Review Article

Multidrug-resistant pulmonary tuberculosis

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Abstract: The advent of effective antituberculous medication has greatly diminished the role of surgery in the management of tuberculosis (TB). More recently, diseases that are resistant to medical treatment have emerged as a major challenge. Multidrug-resistant tuberculosis (MDRTB) is defined as resistance to two or more drugs, including rifampin and isoniazid. In such cases, high relapse rates with medical therapy alone have been reported and adjuvant surgical resection has been proposed as a therapeutic option in selected patients. Although many studies have shown good results with this surgical strategy, the role of minimally invasive surgery in this scenario has yet to be established. Here we review the indications of surgical resection for MDRTB and the role of minimally invasive surgery for infectious / inflammatory diseases of the lungs.

Keywords: Tuberculosis (TB); multidrug-resistant; thoracic surgery; video-assisted; robotic surgical procedures

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Introduction

Throughout the 19th century surgery was an important form of treatment of diseases caused by Mycobacterium tuberculosis (TB). In fact, modern thoracic surgery was developed mainly with the escalating increase of indications for the surgical treatment of pulmonary TB between World Wars I and II. Up until 1930 the therapeutic approach to pulmonary TB consisted basically of isolated bed rest in a healthy climate. Patients spent years in sanatoriums waiting for cure.

Surgical procedures were then conceived and performed by physicians, often themselves former TB patients, who tried to break away from the frustrating passivity of bed rest (1). The main purpose of these procedures was collapsing regions of the lungs that contained cavitary lesions with the hope of reducing the availability of oxygen to the aerobic mycobacteria. Examples of collapse therapy included thoracoplasty, plombage, pneumothorax, pneumoperitoneum, and phrenic nerve crush (2). Surgical resection of the diseased area of the lung was also attempted in the era prior to antibiotic chemotherapy. However, this form of surgical treatment was received with skepticism and most thoracic surgeons still favored collapse therapy as the primary form of treatment for pulmonary TB.

With the advent of streptomycin in 1944 and later the use of isoniazid, chemotherapy became the gold standard in the treatment of TB, with cure being achieved in most patients. Soon surgery became superfluous as a primary form of therapy and basically used in the treatment of sequelae of the disease and complications of previous procedures (3). Interest in surgical treatment for TB has resurged due to the development of strains of M. tuberculosis that are resistant to many or all of the first-line agents.

Multidrug-resistant tuberculosis (MDRTB)

MDRTB refers to Mycobacterium TB strains with *in vitro*

resistance to the two most effective anti-TB drugs, isoniazid and rifampin. In fact the World Health Organization has defined many forms of drug resistance to address this problem (4).

Despite the singularities of each classification, drug resistance has become a major challenge in TB control, with high relapse and treatment failure rates that lead to development of further resistance. There's little randomized control trials on the medical treatment of MDRTB (5) and the limited number of second line drugs available makes treatment more costly and associated with more adverse events.

Since individualized treatment regimens appear to have higher treatment success than standardised regimens, chemotherapy for MDRTB requires assessment of the history of treatment as well as meticulous laboratory studies to characterize susceptibility of the specific strain (6). Even with the best therapeutic options available MDRTB is still regarded as having a poor prognosis and most studies show treatment success estimates at around 40% to 60% (7,8).

Surgical resection of diseased areas of the lungs has therefore been tried as an adjuvant therapy in MDRTB. The rationale behind this form of treatment is to remove segments of the lungs containing high concentrations of drug resistant bacilli as reducing the population of mycobacteria will enhance the sterilizing properties of post-surgical chemotherapy and increase the likelihood of treatment success (9).

Most data available today supports the role of surgery in the management of MDRTB (10) although there has been an important selection bias since patients that are fit for surgery usually show more localized disease, with better response to medical treatment and have an overall better clinical status than patients that are not surgical candidates. Even with surgical patients appearing to have superior outcomes there is still no definitive evidence on the topic and surgery should be considered in selected cases by a multidisciplinary panel of specialists.

Indications for surgical treatment

Indications for surgical resection in the treatment of MDRTB were first described by Iseman *et al* in 1990 (11) and are still used except for minor adaptations due to development of further resistance. Surgery is indicated for patients with such extensive drug resistance that treatment failure or relapse is highly likely, in those with localised disease amenable to resection, and those who have sufficient drug activity to reduce remaining mycobacterial burden enough to allow bronchial stump healing and prevent postoperative complications. However, the lack of effective chemotherapy for some strains of *M. tuberculosis* classified as extensively resistant tuberculosis (XDRTB) means that even "cured" patients remain at high risk for relapse, and may be considered candidates for resection regardless of sputum culture status. The prerequisite of the presence of sufficient susceptible drug activity to facilitate healing of the bronchial stump is also less relevant in the setting of XDRTB, where extended resistance patterns mean that surgery often remains the only option for cure (12).

Guidelines for the management of drug-resistant TB from WHO (13) and Partners in Health (14) use these same indications for surgery. The American Thoracic Society and Centers for Disease Control and Prevention, and Infectious Diseases Society of America treatment of TB publication (15) state only that surgical resection should be considered for patients with MDRTB. According to most reports, a specialised surgical team with experienced thoracic surgeons in a dedicated center is considered a prerequisite for offering surgical resection to these patients (13,15). Other than that patients have to have sufficient cardiopulmonary reserve to tolerate resection (16).

Timing of surgery and preop evaluation

Most authors advocate that surgery should be performed after culture-conversion has been achieved to minimize the risk of post-surgical complications. A minimum of three to six months of preoperative chemotherapy is usually given. Another advantage in performing surgery later in the course of treatment is to allow time for nutritional supplementation and control of coexisting medical conditions. However, particularly in the case of XDRTB, this is unlikely to ever be achieved. Delaying surgery and persisting with ineffective chemotherapy may only facilitate progression of disease, and further promote the development of drug resistance (17).

The preoperative workup is directed at estimating cardiopulmonary reserve. Due to the lack of a standardized method for preoperative evaluation in patients undergoing resection for infectious disease we extrapolate the data available for lung cancer surgery. We routinely perform a complete pulmonary function test to estimate pulmonary reserve. In borderline cases, a quantitative lung perfusion scintigraphy can help to define nonperfused areas of parenchyma and thus provide a more reliable evaluation. Another useful tool for borderline patients is the

Figure 1 RATS left upper lobectomy for inflammatory/infectious lung disease (36).
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cardiopulmonary exercise test. A VO_{2max} of 15 mL/kg/min has been used as the cutoff for operability (18). An ECG followed by an echocardiogram, where indicated, may be useful in excluding pulmonary hypertension.

The role of minimally invasive surgery

Since its first introduction in the 1980s video assisted thoracic surgery (VATS) has evolved to become the preferred method for the treatment of early stage lung cancer in many centers (19). Equivalent oncological outcomes have been extensively reported by large series when compared to open thoracotomy (20,21). Among the biggest advantages of VATS are less morbidity and postoperative pain (22-24), better functional status, and the improved ability to deliver adjuvant medical therapy (25). Other potential advantages include shorter length of hospital stay (26) and possible cost-minimization (27). Despite these advantages, much less is known about the use of these techniques in the setting of benign lung disease, and specifically infectious lung disease. In theory, patients with focal bronchiectasis or cavitary infectious lung disease that meet indications for surgical resection would be excellent candidates for a minimally invasive approach (28).

The main technical difficulties for VATS resections in infectious lung disease include the presence of firm pleural adhesions, hypertrophy of the bronchial circulation, hilar lymphadenopathy and presence of a thicker, difficult to compress lung parenchyma.

Careful preoperative evaluation can help to predict most of the intraoperative complications. A high-resolution computed tomography will usually show the presence of dense adhesions. Although the need of an extrapleural dissection is an indication for conversion, most of the adhesions can be divided by VATS. In fact the better visualisation provided by the scope can make this part of the procedure easier than in some open approaches.

Since hilar lymphadenopathy is a very common finding in these patients, additional care should be taken when dissecting the hilar vessels. Lymphadenectomy is not necessary but careful dissection of the hilar lymph nodes will increase exposure of the hilar vessels and make vascular control safer.

Although these characteristics make VATS resections for infectious lung disease somewhat more challenging and with higher conversion rates than resection for lung cancer, many authors have reported good results by a minimally invasive approach, therefore VATS resection has been deemed feasible and its use has increased substantially (28-31).

More recently, robotic pulmonary resection (RATS) has emerged as another form of minimally invasive approach in the treatment of non-small cell lung cancer. Initial reports assure the safety and oncological equivalency of this method (32-35). Despite the lack of published data on the use of RATS for infectious lung diseases, we believe that the robotic platform offers many advantages desirable in the treatment of these patients. Improved ergonomics, increased dexterity and precision, better visualisation with 3D high definition images and a higher magnification rate are the main advantages mentioned by robotic surgeons. Since nodal dissection seems to be more delicate the robotic system may help overcome the technical challenges of resection for infectious disease. The main disadvantages of this method are the lack of tactile feedback, increased operating room time for setup and increased costs.

Here we present a case of a left upper lobectomy for infectious/inflammatory lung disease operated in our institution by a robotic approach (*Figure 1*).

Conclusions

MDRTB is a major global challenge in TB control with high rates of treatment failure and relapse. Surgical resection of grossly diseased areas of lung parenchyma seems to be an important adjuvant in the treatment of this condition. Most reports confirm this hypothesis, but further investigation is still necessary to define the best treatment strategy. From the evidence available today we suggest that a panel of specialists should be consulted when selecting

patients for surgical treatment.

When surgery is indicated patients should undergo a thorough preoperative evaluation to assess cardiopulmonary risk. Furthermore, we believe patients should have at least 3 months of adequate chemotherapy before surgery with culture conversion being necessary but not mandatory. This extra time should allow for an improvement in nutritional status and control of comorbidities.

From a technical standpoint, lung resection for infectious/inflammatory disease post several challenges. Most difficulties are related to the presence of pleural adhesions and lymphadenopathy. Granting most authors have used an open approach to report their surgical results for MDRTB, we believe that minimally invasive surgery is feasible in this scenario and should be considered in selected cases.

The use of VATS has been increasing in the treatment of benign disease, with several authors publishing their experience with the method. Despite the lack of publications for this specific purpose, we consider that RATS has potential to develop as an excellent platform for delivering a minimally invasive technique in such difficult cases, mainly due to the improved ergonomics and dexterity provided by the robotic system.

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Footnote

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Ethical Statement: 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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