



Expectancy survival of malignant pleural effusion patients treated with thoracoscopic pleurodesis related to histology

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Introduction

Malignant pleural effusion (MPE) affects 150,000 people in the US and over 250,000 people in Europe each year and it represents a common finding, up to 15%, in the advanced stage cancers (1). Lung cancer in men and breast cancer in women account for 50–65% of all MPE (2), followed by ovarian metastatic cancer, hematological malignancies and malignant pleural mesothelioma (MPM). The main causes of MPE are the direct infiltration of the pleural layers by malignant cells, resulting in increased filtration across systemic or pulmonary capillary, or to indirect effects as the obstruction of lymphatic vessels and lymph nodes. Symptoms are strictly related to the amount/volume of the pleural effusion and are represented by dyspnea, caused by reduction of chest wall compliance and of the lung vital capacity, cough and chest pain as epiphenomenon of the involvement of parietal pleura or other thoracic structures (1).

MPE represents a manifestation of a metastatic disease whereby survival is generally less than 12 months depending on the tumor features and the underlying clinical conditions of the patients (1). Although selected cases of MPE caused by highly chemo-sensitive cancer such as lymphoma or breast cancer initially respond to the medical therapy, the effusion's management usually requests an intervention during the disease course. The main goal of MPE treatment consists in relieving symptoms and reducing repeated invasive procedures, therefore, in the last decades, several prognostic scoring systems have been developed to stratify the patient risk and facilitate

the subsequent handling. LENT is one of the most used prognostic scores worldwide and it is based on 4 parameters: LDH level of the pleural fluid, the Eastern Cooperative Oncology Group (ECOG) performance-score, serum neutrophil-to-lymphocyte ratio and the tumor's histology (3); while, more recently, an European multicohort study has developed the PROMISE score, a risk-stratification system, which combine clinical and biological parameters to estimate 3-month mortality (4); nevertheless, data about the score's impact on the daily practice are still lacking (5).

Strategy to manage MPE are mainly represented by therapeutic thoracentesis, pleurodesis (using chemical agents or physical abrasion) and long-term chest drainage with indwelling catheters while pleuroperitoneal shunting and surgical pleurectomy are reserved in case of failure of other procedures. Pleurodesis using 4–6 g of sterile talc is, by far, the most common procedure to manage recurrent symptomatic MPE, reducing repeated hospitalization and avoiding recurrent thoracentesis; moreover, some authors postulated also an anti-tumor effect of talc pleurodesis as consequence of the improvement of the immunological response (1-2,6).

Indications are mainly the presence of symptoms, the evidence of expandable lung after thoracentesis and a life expectancy >1 month (*Table 1*); while, it should be avoided in case of lung entrapment (nearly 30% of MPE) where indwelling catheter should be preferred (2).

Thoracoscopic pleurodesis provides several advantages: it allows a more effective fluid evacuation, a safe lysis of

Table 1 Pleurodesis indications according to guidelines of the major society

Society	Pleurodesis indications
British Thoracic Society [2010]	Life expectancy >1 month Symptomatic and recurrent MPE No trapped lung Good performance status Talc should be preferred for pleurodesis
European Respiratory Society; European Association for Cardio-Thoracic Surgery [2018]	Symptomatic and recurrent MPE Talc is the most effective agent for chemical pleurodesis Talc poudrage may be slightly more effective than talc slurry
American Thoracic Society; Society of Thoracic Surgeon; Society of Thoracic Radiology [2018]	Symptomatic and recurrent MPE (symptoms attributable to effusion) Known or suspected expandable lung About talc pleurodesis: poudrage and slurry are both recommended

MPE, malignant pleural effusion.

adhesions and loculations that may be detrimental on the pleurodesis success and on the lung expansion, lastly, it may be performed via different techniques, using several sclerosant agent that can be spread in a wider way on the pleural surfaces. Thoracoscopic approach, moreover, has an unquestionable diagnostic and stadiative role in absence of clear diagnosis or in case in evaluation of more aggressive procedure (namely pleurectomy/decortication or extended pleuropneumectomy), and to create a pericardial window when symptomatic pericardial effusion is associated to the pleural one.

Hereby, we report a review of recent articles on the expected survival of patients affected by the most common malignant causes of pleural effusion after thoracoscopic pleurodesis (*Table 2*).

MPM

MPM is a relatively rare and aggressive cancer arising from mesothelial cell, highly correlated with asbestos exposure. The prognosis is generally poor with mean life expectancy going from 12 to 21 months, depending on histological subtype and stage. The disease treatment as well as symptoms palliation management is still under debate.

Surgery has a role in different stage of MPM management. Video assisted thoracoscopy has excellent sensitivity and specificity in terms of diagnosis, offers a direct view of pleural cavity to verify the extent of the tumor, beside being the best option for palliative surgery

as pleurodesis with talc (12). Several studies showed good results in MPM patients undergone talc pleurodesis in terms of overall survival and pleural effusion recurrence rates. Moreover, talc seems to have an antitumor effect by inducing apoptosis of MPM cells *in vitro* and promoting the natural secretion of endostatin from normal mesothelial cells, balancing the angiogenic environment present in MPM (6).

In a 2009 paper, Ak *et al.* described their experience on 42 patients with MPE due to MPM underwent talc pleurodesis for recurrent massive or moderate pleural effusion associated to dyspnoea. Pleurodesis was successful in 26 patients (90 days success rate: 62%); these patients presented a median survival of 12 months (range, 8.7–15.3 months) versus 6 months (range, 5.1–6.9) of patients in which the procedure was unsuccessful (13).

In the MesoVATS trial, Rintoul *et al.* compared video-assisted thoracoscopic partial pleurectomy (VAT-PP) and talc pleurodesis in managing MPE due to MPM, showing that the overall survival rates were comparable in the two groups, but VAT-PP was associated to significantly more post-operative complications and longer hospital stay. For these reasons, VAT-PP was not recommended, and talc pleurodesis was considered to be preferred, except for patients with life expectancy over 6 months, in which VAT-PP had a rationale due to the observed improvement of quality of life at 6 and 12 months postoperatively (14).

Comparing survival rates of MPE patients affected by MPM with those affected by other tumors who

Table 2 Expectancy survival of malignant pleural effusion according to the histology in the comparative studies

Comparative studies	Histology	Lung cancer	MPM	Breast cancer	Ovarian cancer	Hematologic malignancies
Barbetakis (7)	No. patients	176 (44%)	10 (2.5%)	97 (24.2%)	24 (6%)	13 (3.2%)
	MOS (month)	6.7	9.6	13.6	13.1	10.2
	SA	Talc, 6 g, thoracoscopic insufflation				
Love (8)	No. patients	11 (18.3%)	14 (23.3%)	18 (30%)	1 (1.7%)	4 (6.7%)
	MOS (month)	~3.8	~5.8	~9.5	–	~8
	SA	Talc, 4–5 g, thoracoscopic insufflation				
Schniewind (9)	No. patients	27 (22%)	13 (10.5%)	51 (41.5%)	6 (4.9%)	–
	MOS (month)	7.6	18.8	7.6	6.7	–
	SA	Talc, 4 g, thoracoscopic procedure				
Steger (10)	No. patients	196	76	135	–	–
	MOS (month)	~7.9	~9.7	~10.7	–	–
	SA	Talc, 5 g, thoracoscopic procedure				
Laisaar (11)	No. patients	30	7	25	11	2
	MOS (month)	9.1	–	7.7	3.3	–
	SA	Talc, 5 g, thoracoscopic insufflation				

MPM, malignant pleural mesothelioma; No. patients, number of patients; MOS, medium overall survival; SA, sclerosant agent.

underwent thoracoscopic talc pleurodesis, Kolschmann *et al.* Observed that MPM was a cancer type with better overall survival after 180 days (15). Similarly, Barbetakis and Steger reported an average survival of 9.6 and 9.7 months respectively in MPM patients who underwent thoracoscopic talc insufflation (7,10).

Lung cancer

Lung cancer is the leading cause of cancer death in the world and about 40% of patients with advanced stage develops pleural effusion, especially in case of adenocarcinoma, due to its peripheral origin. MPE in lung cancer is an independent adverse prognostic indicator (16). As reported in a recent review article by Epelbaum and Rahman, traditional chemotherapy has limited efficacy in controlling the recurrence of pleural fluid in these patients and the observed overall survival ranges from 11 weeks to 11 months (17). For these reasons, local treatments such as chemical pleurodesis are generally performed with palliative purposes, even though its efficacy in stage IV lung cancer seems to be lower than for other kind of tumors.

Chen and colleagues in 2015 performed a retrospective

study on 1,061 patients with MPE treated with medical thoracoscopic pleurodesis; they encountered an overall response rate of 72.3% for lung cancer patients, worse than breast cancer (84.4%) and other metastatic tumors (87.8%) rates (18). In a 2005 study, conversely, Kolschmann *et al.* described no significant influence on thoracoscopic talc poudrage success rate due to the primary neoplasm type, but life expectancy resulted shorter in patients with lung cancer (cumulative survival rate: 29%) than other malignancies (15). Nevertheless, Korsic and coauthors reported that talc pleurodesis allows a longer average survival in MPE caused by advanced lung cancer in patients compared with those without pleurodesis (20 *vs.* 9 weeks, respectively) due to the strong apoptotic effect of the talc on the tumour cells and to the improved quality of life (19).

In their 2010 paper, Barbetakis *et al.* reported their experience on videothoracoscopic talc poudrage in 400 MPE patients (176 patients with metastatic lung cancer), demonstrating the safety and efficacy of this technique. Also in this study, lung cancer patients had one of the worst post-pleurodesis average survival rates (6.6 months for SCLC, 6.7 months for NSCLC patients) (7). Similarly, Laisaar and colleagues (11) reported a median survival after

thoroscopic talc pleurodesis of 9.1 months in line with the 7.9 months reported by Steger (10) and the 7.64 months found by Schniewind (9).

Breast cancer

Breast cancer is the second most prevalent cause of all pleural metastases and accounts for approximately 25% of all malignant effusions (20). The mean survival in these patients is generally shorter than 6 months even though it has been demonstrated that oncological outcomes in terms of survival and pleural progression-free survival is better in patients who received chemotherapy following initial pleurodesis rather than systemic therapy alone (19).

Mohsen and colleagues in 2011 published a prospective randomized control trial on 42 patients with MPE caused by breast carcinoma without extrathoracic disease; authors described a mean survival of 27.7 months in 22 patients underwent thoroscopic talc pleurodesis and 33.8 months in 20 patients who received bedside pleurodesis with 10% povidone-iodine (21). In 2006 Gasparri and colleagues described a median survival of 17 months in 71 consecutive patients underwent talc pleurodesis via VATS (22). In 2007 Steger *et al.* reported their experience on thoroscopic talc pleurodesis in 543 with MPE and described a median survival time of 321 days (approximately 10.7 months) in patients affected by advanced breast cancer (10), while Laisaar (11), Love (8) and Barbetakis (7) reported a median survival of 7.7 months, 285 days (~9.5 months) and 13.6 months, respectively, for the same subset of patients.

Ovarian cancer (OC)

Advanced OC is the second gynecologic cause of MPE (following breast cancer) since pleural surface result the most common extra-abdominal site of diffusion due to the pleural invasion from contiguous structures, such as the diaphragm or to the migration of malignant cells through pleuroperitoneal communication, in fact, about 15% of women with a new diagnosis of OC present pleural effusion (23).

Whitworth and colleagues analyzed outcomes of 29 patients with OC underwent VATS pleurodesis, observing a median survival of 104 days (~3.5 months) (24); 6% of patients analyzed in the aforementioned work of Barbetakis *et al.* study was affected by OC, and the average survival founded after pleurodesis was 13.1 months (7). Schniewind *et al.*, instead, conducted a study on patient's Quality of Life

after Thoracoscopic Talc Pleurodesis for MPE, showing decreases of respiratory symptoms after the procedure. In a total of 123 patients, 6 (4.9%) was affected by OC, their median survival after pleurodesis was 6.7 months (9). Lastly, Laisaar *et al.* in their report of the survival after VATS talc pleurodesis found a median survival of 3.3 months in 11 patients with advanced OC (11).

Hematologic malignancies

MPE may be found in up to 20% of patients with non-Hodgkin's lymphoma (NHL) and 30% of those with Hodgkin disease (HD) as first presentation or during the disease's course while it is rarely found in other malignancies as acute or chronic leukaemia and myeloma.

The prognostic role of the MPE in NHL has not been determined for low- and intermediate-grade lymphoma while in case of high-grade NHL, MPE is an adverse prognostic factor in term of relapse-rate and overall survival (25). HD, on the other hand, usually respond to conventional therapeutic regimens and the presence of MPE seems not to be associated with a worse prognosis.

Unfortunately, few data are available in literature on the expectancy survival in MPE caused by lymphoma. Love and colleague (8) in 2003 reported the median survival of patients with MPE caused by different primary cancer who underwent thoroscopic talc pleurodesis. Out of 66 patients, 4 were affected by NHL and their median survival time was 240 days (approximately 8 months). Martínez-Moragón in 1998 reported a median survival of 10 months after chemical pleurodesis through a chest tube in 10 patients out of 120 patients with different primary cancer (26) while Barbetakis in 2010 reported an average survival of 10.2 months in those affected by lymphoma (7).

Conclusions

MPE represent the end-stage of nearly the totality of cancers. With the exception of very selected cases, any treatment has the exclusively role of relieving symptoms and improving as much as possible the quality of life. In this scenario, to date, videothoroscopic pleurodesis, especially by using 4 to 6 g of sterile talc, represents a safe and effective method to achieve these goals. In literature, VATS pleurodesis is associated with the highest successful rate in controlling the effusion and improving the quality of life; moreover, in many cases it allows an overall survival extension with minimal side effects.

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