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ORIGINAL ARTICLE

Outcomes and risk factors after adjuvant surgical treatments for *Mycobacterium avium* complex lung disease

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Abstract

Background Limited information is currently available on the postoperative outcomes of *Mycobacterium avium* complex lung disease (MAC-LD).

Objective To show the outcomes of pulmonary resection and identify risk factors after adjuvant surgical treatments for MAC-LD.

Methods One hundred and eight patients underwent adjuvant lung resection for MAC-LD at two hospitals between January 2008 and July 2016. We retrospectively evaluated outcomes and risk factors.

Results Postoperative complications occurred in 14 patients (13%). After lung resection, 98 out of 108 patients (91%) achieved sputum culture conversion, eight (8.2%) of whom developed microbiological recurrence during the follow-up period. As a result, the success rate of adjuvant surgical treatments for MAC-LD with drug resistance was 83%. A multivariable analysis showed that a longer period from the initial medical treatment to surgery (hazard ratio, 1.01; 95% confidence interval, 1.00–1.02; $p=0.008$) was independently associated with an increased risk of unfavorable outcomes after adjuvant surgery.

Conclusions Adjuvant surgical treatments for MAC-LD have acceptable outcomes. Better control of the disease may be achieved in some patients with drug resistance and indications for surgery through surgical treatments, and pulmonary resection needs to be performed earlier rather than continuing chemotherapy in these patients because it reduces unfavorable outcomes.

Keywords MAC · NTM · Adjuvant surgery · VATS · Recurrence

Introduction

Although the incidence of lung disease caused by nontuberculous mycobacteria has been increasing worldwide [1, 2], definitive drugs have not yet been developed. Antimicrobial chemotherapy is the mainstay of treatment for nontuberculous mycobacterial lung disease (NTM-LD); however, treatment success rates for patients receiving combination antibiotic treatments are still unsatisfactory even after the introduction of newer macrolide-containing regimens [3–6]. Therefore, surgery may play an important adjunct role to antimicrobial treatments in patients with drug resistance and indications for surgery.

However, information on the outcomes of adjuvant surgery remains limited. We only found two studies on surgery for NTM-LD that met the 2007 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines [7, 8]. Furthermore, most subjects for adjuvant surgical treatments in NTM-LD are etiologically *Mycobacterium avium* complex (MAC) and *M. abscessus*; however, MAC and *M. abscessus* belong to different *Runyon* classifications, which classifies nontuberculous mycobacteria into four groups based on the rate of growth, production of yellow pigment and whether this pigment is produced in the dark or only after exposure to light, and are treated by different drug regimens [9, 10]. Therefore, when examining outcomes after adjuvant surgery, MAC-LD and *M. abscessus* lung diseases

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need to be considered separately. Although more than two-thirds of NTM-LD cases are caused by MAC [11, 12], the outcomes of adjuvant surgical treatments for MAC-LD have not yet been investigated. Furthermore, there is currently no detailed information on recurrence after surgery.

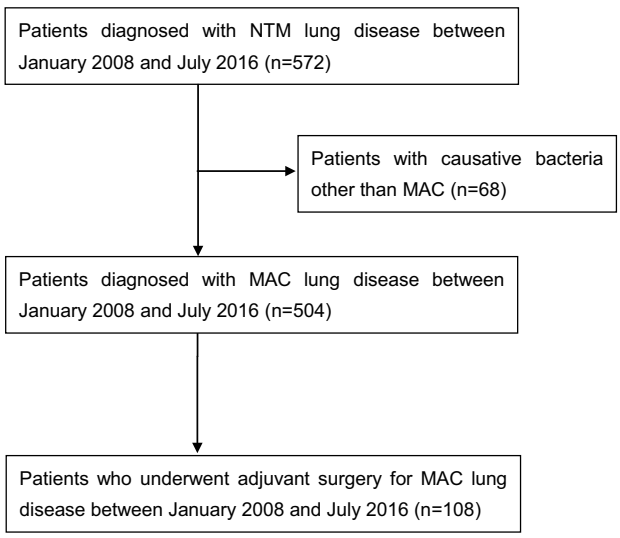
Therefore, the present study was performed to examine the outcomes of pulmonary resection and identify risk factors for unfavorable outcomes after surgery in order to clarify the optimal role of adjuvant surgical treatments for MAC-LD that meets the 2007 ATS/IDSA guidelines.

Methods

Study subjects

We retrospectively reviewed the medical records of all patients who underwent adjuvant pulmonary resection for MAC-LD at the National Hospital Organization Higashinagoya National Hospital (a 415-bed referral hospital in Nagoya, Japan) and the National Hospital Organization Nagoya Medical Center (a 740-bed referral hospital in Nagoya, Japan) between January 2008 and July 2016. During that period, 572 patients were diagnosed with NTM-LD. Excluding other causative bacteria, 504 patients were diagnosed with MAC-LD, 108 (21%) underwent adjuvant surgical treatments (Fig. 1).

All patients fulfilled the 2007 ATS/IDSA diagnostic criteria for MAC-LD: (1) pulmonary symptoms, nodular or cavitary opacities on chest radiographs or multifocal bronchiectasis with multiple small nodules on high-resolution computed tomography scans; (2) positive culture results from at least two separate expectorated sputum samples or from at least one bronchial wash or lavage, and (3) the exclusion of other diagnoses [10].



MAC Mycobacterium avium complex; *NTM* nontuberculous mycobacteria

Fig. 1 Selection of patients in the present study

We classified chest radiography and computed tomography (CT) scan findings as showing the nodular-bronchiectatic form, fibrocavitary form, or nodular-bronchiectatic + fibrocavitary form [13]. When the disease did not belong to the three groups, it was deemed unclassifiable.

The study protocol was approved by the Institutional Review Board of the National Hospital Organization Higashinagoya National Hospital to review and publish information obtained from patient records (IRB No. 29-7). The requirement for informed consent was waived because of the retrospective nature of the analysis.

Pre- and postoperative antibiotic treatments

All patients with MAC-LD, excluding two with clarithromycin-resistant infections, received standard combination antibiotic therapy consisting of an oral macrolide (clarithromycin), ethambutol, and rifampicin for at least 3 months. When necessary, an intramuscular aminoglycoside injection and/or oral fluoroquinolone was added to the regimen.

The same oral antibiotic regimen was maintained after surgical resection.

Surgical treatments

Patients were selected for pulmonary resection based on discussions in a multidisciplinary conference including pulmonary physicians and surgeons. Indications for pulmonary resection generally included (a) a poor response to medical therapy and disease progression; (b) remnant cavity lesions and/or severe focal bronchiectasis, and (c) the development of complications, such as massive hemoptysis, with reference to the 2007 ATS/IDSA guidelines. We carefully selected patients who may benefit from pulmonary resection. Surgical candidates had to have sufficient pulmonary function [> 40% of the predictive postoperative forced expiratory volume in one second (FEV_1)] to tolerate pulmonary resection [14]. Patients generally performed respiratory function training every day for more than 3 months before surgery, except for massive hemoptysis cases.

The standard preoperative work-up included chest radiography, chest CT, pulmonary function tests, and electrocardiography. Surgery was performed under general anesthesia using a double-lumen endobronchial tube. Anatomical resection, such as lobectomy or segmentectomy, was performed to resect pulmonary lesions. Video-assisted thoracoscopic surgery (VATS) without minithoracotomy was generally performed. In patients in whom dense pleural adhesion was recognized, VATS was transferred to minithoracotomy with video assistance or posterolateral thoracotomy.

Data collection

The medical records of 108 patients with adjuvant surgical treatments were retrospectively analyzed in August 2017. Data including age, sex, body mass index (BMI), medical history, pathogenic bacteria, chest CT findings, treatment durations, and antimicrobial treatment were recorded. The following variables were evaluated for their relationship with surgical treatments: (1) the type of pulmonary resection; (2) surgical approach; (3) postoperative complications; (4) postoperative hospitalization period, and (5) follow-up period after surgery.

Favorable and unfavorable outcome groups

We defined the unfavorable outcome group as follows: patients who failed sputum conversion to negative for MAC or who had microbiological recurrence during the follow-up period after surgery. Microbiological recurrence was defined by two or more positive sputum cultures regardless of radiological findings [15]. Patients who achieved sputum conversion and had no recurrence after surgery were designated as the favorable outcome group.

Statistical analysis

Times to unfavorable outcomes were assessed by the Kaplan–Meier method. Cox's model was used to calculate the effects for unfavorable outcomes. Independent variables were selected based on their significance in a univariate analysis. All tests of significance were two-sided; *P* values of <0.05 were considered to be significant. All analyses were performed with EZR software (version 1.35; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.0.3; The R Foundation for Statistical Computing, Vienna, Austria) [16].

Results

Subject characteristics

A total of 108 patients included 71 females (66%) with a median age of 55 years [interquartile range (IQR), 48–64 years]. Median BMI was 19.0 (IQR, 18.3–21.1) kg/m^2. None of the patients had a previous history of lung resection.

The etiological species was *M. avium* in 81 patients (75%) and *M. intracellulare* in 27 (25%). Radiographic features included the nodular-bronchiectatic form in 61 patients (56%), the fibrocavitary form in 17 (16%), the nodular-bronchiectatic + fibrocavitary form in 27 (25%), and an unclassifiable form in three (2.8%) (Table 1).

Medical and surgical treatments

Two patients had clarithromycin-resistant infections. Twenty-seven patients (25%) were orally administered fluoroquinolone, while 83 (77%) were given an intramuscular aminoglycoside injection. However, nine patients discontinued rifampicin due to side effects, such as liver damage and/or skin rash, ten discontinued ethambutol due to visual impairment, and four discontinued aminoglycoside due to hearing loss or skin rash. The median duration from initial chemotherapy to surgery was 35 (IQR, 14.5–80) months (Table 1).

All patients indicated for surgery showed poor responses to medical therapy and disease progression, and had remnant cavity lesions and/or severe focal bronchiectasis. Four patients had massive hemoptysis. Regarding the surgical approach, VATS without minithoracotomy, minithoracotomy with video assistance, and open thoracotomy were performed in 87 (75%), 19 (16%), and 10 (9%) resections, respectively. None of the patients underwent bronchial stump reinforcement (Table 2).

Table 1 Demographic and clinical characteristics of 108 patients who underwent adjuvant surgery for MAC lung disease

Characteristic (unit)	No. (%) or median (IQR)
Age (year)	55 (48–64)
Female gender	71 (65.7)
BMI (kg/m^2)	19.0 (18.3–21.1)
History of pulmonary TB	1 (0.9)
Pathogenic bacteria	
Mycobacterium avium	81 (75.0)
Mycobacterium intracellulare	27 (25.0)
Type of disease	
Nodular-bronchiectatic	61 (56.5)
Fibrocavitary	17 (15.7)
Nodular-bronchiectatic + fibrocavitary	27 (25.0)
Unclassifiable	3 (2.8)
Oral fluoroquinolone	27 (25.0)
Intramuscular aminoglycoside injection	83 (76.9)
Period from initial chemotherapy to surgery (months)	35 (14.5–80)

Data are presented as medians and interquartile ranges or as numbers (%)

BMI body mass index, *MAC Mycobacterium avium* complex, *TB* tuberculosis

Table 2 Surgical characteristics of 116 adjuvant surgical treatments for MAC lung disease

Surgical characteristic (unit)	No. (%)
Type of pulmonary resection	
Bilobectomy	8 (6.9)
Bilobectomy + segmentectomy	1 (0.9)
Lobectomy	49 (42)
Lobectomy + segmentectomy	10 (8.6)
Lobectomy + wedge resection	12 (10)
Segmentectomy	27 (23)
Segmentectomy + wedge resection	3 (2.6)
Wedge resection	6 (5.2)
Surgical approach	
VATS without minithoracotomy	87 (75)
Minithoracotomy with video assistance	19 (16)
Open thoracotomy	10 (8.6)

MAC Mycobacterium avium complex, *VATS* video-assisted thoracoscopic surgery

Outcomes after surgery

Although there were no intraoperative deaths, there was one postoperative death (0.9%) during hospitalization; a 65-year-old man with *M. avium* lung disease died of the acute exacerbation of interstitial pneumonia 40 days after undergoing right upper and middle lobectomy. Postoperative complications occurred in 14 patients (13%). No patients developed bronchopleural fistulas. The median postoperative hospitalization period was 6 (IQR, 6–7.5) days and the median postoperative follow-up period was 48 (IQR, 34–72) months (Table 3).

Table 3 Characteristics after adjuvant surgical treatments for MAC lung disease

Characteristic after surgery (unit)	No. (%) or median (IQR)
Postoperative complications	
Postoperative mortality	1 (0.9)
Lung fistula	10 (9.2)
Bronchopleural fistula	0 (0)
Empyema	2 (1.9)
Arrhythmia	1 (0.9)
Acute exacerbation of interstitial pneumonia	1 (0.9)
Postoperative hospitalization period (days)	6 (6–7.5)
Follow-up period after surgery (months)	48 (34–72)

Data are presented as medians and interquartile ranges or as numbers (%)

MAC Mycobacterium avium complex

After lung resection, 98 out of 108 patients (91%) achieved sputum culture conversion, eight of whom (8.2%) developed microbiological recurrence during the follow-up period. As a result, the success rate of adjuvant surgical treatments was 83% (90/108). Figure 2 shows Kaplan–Meier curves for the probability of unfavorable outcome-free survival.

Predictors of unfavorable outcomes

We examined the effects of preoperative baseline and surgical characteristics on favorable outcomes.

In the univariate analysis, a longer period from the initial medical treatment to surgery (HR, 1.01; 95% CI, 1.00–1.02; $p = 0.004$) was identified as a risk factor for unfavorable outcomes after lung resection for MAC-LD. This was also a risk factor in the multivariable analysis (HR, 1.01; 95% CI, 1.00–1.02; $p = 0.008$) (Table 4).

Discussion

The present study investigated the outcomes of pulmonary resection and risk factors for unfavorable outcomes after adjuvant surgical treatments for MAC-LD. The results obtained showed that adjuvant surgical treatments for MAC-LD had acceptable outcomes and the only risk factor was a longer period from the initial medical treatment to surgery.

Previous studies reported the outcomes of surgical treatments for MAC- or NTM-LD. However, only 6 studies had more than 50 patients [7, 8, 17–20], while 4 had more

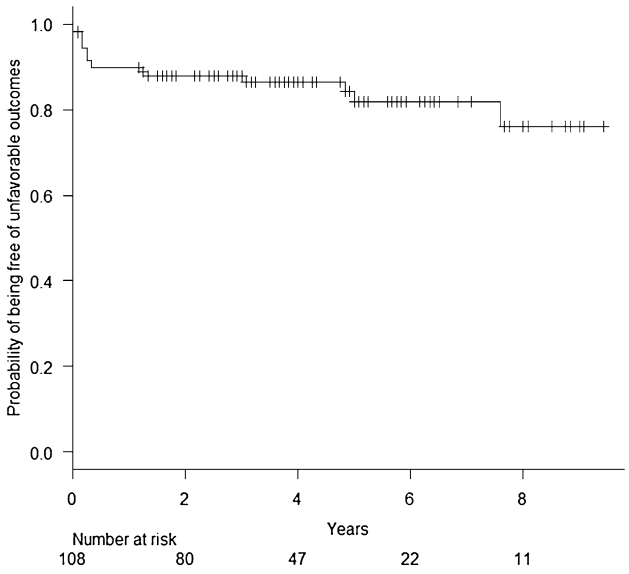


Fig. 2 Kaplan–Meier curve for the probability of being free of unfavorable outcomes in patients after adjuvant surgery for MAC lung disease

Table 4 Predictors of unfavorable outcomes in 108 patients after surgery for MAC lung disease

Characteristic	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Period from initial chemotherapy to surgery	1.01 (1.00–1.02)	0.004	1.01 (1.00–1.02)	0.008
Nodular-bronchiectatic form	0.40 (0.13–1.24)	0.11	0.45 (0.15–1.39)	0.16
Aminoglycoside	2.24 (0.62–8.08)	0.22		
Sex	0.57 (0.19–1.75)	0.33		
Cavitary lesion	0.59 (0.21–1.69)	0.33		
Age	1.02 (0.98–1.06)	0.41		
Mycobacterium avium	1.34 (0.47–3.83)	0.59		
BMI	1.03 (0.81–1.31)	0.81		

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *MAC Mycobacterium avium* complex

than 100 patients [17–20]. All studies with more than 100 patients examined NTM-LD, and we were unable to find studies that reported the outcomes of surgery that targeted MAC-LD. Furthermore, there were only two studies that examined patients after adjuvant surgical treatments that met the 2007 ATS/IDSA guidelines [7, 8]. One study comprised 60 patients and the other had 70, and both of them treated NTM-LD. We were also unable to find any studies that reported risk factors for the unfavorable outcomes of adjuvant surgical treatments for MAC- or NTM-LD that met the 2007 ATS/IDSA guidelines. Therefore, to the best of our knowledge, the present study is the first to have investigated the outcomes of pulmonary resection and risk factors for unfavorable outcomes after adjuvant surgical treatments for MAC-LD that met the 2007 ATS/IDSA guidelines.

Regarding the type of pulmonary resection, a feature of the present study was the relatively high percentage of combinational resection. Simple resection, such as lobectomy, segmentectomy, and wedge resection, was performed in 82 out of 116 surgical procedures (71%), while combinational resection was performed in 34 (29%). The aim of adjuvant surgery for NTM-LD is to control the disease by decreasing the amount of bacteria in the lungs through the resection of lesions. Cavitary and bronchiectatic lesions are referred to as destructive lesions. When surgery is performed for NTM-LD, destructive lesions need to be completely resected. This may be one of the reasons why there was a relatively high percentage of combinational resection in the present study. One of the key points of surgery for NTM-LD is to avoid leaving destructive lesions.

A previous study reported thoracoscopic lobectomy and segmentectomy for infectious lung diseases, including MAC-LD [19]. Regarding the surgical approach in this study, resection was attempted thoracoscopically in 83% of cases. Our rate of thoracoscopic resection was 91% (VATS without minithoracotomy: 75%, minithoracotomy with video assistance: 16%). We consider many surgeries for MAC-LD to be feasible with VATS, except dense adhesion cases. Furthermore, this study reported that they did not routinely buttress the bronchial stump and did not note any bronchopleural fistulas postoperatively. This is consistent with our experience. Buttressing of the bronchial stump may not be needed in pulmonary resection for MAC-LD, except in special cases.

In the present study, outcomes after adjuvant surgical treatments for MAC-LD were as follows: the sputum culture conversion rate was 91%, the recurrence rate was 8.2%, the mortality rate was 0.9%, and the postoperative complication rate was 13%. In previous studies comprising more than 50 patients, the treatment outcomes of adjuvant surgery for NTM-LD had a sputum culture conversion rate between 81 and 100%, recurrence rate between 3 and 7%, mortality rate between 0 and 3%, and postoperative complication rate between 7 and 20% [7, 8, 17–20]. Although MAC- and NTM-LD differ, our results were consistent with previous findings obtained for NTM-LD.

The treatment success rate with antimicrobial chemotherapy in patients with MAC-LD has been unsatisfactory. Newer macrolide-containing regimens have been found to successfully eradicate MAC-LD in only 60–80% of patients, with 20–40% failing to respond to this treatment [3, 5]. In a meta-analysis on the treatment of MAC-LD, the treatment success rate was 60% and the proportion of defaults from the treatment was 16% [21]. If the success of surgical treatments for MAC-LD is regarded as sputum culture conversion, the success rate was 83% in the present study. Since some bias is applied at the stage of indications for surgery, adjuvant surgical treatments cannot simply be compared with medical treatments alone. However, some patients whose medical treatment was not effective may achieve better control of the disease by adjuvant surgical treatments for MAC-LD.

To date, several studies have analyzed factors associated with recurrence in patients successfully treated for MAC-LD [11, 22, 23]. However, risk factors for recurrence after adjuvant surgical treatments for MAC- or NTM-LD that met the 2007 ATS/IDSA guidelines have not been identified. In

the present study, a longer period from the initial medical treatment to surgery was independently associated with an increased risk of unfavorable outcomes after adjuvant surgical treatments for MAC-LD. If the waiting period becomes longer, lesions may expand accordingly in spite of antibiotic treatment. Surgery at an earlier stage is needed rather than continuing the administration of drugs in some cases in which medical treatment is not effective and the disease is progressing.

There is currently no evidence to support the optimal duration of antibiotic treatment after surgery. We extended the duration of antibiotic chemotherapy by 1 year in cases in which bacterial cultures of resected tissue at surgery were positive. A longer duration of antibiotic treatment after surgery may suppress recurrence after surgery; thus, further studies are warranted.

Our study has several limitations, the most significant of which were its performance at two referral centers, its retrospective design, and its inclusion of a small number of patients. In addition, a large number of surgical patients were selected, which biased beneficial outcomes. Prospective multicenter studies with a large number of patients are required to confirm the present results. Furthermore, the unfavorable outcome group consisted of two groups: one that failed sputum culture conversion and the other that had microbiological recurrence during the follow-up period after surgery. As the number of cases in each group increases, it will be necessary to analyze them again separately.

Conclusion

Adjuvant surgical treatments for MAC-LD have acceptable outcomes and many surgeries are feasible with minimally invasive thoracoscopic surgery. Some patients with drug resistance and indications for surgery may achieve better control of the disease by adjuvant surgical treatments and need to undergo pulmonary resection earlier rather than continuing chemotherapy to reduce unfavorable outcomes.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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