Journal of the Formosan Medical Association (2020) 119, S76—S83

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

Review Article

Recent advances and controversies in surgical intervention of nontuberculous mycobacterial lung disease: A literature review

Yu-Ting Tseng [a,b], Chien-Te Pan [a,b], Shun-Mao Yang [a,c], Sheng-Pin Yu [a,d], Pei-Ming Huang [a,b,*]

[a] *Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[b] *Thoracic Medicine Center, Department of Medicine and Surgery, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan*
[c] *Department of Surgery, National Taiwan University Hospital, Hsin-Chu Branch, Taiwan*
[d] *Cardiovascular Medical Center, Department of Medicine and Surgery, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan*

Received 8 March 2020; received in revised form 14 April 2020; accepted 27 April 2020

KEYWORDS
Surgery;
Nontuberculous mycobacteria;
Lung disease;
Macrolide

The prevalence of nontuberculous mycobacterial lung disease (NTM-LD) has increased in Western and Asian nations in recent decades. While surgery may improve the outcome of more complex cases, many inconsistencies exist in the current literature regarding the management, growing emergence, and challenges of drug-resistant forms of NTM-LD, the indications and timing of surgical treatment, and perioperative multimodal therapy of NTM-LD. Moreover, data regarding the comparative treatments, risk factors of pulmonary resection for NTM-LD, and the long-term outcomes of microbiological recurrence are limited. This review will focus on outlining the outcomes of recently optimized surgical approaches, as well as providing an overview of the roles of perioperative multimodalities therapies in the treatment of NTM-LD.

* Corresponding author. Department of Surgery, Yunlin Branch, National Taiwan University Hospital and National Taiwan University College of Medicine, New Medical Building- No.579, Sec. 2, Yunlin Rd., Douliou City, Yunlin County, 640, Taiwan. Tel.: +886 2 2312 3456 ext 63509; fax: +886 2 2322 2890.
E-mail address: phuang3@ntuh.com.tw (P.-M. Huang).

https://doi.org/10.1016/j.jfma.2020.04.029

Introduction

Nontuberculous mycobacteria (NTM) infection is difficult to treat, and nontuberculous mycobacteria lung disease (NTM-LD) most commonly causes chronic pulmonary destruction that is refractory to antimicrobial therapy.[1–3] The incidence of NTM-LD has increased in Western and Asian countries during recent decades,[4–6] and more than 90% of patients will have persistent disease. NTM-LDs have different geographic incidences, etiologies, and biology,[7] and the symptoms of NTM-LD are generally nonspecific and usually reflect advanced disease. Lung resection is considered in patients with NTM-LD when medical therapy alone fails to control disease.[1] However, treatment approaches for resectable NTM-LD are largely based on the location of infection, bacteriological subtype, and patient co-morbidities; whether surgery remains fundamental to the treatment of resectable NTM-LD is uncertain. Nevertheless, these reports provide guidance on patient management and future studies will improve outcomes in the newer macrolide era. This review of the recent scientific literature is intended to assist clinicians in the management of resectable NTM-LD patients, regarding the decision of indication of surgical treatment or perioperative therapy of these pulmonary diseases.

Surgical roles of NTM-LD

The main treatment of NTM-LD is antimicrobial therapy; however, antimicrobials penetrate poorly into areas of destructive lung parenchyma, and liquefacted lungs tend to act as microbe reservoirs which can lead to yield relapse at a later date. Several case series revealed superiority of a combined approach over antibiotics alone, with an acceptable rate of sputum culture conversion after surgical resection for NTM-LD and a low rate of morbidity and mortality.[1,8–13] Based on these data, the ATS/IDSA guideline also recommends the combination of a multidrug treatment regimen and adjuvant surgery for intractable NTM-LD patients with resectable lesions. However, poor performance status or other contraindications to surgery occasionally force its use in certain patients. A complete cure is not always achievable, and severe perioperative complications, with limited treatment options, may occur (Table 1); as a result, further evidence of the benefits of surgical resection is required before it can be used widely. The policy places great emphasis on the importance of pre- and post-operative antimicrobial therapy, proposing the necessity of a multidisciplinary approach for these types of NTM-LD.

Preoperative evaluation of NTM-LD

Extensive preoperative evaluation is essential to allow selection of the appropriate therapeutic strategy for patients with NTM-LD. The recommended preoperative evaluation includes chest X-ray, mycobacterial culture, pulmonary function tests, electrocardiogram, echocardiography, chest computed tomography (CT), quantitative lung perfusion scan, and bronchoscopy. Chest CT is the cornerstone for assessing the surgical extent of major lesions due to NTM-LD. Early CT scans allow the identification of nonresponse patients for earlier surgery and discontinuation of ineffective preoperative antimicrobial therapy.[14,15] Depending on the disease heterogeneity, imaging studies may have the potential to generate false positive and false negative results. The verification bias is due to different follow-up characteristics. Although imaging may suggest NTM-LD, microbiologic evaluation is the most accurate method of diagnosis. Acid-fast bacilli in the sputum smear can support the diagnosis of NTM but is less sensitive or specific than the sputum culture, and airway assessment remains inaccurate with non-invasive imaging examinations. Refractory NTM-LD might be explained by more diffuse or aggressive infection; thus, bronchoscopy is mandatory in the preoperative assessment of NTM-LD in order to detect major excretory lesions with purulent sputum that can spread to other lobes.[8,9,16] Excision of major excretory NTM lesions is effective in suppressing disease progression. However, the involvement of NTM-LD at the resection margin can increase the risk of non-healing pulmonary leaks or bronchopleural fistula. Bronchoscopy can facilitate the evaluation of mucosal architecture that can be correlated with the histology. Therefore, it is crucial to confirm by bronchoscopy whether or not an excretory lesion or inflamed bronchus is present and considering delaying the surgical resection if inflamed proximal bronchial mucosa is found.[9,12]

Surgical indication of NTM-LD

There is limited evidence that antimicrobials without surgery is a beneficial approach for NTM-LD, but for patients who are not candidates for surgery it is often considered (Table 1). Adjuvant surgical resection of NTM-LD removes focal damaged parenchyma to enhance the effectiveness of medical treatment,[17] and a previous study has demonstrated that the sputum culture conversion was persistently higher in the surgical group than the medical alone group (87.5% vs. 45.8%).[12] However, a majority of studies were from centers in the Unites States and Japan, and the inclusion criteria for surgical selection was controversial.[18,19] Because of the unsteady presentation of NTM-LD, clinicopathological characters and treatment policies have not been integrated, and surgery alongside multidrug treatment is an alternative and effective therapy for some NTM-LD patients.

Patients who are considered for surgery may have different characteristics than those who are not, including history, CT scan, and sputum culture examination. Confusion can be largely due to the borderline pulmonary condition of these infections; the image pattern of NTM-LD, the NTM organism involved, and the patient's general response should be considered for further treatment (Fig. 1). Therefore, a multidisciplinary approach, involving pulmonary physicians, infectious disease specialists, interventional radiologists, and thoracic surgeons, is favored. There is no published selection criteria for the surgical treatment of NTM-LD, and the indications for surgery include complex cases, the existence of macrolide-resistance, or significant symptoms such as hemoptysis, irrespective of the status of

Table 1 Indication, related factors of outcomes, and complication of adjuvant surgery in nontuberculous mycobacterial lung disease.

Surgical indication
• Complicated cases (a failed sputum culture conversion after 6 months of therapy)
• Significant symptoms (hemoptysis, persisting bronchiectasis)
• Localized disease (destroyed lung)
• Cavitary lesions (regardless of achieving negative sputum conversion in response to antimicrobial therapy)
• Suspicion of cancer
Related factors of surgical outcomes
• The patient's general condition
• Preoperative pulmonary rehabilitation
• Nutritional status of thin patients.
• The imaging pattern of NTM-LD (the extent of disease)
• The bacterial organism involved
• The risk of postoperative complications
• Quality of life
• Remnant cavitary lesions after pulmonary resection
Perioperative complications
• Bronchopleural fistula
• Pericardial effusion
• Empyema
• Pneumonia
• Acute respiratory distress syndrome

bacterial discharge (Table 1). Resection is recommended for patients with contagious persisting bronchiectasis, destroyed lung, and cavitary disease on imaging, irrespective of whether the patients had achieved negative sputum conversion in response to antimicrobial therapy. Although the decision to proceed to surgery is usually personalized, the risk of postoperative complications and a reduction in the quality of life are important factors to consider. Surgery alone can no longer be considered the standard of care given the limited improvement in the poor prognosis associated with end-stage NTM-LD. Localized disease, particularly in intractable cases of NTM-LD, may

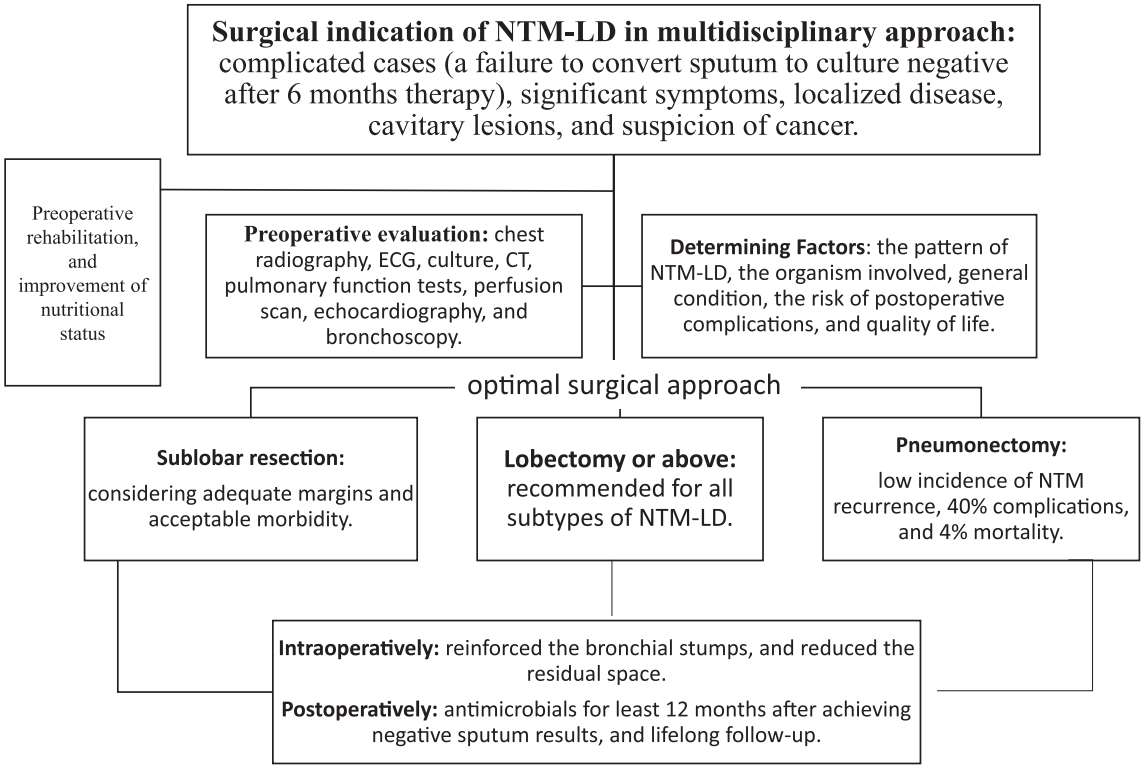

Figure 1 Perioperative management of nontuberculous mycobacterial lung disease.

benefit from surgical resection,[20] a finding that has led to an ongoing debate about the optimal surgical approach and extent of resection. Observation without treatment may be appropriate for some patients with slowly progressive NTM-LD, while NTM-LD that affects extensive areas of the lung or poor surgical candidates favors exclusive medical treatment. Usually, the patients were highly selected, and chronic obstructive pulmonary disease/emphysema were more frequent in surgical NTM-LD patients.[12]

Preoperative medication and the timing of surgery for NTM-LD

Preoperative antimicrobials remain a common option for treatment of NTM-LD in the United States. The use of preoperative antimicrobials has been investigated extensively and they have several potential advantages including an improved chance of complete resection and a reduction in lesion infections. The optimal duration of antibiotic therapy before surgery remains controversial,[19,21] but the standard recommendation for most NTM species is at least three antimicrobials for 16—20 months.[5] Clinical improvement of the symptoms are expected within 3—6 months, and the duration of therapy for the sputum culture results converts to negative within 12 months for most NTM-LD patients.[18,22] However, adverse effects of multidrug treatment are common, and the success rate can be poor.[23,24] Repeated sputum culture test maybe particularly helpful if the patients do not respond to therapy or if there is a relapse. Patients are considered to be treatment failures if there has been no response after 6 months of appropriate therapy or if negative sputum conversion has not been achieved after 12 months of appropriate therapy.[18] Complete response is not necessary to achieve a negative culture, and infection control may be sufficient. A long duration of antimicrobials might worsen the patient's condition if NTM-LD progresses, and there is a risk of contamination of the healthy lung. This is particularly true for *Mycobacterium abscessus* complex, where the use of perioperative antimicrobials results in significant infection control though relatively few complete infection regressions.[25] Although the optimal timing of surgical therapy remains ambiguous, if the patients fail to respond after 6 months of appropriate therapy, the potential role of surgery for the reduction of the bacterial load should be considered.[10]

Surgery is dependent on the image pattern of NTM-LD

The image patterns, clinicopathology, and systemic therapies vary according to NTM species, and the disease can be either nodular/bronchiectatic or cavitary radiographically. NTM-LD likely presents as three radiological types: Upper lobes of a tuberculosis-like pattern in older males with COPD,[26] nodular bronchiectasis in slender older nonsmoking females,[27] and hypersensitivity pneumonitis with diffuse ground-glass infiltrates.[22,28] However, variants of these image types and one or another of them can also exist simultaneously. The optimal route and extent of resection for the various types of NTM-LD depends on the involved lung, overall condition of the patient, and the role of preoperative antimicrobials. The cavitary/tuberculoid type usually (90%) develops in the upper lobes of elderly patients with preexisting lung disease.[29] Surgical candidates more frequently have a cavitary radiologic pattern than patients who are treated exclusively with antimicrobials. The prognosis in cavitary NTM-LD patients is extremely poor as it generally progresses rapidly and can cause extensive lung destruction and respiratory failure. It is particularly associated with *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*, *M. malmoense*, *Mycobacterium xenopi*, and rapidly growing mycobacteria.[22] *M. xenopi* infection is more likely associated with cavitary lesions and rapid lung destruction, so a more aggressive treatment with favorable outcomes after surgery is preferred.[12,30] A combination of bronchiectasis and multiple small nodules, particularly involving the right middle lobe and/or the left lingular lobe in non-smoking women (*Lady Windermere syndrome*) is usually associated with MAC.[27] Patients with the nodular bronchiectatic form were more likely to be non-smoking females, and also had lower pre-operative sputum positive culture rates compared to patients with the cavitary form of NTM-LD.[10] Nodular lesions can be left because they are indolent and have lower microbial burden and rates of relapse or reinfection. There was no correlation between CT patterns and the requirement for antimicrobials after lung resection[12]; after pulmonary resection, 13% of patients exhibited remnant cavitary, which is known to be a predictor of microbiological recurrence.[11]

Classification of bacterial species in NTM-LD surgical outcomes

Since the biology of NTM-LDs differ, they need to be considered individually and optimally treated with different management; this includes different surgical considerations with a different pattern of cavitary lesions in the contralateral lung, patient condition, persistent sputum positivity, and drug resistance.[31—34] Although the current therapeutic decisions of NTM-LD were obtained from a combination of NTM-LDs, several reports provide justification for differentiating epidemiological and morphological features between each subtype of NTM-LD.[5,35,36] Moreover, some patients may have NTM-LD that involves multiple strains, the significance of this for treatment is uncertain.

Bailey[37] categorized NTM-LD as easy to treat and hard to treat: *M. kansasii* was categorized in the easy to treat group, and *M. xenopi*, MAC, *M. simiae*, *M. malmoense*, and others fall into the latter, especially when disease is extensive. An important specified aim of this definition and classification was to describe and compare the optimal treatment approach. Treatment of rapidly growing mycobacteria species, including *M. fortuitum*, *M. abscessus*, and *M. chelonae*, with "standard" mycobacteria agents is likely difficult.[38] If *M. abscessus* or MAC pulmonary disease is localized and if the patient is a suitable surgical candidate, surgery may provide a local control advantage for patients who did not respond to initial antimicrobial therapy.[21,35] Two papers have reported that surgical resection continues to play an important role in the management of MAC-

LD, along with the new macrolide-based combined chemotherapy.[39,40] In 2011, Jarand also reported that surgery along with antimicrobial treatment could control prolonged infection in patients with *M. abscessus* NTM-LD.[25] The development of wound dehiscence was frequent in patients with *M. abscessus*.[10] Moreover, NTM-LD caused by *M. xenopi*, *M. kansasii*, and *M. malmoense* may be associated with a combination of bronchiectasis and *Aspergillus* lung disease, and the presence of *Aspergillus* appeared to be indicative of adverse prognosis.[41] Patients who underwent surgery for non-responding NTM-LD had a higher rate of post-operative complications than patients whose disease was being controlled medically (OR 10; 95%CI, 1.34−74.51; $p = 0.025$).[12] However, the difference in survival among patients with different species of NTM were not statistically significant.[11]

Surgical approach for NTM-LD

Persistent NTM-LD is significantly related to survival outcome, and surgical considerations specific to NTM-LD include a range of destructive lung parenchyma, adhesionlysis, and the choice of surgical approach. The extent of resection, and the approach, including en bloc pneumonectomy, sublobar lobectomy, lobectomy, and limited resection, should be selected based on the ability to achieve a resection with adequate margins and acceptable morbidity. A complete resection of NTM-LD is the primary goal of any surgical approach to improve survival outcome compared to limited surgery. Limited resection of NTM-LD offers only a limited benefit and lobectomy is recommended for all subtypes of NTM-LD, especially in the fibrocavity; indeed, consolidation or cavitation near the central airway is mostly treated with lobectomy. In patients with localized NTM-LD, a limited wedge resection of the infected lung allows adequate resection and excellent functional results, while contralateral bronchiectatic and cavitary lesions can be managed with staged bilateral resections.

It is clear that a variety of approaches exist using thoracotomy or video-assisted techniques to achieve a destructive lung resection. With regards to the surgical approach for NTM-LD, thoracotomy has lower rates of survival and increased morbidity compared to a video−assisted approach.[42] The survival outcome is similar to the traditional approaches of lobectomy, with selection based on surgical expertise. For patients with dense pleural adhesions, especially in apical cavitary disease, a thoracotomy is favored. In patients without severe pleural adhesions, video-assisted thoracoscopic surgery (VATS) is the preferred mode.[19] CT is moderately sensitive and specific for preoperative prediction of pleural adhesion, while lots of patients with pleural adhesions demonstrated no pleural finding on CT.[43] The correlation factors between image characteristics on preoperative chest CT and severe pleural adhesion during surgery are large pulmonary calcified nodules, impaired pulmonary function test, and moderate emphysema.[44] However, the association of localized pleural thickening on CT with severe pleural adhesion was not found. Limited resection and VATS approach should be considered for select patients who have localized lesions or marginal lung function.[10] Matsuoka completed surgical resection of NTM-LD under VATS and none required conversion to thoracotomy.[45] In the current study, the mean duration of hospitalization was 5.5 days. This approach leads to less postoperative pain, better functional status, and shorter hospital stays than thoracotomy. Postoperatively, air leaks lasting for 7 days occurred in 2 patients, but there were no severe complications. The VATS approach was more widely used in another study consisting 126 lobectomies, 73 segmentectomies, 10 lobectomies plus segmentectomies, and 3 bilobectomies.[14] Ten patients (4.7%) required a switch to thoracotomy without any mortality, while complications including prolonged air leak and atrial fibrillation occurred in 9% of the patients. The mean volume of blood loss during surgical resection of NTM-LD was usually less than 150 mL.[11] However, resection via thoracotomy approaches allowed more extensive resection of destructive tissues and muscle flap reconstruction than thoracoscopic resection. Despite this, recurrence and mortality were similar, although morbidity was substantially less with the thoracoscopic resection. The combination of VATS and preoperative pulmonary rehabilitation in patients with NTM-LD may be effective in preventing postoperative pneumonia and atelectasis. The mean duration between the day of the preoperative pulmonary rehabilitation instructions and the day of surgery was 51.4 days.[42] However, early rehabilitation may lead to faster recovery of quality of life when patients are in a stable state.[46]

There is insufficient data to recommend the use of pneumonectomy for NTM-LD, and despite the low recurrence rate of NTM-LD following pneumonectomy, this technique has a high probability of surgical complications (40%)[11] as well as a hospital mortality of 3%−4%. In another Japanese study involving 11 patients who received pneumonectomy for NTM-LD, 4 patients (36%) developed complications,[47] all the patients showed sputum conversion, and 1 patient experienced a relapse. Pomerantz and colleagues reported a high incidence of bronchopleural fistula after right pneumonectomy (6%).[48] Consequently, earlier resection in localized NTM-LD, before entire right lung destruction and extensive polymicrobial contamination, is recommended.

Factors related to surgical outcomes of NTM-LD

Low BMI has been reported as a factor for poor outcome in patients with NTM-LD undergoing surgical therapy.[49] Therefore, an improvement of preoperative nutritional status of thin patients is essential. Preoperative albumin (<3.5 g/dL), prealbumin (<15 mg/dL), and transferrin (<200 mg/dL) values deteriorating below the normal range are useful biomarkers of malnutrition and represent an increased risk for postoperative complications.[50,51] A nutritional support team prepares a plan for preoperative and postoperative care of NTM-LD patients, highlighting the need for patient selection for surgery in this regard. Old age, low BMI, pneumonectomy,[47] and remnant cavitary lesions after pulmonary resection are known predictors of both microbiological recurrence and poor prognosis.[11] Preoperative immune-

modulating nutrients, using mixtures of omega-3 fatty acids, arginine, and other nutrients, can improve the metabolic response to stress and promote both wound healing and immune function.[52]

Despite satisfactory results in terms of sputum culture conversion, the surgical mortality and morbidity rate are 7% and 20%, respectively, while the survival rates at 1, 5, and 10 years after surgery were 94%, 84%, and 76%, respectively.[11] However, the favorable treatment outcomes and postoperative complications are variable in previously reported case series of NTM-LD surgery (Table 2). These are also affected by individual patient variations, as well as the center-specific experience. In one study, all patients who developed bronchopleural fistula had the cavitary form of NTM-LD.[10] Therefore, the bronchial stumps have to be sutured after stapling and reinforced with muscle flaps in patients with a higher risk of bronchopleural fistula, including those with persistent positive sputum culture and those who have undergone pneumonectomy.[8,9] If the residual space is considerable, a pedicled latissimus dorsi muscle flap or limited thoracoplasty was attempted in order to reduce it. Use of the serratus anterior muscle was poorly tolerated in underweight patients due to the resulting winged scapula.

Postoperative management of NTM-LD

The majority of patients with NTM-LD are likely to relapse; therefore, the systemic approach with postoperative antimicrobials is likely to be more beneficial than a localized treatment strategy for these patients. Although the optimal duration of antimicrobial therapy after lung resection is unclear, the duration of antimicrobial regimens are based on the presence of residual disease.[9,11] The expert guidelines recommended that all patients with an NTM-LD infection who undergo lung resection and achieve culture conversion are treated for least 12 months after achieving negative sputum results, defined as three consecutive negative sputum cultures.[1,10,18,21] Moreover, a reduction in the duration of therapy has also been attempted given the high cost of these therapies.[53] Some clinicians recommend a longer period of postoperative antimicrobials (for 2 years instead of a year) for patients whose surgical specimens were positive for culture.[21] However, the postoperative complication rates do not differ between patients who received perioperative antimicrobials and those who did not.[10] The difference in the rate of recurrence among the NTM species did not reach a statistical significance, either.[11]

Table 2 Summary of surgical outcome in recent studies.

	Sakane (2018)[13]	Aznar (2018)[12]	Asakura (2017)[11]	Kang (2015)[10]	Shiraishi (2013)[9]	Mitchell (2008)[8]
Patient No.	25	27	125	70	60	236
Study period	2004–2014	2003–2016	1994–2015	2007–2013	2007–2011	1983–2006
Case Gender	10M:15F	7M:20F	59M:66F	28M:42F	19M:41F	40M:196F
Mean Age (yr)	63.1	55	60	50	50	54.8
Preoperative regimen duration (mean)			7 months	8.3 months	14.2 months	2–6 months
Surgical indication						
Poor response to drug therapy	16 (64%)		36 (29%)	52 (74.3%)	52 (86.7%)	
Symptoms	5 (20%)		19 (15%)	4 (5.7%)	6 (10%)	
Prolonged smear positivity	1 (4%)		70 (56%)			
Cavitary lesions				14 (20%)	25 (41.7%)	29%
Suspicion of cancer	5 (20%)					
Resected extent						
Pneumonectomy	4 (16%)	8 (29.6%)	31 (24.8%)	8 (11%)	1 (1.7%)	44 (18.6%)
Lobectomy or above	13 (52%)	21 (77.8%)	80 (64%)	54 (73%)	45 (75%)	164 (69.5%)
Segmentectomy	8 (32%)	1 (3.7%)	13 (10.4%)	11 (15%)	17 (28.3%)	57 (24.2%)
Sublobar resection			1 (0.8%)	1 (1%)	2 (3.3%)	
Thoracotomy	8 (32%)		120 (96%)	47 (65%)	55 (91.6%)	168 (65.6%)
VATS	17 (68%)		5 (4%)	26 (35%)	5 (8.4%)	68 (34.4%)
No sputum conversion			7 (5.6%)	19%	0%	
relapse	5 (20%)	11 (40.7%)	19 (15.2%)		2 (3%)	
Complication			22%	15 (21%)	8 (12%)	18.5%
ARDS		2 (7.4%)	2 (1.6%)	1 (death)	11 (18.3%)	6 (2.5%)
Bronchopleural fistula/ prolonged air leak		1 (3.7%)	8 (6.4%)	5 (7.1%)	5 (8.3%)	23 (9.7%)
Pericardial effusion		1 (3.7%)	1 (0.8%)	1 (1.4%)		
Empyema		1 (3.7%)	7 (5.6%)	3 (4.3%)		
Others			9 (7.2%)	2 (2.9%)		28 (11.9%)
Mortality	1 (4%)	0%	4 (3%)		0%	2.6%

ARDS: acute respiratory distress syndrome; F: female, M: male; VATS: Video-assisted thoracoscopic surgery.

Moreover, lifetime follow-up is necessary after resection because a relapse or reinfection may occur years after the completion of therapy. NTM therapy was re-initiated in 27.8% of surgical patients after the completion of 12 months of antimicrobial therapy.[12] Therefore, antimicrobials is reasonable for multiple modality therapy when treatment volumes are judged to be safe and there are no other substantial contraindications. Regardless of the above mentioned advancements, patients should undergo regular chest radiographs and sputum culture after the completion of postoperative antimicrobials.[54] Indeed, a follow-up CT scan performed 12 months after surgery showed deterioration of the non-resected lung in 25% patients, stability in 45% of patients, and improvement in 30%. Whenever reactivation or relapse is suspected, resumption of antimicrobials is encouraged to improve outcomes.

Further directions in the surgical management of NTM-LD

Clinical guidelines, surgical techniques, and postoperative care have improved in the recent years, and therefore treatment decisions between early and newly diagnosed patients are different. Even if the patients are treated similarly, the outcomes could vary greatly. Furthermore, perioperative treatment strategies can result in significant undesirable antimicrobial-related toxic effects. An improvement of predictive markers may also help to identify patients who are more responsive, and help prevent expensive and non-effective therapies. Predictive markers can be evaluated through factors such as the response to specific therapy, or the time to progression. Molecular markers can be protein targets or gene expression levels in the bacteria or the host. With a greater emphasis on NTM-LD as a well-defined entity, it is likely that further studies will provide more precise optimal management of adjuvant lung resection in NTM-LD patients with the introduction of new chemotherapeutic regiments.

Conclusion

In summary, pulmonary resection of the lung destroyed by NTM, in addition to newer macrolide therapy, can improve the outcome if antimicrobial therapy alone has failed. Although NTM-LD patients who undergo lung resection have significant morbidity, sputum culture conversion is frequently achieved. Due to the development of surgical techniques and tools, minimal invasive surgery has become an early approach for thoracic surgery in NTM-LD patients, as it has been more widely used with good results.[8,13] After carefully considering age, BMI, remnant lesions after surgery, and type of pulmonary resection, surgery is the most effective option for many patients, including early localized disease, good performance status, or increasingly poor response to drug therapy. Moreover, surgical resection of the destroyed lung does not avoid the need for lifelong follow-up in patients with NTM-LD, and some patients continue to need long-term antibiotics.

Declaration of Competing Interest

This study had no possible conflict of interest.

Acknowledgements

This work is supported by Taiwan Society of Pulmonary and Critical Care Medicine.

References

1. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;**175**(4):367—416.
2. Lee MR, Lee CH, Wang JY, Lee SW, Ko JC, Lee LN. Clinical impact of using fluoroquinolone with low antimycobacterial activity on treatment delay in tuberculosis: hospital-based and population-based cohort study. *J Formos Med Assoc* 2020; **119**(1 Pt 2):367—76.
3. Hsieh MJ, Huang YW, Tsai YH, Feng JY, Su WJ, Taiwan Society of T, et al. Improved appropriateness of anti-tuberculosis prescription by the expert prescription review program in Taiwan. *J Formos Med Assoc* 2020. https://doi.org/10.1016/j.jfma.2019.12.011 [in press].
4. Falkinham 3rd JO. Nontuberculous mycobacteria in the environment. *Clin Chest Med* 2002;**23**(3):529—51.
5. Khan K, Wang J, Marras TK. Nontuberculous mycobacterial sensitization in the United States: national trends over three decades. *Am J Respir Crit Care Med* 2007;**176**(3):306—13.
6. Gadallah MA, Mokhtar A, Rady M, El-Moghazy E, Fawzy M, Kandil SK. Prognostic factors of treatment among patients with multidrug-resistant tuberculosis in Egypt. *J Formos Med Assoc* 2016;**115**(11):997—1003.
7. Brode SK, Daley CL, Marras TK. The epidemiologic relationship between tuberculosis and non-tuberculous mycobacterial disease: a systematic review. *Int J Tubercul Lung Dis* 2014;**18**(11): 1370—7.
8. Mitchell JD, Bishop A, Cafaro A, Weyant MJ, Pomerantz M. Anatomic lung resection for nontuberculous mycobacterial disease. *Ann Thorac Surg* 2008;**85**(6):1887—92. discussion 92-3.
9. Shiraishi Y, Katsuragi N, Kita H, Hyogotani A, Saito MH, Shimoda K. Adjuvant surgical treatment of nontuberculous mycobacterial lung disease. *Ann Thorac Surg* 2013;**96**(1): 287—91.
10. Kang HK, Park HY, Kim D, Jeong BH, Jeon K, Cho JH, et al. Treatment outcomes of adjuvant resectional surgery for nontuberculous mycobacterial lung disease. *BMC Infect Dis* 2015; **15**:76.
11. Asakura T, Hayakawa N, Hasegawa N, Namkoong H, Takeuchi K, Suzuki S, et al. Long-term outcome of pulmonary resection for nontuberculous mycobacterial pulmonary disease. *Clin Infect Dis* 2017;**65**(2):244—51.
12. Aznar ML, Zubrinic M, Siemienowicz M, Hashimoto K, Brode SK, Mehrabi M, et al. Adjuvant lung resection in the management of nontuberculous mycobacterial lung infection: a retrospective matched cohort study. *Respir Med* 2018;**142**:1—6.
13. Sakane T, Matsuoka K, Kumata S, Watanabe R, Yamada T, Matsuoka T, et al. The outcomes of anatomical lung resection for nontuberculous mycobacterial lung disease. *J Thorac Dis* 2018;**10**(2):954—62.
14. Mitchell JD, Yu JA, Bishop A, Weyant MJ, Pomerantz M. Thoracoscopic lobectomy and segmentectomy for infectious lung disease. *Ann Thorac Surg* 2012;**93**(4):1033—9. discussion 9-40.

15. Moon SM, Park HY, Kim SY, Jhun BW, Lee H, Jeon K, et al. Clinical characteristics, treatment outcomes, and resistance mutations associated with macrolide-resistant Mycobacterium avium complex lung disease. *Antimicrob Agents Chemother* 2016;**60**(11):6758—65.
16. Lin CK, Keng LT, Lim CK, Lin YT, Lin SY, Chen LY, et al. Diagnosis of mediastinal tuberculous lymphadenitis using endobronchial ultrasound-guided transbronchial needle aspiration with rinse fluid polymerase chain reaction. *J Formos Med Assoc* 2020; **119**(1 Pt 3):509—15.
17. Mitchell JD. Surgical treatment of pulmonary nontuberculous mycobacterial infections. *Thorac Surg Clin* 2019;**29**(1):77—83.
18. Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. *Curr Opin Infect Dis* 2012;**25**(2): 218—27.
19. Yu JA, Weyant MJ, Mitchell JD. Surgical treatment of atypical mycobacterial infections. *Thorac Surg Clin* 2012;**22**(3):277—85.
20. Tsunezuka Y, Sato H, Hiranuma C. Surgical outcome of mycobacterium other than mycobacterium tuberculosis pulmonary disease. *Thorac Cardiovasc Surg* 2000;**48**(5):290—3.
21. Shiraishi Y. Surgical treatment of nontuberculous mycobacterial lung disease. *Gen Thorac Cardiovasc Surg* 2014;**62**(8):475—80.
22. Glassroth J. Pulmonary disease due to nontuberculous mycobacteria. *Chest* 2008;**133**(1):243—51.
23. Kwak N, Park J, Kim E, Lee CH, Han SK, Yim JJ. Treatment outcomes of Mycobacterium avium complex lung disease: a systematic review and meta-analysis. *Clin Infect Dis* 2017; **65**(7):1077—84.
24. Xu HB, Jiang RH, Li L. Treatment outcomes for Mycobacterium avium complex: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2014;**33**(3):347—58.
25. Jarand J, Levin A, Zhang L, Huitt G, Mitchell JD, Daley CL. Clinical and microbiologic outcomes in patients receiving treatment for Mycobacterium abscessus pulmonary disease. *Clin Infect Dis* 2011;**52**(5):565—71.
26. Kim HO, Lee K, Choi HK, Ha S, Lee SM, Seo GH. Incidence, comorbidities, and treatment patterns of nontuberculous mycobacterial infection in South Korea. *Medicine (Baltim)* 2019;**98**(45):e17869.
27. Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease. Incidence, presentation, and response to therapy in a community setting. *Am Rev Respir Dis* 1991;**143**(6):1381—5.
28. Marras TK, Wallace Jr RJ, Koth LL, Stulbarg MS, Cowl CT, Daley CL. Hypersensitivity pneumonitis reaction to Mycobacterium avium in household water. *Chest* 2005;**127**(2):664—71.
29. Hsiao CH, Lin YT, Lai CC, Hsueh PR. Clinicopathologic characteristics of nontuberculous mycobacterial lung disease in Taiwan. *Diagn Microbiol Infect Dis* 2010;**68**(3):228—35.
30. Lang-Lazdunski L, Offredo C, Le Pimpec-Barthes F, Danel C, Dujon A, Riquet M. Pulmonary resection for Mycobacterium xenopi pulmonary infection. *Ann Thorac Surg* 2001;**72**(6):1877—82.
31. van Ingen J, Verhagen AF, Dekhuijzen PN, van Soolingen D, Magis-Escurra C, Boeree MJ, et al. Surgical treatment of nontuberculous mycobacterial lung disease: strike in time. *Int J Tubercul Lung Dis* 2010;**14**(1):99—105.
32. Sherwood JT, Mitchell JD, Pomerantz M. Completion pneumonectomy for chronic mycobacterial disease. *J Thorac Cardiovasc Surg* 2005;**129**(6):1258—65.
33. Chen CH, Chen YM, Lee CW, Chang YJ, Cheng CY, Hung JK. Early diagnosis of spinal tuberculosis. *J Formos Med Assoc* 2016;**115**(10):825—36.
34. Chan MJ, Huang YB, Wen YH, Chuang HY, Tain YL, Wang YC, et al. Compliance with risk management plan recommendations on laboratory monitoring of antitumor necrosis factor-alpha therapy in clinical practice. *J Formos Med Assoc* 2016;**115**(2):83—93.
35. Vande Weygaerde Y, Cardinaels N, Bomans P, Chin T, Boelens J, Andre E, et al. Clinical relevance of pulmonary nontuberculous mycobacterial isolates in three reference centres in Belgium: a multicentre retrospective analysis. *BMC Infect Dis* 2019;**19**(1):1061.
36. Sood G, Parrish N. Outbreaks of nontuberculous mycobacteria. *Curr Opin Infect Dis* 2017;**30**(4):404—9.
37. Bailey WC. Treatment of atypical mycobacterial disease. *Chest* 1983;**84**(5):625—8.
38. Griffith DE, Girard WM, Wallace Jr RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria. An analysis of 154 patients. *Am Rev Respir Dis* 1993;**147**(5):1271—8.
39. Nelson KG, Griffith DE, Brown BA, Wallace Jr RJ. Results of operation in Mycobacterium avium-intracellulare lung disease. *Ann Thorac Surg* 1998;**66**(2):325—30.
40. 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 Cardio Thorac Surg* 2002; **21**(2):314—8.
41. Kunst H, Wickremasinghe M, Wells A, Wilson R. Nontuberculous mycobacterial disease and Aspergillus-related lung disease in bronchiectasis. *Eur Respir J* 2006;**28**(2):352—7.
42. Morino A, Murase K, Yamada K. Complications after video-assisted thoracic surgery in patients with pulmonary nontuberculous mycobacterial lung disease who underwent preoperative pulmonary rehabilitation. *J Phys Ther Sci* 2015; **27**(8):2541—4.
43. Mason AC, Miller BH, Krasna MJ, White CS. Accuracy of CT for the detection of pleural adhesions: correlation with video-assisted thoracoscopic surgery. *Chest* 1999;**115**(2):423—7.
44. Jin KN, Sung YW, Oh SJ, Choi YR, Cho H, Choi JS, et al. Association between image characteristics on chest CT and severe pleural adhesion during lung cancer surgery. *PloS One* 2016; **11**(5):e0154694.
45. Matsuoka K, Imanishi N, Matsuoka T, Nagai S, Ueda M, Miyamoto Y. Video-assisted thoracoscopic surgery for nontuberculous mycobacterial infection. *Asian Cardiovasc Thorac Ann* 2014;**22**(9):1066—71.
46. Puhan MA, Spaar A, Frey M, Turk A, Brandli O, Ritscher D, et al. Early versus late pulmonary rehabilitation in chronic obstructive pulmonary disease patients with acute exacerbations: a randomized trial. *Respiration* 2012;**83**(6):499—506.
47. Shiraishi Y, Nakajima Y, Katsuragi N, Kurai M, Takahashi N. Pneumonectomy for nontuberculous mycobacterial infections. *Ann Thorac Surg* 2004;**78**(2):399—403.
48. Pomerantz M, Madsen L, Goble M, Iseman M. Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. *Ann Thorac Surg* 1991; **52**(5):1108—11. discussion 12.
49. Gegia M, Kalandadze I, Kempker RR, Magee MJ, Blumberg HM. Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Infect Dis* 2012;**16**(5):e391—6.
50. Roche M, Law TY, Kurowicki J, Sodhi N, Rosas S, Elson L, et al. Albumin, prealbumin, and transferrin may Be predictive of wound complications following total knee arthroplasty. *J Knee Surg* 2018;**31**(10):946—51.
51. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. *Nutrients* 2017;**9**:8.
52. Evans DC, Martindale RG, Kiraly LN, Jones CM. Nutrition optimization prior to surgery. *Nutr Clin Pract* 2014;**29**(1):10—21.
53. Mycobacterium kansasii pulmonary infection: a prospective study of the results of nine months of treatment with rifampicin and ethambutol. Research Committee, British Thoracic Society. *Thorax* 1994;**49**(5):442—5.
54. Wallace Jr RJ, Zhang Y, Brown-Elliott BA, Yakrus MA, Wilson RW, Mann L, et al. Repeat positive cultures in Mycobacterium intracellulare lung disease after macrolide therapy represent new infections in patients with nodular bronchiectasis. *J Infect Dis* 2002;**186**(2):266—73.