Literature Review

Malignant Pleural Effusion: A Contemporary Approach to Diagnosis and Personalized Management

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Abstract

Malignant pleural effusion (MPE) is a manifestation of advanced malignancy characterized by abnormal accumulation of pleural fluid due to tumor cell infiltration. It most commonly originates from lung, breast cancer, or lymphoma and is associated with dyspnea, chest pain, and impaired quality of life. Diagnosis of MPE is established through pleural fluid cytology or histopathological confirmation, supported by radiological imaging. Liquid biopsy offers a minimally invasive approach for detecting molecular alterations. Although diagnostic and therapeutic modalities have improved, management remains primarily palliative. Therapeutic thoracentesis, chemical pleurodesis using talc, and indwelling pleural catheter (IPC) placement are the main palliative strategies. Combination therapy of IPC with talc slurry demonstrates higher rates of spontaneous pleurodesis and shorter hospital stays. Systemic therapies such as chemotherapy, targeted therapy, and immunotherapy provide additional disease control in selected patients. Although current approaches have improved diagnostic and therapeutic outcomes, most treatments remain palliative. Therefore, a multidisciplinary and personalized strategy is essential to optimize patient quality of life. This review underscores the importance of early diagnosis and management of malignant pleural effusion, including cytology, pleural biopsy, imaging, and liquid biopsy, as well as therapeutic approaches such as thoracentesis, pleurodesis, indwelling pleural catheter, systemic therapy, and palliative care.

Keywords: malignant pleural effusion, management, pleurodesis, thoracentesis

INTRODUCTION

Malignant pleural effusion (MPE) is the accumulation of fluid in the pleural cavity due to malignant involvement of the pleura. Early diagnosis is essential to identify the underlying malignancy and guide appropriate therapeutic decisions. MPE is typically exudative in nature, but transudative presentations may occur.[1] It affects approximately 15–20% of patients with cancer and may arise from primary

pleural malignancy, such as mesothelioma, or from metastatic spread, most commonly originating from lung, breast, and ovarian malignancies.[2,3]

Malignant pleural effusion is associated with a considerable symptom burden and a marked reduction in quality of life. Patients commonly present with dyspnea, chest pain, fatigue, cachexia, and diminished daily functioning. The condition also carries a poor prognosis, with median survival ranging from 3 to 12 months depending on the type of primary malignancy, disease stage, and performance status.[2] The presence of malignant cells in pleural fluid generally reflects advanced or metastatic disease and is associated with reduced life expectancy. Despite substantial advances in diagnostic techniques and therapeutic interventions, the management of MPE remains largely palliative.[3]

The goals of management are to relieve symptoms, prevent recurrence, and improve quality of life through interventions such as thoracentesis, pleurodesis, thoracoscopy, chest tube drainage, and indwelling pleural catheter placement. Current clinical guidelines support a patient-centered and individualized approach, with treatment decisions based on comorbidities, rate of fluid reaccumulation, lung expandability, overall clinical condition, tumor characteristics, and patient preferences.[3,4]

DEFINITION

Malignant pleural effusion is a clinical manifestation of malignancy that reflects tumor cell involvement of the pleural cavity. MPE is diagnosed when malignant cells are identified through cytological examination of pleural fluid or histopathological evaluation of pleural biopsy tissue.[5] Approximately 15–20% of cancer patients develop metastatic processes that present as MPE.[6]

Approximately 37% of MPE cases are caused by lung cancer, with the most common causes being lung adenocarcinoma (29–37%), small-cell carcinoma (6–9%), and squamous cell carcinoma (less frequently). The prevalence of MPE in malignant mesothelioma ranges from 54% to 90%. However, the overall number of mesothelioma cases is substantially lower, so its epidemiologic contribution to the total number of MPE cases is relatively small.[7]

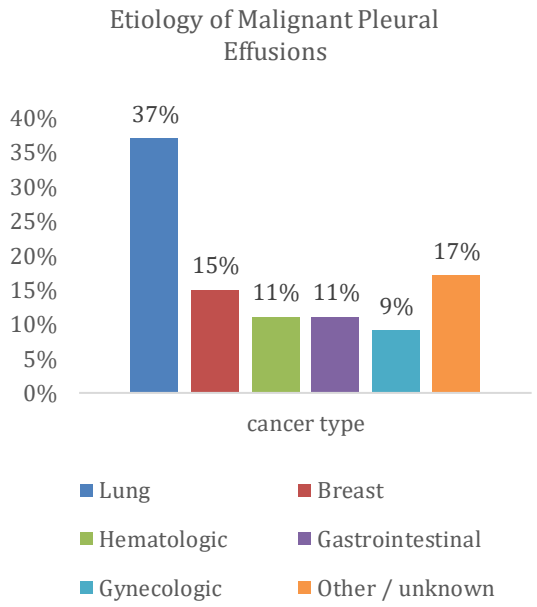

Figure 1. Malignant pleural effusions caused by various primary malignancies

PATHOGENESIS

Malignant pleural effusion may arise either from a primary pleural malignancy or

from metastatic involvement of the pleura through pleural cavity dissemination and lymphatic obstruction.[7] The accumulation of pleural fluid in MPE results from disturbances in the Starling forces that regulate fluid balance, caused by tumor cell infiltration leading to increased production or decreased reabsorption of pleural fluid. The pathogenesis of MPE is complex, involving intricate interactions among tumor cells, host cells, and a variety of chemical mediators.[3]

Several mechanisms contribute to the development of MPE:

1. Tumor spread to the pleura. Pleural invasion by tumor cells may occur through lymphatic dissemination or infiltration from adjacent structures such as the chest wall and diaphragm. However, autopsy studies indicate that the primary mechanism of tumor spread to the pleura is hematogenous dissemination. Once malignant cells reach the visceral pleura, they spread to the parietal pleura either by tumor attachment along the pleural surfaces or through exfoliated tumor cells floating within the pleural fluid.
2. Mechanisms of pleural fluid production in MPE. The pleural microenvironment subsequently becomes immunosuppressive, characterized by impaired macrophage and cytotoxic lymphocyte function, along with increased production of pro-inflammatory mediators. Interactions between tumor cells and host cells trigger the release of vasoactive mediators, disrupting the balance between permeability-stimulating molecules (e.g., vascular endothelial growth factor—VEGF, tumor necrosis factor—TNF, osteopontin—OPN) and inhibitory molecules (e.g., endostatin). This imbalance leads to increased vascular extravasation into the pleural space, resulting in pleural fluid accumulation.
3. Cellular and molecular biology of MPE. The resulting MPE is rich in protein and contains various inflammatory mediators, including:
   - Inflammatory cytokines such as interleukin-2 (IL-2), interleukin-6 (IL-6), and TNF, which promote inflammatory responses and pleural irritation;
   - Pro-angiogenic mediators, including angiopoietin-1 and angiopoietin-2;
   - Molecules that enhance vascular hyperpermeability, such as VEGF, matrix metalloproteinases (MMPs), C-C motif chemokine ligand 2 (CCL2), and OPN.

   These processes are further influenced by tumor-derived activation of pro-inflammatory and pro-angiogenic transcriptional programs, mediated by transcription factors such as nuclear factor kappa-B (NF-κB) and signal transducer and activator of transcription-3 (STAT3). In addition, mast cells contribute to pathogenesis by releasing tryptase alpha/beta-1 and interleukin-1β (IL-1β), which increase vascular permeability within the pleural microvasculature and promote both fluid

accumulation and tumor growth through NF-κB activation.

DIAGNOSIS

Diagnosis of MPE should be structured around confirming pleural malignancy rather than simply identifying pleural fluid. In patients with unilateral or otherwise unexplained pleural effusion, thoracic ultrasound and contrast-enhanced computed tomography (CT) are important early investigations to define the effusion, identify pleural abnormalities suggestive of malignancy, and search for an underlying primary tumor, but a negative CT does not exclude pleural malignancy.[8,9]

Diagnostic thoracentesis with pleural fluid cytology should be the initial test in suspected secondary pleural malignancy. When cytology is positive, then MPE is confirmed, although additional tissue may still be required for histologic subtyping or molecular analysis. When cytology is negative or nondiagnostic, malignancy should not be excluded, and further tissue acquisition should be guided by imaging findings.[8,9]

Image-guided pleural biopsy is appropriate when there is a pleural target, whereas medical thoracoscopy or video-assisted thoracoscopy (VATS) is preferred when suspicion remains high despite nondiagnostic fluid analysis or when direct pleural inspection and biopsy are needed. Tumor markers in pleural fluid may be adjunctive in selected cases but should not replace cytology or pleural biopsy in the diagnostic pathway.[8,9]

Clinical Examination

Ferrer et al described five clinical characteristics suggestive of MPE: 1) presence of symptoms such as dyspnea, chest pain, or constitutional symptoms; 2) symptoms for more than 1 month; 3) absence of fever; 4) hemorrhagic pleural effusion; and 5) thoracic CT findings consistent with malignancy, including masses, atelectasis, or lymphadenopathy.[9]

Physical examination findings in pleural effusion are influenced by the volume of pleural fluid, where small effusions may produce minimal clinical signs, whereas larger effusions usually result in abnormalities on inspection, percussion, and auscultation. In massive effusions, reduced chest wall expansion, widening of the intercostal spaces, and mediastinal deviation may be present.[10]

Radiological Imaging

In addition to clinical findings, supportive imaging plays an essential role. Chest radiography often shows features suggestive of MPE, including pleural effusion, pleural thickening, and mediastinal shift. A lateral view can detect as little as 50 mL of pleural fluid. Malignancy should be suspected if the effusion is loculated, unilateral or asymmetric, massive, or recurrent after drainage.[11] Pleural thickening may appear as focal or diffuse nodular pleural involvement. Widening of the mediastinal contour suggests mediastinal pleural thickening. Radiologic signs may appear singly or in combination.[12]

Thoracic ultrasound (TUS) is a non-invasive, inexpensive, portable imaging modality that avoids radiation exposure and allows real-time assessment. TUS can identify the volume, location, and characteristics of pleural effusion and visualize surrounding structures.[12] It is important for diagnosis, management, and follow-up.

Thoracic ultrasound assists in guiding procedures, evaluating peripheral pleura, visualizing fibrin strands and septations, pleural thickening, and pleural metastases. It also detects small effusions, identifies optimal catheter insertion sites, and assesses lung re-expansion. The strongest ultrasound predictors of pleural malignancy are pleural and diaphragmatic nodularity and pleural thickening >15 mm in B-mode imaging.[12]

Computed tomography of the chest offers superior sensitivity compared with conventional radiography for detecting pleural effusion and pleural thickening. CT also allows detailed evaluation of the lung parenchyma and mediastinal structures.[12] CT findings suggestive of malignant pleural disease include pleural fluid with septations, increased attenuation (Hounsfield units), and loculated collections. Highly suggestive features include nodular pleural thickening, irregular pleural surfaces, mediastinal pleural involvement, circumferential pleural thickening and pleural thickening >10 mm.[13]

Positron emission tomography (PET)/CT is useful in distinguishing benign from malignant pleural disease because most malignancies demonstrate increased uptake of fluorodeoxyglucose (FDG). Yang et al developed and validated a PET-CT scoring system with a sensitivity of 89.7% (95% CI=75.8–97.1%) and specificity of 88.6% (95% CI=73.3–96.8%). Patterns of FDG uptake in MPE include linear, nodular, and encasement types, such as mesothelioma, which commonly shows the encasement pattern, although lung cancer and lymphoma may present similarly. PET/CT is also useful for guiding biopsy by identifying the most metabolically active areas and assessing the extent of disease and treatment response.[12,14]

Thoracentesis

Thoracentesis is a relatively low-risk procedure commonly performed under ultrasound guidance. It plays a key role in confirming malignant disease and providing symptomatic relief from dyspnea in patients with effusion. Collected pleural fluid should be submitted for biochemical testing (around 5 mL) and for cytological assessment (at least 50 mL). Roughly 40% of malignant pleural effusions contain bloody fluid.[12,15]

Cytology remains the most straightforward diagnostic tool for identifying malignancy, with its accuracy affected by the primary cancer type, the number of samples obtained, and laboratory processing methods. The overall sensitivity of pleural fluid cytology for detecting malignant effusion is approximately 58%, improving when two separate specimens are examined using smear staining techniques (such as Papanicolaou or Giemsa) alongside cell-

block preparation with hematoxylin–eosin staining.[12,15]

Pleural Biopsy

Pleural biopsy is the gold standard for diagnosing MPE. Biopsy guided using CT scan or TUS has high diagnostic accuracy (70–83%). Sensitivity increases substantially when a targetable pleural lesion or thickening is present. When pleural thickening exceeds 1 cm, CT-guided biopsy yields sensitivity comparable to thoracoscopy. Diagnostic yields are high for both modalities—84% for TUS and 76–100% for CT—with low complication rates.[12]

Thoracoscopy

Direct visualization of the pleura via medical thoracoscopy or VATS offers superior diagnostic sensitivity, particularly when pleural nodularity is present. Medical thoracoscopy demonstrates a diagnostic sensitivity of 92.6% for pleural malignancy. It may be performed under local anesthesia using rigid or semi-rigid thoracoscopes. Although comparative trials between medical thoracoscopy and VATS are lacking, both have strong diagnostic and therapeutic utility. VATS provides advantages such as more effective drainage in complex loculations and the ability to convert to open thoracotomy when necessary.[8]

Cytology and Histopathology

Pleural fluid cytology remains a common initial diagnostic test, with a mean sensitivity of around 60%. Diagnostic performance depends heavily on tumor type, sample preparation, and the cytopathologist's expertise. Sensitivity is significantly lower in mesothelioma (6%) than in adenocarcinoma (80%), making pleural biopsy the preferred diagnostic modality in suspected mesothelioma.[3,13]

Advances in targeted cancer therapy have increased the importance of obtaining adequate tissue for immunohistochemistry (IHC), which helps differentiate tumor subtypes and identify the primary source of metastatic adenocarcinoma.[3,13] Cell-block techniques offer notable advantages over conventional smears by preserving tissue fragments, cellular architecture, and antigenicity. This increases diagnostic sensitivity and allows for IHC and special staining, making cell-block analysis an invaluable adjunct.[3]

Routine pleural fluid analysis includes pH, glucose, protein, lactate dehydrogenase (LDH), cytology, and microbiology. Several parameters may suggest MPE: LDH >1000 U/L, lymphocyte count >50–70%, pH <7.30, and low glucose levels (30–50 mg/dL). Although MPE is typically exudative, 5–10% may appear transudative.[5,13]

Recent research has focused on pleural fluid protein biomarkers for diagnosis, prognosis, and treatment response. These include tumor-related proteins (mesothelin, CEA, CA 15-3, CA-125, and CYFRA 21-2), immune-cell surface markers (including macrophage-derived RNA), extracellular-matrix proteins (OPN and fibulin-3) and nucleic-acid

signatures (DNA/RNA levels and sequencing).[5,13]

Liquid Biopsy

Liquid biopsy for MPE is a minimally invasive diagnostic method that detects tumor-related biomarkers in pleural fluid. These include circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), extracellular vesicles (exosomes), and circulating tumor cells (CTCs). This method detects oncogenic driver mutations (EGFR, KRAS, ALK) and resistance mutations such as EGFR T790M.[16]

Advantages include the ability to detect malignancy even when cytology is negative, identify molecular targets for therapy, and monitor treatment response or recurrence using a safe and convenient procedure. Limitations include a lack of standardized extraction methods, variation in ctDNA yield depending on tumor burden, and risk of false-negative results in cases with very low tumor load. Technologies such as NGS and ddPCR are costly and require advanced laboratory expertise. Although promising, liquid biopsy for pleural fluid remains investigational pending further clinical validation.[16]

MANAGEMENT

Current management options for MPE include therapeutic thoracentesis, chemical pleurodesis, and an indwelling pleural catheter (IPC). According to treatment objectives, several high-quality, multicentre randomized controlled trials have been conducted to evaluate therapeutic strategies for MPE.[4]

Based on these studies, several guidelines have been published by regional specialist associations to support clinical decision-making, including the American Thoracic Society/Society of Thoracic Surgeons/Society of Thoracic Radiology (ATS/STS/STR), European Respiratory Society/European Association for Cardio-Thoracic Surgery (ERS/EACTS), British Thoracic Society (BTS), and Spanish Society of Thoracic Surgery (SECT).[4]

All four consensus guidelines agree that no pleural intervention should be performed in asymptomatic patients with MPE. Individuals with a very poor prognosis (life expectancy <4 weeks) should receive palliative supportive care. In cases of non-expandable lung (NEL), all guidelines recommend the use of IPC. The BTS guideline is unique in providing a formal definition of NEL. When the lung is able to re-expand, the available therapeutic options become broader. However, both IPC and talc pleurodesis are recommended as first-line options. All guidelines emphasize that assessment of functional status is essential when making treatment decisions.[4,17]

All four guidelines recommend ultrasound-guided thoracentesis as the initial diagnostic step, followed by cytology or pleural biopsy when the diagnosis remains uncertain. The two therapeutic strategies universally endorsed are pleurodesis and IPC, with selection individualized based on lung expandability, prognosis, and patient priorities.[14,18–20]

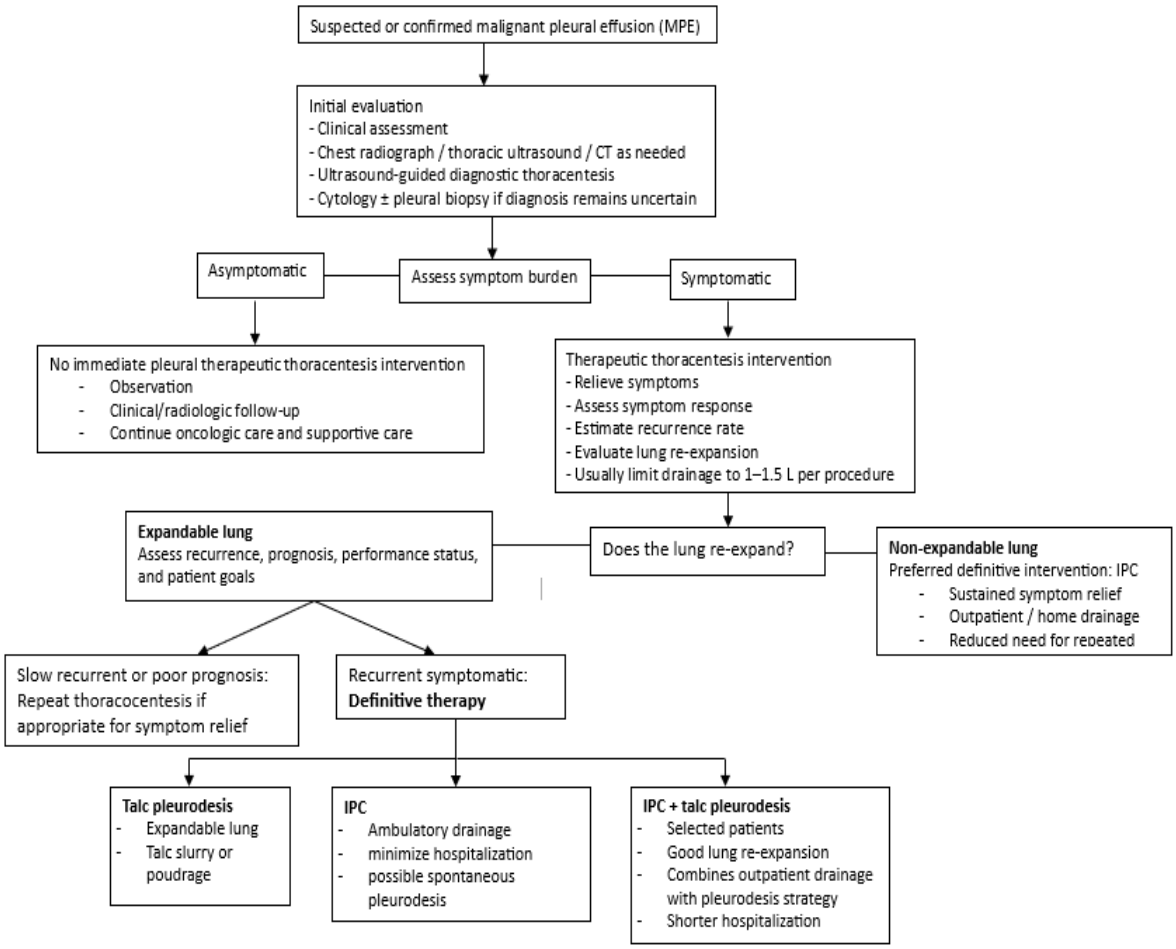

Figure 2. Clinical algorithm for quality of life-oriented management of malignant pleural effusion

The differences among the guidelines lie primarily in their emphasis on clinical practice, where ATS highlights flexibility in choosing IPC, pleurodesis, or a combination of both, while ERS emphasizes evidence derived from randomized clinical trials and the importance of shared decision-making.[14,18–20]

The British Thoracic Society incorporates an approach that distinguishes between ambulatory care and inpatient management. SECT considers the combination of techniques (e.g., talc administration via IPC) as a potential strategy. All guidelines agree that routine prophylactic radiotherapy to prevent tumor-tract seeding is not recommended.[14,18–20]

The primary focus of managing MPE is palliative, to improve and maintain the patient's quality of life. Management begins with confirmation of MPE and assessment of symptom burden, performance status, prognosis, systemic treatment options, and patient priorities.[14]

Therapeutic Thoracentesis

Therapeutic thoracentesis refers to the removal of a certain volume of pleural fluid with the aim of reducing dyspnea in symptomatic patients. The maximum amount of fluid that can be safely removed remains a subject of debate. However, current guidelines recommend draining 1–

1.5 liters per procedure due to the risk of re-expansion pulmonary edema (REPE).

Re-expansion pulmonary edema is a rare but potentially fatal complication that occurs when a collapsed lung rapidly re-expands following evacuation of air or pleural fluid. The clinical manifestations of REPE include anterior chest pain, shortness of breath, and oxygen desaturation. Recognized risk factors include rapid removal of a large volume of fluid, younger patient age, and the presence of a significant pneumothorax or substantial effusion that has caused lung collapse for over a week.[14]

Ultrasound-guided thoracentesis is generally regarded as a safe procedure with a low incidence of complications and can be performed repeatedly, in both inpatient and outpatient settings, particularly for individuals with limited life expectancy. However, over 85% of patients experience recurrent fluid buildup, making definitive treatment necessary for sustained symptom control.[2]

The benefits of therapeutic thoracentesis include assisting in diagnosis, confirming whether fluid removal improves dyspnea or cough (although up to 25% of patients do not experience symptomatic improvement after drainage), monitoring the rate of re-accumulation, and assessing for the presence of non-expandable lung following fluid evacuation.[2]

Pleurodesis

Pleurodesis works by creating adhesion between the parietal and visceral pleura to stop recurrent fluid buildup. Introducing a sclerosing agent into the pleural cavity induces inflammation and fusion of the pleural layers, thereby obliterating the pleural space. Talc is widely used as a safe and effective agent for this purpose, with its particle size optimized to reduce the likelihood of respiratory side effects. Successful pleurodesis requires full contact between the visceral and parietal pleura. Therefore, the procedure is not suitable in the presence of significant visceral pleural thickening that prevents full lung expansion.[13]

Pleurodesis can be performed using talc slurry (a suspension instilled through a chest tube) or talc poudrage (insufflation of talc) during thoracoscopy. Success rates vary but are generally below 80% in randomized controlled trials. Studies report approximately 75% success at 1 month, decreasing to around 50% at 6 months.[5]

Although talc distribution during thoracoscopy has often been considered advantageous, numerous studies have demonstrated no significant differences between talc poudrage and talc slurry in terms of success rates, recurrence of effusion, or complication rates. For this reason, talc poudrage is recommended only when thoracoscopy is already being performed for another indication, such as a pleural biopsy.[5]

The most common side effects of pleurodesis are fever and pain. However, the use of nonsteroidal anti-inflammatory drugs or opioids has not been shown to significantly affect pain severity or procedural effectiveness. Expert consensus recommends reducing or discontinuing

corticosteroids prior to performing pleurodesis, as corticosteroids may impair the inflammatory process required for pleural adhesion.[11]

A newer approach utilizing a thoracic ultrasound–based lung sliding score following talc pleurodesis has been shown to shorten hospital stay compared with the BTS protocol, which relies on chest radiography and monitoring of drainage output. Using the ultrasound-based approach, most patients can be discharged within one day.[11]

Indwelling Pleural Catheter (IPC)

Indwelling pleural catheters are long-term pleural drainage devices that are implanted subcutaneously. The use of IPC allows patients or family members to perform pleural fluid drainage independently at home, thereby reducing hospital admissions and the need for repeat procedures. Spontaneous pleurodesis occurs in approximately 30–40% of patients with IPC. Daily drainage following IPC insertion improves quality of life and increases the rate of spontaneous pleurodesis compared with symptom-guided drainage strategies. The combination of IPC and talc slurry is safe and accelerates pleurodesis without increasing significant complications.[15]

The combined IPC–talc slurry management pathway begins with insertion of the IPC and routine drainage to ensure lung re-expansion. Following satisfactory evacuation of the pleural space, sterile talc slurry is instilled through the IPC, and the catheter is subsequently occluded without the application of continuous negative pressure. Drainage is subsequently resumed at regular intervals to maintain pleural apposition until pleurodesis occurs.[5]

Success is defined as drainage output less than 50 mL on three consecutive drainages, accompanied by radiological evidence of effusion resolution. Once pleurodesis is achieved, the IPC can be removed, reducing long-term infection risk and improving patient comfort.[5] Thus, the IPC–talc slurry strategy represents a modern, adaptive, safe, and evidence-based approach to MPE management.[21]

The advantages of IPC should be carefully weighed against its potential risks, including pain, infection, symptomatic loculation, catheter dislodgement, and catheter-tract metastasis. Overall, most complications can be handled with conservative measures and seldom need the removal of the catheter. For patients who develop symptomatic loculated fluid collections, intrapleural fibrinolytic agents—such as alteplase or urokinase—may be administered to help break down the septations. Infections are generally manageable with antibiotics, whereas catheter-tract metastasis may be treated with localized radiotherapy.[22]

Indwelling pleural catheters are indicated in cases of recurrent pleural effusion, trapped lung, or failed pleurodesis in patients with MPE. The optimal timing for IPC placement is immediately after the first recurrence of effusion or when repeated thoracentesis becomes necessary—there is no need to wait for completion of chemotherapy.[23]

Pigtail and Large Bore Chest Tube

Several studies have compared the effectiveness and risk of complications among pigtail catheters, large-bore chest tubes (LBCTs), and IPC in various conditions such as MPE, pneumothorax, and empyema. Pigtail catheters serve as an alternative option in the management of pleural effusion, pneumothorax, and empyema because they are generally safer, better tolerated in terms of pain, and associated with shorter drainage duration and hospital stay compared with standard chest tubes.[24]

Meanwhile, diagnostic thoracentesis is the initial step to determine pleural fluid characteristics and perform cytological analysis. If the patient is symptomatic and results reveal MPE—or malignancy is strongly suspected—definitive intervention (pleurodesis or IPC) should not be delayed, and there is no need to wait until systemic therapy is initiated or completed. If the patient presents with severe dyspnea, the placement of a temporary chest tube is permissible, even before cytology results are available, to allow decompression and improve symptoms.[18,19]

Table 1. Comparison of Pigtail Catheter, IPC, and LBCTs in MPE

	Pigtail catheter	**IPC**	**LBCTs**
Indication	Recurrent effusion	Effusion with trapped lung	Effective for draining thick, viscous pleural fluid
Lumen Size	Small (8–14 Fr)	Medium (15.5 Fr)	>20 Fr
Pain	Lower pain compared to large tubes	Well tolerated	More significant pain during the procedure
Complications	Higher complication risk in cases of drainage failure	• Increased risk of fluid accumulation in dependent lung areas; • Risk of catheter-tract metastasis, leakage and catheter fracture during removal	Higher incidence of complications such as air embolism, air leak and hypotension
Cost	More expensive than LBCTs	Expensive	Lower cost
Length of hospital stay	Shorter	Shorter	Longer
Disadvantages	• No distal cuff, easily dislodged if not secured properly; • No one-way valve → must remain connected to a drainage bag continuously	More complex insertion technique	• Restricts patient mobility; • Reduces quality of life while in place
Advantages	Low rate of catheter-tract spread, leakage, or fracture	• Possible spontaneous pleurodesis; • Polyester cuff promotes scar formation and catheter stability; • Allows patient-directed drainage based on symptoms and fluid reaccumulation	Rapid and effective drainage for large, viscous, or hemorrhagic effusions

Systemic Therapy

All patients with malignancy and good performance status should be considered for systemic anticancer treatment (SACT) according to national guidelines. Observational data indicate that in certain highly chemosensitive tumors, systemic therapy may help control pleural effusion. However, after adjusting for confounding factors, SACT is not a strong predictor of control of malignant pleural effusion.[19]

Definitive pleural interventions (such as pleurodesis) remain the strongest predictors of effusion control, and there is no evidence supporting the use of SACT to reduce the need for definitive pleural procedures in malignancy. Clinical guidelines such as BTS and ATS emphasize that the management of MPE should remain focused on symptom control through drainage, pleurodesis, or insertion of an indwelling pleural catheter.[19]

Chemotherapy, immunotherapy, targeted therapy, or a combination of these therapies for advanced cancers are selected based on patient compliance, histology, biomarkers, and molecular profile. Systemic chemotherapy for MPE depends on the patient's performance status, tolerance, and overall feasibility. Cisplatin, a potent anticancer drug that inhibits DNA replication, is widely used across various malignancies. In advanced-stage lung cancer, cisplatin is often paired with pemetrexed or paclitaxel, with the choice determined by the tumor's histologic subtype. Cisplatin's effects on MPE include inhibition of the primary tumor, metastatic spread, and pleural fluid accumulation via the pleural circulation.[14]

Immunotherapy targets immune checkpoint receptors that influence the tumor microenvironment and enhance T-cell function. Programmed cell death protein-1 (PD-1) and its ligand (PD-L1) are expressed on T cells, tumor cells, and infiltrating myeloid cells. Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4 represent the best-established pathways. Inhibition of these pathways enhances T-cell cytotoxicity.[12,14]

The KEYNOTE-189 trial demonstrated that adding pembrolizumab (an anti-PD-1 monoclonal antibody) to standard chemotherapy improved overall survival and progression-free survival in patients with lung cancer without EGFR or ALK mutations. The concordance of PD-L1 expression between primary tumor histology and pleural fluid is relatively high. However, several studies suggest that responses to ICI therapy may be reduced in patients with MPE.[12,14]

Anti-angiogenic therapy, such as bevacizumab (a recombinant monoclonal antibody targeting VEGF), combined with carboplatin–pemetrexed chemotherapy, has shown benefit in patients with MPE by improving overall and progression-free survival. Amucirumab, a monoclonal antibody targeting VEGF receptor-2, has demonstrated promising activity in lung cancer and is currently being assessed in phase II studies alongside docetaxel for patients with malignant pleural effusion. Endostatin, a broad-spectrum inhibitor of angiogenesis, may also enhance treatment

outcomes when used with chemotherapy, though further confirmation from prospective randomized trials is required.[14]

The success of combining chemotherapy with ICIs or anti-angiogenic therapy has driven the development of targeted therapies. Several trials have shown improved survival with mutation-specific inhibitors, including EGFR-TKIs (e.g., osimertinib), ROS1 inhibitors (lorlatinib), and ALK inhibitors (alectinib, lorlatinib).[14]

Nevertheless, most patients with EGFR mutations acquire resistance eventually, making repeated molecular analysis of pleural fluid important for treatment adjustments. Newly targetable oncogenic mutations such as KRAS G12C can now be treated with sotorasib and adagrasib, which are currently approved by the Food and Drug Administration for patients with progressive disease after receiving ≥1 line of systemic therapy.[14]

Intrapleural chemotherapy may provide local cytotoxic effects with minimal systemic absorption. A meta-analysis of intrapleural bevacizumab combined with chemotherapy demonstrated higher complete remission rates compared with intrapleural chemotherapy alone, with only a small increase in adverse events. One study comparing intrapleural versus intravenous bevacizumab in non-small cell lung cancer with MPE reported better complete/partial response rates and longer response duration in the intrapleural group, although these findings were not statistically significant.[14]

An improvement in overall response in patients with MPE also occurred with the addition of intrapleural endostatin to standard chemotherapy. Several phase I and II trials of intrapleural chemotherapy have shown short-term partial or complete responses. However, direct comparisons with standard systemic therapy are lacking, and further randomized trials are needed.[14]

Meanwhile, hyperthermic intrathoracic chemotherapy (HITHOC) is an intraoperative technique involving direct administration of heated chemotherapeutic agents into the thoracic cavity, with perfusate temperatures maintained at 41–43°C. This technique enhances local cytotoxicity against neoplastic cells by combining the synergistic effects of chemotherapy and hyperthermia while minimizing systemic toxicity.[25]

It is used as part of multimodal therapy for malignant pleural mesothelioma, thymic carcinoma, advanced lung cancer with pleural involvement, and selected cases of secondary pleural metastases from breast or ovarian cancer. The most commonly used agent is cisplatin, which may be combined with doxorubicin or mitomycin C at 41–43°C with infusion durations of 60–90 minutes in various studies.[25]

A combination of hyperthermia and intrapleural cisplatin (200 mg/m² BSA for 120 minutes at 43°C) has been shown to induce significant apoptosis in neoplastic cells. Apoptotic activity begins immediately after perfusion and peaks at approximately 24 hours. The mechanisms of chemotherapy include mitochondrial

depolarization, phosphatidylserine translocation, and caspase activation. Hyperthermia contributes via cancer cell protein denaturation, inhibition of RNA and DNA synthesis, mitotic arrest, increased reactive oxygen species (ROS), destabilization of lysosomes, increased membrane permeability, and enhanced membrane transport. These changes affect cellular metabolism, excretion, and drug pharmacokinetics, thereby amplifying chemotherapeutic cytotoxicity.[25,26]

Palliative Therapy

Dyspnea, pain, cough, and anxiety are the most common physical and emotional symptoms experienced by patients with MPE. Pharmacological therapy typically involves the use of opioids, which play a central role in relieving symptoms and improving patients' quality of life.[23]

Although morphine is the most extensively studied opioid, several studies have demonstrated that other opioids—such as oxycodone, fentanyl, and methadone—have comparable efficacy. The use of benzodiazepines in combination with opioids may help alleviate dyspnea, particularly in patients with significant anxiety. Additionally, codeine and levodropropizine are effective in controlling cough symptoms.[12]

COMPLICATIONS

Nonexpandable Lung (NEL)

Nonexpandable lung develops when a fibrotic peel forms on the visceral pleura, when the visceral pleura becomes thickened by malignancy, or when multiple metastatic nodules impair lung expansion and prevent adequate contact between the visceral and parietal pleura. NEL occurs in over 30% of malignant pleural effusion cases and substantially reduces the effectiveness of standard pleurodesis for long-term fluid control. It is often recognized only after pleural fluid has been drained.[14]

Thoracentesis with pleural manometry may aid in identifying NEL, as poor lung compliance leads to marked drops in pleural pressure and elevated pleural elastance. However, studies suggest that routine manometry does not lower the risk of re-expansion pulmonary edema or procedure-related chest pain.[14]

Noninvasive methods to predict NEL include the absence of the sinusoid sign on thoracic ultrasound—a dynamic M-mode indicator of atelectatic lung movement—and reduced mobility of the collapsed lung. For patients with NEL, an indwelling pleural catheter remains the primary treatment option. In the AMPLE-2 trial, approximately 30% of patients developed spontaneous pleurodesis within six months of IPC placement, particularly in those undergoing daily rather than symptom-guided drainage.[10]

Selected patients may undergo surgical intervention, such as VATS pleurectomy or decortication to remove the visceral pleural layer. However, attempts to surgically re-expand the lung are often associated with lengthy operative times

and a high likelihood of persistent postoperative air leaks.[10]

Loculated Malignant Pleural Effusion

Septations in MPE can hinder drainage through chest tubes. Pleural fluid that remains in the pleural cavity may cause persistent dyspnea and reduce the rate of successful pleurodesis because the visceral and parietal pleura cannot adequately appose. Adhesiolysis can be performed during thoracoscopy, but surgery is often too invasive.[2]

Intrapleural fibrinolytics as monotherapy are ineffective for pleural infection but have shown benefit in improving drainage in MPE. The BTS guideline states that fibrinolytic therapy (urokinase) can reduce hospital length of stay in patients with loculated effusions. Intrapleural fibrinolytics can enhance drainage and improve dyspnea in loculated effusions, especially in patients with an IPC.[2]

Re-expansion Pulmonary Edema (REPE)

Removing more than 1.5 liters of pleural fluid increases the risk of developing REPE. This complication typically emerges within the first hour after thoracentesis and most commonly manifests within the first 24 hours. REPE occurs when capillary permeability rises as a result of endothelial injury, which may be driven by hypoxia, oxidative stress, surfactant loss, shifts in pulmonary arterial pressures, increased blood flow, and rapid capillary dilation. Additional contributing factors include heightened perfusion following prior vasoconstriction, abrupt pressure changes, impaired lymphatic drainage, and venous constriction.[10]

Chest Pain and Catheter-related Infection

Active pleurodesis works by intentionally inducing pleural injury—either mechanically, such as via abrasion during VATS, or through chemical irritation using agents like talc, bleomycin, povidone-iodine, doxycycline, autologous blood, or *Corynebacterium parvum*. These sclerosing agents can be delivered through pleural catheters or during medical thoracoscopy. Major contraindications include the presence of a trapped lung or a loculated effusion.[13]

The most frequent adverse effect is chest pain, followed by fever. Although uncommon, serious complications such as acute respiratory distress syndrome (ARDS) from talc or vision loss from high-dose povidone-iodine have been documented. Thus, povidone-iodine should be used only when talc cannot be administered.[13]

Indwelling pleural catheters carry risks, including chest discomfort, infection, catheter obstruction, pleural loculations, and, rarely, tumor seeding along the catheter tract. Pain typically lessens within two weeks, and studies show similar pain levels between IPC use and talc pleurodesis.[27]

Loculations can be successfully treated with intrapleural fibrinolytics, and catheter blockage—an infrequent problem—can usually be resolved with

saline flushing or fibrinolytic therapy, though catheter replacement may occasionally be required. Infections are a primary concern, especially in patients on chemotherapy or with long-term catheters, but large studies show an overall infection rate of about 5%, with very low mortality (<1%), and most cases respond well to antibiotics without the need for catheter removal.[27]

For loculated effusions, agents such as tPA and DNase are considered safe. Thomas et al demonstrated high effectiveness, reporting 93% improvement in drainage, 83% relief of dyspnea, and only 3% incidence of non-fatal bleeding. Lower starting doses are advised in frail or elderly patients.[28] Tumor seeding along the pleural puncture or catheter tract may occur, especially in malignancies like mesothelioma or after procedures such as thoracoscopy or IPC placement. Minimizing tissue trauma helps reduce this risk. If tumor seeding develops, palliative radiotherapy is generally used for symptom control and management of local lesions.[29]

Persistent Air Leak

The risk of pneumothorax after an ultrasound-guided thoracentesis is relatively low at about 3–4%, though some cases may still require chest tube placement. A persistent air leak is identified when continuous bubbling is seen in the chest tube drainage system, and it is defined as an air leak that persists for more than 5–7 days after tube insertion. This condition is often caused by a communication between the pleural space and the airways, such as an alveolar-pleural or bronchopleural fistula. According to the American College of Chest Physicians, an initial 4-day period of conservative management is advised to allow spontaneous closure of the fistula.[10]

If the leak does not resolve, treatment options include autologous blood pleurodesis, use of a Heimlich valve, endobronchial valves, tissue adhesives, or other occlusive devices. In cases requiring definitive intervention, surgical approaches such as open thoracotomy with chemical or mechanical pleurodesis or pleurectomy may be necessary.[10]

CONCLUSION

Malignant pleural effusion is a clinically significant manifestation of advanced cancer that requires a patient-centered and symptom-oriented approach. Despite advances in diagnosis, management remains largely palliative, with the principal goals of relieving symptoms, preventing recurrence, and improving quality of life. Current international guidelines are largely concordant in recommending ultrasound-guided thoracentesis for initial evaluation and individualized selection of pleurodesis or IPC according to symptoms, prognosis, and lung expandability, with IPC preferred in non-expandable lung.

The role of ambulatory pleural care, particularly IPC-based strategies with or without talc pleurodesis, reflects a new paradigm in MPE management that emphasizes personalization, reduced

hospitalization, and preservation of patient autonomy. Future efforts should focus on refining outpatient pathways, integrating molecular diagnostics, and improving treatment selection to further optimize quality of life outcomes.

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