INTRODUCTION

The lung is the second most common site of metastasis, and the incidence of pulmonary metastases has increased despite general improvements in the survival rates of cancer patients. Pulmonary metastasectomy (PM) is mainly performed via two surgical approaches: traditional open thoracotomy (OT) and video-assisted thoracoscopic surgery (VATS). Traditional OT is considered a standard component of treatment for patients with pulmonary metastases [1].

As a result of improvements in endoscopic instruments and surgeons' skills, the role of VATS in thoracic surgery has expanded. PM performed via VATS has advantages over that performed via traditional OT in the preservation of lung function, pain control and tolerance of postoperative chemotherapy [2]. In addition, at least 40% of patients with pulmonary metastases from sarcoma may experience recurrence after metastasectomy [3], and several studies have indicated that repeated resection is beneficial for patients with recurrent pulmonary metastases [4–6]. These findings make VATS an alternative strategy for PM.

Nevertheless, the safety of VATS for PM is questioned. Despite improvements in imaging technology, occult lesions still remain a concern [7], and VATS allows only limited intraoperative palpation, which may increase the risk of undetected metastases and lead to a higher recurrence rate, greater mediastinal lymph node involvement and reduced long-term survival rates [8]. No randomized controlled trials have examined the reliability of PM performed via VATS. Hence, we undertook this meta-analytic study to determine whether VATS is justified for PM compared with traditional OT in terms of survival rates. The overall survival (OS) and recurrence-free survival (RFS) rates are the main outcomes used to reflect the surgical effects.

MATERIALS AND METHODS

Eligibility criteria

We established our eligibility criteria before conducting our search. Two authors (Di Meng and Linhai Fu) independently...
evaluated potential eligible articles using the following inclusion criteria: (i) the article was published in English in the past 20 years; (ii) the study subjects were undergoing their first resection surgery for pulmonary metastases; (iii) the survival data for PM performed via VATS were compared with those for conventional OT and (iv) the survival data were reported in detail, including OS and/or RFS data. When studies from the same institutions or based on the same populations were identified, we included only the most recent articles with the most up-to-date data to avoid duplication. Disagreements were judged by the senior reviewer (Wang Lv) after referring to the original articles.

Search strategy

Medline was searched for relevant studies published up to December 2014 as the primary source. This search was performed with the following terms: (‘pulmonary’ or ‘lung’) and (‘metastasec-tomy’ or ‘metastatectomy’ or ‘metastectomy’ or ‘metastasis’ or ‘metastases’) and (‘VATS’ or ‘thoracoscopic’ or ‘thoracotomy’ or ‘thoracic surgery’). The search results were supplemented by manual searches of relevant meeting reports, letters and editorials. We also cross-referenced for relevant studies that met our eligibility criteria.

Data extraction and quality assessment

Two authors extracted the following items from the included articles: the authors, the year of publication, the country, the study design, the number of cases in which VATS or OT was used and the OS and/or RFS data. For articles that were available only as abstracts or that had not yet been published, we attempted to obtain the necessary data by contacting the corresponding authors via e-mail. The RFS rate was identified from the period from the first metastectomy to pulmonary recurrence.

Two authors (Luming Wang and Yining Dai) independently assessed the included studies with the evaluation system based on the MINORS [9]. The full score was 24 points, and a high-quality study was defined as one with more than 18 points. Disagreements were judged by the senior reviewer (Jian Hu).

Statistical analysis

The OS and RFS rates were measured by hazard ratio (HR), which was calculated by comparing the VATS group with the OT group. We extracted the HRs and their associated 95% confidence intervals (CIs) directly from the included articles when they were clearly reported; otherwise, the values were calculated or extracted from

![Figure 1: Flow diagram of the search results for studies comparing metastatectomy through open thoracotomy with that through VATS. VATS: video-assisted thoracic surgery; From [12].](image-url)
the provided Kaplan–Meier curves by the methods of Parmar and Tierney [10, 11]. The Kaplan–Meier curves were read with Engauge Digitizer version 4.1 (http://sourceforge.net/projects/digitizer/files/Engauge%20Digitizer/digitizer-4.1/).

The χ² test and I² test were used to assess statistical heterogeneity beyond chance. P-values of greater than 0.1 for the χ² test and I² values of less than 25% were considered to indicate homogeneity. We calculated the pooled HRs with a fixed-effect model or a random-effect model according to the heterogeneity. Publication bias was assessed with funnel plots and Egger’s test.

We conducted a sensitivity analysis by omitting each study in sequence. All statistical analyses were conducted with Stata version 12.0 (StatCorp, College Station, TX, USA).

RESULTS

Study characteristics and quality assessment

As shown in Fig. 1, eight retrospective cohort studies [13–20] including 822 patients were included in this meta-analysis. The pulmonary metastases originated from carcinoma in 585 patients and from sarcoma in 190. We allocated 337 patients into the VATS group and 485 patients into the OT group. We also extracted data regarding histological studies, the treatment of the primary malignancy, other metastatic sites, the surgical margin of PM and other treatments performed before or after PM, which are listed in Tables 2 and 3. The patients included had a similar condition and treatment process according to the available information. Seven of the studies were considered to be of high quality (quality scores ranging from 19 to 21). Overall, the principal characteristics of each study are listed in Table 1, and the surgical and clinical details of the studies are exhibited in Tables 2 and 3.

Overall survival and recurrence-free survival data

All eight studies provided data for the OS rate [13–20]. The pooled HR for OS was 0.69 (95% CI, 0.55–0.87) and was statistically significant (P = 0.002); there was no evidence of heterogeneity among the studies (I² = 0.0%; P = 0.575).

Data on RFS were available from seven studies [13, 15–20]. The pooled HR for RFS was 0.86 (95% CI, 0.69–1.08; P = 0.200), and no statistically significant heterogeneity was detected among the studies (I² = 0.0%; P = 0.920) (Fig. 2).

Subgroup analysis

We conducted a subgroup analysis according to the histological data of the primary cancer (Fig. 3). Three studies [15, 17, 19]
focused on metastases from colorectal cancer. The pooled HR for OS was 0.72 (95% CI, 0.50–1.04; $I^2 = 0.0\%$, $P = 0.486$), and the pooled HR for RFS was 0.79 (95% CI, 0.59–1.08; $I^2 = 0.0\%$, $P = 0.517$); neither result was statistically significant.

Sensitivity analysis

Sensitivity analyses were performed to investigate the influence of each study on the overall effects. Exclusion of the study with the lowest score [14] yielded an HR of 0.78 (95% CI, 0.59–1.03) for OS, as shown in Fig. 4. Exclusion of each of the other studies did not materially alter the overall results.

Publication bias

The funnel plot did not show any obvious asymmetry. In addition, Egger’s test indicated no evidence of publication bias ($P = 0.169$).

DISCUSSION

The first PM performed by VATS was reported in the early 1990s, and the National Comprehensive Cancer Network (NCCN) guidelines of 2014 strongly suggested its use in primary lung cancer patients with no anatomical or surgical contraindications. Although VATS was not recognized as a routine approach for PM in the clinical guidelines, 40% of the members of the European Society of Thoracic Surgeons conducted PM via VATS in 2008 [21]. It has been reported that intraoperative palpation could be used to identify metastases that are not detected by a preoperative helical chest computed tomographic scan in 20–25% of patients [22, 23]. The VATS approach has limitations in the location of occult nodules in preoperative imaging studies, which may lead to a higher pulmonary recurrence rate and a reduced long-term survival rate. It is therefore urgent to identify whether VATS leads to equivalent survival rates in patients with pulmonary metastases.

The primary results of our meta-analysis indicate that the VATS group may have had a better OS rate in PM than that in the OT group (HR, 0.69; 95% CI, 0.55–0.87; $P = 0.002$) and that the VATS group still had a superior OS rate after exclusion of the one low-quality study [14] (HR, 0.78; 95% CI, 0.59–1.03); however, the results lack statistical significance. The standard benefits of minimally invasive surgery, including less pain, better mobility, faster rehabilitation, a decreased length of stay and better tolerance of postoperative chemotherapy [2], may be the main reasons for the improved survival rates. Furthermore, Hornbech et al. [24] found that ~18.9% of patients may have recurrence of pulmonary metastases and that repeated surgical procedures could improve the long-term survival rate in those patients [5]. Thus, VATS has the potential to be a recommended surgical approach for PM.

Surgical margins and occult nodules are the main concerns with the VATS approach. Our results suggest no difference in the RFS rate between the VATS group and the OT group (HR, 0.86; 95% CI, 0.69–1.08). Tumour-free margins were achieved in most patients in the VATS group according to the included articles, as presented in Table 2. Although VATS may not have allowed the removal of all of the non-imaged nodules, the clinical significance of these nodules is unclear [7]. In a prospective study, Eckardt et al. [8] found that most nodules detected by bimanual palpation during thoracotomy were benign. In addition, there is no
evidence to confirm that the presence of occult nodules reduces the survival rates of patients with pulmonary metastases. Our results suggest no difference in the RFS rate between the VATS group and the OT group (HR, 0.86; 95% CI, 0.69–1.08), which to some degree supports the opinion that nodules missed during PM did not increase the recurrence rate. In addition, the evolution of

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
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<th>OT</th>
<th>HR (95% CI)</th>
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<tr>
<td>Han</td>
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<td>31</td>
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<td>8</td>
<td>12</td>
<td>1.16 (0.18, 7.59)</td>
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Subtotal (I² = 0.0%, P = 0.575) 1.53

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Subtotal (I² = 0.0%, P = 0.920) 1.53

NOTE: Weights are from random-effect analysis
Computed tomographic scanning has increased the rate of false-positive intrapulmonary nodules in patients in whom pulmonary metastases are suspected and has led to excessive pulmonary resections. The necessity of removing every single nodule, especially those that are occult on imaging studies but detected by intraoperative palpation, remains to be determined.

The issue of whether the histological findings on the primary malignancy affect the survival rate remains controversial [1, 25]. Our subgroup analysis included patients with pulmonary metastases from colorectal cancer. No significant statistical differences were found between the two groups in either the OS rate (HR, 0.72; 95% CI, 0.50–1.04) or the RFS rate (HR, 0.79; 95% CI, 0.59–1.08), which suggests that VATS was a suitable approach for pulmonary metastases from colorectal cancers. This finding remains to be confirmed by a large randomized, controlled trial.

A similar meta-analysis was conducted in 2013 [26]. The authors estimated the data by odds ratio and concluded that VATS was a safe and feasible treatment for metastatic lung cancer in terms of survival rate when compared with thoracotomy, which was consistent with the results of the current study. The difference between these two meta-analyses may be a result of the updated studies. In addition, we assessed the OS and RFS rates by HR, which has the advantage of using all available information and is more effective in the evaluation of time-to-event data [11]. Seven of the included studies depicted the data with a Kaplan–Meier curve, which provided information on patients who failed to complete the trial.

Admittedly, our study has some limitations. Firstly, we are unable to conduct this meta-analysis of a specific type of original malignancy because of the scarcity of available studies. And there was no certain evidence that survival rates after PM differed among different histological types. Secondly, it was based on retrospective studies that have unavoidable potential selection bias and inherent limitations. As depicted in Table 2, multiple nodules were found in 20.4% of the patients in the VATS group and in 51.1% of the patients in the OT group; wedge resection was performed in 91.5% of metastases in the VATS group but in only 61.6% of those in the OT group (Table 2). Patients with large or multiple nodules were more likely to consent to an open approach, which acted in favour of VATS. In addition, other treatment given for the primary malignancy, including neoadjuvant treatment or surgery, was not reported in detail. Considering the lack of relevant randomized controlled trials available for use in this meta-analysis, our results still provide the most convincing evidence of the clinical effects of VATS performed for PM. VATS is an alternative surgical approach in the newly launched Pulmonary Metastasectomy in Colorectal Cancer trial, which may be able to answer these questions and clarify the indications for VATS.

In conclusion, VATS is an alternative surgical approach for PM in patients with resectable pulmonary metastases. With developments in imaging and surgical technology, minimally invasive surgery will be an important surgical approach for PM. Further prospective studies are needed to identify the indications for VATS in patients with pulmonary metastases.

**Funding**

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**Conflict of interest:** none declared.
REFERENCES


eComment. Video-assisted thoracoscopic pulmonary metastasectomy: can the “ultrasound eye” do what the surgeon’s finger cannot?

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We read with great interest the meta-analytic study by Di Meng et al. [1], analyzing the effectiveness of video-assisted thoracoscopic surgery (VATS) for the treatment of pulmonary metastases compared to open thoracotomy. Authors concluded that, although open thoracotomy is considered the standard approach for pulmonary metastasectomy [2], VATS is a suitable alternative in patients with resectable pulmonary metastases, and in particular in patients with metastases from colorectal cancer, both in terms of overall survival rate and recurrence-free survival rate. However, localization of occult nodules in preoperative imaging studies is the main concern in VATS technique (although the clinical significance of these nodules is still unclear), because intraoperative palpation is very limited and often difficult. In last years, different works [3] have evaluated the role of intracavitary ultrasonography in the localization of intraparenchymal pulmonary nodules during VATS and have suggested it as a real-time, reliable and effective method, which helps surgeon to detect all lesions not identifiable by using standard techniques (visually, using finger palpation or using the instrument sliding method) or to diagnose occult nodules. The possible costs of a laparoscopic ultrasound probe would be compensated by decreased length of hospital stay after minimally invasive surgery, thanks to less pain and faster rehabilitation of patients. In light of the above considerations, we agree with the authors that further prospective and randomized studies are needed to standardize the indications for VATS in pulmonary metastasectomy and also to clarify the role of different methods of nodule localizations, such as intraoperative ultrasonography.

Conflict of interest: none declared.

References


eComment. Open thoracotomy or minimally invasive thoracoscopic surgery in pulmonary metastasectomy?

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Thoracic and Vascular Surgery Division, Valenciennes Hospital, Valenciennes, France
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I read with great interest the meta-analysis of observational studies by Di Meng et al. [1], in which they compared video-assisted thoracoscopic surgery (VATS) with