



SYSTEMATIC REVIEW

**REVISED** Malignant pleural effusions and the role of talc poudrage and talc slurry: a systematic review and meta-analysis [v2; ref status: indexed, <http://f1000r.es/52v>]

Srinivas Mummadi<sup>1,2</sup>, Anusha Kumbam<sup>1,3</sup>, Peter Y. Hahn<sup>1,2</sup>

<sup>1</sup>Division of Pulmonary and Critical Care Medicine, Tuality Healthcare, Hillsboro, OR, 97123, USA

<sup>2</sup>Division of Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, 97239, USA

<sup>3</sup>Department of Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, 60614, USA

**v2** First published: 27 Oct 2014, 3:254 (doi: [10.12688/f1000research.5538.1](https://doi.org/10.12688/f1000research.5538.1))  
 Latest published: 17 Feb 2015, 3:254 (doi: [10.12688/f1000research.5538.2](https://doi.org/10.12688/f1000research.5538.2))

**Abstract**

**Background:** Malignant Pleural Effusion (MPE) is common with advanced malignancy. Palliative care with minimal adverse events is the cornerstone of management. Although talc pleurodesis plays an important role in treatment, the best modality of talc application remains controversial.

**Objective:** To compare rates of successful pleurodesis, rates of respiratory and non-respiratory complications between thorascopic talc insufflation/poudrage (TTI) and talc slurry (TS).

**Data sources and study selection:** MEDLINE (PubMed, OVID), EBM Reviews (Cochrane database of Systematic Reviews, ACP Journal Club, DARE, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database), EMBASE and Scopus. Randomized controlled trials published between 01/01/1980 - 10/1/2014 and comparing the two strategies were selected.

**Results:** Twenty-eight potential studies were identified of which 24 studies were further excluded, leaving four studies. No statistically significant difference in the probability of successful pleurodesis was observed between TS and TTI groups (RR 1.06; 95 % CI 0.99-1.14; Q statistic, 4.84). There was a higher risk of post procedural respiratory complications in the TTI group compared to the TS group (RR 1.91, 95% CI= 1.24-2.93, Q statistic 3.15). No statistically significant difference in the incidence of non-respiratory complications between the TTI group and the TS group was observed (RR 0.88, 95% CI= 0.72-1.07, Q statistic 4.61).

**Conclusions:** There is no difference in success rates of pleurodesis based on patient centered outcomes between talc poudrage and talc slurry treatments. Respiratory complications are more common with talc poudrage via thoracoscopy.

**Open Peer Review**

Referee Status:

|  | Invited Referees |   |        |
|--|------------------|---|--------|
|  | 1                | 2 | 3      |
| <b>REVISED</b>                               |                  |   |        |
| <b>version 2</b><br>published<br>17 Feb 2015 |                  |   | report |
| <b>version 1</b><br>published<br>27 Oct 2014 |                  |   | report |

- 1 **Gary Lee**, The Lung Institute of Western Australia Australia
- 2 **Pyng Lee**, National University Hospital Singapore
- 3 **Fabien Maldonado**, Mayo Clinic USA

**Discuss this article**

Comments (0)

**Corresponding author:** Srinivas Mummadi ([mummadis@ohsu.edu](mailto:mummadis@ohsu.edu))

**How to cite this article:** Mummadi S, Kumbam A and Hahn PY. **Malignant pleural effusions and the role of talc poudrage and talc slurry: a systematic review and meta-analysis [v2; ref status: indexed, <http://f1000r.es/52v>]** *F1000Research* 2015, **3**:254 (doi: [10.12688/f1000research.5538.2](https://doi.org/10.12688/f1000research.5538.2))

**Copyright:** © 2015 Mummadi S *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Competing interests:** No competing interests were disclosed.

**First published:** 27 Oct 2014, **3**:254 (doi: [10.12688/f1000research.5538.1](https://doi.org/10.12688/f1000research.5538.1))

**First indexed:** 27 Mar 2015, **3**:254 (doi: [10.12688/f1000research.5538.2](https://doi.org/10.12688/f1000research.5538.2))

**REVISED Amendments from Version 1**

In response to the reviewers' comments we have made the following changes:

- 1) Footnotes to the tables have been added reiterating the existing form of publication of one of the included studies (Manes 2000). New tables replacing the old ones have been included.
- 2) Outcomes of pleurodesis have been measured as rates of successful pleurodesis rather than failure. We agree with the reviewer's comments that the visibility of the message is improved by reporting success. Relevant changes have been made in the abstract, body of the manuscript as well as revised figures have been supplied.

See referee reports

## Introduction

Malignant Pleural Effusion (MPE) is a well described event in the natural history of advanced malignancy. Malignant etiology accounts for 22% of the diagnosed pleural effusions<sup>1</sup>. Using data from the 2012 Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP) and Agency for Healthcare Research and Quality, it is estimated that the aggregate charges (the "national bill") were 722 million dollars in the USA<sup>2</sup>.

Palliation with minimal adverse events remains the cornerstone of management<sup>3</sup>. Talc pleurodesis and Indwelling Pleural Catheters (IPC) are the two most commonly used palliative approaches.

Talc pleurodesis can be achieved either by thoracoscopic instillation i.e.; talc insufflation/poudrage (TTI) or via a bedside chest tube i.e. talc slurry (TS). Existing systematic reviews concluded that thoracoscopic talc insufflation/poudrage was more efficacious when compared to bedside chest tube talc slurry<sup>4,5</sup>. New prospectively designed studies comparing TTI and TS have been published since then<sup>6-8</sup>. However the best initial approach for talc pleurodesis remains still unclear. To address the need for an update, a systematic review and meta-analysis of studies comparing thoracoscopic talc insufflation/poudrage and talc slurry in terms of patient centered outcomes was performed.

## Materials and methods

### Data sources and search

We conducted a systematic review with meta-analysis of studies undertaken between 01/01/1980 and 12/31/2014 using MEDLINE (PubMed, OVID), EBM Reviews (Cochrane database of Systematic Reviews, ACP Journal Club, DARE, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database), EMBASE and Scopus. Unpublished data sets such as conference abstracts and [ClinicalTrials.gov](http://ClinicalTrials.gov) were also included in the full review phase to reduce the effect of publication bias<sup>9</sup>.

The following keywords were used: *chemical pleurodesis, pleurodesis, talc pleurodesis, bedside pleurodesis, surgical pleurodesis, medical pleurodesis, thoracoscopicpleurodesis, thoracoscopic talc pleurodesis, thoracoscopicpoudrage, thoracoscopic talc poudrage,*

*talc insufflation, thoracoscopic talc insufflation, pleuroscopy, medical thoracoscopy, talc poudrage, talc slurry, tube thoracoscopy, chest tube talc slurry and malignant pleural effusion.* Both keywords and medical subject headings were used in a Boolean search strategy. An example search strategy can be found in the [Appendix 1](#).

In addition, a pearl growing strategy was employed using frequently cited reviews of malignant pleural effusion treatments. They were included to be analyzed in the full review phase of the study. Approval from the Institutional Review Board was unnecessary because this is a meta-analysis.

### Study selection

Inclusion and exclusion criteria were framed prior to the implementation of the search strategy. To evaluate outcomes in adult malignant pleural effusion patients (18 + years) undergoing talc pleurodesis, we included studies based on the following criteria:

- 1) A randomized design was used in studying talc pleurodesis in patients with malignant pleural effusion between 01/01/1980 and 12/31/2014.
- 2) Patients undergoing bedside TS were compared with patients undergoing thoracoscopic talc insufflation/poudrage (TTI) in the above fashion.
- 3) Sufficient outcomes data were reported [Efficacy of pleurodesis, respiratory complications and non-respiratory complications].

Non-English publications, case reports and series, pediatric studies, descriptive studies without a control group, retrospective studies and prospective controlled studies without randomization were excluded. Eligible articles were reviewed by two reviewers for inclusion; disagreements were resolved via discussion. An examination of the full-length articles was carried with the intent of eliminating duplicate studies or same patient cohorts.

### Data extraction and outcome measures

Two reviewers independently extracted and rated the data from the selected full length articles using a standardized form. From each study, the data abstracted included study name/year, study design (prospective controlled, randomized controlled trial, retrospective etc.), cancer cell type, patient inclusion criteria, sample sizes for the bedside/surgical pleurodesis arms, technique employed in the bedside/surgical arms and the follow-up schedule.

Outcomes data pertaining to pleurodesis efficacy, respiratory complications, and non-respiratory complications were also extracted.

Talc pleurodesis for recurrent malignant pleural effusion is a palliative procedure and does not aim to have a mortality benefit. Therefore, measuring mortality outcomes was not the focus of the meta-analysis.

Various endpoints (pleurodesis failure vs success; radiological recurrence vs further need for pleural procedures) have been used to measure efficacy of the intervention in prior studies<sup>6,10</sup>.

To define efficacy, we chose to measure the success rates of pleurodesis rather than failure rates due to the relative ease of applicability of this measure in the real world clinical setting. A successful pleurodesis was defined *a priori* as accompanied by the lack of a need for repeat pleural procedures. Where clearly defined, asymptomatic radiological recurrences were included in the “successful” group (three asymptomatic recurrences in a total of four recurrences in the study by Yim *et al.*, 1996).

Respiratory complications were defined as occurrence of respiratory conditions such as pneumonia, Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, re-expansion pulmonary edema, bronchospasm, empyema, pulmonary embolism, prolonged air leak, bronchopleural fistula, atelectasis requiring bronchoscopy and subcutaneous emphysema.

Immediate non-respiratory complications were tabulated from the complications mentioned in the full length articles. These included fever, wound infection, chest pain, tumor recurrence at site, myocardial infarction, need for blood transfusions, arrhythmias and immediate post procedural death.

#### Quality assessment criteria

The randomized controlled trials that met inclusion criteria were evaluated for quality using components of the modified Jadad scale<sup>11</sup>. The presence of the following features was appraised:

- A) A description of the study confirming the randomized nature.
- B) Method of allocation to the study arms described and whether adequate/inadequate.
- C) Description of withdrawals and dropouts.

Due to the nature of the comparison (surgical vs bedside procedure), we felt that other features of the scale (description of a double blind nature) could not be appraised during our quality assessment. Two raters independently determined the quality of the studies included. Disagreements were resolved by discussions and final consensus.

#### Statistical analysis

Outcomes data for successful pleurodesis, respiratory and non-respiratory complications were summarized using descriptive statistics (simple count, proportion of the study sample). They were visually presented in Forest plots. The Mantel-Haenszel method<sup>12</sup> was used to combine data from individual studies and the results were reported as pooled relative risks (RR). Heterogeneity among the studies included was investigated by performing the  $I^2$  test<sup>13</sup>. Meta-analyses were conducted using the fixed effects model when heterogeneity between studies was low ( $I^2 < 40\%$ ) and the random effects model otherwise<sup>9</sup>.

To confirm the robust nature of the results, a sensitivity analysis was performed by removing one study at a time and determining the outcome.

Publication bias was examined by visually examining the filled funnel plots using trim and fill method. Other methods (Begg’s correlation<sup>14</sup> and Egger’s linear regression intercept)<sup>15</sup> were additionally used.

All analyses were performed using a statistical software package (Comprehensive Meta-Analysis, version 2.2.064; Biostat, Englewood, NJ).

#### Results

Based on initial search, 137 articles were obtained and reviewed independently by two reviewers. Pearl growing strategy was employed to seek additional articles and resulted in five articles. A clinical trial registry ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) was also examined and resulted in one additional article. These 143 articles were reviewed and 115 articles were excluded based on title and abstract. A total of 28 potential studies were thus identified with our search strategy. Twenty-four studies were further excluded, leaving four studies<sup>6,10,16,17</sup> for the final analysis. The sequence describing the above process can be found in [Figure 1](#).

None of the studies restricted the study population to a single cancerous cell type.

None of the included studies employed thoracoscopic evacuation of the malignant pleural effusion prior to bedside TS insertion via a chest tube.

Follow-up periods varied through the studies (Range = 30–425 days). Where available, recurrence data for the most distal available time point were selected for the meta-analysis.

All of the studies included in the analysis underwent quality assessment. The average Jadad score<sup>11</sup> was 1.5 out of a maximum possible score of 4 (Ranges 1–2). Out of the possible seven ways to assess the quality<sup>11</sup>, only four questions could be answered due to the nature of the intervention. It was not possible reliably or ethically for the original investigators to have carried out efficient blinding in a surgical versus bedside clinical experiment.

#### Measures of successful pleurodesis

The results of the pooled RR are shown in [Figure 2](#). The four studies included in this analysis enrolled a total of 454 patients with malignant pleural effusion ([Table 1](#)). There was no statistically significant difference in the proportion of successful pleurodesis between the bedside TS (successful pleurodesis/patients who underwent pleurodesis,  $n/N = 167/218$  pts) and the TTI groups (successful pleurodesis/patients who underwent pleurodesis,  $n/N = 197/236$  pts, pooled RR 1.06; 95% CI 0.99-1.14; Q statistic, 4.84;  $I^2$  statistic, 38%). There was no evidence of publication bias (P-value = 0.49 for the Begg’s test, P-value = 0.54 for the Egger’s regression intercept). After using the trim and fill methodology ([Figure 3](#)), these results did not change (RR= 1.04, 95% CI =0.97-1.11, Q statistic, 9).

The definitions of an efficacious pleurodesis intervention varied in the included studies. Three studies<sup>10,16,17</sup> reported procedure failure by measuring clinically significant recurrences and one study reported the number of successful procedures defined as the lack of recurrence. This study defined recurrence based on radiological data alone<sup>6</sup>. The remainder of the studies clearly mentioned the number of patients who were symptomatic and required further pleural procedures once a recurrent pleural effusion was diagnosed<sup>10,16,17</sup>.

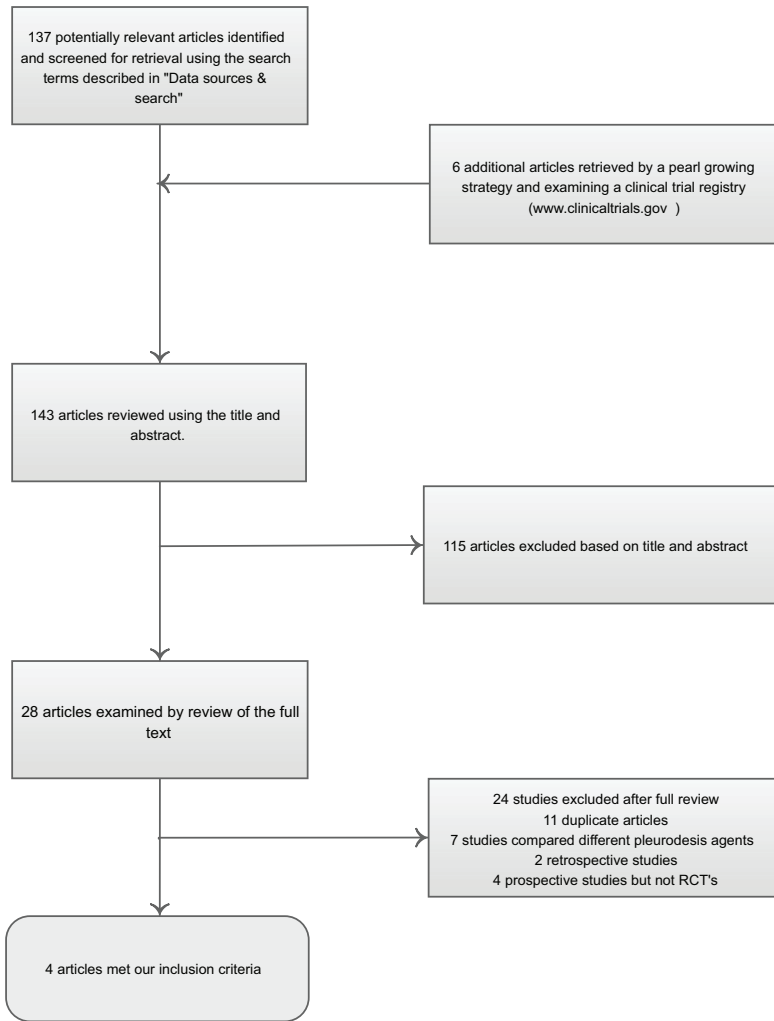


Figure 1. Flowsheet of study selection process.

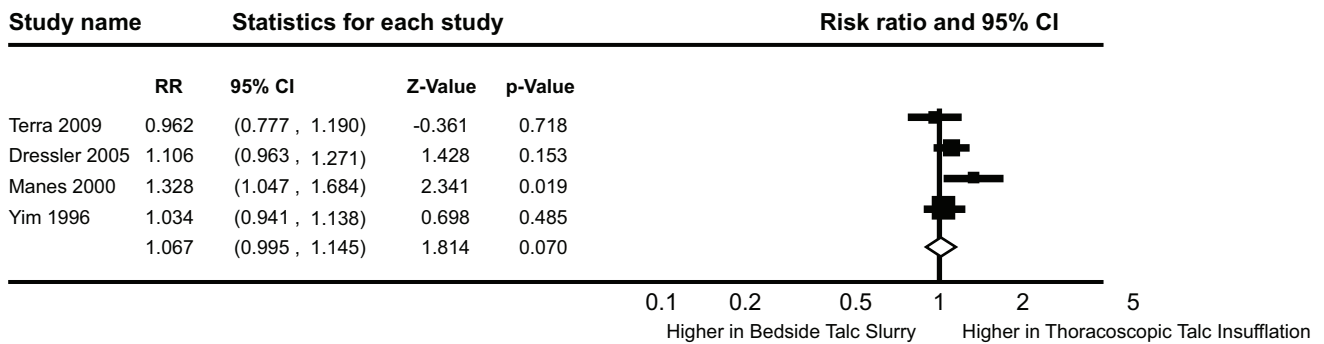


Figure 2. Pooled relative risks (RRs) of success rates post talc pleurodesis. RR, risk ratio, CI, confidence interval.

**Table 1. Characteristics of studies comparing rates of successful pleurodesis.**

| Study/Year Country | Intervention Design | Cancer Type | Definition of Success   | Successful Pleurodesis in TTI Group n/N, (%) | Successful Pleurodesis in TS group n/N, (%) | Follow up schedule                                      | Quality score | Quality problems   |
|--------------------|---------------------|-------------|---|--|---|---|---------------|--|
| Terra/2009 Brazil  | TTI vs TS RCT       | All cancers | Lack of both symptoms and further need for pleural procedures   | 25/30 (83.3%)                                | 26/30 (86.6%)                               | 1,3,6 months followed by q3 months or if symptoms arose | 2             | Allocation process unclear   |
| Dresler/2005 USA   | TTI vs TS RCT       | All cancers | No radiological recurrence  | 119/152 (78.2%)                              | 92/130 (70.7%)                              | 1-6 months  | 2             | Allocation process unclear   |
| Manes*/2000 Spain  | TTI vs TS RCT       | All cancers | Not defined but recurrences randomized to further pleural procedures                                      | 25/26 (96.1%)                                | 21/29 (72.4%)                               | 1-12 months   | 1             | Inappropriate allocation process, Potential "recycling" of patients into intervention arms |
| Yim/1996 China     | TTI vs TS RCT       | All cancers | No radiological recurrence, however symptomatic patients who needed further procedures clearly identified | 28/28 (100%)                                 | 28/29 (96.5%)                               | q6 weeks from 1-4.5 months, then q3 months              | 2             | Allocation process unclear   |

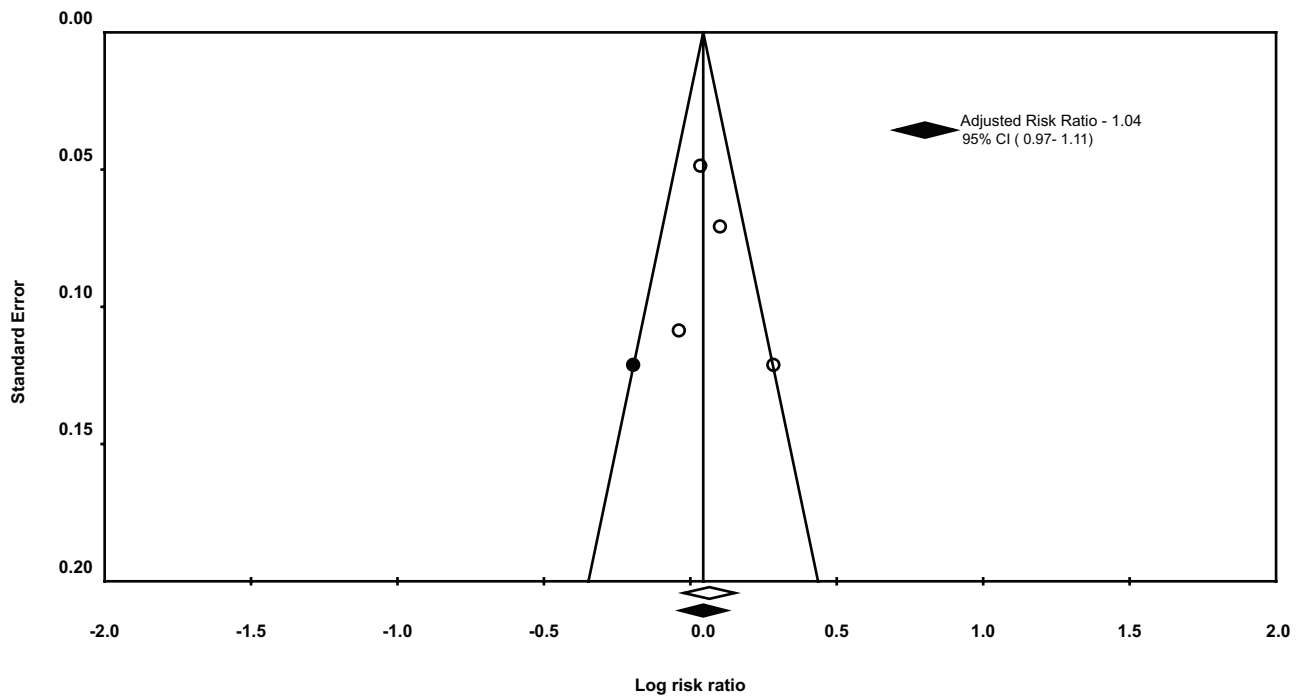
\*Study published only as an abstract form

TTI, Thoracoscopic talc insufflation, Also known as Thoracoscopic talc poudrage

TS, Talc slurry applied via a bedside chest tube

RCT, Randomized Controlled Trials

q- Every



**Figure 3. Filled funnel plot using the trim and fill method for succesful pleurodesis rates post talc pleurodesis: imputed studies - ●, observed studies - ○, CI – confidence interval.**

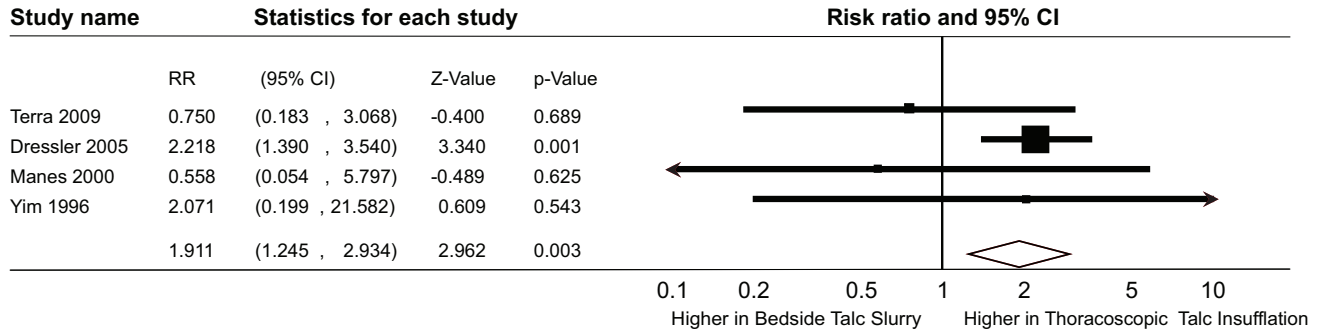
A sensitivity analysis pooling data from studies reporting only clinically significant recurrences was performed leaving out one study<sup>6</sup>. This did not result in a different statistical outcome (pooled RR 1.07; 95% CI 0.92-1.25; Q statistic, 4.49; I<sup>2</sup> statistic 55.53%).

As follow-up periods varied widely, a sensitivity analysis pooling the data from studies reporting 30 day outcomes was carried out and did not result in a different statistical outcome.

**Risk of respiratory complications**

The results of the pooled RR are shown in Figure 4. The four studies included in this analysis reported outcomes on a total of 591 patients who underwent talc pleurodesis for palliation of malignant pleural effusion (Table 2).

There was a statistically significant higher risk of post procedural respiratory complications in the TTI group (Incidence of respiratory



**Figure 4.** Pooled relative risks (RRs) for respiratory complications post talc pleurodesis. RR, risk ratio, CI, confidence interval.

**Table 2.** Characteristics of studies included for studying risk of respiratory complications.

| Study/Year Country | Intervention Design | Talc description  | Anesthesia  | Respiratory complications   | Incidence in TTI Group n/N, (%) | Incidence in TS Group n/N, (%) | Quality score | Quality problems   |
|--------------------|---------------------|---|---|---|---------------------------------|--------------------------------|---------------|--|
| Terra/2009 Brazil  | TTI vs TS RCT       | Noncalibrated talc (Mean diameter = 25 µm, 10% of the particles had a diameter < 10 µm) | TTI- General anesthesia<br>TS- IV, Local anesthesia | Pneumonia, Pulmonary edema, Subcutaneous emphysema                          | 3/30 (10%)                      | 4/30 (13.3%)                   | 2             | Allocation process unclear   |
| Dresler/2005 USA   | TTI vs TS RCT       | Non calibrated talc   | TTI- General anesthesia<br>TS- N/A                  | Empyema, BP fistula, Atelectasis, Pneumonia, Respiratory failure, PE        | 53/223 (23.7%)                  | 21/196 (10.7%)                 | 2             | Allocation process unclear   |
| Manes*/2000 Spain  | TTI vs TS RCT       | N/A   | TTI- Local anesthesia<br>TS- Local anesthesia       | Empyema, Bronchospasm   | 1/29 (3.4%)                     | 2/29 (6.8%)                    | 1             | Inappropriate allocation process, Potential "recycling" of patients into intervention arms |
| Yim/1996 China     | TTI vs TS RCT       | Purified talc from the U.K, no information on calibration                               | TTI-General anesthesia<br>TS-Local anesthesia       | Acute respiratory failure, Reexpansion pulmonary edema, Persistent air leak | 2/28(7.1%)                      | 1/29 (3.4%)                    | 2             | Allocation process unclear   |

\*Study published only as an abstract form

TTI, Thoracoscopic talc insufflation, also known as Thoracoscopic talc poudrage

TS, Talc slurry via a bedside chest tube

RCT, Randomized Controlled Trials

N/A, Not available

U.K, United Kingdom

IV, Intravenous

BP fistula, Bronchopleural fistula

PE, Pulmonary Embolism

complications/Pts who underwent pleurodesis, n/N = 59/307 pts) compared to the TS group (Incidence of respiratory complications/Pts who underwent pleurodesis, n/N = 28/284 pts, pooled RR 1.91, 95% CI= 1.24-2.93, Q statistic 3.15, I<sup>2</sup> statistic 4.79%). There was no evidence of publication bias (P-value = 1.0 for the Begg's test, P-value= 0.24 for the Egger's regression intercept). After using the trim and fill methodology (Figure 5), these results did not change (RR- 1.99, 95% CI = 1.30-3.04, Q statistic, 4.32).

A sensitivity analysis pooling data from studies with ≥ 2 score on the Modified Jadad scale was performed leaving out one study with a score of 1<sup>17</sup>. This did not result in a different statistical outcome (pooled RR 1.99, 95% CI= 1.29-3.08, Q statistic 2.05, I<sup>2</sup> statistic 2.49).

### Risk of non-respiratory complications

The results of the pooled RR are shown in Figure 6. The four studies included in this analysis reported outcomes on a total of 591 patients who underwent talc pleurodesis for palliation of malignant pleural effusion (Table 3).

There was no statistically significant difference in the incidence of non-respiratory complications between the TTI group (Incidence of non-respiratory complications/Pts who underwent pleurodesis, n/N = 110/307 pts) and the TS group (Incidence of non-respiratory complications/Pts who underwent pleurodesis, n/N = 116/284 pts, pooled RR 0.88, 95% CI = 0.72-1.07, Q statistic 4.61, I<sup>2</sup> statistic 34.96%). There was no evidence of publication bias (P-value = 1.0

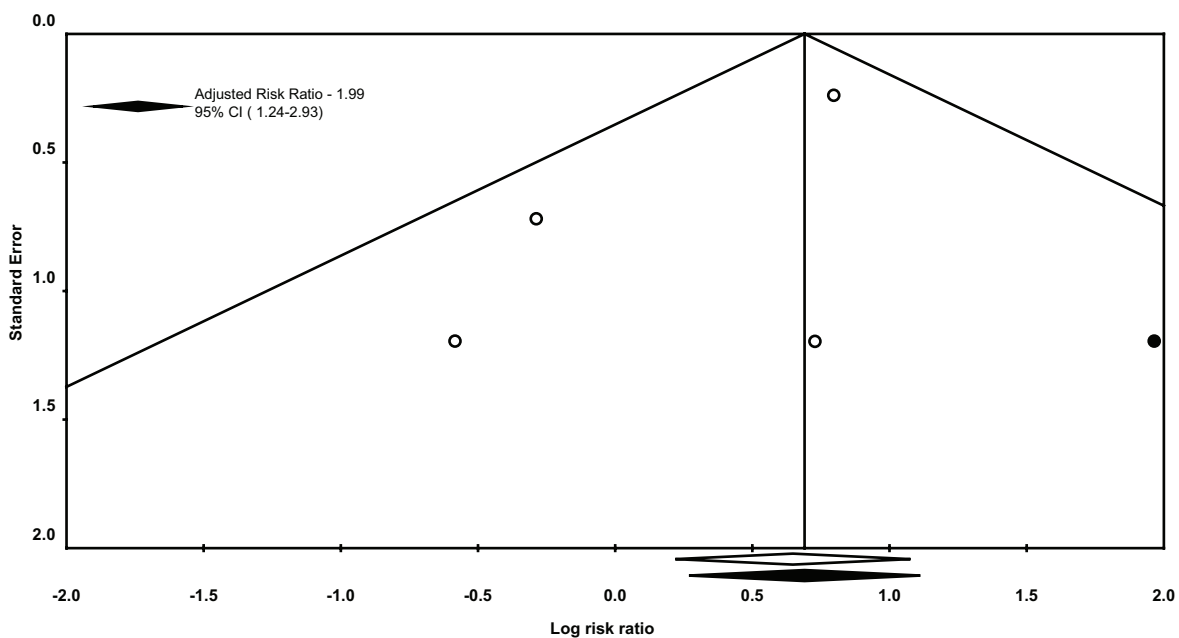


Figure 5. Filled funnel plot using the trim and fill method for risk of respiratory complications: imputed studies - ●, observed studies - ○, CI – confidence interval.

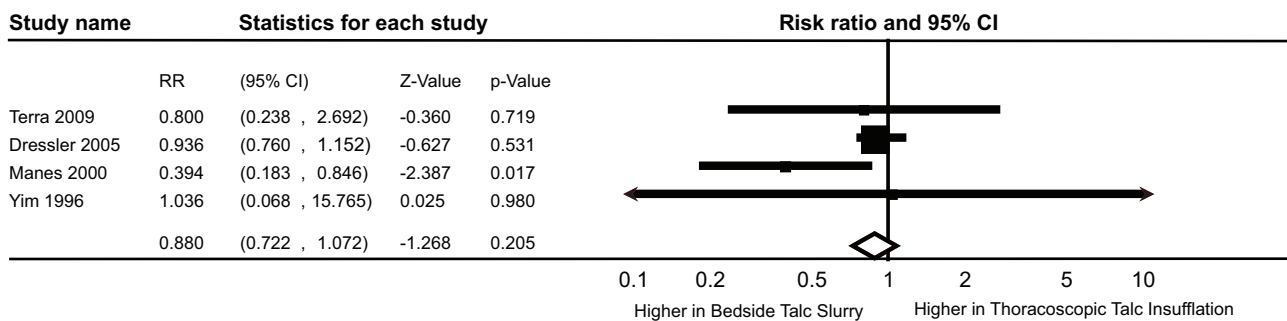


Figure 6. Pooled relative risks (RRs) for non-respiratory complications post talc pleurodesis. RR, risk ratio, CI, confidence interval.



for the Begg’s test, P-value = 0.48 for the Egger’s regression intercept). After using the trim and fill methodology (Figure 7), these results did not change (RR- 0.93, 95% CI = 0.76-1.12, Q statistic, 9.8).

A sensitivity analysis pooling data from studies with ≥2 score on the Modified Jadad scale was performed leaving out one study with a score of 1<sup>17</sup>. This did not result in a different statistical outcome (pooled RR 0.93, 95% CI= 0.76-1.14, Q statistic 0.06, I<sup>2</sup> statistic 0.0).

**Table 3. Characteristics of studies included for studying risk of non-respiratory complications.**

| Study/Year Country | Intervention Design | Immediate non respiratory complications  | Incidence in TTI Group n/N, (%) | Incidence in TS Group n/N, (%) | Quality score | Quality problems   |
|--------------------|---------------------|--|---------------------------------|--------------------------------|---------------|--|
| Terra/2009 Brazil  | TTI vs TS RCT       | Fever, Wound infection, prolonged drainage   | 4/30 (13.3%)                    | 5/30 (16.6%)                   | 2             | Allocation process unclear   |
| Dresler/2005 USA   | TTI vs TS RCT       | Fever, Wound infection, RBC transfusion, Dysrhythmia, MI, DVT, Immediate post procedural death | 99/223 (44.3%)                  | 93/196 (47.4%)                 | 2             | Allocation process unclear   |
| Manes*/2000 Spain  | TTI vs TS RCT       | Fever, Chest pain  | 6/26 (23%)                      | 17/29 (58.6%)                  | 1             | Inappropriate allocation process, Potential “recycling” of patients into intervention arms |
| Yim/1996 China     | TTI vs TS RCT       | Tumor recurrence at wound site, Wound infection  | 1/28 (3.5%)                     | 1/29 (3.4%)                    | 2             | Allocation process unclear   |

\*Study published only as an abstract form

TTI, Thoracoscopic talc insufflation, Also known as Thoracoscopic talc poudrage

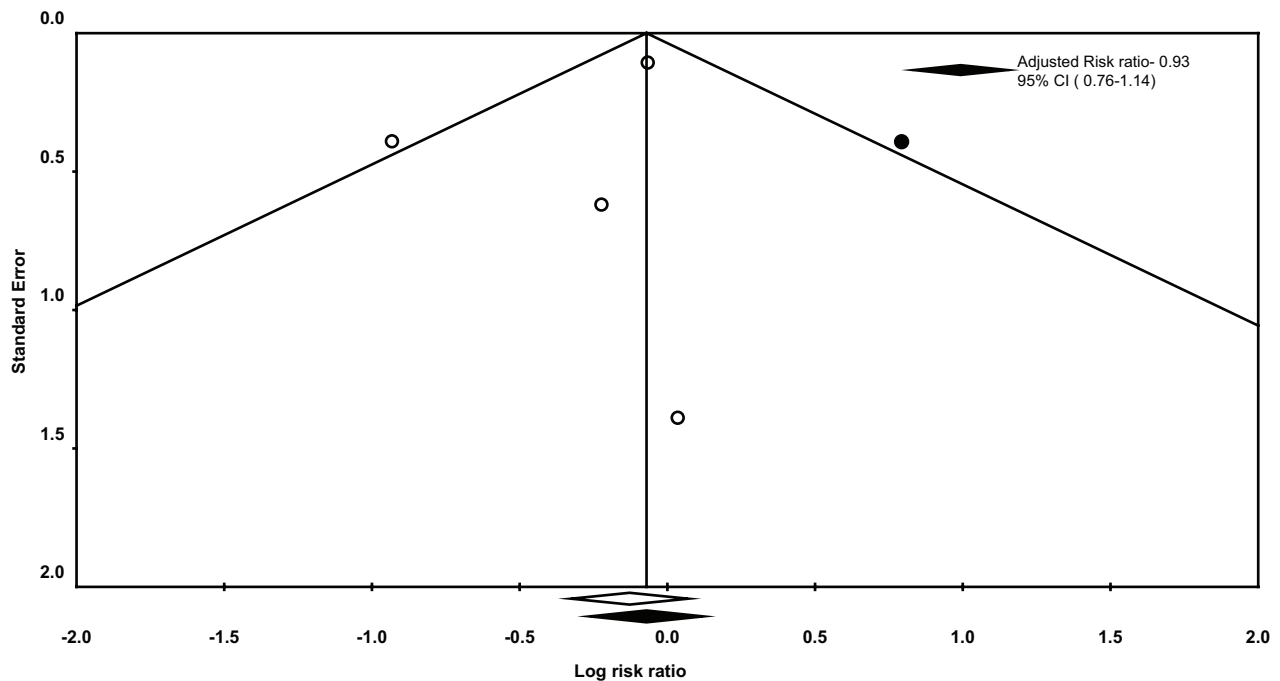
TS, Talc slurry applied via a bedside chest tube

RCT, Randomized Controlled Trials

RBC-Red Blood Cell

MI-Myocardial Infarction

DVT- Deep Venous Thrombosis



**Figure 7. Filled funnel plot using the trim and fill method for risk of non-respiratory complications: imputed studies - ●, observed studies - ○, CI – confidence interval.**

## Discussion

Many experts believe that serial thoracentesis is not an ideal choice for treating the recurrent malignant pleural effusion<sup>18,19</sup>.

Talc pleurodesis was first performed in 1935<sup>20</sup> and is still commonly employed in the treatment of malignant pleural effusions. Although studies have shown talc to be the best chemical agent in terms of pleurodesis success and risk of recurrence<sup>21,22</sup>, the best method of applying talc remains controversial. Our meta-analysis demonstrates that both talc poudrage (TTI) and talc slurry (TS) offer similar rates of efficacy. There was no difference in the rates of successful pleurodesis (i.e., lack of need for further pleural procedures or symptoms). TTI did have a greater risk of respiratory complications. There was, however, no difference in the rate of non-respiratory complications such as fever and need for blood transfusions.

Our results are in contrast to those of previous meta-analyses<sup>5</sup>, including the recently withdrawn Cochrane analysis which suggested improved success rates of talc pleurodesis utilizing TTI. The conclusion of these analyses was that thoracoscopic pleurodesis with talc was the optimal method for pleurodesis in patients with malignant pleural effusions. However, several newer prospective studies have been published since<sup>6,7</sup> and have been incorporated into the present analysis.

Arguments in favor of TTI include the observation that there is more complete lung expansion after the procedure<sup>18</sup>. This is certainly understandable given that take-down of adhesions is typically performed during the procedure itself as opposed to TS. Interestingly, Terra *et al.* using CT scanning post-TTI and TS to assess degree of post procedure lung expansion did not find a correlation between clinical outcomes and initial degree of lung expansion<sup>7</sup>. These authors postulated that factors other than the degree of visceral and parietal pleura apposition were important in determining the success of pleurodesis. Likewise, there are no data to substantiate an existing notion that TTI would result in a superior dispersion of talc in the pleural space. Mager *et al.* used 99m Tc-labeled talc to show that rotation protocols did not affect the overall dispersion of talc suspensions after TS<sup>23</sup>. The degree of dispersion also did not affect pleurodesis success<sup>23</sup>.

In comparing TTI and TS, several difficulties arise. Pleurodesis success rates vary in the literature, due to the inconsistent definition of pleurodesis success and failure used in different studies. Failure or recurrence has been defined radiologically in some studies<sup>6</sup> but it has been argued that patient centered outcomes such as new symptoms and need for further pleural procedures are more pertinent outcomes<sup>7</sup>. In our meta-analysis, we determined success *a priori* as the lack of need for further pleural procedures and disregarded asymptomatic radiological recurrences where possible.

The technique of both TS and TTI vary significantly between centers and this is evident in the included studies. TS varied in regard to length of chest tube clamping, rotating or not-rotating the patient, size of chest tube, and timing of chest tube removal. With regard to TTI, in three of the four studies TTI was performed under general anesthesia and the ability to tolerate general anesthesia was in fact

an entry criteria. Overall, 88% of patients in our analysis underwent general anesthesia for TTI. One could argue that the increased respiratory complications observed with TTI may be related to general anesthesia and single lung ventilation. Despite the concerns of ARDS with the use of ungraded talc, the studies included in our meta-analysis did not report specific cases of ARDS. Non-specific respiratory failure was, however, reported in patients in the study by Dresler<sup>9</sup> and Yim *et al.* reported a case of acute respiratory failure in the TS group<sup>16</sup>.

With the increasing numbers of interventional pulmonologists performing pleuroscopy (medical thoracoscopy)<sup>24</sup> under local and/or moderate sedation, the question of which procedure is the most optimal for talc pleurodesis is increasingly relevant. Whether talc poudrage performed during pleuroscopy with local or moderate sedation and dual lung ventilation is equivalent to surgical thoracoscopy (VATS) in terms of pleurodesis success and complications is unknown. Further studies are needed to compare talc poudrage performed with pleuroscopy versus TS.

One may wonder whether the question of TTI versus TS is still relevant in the era of indwelling pleural catheters (IPCs). Certainly, in the patient with trapped lung, both TS and TTI would likely be ineffective and indeed all of the studies in this meta-analysis excluded patients with possible trapped lung physiology. In the patient with malignant effusion without trapped lung, however, clear superiority of IPCs has not been demonstrated<sup>3</sup>. In fact, talc pleurodesis may be more economical compared to IPC in patients with good performance status and projected life expectancy of >6 weeks<sup>25,26</sup>. The issue of cost is especially relevant in the era of health care reform and accountable care organizations. With the advent of newer molecular/hormonal therapies especially in breast cancer, malignant pleural effusion is increasingly recognized as a non-terminal event<sup>27</sup>. Perhaps most importantly, patient preference is paramount<sup>28</sup> and no study has clearly demonstrated the superiority of IPCs compared to talc pleurodesis.

Our study has several limitations. The results of meta-analyses are dependent on the quality of the studies included. Of note, one of the included studies (Manes *et al.*, 2000) has several potential quality concerns as reflected by a modified Jadad score of 1. These include existing only in an abstract form, inappropriate randomization allocation and possible recycling of patients into treatment arms. We included this study due to its unique conclusion (TTI is superior to TS in terms of efficacy) and a large treatment effect. Reassuringly, sensitivity analysis performed by leaving this study out did not change the final estimates of all the studied outcomes. The inclusion of only randomized controlled trials was necessary due to significant bias inherent in non-randomized prospective studies. Despite the lack of heterogeneity between studies, the individual studies varied substantially (technique of talc pleurodesis, varying definitions of recurrence and follow-up schedule). Sensitivity analyses performed leaving out one study at a time did not impact the results, suggesting robust data. Publication bias is an inherent limitation of meta-analyses. It is reassuring to see that accounting for it did not result in a statistically significant departure from the original point estimates.

In conclusion, our meta-analysis demonstrates that there is no difference in success rates of pleurodesis based on patient centered outcomes between talc poudrage and talc slurry. Respiratory complications are more common with talc poudrage via thoracoscopy. Further studies are needed, however, to look at the role of talc pleurodesis via pleuroscopy. The decision of which procedure to perform needs to take into account also the patient preferences.

### Author contributions

**SM** co-conceived the study, participated in the design of the study, search strategy execution, performance of the statistical analysis, and writing of the manuscript.

**AK** participated in the search strategy execution, performance of the statistical analysis and writing of the manuscript.

**PH** co-conceived the study, participated in the design of the study, performance of the statistical analysis, and writing of the manuscript. All authors read and approved the final manuscript.

### Competing interests

No competing interests were disclosed.

### Grant information

The author(s) declared that no grants were involved in supporting this work.

## References

- Marel M, Zrustova M, Stasny B, *et al.*: **The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia.** *Chest.* 1993; **104**(5): 1486–1489.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- HCUP national inpatient sample (NIS). **The Healthcare cost and utilization project (HCUP).** Agency for healthcare research and quality, Rockville, MD. 2012. Updated 2014.  
[Reference Source](#)
- Davies HE, Mishra EK, Kahan BC, *et al.*: **Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial.** *JAMA.* 2012; **307**(22): 2383–2389.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Shaw P, Agarwal R: **Pleurodesis for malignant pleural effusions.** *Cochrane Database Syst Rev.* 2004; (1): CD002916.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tan C, Sedrakyan A, Browne J, *et al.*: **The evidence on the effectiveness of management for malignant pleural effusion: a systematic review.** *Eur J Cardiothorac Surg.* 2006; **29**(5): 829–838.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dresler CM, Olak J, Herndon JE 2nd, *et al.*: **Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion.** *Chest.* 2005; **127**(3): 909–915.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Terra RM, Junqueira JJ, Teixeira LR, *et al.*: **Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis?** *Chest.* 2009; **136**(2): 361–368.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stefani A, Natali P, Casali C, *et al.*: **Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study.** *Eur J Cardiothorac Surg.* 2006; **30**(6): 827–832.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Crowther M, Lim W, Crowther MA: **Systematic review and meta-analysis methodology.** *Blood.* 2010; **116**(17): 3140–3146.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Terra RM, Junqueira JJ, Teixeira LR, *et al.*: **Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis?** *Chest.* 2009; **136**(2): 361–368.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jadad AR, Moore RA, Carroll D, *et al.*: **Assessing the quality of reports of randomized clinical trials: is blinding necessary?** *Control Clin Trials.* 1996; **17**(1): 1–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mantel N, Haenszel W: **Statistical aspects of the analysis of data from retrospective studies of disease.** *J Natl Cancer Inst.* 1959; **22**(4): 719–748.  
[PubMed Abstract](#)
- Higgins JP, Thompson SG, Deeks JJ, *et al.*: **Measuring inconsistency in meta-analyses.** *BMJ.* 2003; **327**(7414): 557–560.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Begg CB, Mazumdar M: **Operating characteristics of a rank correlation test for publication bias.** *Biometrics.* 1994; **50**(4): 1088–1101.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Egger M, Davey Smith G, Schneider M, *et al.*: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ.* 1997; **315**(7109): 629–634.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yim AP, Chan AT, Lee TW, *et al.*: **Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion.** *Ann Thorac Surg.* 1996; **62**(6): 1655–1658.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Manes M, Rodriguez-Panadero F, Bravo JL, *et al.*: **Talc pleurodesis prospective and randomized study.clinical follow up.** *Chest.* 2000; **118**(4): 131S.
- Lee P: **Point: Should thoracoscopic talc pleurodesis be the first choice management for malignant effusion? Yes.** *Chest.* 2012; **142**(1): 15–7; discussion 20–1.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Light RW: **Counterpoint: should thoracoscopic talc pleurodesis be the first choice management for malignant pleural effusion? No.** *Chest.* 2012; **142**(1): 17–9; discussion 19–20.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bethune N: **Pleural poudrage: New technique for the deliberate production of pleural adhesion as preliminary to lobectomy.** *J Thorac Surg.* 1935; **4**: 251.
- Diacon AH, Wyser C, Bolliger CT, *et al.*: **Prospective randomized comparison of thoracoscopic talc poudrage under local anesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions.** *Am J Respir Crit Care Med.* 2000; **162**(4 Pt 1): 1445–1449.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Xia H, Wang XJ, Zhou Q, *et al.*: **Efficacy and safety of talc pleurodesis for malignant pleural effusion: a meta-analysis.** *PLoS One.* 2014; **9**(1): e87060.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mager HJ, Maesen B, Verzijlbergen F, *et al.*: **Distribution of talc suspension during treatment of malignant pleural effusion with talc pleurodesis.** *Lung Cancer.* 2002; **36**(1): 77–81.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mori PA, Casalini AG: **Therapeutic medical thoracoscopy.** *Monaldi Arch Chest Dis.* 2011; **75**(1): 89–94.  
[PubMed Abstract](#)
- Olden AM, Holloway R: **Treatment of malignant pleural effusion: PleuRx catheter or talc pleurodesis? A cost-effectiveness analysis.** *J Palliat Med.* 2010; **13**(1): 59–65.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Puri V, Pydeck TL, Crabtree TD, *et al.*: **Treatment of malignant pleural effusion: a cost-effectiveness analysis.** *Ann Thorac Surg.* 2012; **94**(2): 374–379.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mohsen TA, Zeid AA, Meshref M, *et al.*: **Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial.** *Eur J Cardiothorac Surg.* 2011; **40**(2): 282–286.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Maskell NA: **Treatment options for malignant pleural effusions: patient preference does matter.** *JAMA.* 2012; **307**(22): 2432–2433.  
[PubMed Abstract](#) | [Publisher Full Text](#)

## Supplementary materials

### PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page #  |
|------------------------------------|----|---|---------------------|
| <b>TITLE</b>                       |    |   |                     |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | Page 1              |
| <b>ABSTRACT</b>                    |    |   |                     |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Page 1              |
| <b>INTRODUCTION</b>                |    |   |                     |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | Page 3              |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Page 3              |
| <b>METHODS</b>                     |    |   |                     |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | N/A                 |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | Page 3              |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Page 3              |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | Appendix 2          |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | Page 3              |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Page 3              |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | Page 3              |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | Pages 3–4           |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | Pages 4–7           |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.  | Pages 4–7           |
| Risk of bias across studies        | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | Pages 4–5           |
| Additional analyses                | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | Pages 4–7           |
| <b>RESULTS</b>                     |    |   |                     |
| Study selection                    | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.   | Figure 1, Pages 4–5 |
| Study characteristics              | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Tables 1–3          |
| Risk of bias within studies        | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).   | Pages 4–7           |
| Results of individual studies      | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | Figures 2,4,6       |

| Section/topic               | #  | Checklist item   | Reported on page # |
|-----------------------------|----|--|--------------------|
| Synthesis of results        | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Pages 4–7          |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | Pages 4–7          |
| Additional analysis         | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | Pages 4–7          |
| <b>DISCUSSION</b>           |    |  |                    |
| Summary of evidence         | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Pages 7,9,10       |
| Limitations                 | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                        | Page 10            |
| Conclusions                 | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Page 11            |
| <b>FUNDING</b>              |    |  |                    |
| Funding                     | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | Page 11            |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

## Appendix 1

### Search strategy for MEDLINE using PubMed

1. Search “talc poudrage” [MeSH OR tw] – 162 results
2. Search “chemical pleurodesis” [MeSH OR tw] – 266 results
3. Search “pleurodesis” [MeSH OR tw] – 2154 results
4. Search “thoroscopic pleurodesis” [MeSH OR tw] – 52
5. Search “thoroscopic talc pleurodesis” [MeSH OR tw] – 42
6. Search “thoroscopic poudrage” [all terms] – 87
7. Search “thoroscopic talc poudrage” [MeSH OR tw] – 49
8. Search “talc insufflation” [MeSH OR tw] – 57
9. Search “thoroscopic talc insufflation” [MeSH OR tw] – 19
10. Search “pleuroscopy” and “talc pleurodesis” [All Fields] – 329
11. Search “pleuroscopy” and “talc insufflation” [All Fields] – 69
12. Search “pleuroscopy” and “talc poudrage” [All Fields] – 119
13. Search “talc slurry” [MeSH OR tw] – 95
14. Search 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 – 2206 results
15. Search “malignant pleural effusion” [MeSH OR tw] – 3426 results
16. Search “malignant pleuritis” [MeSH OR tw] – 29
17. Search 14 and 15 – 580 results. Subsequently, the following filters were applied [Clinical trials including Phase I–IV, Controlled Clinical Trials, Randomized Controlled Trials, Reviews, Systematic Reviews, Meta-Analyses, observational studies, abstract availability, publication dates from 01/01/1989 to 12/31/2014, adult human studies, English-language publications] – 71 results.
18. Search 14 and 16. Filters applied [Clinical trials including Phase I–IV, Controlled Clinical Trials, Meta-Analyses, observational studies, randomized controlled trials, systematic reviews, review articles, abstract availability, publication dates from 01/01/1989 to 10/1/2014, adult human studies, English-language publications] – 0 results.  
Terms such as thoroscopic poudrage, chest tube talc slurry, thoracostomy talc slurry, chest tube talc pleurodesis, talc slurry sclerosis did not reveal any results in the [MeSH OR tw] category.

# Open Peer Review

Current Referee Status:



---

## Version 2

Referee Report 27 March 2015

doi:[10.5256/f1000research.6583.r6534](https://doi.org/10.5256/f1000research.6583.r6534)



**Fabien Maldonado**

Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

This is a very well-written and conducted systematic review and metaanalysis.

I would have liked to get a sense of the level of agreement between the two reviewers for study inclusion, though I suspect the search was relatively straightforward.

It would be worthwhile pointing out in the discussion that the Dresler paper weighs heavily in the results, particularly with respect to respiratory complications, inherent in surgical procedures and perhaps, in some instances, unrelated to the talc pleurodesis itself. The methodological flaws of this study (exclusion of a substantial number of patients after randomization limiting the benefits of randomization) should have been specifically highlighted in my opinion.

Nonetheless, this is an important meta-analysis that should be indexed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

---

## Version 1

Referee Report 31 December 2014

doi:[10.5256/f1000research.5917.r7143](https://doi.org/10.5256/f1000research.5917.r7143)



**Pyng Lee**

Division of Respiratory and Critical Care, National University Hospital, Singapore, Singapore

Malignant pleural effusion is also one of the leading causes of exudative effusion; studies have demonstrated that 42 to 77% of exudative effusions are secondary to malignancy ([Marel et al., 1993](#);

Valdés *et al.*, 1996)

Need statistician review.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

Referee Report 31 October 2014

doi:10.5256/f1000research.5917.r6535



**Gary Lee**

Pleural Medicine Unit, The Lung Institute of Western Australia, Nedlands, WA, Australia

**Overview:**

The topic is important and clinically relevant. Talc pleurodesis is commonly practiced. The debate on the superiority of thorascopic poudrage (TTI) versus talc slurry (TS) has been ongoing for decades. A meta-analysis incorporating the most recent data is useful.

The methodology appears sound. The four selected articles are well described and acknowledged in most review articles as the only randomized studies directly addressing this topic.

The interpretation of the data is fair and balanced. The endpoints chosen are clinically relevant and important. Most other reviews or book chapters on the issue have only focused on the success/failure rate of the pleurodesis. The authors rightly highlighted the increased complication rates of TTI. The figures and graphs are clear and easy to understand.

The discussion is based on the analyses and the postulations for the observed results are sound and reasonable.

Overall this is an excellent paper and I would support its indexing.

There are several few points that the authors may wish to consider. I believe that this article may be improved if the authors can address the following:

**1. The study by Manes *et al.* (2000)**

The authors quite rightly included not only peer reviewed papers but also all published abstracts. This approach is according to standard meta-analysis practice, in order to avoid publication bias such that 'negative' studies (often not published in full) are not excluded. However, including data from published abstracts preclude scrutiny of the detailed methods, analyses and thus raises questions on the quality of the results. The situation in the meta-analysis of TTI vs TS highlights the pros vs cons of including data that were not peer reviewed.

Three of the four selected studies were published in respected journals and were subjected to peer-reviewing processes. The study by Manes however was published only as an abstract 14 years ago, and to date had not been published as a full paper. This by itself raises great concerns. The results of this particular study deviated significantly from all the other three. The authors have

identified clear methodological concerns (especially ‘recycling’ of patients into randomization after failing pleurodesis). Unless the authors have obtained details from the primary research group, it is doubtful that a short abstract could provide adequate details for proper critique of the methods and results. Including this study without qualifying its many limitations may distort the interpretation of the readers.

I suggest that the authors should:

1. Highlight the point that the Manes study was never published in full in the text/legends;
2. Perform and show a separate analysis excluding the Manes study;
3. Discuss the rationale of including/excluding this single study in the Discussion section.

I believe the above measures are justified as the Manes study was not a ‘negative’ study and would never have been biased against if ever submitted for full publication.

## 2. An alternate way of presenting the data

Although it would not change the actual conclusion or the raw data, presenting the results as ‘success’ rather than ‘failure’ rates would quite significantly change the ‘visual effects’ of the graphs. Take for example the Dresler study. The RR for failure is 0.74 but if expressed as ratio of success rates it would become 1.11, the Yim study 1.04 and the Terres study 0.96. This probably presents a more useful interpretation for clinicians and patients – that the magnitude of superiority of TTI in any of the studies is at best 1.11 times over TS (excluding Manes *et al.*).

## 3. Discussion

It would be useful to include that there are no scientific grounds why insufflation should be more advantageous than slurry. Talc does not work as a glue (otherwise we would have had major problems when talc was still included in baby nappy powders). Even distribution of talc over the pleural surface is not therefore critical. Radio-active isotope studies have shown that talc, even when applied as a slurry, can distribute around the pleural cavity via respiratory motions.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Reader Comment 17 Feb 2015

**Srinivas Mummadi**, Tuality Community Hospital/Oregon Health and Science University , USA

Thank you very much your comments and a detailed critique of our manuscript.

### 1. Response to “The study by Manes *et al.* (2000)”

We agree with your assessment of the pros and cons of including the study by Manes *et al.* (2000) published only as an abstract. As our inclusion criteria were defined *a priori*, we included the study in our analysis.



We agree with your comments that it suffers from potential quality concerns. In addition to our stated concerns regarding the inappropriate allocation of randomization, we have made efforts to highlight additional quality concerns outlined below.

Footnotes to the tabular data have been added, highlighting the existing form of publication as an abstract. We also discussed in detail the lack of change in point estimates for all the predefined outcomes after removing the study as a part of the sensitivity analysis.

Due to its unique conclusion (TTI is superior to TS in terms of pleurodesis success rates) and a relatively large treatment effect, we believe that the inclusion of this study with the clear mentioning of its inherent limitations gives us a unique opportunity to present both sides of the talc poudrage versus talc slurry debate in a systematic review.

Inclusion of this study in the analysis allows meta-analysis to play the role of an adjudicator.

As mentioned earlier, removal of this study in the sensitivity analysis did not influence the results.

For the sake of clarity, we would like to report the results for all the studied outcomes after removing the above mentioned study in this reply.

1) Pooled relative risks (RRs) of success rates post talc pleurodesis (TTI vs TS)

Point estimate (RR) = 1.04, 95% CI (0.97-1.1), P-value – 0.24, Q statistic -1.28

2) Pooled relative risks (RRs) for respiratory complications post talc pleurodesis (TTI vs TS)

Point estimate (RR) = 1.99, 95% CI (1.29-3.08), P-value – 0.002, Q statistic -2.05

3) Pooled relative risks (RRs) for non-respiratory complications post talc pleurodesis (TTI vs TS)

Point estimate (RR) = 0.93, 95% CI (0.76-1.14), P-value – 0.5, Q statistic - 0.06

## 2. An alternate way of presenting the data

We agree with your suggestion that the clarity of the take-home message would be improved by presenting the data as rates of success rather than rates of failure. We have therefore renamed the outcome as “successful pleurodesis” [defined as no need for further pleural procedures despite asymptomatic radiological recurrence in a few cases]. Measuring patient centered outcomes was the predefined objective of the study, therefore asymptomatic radiological recurrences where clearly defined were counted towards success (3 patients)

Relevant changes have been made in the body of the manuscript, figures, and tables. Reassuringly, measuring the outcome as either relative rates of success or relative risks of recurrence did not influence the existing conclusion.

### 3. Discussion

We agree that there are no quality data to substantiate the “intuition” that thoracoscopic talc insufflation is superior to talc slurry in terms of talc dispersion in the pleural space. We would like to draw your attention to our mentioning of these points in the existing discussion section (Mager *et al.*). We have fine-tuned the write up to buttress the above point to increase the visibility to the reader.

***Competing Interests:*** None

---