

# Malignant Pleural Effusions: Appropriate Treatment Approaches

## *Malign Plevral Effüzyonlar: Uygun Tedavi Yaklaşımları*

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### Abstract

Malignant pleural effusion (MPE) is a common and important clinical condition. A complication in many types of tumors, its presence indicates the onset of the terminal stages of cancer. Dyspnea is the most common symptom of MPE. The most common underlying tumors are lymphomas and cancers of the lung, breast and ovaries, which account for 75% of cases. The diagnosis of MPE can be established by the presence of malignant cells in the pleural fluid or tissue. Median survival in these patients ranges from 3 to 12 months, with the shortest survival period presenting in lung cancer patients. The aim of MPE therapeutic approaches should be effective treatment and a short hospital stay. There are many different treatment options for patients who suffer from MPE, including serial thoracentesis, tube thoracostomy, pleurodesis, long term pleural catheter, pleuroperitoneal shunt, decortication, chemotherapy and radiotherapy. The choice of therapy is determined based on a patient's clinical situation as well as the underlying disease. Today, intercostal tube insertion and chemical pleurodesis are the most commonly prescribed treatment modalities.

**Keywords:** Malignant pleural effusions, Diagnosis, Treatment

### Özet

*Malign plevral effüzyon (MPE) sık görülen ve önemli bir klinik durumdur. Kanser hastalarında terminal dönemin bir göstergesidir. En sık semptom dispnedir. Etiyolojide en sık akciğer kanseri, meme kanseri, lenfoma ve over kanseri yer almakta olup tüm MPE olgularının %75'ini oluşturur. MPE tanısı plevral mayide veya plevra dokusunda malign hücreler görüldüğünde konulabilir. Bu hastalarda ortalama yaşam beklentisi 3-12 ay arasında değişmekte olup en az yaşam beklentisi olan akciğer kanserli hastalardır. Terapotik yaklaşımda amaç etkili tedavi ve kısa hastane yatış süresi olmalıdır. Seri torasentez, tüp torakostomi, plörodez, kalıcı plevral kateter, plöroperitoneal şant, dekortikasyon, kemoterapi ve radyoterapi gibi farklı tedavi modaliteleri kullanılmakta olup, tedavi seçeneği hastanın klinik durumunu ve alta hastalığa bağlı olarak değişmektedir. Günümüzde en sık kullanılan tedavi seçeneği göğüs tüpü yerleştirilmesi ve kimyasal plörodezdır.*

**Anahtar Kelimeler:** Malign plevral effüzyon, Teşhis, Tedavi

## Introduction

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**P**leural effusions that are due to malignancy are either malignant pleural effusions (MPE) or paramalignant pleural effusions (PMPE). MPEs are diagnosed by the presence of malignant cells in the pleural fluid or tissue. In the case of PMPE, there is a malignant focus in the body, but no evidence of pleural invasion or the presence of malignant cells in the pleural fluid or tissue [1]. Any organ's cancer can metastasize to the pleura and result in effusion. Today, the exudative type of pleural effusion is mostly secondary to malignancy. Even though there have been no epidemiologic studies, it is estimated that, in the United States, the incidence of MPE is approximately greater than 175,000 cases per year [2,3]. In postmortem studies, MPE is found in 15% of patients [4].

In this study, we aim to review MPEs, one of the most common clinical situations that doctors face, including their clinical presentation, diagnosis, and available treatment modalities according to data presented in the literature.

## Etiology

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Approximately 35% of MPE cases are secondary to lung cancer [5]. At the time of diagnosis, 15% of lung cancer patients have pleural effusions, and over time, this rate increases to 50% [6]. In most cases, the MPE is of the paramalignant effusion type. Adenocarcinoma is the most common lung cancer type causing MPE. Small cell lung cancer rarely results in MPE [7].

Breast cancer is the second most common cause of MPE, with 23% of cases resulting in the development of the complication [5]. In a study evaluating 2,147 cases, Lee [8] reported that 50% of breast cancer patients have different degrees of invasion. Banarjee et al. [9] showed that, in breast cancer patients, 70% of effusions occur on the same side of the cancer, 20% contralaterally and 10% bilaterally.

Lymphomas are responsible for 10% of MPE cases. In Hodgkin's lymphoma, effusion can be seen during the late stages disease progression, while in non-Hodgkin's lymphoma, effusion can be seen as early as the time of diagnosis [10].

Interestingly, MPE rarely results from gynecologic, gastrointestinal and genitourinary tract cancers. The primary origin of cancer that underlies MPE cannot be determined in 12% of cases [5].

## Pathophysiology

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MPE means that there are malignant cells in pleural space. MPE can result from 3 methods of metastasis [11]:

1) The direct invasion of pleura with malignant cells by neighboring organs like the lung, breast, and chest wall.

2) The spread of visceral pleura by the embolization of malignant cells, with invasion of the pulmonary vascular system

3) The spread of parietal pleura by the hematogenous spread of distant organ metastasis.

The presence of malignant cells in the intrapleural space lying through parietal pleura can occlude lymphatic orifices and, consequently, disrupt the drainage of intrapleural fluid. Malignant cells also enable ongoing effusion by stimulating the release of chemokines, which increases the permeability of vascular and pleural membranes.

In PMPE, there are no malignant cells in the pleural space. Tumoral invasion of mediastinal lymph nodes, bronchial obstruction, pulmonary embolization, radiochemotherapy, vena cava superior syndrome and decrease in oncotic pressure could cause PMPE [12].

Angiogenesis is an important factor in the development of MPE by enabling new capillary formation at the parietal pleura. Angiopoietin and its receptor Tie2 enable MPE by stimulating tumor angiogenesis. Vascular endothelial growing factor (VEGF) plays a key role in the development of MPE by enabling endothelial cell maturation [13].

## Diagnosis

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### Symptoms and Findings:

The most important clinical finding in MPE patients is varying degrees of respiratory stress. The degree of dyspnea depends on both the volume of effusion and the relationship of the lung and pleura to each other. together. Another important finding is chest pain due to the invasion of cells into the parietal pleura, ribs and chest wall. Chest pain is very severe in mesothelioma patients with same side effusion. Interestingly, chest pain usually does not present in MPEs that are secondary to adenocarcinomas. Hemoptysis can be seen in bronchial carcinoma patients. Pneumothorax can be seen in MPEs secondary to sarcoma metastases. Fever is rarely observed. Weight loss, malaise, anorexia, nausea and emesis, which can be seen in malignant patients, are generally present. Other clinical situations are cachexia and lymphadenopathy due to cancer [2,14].

During physical examination intercostal distinctions are present, such as dullness with percussion and a decrease of respiratory sounds. Pleural friction rub can be heard in massive effusions. There are no symptoms in 15% of patients [15].

### Radiology:

The amount of effusion ranges between 500-2000 ml in 75% of MPE cases. In 10% of MPE cases, massive effusion can be observed. Bilateral pleural effusion is due to malignancy in 50% of cases if there is no sign of cardiomegaly [1]. Effusions that range from 200-300 ml can cause costophrenic angle opacification at anteroposterior chest x-ray. Even 100 ml of pleural fluid can be seen in a lateral decubit x-ray. Effusions that cannot be visualized by x-ray can be detected by computerized tomography. Mediastinal lymph nodes and parenchymal pathologies, which may enable pleural effusion, can also be detected. Ultrasonography (USG) is also helpful in cases with low amounts of fluid and for guiding thoracentesis. In 50% of cases, the amount of effusion is less than 500 ml cc. In these cases, the use of USG is

most appropriate [1]. In general, MRI and PET are not used to diagnose MPEs. However, they do give important clues regarding malignant pleural mesothelioma [16].

**Diagnostic Thoracentesis:**

The first step in the histopathological diagnosis of MPE is obtainment of pleural fluid via thoracentesis. Effusions can be blurry, yellowish or have a serohemorrhagic character. Effusions should be analyzed to identify the etiology. Cytological examinations are positive in 40-80% of MPE cases [15,17].

For the diagnosis of MPE, the presence of malignant cells in the pleural fluid or tissue should be demonstrated by histological or cytological means. In 95% of malignant effusions, there appears to be an exudative characteristic [18].

It is estimated that the rate of diagnosis increases with repeated thoracentesis. Within the first thoracentesis, the success rate of cytological diagnosis is 65%. The 2nd thoracentesis adds 27% to the success rate, while the 3rd thoracentesis only adds 5%. Importantly, an increase in the volume of cytological material does not affect the diagnostic rate [11].

The level of glucose in the pleural fluid is similar to that of plasma. In cases of high concentration of malignancy in the pleural space, the level of glucose is usually lower than 60 mg/dl [19]. This situation is explained by the diminution of glucose passage from the blood to the pleura and by the consumption of glucose by tumoral tissues. Thus, low glucose level is a poor prognostic factor [20].

The pH level of pleural fluid is lower than 7.3 in 1/3 of MPE cases [2,21]. As seen in cases with low glucose levels, cytological positivity is high. Similarly, low pH level is a poor prognostic factor, and the response to pleurodesis is not good [19,21]. On the other hand, other authors don't find a significant correlation between low pH and survival or the success of pleurodesis [22-24].

The level of amylase is increased in 10% of MPE cases. Adenocancer is mostly found in these patients [16].

Immunohistochemical studies are helpful in the differential diagnosis of adenocarcinoma and mesothelioma. Metastatic adenocancers generally stain with Anti-CEA, Anti-Leu M1 and Musin, but reactive or mesothelial cells do not. Also, immunohistochemical tests help in the diagnosis of pleural fluid that originated from lymphomas [25].

A high level of tumor marker in the pleural fluid does not help diagnosis in the diagnosis of MPE. The CEA level is estimated to be greater than 10 ng/ml in 30-40% of MPE cases [25]. Moreover, cytological positivity is seen in most patients with high levels of CEA.

In addition, chromosomal analysis of pleural effusions that result from lymphomas or leukemias could be helpful in the diagnosis of MPE [26].

**Closed Pleural Biopsy:**

In addition to thoracentesis, pleural biopsies can further contribute to the diagnosis of MPE. However, it is important for the exclusion or diagnosis of tuberculosis pleuritis in areas where tuberculosis is endemic [27]. A pleural biopsy should be performed after the first negative thoracentesis. If the pleural biopsy is negative within the second cytology, then with high probability, a se-

cond pleural biopsy will not give a positive result [1]. The success rate is 40-75% in blind percutaneous pleural biopsies [2,28,29]. Additionally the pleural biopsy diagnosis rate is approximately 7-12% when the pleural fluid cytology is negative [27,30].

**Thoracoscopy:**

Today thoracoscopy is the gold standard in the diagnosis of unknown etiology and undiagnosed pleural fluids [31]. Medical thoracoscopy should be planned if thoracoscopy is going to be done in patients who cannot tolerate single lung ventilation. In contrast with surgical thoracoscopy, non-disposable rigid instruments can be used with local anesthesia or low sedation in medical thoracoscopy, which is much cheaper and less invasive. Technically, it is similar to the insertion of a chest tube. Additionally, a biopsy can be taken from the pleural areas of the chest wall, diaphragm, mediastinum, lung and pleural cavity, which can be visualized. Medical thoracoscopy is primarily a diagnostic procedure [2]. Within medical thoracoscopy, a tumor is much more easily established by taking a biopsy from the metastatic pleural disease under direct observation. Higher positive results can be observed by examining the morphological classification of lymphomas and the hormonal receptors of breast cancer [10,32,33]. Pleurodesis can be done during thoracoscopy. Therefore, thoracoscopy is a procedure that is used for both the treatment and diagnosis of MPE.

Thoracoscopy has a diagnostic success rate of 90% for pleural effusions that are secondary to malignancy and tuberculosis [34]. The pleural cytology diagnosis rate and the percutaneous pleural biopsy rate was 66% and 46%, respectively. Both procedures together had a 73% diagnostic rate in a study involving 500 MPE patients [35]. Boutin et al. [32] performed pleural biopsies and took samples for cytological examination in all patients one day before thoracoscopy. The pleural biopsy and cytology diagnosis rates were 41%, whereas VATS had an 87% diagnosis rate.

The experience of the thoracoscopist and adherence preventing the reach of neoplastic tissue are important reasons for the lack of tumoral tissue biopsy material, which results in false negative/false-negative reports. Adhesions are generally a result of repeated serial thoracentesis [31, 32].

**Treatment**

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Therapeutic approaches to MPE cases depend on the age, histology of the primary tumor, response to cancer therapy and the survival expectancy. In most MPE patients, disease is not curable and the aim is palliative. The short-term aim is to relieve dyspnea. In the long term, the obliteration of pleural space to prevent the recollection of pleural fluid should be the main aim. There are many methods of palliative care including systemic cancer therapy, thoracentesis, tube thoracostomy, pleurodesis with a sclerosant agent, insertion of a pleural catheter, pleuroperitoneal shunt and pleurectomy. In a small number of patients, there is a balance between the formation and absorption of pleural fluid so that dyspnea doesn't occur and observation is enough [2,15].

### Therapeutic Thoracentesis:

Thoracentesis is preferred for the treatment of MPE when other treatment modalities are not used and in patients with low survival expectancy. The primary disadvantage of thoracentesis is the recollection of pleural effusion, which occurs in 96% of patients within a month [36]. For this reason, this treatment modality is not preferred in well-conditioned patients.

Pleural drainage by thoracentesis is used to relieve symptoms temporarily caused by MPE. It is generally well tolerated by patients. The procedure is easy and early outcomes are perfect. In the literature, it is advised that draining more than 1500 cc at a time is recommended to avoid re-expansion pulmonary edema (RPE) [2,15]. The procedure should be stopped if chest pain, dyspnea and cough are observed. Potential complications of the procedure are pain in the side, subcutaneous hemorrhage, pneumothorax, empyema, pulmonary edema and spleen or liver damage. Pneumothorax is seen in 12% of thoracentesis cases, but only 5% of cases required treatment with a tube insertion [37]. The possible presence of lymphangitis carcinomatosa, atelectasis, thromboembolism and tumor emboli should be investigated if dyspnea is not relieved after drainage of the pleural effusion by thoracentesis. Similarly, the presence of endobronchial obstruction or a trapped lung should be suspected if mediastinal shift is not seen at chest x-ray or the lung does not fully expand after a large amount of pleural drainage. Bronchoscopy or thoracoscopy should be performed for diagnosis [2].

Increased symptoms and loculated effusion can be seen after repeated thoracentesis. Other treatment modalities should be kept in mind when recurrent effusions occur. Tube thoracostomy is effective in the drainage of effusions but is unable to prevent the recollection of effusion. The success rate for 30 days ranges between 11-40% [38].

Chang et al. [39] documented that repeated thoracentesis can cause pleural inflammation and increased TNF- $\alpha$  release. They also declared that fibrin formation can be seen secondary to thoracentesis in MPE and that the presence of fibrin increased the success of later pleurodesis.

### Intercostal Tube Drainage and Intrapleural Instillation of Sclerosant Agent:

It is reported that tube thoracostomy and instillation of sclerosant agent is the most effective and least morbid treatment modality for MPE [25]. Effusion drainage by tube thoracostomy and the instillation of sclerosant treatment was first described in 1976 by Adler and Sayek [40]. Initially, 24F or 32F large bore tubes were used. However, 8-14 F small bore tubes were later used, which are more comfortable for patients. There are no observed differences in efficacy against pleurodesis in studies where large and small bore tubes are used [41]. Parulekar et al. [42] evaluated the usage of small bore and large bore tube catheters in MPE treatment. In this study, small bore catheters are used in 58 MPE cases, and large bore catheters are used in 44 MPE cases. It is estimated that the 6 weeks and 4 months recurrence rate when small bore tubes are used is 45% and 53%, respectively, compared to 45% and 51% when large bore tubes are used. Univariate and multivariate analysis showed that the size of the tube does not have an effect on the recurrence rate.

Patients can be followed as outpatients, and pleurodesis can be performed after the positioning small bore catheters. In this way, costs will be reduced and patients can be more active [43]. This may allow patients to spend some time out of the hospital. This is especially true for patients who are incurable and have limited survival expectancy.

Pleurodesis enables the obliteration of intrapleural space and scar formation at the visceral and parietal pleura. A sclerosant agent is given to the hemithorax, which obliterates small pleural blood vessels and results in mesothelial fibrosis [44]. For successful pleurodesis, inflammatory and fibrotic mediators should be used and released by mesothelial cells. By instillation of a sclerosant agent, intrapleural and intensive inflammation occurs, and as a result of chemical pleuritis, pleural leaves are adhered [45]. Commonly used sclerosant agents are; talc, antibiotics (doxycycline, monocycline, tetracycline), cytotoxic chemotherapeutic agents (bleomycin, cisplatin, cytarabine, doxorubicin, fluorouracil, mitomycin) and various other agents (corynebacterium parvum, interferon, methylprednisolone acetate, radioactive isotopes, recombinant interleukin-2) [44].

### Pleurodesis Technique:

Chemical pleurodesis with tube thoracostomy is the most commonly used method in MPE treatment. Most doctors delay pleurodesis until drainage per day is less than 150 cc [46]. It is generally believed that pleurodesis will be more effective when the effusion is completely drained. Also, expansion of the lung is required for the effectiveness of this procedure, but the same success can be achieved by performing pleurodesis after a short period of total lung expansion. This approach is now advised due to decreasing duration of hospital stays and the minimal insertion of tubes [47]. The tubes are generally clamped for 2 hours and then reopened for drainage by coupling the tube to an aspirator. Then, the chest tube is withdrawn when daily drainage is less than 100 ml. In a randomized study, Villanueva et al. [48] instilled a sclerosant agent when the daily drainage was fewer than 150 ml in one group or after total lung expansion without considering daily drainage in another group. They did not find a difference in success rate. However, withdrawal of the tube occurred 2 days later in the second group.

The most common side effect from pleurodesis is pain. For this reason, narcotic analgesia and/or midazolam should be used if there is no contraindication. Although there are very few human and animal data supporting the application of lignocaine intrapleurally, it is a practice that is generally used [46].

### Talc Pleurodesis:

Talc ( $Mg_3Si_4O_{10}(OH)_2$ ) is a trilayered magnesium silicate sheet. It was first used as a pleurodesis agent in 1935. Talc used for intrapleural administration is asbestos free and sterilized effectively by dry heat exposure, ethylene oxide, and gamma radiation [49].

It may be administered in two ways: at thoracoscopy using an atomizer termed 'talc poudrage' or via an intercostal tube in the form of a suspension termed 'talc slurry'. Comparing talc poudrage and talc slurry, both methods have 91% success rates [2]. In animal studies better pleurodesis results were obtained

with talc poudrage compared to slurry [50].

Instillation of talc poudrage to the intrapleural space by thoracoscopy is thoroughly documented. Talc poudrage can be done under local anesthesia with medical thoracoscopy or VATS. Some techniques should be known well in order to do a successful pleurodesis and avoid complications. Before atomizing the talc, the pleural fluid should be completely drained. During thoracoscopy, air entering the pleural cavity passively can be easily excreted, and in this way, the desired pressure balance can be maintained. Complete lung collapse is important in order to see the pleural cavity, take a biopsy from the suspected lesions and enable talc lying widely. Antony et al. [51] applied talc in 28 cases with VATS and in 29 cases with tube thoracostomy, but they did not find significant a difference in success rate between the two groups.

Talc slurry is also an effective agent for pleurodesis in MPE. Potential disadvantages, which decrease efficacy of the procedure, are incomplete uniform laying, incomplete pleurodesis, and short duration of contact with the pleural surface. The pleurodesis technique is similar to dissolving chemical agents. Before the procedure, it is advised that the use of intravenous narcotics and anxiolytics-amnestic agents occurs in low doses [2]. Standard chest tubes (18-24 F) or small bore catheters (10-12 F) can be used effectively in talc slurry forming pleurodesis.

Mitchem et al. [52] compared the results of pleurodesis with doxycycline, autologous blood and talc in rabbits. Talc was found to be the most effective agent. Walker-Renard et al. [53] estimated a 54% success rate with bleomycin, 68% with tetracycline, and 98% with talc in their study. Kilic et al. [54] evaluated the results of chemical pleurodesis applied to patients using talc, tetracycline and bleomycin. They declared that the use of talc resulted in minimal drainage and earlier removal of the catheter or tube. Today, the most frequently used sclerosant agent is talc because of its relative low cost, easily handling and high success rate.

Talc is usually well tolerated. The most common side effects are fever (16%) and chest pain (7%) [53]. Cardiac complications like arrhythmias, cardiac arrest, myocardial infarction or hypotension are noted. Adult respiratory distress syndrome (ARDS) following talc pneumonia is rare but is a fatal complication. Both in talc poudrage and in slurry associated ARDS, acute pneumonia and respiratory failure are observed [55]. It is unknown whether the poudrage or slurry method is a major factor causing the respiratory failure, even though it is known that talc dosage or particle size is important. Other causes of acute respiratory failure are high doses of talc, active air leakage, over-premedication during the procedure, underlying lung disorder, re-expansion pulmonary edema and sepsis secondary to nonsterile procedure, or endotoxin containing talc usage [2]. Talc particles are seen in distant organs like the liver, kidney and even the brain following pleurodesis [56].

ARDS is the most common complication secondary to intrapleural talc usage, ranging between 1.3% and 9% [57,58]. However, there are large studies that use talc in which ARDS is not observed [59,60]. In the literature, it is estimated that more than 5 g talc usage is a major risk factor for ARDS [57].

York et al. [61] used talc slurry in 125 patients. Talc pneumonia is seen in 8 patients and ARDS is observed in 5 patients. The mechanism of acute pneumonia is still not understood. There is

a hypothesis about the absorption of talc with inflammatory mediators for systemic circulation [62]. In some studies, it is shown that there is a relationship between more than 10 g talc usage and the development of ARDS and pneumonia [63]. Also, in a study with rats, the spread of particles to other organs does not seem to be dependent on dosage [64].

#### **Tetracycline:**

Tetracycline hydrochloride is a very frequently used chemical pleurodesis agent. The direct effects of this drug are similar to growth factors that are released from fibroblasts. Tetracycline can be applied by small bore catheter or tube thoracostomy. There are no significant differences in the success rate between one and multiple administrations [65].

The advantages of tetracycline are its reasonable efficacy, excellent safety profile, ease of administration and low cost. The estimated success rate of treatment with tetracycline varies from 50% to 92% with a mean of 65% [49,65]. The most common side effects are chest pain (30%) and fever (10%), which are usually transient and respond to antipyretics and analgesia. The optimal dose for intrapleural administration is 1.0-1.5 g or 20 mg/kg [49]. Studies using smaller doses such as 500 mg have reported a lower response rate, but there is no evidence to support the use of larger doses of tetracycline [66].

Thoracoscopic instillation of tetracycline has been studied in two randomized trials of malignant effusions in breast cancer. Evans et al. [67] compared thoracoscopic instillation of 500 mg of tetracycline with 1.5 g by chest tube. The complete response rate at one month for both groups was 76%. Fentiman et al. [68] compared talc poudrage with thoracoscopically administered 500 mg of tetracycline. The talc group was found to have a successful palliation rate of 92% after one month compared to 48% for tetracycline group. Tetracycline pleurodesis may also be performed using a needle aspiration technique in which effusion is completely drained. However, in a randomized trial, McAlpine et al. [69] reported a success rate for this method of 29% at 6 weeks compared with 80% with intercostal tube drainage.

#### **Bleomycin:**

Many antineoplastic agents have been used to form a sclerosant effect in the management of MPE in previous trials. However, other agents, with the exception of bleomycin, were not used widely because of their low sclerosant effect and many side effects. In many studies, the bleomycin dose is 60 IU mixed with 50-100 ml saline solution [49].

Bleomycin is widely used in lymphomas and cancers of the neck and head. The success rate of intrapleural administration of bleomycin ranges between 31-85% [49,70]. The most common side effects are fever, localized chest pain and gastrointestinal complaints. It rarely causes systemic toxicity because of its limited absorption. It can be used safely in immunodeficient patients or during simultaneous chemotherapy administrations because of its inability to cause myelosuppression [49].

Similar success results are observed comparing pleurodesis following treatment with doxycycline and bleomycin using small bore catheters (with bleomycin 72%, doxycycline 79%) [71]. The success with talc was found to be much higher than bleomycin

in trials where both treatments are compared [53]. When compared with talc and tetracycline, the disadvantages of bleomycin were a low success rate and a high cost [54]. Because of its high cost and ineffectiveness, bleomycin is not advised, except in one study conducted by Ruckdeschel et al. [72].

#### **Rarely Used and Historical Agents:**

Doxycycline is analogous to tetracycline. In a few number of studies, pleurodesis results with doxycycline are evaluated. The success rate was estimated as 76% [49,71]. The side effects from doxycycline treatment are similar to those from tetracycline treatment, which includes pleurotic chest pain (60%) and fever (30%) [49]. One major disadvantage of doxycycline therapy is the need for repeated treatment practice to reach success. This situation may cause a long duration of catheter or intercostal tube insertion, increasing the risk of infection, patient discomfort and cost.

Monocycline was used as a sclerosant agent. However, limited numbers of studies have reported the effects in humans [73]. One study done with rabbits has shown that it can be as effective in pleurodesis as tetracycline [74].

Corynebacterium parvum extract, interferons, interleukins and several chemotherapeutic drugs (cisplatin, cytosine arabinoside and mitoxantrone) are agents used for pleurodesis. Most studies are uncontrolled and have small numbers of patients. Corynebacterium parvum, interferon's and interleukins require multiple administrations, while significant toxicity is encountered with the use of the chemotherapeutic drugs [49].

#### **Systemic Therapy:**

Therapeutic thoracentesis or chemotherapy combined with pleurodesis can be used to treat started in small cell lung cancer, which has high response rate to chemotherapy if there is no contraindication. Even effusions secondary to breast cancer, lymphomas, prostate, ovarian, thyroid and germ cell tumors respond to chemotherapy. Local treatment such as pleurodesis could be applied if systemic treatment choices cannot be used or are contraindicated or ineffective [2,49,56].

#### **Long term indwelling pleural catheter drainage:**

The insertion of a long-term pleural catheter is an alternative method for controlling recurrent and symptomatic MPE in patients with a trapped lung. A specific catheter has been developed for this aim and studies using this catheter have reported encouraging results [75,76].

Putnam et al. [75] compared treatment with a long term indwelling pleural catheter with doxycycline pleurodesis by a standard intercostal tube. The length of hospitalization for the indwelling catheter group was significantly shorter than that of the doxycycline treated group (1 day and 6 days, respectively). Spontaneous pleurodesis was achieved in 42 of the 91 patients in the indwelling catheter group. A late failure rate (defined as reaccumulation of pleural fluid after initial successful control) of 13% was reported compared with 21% for the doxycycline group. The complication rate was higher (14%) in the indwelling catheter group and most commonly included local cellulites and, in rare cases, tumor seeding of the catheter tract.

An indwelling pleural catheter is an effective method for

controlling MPE and reducing hospital stays in the treatment of recurrent and symptomatic MPE.

#### **Pleuroperitoneal Shunt:**

If pleurodesis cannot be applied due to the inability to expand the lung or because of the presence of thick visceral pleura, endobronchial lesions, cancer infiltrated lungs, respiratory distress or mediastinal shift, the use of a chronic catheter or pleuroperitoneal shunt should be kept in mind as the treatment choice [77]. In selected patients with trapped lungs and large effusions that are refractory to chemical pleurodesis, pleuroperitoneal shunting is an acceptable palliative option. Here, a shunt can be replaced via thoracoscopy or mini thoracotomy during a hospital stay. The procedure is usually well tolerated. The postoperative morbidity and mortality rate are low [78]. It is a chronic drainage system, which consists of a subcutaneous pump (Denver Biomaterials, Golden, CO) that transfers pleural fluid to peritoneal cavity. Ponn et al. [79] describe in detail the insertion of a shunt. In this procedure, serious patient education is needed and the success rate is very high in patients that cooperate.

These patients have a risk of infection due to prior chest tube insertion. For this reason and before implanting the shunt, the examination of pleural fluid by gram staining and culture should be performed to determine the sterility. Otherwise, sepsis risk may occur due to infection of the peritoneal cavity with infected pleural fluid.

Genc et al. [80] estimated early and late complications for 21 of 160 (14.8%) patients that were treated with a pleuroperitoneal shunt. Complications include shunt occlusion, infection and tumor seeding or implantation into the peritoneal cavity. Shunt occlusion rates vary from 12% to 25%, and treatment normally requires replacement of the shunt [78,81]. The presence of pleural infection, multiple pleural loculations and an inability to compress the pump chamber are contraindications to pleuroperitoneal shunting [49].

#### **Pleurectomy:**

If the malignant tissue surrounding the pleural surface has a cortex, pleurodesis can be insufficient. Pleurectomy is an effective but invasive method for treating MPE. The cortex can be extracted via open thoracotomy and pleurodesis can be applied. Complications may include empyema, hemorrhage and cardio-respiratory failure. This procedure has a 12% perioperative mortality, so patient selection is important [82]. This method should be reserved for those who have failed to respond to other forms of treatment. The advent of VATS has enabled the use of parietal pleurectomy without thoracotomy. In a study of 19 patients (13 with mesothelioma and 6 with metastatic adenocarcinoma), it was found that this thoracoscopic method was safe and associated with an effusion recurrence rate of 10%. The median postoperative stay was 5 days and no mortality was observed [83]. A pleuroperitoneal shunt should be replaced if adequate lung expansion cannot be achieved after effusion drainage due to malignant tissue cortex or fibrosis

## Factors Affecting Prognosis

Increased pleural fibrinolytic activity is associated with the failure of pleurodesis. Rodriguez-Panadero et al. [84] showed that a rapid reduction in fibrinolytic activity within 24 hours using pleural D-Dimer levels was associated with a good outcome of talc pleurodesis. In contrast, treatment was unsuccessful in the group where the D-Dimer levels were high.

In animals, the effectiveness of pleurodesis may be reduced by concomitant use of corticosteroids. Recent evidence in rabbits has shown a reduced pleural inflammatory reaction and, in some cases, the prevention of pleurodesis with the administration of corticosteroids at the time of talc pleurodesis [85]. Similarly, the

coagulation cascade has an important role in organ fibrosis involving pleurodesis [84,86]. In animal trials, it was shown that heparin usage could inhibit pleural fibrosis [87]. The administration of non-steroidal anti-inflammatory agents at the time of pleurodesis is more contentious and, at present, evidence against their use is lacking.

In some trials for pleurodesis results and survival expectancy, the best correlation is found with pleural fluid pH and glucose [20, 88]. In a meta-analysis study involving more than 400 patients for the success of pleurodesis, these are found to be low predictive factors [89]. A patient's clinical situation and type of tumor should be the factors to decide the appropriateness of pleurodesis.

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