Recent Advances in the Diagnosis and Management of Malignant Pleural Effusions

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Malignant pleural effusions (MPEs) are an important complication for patients with intrathoracic and extrathoracic malignancies. Median survival after diagnosis of an MPE is 4 months. Patients can present with an MPE as a complication of far-advanced cancer or as the initial manifestation of an underlying malignancy. Common cancer types causing MPEs include lymphomas, mesotheliomas, and carcinomas of the breast, lung, gastrointestinal tract, and ovaries. However, almost all tumor types have been reported to cause MPEs. New imaging modalities assist the evaluation of patients with a suspected MPE; however, positive cytologic or tissue confirmation of malignant cells is necessary to establish a diagnosis. Even in the presence of known malignancy, up to 50% of pleural effusions are benign, underscoring the importance of a firm diagnosis to guide therapy. Rapidly evolving interventional and histopathologic techniques have improved the diagnostic yield of standard cytology and biopsy. Management of an MPE remains palliative; it is critical that the appropriate management approach is chosen on the basis of available expertise and the patient's clinical status. This review summarizes the pathogenesis, diagnosis, and management of MPE. Studies in the English language were identified by searching the MEDLINE database (1980-2007) using the search terms *pleura*, *pleural*, *malignant*, *pleurodesis*, and *thoracoscopy*.

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CT = computed tomography; EGFR = epidermal growth factor receptor; FDG = fluorine 18–labeled fluorodeoxyglucose; LDH = lactate dehydrogenase; MPE = malignant pleural effusion; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PET = positron emission tomography; PF = pleural fluid; SMRP = serum mesothelin-related protein; VATS = video-assisted thoracoscopic surgery

Malignant pleural effusions (MPEs), which comprise a heterogeneous group of conditions, represent an important source of morbidity for patients with underlying cancer. They can occur as the initial presentation of cancer, as a delayed complication in patients with previously diagnosed malignancies, or as the first manifestation of cancer recurrence after therapy. Malignant pleural effusions can result from primary malignancies of the pleurae or from underlying intrathoracic or extrathoracic malignancies that reach the pleural space by hematogenous, lymphatic, or contiguous spread. Although virtually any malignant cell type can cause an MPE, more than 75% of MPEs are caused by neoplasms of the lung, breast, or ovary or by lymphomas.[1-4] Metastatic adenocarcinoma is the most common tumor type.[5] Mesotheliomas develop from malignant transformation of mesothelial cells in the pleural membranes.[6] Regardless of the etiology of an MPE, the median survival from clinical recognition is 4 months; however, prolonged survival is possible in some patients.[7]

This article reviews the current evidence on the pathogenesis, diagnosis, and management of MPEs. Relevant studies in the English language were identified by searching the MEDLINE database (1980-2007) using the search terms *pleura*, *pleural*, *malignant*, *pleurodesis*, and *thoracoscopy* and by hand searching selected reference lists.

PATHOGENESIS

An MPE is defined by the presence of cancer cells in the pleural space. Metastatic MPEs result from direct extension of malignant cells from an adjacent cancer (such as malignancies of the lung, breast, and chest wall), invasion of the pulmonary vasculature with embolization of tumor cells to the visceral pleura, or hematogenous metastases from distant tumors to the parietal pleura. Once established in the pleural space, tumor deposits spread along parietal pleural membranes and obstruct lymphatic stomata, which drain intrapleural fluid. Pleural tumor deposits also stimulate the release of chemokines that increase vascular and pleural membrane permeability, thereby promoting pleural effusions.[8,9] Patients with cancer can develop pleural effusions as an indirect effect of cancer even when cancer cells are absent from the pleural space. These effusions, termed paraneoplastic or paramalignant effusions, can result from mediastinal lymph node tumor infiltration, bronchial obstruction, radiochemotherapy, pulmonary embolism, superior vena cava syndrome,[10] or decreased oncotic pressure.[11]

Between 20% and 30% of patients with non-Hodgkin lymphoma and Hodgkin disease develop pleural effusions.[9] Most effusions in patients with Hodgkin disease are paraneoplastic and result from thoracic duct obstruction. Most patients with effusions due to non-Hodgkin lymphoma have T-cell–type lymphomas and direct pleural infiltration.[9] Nevertheless, non-Hodgkin lymphoma is the most common malignancy-related cause of chylous pleural effusions.[4]

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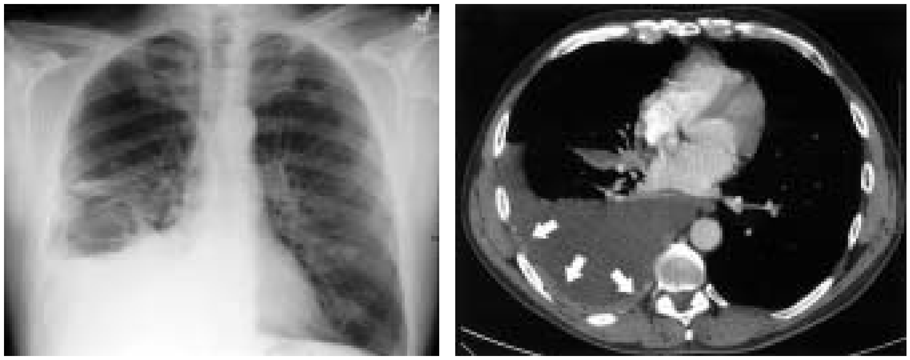

FIGURE 1. Left, Frontal chest radiograph of a 54-year-old man with a mass on the left kidney and dyspnea showing a moderate-sized right pleural effusion without unique diagnostic features of a malignant effusion. Right, Contrast-enhanced computed tomogram with mediastinal windows showing a right pleural effusion with irregular thickening of the parietal pleura (arrows). Computed tomography–guided pleural biopsy revealed metastatic renal cell carcinoma.

Patients with lymphoma usually do not present with an isolated pleural effusion in the absence of other signs of lymphoma. An exception is primary effusion lymphoma, which is typically a large-cell lymphoma that exclusively or predominantly involves serous cavities without clinically apparent solid tumor mass elsewhere. These body-cavity lymphomas have been reported primarily in patients with AIDS complicated by herpesvirus/human herpesvirus 8 infections. These patients might or might not have coexisting Kaposi sarcoma. Pleural fluid (PF) generation in primary effusion lymphoma appears mediated by vascular endothelial growth factor or vascular permeability factor, which alters permeability of vascular and pleural membranes.[8,9] Patients with chronic intrapleural infections can develop pyothorax-associated lymphoma as a unique expression of a non-Hodgkin lymphoma.[12]

DIAGNOSIS

Patients with MPEs present with nonspecific histories and physical findings and require cytopathologic analysis of PF or pleural tissue to establish a diagnosis. Patients usually experience dyspnea, cough, and decreased exercise tolerance at presentation, but an MPE could be first noted as an incidental finding on imaging studies in an asymptomatic patient. Most patients with an MPE due to adenocarcinoma do not have chest pain, whereas 60% of patients with mesothelioma can experience a constant dull or occasionally localized pleuritic chest pain.[13] Patients with an MPE due to sarcoma can present with a pneumothorax.[14] Chest physical findings are typical for pleural effusions; however, extrapleural findings could direct attention toward a previously undiagnosed underlying malignancy. The detection of an effusion coincident with a newly diagnosed cancer does not establish an MPE because 50% of such effusions are nonmalignant.

In some circumstances, establishing the malignant etiology of a pleural effusion might not offer prognostic or therapeutic benefit. A fragile patient with multiple comorbid conditions and an undiagnosed small effusion, for instance, might benefit from observation rather than invasive diagnostic interventions. Conversely, the occurrence of an effusion in a patient with an underlying malignancy should not be assumed to be malignant if the presence of an MPE would alter tumor staging and therapeutic decisions. The presence of an MPE is required to stage a non–small cell lung cancer as IIIB (T4M0). However, it has been recently reported that patients with an MPE but without other evidence of metastatic disease have a median survival of 8 months vs 13 months for patients with other T4M0 disease (stage IIIB) without MPE.[15] This observation underlies recent recommendations from the International Association for the Study of Lung Cancer to classify non–small cell lung cancer with MPE as stage IV disease.[15]

IMAGING

Although standard chest radiographs can detect as little as 50 mL of PF on a lateral view,[16] they provide only suggestive findings for the diagnosis of MPE (Figure 1). A massive effusion increases the probability of a malignant etiology and commonly produces a meniscus sign with fluid tracking up the lateral chest wall, a shift of the mediastinum to the contralateral side, and an inversion of the diaphragm.[17] Radiographic signs of an MPE include circumferential lobulated pleural thickening, crowding of ribs, and elevation of the hemidiaphragm or ipsilateral mediastinal shift consistent with lung atelectasis due to airway obstruction by a tumor (Figure 2).[17]

Chest ultrasonography is increasingly used to evaluate patients with pleural effusions because it detects small

FIGURE 2. Frontal chest radiograph of a 71-year-old man with mesothelioma showing lobulated circumferential right pleural thickening. A mesothelioma was diagnosed by thoracoscopic pleural biopsy.

volumes (5 mL) of fluid,[18] identifies imaging features suggestive of an MPE, and guides thoracentesis and chest-catheter insertion. Findings that suggest MPE include solid pleural densities, hypoechoic pleural thickening with irregular or unclear borders,[19] invasion of pleura-based masses into neighboring structures, and swirling patterns within PF that represent cellular debris.[20] Pleural metastases can appear circular, nodular, hemispheric, or broad based with frond-like extensions into the pleural space (Figure 3).[19]

Contrast-enhanced chest computed tomography (CT) provides the most useful imaging information for evaluating patients with suspected MPE (Figure 1, right). Images that include the upper abdomen allow detection of adrenal and hepatic metastases. An occult primary tumor could be identified in the form of a breast mass (breast cancer), lung nodule (lung cancer), mediastinal mass (thymoma), or air-space consolidation (lymphoma).[17] Performance of CT before large-volume thoracentesis improves diagnostic sensitivity by allowing both the visceral and parietal pleurae to be imaged.

The following chest CT findings suggest MPE: (1) circumferential pleural thickening, (2) nodular pleural thickening, (3) parietal pleural thickening greater than 1 cm, and (4) mediastinal pleural involvement or evidence of a pri-

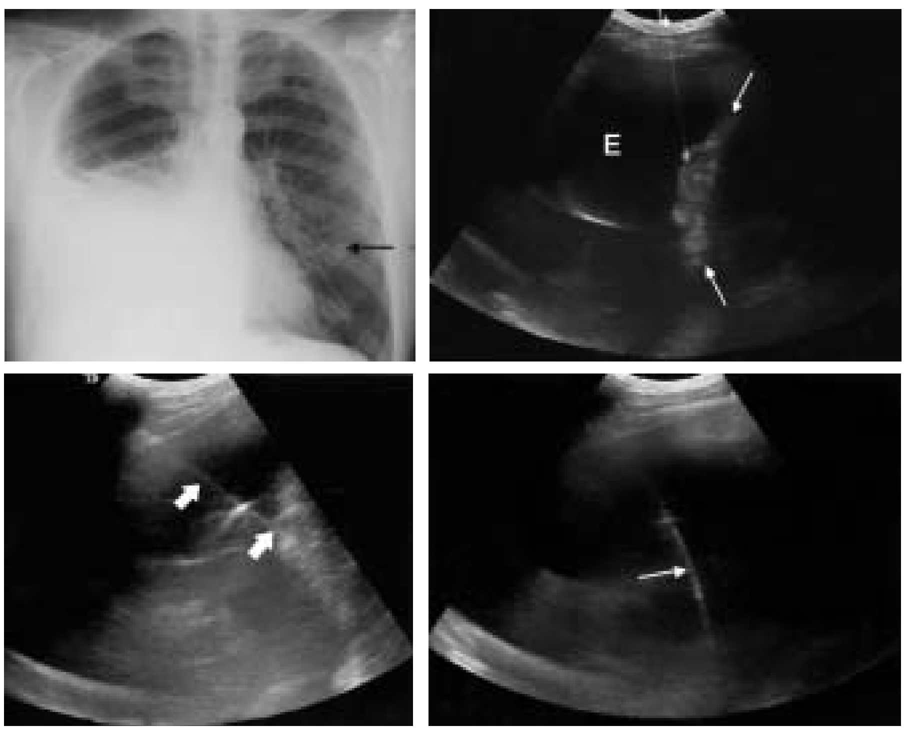

FIGURE 3. Top left, Frontal chest radiograph showing a moderate-sized right pleural effusion with opacification of the middle and right lower lobes and a left lung metastatic nodule (arrow). Top right, Sagittal ultrasonogram of the lower right side of the chest showing an anechoic effusion (E) with a lobulated echogenic mass along the diaphragmatic pleura (arrows). Bottom left, Image obtained during ultrasonographic biopsy showing biopsy needle (arrows) traversing effusion and entering diaphragmatic mass. Cytologic evaluation confirmed metastatic adenocarcinoma consistent with a renal primary tumor. Bottom right, Image obtained during placement of a guidewire (arrow) for insertion of a 14F catheter for drainage and subsequent talc sclerosis.

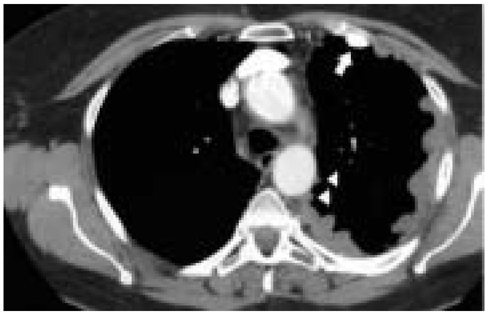

FIGURE 4. Contrast-enhanced computed tomogram at the level of the aortopulmonary window of a 67-year-old man with mesothelioma showing lobulated left pleural thickening that extends along the mediastinal pleura (arrowheads). Note the presence of associated calcified left pleural plaques (arrow) reflective of prior asbestos exposure.

mary tumor (Figure 4).[21,22] Each of these findings has a reported specificity of between 22% and 56% and a sensitivity of between 88% and 100%.[21-23] Findings suggestive of a mesothelioma include involvement of interlobar fissures and pleural thickening greater than 1 cm.[22] Coexistence of calcified pleural plaques with diffuse pleural thickening further suggests mesothelioma. If pleural nodularity or thickening are found on preoperative chest CT even in the absence of a pleural effusion, assessment for pleural metastases is warranted before patients undergo resection of lung cancer.[24] Chest CT can help determine the etiology of a paraneoplastic pleural effusion by revealing tumor involvement of thoracic structures, such as the superior vena cava (Figure 5).

Magnetic resonance imaging (MRI) provides better imaging of soft tissues than chest CT and can detect tumor invasion into the chest wall and diaphragm.[25] Magnetic resonance imaging with triple-echo pulse sequences is highly sensitive for small effusions and can identify features of fluid that differentiate exudative from transudative effusions.[26] In addition, MRI has a sensitivity and specificity similar or superior to chest CT for diagnosing pleural malignancies when CT criteria for malignant pleural disease are used in combination with MRI signal intensity findings (Figure 6).[17,27-30] Despite these favorable features, chest MRI is reserved for more complex pleural effusions because MRI is not as effective as contrast CT for imaging the lung parenchyma.

Chest imaging with positron emission tomography (PET) with fluorine 18–labeled fluorodeoxyglucose (FDG) has a reported sensitivity for malignant pleural disease of 93% to 100%, negative predictive value of 94% to 100%, specificity of 67% to 89%, and positive predictive value of 63% to 94%.[31-33] False-positive results occur in patients with uremic pleuritis, parapneumonic effusions, and other inflammatory pleural conditions that include posttreatment with talc instillation for pleurodesis.[34] Particularly when PF cytology is negative, negative PET-FDG results provide the most useful clinical information for ruling out an MPE.

Fused images can be created by combining PET-FDG and CT, allowing improved localization of PET-detected abnormal FDG activity for guiding biopsy (Figure 7).[35] In a series of 31 patients, Toaff et al[36] reported that the presence of focal increased FDG activity in the pleural space combined with CT detection of a concomitant solid pleural density had a sensitivity of 95%, a specificity of 80%, a positive predictive value of 91%, a negative predictive value of 89%, and an accuracy of 90% for malignant pleural disease.[36] Combined PET-CT imaging can also be used to differentiate increased FDG activity due to talc pleurodesis from intrapleural tumor recurrence by detecting pleu-

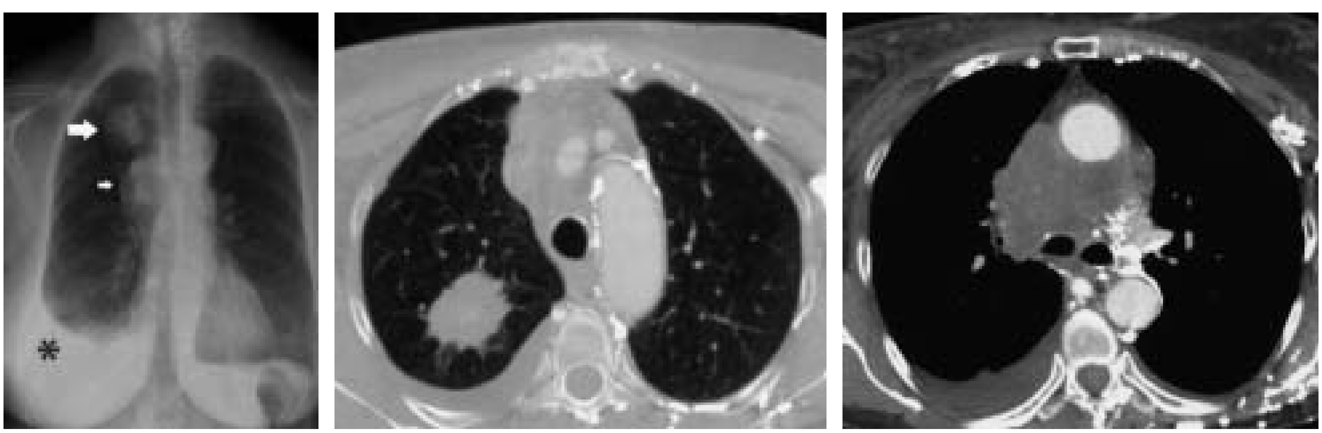

FIGURE 5. Left, Frontal chest radiograph of a 62-year-old woman with superior vena cava syndrome showing a right upper lobe nodule (large arrow) with a right hilar/mediastinal mass (small arrow) and a right transudative pleural effusion (asterisk). Middle, Contrast-enhanced computed tomogram at the level of the aortic arch revealing a right upper lobe mass confirmed by transthoracic biopsy as a non–small cell carcinoma. Right, Contrast-enhanced computed tomogram showing a right mediastinal and hilar mass that occludes the superior vena cava. Note the mediastinal and left chest wall venous collaterals and edema of the subcutaneous fat resulting from superior vena cava occlusion.

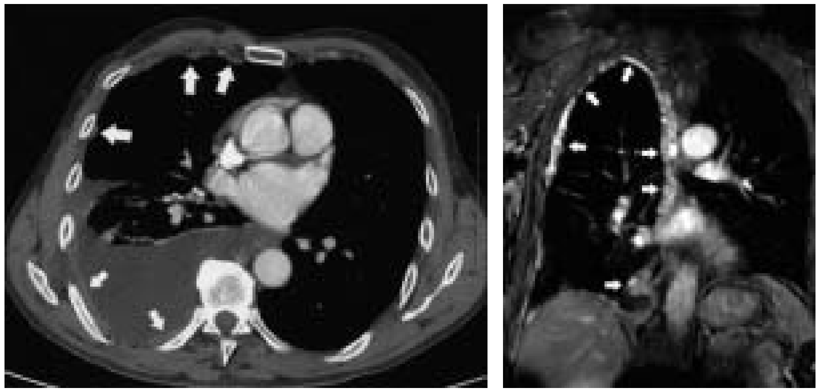

FIGURE 6. Left, Contrast-enhanced computed tomogram at the level of the left atrium shows a right pleural effusion with foci of pleural nodularity (large arrows) and thickening (small arrows). Right, Coronal gradient-echo magnetic resonance imaging obtained after gadolinium administration showing irregular pleural enhancement involving the mediastinal, costal, and diaphragmatic pleural surfaces (arrows) diagnosed by thoracoscopic biopsy as mesothelioma.

ral thickening (characteristic of talc pleurodesis) with increased CT attenuation.[34,37]

PLEURAL FLUID ANALYSIS

Despite the improved diagnostic accuracy of new chest-imaging modalities, cytologic or tissue biopsy confirmation is required to establish a diagnosis of MPE. Most patients who present with undiagnosed pleural effusions benefit from thoracentesis. Although 15% of patients who present with non–small cell lung cancer have an MPE,[38] bronchoscopy has a low diagnostic yield in evaluating patients for possible MPE if evidence of a pulmonary parenchymal or airway lesion is lacking.[39,40]

The selection of a site for thoracentesis has traditionally been guided by chest radiographic and physical findings.[41] However, recent studies show that chest ultrasonographic guidance improves the appropriateness of needle-insertion–site selection[42]; some experts recommend the routine use of ultrasonographic guidance for thoracentesis.[42-45]

Certain characteristics of PF can signal an increased likelihood of MPE and can guide decisions for further diagnostic studies. For example, an exudative effusion has a higher probability of being malignant than a transudative effusion; however, the finding is nonspecific because of the multiple inflammatory causes of exudative effusions. It should be noted that 3% to 10% of MPEs are transudates.[46,47] Malignant transudative effusions result from the imperfect application of diagnostic rules that categorize pleural effusions or comorbid conditions associated with transudates, such as hypoalbuminemia, cirrhosis with ascites, or chronic heart failure.

FIGURE 7. Left, Frontal chest radiograph showing a left pleural effusion. Middle, Fused axial positron emission tomogram/computed tomogram showing a right pleural effusion and irregular thickening of the left pleural surface with a focal area of increased metabolic activity (thin arrow) and calcified left pleural plaques (thick arrows). Right, Image obtained during computed tomography–guided biopsy showing a cutting needle within the area of focal increased metabolic activity seen in Figure 7, middle. Metastatic adenocarcinoma was revealed on biopsy.

TABLE 1. **Criteria-Based Rules to Identify Exudative Pleural Effusions***

Rule†	PF/S LDH >0.6	PF/S protein >0.5 PF	LDH >67% serum normal	PF cholesterol >45 mg/dL	PF protein >3 g/dL
Light criteria	X	X	X		
Abbreviated Light criteria		X	X		
2-Criteria rule without need for blood test			X	X	
3-Criteria rule without need for blood test			X	X	X

*LDH = lactate dehydrogenase; PF= pleural fluid; S = serum.
†Fulfillment of any 1 criterion defines an exudative effusion. X denotes that a criterion is used in the rule.

Light Criteria

Pleural effusions are most commonly categorized as transudates or exudates by the diagnostic rule termed Light criteria (Table 1). This rule defines an exudate if any 1 of the 3 criteria are met. Light criteria have an overall diagnostic accuracy of 93% but commonly misclassify effusions (approximate diagnostic accuracy, 65%) when any 1 of the 3 criteria has a value near its cutoff point.[48] Moreover, a meta-analysis of studies that evaluated Light criteria showed that the 2 criteria that incorporate serum lactate dehydrogenase (LDH) values (PF LDH and PF-to–serum LDH ratio) have a high coefficient of correlation, as would be expected by mathematical coupling.[49] Consequently, either of the 2 LDH criteria can be removed from the Light rule without affecting its overall diagnostic performance. This 2-criteria rule has been termed the "abbreviated Light criteria."[49]

Light criteria can be effectively used to categorize effusions as exudates because they are associated with the increased permeability of pleural membranes or the breakdown of intrapleural cells, allowing high–molecular-weight constituents to concentrate in the pleural space. Therefore, other PF tests that measure high–molecular-weight compounds would be expected to be similarly useful for categorizing effusions as exudates. Confirming this expectation, a meta-analysis found that the monitoring of PF cholesterol or albumin was as effective as Light criteria in categorizing an effusion as an exudate.[49] Unlike Light criteria, the proposed 2- and 3-criteria rules that use PF protein, cholesterol, and LDH levels do not require concomitant blood tests (Table 1). As with all diagnostic rules that combine different tests in "or" rules, the 3-test combination has a higher sensitivity but a lower specificity than the 2-test rule. Other characteristics of PF can suggest the presence of an MPE (Table 2), but none has sufficient diagnostic accuracy to obviate cytopathologic confirmation.

TABLE 2. **Pleural Fluid Findings Suggestive of Malignant Pleural Effusion (MPE)**

Cell counts	
Lymphocytes	More than 50% of MPEs have lymphocyte-predominant effusions (lymphocytes = 50%-70% of nucleated cells). Lymphocyte counts >85% suggest tuberculous pleurisy, lymphoma, sarcoidosis, chronic rheumatoid pleurisy, yellow-nail syndrome, or chylothorax
Erythrocytes	Bloody effusions common with MPE but also found with benign asbestos pleurisy, postcardiac injury syndrome, trauma, and pulmonary infarction
Eosinophils	From 12%-24% of eosinophilic effusions (>10% eosinophils) are malignant in etiology[50-52]
Chemical analysis	
Protein and LDH	Most MPEs are exudates according to Light criteria; 3%-10% are transudates.[46,47] LDH >1000 IU/L narrows the differential diagnosis to MPE, empyema, rheumatoid pleurisy, and pleural paragonimiasis
Amylase	1%-8% of pleural effusions are rich in amylase (>100 IU/L)[53,54] and so routine amylase measurement is not cost-effective unless pancreatic disease or ruptured esophagus is strongly suspected before the test.[53] Higher pleural fluid concentrations are associated with shorter survival times among patients with MPE[54]
pH	Levels <7.30 in 30% of MPE cases[55-57]; decreasing pleural fluid pH correlates with decreasing survival and success rates with pleurodesis[55-58]; however, in the absence of other clinical information, the correlation does not assist patient selection for pleurodesis[7,59,60]
Glucose	Levels <60 mg/dL suggest MPE, rheumatoid pleurisy, complicated parapneumonic effusion, tuberculous pleurisy, lupus pleuritis, or esophageal rupture

Cytology

Standard PF cytology can provide confirmation of an MPE but has a diagnostic yield of only 65% in general categories of patients with MPE.[61-66] The reported diagnostic yield for lymphomatous MPE ranges from 22% to 94%.[9] The diagnostic yield could increase with repeated thoracenteses[66,67] but not with the submission of larger volumes of PF for cytologic analysis.[65] Positive results on standard cytology might not differentiate between pleural adenocarcinoma and mesotheliomas or between lymphomas and reactive lymphocytosis without special studies.

Additional PF studies could complement standard cytology. Electrochemiluminescence and microparticle enzyme immunoassays of PF can detect tumor markers, such as carcinoembryonic antigen, carbohydrate antigen 15-3, cytokeratin 19 fragments, and cancer antigen 125. Unfortunately, none of the available tumor markers has sufficient diagnostic yield to be used in routine clinical practice. Combinations of tumor markers, however, could help select patients with negative PF cytologic results for additional diagnostic studies.[68-70] Groups of immunohistochemical markers could lead to a diagnosis in approximately 80% of patients with malignant mesothelioma.[71,72]

Genetic analysis of PF offers opportunities to improve the sensitivity of thoracentesis for MPE.[63,64,73,74] Common features of early malignancy, which include DNA methylation and other genetic mutations and microsatellite alterations, can be detected by polymerase chain reaction (PCR) and microarray techniques that measure simultaneously the expression of thousands of genes in a single sample. In a study of 31 patients with various pleural effusions, DNA methylation was observed in 59% of PF samples from patients with MPEs but in none of the benign effusions.[74] The addition of DNA methylation raised the sensitivity of cytology alone from 63% to 88%. Another study confirmed this finding, establishing the promise of PF epigenetic analysis as a rapid and reliable test when combined with standard cytology.[64]

Holloway et al[75] suggest that PF gene-expression tests can establish the cancer cell type and estimate the likely response to cancer therapy. Using a real-time PCR–based assay of 17 genes, they differentiated between biopsy-proven malignant mesothelioma and lung adenocarcinoma.[75] Detection of epidermal growth factor receptor (EGFR) mutations in malignant PF cells can predict a favorable response to gefitinib therapy in patients with non–small cell lung cancer.[76] However, absence of EGFR mutations does not preclude a therapeutic response.[77] Detection of Kristen ras oncogene mutations is a negative predictor of responsiveness to EGFR tyrosine kinase inhibitors.[78] Elevated levels of serum mesothelin-related protein (SMRP) are found in 84% of patients with malignant mesothelioma, but in fewer than 2% of patients with lung cancer,[79] making them a promising marker for the diagnosis of mesothelioma. They can also be used to clinically monitor patients with mesothelioma and to determine their prognosis. For the differentiation of mesothelioma from lung cancer controls, the area under the receiver operating curve for serum SMRP is 0.77 (95% confidence interval, 0.71-0.83), with a best cutoff of 1.00 nmol/L (sensitivity, 68.2%; specificity, 80.5%).[80] Other promising markers and combinations of markers have been recently reported and reviewed.[79,81-83]

Accessible techniques for detecting aneuploidy in PF samples, such as fluorescence in situ hybridization analysis, image analysis cytometry, and PCR, are more sensitive than standard cytologic studies.[84] Investigations are under way to determine if the detection of aneuploidy adds diagnostic value and meaningful therapeutic consequences to standard PF analysis for the detection of MPE.[84,85] Evidence to date suggests that detection of aneuploidy is a useful marker for identifying malignant cells[85,86] and that genetic changes often precede morphologic changes in a developing malignancy.[86]

Lymphomatous MPEs present a special diagnostic challenge. It can be difficult to classify the subtype of lymphoma and to differentiate between lymphoma and small round-cell tumors or reactive lymphocytosis. Lymphoma subtypes commonly associated with MPEs include lymphoblastic lymphoma; follicular center cell lymphoma, including Burkitt-type lymphoma; splenic marginal zone lymphoma; mucosa-associated lymphoid tissue lymphoma; and anaplastic large-cell lymphoma. Experienced cytology laboratories can use various immunologic and molecular cytogenetic tests in combination with morphologic examination to establish the presence of a lymphomatous pleural effusion with a 100% sensitivity and specificity and to determine the lymphoma subtype.[9]

Pleural Biopsy

When an MPE is still suspected after thoracentesis and PF analysis but cytology has not established a specific diagnosis, pleural biopsy might be indicated. Image-guided and thoracoscopic biopsy techniques have improved diagnostic yield as compared with traditional closed pleural biopsy using Abrams or Cope needles. The specificity of closed-needle biopsy for MPE is high, but case series report sensitivities that range from 7% to 72%.[40,62,87-90] The most recent case series reported a sensitivity for mesothelioma of 31% and for adenocarcinoma of 69% when adequate tissue was acquired[40]; adequate tissue is obtained in 71% to 91% of closed-needle biopsy specimens.[91,92] However, it should be noted that closed pleural biopsy leads to a diagnosis in only 7% of patients with preexisting negative PF cytologic study results.[62] Only 3 to 4 biopsy samples are necessary to achieve maximal sensitivity with closed-needle biopsy.[40,93]

At most centers, closed-needle biopsy has been supplanted by ultrasonography or chest CT–guided percutaneous pleural biopsy.[90,94,95] Diacon et al[42] reported an 86% sensitivity and a 100% specificity with transthoracic ultrasonography–guided biopsy when they used a 14-gauge cutting needle for pleura-based lesions 20 mm or greater in diameter. Maskell et al[90] reported the results of a randomized study comparing closed pleural biopsy with CT-guided needle biopsy in patients with negative cytologic results for MPE. They observed higher diagnostic yields with CT-guided vs closed pleural biopsy, with sensitivities of 87% vs 47%, specificities of 100% vs 100%, positive predictive values of 100% vs 100%, and negative predictive values of 80% vs 44%, respectively. Many patients in the CT-guided group had minimal (5 mm) pleural thickening that was successfully biopsied.

Although some centers perform thoracoscopic pleural biopsy after a nondiagnostic cytologic analysis of exudative PF, most would first do image-guided pleural biopsy if a region of pleural thickening or a mass were detected. Available thoracoscopic techniques include video-assisted thoracoscopic surgery (VATS)[96] and medical thoracoscopy with either a rigid thoracoscope[97] or a semirigid pleuroscope.[98,99] A wide-field examination of the pleural space is possible with VATS, and large tissue-biopsy samples can be obtained. However, VATS requires general anesthesia and an induced pneumothorax, which might not be tolerated by some patients with impaired lung function. Medical thoracoscopy is performed without pneumothorax under moderate sedation, making it easier for patients with limited pulmonary reserves to tolerate. Pulmonary physicians skilled in bronchoscopy should find the semirigid pleuroscope easy to use because it has the same light source, video equipment, and manual controls as the fiberoptic bronchoscope.[98,99]

Thoracoscopy has a 90% to 100% sensitivity for MPE.[100,101] In some patients, studding of pleural surfaces with tumor can be subtle, or coexisting benign lesions could misdirect biopsy sampling. For such patients, techniques that cause metastases to fluoresce can guide biopsy sampling.[102,103]

For diagnosis of mesothelioma and classification of its subtype, a large pleural biopsy specimen is often necessary. Immunohistochemical staining provides essential information in the diagnostic evaluation.[72] Some specimens could require electron microscopy to differentiate mesotheliomas from adenocarcinomas or fibrous pleuritis.[72] Mesothelioma subtype classification becomes important in centers that recommend aggressive trimodality therapy with extrapleural pneumonectomy for the epithelial but not the mixed or sarcomatoid subtypes. When this is a consideration, patients with suspected mesothelioma could be referred for open pleural biopsy by a limited thoracotomy, which has a sensitivity for epithelial malignant mesothelioma of 97% and specificity of 56%.[104] As many as 44% of patients who receive a pathologic diagnosis of nonepithelial subtype at resection could have been misdiagnosed initially with the epithelial subtype by more limited biopsy techniques.[104]

Despite the high diagnostic yield of thoracoscopy for MPEs, it is less effective in providing a specific diagnosis for nonmalignant pleural disease, leading to a diagnosis in only 50% of patients with unexplained exudative pleural effusions.[105] Therefore, referral of patients for thoracoscopy should be guided by the pretest probability that an exudative effusion is malignant. In a multivariate analysis, Ferrer et al[105] examined clinical predictors of MPE and derived a prediction rule of 4 variables: symptoms lasting longer than 1 month, absence of fever, blood-tinged PF, and chest CT findings suggestive of malignancy. Among 93 patients referred for VATS, 100% of the 28 patients fulfilling all 4 criteria had an MPE, 74% of those fulfilling 3 criteria, 24% of those fulfilling 2 criteria, and none of those fulfilling 0 or 1 criterion.[105]

MANAGEMENT OF MPEs

Because management of MPEs is palliative and does not improve survival, most physicians wait for symptoms or functional limitations related to the MPE to occur before intervening. However, some centers recommend early interventions at first diagnosis of an MPE to prevent pleural loculations that complicate management. Interventions are directed toward removing PF and, when appropriate, performing pleurodesis or initiating long-term drainage to prevent fluid reaccumulation.

Therapeutic Thoracentesis

Management of symptomatic MPE begins with therapeutic thoracentesis, which assesses the response of dyspnea to fluid removal. If symptoms do not improve with large-volume thoracentesis, alternative causes of dyspnea require evaluation, such as microtumor emboli, lymphangitic cancer, or effects of chemotherapy and radiation therapy. The removal of large volumes of PF could rapidly expand atelectatic lung regions beyond their capacity to reinflate and cause alveolar capillary injury resulting in reexpansion pulmonary edema.[106] It has been recommended that intrapleural pressure be monitored during thoracentesis and the procedure discontinued when pleural pressures reach a threshold pressure.[107] These recommendations, however, have not been subjected to prospective study, and many physicians are not trained in intrapleural pressure monitoring. Feller-Kopman et al[108] recently showed that patients' symptoms during thoracentesis correlated with intrapleural pressure and could serve as an indicator of the safe limits of PF removal. They observed that reexpansion pulmonary edema and excessively negative intrapleural pressures can be avoided if thoracentesis is discontinued when patients experience nonspecific chest discomfort.

Although symptoms can improve after thoracentesis, 98% to 100% of patients with MPE experience reaccumulation of fluid and recurrence of symptoms within 30 days.[109,110] Repeated thoracenteses, therefore, should be reserved for patients who (1) reaccumulate pleural effusions slowly after each thoracentesis, (2) have cancers that commonly respond to therapy with resolution of the associated effusions, (3) appear unlikely to survive beyond 1 to 3 months, and (4) cannot tolerate other more interventional procedures to control pleural fluid, such as pleurodesis.[101,111]

For all other patients, pleurodesis or long-term indwelling catheter drainage is recommended.

Before referring patients for pleurodesis, clinicians should assess their suitability for the procedure using a checklist of questions (Table 3), paying special attention to any causes of dyspnea other than the MPE itself (Table 4). Perhaps the most difficult of the questions to answer concerns the estimated survival after pleurodesis. Most physicians consider an expected survival beyond 2 to 3 months necessary to justify the cost, risks, and discomforts of pleurodesis. Multiple clinical factors have been used to estimate survival, including the cell type and stage of the tumor, characteristics of PF, and performance level. Unfortunately, despite careful patient selection at expert centers, up to 32% of patients do not survive 30 days after pleurodesis,[112-116] highlighting the limited ability of physicians to predict survival for patients with MPE. The American Thoracic Society/European Respiratory Society guideline for MPE management recommends that pleurodesis be limited to patients with PF pH values greater than 7.30[111] because of the direct correlation between low PF pH and poor short-term survival.[56,57] Unfortunately, meta-analyses of pH demonstrate poor predictive performance of PF pH for individual patients.[7,60] Among the criteria now in common use, performance status has the most value for estimating postpleurodesis survival.[117]

Pleurodesis should be restricted to patients who have a reasonable likelihood of responding to the procedure. Successful pleurodesis requires apposition of the visceral and parietal pleurae.[118] Patients with airway obstruction from an endobronchial tumor, extensive intrapleural tumor masses, or multiple pleural loculations resulting in trapped lungs are unlikely to respond. Up to 30% of patients who are evaluated for pleurodesis are unsuitable candidates because of trapped lungs.[115] A number of factors should be considered in estimating the likelihood that a patient will respond to pleurodesis. When a chest radiograph after thoracentesis reveals a distribution of intrapleural air that corresponds with the distribution of PF before thoracentesis, a pneumothorax could suggest a trapped lung (Figure 8).[119-121] Such pneumothoraces usually result from trapped lungs that cannot reexpand during thoracentesis and from the entry of air into the pleural space (as negative intrapleural pressure) along the thoracentesis needle track during fluid removal.

Other signs of poor lung expandability include deviation of the trachea toward the side of the MPE noted on a standard radiograph and evidence on chest CT of loculations, thickened visceral pleural membranes, and large intrapleural tumor masses. The generation of extremely low intrapleural pressures during thoracentesis suggests nonexpandable lung[43,122]; however, the predictive performance of pleural manometry has not been established. The American Thoracic Society/European Respiratory Society guideline for MPE recommends use of PF pH as a predictor of pleurodesis outcome, with decreasing pH corresponding to lower probabilities of response.[111] However, a meta-analysis of primary data from multiple case series found that more than 50% of patients with low PF pH values had improved symptoms after pleurodesis.[59] Moreover, in a randomized trial of thoracoscopic vs chest-tube pleurodesis, Crnjac et al[123] observed that more than 50% of patients with low pH effusions had successful pleurodeses. Pleural fluid pH appears to have no value for selecting patients for pleurodesis.

TABLE 3. **Questions to Guide Selection of Patients for Pleurodesis**

Is the underlying tumor and resulting malignant pleural effusion responsive to chemotherapy or radiotherapy?
Are the patient's respiratory symptoms caused by the effusion?
Does the patient's dyspnea improve after therapeutic thoracentesis?
Do alternative causes of dyspnea exist that will not respond to pleurodesis?
Does the patient's life expectancy warrant pleurodesis (eg, is it longer than 2-3 months)?
Will pleurodesis resolve the effusion and sufficiently improve the patient's symptoms?
Does the lung expand to the chest wall after therapeutic thoracentesis?
Do imaging studies suggest multiloculated effusions and thick visceral pleural membranes suggestive of a trapped lung?
Will the amount of intrapleural tumor prevent an effective pleurodesis?
Do imaging studies detect large tumor masses along pleural surfaces?

TABLE 4. **Causes of Dyspnea in Patients With Malignant Pleural Effusions**

Pleural
Malignant effusions
Effusions caused by
Drugs
Pneumonia
Heart failure
Pulmonary embolism
Pulmonary parenchyma
Lymphangitic cancer
Chemotherapy-induced pneumonitis or fibrosis
Radiation fibrosis or pneumonitis
Extensive tumor mass with lung restriction
Airways
Airway obstruction by tumor
Bilateral vocal cord paralysis from recurrent laryngeal nerve praxis
Cardiac and pericardial
Chronic heart failure
Pericardial effusion
Constrictive pericarditis
Restrictive cardiomyopathy due to tumor infiltration
Vascular
Pulmonary thromboemboli
Tumor emboli
Other
Deconditioning
Poor nutrition
Cancer-related cachexia
Myopathy
Chest wall invasion by tumor
Progression of underlying lung disease (eg, emphysema)

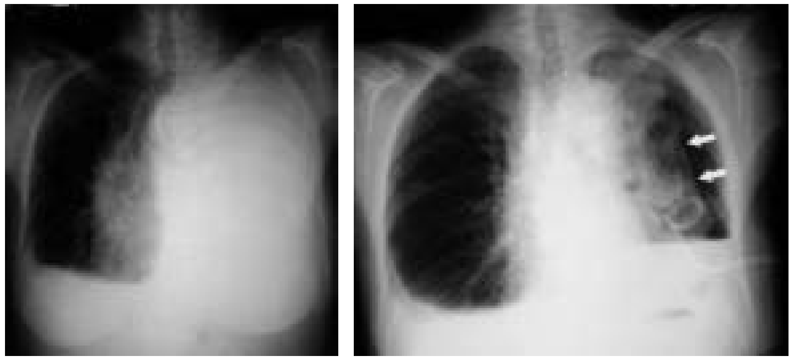

FIGURE 8. Left, Frontal chest radiograph of a 67-year-old woman with a malignant left pleural effusion showing opacification of the left hemithorax with contralateral shift of the mediastinum. Right, Chest radiograph after pigtail catheter placement for planned pleurodesis showing a left hydropneumothorax with persistently collapsed left upper and lower lobes. Note the thickening of the visceral pleural surface (arrows). Because the configuration of the hydrothorax established a trapped lung, the catheter was subsequently removed, and pleurodesis was not attempted.

Little consensus exists as to the ideal procedure for pleurodesis. A survey of physicians in 5 English-speaking countries showed substantial differences in the pleurodesis procedures used in each country.[124] That variability could be due in part to physician dissatisfaction with available techniques, all of which have their shortcomings.

Existing pleurodesis methods include instillation of compounds via an intrapleural chest catheter or various techniques with the use of thoracoscopy. In the traditional approach to chest-catheter pleurodesis, a short-term catheter is inserted for drainage of PF and for instillation of a sclerosing agent and then removed when minimal fluid remains to be drained. Most centers no longer use conventional large-bore (20F-32F) chest tubes because of the equivalent effectiveness of small-bore (9F-14F) catheters,[125-131] which provide opportunities for outpatient pleurodesis.[132] Each of the several protocols that exist for chest-catheter pleurodesis are based on empiric experience and limited comparative studies. Most experts recommend that the sclerosant be instilled only when catheter drainage has decreased to less than 150 mL/d and that the chest catheter be removed after sclerosant instillation when drainage returns to less than 150 mL/day, which usually requires multiple days of hospitalization.

Recently, studies have reported the outcomes of accelerated pleurodesis protocols.[131,133-135] Yildirim et al[134] randomized patients to a standard protocol that required diminished PF drainage vs a protocol that instilled sclerosant immediately after catheter insertion. The success rate for pleurodesis did not differ between the 2 groups, but those following the accelerated protocol had shorter hospital stays. In a randomized controlled trial, Goodman and Davies[133] observed similar pleurodesis success rates when chest catheters were removed 24 hours vs 72 hours after instillation of talc slurry. In an observational study, Sartori et al[131] reported a high rate of success with pleurodesis when small-bore catheters were inserted with ultrasonographic guidance to ensure proper positioning and when serial ultrasonography was used to ensure that the pleural space was free of fluid before instillation of the sclerosant (Figure 3). Ultrasonography-directed thoracenteses were also performed intermittently to drain reaccumulating or loculated PF; catheters were removed when less than 100 mL of catheter drainage occurred during any 12-hour period. Marom et al[136] similarly demonstrated the value of ultrasonographic guidance in chest-catheter insertion. Spiegler et al[135] reported a 79% success rate with pleurodesis when the sclerosant was instilled as soon as 2 hours after catheter insertion with routine catheter removal 2 hours after instillation of the sclerosing agent.[135] Hospital stays could be shortened or even avoided with the use of tunneled pleural catheters[137] or portacath catheters.[138,139] These catheters can be inserted in an outpatient setting, allowing patients to return for instillation of a sclerosant if a spontaneous pleurodesis does not occur after 2 weeks of home drainage.

Sclerosants can cause acute pleuritis and pleuritic chest pain. Instillation of lidocaine through the chest catheter has been proposed to prevent pain but no evidence of efficacy exists.[140] One study reported good pain control with lidocaine spray administered before talc insufflation.[141] No evidence exists that patients should be rotated through 4 quadrant positions to ensure wide dispersal of the sclerosant in the pleural space.[142-144] Observational studies and animal investigations have shown that systemic corticosteroids lower the rate of successful pleurodesis and should be avoided.[101,145-148] The effects of nonsteroidal anti-inflammatory agents on pleurodesis have not been investigated in humans; however, ketoprofen has been shown not to hinder pleurodesis in a rabbit model.[149] Minimal data support the role of intrapleural instillation of fibrinolytic agents for patients with loculations whose lungs do not reexpand after chest-catheter insertion.[150]

Controversy exists regarding the ideal sclerosant for chest-catheter pleurodesis (Table 5). Because of the absence of adequate comparative trials of different agents, extensive practice variation exists.[124] A Cochrane Review[188] and another recent systematic review of the literature[144] concluded that talc had the highest efficacy for preventing MPE recurrence when compared with other commonly used sclerosants; most contemporary studies report a 71% to 96% success rate with talc instilled through a chest-catheter tube.[115,136,142,153,160,163,189,190] Talc could cause pleurodesis by promoting angiogenesis[191] and stimulating mesothelial cells to release basic fibroblast growth factor, interleukin 8, vascular endothelial growth factor, transforming growth factor, and other proinflammatory mediators that stimulate pleural fibrosis.[192,193]

Adverse effects of talc include dyspnea, fever, chest pain, atelectasis, pneumonia, arrhythmias, empyema, and acute respiratory failure.[115,194-196] Up to 16% of patients develop transient unilateral interstitial infiltrates ipsilateral to the side of pleurodesis.[197] Respiratory failure, which could progress to acute respiratory distress syndrome, occurs with equal frequency after talc administration by slurry (chest catheter) or insufflation (thoracoscopy). The small particle size of talc allows its systemic absorption and wide circulation to vascular beds distant from the pleural space, promoting tissue inflammation.[198,199] Different sources of talc vary in particle size, perhaps explaining why centers using larger talc particles for pleurodesis rarely observe acute respiratory failure,[200-203] whereas those that use smaller, noncalibrated talc report a 4% to 8% incidence of respiratory failure and a 30% incidence of severe hypoxemia.[115,204] Experts now recommend the use of talc calibrated to a mean particle size of less than 20 microns with no particles less than 10 microns. Other investigational and available sclerosants (Table 5) have not been compared with talc in large randomized trials, and so little information is available on their toxicity.

Thoracoscopic Pleurodesis

Various thoracoscopic procedures produce pleurodesis by intrapleural instillation of sclerosants or generation of pleural injury by dry-gauze abrasion or other physical techniques. Available instruments include video-assisted thoracoscopes, medical thoracoscopes, and pleuroscopes.[98,99,205] Video-assisted thoracoscopes allow wide access to the pleural space, making possible the lysis of extensive loculations and adhesions for patients who would otherwise not

TABLE 5. **Available and Investigational Sclerosing Agents for Pleurodesis**

Agent	Reported success rates* (%)
Mineral	
Talc	70-100[115,144,151-157]
Antibiotic	
Doxycycline	60-81[158-160]
Quinacrine	64-100[161-165]
Antiseptic	
Iodopovidone	64-96[166-170]
Silver nitrate	96[153]
Anticancer drug	
Bleomycin	64-84[148,156,171,172]
Mitoxantrone	76-88[173-175]
Cisplatin	65-83[176,177]
Bacterial product or component	
Corynebacterium parvum	65-92[178-182]
Staphylococcus aureus superantigen	100[183]
OK432	53-79[176,184,185]
Cytokine	
Interferon alpha-2β	62-100[171,186,187]

*Success rates variably reported as rate immediately after pleurodesis or rate obtained at different time points after pleurodesis.

benefit from pleurodesis. Disadvantages include cost and the need for general anesthesia and induced pneumothorax, which some patients with compromised lung function might not tolerate. However, the performance of VATS without general anesthesia has been recently reported.[206] Medical thoracoscopy and pleuroscopy are usually done with local anesthesia and moderate sedation. Thoracoscopy produces effective pleurodesis in 71% to 97% of patients[115,151,152,154,189,207-210] with a morbidity rate of 3% to 26% and a mortality rate of less than 1%.[123,154,208,210]

Thoracoscopic vs Chest-Catheter Pleurodesis

No large-scale appropriately randomized studies have compared the efficacy of pleurodesis by chest-catheter instillation of sclerosants vs various thoracoscopic techniques in patients with MPE. A recent Cochrane systematic review of 2 studies that treated 112 patients with talc by either chest catheter or thoracoscopy reported slightly better outcomes with thoracoscopy (relative risk of nonrecurrence, 1.19; 95% confidence interval, 1.04-1.36).[188] Although this difference was not supported by a subsequent randomized trial of talc pleurodesis by chest catheter or thoracoscopy, subgroups of patients with underlying lung or breast cancer had better outcomes with thoracoscopy.[115] Crnjac et al[123] observed similar outcomes for thoracoscopy with mechanical pleural abrasion vs chest-catheter pleurodesis with talc slurry; at pH values less than 7.30, better outcomes were observed with thoracoscopy (81% vs 55%). Low pH can be used to identify patients with extensive intrapleural loculations and adhesions that can be lysed by thoracoscopy, perhaps explaining this observed difference.

In the absence of high-quality comparative outcome studies, the available institutional expertise with the various pleurodesis techniques and observed clinical outcomes should determine the local approach to pleurodesis. Some patient-related factors, however, are important to consider. Patients with clinical, radiographic, or ultrasonographic signs of extensive pleural tumor and trapped lung are more likely to respond to pleurodesis by thoracoscopy, which can lyse adhesions or, if lung reexpansion and a successful pleurodesis appear unlikely, indicate that drainage via a long-term indwelling catheter is required.[113] At most centers, patients are referred for chest-tube pleurodesis because of its high success rate, low cost, and low morbidity.[152] Wider adoption of small-bore, tunneled catheters for pleurodesis could further support the use of chest-catheter pleurodesis.

Drainage via Long-Term Indwelling Catheter

Long-term indwelling catheters placed with or without ultrasonographic guidance allow intermittent drainage of up to 1000 mL of PF 2 to 3 times a week for prolonged periods.[211-217] Immediate relief of dyspnea occurs in 94% to 100% of patients,[213-216] persistent relief for 30 days in 90%.[213] Patients tolerate the procedure well with close follow-up for complications of catheter infection, insertion-site skin breakdown, cellulitis, catheter obstruction with tension pleural effusion, empyema, and tumor spread along the catheter track.[212,214,215,218,219]

Several studies report that spontaneous pleurodesis occurs in 40% to 58% of patients with long-term indwelling catheters after 2 to 6 weeks of drainage.[214,216] After several weeks of drainage, sclerosants can be instilled through the catheter if spontaneous pleurodesis does not occur.[213] In a randomized trial, Putnam et al[220] showed equivalent symptom control with long-term indwelling catheters and pleurodesis with doxycycline instillation through a chest tube. Because of the high rate of "spontaneous" pleurodesis and the ability to later instill sclerosants, some experts recommend long-term indwelling catheters as primary MPE therapy for patients who can manage home drainage.[137] Additional prospective studies are needed to compare the cost of drainage using long-term indwelling catheters as primary therapy vs thoracoscopy and inpatient chest-catheter pleurodesis and to assess patients' attitudes toward and outcomes with these procedures.

PLEUROPERITONEAL SHUNTING

Among patients who cannot undergo or do not benefit from pleurodesis, those who can manage long-term indwelling catheter drainage at home could benefit from pleuroperitoneal shunting.[113,221-223] Symptoms subside in 95% of treated patients; complications occur in 15%.[222] Paraneoplastic chylous effusions could also respond to shunting.[224] Shunt complications occur in 15% of patients in the form of skin erosion, infection, and shunt occlusion that requires shunt revision or replacement.[222]

CONCLUSION

Considerable advances have been made in the diagnosis of MPEs through specialized cytologic and imaging studies along with improved methods for pleural biopsy. Although multiple, well-tolerated techniques exist to control MPEs by pleurodesis or long-term catheter drainage, all management approaches remain palliative. In selecting an appropriate intervention, clinicians should consider local expertise, the patient's clinical status, and comparative institutional outcomes from the available techniques.

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The Symposium on Solid Tumors will continue in the March issue.