Review Article



# Possibilities of surgical pleurodesis for malignant pleural effusion

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**Abstract:** Malignant pleural effusion (MPE) is a frequent clinical problem, affecting 15% of patients with cancer. It frequently confers a poor prognosis and causes numerous oppressive symptoms as dyspnoea, dry cough and pain. Several different approaches have been proposed to manage MPE and relieve patients' symptoms. The selected approach depends on predicted patient survival (LENT or PROMISE SCORE), patient preferences and availability of the different techniques. Repeated thoracentesis, chemical pleurodesis via chest tube or thoracoscopy (medical or surgical), mechanical surgical pleurodesis, pleurectomy/decortication and application of indwelling pleural catheter (IPC) or pleuro-peritoneal shunt are the most common utilized approaches. The gold standard procedure for the management of an MPE is pleurodesis. Chemical pleurodesis can be obtained by the instillation of a sclerosant agent into the pleural space through an intercostal chest tube after complete evacuation of fluid ("slurry pleurodesis") or during a thoracoscopy ("poudrage pleurodesis") which also consents to visualize the all pleural cavity, assess the possibility of lung re-expansion and remove the eventually present loculation/pleural bridge. An alternative approach is the use of IPC, which consists of a chest tube tunnelled under the skin allowing intermittent fluid drainage. This approach has shown to have several advantages in trapped lung, a condition in which the lung parenchyma cannot completely rehabilitate the pleural cavity, but also it has been increasingly utilized for the primary management of MPE as an alternative to chemical pleurodesis. The aim of this review is to analyse the role of surgery in pleurodesis for MPE.

**Keywords:** Malignant pleural effusion (MPE); surgery; minimally invasive approach; pleurodesis

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## Introduction

Malignant pleural effusion (MPE) is a common life-threatening condition, affecting more than 1 million people worldwide. About half of patients with tumour develop a pleural effusion and, as the cancer incidence rises and the overall survival improves, the prevalence of MPE is expected to increase (1).

MPE is frequently produced by hematogenous or direct spread of cancerous cells to the visceral/parietal pleura, but it can be also caused by paramalignant effusion, without direct pleural involvement. This disorder occurs for different mechanisms such as lymphatic mediastinal obstruction, pulmonary embolism and superior vena cava syndrome (2-4). Metastatic tumors are much more frequent than primary pleural tumors, however an increasingly common cause of MPE, especially in industrialized nations, is malignant pleural mesothelioma (MPM). Common causes of MPE are lung (37.5%), breast (16.8%), lymphoma (11.5%), genitourinary (9.4%) and gastrointestinal tract tumours (6.9%), MPM (4%) and unknown primary tumours (5–10%) (3-6).

The MPE is often a sign of metastatic disease and when it occurs the survival is generally limited, ranging between

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4 months in lung carcinomas and 12 months in mesothelioma. Malignant effusion caused by unknown primary cancer, that recognize the most common histological type in adenocarcinoma, has an intermediate survival time (6,7).

Most patients with pleural effusion are symptomatic: shortness of breath and dry cough are the most common symptoms (86%).

Surgery has three main aims in the management of MPE: diagnostic, staging and palliative.

During the diagnostic phase a thoracoscopy can be performed to obtain pleural biopsy and to assess the underlying lung capacity to completely re-expand when inflated with positive pressure.

The staging role of surgery is particularly important in lung cancer, lymphoma, thymoma and MPM. In selected patients affected by MPM and stage IV thymoma surgery can be considered for a therapeutic cytoreductive purpose, in that cases the correct staging is crucial.

In most of cases an operation for the management of MPE will be inevitably palliative, as no procedure has yet been revealed to prolong life expectancy. The management of a MPE is a challenging problem in palliative care practice. It is led by an assessment of the patient's prognosis and driven by a balance of the expected benefit and morbidity of the proposed procedure.

Calculating predicted patient survival is paramount, as it will direct decision making. The best validated scoring system in MPE management is the LENT score, that uses Eastern Cooperative Oncology Group (ECOG) performance status score, pleural fluid analysis and tumour type to calculate survival (7).

Recently, a new scoring system has been introduced, the PROMISE scoring, which uses eight variables (haemoglobin, C-reactive protein, white blood cell count, ECOG performance status, cancer type, pleural fluid TIMP1 concentrations, and previous chemotherapy or radiotherapy) to develop a survival score and estimate the 3-month mortality (8).

When an MPE is confirmed, management alternatives are observation, insertion of a tunnelled catheter, pleurodesis or decortication. Several factors influence the management choice, including the patients' performance status and prognosis, whether the underlying lung can expand after fluid drainage, the chemosensitivity of the malignancy and doctors' skill and personal preferences.

The gold standard procedure for the management of an MPE is pleurodesis. Conservative approach or repeated thoracentesis are indicated when life expectancy is very poor and/or the patient is considered unsuitable for pleurodesis.

A reasonable alternative to pleurodesis is the implantation of indwelling pleural catheter (IPC), which permits intermittent pleural fluid drainage, relieves the pressure on the chest and diaphragm and offers good patient satisfaction with prompt palliation of dyspnoea, allowing spontaneous pleurodesis in up to 50% of patients (9,10).

The IPC offers several advantages (e.g., ease of placement and reduced time of hospitalization compared to pleurodesis) and seems to be as effective as pleurodesis in reliving patients' symptoms, however it has not negligible drawbacks (11-15).

Catheter dysfunction is the most frequent complication which implies recurrent thrombolysis to maintain IPC patency; empyema secondary to catheter placement denies any palliation and makes IPC management problematic; in 7% of patients has been reported IPC tract seeding and in 10% of patients an IPC fracture during removal has been described (16-18). The recently published ATS/STS/STR Clinical Practice Guidelines suggest that both IPC and pleurodesis can be used in patients with MPE, inflatable lung and no prior definitive therapy, as first-line definitive intervention for management of dyspnoea (19).

Pleurodesis implicates the administration of a sclerosant agent in the pleural space or mechanical scarification of pleural surface allowing adhesions between the parietal and visceral pleura and preventing fluid accumulation. It can be performed by video-assisted thoracoscopic surgery (VATS) with the instillation of chemical sclerosant agents or with mechanical abrasion, or at the bedside by injection of sclerosant agents into a chest drainage.

### *Sclerosant agents*

*Table 1* shows the most common used pleurodesis agent. Talc, which is a clay mineral composed of hydrated magnesium silicate with the chemical formula $Mg_3Si_4O_{10}(OH)_{2.,}$ is the most broadly utilized pleurodesis product and it has been demonstrated the most effective sclerosant material (20,21).

Medical Talc used in EU is specifically calibrated to a mean particle size of 25 micron in order to avoid systemic dissemination. Talc can be administered during surgical procedure (Talc poudrage) or can be injected, mixed with sterile fluid, through a chest tube (Talc slurry) (22). A Cochrane published in 2016 has shown that several methods are less effective than talc poudrage at inducing pleurodesis:

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**Table 1** Most common used agent for pleurodesis

| Sclerosing agent | Efficacy | Advantages | Disadvantages |
|---|---|---|---|
| Talc poudrage | 80–95% | Simple availability; low cost; very effective | Risk of respiratory distress in case of extra pleural dissemination (particles smaller than 15 μm) |
| | | | Thoracoscopy is required |
| Talc slurry (in suspension) | 70–85% | Simple availability; low-cost; simple application | Risk of respiratory distress in case of extra pleural dissemination (particles smaller than 15 μm) |
| | | | Less successful than poudrage |
| | | | Greater number of loculation than poudrage |
| Doxycycline | 70–85% | Simple availability; simple application | Risk of acute respiratory failure |
| | | | Extremely painful |
| | | | Several applications are usually required |
| Silver nitrate | 89–96% | Simple availability; good side-effect profile; low cost | Long-term efficacy undetermined |
| Iodine povidone | 65–95% | Simple availability; low cost; very effective | Extremely painful |
| | | | Possible thyroid uptake |
| | | | Risk of anaphylaxis by Iodine |
| Bleomycin | 60–85% | Efficacy comparable to talc slurry | Extremely painful |
| | | | Possible toxicity from systemic absorption |
| | | | Extremely expensive |
| Oxytetracycline | 60–80% | Simple application | Several applications are usually required |
| | | | Not worldwide available |

bleomycin [odds ratio (OR) 9.70 (95% CI: 2.10–44.78)], tetracycline [OR 12.10 (95% CI: 1.32–111.30)], and doxycycline [OR 42.69 (95% CI: 2.13–856.61)]. The comparison between talc poudrage and slurry has given weak evidences that talc slurry is less effective [OR 1.31 (95% CI: 0.92–1.85)] (21). A recent randomized controlled trial has shown that there is no significant difference between IPC and talc slurry in symptoms control (23).

The aim of this review is to analyse the literature concerning surgical pleurodesis in MPE.

## Methods

A literature review was conducted by searching PubMed in October 2019, using the search terms {["pleural effusion, malignant" (MESH TERMS)] AND ["pleurodesis"] AND ["surgery" (MESH TERMS)]}.

Inclusion criteria were: (I) the paper described surgical management of MPE; (II) the study was a randomized controlled trial, meta-analysis or single centre/multicentre database study recording on MPE management; (III) the study was published between 2009 and 2019.

After language restriction (English), applying inclusion criteria and eliminating duplicate papers, 107 studies were selected for this analysis, all reporting surgical MPE management.

## Results

VATS procedure in the management of MPE is relatively well standardized (24,25).

Port-size is usually 10 mm and often a thoracoscope with a 5-mm working channel is used, in order to reduce the number of ports (generally two or three). The lung is evaluated for complete expansion during positive pressure insufflation and, if it is acceptable, pleurodesis is executed. Talc poudrage, the most common approach of pleurodesis, consists in the insufflation of 2–10 g of sterile, asbestos-free

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talc. The VATS approach allows to break all fibrin bridges and consequently a uniform distribution of talc on pleural surface, and full re-expansion of the lung. The effectiveness of talc as a sclerosing product has been well recognised, showing a response rate of 90% at 1 month. Alternative agents for chemical pleurodesis and their success-rate have been already mentioned (21,26-28).

After the procedure two large-bore (28–32 Fr) chest tubes or one large and one small-bore (7–16 Fr) chest tube drainage (pigtail catheter) are introduced via the access sites. The management of chest tubes changes among institutions, but generally the drainages are attached to suction and removed when the output is 50–250 mL per day (14,24,29).

The pigtail catheter can be left in place in case of pleurodesis failure.

Other surgical options are mechanical pleurodesis and pleurectomy. Mechanical pleurodesis, which consists in abrasion, "scarification" of the visceral and parietal pleural surfaces, is occasionally utilized, however parietal pleurectomy is less frequently used (30).

The measurement of patient's symptoms control and quality of life (QoL) after VATS pleurodesis has been analysed. Several studies have reported an improvement in dyspnoea and fatigue after VATS pleurodesis compared to slurry pleurodesis (31-33).

VATS pleurodesis, adhesiolysis and decortication as needed, is related with a post-operative mortality rate of 22% in patients with an Anesthetic Society Score (ASA) ≥4, versus 1% in patients with a score of <4 (34). A mortality hazard ratio (HR) of 2.5 at 90 days post-VATS has been reported by Yoon *et al.* for patients with an ECOG of 3–4 versus those of ≤2 (35).

The morbidity of pleurectomy and decortication significantly reduces its palliative benefit in MPE patients. Two exceptions are selected cases of trapped lung and MPM.

### *Particular cases*

#### Trapped lung

This condition has been an important clinical challenge that affects 10–20% of patients with MPE (21). Trapped lung occurs as a result of malignant invasion of the visceral pleura or in case of proximal bronchial obstruction which causes chronic atelectasis of the lung. The both conditions prevent the lung from fully expanding after drainage of the effusion and cause the rapid recurrence of fluid accumulation after interventions and severe symptoms (breathlessness and pain after fluid aspiration) caused by the loss of elasticity of visceral pleura (36-38).

Little evidence is regarding the most effective management of patients with trapped lung, however patients affected by this condition appear best treated by less-invasive treatments (e.g., IPC).

Surgical approach can be indicated with adhesiolysis and/or decortication, to remove as much tumour as possible from the lining lung allowing its re-expansion, however there is a lack of randomised trial on surgery in this population (7). The addition of these procedures to standard pleurodesis significantly increases the duration of the operation, increase the complication rate including persistent air leak and the hospitalization (30).

#### MPM

A great debate around the role of surgery in mesothelioma is currently ongoing. The Extra-pleural pneumonectomy (EPP), an aggressive intervention with a high morbidity and mortality, was considered the treatment of choice for many years. After the Mesothelioma and Radical Surgery (MARS) trial the scientific community has changed its approach in favour of less aggressive and lung sparing surgery, as pleurectomy/decortication (39).

With the aim to compare the benefits of VATS pleurectomy to talc pleurodesis (slurry or poudrage) the MesoVATS study was conducted, showing no survival difference between the two groups at 12 months (52% of the pleurectomy group versus 57% of the talc pleurodesis group). VATS partial pleurectomy (VATS-PP) was also associated with longer hospitalization, increased complications (e.g., persistent air leak in 24% pleurectomy group versus 5% in the talc pleurodesis group) (40). However, there was some evidence that VATS-PP improved EQ5D measured QoL after 6 months particularly in the European Organisation for Research and Treatment of Cancer low-risk subgroup (41).

In case of trapped lung in mesothelioma both IPC and VATS pleurectomy/decortication are offered to patients, but which is the most effective approach at relieving breathlessness it is not known. For this reason, a randomised controlled trial is ongoing in the UK evaluating the efficacy of surgical pleurectomy/decortication versus IPC in patients with mesothelioma and trapped lung (Meso-TRAP trial NCT03412357) (42).

## Conclusions

This paper presented a detailed review of the literature

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relating to the management of MPE, focusing specifically on surgical pleurodesis. Several sclerosant agents are available, but the highest quality evidence supports talc pleurodesis. It is still being debated whether talc poudrage is more effective than talc slurry. IPC are also highly effective approach to relieve symptoms. Regarding the trapped lung, the most effective treatment is still unknown: surgical approach with pleurectomy decortication can be performed, but IPC is a good intervention to improve symptoms, with lower rate of complication and shorter hospital stay (43).

During the last decade an exceptional number of high-quality studies (especially multicentre randomized controlled trial) has been conducted on MPE management. The data have partially clarified the benefits of new approaches and the detrimental effect of some conventional therapies (23,39).

Future randomized controlled studies, as Meso-TRAP, will further enlighten the role of current approaches in MPE management in terms of patient's benefits. Personalized treatment is essential in this area as we better identify sub-groups of MPE patients, recognize those who will benefit the most from each approach and improve management depending on patients' characteristic.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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