REVIEW ARTICLE

MALIGNANT PLEURAL EFFUSIONS

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INTRODUCTION

Pleural effusions are a common complication of advanced malignancies, and cause dyspnea, chest pain and cough. In most cases they signify incurable disease, with a median survival after diagnosis usually measured in months rather than years. Thus treatment focuses on improving patient symptoms rather than cure. Chest tube insertion and sclerotherapy, i.e. pleurodesis, remains the standard of care in most countries, with the goal of preventing fluid recurrence after removal. However newer therapeutic options, such as pleuroscopy and long-term indwelling pleural catheters, can be performed as outpatients or with a minimal hospital stay, may cause less discomfort to the patient than a standard chest tube or video assisted thorascopic surgery (VATS) pleurodesis, are cost effective, and may allow patients to spend more time away from the hospital with loved ones.

Definitions and Pathophysiology

Pleural effusion in the setting of known malignancy can be either a malignant pleural effusion (MPE), or para-malignant effusion (PME)[1]. An MPE is present when there are malignant cells in the pleural fluid, when there is tumor in the pleura on pleural biopsy, or when visible tumor is present in the pleural space on imaging. When there is a pleural effusion but no malignant cells in the fluid, and no imaging or pathology showing pleural involvement by tumor, it is termed a PME. The distinction is important for staging cancers, prognosis, and treatment. MPE's increase the cancer stage, give the patient a worse prognosis, and may affect treatment decisions. Also, PME's may have another treatable cause besides the cancer (see Figure I).

The pleural space is a potential space between the visceral pleura, which covers the lung, and the parietal pleura, which covers the inside of the chest wall. A thin layer of fluid is present in this space to lubricate the pleural interface. Pleural fluid is created by blood filtration through high pressure systemic blood vessels, and is drained through the parietal pleura via lymphatic openings, that then drain into parietal lymphatic vessels. MPE results either from increased fluid production, or decreased fluid drainage[2]. Increased fluid production occurs either from direct tumor invasion into the pleural space, or via hematogenous cancer spread to the parietal pleura. Local inflammatory changes in response to the tumor cause increased vascular permeability, and increased fluid. Decreased drainage occurs most commonly from cancer spread to mediastinal lymph nodes. Tumors block lymphatic drainage, causing increased pleural fluid. Indeed lung cancer, breast cancer, and lymphoma commonly invade mediastinal lymph nodes, and are thus the most common tumors associated with pleural effusions.

Incidence, Etiology and Outcomes

In a post -mortem autopsy study of 191 patients who died with malignancy, pleural effusion was present in 16% (30)[3]. While any carcinoma can metastasize to the pleura, lung carcinoma is the most common malignancy causing pleural effusions in most studies, with pleural effusions reported to occur in 7-15% of patients with lung cancer[1]. The second most common malignancy causing pleural effusion is breast cancer, though in some series it is the most common[1, 6]. Lymphoma also commonly causes pleural effusions, and is the most common malignancy associated with chylothorax[4]. Other examples of cancers causing pleural effusions are pleural mesothelioma, ovarian cancer, melanoma, renal cell carcinoma, sarcoma, pancreatic cancer, gastric cancer, uterine and cervical cancers, colon cancer, thyroid cancer, head and neck cancers, and adenocarcinoma of unknown primary[1]. In a

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2003 review, 5 studies that included a total of 2040 MPE's were summarized, and the primary tumor site causing MPE was lung cancer in 37.5% (764), breast in 16.8% (343), lymphoma in 11.5% (234), unknown primary in 10.7% (219), GU cancers in 9.4% (191), GI cancers in 6.9% (141), and other cancers in 7.3% (148)[5].
In a study of 60 patients from 1988, median survival from the time of pleural effusion discovery was 3.8 months for gastrointestinal cancers, 5.3 months for lung cancer, 7 months for lymphoma, and 14 months for breast[6]. In a 2000 study of 417 patients, the median survival for patients with malignant pleural effusions of all types was 4 months[7]. Median survival for gastrointestinal cancers was 2.3 months, lung cancer 3.0 months, breast cancer 5.0 months, and lymphoma 9 months . In a 2010 thoracic surgery study of 278 patients undergoing palliative procedures for malignant effusions, median survival post-procedure of all cancers was 7 months[8]. Median survival for adenocarcinoma of unknown primary was 4 months, ovarian cancer 4.3 months, lung cancer 4.5 months, breast cancer 8.5 months, and malignant mesothelioma 9.9 months. In a study of 45 patients with breast cancer who had mastectomy, median survival was 48 months in those where pleural effusion was the only evidence of cancer recurrence, and was 12 months in those with additional metastatic disease outside the pleura[9].

Sahn and Good in 1988 noted that among 60 patients with malignant pleural effusions of all types, median survival was lower in those with a pleural fluid pH less than 7.3[6]. Heffner et al in 2000 looked at 417 patients with malignant pleural effusions of all types to assess the accuracy of pleural fluid pH in predicting patient survival[7]. While those with a pleural fluid pH less than 7.28 had a lower 3 month survival (38.9%) compared with those with a pH greater than 7.28 (61.6%), the pleural fluid pH had insufficient predictive accuracy when used to try to select patients for pleurodesis based on estimated survival. Thus while a lower pleural fluid pH typically portends a shorter survival, it should not be used alone, or in conjunction with tumor type, to select patients who should and should not undergo pleurodesis based on predicted survival.

The poor survival of patients with lung cancer and MPE is reflected in the revised staging classification of lung cancer published in 2007[10]. Since the 6th edition of the TNM classification in 1997, malignancy in the pleural space was a T4 lesion, and patients were staged IIIB. However it was recognized that lung cancer patients with a T4M0 lesion in the setting of an MPE had a survival closer to those patients with metastatic disease to the contralateral hemithorax. Thus in the 2007 guidelines, an MPE is an M1a lesion, making all lung cancer patients with an MPE Stage 4.

Diagnosis

The pleural fluid in a malignant effusion is nearly always an exudate by Light's criteria, which is at least one of the following three fluid characteristics being met; pleural fluid to serum protein ratio > 0.5, pleural fluid to serum lactate dehydrogenase (LDH) ratio > 0.6, and pleural fluid LDH greater than 2/3 the upper limit of normal for serum LDH[11]. Approximately 5% of MPEs are transudative, and while tumor cells are often present, the main cause of the pleural effusion in these cases appears to be from another cause such as congestive heart failure or superior vena cava obstruction[12]. MPE's are often bloody, and indeed malignancy is the most common cause of a bloody effusion. Half of MPE's however do not appear bloody[13].
The most common finding on cell differential is a lymphocytic predominance, but mononuclear and eosinophilic predominance can occur. In a study of 460 effusions, 20% of eosinophilic effusions were malignant, and 20% of non-eosinophilic effusions were malignant[14]. Thus the presence or absence of eosinophilia does not alter the likelihood of malignancy.
Pleural fluid cytology is the easiest way to diagnose MPE Since approximately 50% of pleural effusions in patients with malignancy are from a non malignant cause, accurate diagnosis is the first and most important step to determining if an MPE is present, or a PME. If there are no malignant cells, and no tumor seen in the pleural space on imaging, a search for an alternative cause of the pleural effusion should be sought (see Figure I). When an MPE is diagnosed, it is important to recognize that cancer treatment shifts from curative to palliative. Palliative treatment of MPE has not been shown to prolong cancer survival, but can alleviate symptoms including dyspnea, chest pain, and cough. However mismanagement of MPE

may aggravate symptoms and shorten life. Thus a multidisciplinary team including pulmonologists, oncologists, and thoracic surgeons with demonstrated competencies in their treatment modalities, should be sought.

Initial Treatment Decisions

Asymptomatic MPE's do not need to be treated, and can be observed. If they become symptomatic, several factors help guide management decisions. These include tumor type, patient functional status, ability of the lung to re-expand after fluid removal, patient preference for level of invasiveness, and available management options. Primary tumor cell type should be used in decision making only to the extent of the tumor's responsive to chemotherapy or radiation. Small cell lung cancer, lymphoma, breast cancer, ovarian cancer, and prostate cancer may all respond well to chemotherapy with resolution of the effusion. Clinicians are poor at predicting the duration of survival based on tumor cell type. Thus in patients with minimal symptoms and a treatment responsive tumor, treating the underlying cancer may be a reasonable step at resolving the effusion. If cancer treatment will not resolve the effusion, other clinical factors need to be taken into account.

One of the strongest predictors of survival appears to be the Karnofsky Performance Scale, which ranks people on a percentage scale from 10%, which is moribund with a rapidly progressive disease process, to 100%, which is perfect health. In a prospective study of 85 patients with MPEs, patients with a Karnofsky score > 70 had a median survival of 13.2 months, while patients with a Karnofsky score < 30 had a median survival of 1.1 months[15]. Thus a poor performance score may guide clinicians to less invasive therapies. The ability of the lung to re-expand after fluid removal also impacts treatment decisions. If the lung cannot re-expand with apposition of the visceral and parietal pleura, certain therapies such as pleurodesis will be ineffective. A pneumothorax after pleurodesis is strongly suggestive of a trapped lung, especially if the air is in the same shape as the original fluid, termed an "ex vacuo" pneumothorax[16]. Other findings that predict failure of pleurodesis include extensive intrapleural tumor, multiple pleural loculations, airway obstruction from an endobronchial tumor, and a markedly thickened visceral pleura[17].

A treatment algorithm for managing pleural effusions in patients with known or suspected malignancy is presented in Figure I. The initial step is large volume therapeutic thoracentesis in order to document symptom improvement and the presence or absence of trapped lung. Removal of 1-1.5 L of fluid should be attempted. There is a risk of re-expansion pulmonary edema if more fluid than this is removed, though if pleural manometry is available, more fluid has been safely removed as long as the pleural pressure does not go below -20cm H_2O[18]. Table I lists the various available interventions that can be performed if patients do have symptomatic improvement with fluid removal. The intervention, advantages, and disadvantages are listed. A more detailed discussion of each potential intervention follows.

Serial Thoracentesis

Serial thoracentesis may be an option in patients who carry a poor prognosis with short expected survival, and in those who prefer this option to more invasive measures. Thoracentesis is done as an outpatient on a schedule dictated by the patient's symptom recurrence. For patients considering this option, the physician should have a candid discussion about the potential complications, such as infection, bleeding, and pneumothorax, associated with thoracentesis each time it is performed. For patients with rapid fluid re-accumulation, the number of procedures needed during the patients remaining life can be significant. Thus it is not a good option for patients with rapid re-accumulation and a prognosis measured in months rather than weeks.

Standard Chest Tube With Chemical Pleurodesis

Chest tube thoracostomy with chemical pleurodesis is the most commonly used modality for managing MPEs worldwide. This treatment approach is reserved for patient without trapped lung or loculations. If there are loculations, a standard chest tube can be placed with tPA used to try and lyse the adhesions (Figure I). If this is successful, chemical pleurodesis can then be attempted.

Chest tube thoracostomy is an inpatient procedure that requires an average of 5–7 days in the hospital. Chest tube placement is typically done at the bedside, but can also be done in the minimally invasive procedure unit or in the operating room. The tube is inserted into the pleural space using local anesthesia. Pleurodesis can only be performed after complete pleural fluid evacuation with lung re-expansion, and no evidence of trapped lung. After chest tube placement and drainage, a chest radiograph is obtained to document complete lung re-expansion with apposition of the pleural surfaces. When there is complete lung re-expansion, the sclerosing agent of choice is instilled into the pleural space via the chest tube, typically in a solution of 50 ml of sterile normal saline. Available sclerosing agents include talc, tetracycline, bleomycin, and doxycycline (see below and in Table II)[5]. The sclerosing agent may cause significant discomfort to the patient due to pain and fever. Pre-treatment with intravenous narcotics and oral acetaminophen are recommended, as well as intrapleural lidocaine (Table II). The chest tube is then clamped so that the fluid cannot drain. After 1-2 hours, the chest tube is unclamped and reconnected to wall suction. The chest tube can be removed when the 24 hour output is less than 100-150 ml.

Success rates for pleurodesis vary widely based on study and agent. Complete success is generally considered no return of the pleural effusion by the time of patient death. A partial response is some return of fluid, but not enough to require repeat intervention. In a 2003 British Thoracic Society review on the management of MPE's, success rates (complete and partial) for talc in reviewed studies ranged from 88% to 100% with a mean of 90%[5]. Tetracycline success ranged from 50% to 92% with a mean of 65%. Bleomycin success ranged from 58% to 85% with a mean of 61%. Doxycycline success rates ranged from 65% to 100% with a mean of 76%.

In a 2006 review by Tan et al, 31 randomized controlled trials in patients with MPE were examined to determine whether data supported the use of one sclerosing agent over another when they were directly compared to one another[19]. Talc was associated with a non-significant reduction in recurrence when compared with bleomycin (RR 0.64; 95% confidence interval (CI) 0.34–1.20). Similar results were observed when talc was compared to tetracycline (RR 0.5; 95% CI 0.06-4.42). There was no significant difference when tetracycline or doxycycline were compared to bleomycin (RR 0.92; 95% CI 0.61–1.38). Thus while all agents appear to work, and the results were not significant, there is a trend towards greater success in achieving pleurodesis with the use of talc.

In the same study by Tan et al, 3 RCT with a total of 161 patients were examined to see whether VATS or chest tube instillation of sclerosing agents was superior at achieving pleurodesis. VATS talc intillation, also known as talc poudrage, was associated with a reduction in recurrence (RR 0.21; 95% CI 0.05–0.93) when compared with chest tube instillation, but this was only based on 13 events in 112 patients. In the one RCT that compared VATS to chest tube instillation of tetracycline, there was no difference in recurrence. Thus there is no clear evidence that either VATS or chest tube instillation of sclerosing agents is superior. Other techniques examined in the review such as rolling the patient after instillation of the sclerosing agent, protracted drainage of the effusion, and use of larger bore chest tubes were not found to be associated with any substantial benefits[5]. Radio-labeled talc and tetracycline have been used to see if patient rotation after intrapleural instillation resulted in better pleural distribution of the agent, and there was no greater dispersal with rotation[20, 21]. Thus due to patient discomfort, it is recommended that patient rotation not be done, and patients can sit still while the agent sits in the pleural space. It was felt in the past that larger chest tubes (24-36 French) were better for pleurodesis as there was less chance of tube obstruction. However smaller chest tubes (10-14 French) have had equal success to larger chest tubes in numerous studies[5,19] . Smaller chest tubes cause less discomfort for the patient and should thus be considered. Only one study in the review by Tan et al looked at chest tube duration, with removal of the tube 24 hours after sclerosis, versus waiting until there was no output, and there was no difference in success rates. However, this has not been examined in large studies, and we recommend keeping the tube in until output falls to less than 100 to 150ml in 24 hours.

The most common complications of chemical pleurodesis are fever and pain. Other rare complications include local site infection, empyema, hypotension ranging from mild to severe vasodilatory shock, and a fibrotic granulomatous pleural reaction. Acute respiratory distress syndrome (ARDS), acute pneumonitis, and respiratory failure have also been reported after both talc poudrage and slurry. There has been great variability in the reports of ARDS associated with talc use, and it is now believed that these may be due to difference in the talc used. Small particle talc has been suggested as the culprit of ARDS. This led to a multicentre, prospective study of 558 patients with MPE, published in 2007, and using large particle talc with a mean size of 28.5 microns[22]. In this study, none of the patients developed ARDS. Due to concerns over small particle talc, it was felt to be unethical to compare large and small particle talc. Thus current recommendations are for the use of large particle talc with low if any associated risk for ARDS.

Medical Thoracoscopy (Pleuroscopy)

Medical thoracoscopy (MT), also known as pleuroscopy, is becoming a common procedure performed by pulmonologists and thoracic surgeons around the world for the rapid diagnosis and treatment of malignant and nonmalignant pleural disease. MT is performed with a reusable flexible fiberoptic pleuroscope. The benefits of MT include direct pleural space visualization with biopsy capability, the ability to administer sclerosing agents directly during the procedure, and placement of a chest tube in the same incision used for the pleuroscope.

Pleuroscopy is performed under local anesthesia, with or without conscious sedation, in an endoscopy suite or sterile procedure room. General anesthesia, intubation, and single-lung ventilation, as used in VATS, are not required. The pleuroscope is a semi-rigid instrument with a handle similar to that of a standard flexible fiberoptic bronchoscope. The outer diameter of the shaft is 7.0 mm. The length of the insertion portion is 27 cm, which consists of a proximal rigid portion (22 cm) and a bendable distal end (5 cm). The tip is movable in one plane, much like a flexible bronchoscope. A 2.8-mm single working channel accommodates biopsy forceps and other instruments. The pleuroscope connects to a standard video and light source identical to that of a standard flexible bronchoscope, and the two are interchangeable.

MT is performed using a single-puncture technique. Patients are placed in the lateral decubitus position, with the affected side up. Most patients receive conscious sedation, with appropriate monitoring. Local anesthesia is used, and a small incision is made in the mid-axillary line. An 11-mm trocar is inserted into the pleural space. After some pleural fluid is suctioned away, the pleuroscope is introduced into the pleural cavity, and the lung, diaphragm, and pleural surfaces are inspected. More fluid can be evacuated through the pleuroscope as needed to clear the field for visual inspection. Parietal pleural biopsy specimens are obtained when indicated, and the procedure is followed by instillation of a sclerosing agent, typically a talc poudrage. After the procedure, a 24-Fr standard chest tube is inserted through the trocar. A chest radiograph is obtained to verify chest tube position and evaluate for pneumothorax.

Talc poudrage performed during pleuroscopy has a mean pleurodesis success rate of greater than 90%[23,26]. Various major and minor complications may occur with thoracoscopy, but most are infrequent. The most common complication is pneumothorax, occurring in 8.3% of patients in one study[23]. Other complications in the same study included subcutaneous emphysema (5.3%), fever (3.6%), and pain (1.2%). Major complications such as death, severe sepsis, pulmonary embolism, or hypercapnic coma occurred in 0.6% of patients. One of the larger studies of medical thoracoscopy for MPE was published by Steffen et al who reported their experience with 102 patients who underwent medical thoracoscopy and talc pleurodesis for recurrent MPE[27]. The success rate of pleurodesis at 180 days was 82.6% among 46 surviving patients. The type of primary neoplasm had no significant influence on the success rate. Adverse events included empyema in one case and malignant invasion of the trocar-site scar in another patient.

Video-Assisted Thoracoscopic Surgery

Video-Assisted Thoracoscopic Surgery (VATS) is typically performed by surgeons, and provides better access to the pleural space with a greater number of therapeutic and diagnostic options than MT. It requires general anesthesia and single lung mechanical ventilation. After induction of general anesthesia and intubation with a double lumen endotracheal tube for single lung ventilation, the patient is placed in the

lateral decubitus position with the affected side up. A rigid thoracoscope is placed inferiorly in the mid axillary line at about the 7-8 intercostal space. When the camera is in the pleural space, 2 instrument ports are placed under direct visualization, typically in the anterior and posterior chest, and which allow manipulation of structures within the thorax. Any pleural fluid is suctioned away, and the lung is deflated. A thorough inspection of the pleural cavity can then be performed.

VATS allows biopsy of any structure in the thorax, including the visceral pleura and lung, which cannot be safely biopsied using MT. The instrument ports also allow direct lysis of adhesions, which also cannot be done with MT. In selected patients, VATS can be used for decortication, which is removal of any fibrous coating of the lung. Decortication may allow re-expansion of trapped lung. If lung re-inflation and lysis of any adhesions are successful, sclerotherapy can be performed under direct visualization. The success of pleurodesis with VATS is similar to that with a standard chest tube, with reported success rates greater than 90% with talc poudrage[5]. At the end of the procedure, 2 chest tubes are typically placed, one in the anterior instrument port site and directed apically, and one in the inferior thoracoscope port lying posterior. Mortality rates for VATS range in studies from 0 to 9%[28]. Complications vary based on the indication for the procedure, manipulations performed, type of anesthesia, equipment used, and experience of the operator. However known complications include bleeding, empyema, wound infection, prolonged air leak, tumor seeding at the entry site, and death[28].

Tunneled Pleural Catheter

Tunneled pleural catheters (TPCs) are flexible small-bore chest tubes that are placed in the pleural space and are left in place as outpatients. Intermittent drainage by the patient relieves dyspnea and other symptoms caused by MPEs, and spontaneous pleurodesis occurs frequently. By far the most common TPC in use is manufactured by Care Fusion, San Diego, California USA. It is manufactured under the name PleurX, and consists of a 66 cm, 15.5 Fr silicone rubber catheter. The catheter can be inserted in an outpatient setting with local anesthesia. An ultrasound is used to visualize the pleural effusion in the mid axillary line. The catheter is tunneled a short distance under the patients skin, with the posterior portion of the catheter positioned in the pleural space, and the anterior portion external to the patient. The end of the catheter in the pleural space has fenestrations along 24 cm of the tube to aid in fluid drainage. Midway along the tunneled portion of the catheter is a polyester cuff that helps prevent infection, and incites a granulomatous reaction that holds the catheter in place. The anterior portion has a one way valve that prevents fluid drainage. The entire procedure can be done in 15-20 minutes, and afterwards patients are discharged home.

The MPE is drained by attaching vacuum bottles provided by the company to the valve on the external portion of the tube. Kits provided by the company include all sterile equipment needed to attach the bottles to the tube for drainage. An instructional video helps patients and family members learn how to perform drainage themselves in an outpatient setting. Though often assisted by a family member, patients can often perform the drainage themselves or with the help of a visiting nurse. Drainage is typically done every other day, but studies of daily drainage are under way due to recent case reports that suggest daily drainage of all the fluid in the pleural space may result in earlier and more frequent pleurodesis[29]. Drainage takes approximately 10–15 min. When the pleural fluid output drops to less than 50 ml on three consecutive drainages, pleurodesis is assumed, and after pleural effusion resolution is confirmed with a chest radiograph, the pleural catheter may be removed in an outpatient setting.

TPC's were approved by the US Food and Drug Administration in 1997. A well conducted review from 2011 included pooled data from all published studies that used TPCs in the management of MPEs and reported the outcomes[30]. The review identified 19 unique studies (meaning patient data were not duplicated in multiple studies). All were consecutive case series, except for one randomized controlled trial by Putnam et al published in 1999[31].

A total of 1370 patients were included in the analysis, 1348 of which had an MPE[30]. Most patients had recurrent pleural effusions that had failed thoracentesis or pleurodesis, and many had trapped lung or

were not good surgical candidates. In the 1,236 patients who had reports on cancer type, lung cancer was present in 33.5%, breast cancer in 25.9%, and mesothelioma in 10.5%. A variety of malignancies compromised the remaining patients. Survival varied from 3 to 1240 days, with a mean of 87 days. Catheter permanence times varied from 2 to 434 days, with a mean of 51 days.

While the studies reported improvement in a variety of ways, there was symptomatic improvement in 95.6% of patients. Spontaneous pleurodesis occurred in 45.6% of patients (430/943 patients where data were available) with an average time to pleurodesis of 52 days. Reported complications varied between studies, but were relatively uncommon. Bleeding occurred in 0.4%, tract metastasis in 0.8%, empyema in 2.8%, pain beyond post procedure in 3.2%, cellulitis in 3.4%, and catheter obstruction in 3.7%. Other rare complications included catheter dislocation, catheter malfunction, and pneumothorax requiring a standard chest tube. The catheter was removed due to complications in 8.5%. In ten studies that included a total of 591 patients, there were no reported complications in 87.5% of patients (517).

Putnam et al in 1999 published the only randomized trial to date comparing pleurodesis to TPC for the management of MPE[31]. The study included 144 patients with symptomatic MPE randomized to either TPC or intrapleural doxycycline via tube thoracostomy. Equivalent safety and efficacy were shown, and there was no difference in median survival. Similar improvements were seen in quality of life scores, but the TPC group had a trend toward greater improvement in dyspnea after exercise at 1–3 months. The median hospitalization time was 1 day for pleural catheter patients, compared with 6.5 days for sclerotherapy patients. Spontaneous pleurodesis developed in 46% of pleural catheter patients (median 29 days, range 8–223 days), whereas pleurodesis occurred in 54% of sclerotherapy patients. A subsequent single center cost analysis by Putnam et al looked at 100 consecutive TPC patients (60 outpatients, 40 inpatients), and 68 consecutive inpatients treated with tube thoracostomy and pleurodesis[32]. Hospital charges were obtained from date of tube insertion (either TPC or thoracostomy tube) through the 7th day. They found significantly ($P = 0.001$) lower hospital charges for outpatients who received pleural catheters (mean charge: US \$3,339 $\pm$ 1753), compared with inpatients who received pleural catheters (mean charge: US \$11,188 $\pm$ 7964) and inpatients treated with tube thoracostomy and pleurodesis (mean charge: US \$7,830 $\pm$ 4497).

The experience with pleural catheters continues to grow and appears promising. Advantages of pleural catheters include cost-effectiveness, outpatient control of the effusion, a minimally invasive approach, and user-friendly technology. While pleurodesis may occur spontaneously, chemical pleurodesis remains an option with pleural catheters, and any of the sclerosing agents listed previously can be instilled in a pleural catheter. In addition, pleural catheters could potentially be used in the future to administer anticancer agents and novel therapies for the treatment of pleural metastases.

Pleuroperitoneal shunts

The pleuroperitoneal shunt for managing MPEs has gradually fallen out of favor at most centers. Pleuroperitoneal shunts are typically tunneled beneath the skin, with one end in the plural space, and one end in the peritoneal cavity. At the mid-portion of the tunneled tube is a pump that the patient operates to move fluid from the pleural space to the peritoneal cavity. The shunts have been, and at some centers still are, used to treat patients who cannot achieve successful pleurodesis because of trapped lung, in those who have failed chemical pleurodesis, or for patients who cannot undergo surgery. The pleuroperitoneal shunt may be particularly beneficial in refractory chylothorax, as it allows the recirculation of chyle.

The pleuroperitoneal shunt is safe and effective when performed at experienced centers. Genc et al at the Royal Brompton Hospital in London UK, reported their experience with 160 patients (141 with available follow-up data) that had a pleuroperitoneal shunt inserted[33]. The most commons malignancies in decreasing frequency were breast, mesothelioma, lung cancer, and adenocarcinoma of unknown primary. Effective palliation was achieved in 95% of patients. Hospital mortality occurred in 1.87% (3/160). The median survival was 7.7 months after shunt insertion. Shunt complications were reported in 21 (14.8%), with occlusion occurring in 12, and shunt infection or erosion requiring removal in 8.

Sclerosing Agent	Dose and preparation*
Talc (slurry or poudrage)	5 grams sterilized talc powder, asbestos free, and particle size controlled (large particle talc) dissolved in 50 ml normal saline.
Tetracycline	1 to 1.5 grams dissolved in 50 ml normal saline
Bleomycin	60 Units in 50 ml normal saline
Doxycycline	0.5 grams (500 mg) dissolved in 50 ml normal saline

Table I- Available sclerosing agents and doses[18].
* It is recommended to give lidocaine 3mg/kg intrapleurally immediately before administering any of these sclerosing agents into the pleural space.

Options	Advantages	Disadvantages
Serial therapeutic thoracentesis	- Good option of patients with a short life expectancy due to other co-morbidities/poor functional status. - Prompt symptom relief. - No indwelling catheters or tubes, and does not require hospitalization.	- Often rapid re-accumulation. - Repeated procedures with associate increased risk of complications (bleeding, infection, pneumothorax) - Multiple hospital visits. - Often reduced quality of life as symptoms progressively recur until next procedure.
Standard chest tube with chemical pleurodesis	- Highly effective (pleurodesis in 81-93%)	- Generally requires 5-7 day hospitalization. - Invasive. - Sclerosing agent can be quite painful. - Expensive.
Medical thoracoscopy (MT)	- Highly effective (pleurodesis in > 90%) - Diagnosis and pleurodesis can be performed at the same time. - Does not require general anesthesia (as in VATS).	- Invasive inpatient procedure. - Cannot safely lyse adhesions, biopsy the lung or visceral pleura, or relieve trapped lung.
Video assisted thoracoscopic surgery (VATS)	- Highly effective (pleurodesis in > 90%) - Diagnosis and pleurodesis can be performed at the same time. - Can lyse adhesions and potentially relieve trapped lung.	- Invasive inpatient procedure. - Requires general anesthesia with single lung ventilation. - Patients typically with 2 chest tubes post procedure.
Chronic indwelling pleural catheters	- Good option for motivated patients. - Outpatient catheter placement with local anesthesia (minimally invasive). - Outpatient drainage daily or every other day with associated dyspnea control. - Pleurodesis without chemicals in approximately 50% of patients. - Can be used in those with trapped lung for symptom palliation. - Catheter can be used to administer intrapleural chemotherapies. - Cost effective.	- Family member or visiting nurse typically required to assist with home drainage. - Catheter site infections infrequently. - Lower pleurodesis rate compared with chemical pleurodesis with chest tube or MT/VATS. - Daily or every other day drainage required. - Effort associated with catheter care.
Pleuroperitoneal shunts	- Can be an option at experienced centers for those who fail chemical pleurodesis or who have trapped lung. - Can recirculate chyle in those with chylothorax.	- Shunt malfunction - Limited availability due to lack of expertise in placing the shunts. - Infection. - Requires frequent pumping by the patient.

Table II- Management options for symptomatic malignant pleural effusions (MPE).

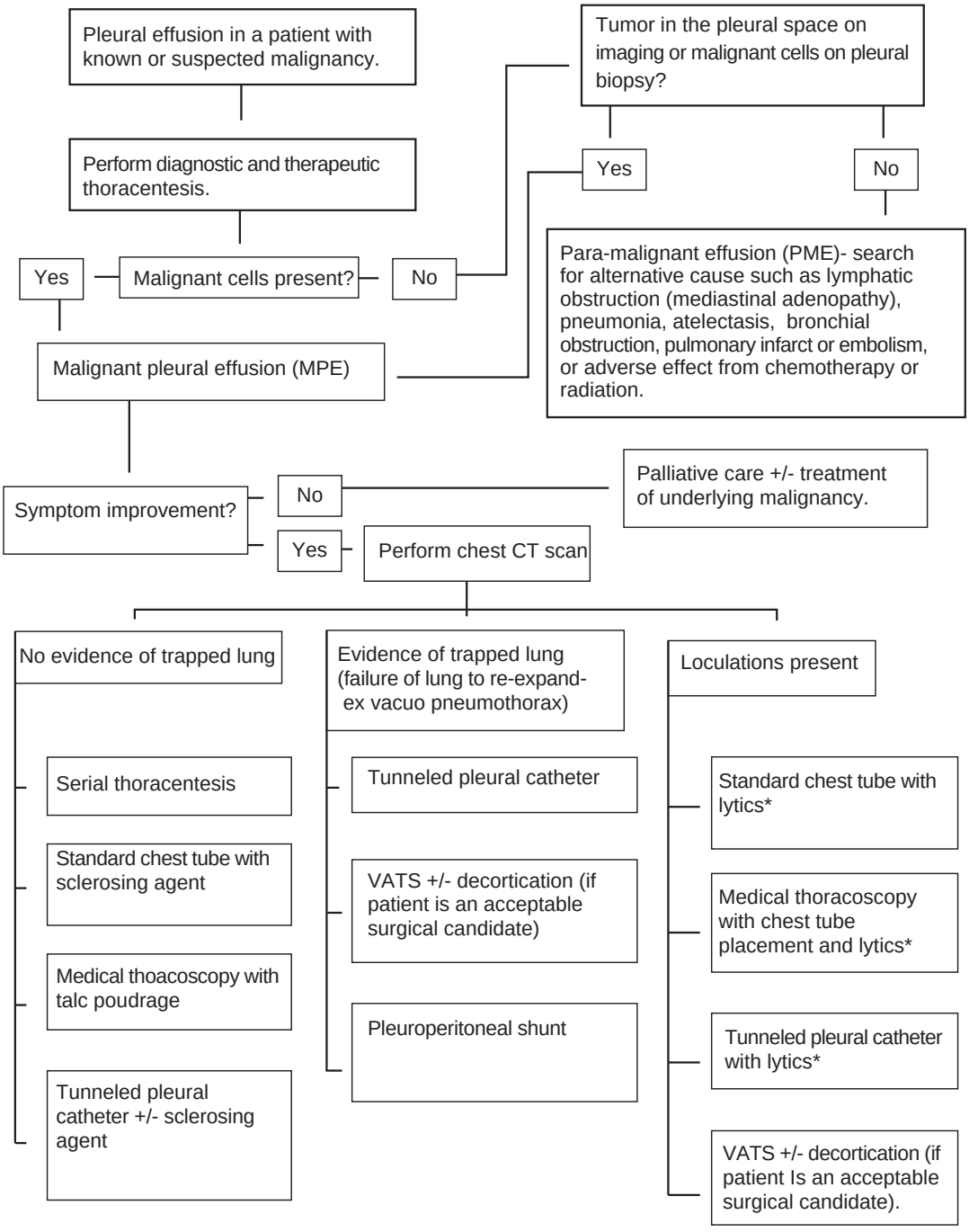

Figure I- Treatment algorithm for pleural fluid evaluation in a patient with known or suspected malignancy. Specific treatment options with advantages and disadvantages are listed in Table 1 and discussed in the text.

*Tissue plasminogen activator (tPA) is commonly used. A standard dose is 10 mg mixed with 50ml normal saline, and instilled into the chest tube, which is then clamped for 2 hours. The tube is then unclamped and the fluid allowed to drain into a pleurovac. This is repeated twice a day for 3 days. Imaging is then repeated to determine if the adhesions have been successfully lysed. If successful, sclerotherapy may then be attempted (see Table 2 and section 'Standard chest tube and chemical pleurodesis').

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