduction of new antimycobacterial therapy improved the outcome of using medical treatment alone (4,5). However, the most common indication in our case for surgery was the diagnosis of pulmonary nodules suspected to be lung cancer (untreated group). The second indication was a poor response to antibiotic therapy (treated group). Pathological findings showed that *M. avium* was the most frequent pathology in both the groups, and gsNTM (46%) of the untreated group. We performed VATS in all 82 patients (83 cases,

100%); the surgical procedures were lobectomy in 3 cases and segmentectomy in 3 cases in the preoperative treated group; the procedure was wedge resection in 64 cases (65 surgeries), lobectomy in 7 cases, segmentectomy in 3 cases, and mediastinal lymph node biopsy in 2 cases in the preoperative untreated group. The postoperative complication rate was none in both the groups. In recent studies, resected NTM cases were reported after the diagnosis was confirmed; however, there are few reports of undiagnosed cases (6-10). Thus, the present study is the first case series to evaluate the role of resection surgery for undiagnosed NTM lung disease.

NTM is found in the soil and water, and can produce opportunistic lung infections. The indolent nature of NTM disease may result in extensive parenchymal destruction,

resulting in respiratory failure and vulnerability to airway infection; this may prove fatal (6,7). However, the true incidence and prevalence of pulmonary NTM disease remains unclear, and reports suggest that the prevalence of pulmonary NTM disease is increasing (3). In many species of mycobacteria classified as NTM, only a few species of NTM are known to cause pulmonary disease (4). In Japan, *M. avium* complex (MAC) are the most common, and *M. kansasii* is the second most common NTM (8). Moreover, *M. kansasii* is the only NTM disease that can be successfully treated with a multidrug regimen alone (9). In our cases, only 3 patients were infected with *M. kansasii*, were given only surgery and postoperative progression or recurrence was not observed.

With respect to surgeries for pulmonary NTM, based on the 2007 ATS/IDSA statement, in 2008, guidelines were published for surgical therapy for pulmonary NTM disease (1). The guideline showed that surgical therapy is intended to control the patients' disease condition. NTM is caused by environmental mycobacteria, as previously described, therefore, patients who have undergone surgery may exhibit relapse or reinfection in the remaining lungs. It is difficult to achieve complete cure with only surgery. The policy also emphasizes the importance of pre- and post-operative chemotherapy. Whether patients who undergo surgical resection of a solitary nodule related NTM can be exempted from post-operative chemotherapy remains controversial.

Concerning the procedure of lung resection, segmentectomy or greater resection is recommended because NTM can progress throughout the airways. However, the optimal timing of surgery remains ambiguous; the guidelines (1) recommend that surgery should be performed after at least 3–6 months of chemotherapy. In clinical practice, the duration of pre-operative chemotherapy tends to be longer. Shiraishi and colleagues reported that the duration of preoperative chemotherapy ranged from 3.3 to 75.2 months (median, 14.2 months) (9). However, there are cases that cannot be treated because of adverse events, such as liver damage; early surgery is performed in these cases.

Post-operative chemotherapy should also be performed according to Japanese Society for Tuberculosis (JST) guideline for management of pulmonary NTM. The regimen may be the same as that for preoperative therapy. However, the optimal duration of post-operative chemotherapy remains controversial. So far, there is no evidence to support any particular duration. The JST guidelines recommend that chemotherapy be continued for

at least 1 year postoperatively (4). Shiraishi and colleagues reported that the duration of post-operative chemotherapy ranged from 5.7 to 62 months (median, 24 months) (9).

In our cases, we started induction chemotherapy for all the cases with a preoperative diagnosis (treated group); however, in 1 case, we stopped treatment because of adverse events. Further, segmentectomy or lobectomy was performed for all cases and all cases we diagnosed NTM met the AST/IDSA criteria for NTM pulmonary disease. Three patients received adjuvant chemotherapy, 3 did not because of adverse events and comorbidities. The postoperative recurrence or progression of NTM was confirmed in 1 case (16.7%) in the treated group and in 6 cases (7.9%) of the untreated group. In 3 cases on untreated group, adjuvant chemotherapy could not be given because of immunodeficiency state. In the untreated group, postoperative therapy was performed for 5 patients because of residual diseases, in which NTM progression was confirmed in 2 cases (40.0%). However, in localized and untreated cases (71 cases), recurrence or progression was confirmed only in 3 cases (4.2%). Recent studies have reported a postoperative recurrence or progression rate of 10% in the wedge resection group and 23% in the lobectomy group (10). In our cases, postoperative recurrence or progression rate was lower than the previous report. Moreover, we could not detect any significant difference in prognostic factors in the preoperatively treated and untreated groups. Based on these results, there is a possibility that lobectomy or adjuvant chemotherapy need not be performed in cases in which the diagnosis was NTM in isolated undiagnosed pulmonary nodules.

This study has certain limitations. First, there was a selection bias in the decision-making regarding surgery. Patients with multiple comorbidities were excluded from surgery. These selection criteria favor surgical outcomes by eliminating patients who were expected to have poor prognosis. If all the patients underwent surgery, the outcomes might have been similar to those with only medical therapy. Second, we did not compare our patients with those who developed NTM but did not undergo surgical resection. This would have given context to the surgery indications and may have allowed us to compare the duration of antimycobacterial treatment and long-term outcomes in both the groups. Another limitation of this study was the relatively small size and heterogeneity of the patient sample that considerably limited our ability to analyze the predictors of progression.

Despite these limitations, as a few cases were reported on



resected proven or probable NTM, multicenter prospective study including surgical indication is aimed.

## Conclusions

We analyzed patients who underwent VATS biopsy for pulmonary NTM infections. We need to reconsider the surgical procedure for single pulmonary NTM lesion and whether adjuvant chemotherapy is necessary for NTM treatment.

## Acknowledgments

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* Data collection and analyses were approved (No. 2092), and the need to obtain written informed consent from each patient was waived by the Institutional Review Board of Komagome Hospital. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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