

## Original Article

# Efficacy of medical thoracoscopic talc pleurodesis in malignant pleural effusion caused by different types of tumors and different pathological classifications of lung cancer

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Received June 23, 2015; Accepted September 23, 2015; Epub October 15, 2015; Published October 30, 2015

**Abstract:** The aim of this study was to assess the efficacy and complications and compare the efficacy of medical thoracoscopic talc pleurodesis among patients with different types of tumors and different pathological classifications of lung cancer as well as to evaluate the role of postoperative negative pressure chest tube drainage. A total of 1061 patients with malignant pleural effusion who underwent thoracoscopic pleurodesis were analyzed retrospectively. The complications, postoperative drainage time, and efficacy of pleurodesis among patients with different types of tumors and different pathological classifications of lung cancer were assessed. The overall response rate (ORR) was 88.03%. Major complications included chest pain (68%) and fever (47%). The postoperative drainage time was  $4.74 \pm 1.56$  days. Postoperative negative pressure chest tube drainage significantly shortened the drainage time (negative vs. non-negative:  $4.56 \pm 1.49$  days vs.  $4.81 \pm 1.59$  days,  $P = 0.037$ ). Pleurodesis was less effective in treating effusion caused by lung cancer (72.3%) and mesothelioma (68.2%) than that caused by breast cancer (84.4%) and other tumors (87.8%) ( $P = 0.009$ ). The efficacy in the treatment of effusion caused by adenocarcinoma (66.7%) was slightly less than that caused by other types of lung cancer ( $P = 0.311$ ). In conclusion, medical thoracoscopic talc pleurodesis is a palliative and effective treatment for malignant pleural effusion. In addition, postoperative simple negative pressure chest tube drainage significantly shortens the drainage time. However, thoracoscopic pleurodesis is less effective for the treatment of effusion caused by lung cancer and pleural mesothelioma compared with that caused by other types of cancers.

**Keywords:** Malignant pleural effusion, medical thoracoscopy, pleurodesis, cancer

## Introduction

Malignant pleural effusion is the most common complication of late-stage malignancies. It has been reported that there are 150,000 cancer patients with malignant pleural effusion in the United States [1]. It is caused by invasion and metastasis of malignant tumor cells into the pleura. Pleural malignant mesothelioma, lung cancer, and breast cancer are the main primary causes [2]. Other origins of tumors such as the gastrointestinal and genitourinary systems can also cause pleural effusion. Rapidly growing pleural effusion causes direct lung compression and a mediastinal shift to the contralateral side, leading to atelectasis, pulmonary infection, dyspnea, and respiratory failure. If it is not

treated in a timely manner, the average survival time of patients is less than a year [3].

The principal treatment for malignant pleural effusion is to drain out the pleural effusion in order to alleviate the compressive symptoms. Various measures are available to reach this goal. Repetitive thoracentesis is the most commonly used method, which enables immediate relief of symptoms in the most cost-effective way [4]. However, pleural effusion usually recurs within one month [5]. A large number of protein loss caused by thoracentesis further speeds up the production of pleural effusion.

The insertion of a tunneled pleural catheter (TPC) is considered as the preferred treatment

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**Table 1.** Characteristics of patients with malignant pleural effusion

Characteristics		Number of patients	%
Total		1061	100
Age (years)	65.3 ± 11.3		
Gender	Male	610	57.49
	Female	451	42.51
Pleural effusion Site	Left	401	37.79
	Right	534	50.33
	Bilateral	126	11.88
Amount	Large	596	56.17
	Medium	359	33.84
	Small	106	9.99
Cause	Pleural mesothelioma	351	33.1
	Lung cancer	473	44.58
	SCC	109	10.27
	ADC	227	21.39
	LCLC	41	3.86
	SCLC	96	9.05
	Breast cancer	81	7.6
	Other tumors	156	14.7
Pleurodesis	Negative pressure	297	27.9925
	Non-negative pressure	764	72.0075
Adjunctive chemotherapy	No	379	35.721
	Yes	682	64.279
Complications	Fever	502	47.31
	Chest pain	723	68.11
	Pulmonary edema	3	0.28
Drainage time (days)	4.74 ± 1.56		

Note: SCC, squamous cell carcinoma; ADC, adenocarcinoma; LCLC, large cell lung carcinoma; SCLC, small cell lung carcinoma. Other tumors include lymphoma, ovarian cancer, gastrointestinal cancer, liver cancer, skin cancer, and tumors of unknown origin.

for patients with malignant pleural effusion [4]. However, Olden *et al.* compared TPC and talc pleurodesis for patients with expected survival time of 6 months and found that pleurodesis dominated TPC, though the differences in both costs and efficacies between the two options were small [6]. Chemical pleurodesis mainly includes bedside pleurodesis, medical thoracoscopic pleurodesis, and surgical thoracoscopic pleurodesis. With the development of modern thoracoscopic techniques in recent years, increasing numbers of reports have suggested that thoracoscopic pleurodesis is one of the most efficient methods to treat malignant pleural effusion because it has the lowest mortality rate and fewest complications [7-11]. Studies

have suggested that thoracoscopic pleurodesis is more effective than bedside pleurodesis [4, 12], although there is no significant difference in the occurrence of side effects. Compared with surgical thoracoscopic pleurodesis, medical thoracoscopic pleurodesis hurts less and is safer.

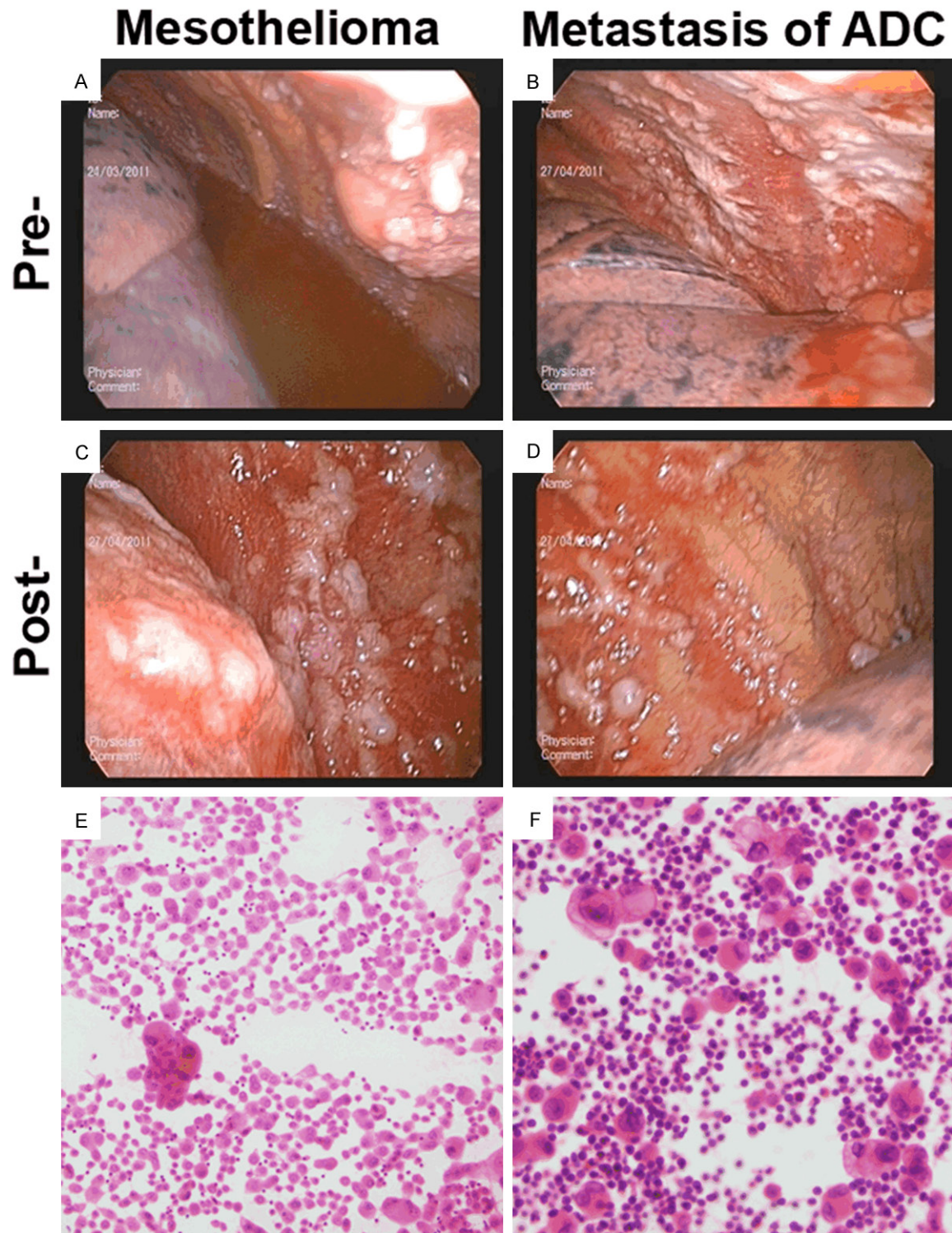
Thoracoscopic pleurodesis has been recommended as the primary choice to treat malignant pleural effusion [8, 9]. Talc is believed to be one of the safest, cheapest, and most effective agents for promoting pleural symphysis. Medical thoracoscopic talc powder spraying enables the talcum powder to be evenly dispersed into the pleural cavity so as to improve the efficacy and safety of the treatment. However, there are few reports comparing the efficacy and safety of this technique in treating effusion caused by different types of tumors or different types of lung cancers. To compare the efficacy of medical thoracoscopic talc pleurodesis in patients with different types of tumors and lung cancers, as well as to evaluate the role of postoperative negative pressure chest tube drainage in medical thoracoscopic talc pleurodesis, We retrospectively analyzed

1061 patients who underwent medical thoracoscopic talc pleurodesis.

### Materials and methods

#### Patients

This retrospective study was approved by the Ethics Committee of Shangdong Provincial Hospital. The study sample covers patients admitted from March 1992 to September 2013. A total of 1412 hospitalized patients with malignant pleural effusion were screened. The inclusion criteria for the implementation of medical thoracoscopic talc pleurodesis were as follows: 1) the patients were able to tolerate the thora-



**Figure 1.** Representative thoracoscopic images of the pleura following thoracoscopic talc powder spraying. Panels A (pleural mesothelioma) and B (pleural metastasis of lung adenocarcinoma) show the thoracoscopic images of patients. Panels C (pleural mesothelioma) and D (pleural metastasis of lung adenocarcinoma) show the images after talcum powder spraying, respectively. Panels E (pleural mesothelioma) and F (pleural metastasis of lung adenocarcinoma) show pleural effusions in pathology samples (HE staining, 200 ×).

oscopic talc pleurodesis procedure; 2) according to the tumor staging, the patients were

unsuitable for a surgical operation; and 3) the patients and/or their families agreed to receive

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the treatment of thoracoscopic talc pleurodesis. The exclusion criteria were as follows: 1) the expected survival time of the patients was less than 1 month; 2) patients who were suspected of having an intrathoracic infection; and 3) patients and/or their families refused to accept the treatment of thoracoscopic talc pleurodesis. A total of 1173 eligible patients underwent thoracoscopic talc pleurodesis; and a total of 112 patients were excluded from this study because of poor lung expansion (4%), further treatment in another hospital (3.6%), or refusal of further treatment (2%). None of the patients died. A total of 1061 patients were analyzed. Of these, 682 patients received regular chemotherapy according to the type of primary tumor at 1 week after the operation, and 379 patients did not receive chemotherapy because they were either intolerant to chemotherapy or did not consent to chemotherapy. This study compared the efficacy of medical thoracoscopy talc pleurodesis to treat the pleural effusion caused by different types of tumors in patients who did not receive chemotherapy. We also compared the efficacy in different pathological types of lung cancers. All patients had certain symptoms of chest tightness and shortness of breath before they received the operation. The baseline patient characteristics are summarized in **Table 1**.

### *Surgical procedures*

All patients and/or their family members fully understood the purposes and risks of the operation and agreed to sign the consent form for the operation. Preoperative electrocardiogram examination and blood tests were routinely conducted. Preoperative chest radiograph and/or lung ultrasound examination were carried out at 1-3 days before the thoracoscopic operation to determine the amount of pleural effusion and whether there was an intrathoracic infection. For patients with severe dyspnea, preoperative thoracentesis and chest tube drainage were performed to relieve symptoms. Lung ultrasonography and chest radiography were performed 4 weeks after the therapy to evaluate the outcome of the therapy. The amount of pleural effusion was defined as large, medium, or small, corresponding to more than 800 mL, 500-800 mL, and less than 500 mL, respectively. Dolantin (50 mg) was injected intramuscularly 30 min prior to the operation.

Oxygen inhalation was carried out during the operation. Meanwhile, heart rate, blood pressure, and peripheral oxygen saturation were monitored. Patients were awake and placed in the lateral recumbent position, the skin was routinely disinfected, local anesthesia was administered by a local injection of 2% lidocaine, and a skin incision of 1.0-1.5 cm was made. After blunt separation of tissue in the chest wall, a Trocar (7 mm) was inserted into the pleural cavity at the posterior axillary line between costa 6-8. When sensing a breakthrough, the core of the Trocar was removed, and a thoracoscope (6.5 mm) was inserted through the Trocar. After slowly sucking out all of the fluid, the pleura was fully exposed by blunt separation or electrical cuttings. Diaphragmatic pleura, mediastinal pleura, pulmonary surface and interlobar fissure visceral pleura, lung inflation, and diaphragm muscle activity were sequentially examined. Pleural adhesions were separated as far as possible using biopsy forceps. A total of 4-5 g of sterilized medical talc powder was widely and uniformly sprayed onto the pleura through a catheter (**Figure 1**) before spraying A (pleural mesothelioma) and B (pleural metastasis of lung adenocarcinoma), and after spraying C (pleural mesothelioma) and D (pleural metastasis of lung adenocarcinoma). The thoracoscope was then withdrawn at the end of the treatment. A drainage tube was inserted into the pleural cavity through the Trocar to continuously drain the air and fluid. Meanwhile, patients were encouraged to cough so as to promote lung re-inflation. We designed a simple negative pressure suction device. The pumping speed could be adjusted by squeezing the balloon frequency arbitrarily. The patients controlled it by themselves. Thus, gas and liquid in the thoracic cavity were removed constantly. A negative pressure suction device was applied in 297 patients (negative pressure group) randomly, and a non-negative pressure suction device was applied in the remaining 764 patients (non-negative pressure group). Once the output of pleural effusion was less than 50 mL and the artificial pneumothorax had disappeared based on the chest X-ray examination, the drainage tube was withdrawn within 24 h.

### *Evaluation of the efficacy*

The response was evaluated by ultrasound or chest X-ray based on the posteroanterior find-

**Table 2.** Responses to thoracoscopic talc pleurodesis in patients with and without negative pressure suction

	Negative pres- sure		Non-negative pressure		X <sup>2</sup>	P value
	Number	%	Number	%		
Total	297	100	764	100		
CR	226	76.09	476	62.3	18.186	< 0.01
PR	53	17.85	228	29.84		
NR	18	6.061	60	7.853		
OR = CR+PR	237	79.8	495	64.79	1.009	0.315
Drainage time (days)	4.56 ± 1.49		4.81 ± 1.59		4.379	0.037

Note: CR, complete response; PR, partial response; NR, no response; OR, overall response (CR+PR).

ings at 4 weeks after the treatment. The response criteria used were as follows [13]: a complete response (CR) when no pleural effusion was observed; a partial response (PR) when pleural effusion was significantly decreased (> 50%); and no response (NR) when effusion was larger than that defined by the PR. The overall response rate (ORR) was defined as CR+PR. The effect of negative pressure chest tube drainage on the treatment was also evaluated. The postoperative drainage time as well as the effects of different lung cancer pathological classifications and different primary malignant tumor types on the treatment were evaluated.

#### Evaluation of complications

Complications due to medical thoracoscopic talc pleurodesis were evaluated after the operation. In this study, the complications included fever, chest pain, and pulmonary edema; and no other complications occurred.

#### Statistical analysis

SPSS 20.0 software was used for the statistical analysis. The mean and standard deviation of the postoperative drainage time was calculated. The Chi-squared test was applied to compare the drainage time of the negative pressure group and the non-negative pressure group. The Chi-squared test was also used to compare the efficacy of thoracoscopic talc pleurodesis in patients with different types of tumors and the efficacy of the operation in patients with different lung cancers. All analyses were tested at the 5% significance level.

## Results

### Baseline patient characteristics

A total of 1173 patients underwent medical thoracoscopic talc pleurodesis. In the final study, 1061 patients were analyzed. Their average age was 65.3 years old, with 57% males and 43% females. In total, 38% of the patients had left side pleural effusion, 50% had right side pleural effusion, and 12% had bilateral pleural effusion. For patients with bilateral pleural effusion, their cardiac function and plasma albumin levels were evaluated. Abnormalities were corrected in a timely manner. In addition, 56% had a large amount of pleural effusion, 34% had a medium amount, and 10% had a small amount. The patients with a small amount of pleural effusion had undergone thoracocentesis in other hospitals. The main causes of pleural effusion were lung cancer (44.6%) and pleural mesothelioma (33.1%). Breast cancer accounted for 7.6%, and other types of cancer accounted for 14.7% of causes of pleural effusion. Of lung cancers, there were 10.27% squamous cell carcinoma (SCC), 21.39% adenocarcinoma (ADC), 3.86% large cell lung carcinoma (LCLC), and 9.05% small cell lung carcinoma (SCLC) (Table 1).

### Negative pressure chest tube drainage improves the efficacy of thoracoscopic talc pleurodesis

To determine whether simple negative pressure suction after the operation had any effect on the efficacy of medical thoracoscopic talc pleurodesis, patients were divided into two drainage groups randomly: with and without negative pressure suction. We found that 226 (76%) patients with negative pressure suction and 476 (62%) patients without negative pressure suction achieved CR. In addition, 53 (18%) patients with negative pressure suction and 228 (30%) patients without negative pressure suction had PR, while 18 (6.1%) patients with negative pressure suction and 60 (7.9%) patients without negative pressure suction had

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**Table 3.** Responses to thoracoscopic talc pleurodesis in patients with different types of tumors

Primary tumor	CR	PR	NR	ORR (%)	CR (%)	
Total	379	228	55	96	74.7	60.2
Lung cancer	191	111	27	53	72.3	58.1
Pleural mesothelioma	107	57	16	34	68.2	53.3
Breast cancer	32	24	5	3	84.4	75
Other tumors	49	36	7	6	87.8	73.5
X <sup>2</sup>					11.684	9.014
P value					0.009	0.029

Note: CR, complete response; PR, partial response; NR, no response; ORR, overall response rate.

**Table 4.** Responses to thoracoscopic talc pleurodesis in patients with different lung cancers

Lung cancer	CR	PR	NR	ORR (%)	CR (%)	
Total	191	111	27	53	72.3	58.1
SCC	45	28	7	10	77.7	57.8
ADC	96	50	14	32	66.7	52.1
LCLC	14	9	3	2	85.7	64.3
SCLC	36	24	3	9	75	66.7
X <sup>2</sup>					3.58	3.047
P value					0.311	0.384

Note: CR, complete response; PR, partial response; NR, no response; ORR, overall response rate.

NR, respectively. Negative pressure chest tube drainage significantly improved the CR rate compared with that in the non-negative pressure group ( $P < 0.01$ ). However, the ORRs were similar (80% vs. 65%,  $P = 0.315$ ). The drainage time was significantly shorter in the negative pressure group than that in the non-negative pressure group ( $4.56 \pm 1.49$  days vs.  $4.81 \pm 1.59$  days,  $P = 0.037$ ) (Table 2).

### Overall efficacy and complications of medical thoracoscopic talc pleurodesis

A total of 1061 patients who received medical thoracoscopic talc pleurodesis treatment were included in this study. The majority of the patients acquired CR (694/1061, 65.41%) or PR (240/1061, 22.62%), while a few patients had NR (127/1061, 11.97%). The ORR was 88.03%. After the treatment, the most common complication was chest pain (68%), followed by fever (47%). Pulmonary edema was only seen in 0.28% of patients. The drainage time was  $4.74 \pm 1.56$  days (Table 1).

### Efficacy of medical thoracoscopic talc pleurodesis was similar among patients with different types of cancer

To determine the different outcomes of medical thoracoscopic talc pleurodesis in patients with different types of cancers, we divided the patients into four groups based on the causes of pleural effusion: lung cancer, pleural mesothelioma, breast cancer, and other tumors (including lymphoma, ovarian cancer, gastrointestinal cancer, liver cancer, skin cancer, and tumors of unknown origin). The overall effective rates for pleural effusion caused by lung cancer and pleural mesothelioma were 72.3% and 68.2%, which were significantly less than that caused by breast cancer and other cancers (84.4% and 87.8%, respectively;  $P = 0.009$ ). The CR rates in the treatment of pleural effusion caused by lung cancer (58.1%) and pleural mesothelioma (53.3%) were also significantly less than that of breast cancer (75%) and other tumors (73.5%) ( $P = 0.029$ ) (Table 3).

### Efficacy of medical thoracoscopic talc pleurodesis was similar among patients with different pathological classifications of lung cancer

To determine the efficacy of medical thoracoscopic talc pleurodesis among patients with different pathological classifications of lung cancer, we evaluated the efficacy of pleurodesis among patients with SCC, ADC, LCLC, and SCLC. The thoracoscopic pleurodesis were slightly less effective in the treatment of pleural effusion caused by ADC (ORR: 66.7%; CR: 52.1%) than that caused by SCC (ORR: 77.7%; CR: 57.8%), LCLC (ORR: 85.7%; CR: 64.3%), and SCLC (ORR: 75%; CR: 66.7%). However, the difference was not statistically significant (ORR:  $P = 0.311$ ; CR:  $P = 0.384$ ) (Table 4).

## Discussion

The technique and clinical applications of medical thoracoscopy have substantially evolved in the last few decades. The recent development of a semirigid thoracoscope, which is handled similarly to a bronchoscope, has made this procedure more attractive. Medical thoracoscopy

offers essential information to clarify the diagnosis of pleural effusions and is also a fundamental technique to intervene in the pleural cavity. Thoracoscopic pleurodesis is generally a well-tolerated procedure. As the most effective agent for pleurodesis, talcum powder has been widely used in clinical practice for various diseases, such as pleural effusion, intractable pneumothorax, chylothorax, and refractory empyema. Talcum powder stimulates widespread pleural inflammation, which is characterized by a large amount of inflammatory cell infiltration. Pleural inflammation leads to granulation formation, pleural adhesions, and pleural fibrosis. Application of medical thoracoscopy enables the talcum powder to be uniformly sprayed into the pleural cavity, thus improving the efficacy of pleural adhesions and fixation. The uniformity is the key to success. In the present large sample study, the ORR of thoracoscopic talc pleurodesis reached up to 88.03%. These results suggest that this method efficiently treats malignant pleural effusion. Consistent with our findings, previous reports have shown that the success rate of thoracoscopic talc pleurodesis is 90-96% [11, 14, 15]. However, other reports have shown that thoracoscopic talc pleurodesis is less efficient, with efficacies of 65-85% [2, 16]. This discrepancy of response in studies reflects the use of different selection criteria and outcome definitions. In the present study, we excluded elderly patients with severe cardiovascular or pulmonary insufficiency, and those with an expected survival time of less than 1 month.

The major postoperative complications of talc pleurodesis are chest pain and fever. Our current study showed that the incidence of chest pain was 68%. A low dose of analgesic drug was able to alleviate the pain effectively. Chest pain in our patients disappeared within 1-2 days after the treatment. Local irritation due to talc on the pleural and inflammatory responses was the main cause of chest pain. A low- to mid-grade fever was present in 47% of our patients. After symptomatic treatment, the patient body temperature usually dropped to normal within 1-3 days. Acute respiratory distress syndrome (ARDS) is the most severe complication of talc pleurodesis. However, the incidence is relatively low [11]. In our study, none of the patients had ARDS. Kolschmann *et al.* [17] have suggested that ARDS is positively correlated with

the amount of talcum powder administered. In recent years, studies have found that ARDS is significantly correlated with the particle size of the talcum powder [18-20]. Small particles (less than 10  $\mu\text{m}$ ) can easily induce an inflammatory response; therefore, it can increase the occurrence of ARDS. Three patients in the current report had postoperative re-expansive pulmonary edema. This complication was likely caused by the fast drainage speed. The symptoms were improved quickly after active treatment that included slowing down the drainage speed, using a negative pressure device, and intermittently draining the residual gas and liquid. Pulmonary edema happened in only 0.28% of our patients. Studies suggest that the severity of side effects as well as elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, and white blood cell count) are positively correlated with the postoperative performance of pleurodesis and indirectly predicate its efficacy [21, 22].

The purpose of postoperative thoracic tube drainage after medical thoracoscopic talc powder spraying is to discharge the intrathoracic residual air and liquid. In order to overcome the pressure caused by the sealed water bottle, patients must continue to cough or hold their breath. These actions may worsen the chest pain. We designed a simple intermittent negative pressure suction device that can effectively reduce severe chest pain or chest tightness and even the occurrence of pulmonary edema by the continuous pressure suction. The application of a negative pressure suction device can speed up the drainage of air and liquid, improve the efficacy of talc pleurodesis, and shorten the drainage time. In the present study, although negative pressure suction after the operation was unable to increase the ORR of pleurodesis, it significantly improved the CR rate. Meanwhile, it effectively shortened the drainage time, thus reducing the occurrence of side effects arising from the drainage.

Lung cancer, pleural mesothelioma, and breast cancer are the major primary disorders that cause malignant pleural effusion. Previous studies have revealed that the efficacy of talc pleurodesis is not significantly different among patients with different tumors [23-25]. The present study showed that the ORRs and CRs of pleurodesis were lower in patients with lung

cancer and mesothelioma than in those with breast cancer or other types of tumors. The difference was statistically significant, similar to Bielsa's report. Bielsa *et al.* [25] have reported that the CRs of patients to pleurodesis were 63% (lung cancer), 61% (mesothelioma), 77% (breast cancer), and 74% (other types of tumors), respectively. Our CRs were 58.1% (lung cancer), 53.3% (mesothelioma), 75% (breast cancer), and 73.5% (other types of tumors), respectively. The ORR rates were 72.3% (lung cancer), 68.2% (mesothelioma), 84.4% (breast cancer), and 87.8% (other types of tumors). The differences were likely caused by different definitions of outcomes and sample sizes as well as whether the patients received chemotherapy. In the report by Bielsa *et al.* [25], CR was defined as patients who had no recurrent pleural effusion until death. In our study, CR was defined as patients who had no recurrent pleural effusion for up to 4 weeks. In addition, because different chemotherapeutic agents are used to treat different types of tumors, we only analyzed patients who did not receive chemotherapy. The severity of pleural invasion likely explains the significantly different efficacies of pleurodesis in different types of pleural effusion. Pleural mesothelioma had the most severe pleural involvement, and the multiple pleural nodules present in pleural mesothelioma had an important effect on the efficacy of pleurodesis.

Lung cancer is one of the most common causes of malignant pleural effusion. The severity of lung cancer malignancy is different in different pathological classifications. The incidences of pleural metastases are also not identical. Until now, there has been no comparison of the efficacy of thoracoscopic talc spraying in patients with different pathological classifications of lung cancer. Our results revealed that the ORR rates were 77.7% (SCC), 66.7% (ADC), 85.7% (LCLC), and 75% (SCLC). The CRs were 57.8% (SCC), 52.1% (ADC), 64.3% (LCLC), and 66.7% (SCLC), respectively. Although its efficacy in pleural effusion caused by ADC was relatively lower than that of SCC, LCLC, and SCLC, the differences were not statistically significant.

As a retrospective study, our study has certain limitations. At the early stage of this therapy, we were unable to score the quality of life of patients; thus, it was difficult to evaluate the improvement of quality of life. In addition, the

quality of life, survival time, and efficacy should be further studied in patients receiving medical thoracoscopic talc pleurodesis and chemotherapy.

In conclusion, medical thoracoscopic talc pleurodesis is a palliative and effective treatment for malignant pleural effusion. Moreover, it is safe and has few complications. Although postoperative simple negative pressure chest tube drainage is not able to improve the ORR of pleurodesis, it can shorten the drainage time and improve the quality of life of the patients. The efficacy of thoracoscopic talc pleurodesis is different for the treatment of pleural effusion caused by different primary tumors. It is relatively lower in lung cancer and pleural mesothelioma. In addition, the efficacy is not affected by the different pathological classifications of lung cancer.

### Disclosure of conflict of interest

None.

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