Management of Malignant Pleural Effusions

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INTRODUCTION

Accumulation of pleural fluid is a common clinical problem associated with malignancy. In the United States alone, more than 150,000 patients are diagnosed with malignant pleural effusions annually.\(^1\) Malignant effusions are the second most common cause of a pleural exudate.\(^2\) Malignant pleural effusions represent advanced disease and are generally a poor prognostic indicator. Median survival following the diagnosis of a malignant effusion ranges from 3 to 12 months and depends on the tumor origin.\(^3\)–\(^8\) However, not all effusions will progress in size and become symptomatic. In one retrospective study, only 7% of asymptomatic patients with small effusions from lung cancer had progression of fluid accumulation and required therapeutic intervention.\(^9\) Nevertheless, patients with large symptomatic effusions requiring therapeutic drainage will almost invariably experience re-accumulation of fluid within 30 days, thus making long-term therapeutic interventions necessary.\(^10,11\)

Malignant effusions are a frequent cause of dyspnea and discomfort, thereby adversely affecting a patient’s quality of life. Therapeutic management remains a clinical challenge for both patients and clinicians. This review discusses the pathophysiology of malignant pleural effusions and focuses on the available management options for this common clinical problem.

PATHOGENESIS AND ETIOLOGY

Normally, the thoracic cavity contains less than 15 mL of pleural fluid, resulting in a potential space between the visceral and parietal pleura. The negative intrapleural pressure creates a gradient for fluid movement into the pleural space dictated by Starling forces. Pleural fluid normally has low protein content and is primarily removed via stomata located on the parietal pleura which are connected to lymphatics. This system’s capability to remove pleural fluid exceeds normal fluid production by more than 30 times, suggesting that accumulation of excess pleural fluid likely requires a combination of both increased fluid production and impaired fluid removal.\(^12,13\)

Several mechanisms have been associated with the development of malignant effusions. Pleural involvement by malignancy may occur from direct invasion of the pleural cavity by tumor (eg, lung cancer, breast cancer, chest wall neoplasms) or hematogenous spread of tumor to the pleura (eg, metastasis, non-Hodgkin lymphoma).\(^14,15\) Pleural
malignancies can directly result in increased fluid production. Increased cytokine and inflammatory mediators may also affect vascular permeability, resulting in pleural fluid production. Vascular endothelial growth factor (VEGF) is produced by many tumors and may be involved in the pathogenesis of malignant effusions. VEGF and soluble intercellular adhesion molecule-1 levels have also been identified as independent prognostic factors for progression-free survival.

Tumor cells can also disrupt lymphatic drainage by occluding either pleural stomata or downstream lymphatic drainage. However, tumor involvement of the pleura does not always result in the development of an effusion; pleural fluid accumulation is present in approximately 60% of such cases. Malignant pleural effusions have also been strongly associated with mediastinal metastases, likely resulting from obstruction of mediastinal lymphatics. Paramalignant effusions result from secondary effects of tumor burden. Such causes include thoracic duct obstruction (eg, Hodgkin lymphoma), bronchial obstruction, pneumonia, atelectasis, pulmonary embolism, trapped lung, and effects related to radiation or chemotherapy. Pleural fluid cytology and pleural biopsy are negative in these situations because tumor is not directly affecting the pleural space.

Lung cancer is the most common cause of malignant effusions and accounts for more than one-third of cases. Other frequently encountered primary tumor sites include breast, lymphoma, ovary, and stomach. Combined, these sites comprise more than 75% of cases (Table). Mesothelioma-related effusions may be more prevalent in certain parts of the world due to associated exposure to asbestos. The primary tumor origin remains unknown in approximately 10% of cases.

**CLINICAL PRESENTATION AND DIAGNOSIS**

More than 75% of patients with malignant pleural effusion are symptomatic. Dyspnea is the most common symptom and is present in more than half of patients. The mechanism of dyspnea caused by large effusions may not be solely impaired lung volumes or gas exchange. Other associated factors include decreased chest wall compliance, mediastinal shift causing decreased volume of the contralateral lung, paradoxical motion of the diaphragm, stretch of respiratory muscles resulting in inefficient muscle length-tension relationships, and reflex stimulation from the lungs and chest wall. Other common presenting symptoms include cough, orthopnea, and chest pain. Hemothorax suggests involvement of the large airways. And, given the advanced nature of most malignant pleural effusions, patients may also present with weight loss and cachexia.

Diagnostic thoracentesis is the most common method by which tumor involvement of the pleural cavity is diagnosed. Diagnostic sensitivity of fluid cytology ranges from 62% to 90%, with variability...
resulting from the extent of disease and primary malignancy. If thoracentesis is initially nondiagnostic, repeat thoracentesis can improve diagnostic yield, but subsequent sampling has diminishing utility. In one series, the diagnosis of malignancy was made in 65% of patients by fluid cytology analysis from the initial sample and 27% from the second sample, but only 5% from the third sample.

However, it is also important for the clinician to assess how the patient responds to large volume drainage as the effect on the patient’s symptoms and their physiologic responses to fluid removal will influence management options. Up to 50% of patients will not have significant symptom palliation because they may be symptom-limited by other comorbid conditions, generalized deconditioning, or incomplete lung reexpansion. A trapped lung is generally described as a lung that cannot expand completely after removal of pleural fluid; it may result from pleural-based malignancies or metastases, loculations and adhesions, or bronchial obstruction. Trapped lung is associated with high elastance ($P_{EL}$) affecting pleural pressure-volume relationships (Figure 1). While clinically often considered together, some authors differentiate the category of incomplete lung expansion into 2 subgroups. In this context, the term trapped lung is used specifically to describe a mature, fibrous membrane that prevents lung reexpansion and is caused by a prior inflammatory pleural condition. Entrapped lung describes incomplete lung expansion resulting from an active disease process, such as ongoing infection, rheumatologic pleurisy, or malignancy. Differences in pleural manometry can be seen in the 2 subgroups. Pleural manometry can be helpful to monitor for the generation of high negative intrapleural pressures during fluid removal; negative pressures in excess of $-19$ cm H$_2$O are suggestive of trapped lung. Patients may develop symptoms of chest pain or discomfort during fluid drainage in these situations.

While most malignant pleural effusions are protein-rich exudates, approximately 2% to 5% may be transudates. Pleural fluid may frequently appear hemorrhagic, but comparison of the hematocrit in the pleural fluid to the serum with a ratio greater than 0.5 is used to distinguish a true hemothorax from bloody appearing pleural fluid. The cell count may be lymphocyte-predominant, but other cell types, such as eosinophils, do not exclude malignancy. Fluid may have a low glucose concentration and pH as well. While there is conflict-

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**Figure 1.** Pressure/volume curves in normal lung compared to entrapped and trapped lung physiology. There is minimal pleural pressure change in normal lung as fluid is removed. Entrapped lung initially has a pleural space elastance ($P_{EL}$) that mirrors normal lung but then increases significantly. Trapped lung has a high $P_{EL}$ throughout the course of volume removal. (Adapted from Huggins JT, Doelken P, Sahn SA. The unexpandable lung. F1000 Med Rep 2010;2:77.)
ing data associating fluid pH with patient survival, meta-analysis of 433 patients suggested that pH of 7.28 or less is an independent predictor of less than 3-month survival.8

**PLEURAL DRAINAGE OPTIONS**

**THERAPEUTIC THORACENESIS**

Evaluation of pleural fluid cytology is a crucial step in the diagnosis and staging of disease. As a result, large-volume fluid removal is often the first therapeutic intervention for patients who present with symptomatic effusions. A patient’s response to therapeutic thoracentesis dictates which additional therapeutic options are appropriate for palliation. Lack of symptom relief suggests that other comorbid conditions or trapped lung physiology may be the primary cause of the patient’s symptoms and discourages further invasive therapies. Radiographic evidence of successful post-drainage lung reexpansion is also an important predictor of success for potential pleurodesis.37,38

There are no absolute contraindications to thoracentesis. However, special consideration should be given to patients with clinical risk factors such as coagulopathy, use of anticoagulation medications, thrombocytopenia, platelet dysfunction (eg, use of antiplatelet medications, uremia), positive pressure ventilation, and small effusion size. These factors may increase the potential risk for the principle complications of bleeding and pneumothorax. These factors should only be considered relative contraindications, however, as thoracentesis can still be safely performed under these circumstances by experienced operators using guidance technology such as ultrasonography.

Hibbert and colleagues reported on a retrospective review of 1009 ultrasound-guided thoracenteses with risk factors of an international normalized ratio (INR) greater than 1.6, platelet values less than 50,000/μL, or both.39 The overall rate of hemorrhagic complication was 0.4%, with no difference between procedures performed with \( n = 303 \) or without \( n = 706 \) transfusion correction of the coagulopathy or thrombocytopenia. A similar retrospective evaluation of 1076 ultrasound-guided thoracenteses, including 267 patients with an INR greater than 1.5 and 58 patients with platelets less than 50,000/μL, reported a 0% complication rate.40 Small case series have also demonstrated low hemorrhagic complication rates for thoracentesis in patients treated with clopidogrel41,42 and with increased bleeding risk from elevated INR (liver disease or warfarin therapy) and renal disease.43

Complications from pneumothorax can similarly be affected by patient and operator-dependent risk factors. Meta-analysis of 24 studies including 6605 thoracenteses demonstrated an overall pneumothorax rate of 6.0%, with 34.1% requiring chest tube insertion.44 Lower pneumothorax rates were associated with the use of ultrasound guidance (odds ratio [OR] 0.3; 95% confidence interval [CI] 0.2–0.7). Experienced operators also had fewer pneumothorax complications in studies reporting this data, though this factor was not significant in the studies directly comparing this variable. Therapeutic thoracentesis and use of a larger-bore needle were also significantly correlated with pneumothorax, while mechanical ventilation had a nonsignificant trend towards increased risk.

While there is no consensus on the volume of pleural fluid that may be safely removed, it is commonly recommended not to remove more than 1.5 L at a time in order to prevent reexpansion pulmonary edema.2,26 Use of excessive negative pressure, such as from a vacuum bottle, should also be avoided for this same reason. However, reexpansion pulmonary edema rates remain low
even when larger volumes are removed if the patient remains symptom-free during the procedure and pleural manometry pressure does not exceed \(-20\) cm H\(_2\)O\(^4\)). Patient symptoms alone, however, are not a sensitive or specific indicator that pleural pressures exceed \(-20\) cm H\(_2\)O\(^4\)).

Given the low morbidity and noninvasive nature of the procedure, serial large-volume thoracentesis remains a viable therapeutic intervention for patients who are unable or unwilling to undergo more invasive interventions, especially for patients with a slow fluid reaccumulation rate or with a prognosis of less than 1 month survival. Unfortunately, almost all symptomatic effusions will recur within 30 days of drainage, which necessitates repeat procedures\(^10,11\).

Therefore, factors such as diminishing symptom control prior to repeat drainage, patient inconvenience, recurrent procedural risk, and utilization of medical resources need to be considered.

**TUNNELED PLEURAL CATHETER**

Tunneled pleural catheters (TPC) are a potentially permanent and minimally invasive therapy which allows intermittent drainage of pleural fluid (Figure 2). The most common catheter system in use is a 15.5 Fr fenestrated catheter inserted into the pleural space (PleurX; CareFusion, San Diego, CA). The catheter is tunneled under the skin to prevent infection and secured in place by a polyester cuff, which induces a fibrotic reaction within the tunnel path. Placement can be performed under local anesthesia at the patient’s bedside or as an outpatient. Fluid can then be drained via specialized drainage bottles by the patient, a family member, or a visiting home nurse. The catheter can also be removed in the event of a complication or the development of spontaneous pleurodesis.

TPCs have been shown to be an effective palliative management strategy for patients with recurrent effusions\(^21,47–49\) and are an efficacious alternative to pleurodesis\(^50\). Meta-analysis of 19 studies showed symptomatic improvement in 95.6% of patients, with development of spontaneous pleurodesis in 45.6% of patients (range 11.8% to 76.4%) after an average of 52 days\(^51\). TPCs are commonly used in patients with a poor prognosis (<6 months), patients with trapped lung, or patients who have failed prior pleurodesis\(^52–54\). Small case series also demonstrate that TPC placement may induce spontaneous pleurodesis in almost half of patients with a trapped lung\(^53\).

The catheter may not be able to be successfully placed in approximately 4% of cases\(^49\). Increased bleeding risk, significant malignancy-related skin involvement on the chest wall, and pleural locula-
tions can complicate TPC placement. TPC-related complications are relatively uncommon, but include pneumothorax (5.9%), catheter malfunction (9.1%) and obstruction (3.7%), and infections including cellulitis (3.4%) and empyema (2.8%).

Retrospective analysis suggests that TPCs do not increase the risk of infection with chemotherapy. Tumor metastasis along the catheter tract is a rare occurrence (<1%), but is most notable with mesothelioma, with an incidence as high as 10%.

PLEUROPERITONEAL SHUNT

Pleuroperitoneal shunts are used in patients with refractory malignant effusions, failed chemical pleurodesis, and trapped lung or in patients who are not pleurodesis candidates. Pleuroperitoneal shunts transfer fluid from the pleural space to the peritoneal cavity when manually pumped (Denver shunt) or passively from pressure changes related to the respiratory cycle (LeVeen shunt). Use of these devices, however, has largely been supplanted by TPC. Palliation is achieved in 80% to 90% of properly selected patients. This method of pleural fluid drainage is particularly useful with chylothorax because it allows recirculation of chyle. Infection and shunt occlusion are the most significant complications associated with pleuroperitoneal shunts. Shunt occlusion, usually from clotting of the catheter, occurs in up to 25% of cases, with a median patency duration of 2.5 months.

PLEURODESIS

PROCEDURAL OPTIONS

Pleurodesis obliterates the potential pleural space by inducing inflammation and fibrosis, resulting in adherence of the visceral and parietal pleura together. This process can be induced through mechanical abrasion of the pleural surface, introduction of chemical sclerosants, or from prolonged use of a chest tube. Chemical sclerosants are the most commonly used method and are introduced through a chest tube or under visual guidance such as medical thoracoscopy or video-assisted thoracoscopic surgery (VATS). The pleurodesis process is thought to occur by induction of a systemic inflammatory response with localized deposition of fibrin. Activation of fibroblasts and successful pleurodesis have been correlated with higher basic fibroblast growth factor (bFGF) levels in pleural fluid. Larger tumor burden is associated with lower bFGF levels, suggesting a possible mechanism for reduced pleurodesis success in these cases. Corticosteroids may reduce the likelihood of pleurodesis due to a reduction in inflammatory response demonstrated in a rabbit model using talc and doxycycline. Similarly, animal data suggest that use of nonsteroidal anti-inflammatory drugs may hinder the likelihood of successful pleurodesis. Unfortunately, human data evaluating the effect of these medications on pleurodesis is lacking.

Patients selected for pleurodesis should have significant symptom relief from large-volume removal of pleural fluid, good functional status, and evidence of full lung reexpansion after thoracentesis. Lack of visceral and parietal pleural apposition will prevent pleural adhesion from developing. As a result, trapped lung is associated with chemical pleurodesis failure and is an absolute contraindication to the procedure. Discussion of different methods of performing the procedure and sclerosing agents will follow. The pleurodesis process typically requires 5 to 7 days, during which time the patient is hospitalized for chest tube drainage and pain control. When pleural fluid output diminishes, the chest tube is removed and the patient can be discharged.
Chest Tube Thoracostomy

Chest tube thoracostomy is an inpatient procedure performed under local anesthesia or conscious sedation. It can be used for measured, intermittent drainage of large effusions for immediate symptom relief as well as to demonstrate complete lung reexpansion prior to instillation of a chemical sclerosant. Pleurodesis using a chest tube is performed by instillation of a slurry created by mixing the sclerosing agent of choice with 50 to 100 mL of sterile saline. This slurry is instilled into the pleural cavity through the chest tube. The chest tube is clamped for 1 to 2 hours before being reconnected to suction. Intermittent rotation of the patient has not been shown to result in better distribution of the sclerosant or improved procedural outcomes. Typically, a 24 to 32 Fr chest tube is used because of the concern about obstruction of smaller bore tubes by fibrin plugs. However, these caliber tubes are also associated with greater patient discomfort compared to smaller bore tubes, and several randomized trials have shown that smaller bore chest tubes have similar efficacy with pleurodesis.

Medical Thoracoscopy

Medical thoracoscopy, also referred to as pleuroscopy, is a minimally invasive means to visualize the pleural space and perform guided biopsy of the parietal pleura and lysis of adhesions and introduce chemical sclerosants to induce pleurodesis (Figure 3). It can be performed under local anesthesia with procedural sedation in an endoscopy suite or procedure room. In contrast, VATS is performed in an operating room setting and requires general anesthesia, intubation with a double-lumen endotracheal tube, and multiple trocar incisions. For medical thoracoscopy, the patient is placed in the lateral decubitus position. The medical thoracoscope is introduced into the pleural space through 1 or more trocars. Trocar sizes range from 5 to 13 mm depending on the type of thoracoscope used. The body of the thoracosopes may be rigid or semi-rigid (Figure 4). Rigid thoracoscopes have direct (0º) and angled cameras, while semi-rigid thoracoscopes have a flexible tip that can be manipulated similar to a flexible bronchoscope to direct visualization and biopsies. Following the procedure, a chest tube is typically introduced through the trocar insertion site for drainage.

Diagnostic accuracy of medical thoracoscopy is reported to be as high as 97% for malignant pleural effusions and pleural disease such as mesothelioma, thereby allowing both diagnostic and therapeutic interventions to be performed simultaneously. Medical thoracoscopy also creates optimal conditions for pleurodesis through removal of pleural adhesions, accessing loculated spaces, and using visual guidance to ensure complete drainage of pleural fluid and uniform distribution of the chemical sclerosant. Pleurodesis rates for talc poudrage with medical thoracoscopy have been reported to be as high as 95% after 90 days. Patient selection for medical thoracoscopy is important as patients

Figure 3. Thoracoscopic images of the pleural space. (A) Thin adhesions which can be safely removed with thoracoscopy. (B) Thick adhesions between the lung and chest wall. (C) Large tumor plaques on the chest wall from metastatic gastric adenocarcinoma.
must be able to tolerate spontaneous respiration under procedural sedation with 1 lung partially collapsed. Procedure-related complications include pneumothorax, subcutaneous emphysema, fever, and pain.  

**Surgical Interventions**

While similar in many ways to medical thoracoscopy, VATS has several distinct and clinically important differences. The equipment is slightly larger but otherwise similar in concept to rigid medical thoracoscopes. A greater number of diagnostic and therapeutic options, such as diagnostic biopsy of lung parenchyma and select hilar lymph nodes, are also available with VATS. However, VATS requires surgical training and is performed in an operating room setting, which necessitates additional ancillary and logistical support. VATS also uses at least 2 trocar insertion sites, requires general anesthesia, and utilizes single-lung ventilation through a double-lumen endotracheal tube. Nevertheless, it is a viable alternative to medical thoracoscopy to obtain diagnostic samples and perform pleurodesis.

Thoracotomy with decortication is rarely used as treatment of malignant effusions complicated by loculations or trapped lung due to the significantly increased procedural morbidity and mortality. Therefore, it is reserved for the limited population of patients in whom other therapeutic interventions have failed but who otherwise have significant symptoms with a long life expectancy. Mesothelioma is a specific situation in which variations of pleurectomy, such as radical pleurectomy with decortication, lung-sparing total pleurectomy, and extrapleural pneumonectomy (EPP), have been used as front-line therapy. The Mesothelioma and Radical Surgery (MARS) trial is the only randomized, controlled evaluation of EPP and had decreased median survival in patients who underwent EPP compared to those who did not undergo the procedure (14.4 months vs 19.5 months).  

EPP is also associated with approximately 50% procedure-related morbidity and a mortality rate ranging from 4% to 15%. While successful at achieving pleurodesis, use of EPP as a treatment for mesothelioma is now discouraged. Less invasive surgical approaches, such as pleurectomy with decortication, are able to palliate symptoms with significantly less operative risk.  

**PLEURODESI S AGENTS AND ADMINISTRATION**

An ideal sclerosing agent should be efficacious, readily accessible, and easily administered and possess a good safety profile. A variety of chemical sclerosants have been used for pleurodesis, including talc, bleomycin, tetracycline, doxycycline,
iodopovidone, and mustine. Meta-analysis indicates that pleurodesis is more successful with talc compared to other agents or chest tube drainage alone (relative risk [RR] 1.34, 95% CI 1.16–1.55). Meta-analysis indicates that pleurodesis is more successful with talc compared to other agents or chest tube drainage alone (relative risk [RR] 1.34, 95% CI 1.16–1.55). Modern talc (Mg₃Si₄O₁₀(OH)₂) used for pleurodesis is an inert, hydrated magnesium silicate sheet that is sterilized and asbestos-free. Published pleurodesis success rates range from 81% to 93%, compared to 80% to 85% with tetracycline/doxycycline and 70% to 79% with bleomycin. As a result, talc is now the preferred pleurodesis agent.

Chemical sclerosing agents can be delivered into the pleural space either through a chest tube as a liquid suspension (slurry) or insufflated as a dry powder during medical thoracoscopy or VATS (poudrage). Several studies suggest similar or better pleurodesis rates with talc poudrage compared to talc slurry, though these data are not completely conclusive. The largest of these trials compared talc poudrage versus talc slurry in 501 randomly assigned patients; 30-day pleurodesis rates were similar at 78% versus 71%, respectively. However, subgroup analysis demonstrated increased success with talc poudrage (82% versus 67%) in patients with primary lung or breast cancer compared to other primary malignancies. Meta-analysis of the studies directly comparing talc poudrage with slurry suggest that poudrage is more effective than slurry (RR 1.12, 95% CI 1.01–1.23). Talc poudrage also has situational benefits due to the procedural advantages offered by medical thoracoscopy or VATS. Thoracoscopic approaches also allow diagnostic biopsy and therapeutic pleurodesis to be performed simultaneously, manual lysis of adhesions, visual confirmation of adequate drainage of the pleural cavity, and uniform dispersal of the sclerosing agent.

Additional factors have been shown to be associated with pleurodesis outcomes. Pleurodesis success is negatively associated with low pleural pH, with receiver operating curve thresholds of 7.28 to 7.34. Trapped lung, large tumor bulk lining the pleural surfaces, and elevated adenosine deaminase levels are also associated with poor pleurodesis outcomes. In contrast, pleural fluid output less than 200 mL per day treated with talc slurry and the presence of epidermal growth factor receptor mutation treated with erlotinib and talc poudrage are associated with successful pleurodesis.

The most common complications associated with chemical pleurodesis are fever and pain. Other potential complications include soft tissue infections at the chest tube site, pleural space infections and empyema, arrhythmias, cardiac arrest, myocardial infarction, and hypotension. Doxycycline is commonly associated with greater pleuritic pain than talc. Acute respiratory distress syndrome (ARDS), acute pneumonitis, and respiratory failure have been described with talc pleurodesis. ARDS secondary to talc pleurodesis occurs in 1% to 9% of cases, though this may be related to the use of ungraded talc. Janssen and colleagues prospectively treated 558 patients using large particle talc (>5 µm) without any occurrences of ARDS, suggesting the safety of graded large particle talc.

**MANAGEMENT CONSIDERATIONS**

When evaluating therapeutic options for patients with malignant pleural effusions, it is important to consider factors including the severity of symptoms, fluid quantity, fluid reaccumulation rate, pleural physiology, functional status, overall prognosis, and anticipated response of the primary malignancy to therapy. Management strategies focus on either drainage of pleural fluid or prevention of recurrence (Figure 5). It is also crucial for patients to understand these therapeutic interven-
tions are palliative rather than curative. An appropriate management plan should be selected after comprehensive discussion with the patient and should fit within the context of their desired goals of care. The ideal management strategy provides both immediate and long-term symptom palliation, has minimal associated morbidity and side effects, minimizes hospitalization time and clinic visits, avoids the risks and inconvenience of recurring procedures, is inexpensive, and minimizes utilization of medical resources.

When compared directly with pleurodesis, TPC provides similar control of symptoms but with a reduction in hospital length-of-stay by a median of 3.5 to 5.5 days.98,99 In a nonrandomized trial where patients chose palliation by TPC or talc pleurodesis, more TPC patients had a significant immediate improvement in quality of life and dyspnea after the first 7 days of therapy.100 This is reasonably attributed to the differences between the immediate relief from fluid drainage after TPC placement compared to the time required for pleural symphysis to occur with pleurodesis. However, in a randomized comparison of TPC to pleurodesis by talc slurry, improvement in dyspnea between the 2 groups was similar after 42 days as measured by a visual analog scale.99

Using a decision analysis cost model comparing TPC to talc slurry pleurodesis, Olden and Holloway showed that cost of TPC is initially favorable due to decreased hospitalization time, but is
offset after 6 weeks due to costs associated with disposable drainage bottles.\textsuperscript{101} Puri and colleagues used a similar model to compare serial thoracentesis, TPC, bedside pleurodesis, and thoracoscopy pleurodesis.\textsuperscript{102} In their analysis, TPC optimized cost and quality-adjusted life-years assuming 3-month survival, while bedside pleurodesis was preferred based on 12-month survival. Of course, cost should not be the primary consideration when developing a therapeutic management strategy.

Combinations of different therapeutic interventions are now being explored as a means for patients to achieve long-term benefits from pleurodesis while minimizing hospitalization time. Reddy and colleagues treated 30 patients with recurrent symptomatic malignant pleural effusions with combined therapies. Patients underwent thoracoscopic talc poudrage with chest tube insertion and simultaneous TPC insertion.\textsuperscript{103} The chest tube was removed after 24 hours and intermittent drainage was continued via TPC. Patients were discharged once clinically stable and after the chest tube was removed. Using this approach, 92\% had successful pleurodesis and the TPC was able to be removed after a median of 7.5 days. Median hospitalization time was 1.8 days. While there was no control arm in this pilot study, the pleurodesis success rate and length of hospitalization compare favorably to other published studies and it is encouraging that a multimodality approach may allow for improvements in the delivery of patient care.

Pleural adhesions and trapped lung also pose specific dilemmas. Pleural adhesions can create loculations, thereby complicating drainage by thoracentesis or TPC and hindering dispersal of pleurodesis agents. Adhesiolysis by medical thoracoscopy or VATS may be useful in these patients to free up the pleural space and improve efficacy of long-term drainage options or facilitate pleurodesis. Intrapleural administration of fibrinolytics, such as streptokinase and urokinase, have also been used for treatment of loculated effusions.\textsuperscript{104–106} The only prospective, randomized controlled trial using streptokinase with 10 Fr drainage tubes found improvements in the volume of pleural fluid drainage, lung reexpansion, and success of subsequent doxycycline pleurodesis.\textsuperscript{106} However, if lung reexpansion is unable to be restored, TPC remains the long-term therapy of choice.

**SUMMARY**

Malignant pleural effusions represent advanced stage disease and frequently adversely affect a patient’s quality of life. Ideal therapeutic options should effectively palliate symptoms, provide long-term relief, be minimally invasive with few side effects, minimize hospitalization and reliance on medical assistance, and be cost-effective. There are a variety of therapeutic options available to the treating clinician, though there is no single therapy of choice that is universally superior in all circumstances. Initial thoracentesis is important in evaluating whether removal of a large volume of fluid provides significant symptom relief and restores functional status. Both pleurodesis and TPC provide similar control of symptoms. Pleurodesis is associated with greater procedure-related risk and length of hospitalization and is contraindicated in patients with trapped lung, but does not require long-term catheter care or disposable resources. Cost analysis favors TPC over pleurodesis in patients with poor prognosis. Ultimately, however, determination of the appropriate therapeutic management strategy requires careful evaluation of the patient’s clinical situation and informed discussion with the patient to make sure that the treatment plan fits within the context of their goals of medical care.
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