INTRODUCTION

Tuberculoma is a single caseous tuberculosis lesion surrounded by fibrous tissue or spheroid lesion formed from obstructed cavity filling with caseous substance, more than 2 cm in diameter. Tuberculomas are spherical, avascular and granulomatous tubercle tumors most commonly found in the lungs and central nervous system. Tuberculomas are primarily observed in healed primary tuberculosis infection but can occasionally also exist in post-primary tuberculosis.

Pulmonary tuberculoma develops in approximately 7–9% of tuberculosis patients. Pulmonary tuberculosis usually present as a solitary pulmonary nodule (SPN). SPNs are defined as single, round or oval nodules with well-defined boundaries that are smaller than or equal to 30 mm. The larger the size of the nodule, the greater the risk for malignancy. Natural history of pulmonary tuberculoma can be divided into progressive, stationary, and regressive. Stationary status accounts for 30–50% of all patients with a tuberculoma. The reported progression rate was 5.8% in patients with tuberculomas sized <2 cm vs. 14.8% and 25.0% when tuberculosis is sized <4 and >4 cm, respectively.

The diagnosis of pulmonary tuberculosis often requires invasive procedures such as percutaneous fine needle biopsy or VATS. A correct diagnosis is important because pulmonary tuberculosis may be accompanied by lung cancer in rare cases. The differentiation between pulmonary tuberculosis and lung cancer, as well as between active tuberculosis and inactive tuberculosis remains a clinical challenge. Pulmonary tuberculosis is difficult to differentiate from primary or metastatic lung cancer. Misdiagnosis and loss of diagnosis are common. Treatment of pulmonary tuberculosis should follow the multiple disciplinary team model, including the thoracic surgeon, tuberculosis department, pulmonary department, radiographic department, clinical nutritional department and others.

Surgical resection is valuable to help determine further treatment strategies and decrease the duration and dose of anti-tuberculosis treatment. In the other hand clinical experience has shown that most medical treatment effects on tuberculoma are relatively poor, after the whole anti-tuberculosis treatment, lesions are often not obviously reduced. Hence, this systematic review aimed to summarize the effectiveness of managing pulmonary tuberculosis, including the response to anti-tuberculosis treatment or surgical treatment.

METHODS

This systematic review was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the events evaluated by interventions and healthcare behaviors. Population,
The search on the database was resulted in 288 initial articles (52 articles from Wiley Online Library, 6 from PubMed database, 5 from Cochrane Online Library, 138 from ProQuest and 87 articles from ScienceDirect). Because of the irrelevant titles, 278 articles were excluded, and there were not duplicate titles. After the discussion among the authors, another six articles were excluded because of several reasons. The title and the abstract of the articles were reviewed, and according to the results, only four fitted the eligibility criteria stated in this systematic review (Figure 1).

All four selected studies were conducted in 2013, 2014, 2017, and 2018. There was differentiation treatment in each studies, two studies with surgical treatment, one study with anti-tuberculosis treatment then percutaneous lung puncture, and one review included the both of treatments, anti-tuberculosis and surgical treatment with application of the tubeless video-assisted thoracoscopic surgery (VATS) technique (Table 1).

Xie et al. found that pulmonary tuberculoma responds poorly to anti-tuberculosis treatment and often requires long-term treatment, if the size of pulmonary tuberculoma increases with medical treatment, surgical resection may offer the most appropriate solution. The development of modern thoracic surgery techniques, especially VATS, enables the effective treatment of patients with pulmonary tuberculoma. Complications of pulmonary tuberculoma that are unresponsive to conventional antituberculosis treatment can also be treated with VATS. Resection is also valuable to help determine further treatment strategies and decrease the duration and dose of anti-tuberculosis treatment. Anti-tuberculosis treatment is not necessary preoperatively and is usually administered postoperatively.

Laisaar et al. enrolled forty-three patients (25 men, 18 women) with mean age of 43.3 (range 15-68) years. All patients who underwent thoracoscopic resection of tuberculoma between 1996 and 2008 were retrospectively analyzed. The median postoperative stay in surgical department was four days. No intra-hospital mortality occurred. Eleven patients received preoperative ATT for 8 to 288 (median 115) days and 42 patients were treated postoperatively for 40 to 672 (median 185) days. One patient defaulted in ATT. First-line drugs were prescribed in 37 and second-line in five patients. None of the patients developed relapse during the median follow-up of 9.0 (range 3.2 to 16.1) years. Thoracoscopic pulmonary resection provides a minimally invasive opportunity for morphological and microbiological

**RESULTS**

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### Table 1. Summary of data description from the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject criteria and study design</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xia et al. 2017³</td>
<td>Subject criteria: Unspecified</td>
<td>Anti-tuberculosis treatment and surgical treatments (novel tubeless video-assisted thoracoscopic surgery technique)</td>
<td>VATS as surgical treatment of pulmonary tuberculoma has been found to be safe and feasible and leads to less surgical trauma, which results in reduced length of hospitalization and better post-operative quality of life.</td>
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<td></td>
<td>Study design: Review</td>
<td></td>
<td></td>
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<tr>
<td>Laisaar et al. 2014⁴</td>
<td>Subject criteria: All patients who underwent thoracoscopic resection of tuberculoma between 1996 and 2008</td>
<td>Thoracoscopic lung resection, followed by anti-tuberculosis treatment (ATT)</td>
<td>Thoracoscopic pulmonary resection results in an excellent cure rate in combination with ATT</td>
</tr>
<tr>
<td></td>
<td>Study design: Case report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al. 2013¹</td>
<td>Subject criteria: Patients who were diagnosed with tuberculoma, and the diameter was greater than or equal to 2 cm; After 3-6 months of regular anti-TB treatment, tuberculoma size was unchanged; Aged from 18 to 60 years old;</td>
<td>Anti-tuberculosis treatment, then percutaneous lung puncture (isoniazid and amikacin)</td>
<td>The drug administration via percutaneous lung puncture — “holing” in pulmonary tuberculoma takes a significant effect obviously, good short- and long-term effects and less side effects.</td>
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<tr>
<td></td>
<td>Study design: Experimental</td>
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<tr>
<td>Giller et al. 2018⁹</td>
<td>Subject criteria: 5599 surgeries on patients with pulmonary TB aged from 1 to 87 years. (18.8% patients with tuberculoma)</td>
<td>Surgical treatment</td>
<td>3 years after treatment showed that 93.9% patients had no TB relapse. Post-operative complication: 1.9% and 30-days mortality rate: 0.1%.</td>
</tr>
<tr>
<td></td>
<td>Study design: Case Series</td>
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diagnosis of tuberculoma; and results in an excellent cure rate in combination with ATT.⁸

Yang et al. showed that after two months of drug treatment by lung puncture, the sputum smear test showed the negative conversion rate of tubercle bacillus was 87%, and the positive conversion rate was 8%. The tuberculosis bacillus culture indicated that the negative conversion rate was 100%. The re-examination after one year showed the negative conversion rate of tubercle bacillus in the sputum smear test was 80%. About 58% of tuberculosis disappeared or significantly reduced, in which, 40% of tuberculoma disappeared. The tuberculoma diameter reduced from 3.6 cm × 2.8 cm to 1.7 cm × 1.1 cm on average. Side effects included postoperative pneumothorax 9%, hemoptysis 7% and fever 11%. A total of 34 patients were followed up for five years, and the disappearance rate of tuberculoma was up to 47%, with no recurrence.¹

Giller et al. reported that surgical treatment is necessary in regions with a high frequency of drug-resistant cases. Though the study of the results 3 years after treatment showed that 93.9% (149 of 159 cases) of patients had no TB relapse. Treatment efficacy in the long term, which is estimated after 2–3 years of observation and defined by the index of clinical recovery, exceeded countrywide results by 2.8 times that for the experimental group of 334 patients (83.2% vs 29.3%).⁹

### DISCUSSION

Based on four studies that have been analyzed, two studies were related to surgical treatment, one study related to anti-tuberculosis treatment then percutaneous lung puncture, and one review included the both of treatments, anti-tuberculosis and surgical treatment. Clinical experience has shown that: most medical effects treatment on tuberculoma are relatively poor, after the whole anti-tuberculosis treatment, lesions are often not obviously reduced. The possibility of complete drug absorption is even smaller. Tuberculoma patients should also be regularly re-examined though the treatment has been finished. Because the immunity will be weakened or allergic reaction increased once the body is affected by certain factors, tubercle bacillus in tuberculoma can be re-active and multiply, tuberculoma capsule is damaged. The lesions extends to the surrounding lung tissue or are caseated liquefied, dissolved and penetrates the bronchia to discharge, thus forming a cavity. Tubercle bacillus can also spread to the lung or pleura via lymph or bronchia, causing new lesions, worsening tuberculosis. Therefore, the way to control and treat tuberculoma becomes another anti-tuberculosis problem.¹

The diagnosis of pulmonary tuberculoma often requires invasive procedures such as percutaneous fine
needle biopsy or VATS. A correct diagnosis is important because pulmonary tuberculosis may be accompanied by lung cancer in rare cases. Therefore, the clinician must be aware of the various responses of pulmonary tuberculosis to anti-tuberculosis treatment. Pulmonary tuberculosis responds poorly to anti-tuberculosis treatment and often requires long-term treatment. If the size of pulmonary tuberculosis increases with medical treatment, surgical resection also the most appropriate solution.\textsuperscript{5,6} In 2004, a retrospective study published by the European Respiratory Journal assessed the response to anti-tuberculosis treatment in 45 cases of pulmonary tuberculosis. After a mean treatment duration of 11.5±3.6 months, only 40% of patients showed a reduction in tuberculosis size (>25% reduction in area versus its initial area) after 3 months of treatment, while 55.6% remained unchanged, two patients had an increased tuberculosis size (>25% increase in area versus its initial area).\textsuperscript{11}

The natural progression of pulmonary tuberculosis commonly includes three phases: a progressive period, a steady period (most common, 30–50% of all affected patients) and a regression period. Cases of SPN containing both tuberculosis and tuberculosis have been reported, and lung cancer misdiagnosis can occur. If the size of pulmonary tuberculosis increases with medical treatment, surgical resection may offer the most appropriate solution.\textsuperscript{5}

The indications for surgical treatment of tuberculosis are the following: long-lasting sub febrile temperature, tuberculosis intoxication, diameter >3 cm, positive sputum culture, lung parenchymal destruction, multiple tuberculosis in one lobe, and suspected primary or metastatic lung cancer. Resection is also valuable to help determine further treatment strategies and decrease the duration and dose of anti-tuberculosis treatment.\textsuperscript{1,5} In tuberculosis, surgery is subsegmental or a segmental resection of the lung in the majority of cases and rarely, a lobectomy.\textsuperscript{9}

Pulmonary tuberculosis usually present as a solitary pulmonary nodule (SPN). SPNs are defined as single, round or oval nodules with well-defined boundaries that are smaller than or equal to 30 mm. The larger the size of the nodule, the greater the risk for malignancy.\textsuperscript{12} Resection of benign SPNs, including tuberculosis, is performed using pulmonary wedge resection. However, the resection technique is very different for malignant SPNs, which require radical surgery with lobectomy and systemic lymph node dissection.\textsuperscript{3,5}

Differentiation between active tuberculosis and primary or metastatic lung cancer remains a clinical challenge. Active tuberculosis has a central mass of epithelioid cells with Langhans type giant cells and varying degrees of caseation, and inactive tuberculosis is primarily composed of acellular caseous material and fibrosis.\textsuperscript{13} Because of increased glucose metabolism caused by granulomatous inflammation, they can accumulate F-18 fluorodeoxyglucose (FDG) during positron emission tomography (PET); then, they could be misdiagnosed with pulmonary tumours. Choline C-11 PET scans can differentiate between lung cancer and tuberculosis, being tuberculosis's choline C-11 uptake lower if compared with lung cancer.\textsuperscript{4}

Tuberculomas can be found in the upper lobes, often surrounded by satellite nodules in 80% of the cases. The reported progression rate was 5.8% in patients with tuberculosis size <2 cm vs. 14.8% and 25.0% when tuberculosis is sized <4 and >4 cm, respectively. Atypical and typical mono- and bi-segmental resections are recommended for patients with tuberculosis. Lobectomy may be necessary only for large lesions or for those located near the lung hilum. If anti-TB therapy is not performed pre-operatively (differential diagnosis with lung cancer), it is usually administered post-operatively.\textsuperscript{4,13}

This study’s limitation was that a small number of studies proved the effectiveness of surgical resection compared with medical treatment (anti-tuberculosis treatment) to increase the cure rate of tuberculosis patients, because only four studies fitted to eligibility criteria.

CONCLUSION

This review describes the effectiveness of tuberculosis treatment, including medical treatment (anti-tuberculosis) and surgical resection. The treatment of tuberculosis with surgical resection works effectively, with better short- and long-term effects for tuberculosis. Surgical treatment of pulmonary tuberculosis has been found to be safe and feasible, which results in better post-operative quality of life. Surgical resection followed by post-operative anti-tuberculosis treatment results in an excellent cure rate.

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DISCLOSURE

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ETHICAL CONSIDERATION

Ethical clearance is not mandatory in systematic review.

AUTHOR CONTRIBUTION

All authors had contributed in manuscript writing and agreed for the final version of manuscript for publication.

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5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that