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REVIEW

Management of Malignant Pleural Effusions

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ABSTRACT

Malignant pleural effusions are a common clinical problem in patients with primary thoracic malignancy and metastatic malignancy to the thorax. Symptoms can be debilitating and can impair tolerance of anticancer therapy. This article presents a comprehensive review of pharmaceutical and nonpharmaceutical approaches to the management of malignant pleural effusion, and a novel algorithm for management based on patients' performance status.

Keywords: lung cancer; management; pleural effusion; pleurodesis; pleuroscopy; thoracentesis

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INTRODUCTION

With an estimated annual incidence of 150,000 to 175,000 cases per year in the US and 40,000 per year in the UK,[1,2] malignant pleural effusions (MPEs) are a common clinical problem in the setting of cancer. The presence of malignant cells in the pleural fluid is often indicative of advanced disease associated with high morbidity and mortality and precludes the possibility of a curative treatment approach.[2] In many parts of the world, chest tube thoracostomy with subsequent chemical pleurodesis remain standard management of this protracted and often devastating condition. This option is less than optimal given the associated morbidity. Modalities such as pleuroscopy with sclerotherapy and the increasing use of long-term indwelling pleural catheters have shown to be efficacious, cost effective, and patient friendly,[3-5] and may indicate a paradigm shift in the management of this debilitating condition. In this paper we review the current evidence for the available management options for MPE and present an algorithm to aid clinical decision making as to the most appropriate modality.

Etiology

Almost any cancer can produce an MPE. The most common etiologies of MPE are lung cancer in men and breast carcinoma in women, with these two malignancies accounting for approximately 75% of all MPEs.[6,7] Other malignancies associated with MPE include lymphoma, ovarian cancer, gastrointestinal cancer, and mesothelioma in the order of decreasing frequency with about 7% occurring in the setting of an unknown primary cancer.[6,7] Pleural effusions presenting in the setting of an underlying cancer that fail to demonstrate evidence of malignancy in the fluid and pleural surface are described as paramalignant pleural effusions. These effusions may be secondary to local or systemic tumor effects, cancer therapy complications, or concurrent nonmalignant disease.[7]

Pathogenesis

Pleural malignancies may arise from tumor emboli to the visceral pleura[5] or direct extension from neighboring structures and hematogenous metastasis to parietal pleural,[5,7] (Figure 1), but the exact mechanism of malignant pleural fluid accumulation is not entirely understood. The mere presence of pleural metastasis does not appear to be sufficient for its pathogenesis. In fact, only about 60% of patients with proven pleural metastases develop pleural effusions.[8,9] A diagram highlighting the different mechanisms of impaired transpleural flow that can result in the accumulation of pleural fluid in the setting of malignancy is presented in Figure 2.

Many hypotheses exist regarding the pathogenesis of MPE in cancer. Indeed, the accumulation of excess pleural fluid associated with cancer may be the result of a number of separate factors in an individual patient.[9] Postmortem studies have demonstrated a strong relationship between carcinomatous infiltration of the mediastinal lymph nodes and the occurrence of pleural effusion.[8,10] This finding suggests an important role of the impaired lymphatic drainage in the pathogenesis of MPE. However, if this was to be the only mechanism, one would expect MPEs to be transudative, but instead, the majority of these effusions are exudates.[9] There is also some evidence that the upregulation of vascular endothelial growth factor (VEGF) may play a significant role in the pathogenesis of MPEs.[11,12]

Figure 1. Pleural involvement in malignancy.

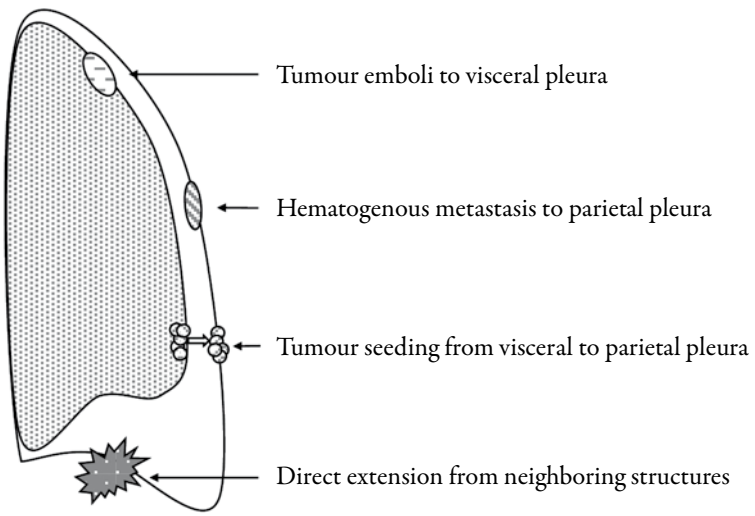
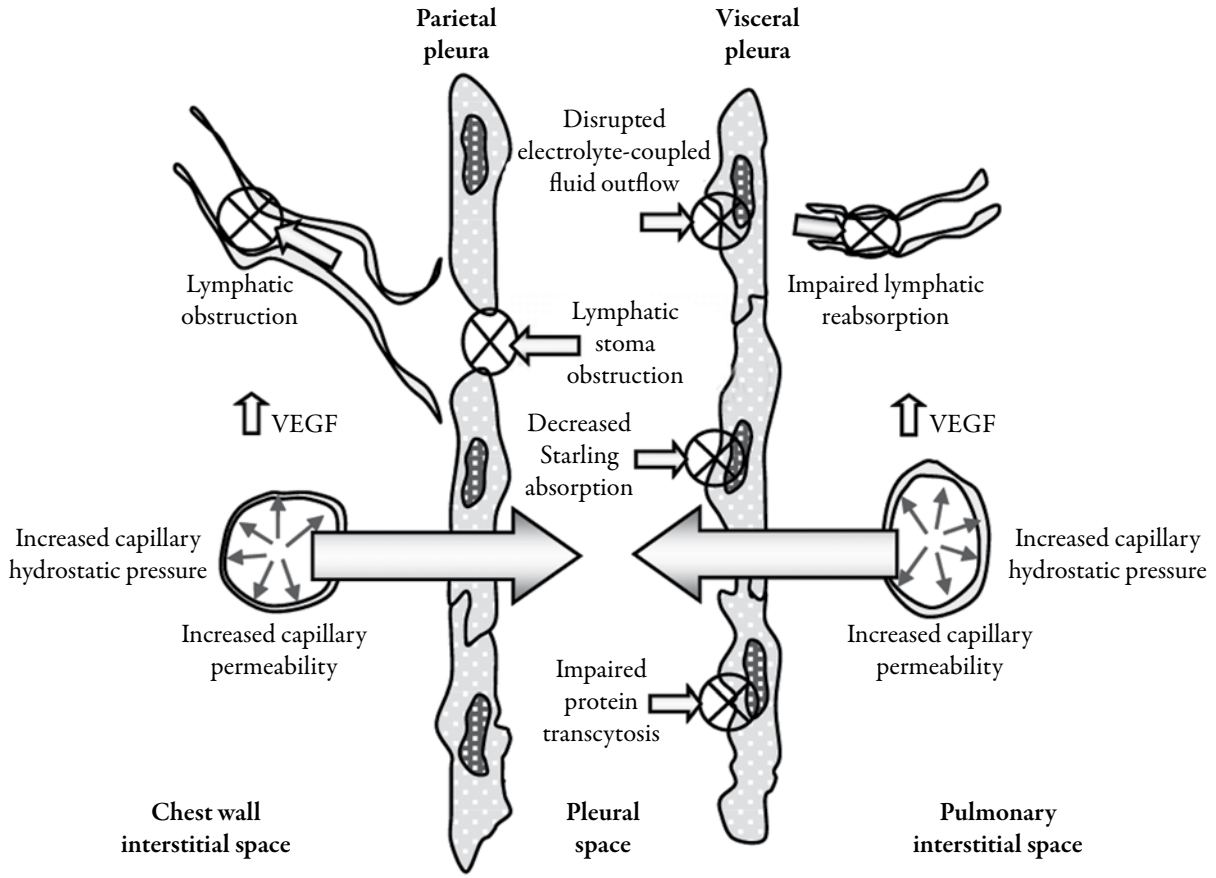


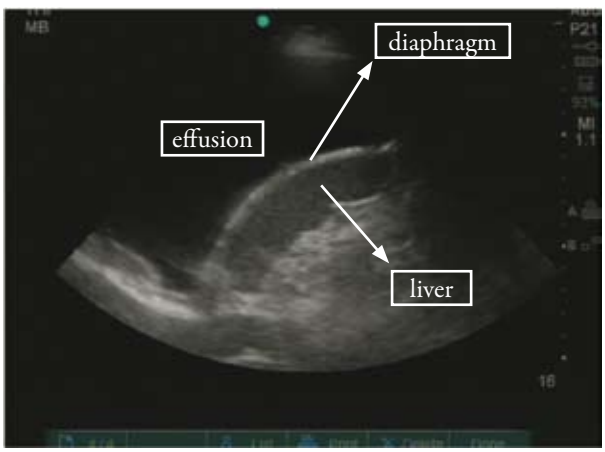
Figure 2. Mechanisms of impaired transpleural flow that can result in the accumulation of pleural fluid in the setting of malignancy. VEGF, vascular endothelial growth factor.



Diagnosis

Typically, patients present with progressive exertional dyspnea.[5] Cough and chest pain may also be troubling symptoms. However, some patients may have no respiratory symptoms at the time a pleural effusion is noted on an imaging study. The history and physical examination should be carried out in the same manner as in the evaluation of any other pleural effusion. Posteroanterior and lateral chest radiographs should be obtained in all patients with suspected pleural effusion. Lateral decubitus radiograph may be necessary when the presence and/or volume of the effusion are in doubt. However, because other conditions may be confused with a pleural effusion on x-rays, other imaging studies may be necessary, such as ultrasound (Figure 3) or computed tomography

Figure 3. A 73-year old female with non-small cell lung cancer (NSCLC). Transthoracic ultrasound image displays a right-sided malignant pleural effusion.



(CT).[5] Ultrasound is in fact more sensitive than radiography and can detect as little as 5 mL of pleural fluid and is superior to CT for characterization of collections for the presence of septations and loculations.[13] Once the presence of a clinically significant pleural effusion has been established, a diagnostic thoracentesis is indicated. Since a significant portion of patients with MPE are dyspneic, a therapeutic thoracentesis is almost always performed at the same time. A large volume thoracentesis is also important to establish if fluid drainage will lead to symptom(s) improvement. In this case, if or when the pleural effusion recurs, one of the more definitive therapeutic options that will be discussed below should be considered. In patients with a known underlying malignancy, it is our practice not only to obtain the usual tests to differentiate a transudate from an exudate (total protein and lactate dehydrogenase both in the fluid and in the serum) but also to obtain total and differential cell count, glucose level, cholesterol and triglycerides, cytological analysis, hematocrit (if fluid is grossly bloody), and cultures. It is important to keep in mind that 2% to 5% of MPEs are transudates.[14,15] The yield of cytological examination in establishing a diagnosis of cancer is quite variable (62% to 90%) and a second thoracentesis may be considered depending on the availability of thorascopy.[2] Its sensitivity may be as low as 10% for effusions due to mesothelioma and over 70% for metastatic adenocarcinomas.[13] Recent data suggests that at least 50 mL of pleural fluid should be studied in order to provide optimal cytological analysis.[16,17] If lymphoma is suspected, flow cytometry should also be performed.[5] Pleural fluid mesothelin measurement, where available, appears to be a promising tumor marker in the diagnosis of mesothelioma-related pleural effusions.[18] However, other tumor marker measurements are not indicated at this time. If pleural fluid analysis is negative for malignancy, thoracoscopy should be the next procedure of choice among patients in whom cancer is suspected;[2,5,13] its sensitivity for pleural malignancy is generally >90%.[2,19,20]

Prognosis

Despite recent advances in cancer therapy, the prognosis of patients with MPE remains poor. The median survival after a malignant effusion diagnosis is between 4 and 9 months.[21]

THERAPEUTIC OPTIONS FOR MPE

Deciding on therapeutic options for MPE should take into account the etiology, prognosis, symptoms, and the patients' overall performance status. Although MPE secondary to breast cancer, small cell lung carcinoma, and lymphoma may respond to systemic chemotherapy and radiation,[2] most malignant effusions also require local palliative therapy. The local treatment options include frequent thoracentesis, placement of nontunneled or tunneled drainage catheters, tube thoracostomy or thoracoscopic pleurodesis, pleuroperitoneal shunting, pleurectomy, and decortication (Table 1).

A flow diagram for the different management options for MPE developed and used in our institution is given in Figure 4.

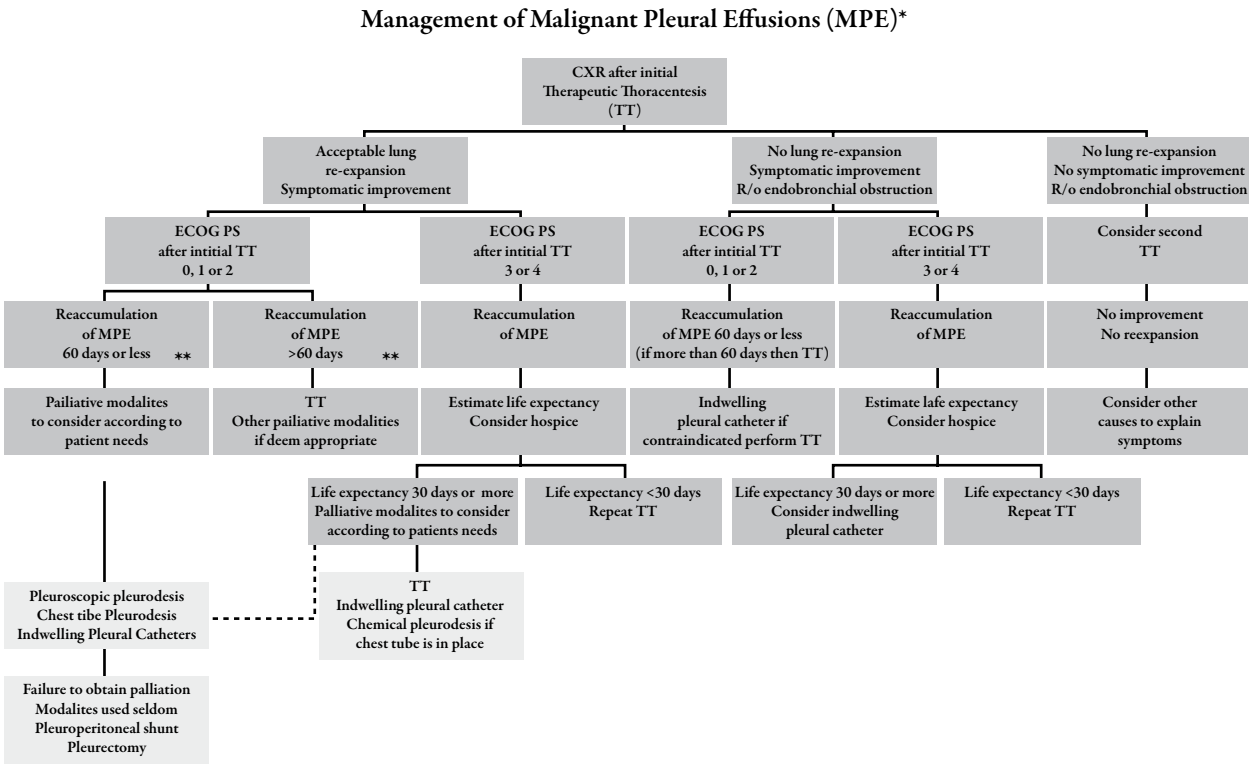
Therapeutic Thoracentesis

Thoracentesis is typically the first step in the management of a newly diagnosed pleural effusion. As discussed previously, the initial thoracentesis usually has a diagnostic and therapeutic role and can segregate patients into responders, where repeated fluid evacuation may be a therapeutic option and nonresponders, where due to coexisting morbidities or the presence of non re-expandable lung the

Table 1. Treatment options for malignant pleural effusions (MPEs).

	Repeated thoracentesis	Indwelling catheter	Tube plus slurry	Thoracoscopy plus poudrage
Morbidity	+	+	++	+++
Prolonged effect	-	+++	+++	+++
Inpatient stay	-	-	++	++
Continuous outpatient care	+	+++	-	-
Repeat intervention required	+++	+	+	+
Cost per procedure	+	++	++++	++++

Figure 4. Algorithm for the management of malignant pleural effusions (MPEs) based on patient's performance status. Lighter grey boxes represent virtual multimodality evaluation. *Patients with chemoradiosensitive tumors on initial treatment (lymphoma, breast cancer, small cell lung cancer, germ cell, ovarian, prostate, and thyroid neoplasms) could obtain palliation with therapeutic thoracentesis while waiting on systemic treatment results. **The 60-day time point for reaccumulation is our institution's cut-off and based on unpublished data. CXR=chest x-ray; ECOG PS=Eastern European Cooperative Oncology Group Performance Status; r/o=rule out; TT=therapeutic thoracentesis.



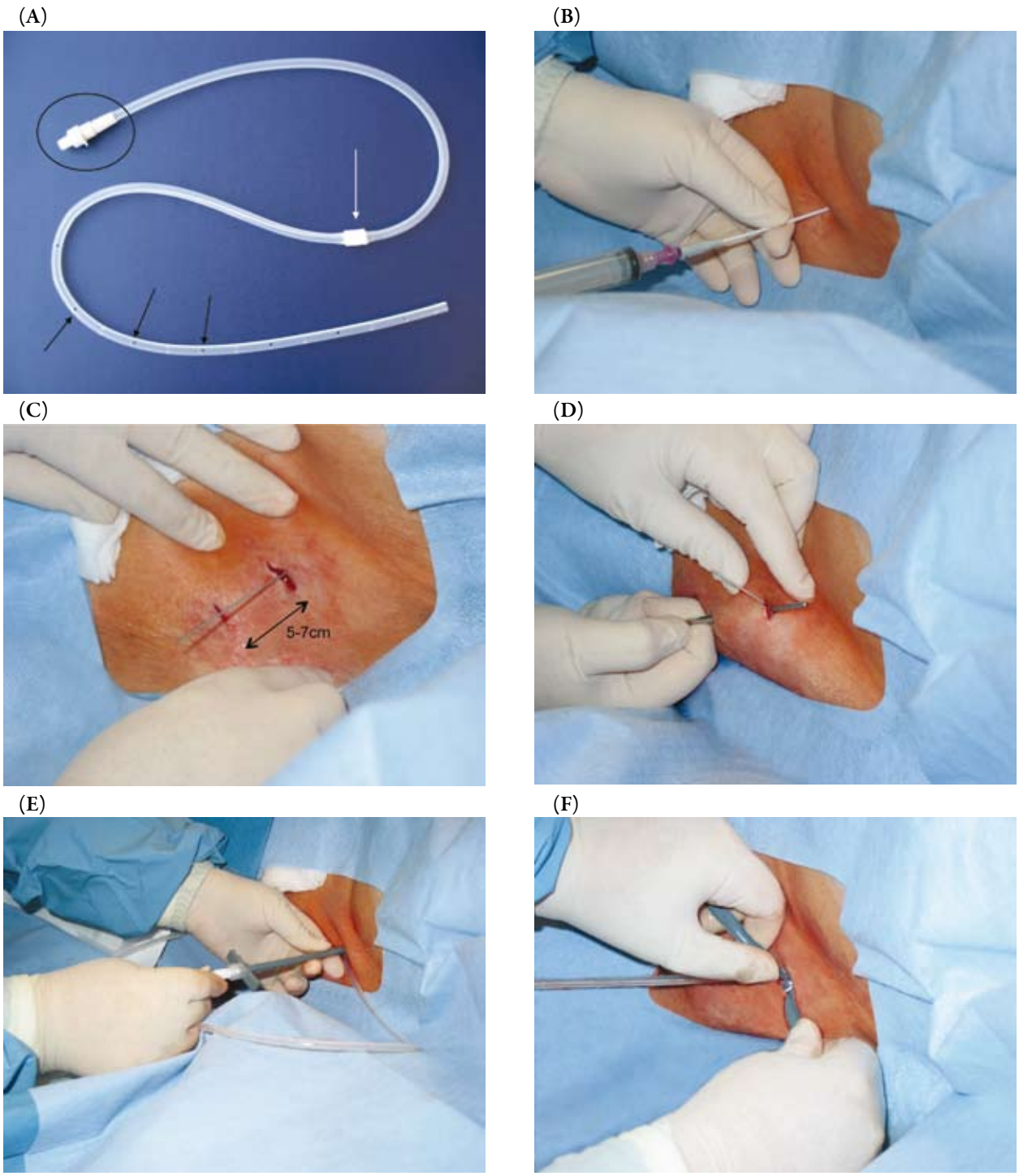
removal of fluid does not have significant impact on symptoms and additional procedures may have a limited role. In patients who are unable to undergo invasive procedures or who have advanced disease with <30 days to live, repeated thoracentesis along with opiods to palliate dyspnea may be an option especially as it can be performed on an outpatient basis avoiding prolonged hospitalizations. The optimal amount of fluid that should be removed remains controversial, with the consensus statement by the American Thoracic

Society and the European Respiratory Society recommending not more than 1.0-1.5 L of fluid to be slowly evacuated in one sitting and that drainage should be discontinued if the patient develops symptoms of dyspnea, cough, or chest discomfort.[22] However, in recent studies the risk of re-expansion pulmonary edema was shown to be unrelated to the amount drained, and it has been suggested that no upper limit is necessary.[23] In our experience, patients with radiographic evidence of contralateral mediastinal shift from large pleural effusions may safely tolerate the removal of 2.0-2.5 L of fluid in one sitting as long as there are no procedure-related symptoms of chest pain, cough, or dyspnea. However, large volume pleural fluid drainage during a single procedure should be approached cautiously, especially when radiological studies reveal a centered or ipsilaterally shifted mediastinum.[5] Ultrasound-directed thoracentesis is increasingly being accepted as the standard of care and we routinely use ultrasound for all our diagnostic and therapeutic pleural procedures. A recent meta-analysis shows reduced pneumothorax rates with the use of real-time ultrasound guidance.[24] Other complications related to thoracentesis include vasovagal reactions, cough, chest pain, and hemothorax. Pneumothorax can result from an accidental disruption of the visceral pleura, from the introduction of air along the needle/catheter tract, or due to the presence of nonre-expanding lung.[5] If the patient remains symptomatic despite adequate re-expansion, causes such as lymphangitic spread, pulmonary embolism, or malignant airway obstruction should be suspected and investigated appropriately. In nearly all patients the fluid reaccumulates within 30 days of thoracentesis.[25] Therefore, for patients with limited life expectancies, poor performance status, or those in whom pleural fluid reaccumulation is slow, repeated therapeutic thoracentesis is a viable option. Frequent repeated thoracenteses may trigger fluid loculation by inducing local cytokines and fibrin, which can make further thoracenteses difficult, and can also complicate future modes of palliation.[5]

Indwelling Tunneled Pleural Catheter

The US Food and Drug Administration approved the use of the only commercially available indwelling tunneled pleural catheter (IPC [Pleurx; Denver Biomedical, Golden, CO, USA]) in 1997. Ever since, several studies have demonstrated its safety and efficacy in the treatment of MPEs.[26-29] The IPC placement with intermittent outpatient drainage is our preferred method of treatment for the majority of patients with recurrent MPEs. The IPC is a 15.5 Fr silicone catheter and 66 cm in length (Figure 5A). It has fenestrations at its distal 24 cm. A safety valve at its proximal end prevents passage of air or fluid through the catheter unless the matched drainage line is attached. The IPC has a polyester cuff situated 14 cm from the proximal end and lies within the subcutaneous tract (tunnel). This cuff anchors the catheter in position and it is believed to form a barrier to infection.[26] Placement is simple and is generally performed on an outpatient basis with local anesthesia. The IPC is generally placed at the anterior or mid axillary line. Once the pleural fluid is identified with a "finder" needle, a soft tipped guidewire is inserted through this needle into the pleural space and the needle is removed (Figure 5B,C). Two separate small incisions (0.5-2.0 cm) are made, one at the site of the guidewire and one approximately 5-7 cm inferiorly (Figure 5C). A trocar attached to the distal end of the IPC guides the catheter and creates a subcutaneous tunnel starting at the inferior incision (Figure 5D). Once the IPC comes out of the superior incision, the polyester cuff is placed within 1 cm of the inferior

Figure 5. Indwelling pleural catheter. (**A**) Indwelling tunneled pleural catheter (IPC) with its fenestrations (black arrows), safety valve (in circle), and polyester cuff (white arrow). (**B**) A syringe attached to the "finder" needle is used to identify the pleural fluid. (**C**) Soft tipped guide wire in place after removal of the finder needle and the two separate small incisions (0.5-2.0 cm) to create the subcutaneous tunnel. (**D**) Trocar attached to the distal end of the IPC, creating the subcutaneous tunnel starting at the inferior incision. (**E**) Dilator with a peel-away sheath being placed over the guide wire using a modified Seldinger technique. (**F**) IPC introducer being peeled away.



incision. The trocar is removed and a dilator with a peel-away sheath is placed over the guidewire using a modified Seldinger technique (Figure 5E). The dilator and wire are removed and the IPC is threaded through the peel-away introducer into the pleural space (Figure 5F). The introducer is then removed and the incisions are sutured. Initial drainage is performed immediately after the procedure, and then subsequently the IPC is drained using a dedicated vacuum bottle on a daily basis or every other day.

We favor this modality of treatment for the majority of our patients because of its minimally invasive outpatient approach. It is less onerous for patients with poor performance status and rarely interferes with ongoing active cancer treatments. Pleurodesis has been reported to occur in 40% to 70% of patients, and it may occur in as little as 7 days.[22,28,30] Tremblay and Michaud[28] reported their experience of 250 IPCs. Lack of symptom control occurred in <4% of patients. Complication rates were relatively low. Infection was reported in <5% of cases and symptomatic loculations in 8%. Using the same database, they reported that in patients that could otherwise tolerate other pleurodesis modalities, such as talc slurry or poudrage, 70% achieved pleurodesis with the IPC.[30] In Warren et al.'s retrospective analysis of 231 IPCs placed,[29] the incidence of infection was only 2%, and pleurodesis was achieved in about 54% of cases. A recent retrospective cohort of 311 patients with MPEs treated with IPC demonstrated that pleurodesis was an independent predictor of survival.[31] Whether IPC induced pleurodesis or pleurodesis per se (independent of treatment modality) is responsible for this finding is unclear. Unfortunately, no randomized controlled studies have been performed to compare IPC and talc pleurodesis, which remains the preferred method of treatment of MPEs by many. Some have attempted the injection of sclerosing agents through the IPC such as bleomycin or doxycycline, but no studies on the use of sclerosing agents with IPC have been reported. Our limited experience has demonstrated that the instillation of talc through the IPC already in place is limited by frequent clogging of the catheter. Talc poudrage followed by the placement of IPC instead of tube thoracostomy has not been studied. A recent phase 1 study on the administration of interferon (IFN) beta through IPC for mesothelioma has shown promising results.[32] The IPC has also been shown to be successful for the treatment of trapped lung in the setting of MPE[33] and refractory chylothorax[34] situations in which alternative options are limited. In terms of cost, Putnam et al.[27] reported in 2000 a hospital charge advantage of IPC treatment for outpatients vs. tube thoracostomy and pleurodesis (US $3391±1753 vs. $7830±4497, respectively). However, when hospital charges were evaluated from insertion date until death or last follow-up the difference was not statistically significant (US $21,161±32,617 vs. $32,252±56,682, respectively). Based on current evidence, IPC is clearly a valuable option for the management of MPE.

Chest Tube Thoracostomy

The therapy most widely used for pleurodesis in the palliation of MPE is inpatient tube thoracostomy. A variety of chest tubes can be used for thoracostomy ranging traditionally from a 28-32 Fr,[2] and with emerging data, the use of small bore catheters such as a 14 Fr plastic catheter have proven to be successful.[35,36] The procedure is usually performed at the bedside under local anesthesia with or without conscious sedation and cardiopulmonary monitoring. The patients generally require an inpatient stay averaging 5-7 days. Pleurodesis is attempted after a chest

x-ray can confirm complete lung re-expansion and the absence of trapped lung. Premedication with narcotic analgesics or conscious sedation or both are often administered to reduce the pain and discomfort associated with the instillation of most sclerosing agents, and lidocaine may be administered intrapleurally as a local anesthetic prior to the sclerosant. The sclerosing agent of choice is instilled into the pleural space via the chest tube, typically in a solution of 50-100 mL of sterile saline. The chest tube is then clamped for 1-2 hours. The tube is then reconnected to –20 cm H_2O suction until the 24-hour output is less than 150 mL at which point it can be removed. In the meta-analysis by Tan et al.[37] techniques such as rolling the patient after instillation of the sclerosing agent, protracted drainage of >24 hours and use of larger bore chest tubes were not associated with any substantial advantages.

Medical Thoracoscopy or Video-Assisted Thoracic Surgery (VATS)

Medical thoracoscopy (pleuroscopy) refers to a minimally invasive procedure which allows the pulmonologist to examine the pleural space in a spontaneously breathing patient with local anesthesia and under conscious sedation.[38] It typically involves the insertion of a rigid or semirigid pleuroscope through a single port into the pleural space (although more ports may be used depending on the indication and complexity of pleural disease), evacuation of pleural fluid, biopsy of parietal pleural lesions if indicated, and insufflation of sclerosant into the pleural space. The procedure is safe and well tolerated. Complications include subcutaneous emphysema, fever, and pain. Major complications such as severe sepsis, pulmonary embolism, massive bleeding, and shock are infrequent[38] and death is extremely rare as a direct complication of the procedure.[39]

VATS is performed in an operating room almost exclusively under general anesthesia with a double lumen endotracheal tube allowing for single lung ventilation. Multiple ports of entry are usually used allowing for better visualization of the entire parietal and visceral pleurae and better manipulation of the lung to perform biopsies, lobectomies, and pneumonectomies if necessary. Depending on the type of sclerosant used and expected outcomes, response rates of 60% to 100% have been recorded for chemical pleurodesis via pleuroscopy and VATS.[38]

Both VATS and pleuroscopy can be performed under local or regional anesthesia in an awake or moderately sedated patient or under general anesthesia with one or two lung ventilations.[40] Local anesthesia in the form of intercostal nerve blocks performed at the level of the incision and two interspaces above and below provide adequate procedural analgesia. Both paravertebral blocks with a single dose of local anesthetics[41] and thoracic epidural anesthesia[42] have been shown to provide adequate intraoperative anesthesia with the added advantage of postoperative analgesia. Noteworthy is that in an awake or moderately sedated patient it is recommended that a high FiO^2 is delivered via a facemask to overcome the shunt due to the loss in lung volume caused by the unavoidable pneumothorax. If VATS is planned to involve a more invasive or prolonged procedure on the lung parenchyma than lung biopsies or lobectomy, general anesthesia with one lung ventilation using double lumen tube or bronchial blockers is a more appropriate choice.[40]

Sclerosing Agents and Their Mode of Delivery

Pleurodesis may be performed at the bedside using chest thoracostomy or thoracoscopically

with pleuroscopy or VATS. The aim is to incite chemical or mechanical irritation between pleural layers resulting in inflammation and fibrin deposition, which subsequently results in pleural symphysis, preventing the reaccumulation of fluid. A variety of agents have been used as sclerosants for chemical pleurodesis, some intended to cause an inflammatory response and others that are supposed to act as chemotherapeutic agents as well. This area remains controversial with regards to the sclerosing agent of choice and its method of administration. Sterile asbestos-free talc is readily available and relatively inexpensive. It can be instilled into the pleural space via chest tube as a suspension with sterile saline–talc slurry (TS) or insufflated over the pleural surfaces during thoracoscopy–therapeutic talc insufflation (TTI), or poudrage. Talc consistently appears to be the most effective agent. A 2004 Cochrane review[43] compared the relative efficacy of different sclerosing agents. Based on 10 studies with 308 patients who had pleurodesis for MPEs, it was concluded that talc as slurry or poudrage was the sclerosant of choice with a relative risk (RR) of nonrecurrence of 1.34 (95% CI: 1.16, 1.55) in favor of talc compared with bleomycin, tetracycline, mustine, or tube drainage alone. In the more recent meta-analysis by Tan et al.[37] talc was compared with other agents in nine studies that included 341 patients. A modest reduction in recurrence was found when talc was compared with bleomycin (RR, 0.64; 95% CI: 0.34, 1.20). Similar results were observed when talc was compared with tetracycline (RR, 0.50; 95% CI: 0.06, 4.42).

The main advantages of TTI are that it allows for complete fluid evacuation with visualization, adhesion lysis when indicated, and more even talc distribution during insufflations.[38] Based on the results of two small randomized controlled trials,[44,45] a preference for TTI "poudrage" over TS "slurry" was demonstrated; however, subsequent to these studies, Dresler et al.[46] concluded from their large randomized study with 501 patients that there was no difference in freedom from radiographic recurrence of MPE between the two methods of talc delivery (TTI, 78%; TS, 71%) within 30 days. Respiratory complications were greater with TTI in this study, although symptoms of excess fatigue and pain were noted among recipients of TS. Ad hoc subgroup analysis revealed that patients with primary lung or breast cancer had a higher success rate with TTI (82%) than with talc slurry (67%). Our practice is to consider clinically suitable patients with good performance status (Eastern Cooperative Oncology Group [ECOG] 0-2) who achieve symptomatic relief with lung re-expansion after initial thoracentesis, for pleurodesis with TTI as the preferred modality of talc administration.[5]

The most common complications of chemical pleurodesis are fever and pain. Other rare complications include local site infection, empyema, arrhythmias, cardiac arrest, myocardial infarction, and hypotension.[2] The incidence of respiratory complications including acute respiratory distress syndrome (ARDS) associated with talc pleurodesis varies.[47,48] The exact mechanism whereby talc induces acute lung injury is still not fully understood, however it is hypothesized that this toxicity may result from the systemic absorption of small diameter talc particles (size <15 microns) used in ungraded or mixed talc preparations through the parietal pleural pores, generating a systemic inflammatory response.[49] This hypothesis is given credence by the observation that most cases of ARDS after talc use are reported in the US, where talc particles have the smallest mean diameter, and by a recent European multicenter prospective study of 558 patients with MPE, none of whom developed ARDS after receiving large-particle talc pleurodesis (mean size 24.4 microns).[50]

Despite being the most studied, most readily available, and most cost-effective agent there are doubts about talc being the most efficacious agent and its added safety concerns demand the continued search for an ideal sclerosing agent. Animal studies have demonstrated that transforming growth factor (TGF-B) induces pleurodesis by stimulating the mesothelial cells to produce collagen. This type of pleurodesis is more efficacious compared to that induced by talc, doxycycline, or bleomycin, it occurs faster and since it does not require pleural surface "chemical injury" the inflammatory indices in the pleural fluid after the intrapleural administration of TGF-B are much lower than those after doxycycline or talc.[51,52] A recent study[53] demonstrated a significantly higher effective rate of pleurodesis with intracavitary injections of recombinant adenovirus p53 agent with cisplatin compared with the control group of cisplatin alone over a 4-week period. The treatment group also had a significantly higher quality of life and there were no significant side effects associated with the regimen. Based on the principle that bacterial infection of the pleural space can induce pleurodesis by inflammation, a recent report[54] postulated that therapeutically administered lipoteichoic acid T (LTA-T) from the bacterial cell wall might produce a similar effect and achieve control of MPEs. In this phase 1 study involving 13 patients with MPEs, a therapeutic dose range of LTA-T with mild toxicity was established and there was preliminary evidence of pleurodesis efficacy suggesting a role for this agent in the future.

Thoracoscopic mechanical pleurodesis is achieved by mechanical pleural abrasion of parietal and visceral pleura to induce petechial bleeding resulting in a diffuse inflammatory response. In a series of malignant effusions from breast cancer,[55] mechanical pleurodesis demonstrated similar success rates compared to talc slurry.

Pleuroperitoneal Shunts

Pleuroperitoneal shunts transfer pleural fluid from the pleural space into the peritoneal cavity when manually pumped[56,57] These shunts have a niche in the palliation of chylous effusions refractory to pleurodesis and have been used in the management of patients who cannot achieve successful pleurodesis because of nonre-expandable lung or for patients who cannot undergo surgery. The procedure is safe and effective in the hands of experienced operators, with palliation achieved in 80% to 90% of properly selected patients. However the use of these shunts has declined over time due to the high incidence of shunt blockage due to clotting reported in up to 25%,[56] infected shunts, and quality of life issues as the shunts can be burdensome on the patients due to frequent manual pumping.

Surgery

Major surgical procedures for the management of MPE such as parietal pleurectomy, decortication, or pleuropneumonectomy are associated with high mortality rates. Surgery should be reserved for patients with prolonged life expectancy, significant symptoms, and who either failed other treatments such as pleurodesis or are not suitable for such treatments (complicated effusion with multiple loculations).

Algorithm for the Management of MPE Based on Patients' Performance Status

An algorithm for the management options for MPE that we use at our institution is presented in Figure 4. This algorithm takes

into account aspects of both cancer type and response to treatment and the patient's overall clinical status.[58] A thorough clinical history and exam, information regarding prior thoracenteses including the volume of fluid evacuated, lung re-expansion, symptom relief, and interval between repeated taps is pertinent and helps guide further therapy.

CONCLUSION

MPE is an indicator of advanced disease and carries a poor prognosis especially in the setting of lung cancer. A palliative rather than a curative approach is often needed and significant importance should be given to factors such as response to thoracentesis and lung re-expansion, the patient's life expectancy, and performance status. Social factors, personal preferences, and the availability of specific treatment modalities also impacts the therapeutic options and help tailor a management plan. In clinically suitable patients, pleurodesis with asbestos-free graded large particle talc, preferably via thoracoscopic poudrage or the use of chronic IPC offer efficacious, cost-effective, and minimally invasive options for the management of MPE. Both the use of novel compounds to block VEGF and the use of gene therapy either alone or in combination with other palliative modalities is promising.

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REFERENCES

1. Marel M, Zrustova M, Stasny B, et al. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. Chest. 1993;104:1486-1489.
2. Antony VB, Loddenkemper R, Astoul P, et al. Management of malignant pleural effusions. Am J Respir Crit Care Med. 2000;162:1987-2001.
3. Putnam JB Jr, Walsh GL, Swisher SG, et al. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. Ann Thorac Surg. 2000;69:369-375.
4. Rodriguez-Panadero F, Janssen JP, Astoul P. Thoracoscopy: general overview and place in the diagnosis and management of pleural effusion. Eur Respir J. 2006;28:409-422.
5. Shannon VR, Eapen GA, Jimenez CA, et al. Respiratory complications. In: Kufe DW, Blast Jr RC, Hait WN, et al., eds. Cancer Medicine 7. 7th edition. Philadelphia, PA, USA: BC Decker Inc; 2006:2150-2173.
6. Sahn SA. Malignancy metastatic to the pleura. Clin Chest Med. 1998;19:351-361.
7. Sahn SA. Pleural diseases related to metastatic malignancies. Eur Respir J. 1997;10:1907-1901.
8. Meyer PC. Metastatic carcinoma of the pleura. Thorax. 1966;21;437-443.
9. Light RW, Hamm H. Malignant pleural effusion: would the real cause please stand up? Eur Respir J. 1997;10:1701-1702.
10. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med. 1977;63:695-702.
11. Zebrowski BK, Yano S, Liu W, et al. Vascular endothelial growth factor levels and induction of permeability in malignant pleural effusions. Clin Cancer Res. 1999;5:3364-3368.
12. Yeh HH, Lai WW, Chen HH, et al. Autocrine IL-6-induced Stat3 activation contributes to the pathogenesis of lung adenocarcinoma and malignant pleural effusion Oncogene. 2006;25:4300-4309.
13. Heffner JE, Klein JS, Hampson C. Diagnostic utility and clinical application of imaging for pleural space infections. Chest. 2010;137:467-479.
14. Porcel JM, Alvarez M, Salud A, Vives M. Should a cytologic study be ordered in transudative pleural effusions? Chest. 1999;116:1836-1837.
15. Ashchi M, Golish J, Eng P, O'Donovan P. Transudative malignant pleural effusions:

prevalence and mechanisms. South Med J. 1998;91:23-26.

16. Abouzgheib W, Bartter T, Dagher H, Pratter M, Klump W. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. Chest. 2009;135:999-1001.

17. Swiderek J, Morcos S, Donthireddy V, et al. Prospective study to determine the volume of pleural fluid required to diagnose malignancy. Chest. 2010;137:68-73.

18. Davies HE, Sadler RS, Bielsa S, et al. Clinical impact and reliability of pleural fluid mesothelin in undiagnosed pleural effusions. Am J Respir Crit Care Med. 2009;180:437-444.

19. Menzies R, Charbonneau M. Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med. 1991;114:271-277.

20. Ferrer J, Roldán J, Teixidor J, Pallisa E, Gich I, Morell F. Predictors of pleural malignancy in patients with pleural effusion undergoing thoracoscopy. Chest. 2005;127:1017-1022.

21. Bielsa S, Martin-Juan J, Porcel JM, Rodriguez-Panadero F. Diagnostic and prognostic implications of pleural adhesions in malignant effusions. J Thorac Oncol. 2008;3:1251-1256.

22. Jones PW, Moyers JP, Rogers JT Ultrasound-guided thoracentesis: is it a safer method? Chest. 2003;123:418-423.

23. Feller-Kopman D, Berkowitz D, Boiselle P, Ernst A. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. Ann Thorac Surg. 2007;84:1656-1661.

24. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW. Pneumothorax following thoracentesis: a systematic review and meta-analysis. Arch Intern Med. 2010;170:332-339.

25. Neragi-Miandoab S. Malignant pleural effusion, current and evolving approaches for its diagnosis and management. Lung Cancer. 2006;54:1-9.

26. Musani A, Haas A, Seijo L, Wilby M, Sterman D. Outpatient management of malignant pleural effusions with small-bore, tunneled pleural catheters. Respiration. 2004;71:559-566.

27. Putnam JB, Walsh GL, Swisher SG, et al. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. Ann Thorac Surg. 2000;69:369-375.

28. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest. 2006;129:362-368.

29. Warren WH, Kalimi R, Khodadadian LM, Kim AW. Management of malignant pleural effusions using the Pleur(x) catheter. Ann Thorac Surg. 2008;85:1049-1055.

30. Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. Eur Respir J. 2007;30:759-762.

31. Jimenez CA, Ozcakar B, Morice RC, et al. Pleurodesis after intrapleural catheter insertion is an independent factor for overall survival in patients with malignant pleural effusions. Eur Respir J. 2009;34(Suppl. 53):299.

32. Sterman DH, Recio A, Carroll RG, et al. A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. Clin Cancer Res. 2007;13:4456-4466.

33. Pien GW, Gant MJ, Washam CL, Sterman DH. Use of an implantable pleural catheter for trapped lung syndrome in patients with malignant pleural effusion. Chest. 2001;119:1641-1646.

34. Jimenez CA, Mhatre AD, Martinez CH, Eapen GA, Onn A, Morice RC. Management of recurrent chylothorax in patients with cancer. Chest. 2007;132:1584-1590.

35. Sartori S, Tombesi P, Tassinari D, et al. Sonographically guided small-bore chest tubes and sonographic monitoring for rapid sclerotherapy of recurrent malignant pleural effusions. J Ultrasound Med. 2004;23:1171-1176.

36. Spiegler PA, Hurewitz AN, Groth ML. Rapid pleurodesis for malignant pleural effusions. Chest. 2003;123:1895-1898.

37. Tan C, Sedrakyan A, Browne J, et al. The evidence on the effectiveness of management for malignant pleural effusion: a systematic review. Eur J Cardio-Thorac Surg. 2006;29:829-838.

38. Casal RF, Eapen GA, Morice RC, Jimenez CA. Medical thoracoscopy. Curr Opin Pulm Med. 2009;15:313-320.

39. Viskum K, Enk B. Complications of thoracoscopy. Poumon Coeur. 1981;37:25-28.

40. Wilson WC, Benumof JL. Anesthesia for thoracic surgery. In: Miller RD, Eriksson LI et al., eds. Miller's Anesthesia. 7th edition. Morristown, NJ, USA: Churchill Livingstone; 2009:chapter 49.

41. Hill SE, Keller RA, Stafford-Smith M, et al. Efficacy of single-dose, multilevel paravertebral nerve blockade for analgesia after thoracoscopic procedures. Anesthesiology. 2006;104:1047-1053.

42. Pompeo E. Awake operative videothoracoscopic pulmonary resections. Thorac Surg Clin. 2008;18:311-320.

43. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev. 2004;(1):CD002916.

44. Yim AP, Chan AT, Lee TW, Wan IY, Ho JK. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg. 1996;62:1655-1658.

45. Manes N, Rodriguez-Panadero F, Bravo JL, Hernandez H, Alix A. Talc pleurodesis. Prospective and randomised study. Clinical follow-up. Chest. 2000;118:131.

46. Dresler CM, Olak J, Herndon JE 2nd, et al. Phase III intergroup study of talc poudrage vs. talc slurry sclerosis for malignant pleural effusion. Chest. 2005;127:909-915.

47. Campos JR, Werebe EC, Vargas FS, Jatene FB, Light RW. Respiratory failure due to insufflated talc. Lancet. 1997;349:251-252.

48. Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. Am J Surg. 1999;177:437-440.

49. Maskell NA, Lee YCG, Gleeson FV, et al. Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med. 2004;170:377-382.

50. Julius PJ, Gareth C, Phillippe A, et al. Safety of pleurodesis with talc poudarage in malignant pleural effusion: a prospective cohort study. Lancet. 2007;369:1535-1539.

51. Light RW, Cheng D-S, Lee YC, et al. A single intrapleural injection of transforming growth factor-2 produces excellent pleurodesis in rabbits. Am J Respir Crit Care Med. 2000;162:98-104.

52. Lee YCG, Teixeira LR, Devin CJ, et al. Transforming growth factor-beta(2) induces pleurodesis significantly faster than talc. Am J Respir Crit Care Med. 2001;163:640-644.

53. Dong M, Li X, Hong LJ, et al. Advanced malignant pleural or peritoneal effusion in patients treated with recombinant adenovirus p53 injection plus cisplatin. J Int Med Res. 2008;36:1273-1278.

54. Rahman NM, Davies HE, Salzberg M, et al. Use of lipoteichoic acid-T for pleurodesis in malignant pleural effusion: a phase I toxicity and dose-escalation study. Lancet Oncol. 2008;9:946-952.

55. Crnjac A, Sok M , Kamenik M. Impact of pleural effusion pH on the efficacy of thoracoscopic mechanical pleurodesis in patients with breast carcinoma Eur J Cardiothorac Surg. 2004;26:432-436.

56. Reich H, Beattie EJ, Harvey JC. Pleuroperitoneal shunt for malignant pleural effusions: a one-year experience. Semin Surg Oncol. 1993;9:160-162.

57. Lee KA, Harvey JC, Reich H, et al. Management of malignant pleural effusions with pleuroperitoneal shunting. J Am Coll Surg. 1994;178:586-588.

58. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest. 2000;117:73-78.