Malignant pleural disease

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Shareable abstract (@ERSpublications)
Malignant pleural disease represents a growing healthcare burden and is associated with disabling symptoms and limited life expectancy. This review gives an overview of epidemiology, pathogenesis, diagnosis and key considerations for management. https://bit.ly/3HdzT3L

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Abstract

Malignant pleural disease represents a growing healthcare burden. Malignant pleural effusion affects approximately 1 million people globally per year, causes disabling breathlessness and indicates a shortened life expectancy. Timely diagnosis is imperative to relieve symptoms and optimise quality of life, and should give consideration to individual patient factors. This review aims to provide an overview of epidemiology, pathogenesis and suggested diagnostic pathways in malignant pleural disease, to outline management options for malignant pleural effusion and malignant pleural mesothelioma, highlighting the need for a holistic approach, and to discuss potential challenges including non-expandable lung and septated effusions.

Introduction

Malignant pleural disease (MPD) arises from direct extension of an adjacent tumour, pleural metastases of distant tumours or a primary pleural neoplasm, most commonly malignant pleural mesothelioma (MPM) [1]. MPD can manifest as solid disease and/or malignant pleural effusion (MPE), both associated with high morbidity and mortality [2].

MPE, defined by the accumulation of pleural fluid accompanied by malignant cells in the pleural space, can complicate any cancer [3, 4]. MPE compromises quality of life (QoL) and causes debilitating symptoms, including breathlessness, cough and pain [3, 5, 6]. Lung and breast cancer are the leading causes for MPE in men and women, respectively, accounting for 50–65% of all MPE combined [4]. MPM is associated with MPE in 90% of cases [3].

Despite recent treatment advances, MPE remains incurable, with a median survival of 3–12 months [7], and management is palliative. Given the heterogeneity within the MPE patient cohort, estimating prognosis and survival is challenging; previously reported mortality rates are as high as 37% at 30 days and 77% at 1 year [2]. This high morbidity and mortality mandate a focus on expedited diagnostic work-up in suspected cases and careful consideration of patient and disease factors in management of the debilitating symptoms for this cohort with a limited life expectancy. Minimising patient symptoms, optimising QoL, reducing hospital days and maximising time at home are key aspects to personalised management strategies [8].

Epidemiology

MPD incidence rates and associated healthcare costs are expected to rise, given increasing international cancer rates, improved diagnostics and advances in cancer therapies that improve life expectancy.

Pleural effusion affects up to 1.5 million people in the USA annually [9]. Accounting for one third of exudative effusions, MPE affects 150 000 patients in the USA and 50 000 in the UK each year [7, 10, 11]. In Europe, 100 000 effusions occur each year due to lung cancer alone [12]. This, in turn, leads to significant healthcare resource usage and hospital admission rates; median length of stay is 5.5 days and estimated inpatient charges are USD 5 billion per year in the USA alone [13].

Global incidence of MPM continues to rise worldwide. The World Health Organization (WHO) predicts an exponential rise in MPM in developing countries where asbestos use is not strictly regulated [14–20]. Despite regulations controlling asbestos use in the UK, the reduction in incidence has been only 7%, although a further projected fall over the next 20 years is anticipated [21]. An estimated 2700 new mesothelioma cases are diagnosed in the UK annually, with peak incidence in people aged 85–89 years [22].

Pathogenesis

Pleural fluid accumulates when production outweighs absorption. *Post mortem* studies of patients with MPD suggest the majority of cases occur secondary to haematogenous spread, initially invading the visceral pleura [23, 24]. Parietal disease in the absence of visceral pleural disease is exceptionally rare.

Key mechanisms in MPE accumulation are complex tumour–mesothelial interactions resulting in pleural inflammation, tumour angiogenesis and vascular hyperpermeability with subsequent plasma extravasation into the pleural space. Many host- and tumour-derived factors, including vasoactive mediators such as tumour-derived vascular endothelial growth factor (VEGF), participate in this pathway [25]. VEGF is a potent initiator of vasodilation and increased endothelial fenestration, resulting in increased permeability to protein, in turn leading to fluid exudation into the pleural space. Protective host-derived molecules including endostatin, an endogenous inhibitor of angiogenesis and tumour growth, play a role [26]. The balance between pleural levels of angiogenic and anti-angiogenic mediators is a major determinant of effusion development [25].

Multiple tumour-derived pro-inflammatory molecules have also been implicated, including tumour necrosis factor-α, monocyte chemotactic protein-1 and osteopontin [27–29]. Host and tumour-derived osteopontin work in a synergistic fashion to stimulate macrophage recruitment and tumour angiogenesis while protecting tumour cells from apoptosis. Both directly promote vascular hyperpermeability independently of VEGF [30]. Host-derived interleukin (IL)-5 recruits eosinophils and myeloid suppressor cells that facilitate tumour cell survival in the pleural space and enhance vascular permeability [31]. Mast cells increase pleural vasculature permeability through the release of mediators (tryptase AB1 and IL-1β) and trigger NF-κB activation in pleural tumour cells, promoting fluid accumulation and tumour proliferation [32].

For the excess fluid to remain in the pleural space, impaired removal is also required and may be the predominant factor in MPE development [33]. Parietal pleural invasion can lead to obstruction of stomata, preventing exit of the effusion *via* their lymphatic lacunae [33]. Downstream lymphatic invasion also plays a major role, and the presence of an effusion has been demonstrated to correlate better with nodal involvement than the extent of pleural disease [24, 33].

Diagnosis

A suggested diagnostic algorithm when MPD is suspected is shown in figure 1.

Clinical presentation

The most common presenting symptom of MPE is breathlessness, which is often disabling. Chest discomfort and cough occur less commonly and 15–25% are asymptomatic at presentation [34]. Symptom severity correlates poorly with effusion size [5, 35]; however, breathlessness that appears disproportionate to the volume of fluid present should prompt consideration of comorbid conditions, *e.g.* pulmonary embolism. Effusion is present at diagnosis in >90% of MPM cases, and chest pain is often prominent. Both MPE and MPM are associated with constitutional symptoms, including anorexia, weight loss and night sweats.

Breathlessness in MPE is multifactorial. Pleural effusions cause abnormalities in both gas exchange and respiratory mechanics [36] but post-drainage increases in lung volume correlate poorly with the volume of effusion removed [35, 37, 38] and changes in physiological parameters are minimal [39, 40]. The hypothesis that diaphragmatic dysfunction plays a leading role has been confirmed in studies using advanced ultrasound techniques [41–44]. Abnormal hemi-diaphragm movement pre-drainage was associated with a four-fold increased likelihood of breathlessness improvement post-drainage [41]. Combining data from five randomised controlled trials (RCTs), Mishra *et al.* [45] demonstrated that worse breathlessness at baseline is predictive of shorter survival.

Radiology

Radiography

Chest radiography can detect effusion volumes as low as 200 mL in the posteroanterior view but remains poorly sensitive up to 500 mL [46]. Chest radiography can demonstrate other features of MPD, such as pleural thickening or pleural plaques, indicating prior asbestos exposure [47].

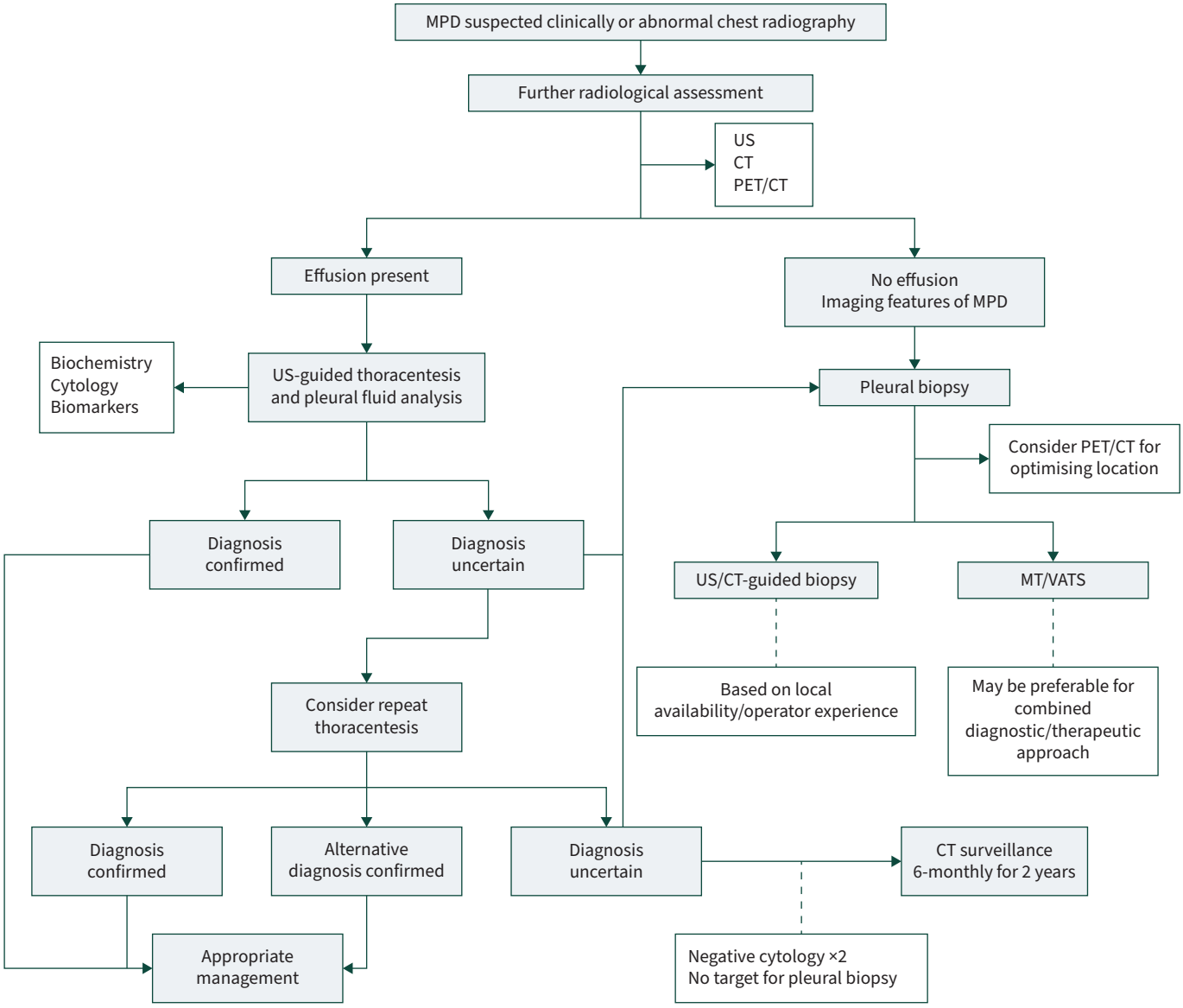

FIGURE 1 Summary of diagnostic work-up in suspected malignant pleural disease (MPD). US: ultrasound; CT: computed tomography; PET: positron emission tomography; MT: medical thoracoscopy; VATS: video-assisted thoracoscopic surgery.

Thoracic ultrasound

Thoracic ultrasound (TUS) is more sensitive than chest radiography in detecting the presence of pleural effusion [48]. TUS can assess both effusion volume and character; anechoic effusions can be transudative or exudative, but echogenicity is indicative of the latter [49, 50]. Pleural thickening >1 cm, pleural nodularity and diaphragmatic thickening >7 mm are suggestive of MPD [49]. The sonographic finding of nodularity of the parietal, visceral or diaphragmatic pleura in the presence of an effusion has a specificity of 96.9% for MPE [51]. Use of TUS is essential with any pleural intervention, due to an abundance of data illustrating reduced complication rates including pneumothorax [52]. Furthermore, periprocedural colour Doppler ultrasound can be used to identify and avoid intercostal arteries and collaterals [53, 54].

Computed tomography

Computed tomography (CT) is highly sensitive in identifying the presence of pleural fluid, although septations are better visualised on TUS [47, 55]. Delayed-phase contrast optimises visualisation of the pleura [56]. CT features that increase suspicion of malignant disease include parietal pleural thickening that is circumferential, nodular, >1 cm or affecting the mediastinal pleura [57]. A 2015 retrospective review demonstrated that the positive predictive value of a malignant CT report was 80%, with a negative

predictive value of 65%, highlighting the need to pursue further investigation if there is a high clinical suspicion [58]. CT can also identify extra-pleural features suggestive of malignancy, such as a lung mass, pericardial effusion, lymphadenopathy, chest wall invasion or rib destruction.

Positron emission tomography

Positron emission tomography (PET)/CT has a sensitivity of 81% and specificity of 74% in discriminating benign pleural effusion from MPE [59]. Malignant pleural thickening is typically 2-fluoro-2-deoxy-D-glucose (FDG)-avid but infection and prior talc pleurodesis can demonstrate a similar appearance (figure 2) [60]. PET/CT has significant value in identifying the presence of nodal or extrathoracic metastases and determining optimal site for tissue biopsy [61]. In the imaging of MPM, PET/CT has been shown to have sensitivity of 95–100% and specificity of 78–92% [62].

Pleural fluid

Biochemical analysis of MPE is generally consistent with an exudative effusion, although 5–10% are transudative by Light's criteria [63–65]. Pleural fluid pH and glucose have been found to correlate inversely with the extent of pleural disease, number of malignant cells in the fluid, cytology positivity and success of pleurodesis [66–68].

The minimum volume of pleural fluid required for cytopathological examination is 60–75 mL [69–71]. At least 20 mL are required to facilitate molecular testing for targetable mutations in MPE secondary to primary lung adenocarcinoma; however, specimen cellularity and particularly tumour cell proportion (tumour to non-tumour ratio >20%) are more important determinants of sample adequacy than fluid volume [72].

Sensitivity for pleural fluid cytology in the diagnosis of MPE is 50–60% [73–75]. Tumour type is an important determinant of diagnostic yield, with higher sensitivity (80%) in adenocarcinoma while haematological malignancies have a lower yield (<50%) [74]. With an average sensitivity of 60%, if the first sample is negative, a second sample can increase sensitivity by 27%, but further samples are unlikely to be useful [73, 76, 77]. Of note, cytological sensitivity for mesothelioma has been reported as low as 6% [74] but recent advances have improved this and reduced the need for pleural biopsy in many cases [78].

Given the limited sensitivity of cytological testing, research into novel pleural fluid biomarkers that may enhance diagnostic yield is ongoing. Cancer ratio, defined as the ratio of serum lactate dehydrogenase to pleural fluid adenosine deaminase, has demonstrated high sensitivity and specificity (84–94% and 92–98%, respectively) as an additional tool to differentiate between MPE and benign effusions [79, 80].

Prior meta-analyses have demonstrated significantly elevated levels of VEGF in MPE compared to benign pleural effusion, but with moderate sensitivity and specificity of 75% and 72%, respectively [81, 82]. Multiple studies have investigated the diagnostic accuracy of conventional cancer biomarkers including

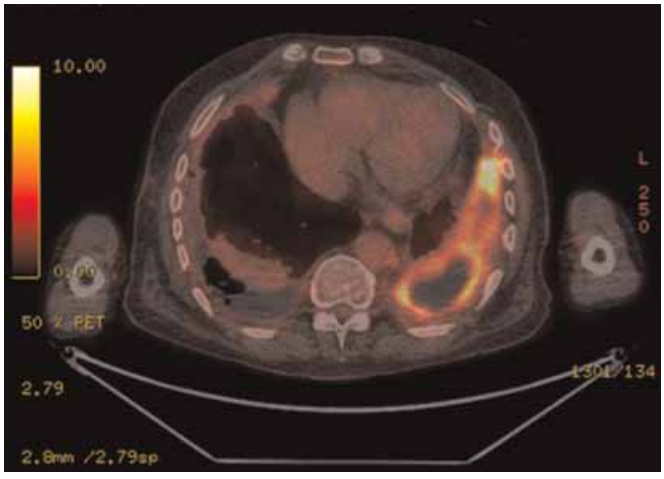

FIGURE 2 2-Fluoro-2-deoxy-D-glucose (FDG)-avid pleural thickening in non-malignant pleural disease following video-assisted thoracoscopic surgery biopsy and talc pleurodesis.

carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), carbohydrate antigens 125 (CA-125), 19-9 (CA19-9) and 15-3 (CA15-3), and a fragment of cytokeratin 19 (CYFRA 21-1). Overall, these have failed to demonstrate significant clinical utility, with high specificity but sensitivity of ∼50% [83]. A 2017 meta-analysis investigated the diagnostic accuracy of the combinations of positive pleural CEA+CA19-9 and CEA+CA15-3, demonstrating an extremely high specificity for MPE of ∼99%, although again sensitivity was low at 65% [84].

Pleural biopsy

In suspected MPD where pleural fluid cytology is negative for malignancy, pleural biopsy may be indicated. Closed or "blind" pleural biopsy is no longer recommended, where resources allow, due to inferior diagnostic yield and higher rates of complications [52]. Both ultrasound- and CT-guided biopsies demonstrate excellent diagnostic yield (93% and 84%, respectively) and are safe, with a low rate of adverse events (7% and 3%, respectively) [85]. In comparison to CT, ultrasound has advantages including lack of ionising radiation and real-time observation of the biopsy needle (figure 3). Choice of modality depends largely on local availability and operator experience.

In lung biopsies, the use of PET/CT guidance to identify targetable areas of increased metabolic activity reduces inconclusive results and the need for repeat sampling *versus* CT alone [86]. An ongoing RCT aims to examine the diagnostic yield of PET/CT- *versus* CT-guided biopsy in suspected MPD and may change best practice where resources allow [87].

Medical thoracoscopy (MT) has a 92.6% sensitivity in the diagnosis of MPD [10]. MT can provide a combined diagnostic and therapeutic procedure, allowing for large volume thoracentesis, direct visualisation, and biopsy of abnormal areas. Talc poudrage can be performed, although this requires certainty about the diagnosis and quality of the biopsy as successful pleurodesis may limit future investigations. MT has been shown to be safe, with a mortality rate of 0.34% and major complication rate of 1.8% [10]. Absolute contraindications to the procedure include severe respiratory distress or uncontrolled cough (causing procedural safety concerns) and a lack of pleural space resulting from adhesions of the pleural layer (*e.g.* pleural infection, pleural fibrosis or prior pleurodesis) [10, 88]. Video-assisted thoracoscopic surgery (VATS) shares many of the advantages of MT and has consistently shown high sensitivity of >90% in the diagnosis of MPD [89, 90]. VATS requires general anaesthesia and single-lung ventilation and is often unsuitable for this cohort with advanced malignancy.

Management

Prognosis is a key consideration in choosing the most appropriate management strategy. Prognostic scoring tools such as the LENT (pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group performance score, neutrophil-to-lymphocyte ratio and tumour type) and PROMISE scores may aid in risk-stratifying and clinical decision-making, but remain imprecise for individual patients [91, 92]. Treatment strategies for MPEs can be largely divided into systemic and procedural categories. Procedural

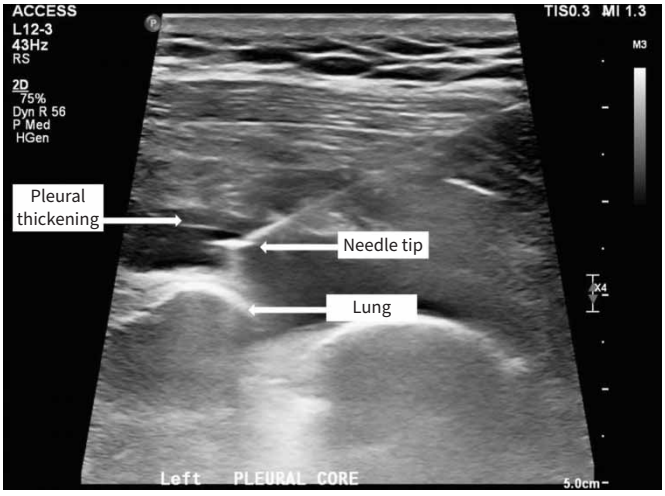

FIGURE 3 Real-time ultrasound-guided pleural biopsy.

treatments are summarised in figure 4. Challenges that may arise during management, such as non-expandable lung (NEL) and septated effusions, will also be discussed in this section.

Procedural treatment

Presence of MPE inherently signifies incurable disease; therefore, the primary focus of management is palliative, aiming to improve and maintain QoL. This is usually achieved through drainage of the effusion, ideally with the least number of minimally invasive interventions, delivered in an affordable manner and with as few hospital days as possible. Drainage options and their advantages and disadvantages should be discussed with the patient and an individualised decision should be made based on patient preference, probability of response to cancer-directed therapy, performance status, home supports, dexterity, comorbidities and available resources.

Therapeutic thoracentesis

Therapeutic thoracentesis involves removal of a large volume (⩾1 L) of fluid. Maximum fluid removal is disputed, although current guidelines would recommend 1–1.5 L drainage at any one time, due to risk of re-expansion pulmonary oedema (RPO) [7, 93]. RPO is a rare, potentially fatal complication that occurs after rapid re-expansion of the lung from a collapsed state secondary to pneumothorax or pleural effusion [94]. Clinical signs of RPO include anterior chest discomfort, dyspnoea and desaturation. Recognised risk factors include rapid removal of fluid over a short period of time, younger age and large pneumothorax or massive effusion causing pulmonary collapse for a duration of >1 week [95, 96].

Therapeutic thoracentesis can 1) aid diagnosis, 2) confirm fluid drainage relieves breathlessness/cough (up to 25% do not improve post-drainage [41]), 3) monitor rate of re-accumulation [3, 7], and 4) assess for NEL post-drainage. Thoracentesis using ultrasound guidance is a safe procedure, with low complication

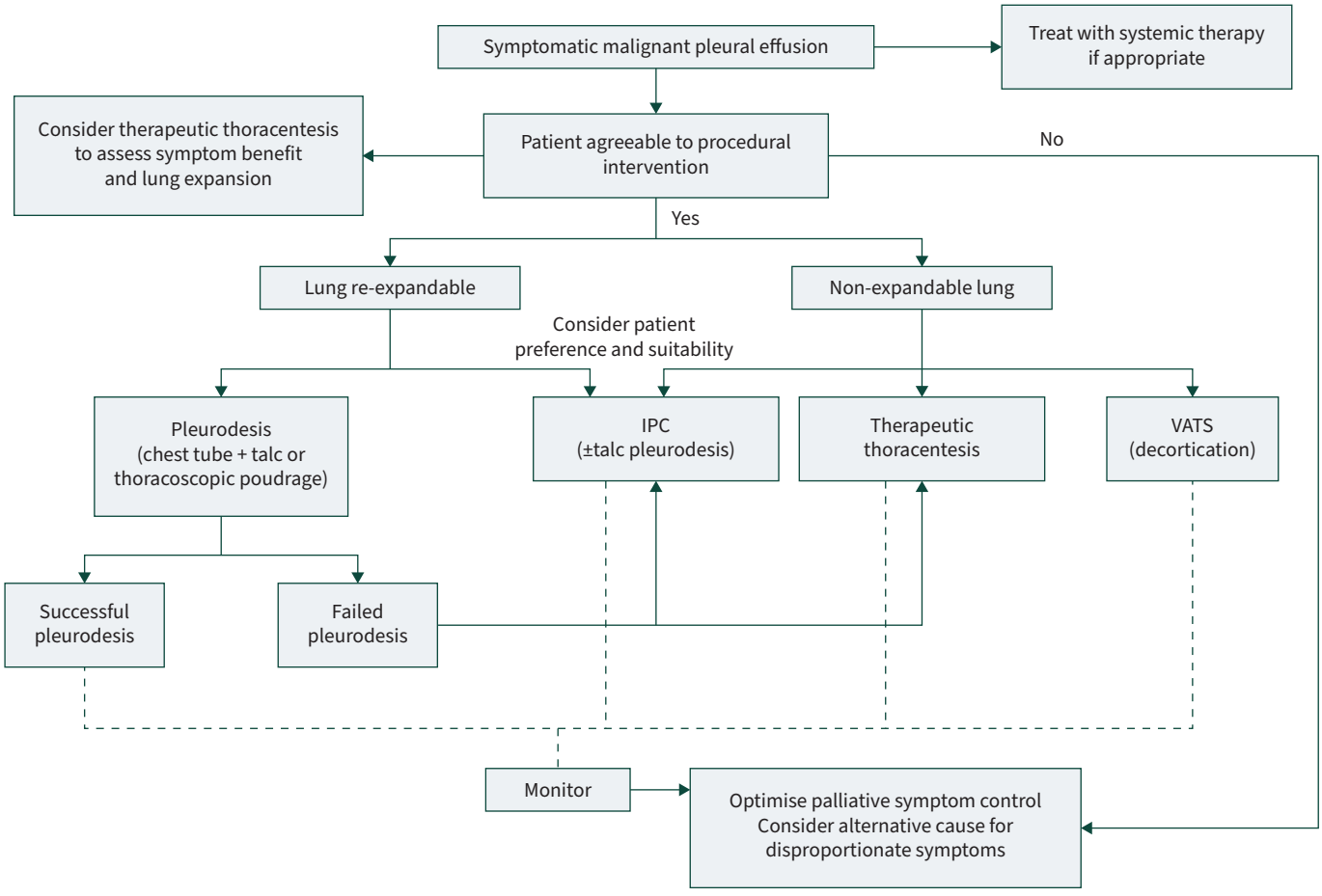

FIGURE 4 Overview of management options for symptomatic malignant pleural effusion. IPC: indwelling pleural catheter; VATS: video-assisted thoracoscopic surgery.

rates, that can be done repeatedly as an inpatient or outpatient management option in patients with poor performance status and prognosis [97]. Fluid re-accumulation occurs in >85% and a definitive procedure is often required for long-term control [98].

Pleurodesis

Chemical pleurodesis involves the fusion of parietal and visceral pleura to prevent fluid re-accumulation. Intrapleural administration of sclerosant generates adhesions and seals the pleural space. Talc is a safe and effective sclerosing agent [99], provided graded-size talc preparation is used to minimise risk of respiratory complications associated with small-particle talc [100, 101]. Visceral and parietal pleural apposition is required to achieve pleurodesis, rendering it an unsuitable intervention where visceral pleural thickening causes incomplete lung re-expansion.

Pleurodesis is performed by administering talc slurry (suspension) *via* chest tube or by talc poudrage (atomised form) at thoracoscopy. Published pleurodesis success rates vary but in general are <80% across randomised studies [102–105]. The largest RCT on talc pleurodesis in MPE reported a success rate of ~75% at 1 month, but progressively reduced to 50% at 6 months [104]. Ability to distribute talc throughout the pleural space at thoracoscopy is often considered an advantage; however, multiple studies have shown that there is no significant difference in successful pleurodesis rates, effusion recurrence or complication rates when comparing talc poudrage to talc slurry instillation [104, 106]. Talc poudrage is therefore only warranted if performing a thoracoscopy for another indication, *e.g.* pleural biopsy. Optimal chest tube size is often disputed; however, if talc slurry pleurodesis is intended, a chest tube size >12 F is recommended, given reduced pleurodesis success seen when directly comparing 12 and 24 F tubes [103]. Pleurodesis success is significantly lower in patients with MPM (73% *versus* 85%, p=0.002) [107]. This may reflect higher rates of NEL or significant tumour bulk preventing chemical adhesive success.

Fever and pain are the most common pleurodesis-related adverse events. There is no significant difference in pain or pleurodesis efficacy when utilising non-steroidal anti-inflammatory medication *versus* opiates [103]. Expert consensus suggests that corticosteroids should be reduced or withheld, if possible, in advance of pleurodesis.

Implementation of lung sliding scores using TUS after talc pleurodesis should be considered. When compared to regular British Thoracic Society standard guidelines (using plain film radiograph and monitoring fluid output), TUS-guided protocols reduce inpatient stay, with most patients discharged home within a day of pleurodesis. This potential pathway is also cost-effective and, infrastructure and staffing permitting, may replace current standard practice [108].

Indwelling pleural catheter

An indwelling pleural catheter (IPC) is a tunnelled ambulatory drainage device that can remain *in situ* long term (figure 5). The latest evidence-based guideline on MPE from the American Thoracic Society in 2018 recommended IPC as first-line therapy for NEL (previously estimated as >30% of patients) and, together with chest tube/talc pleurodesis, recommended these as equally acceptable first-line definitive therapies in patients with expandable lungs [52]. IPC has been demonstrated to improve both breathlessness and QoL at least as well as talc pleurodesis and reduced re-intervention rates from 22% to 4–6% [105, 109]. Immediate (peri-procedural) hospitalisation days were significantly reduced in the IPC arm *versus* chemical pleurodesis [105, 110]. Furthermore, lifetime hospitalisation days were reduced by 3.6 days per patient in the IPC arm *versus* chest tube/talc slurry pleurodesis [109]. On average, there is a modest reduction in hospital stay in the IPC group, but this may be significant in everyday practice for a patient group with limited life expectancy. Importantly, several prospective case series have demonstrated that IPC can provide effective palliation in the presence of NEL [111–114]. Spontaneous pleurodesis (most commonly defined as drainage of <50 mL on three consecutive drainage attempts) occurs in 30–60% of patients [105, 109, 110].

Daily fluid drainage after IPC insertion improved QoL as measured by the EQ-5D-5L questionnaire and improved rates of spontaneous pleurodesis over symptom-guided drainage [115, 116]. Furthermore, IPC and talc pleurodesis are not mutually exclusive. In the IPC-Plus RCT, instillation of talc slurry *via* IPC followed by intermittent drainage was shown to be feasible and safe and to accelerate pleurodesis [117]. If pleurodesis and drain removal is the priority, talc *via* IPC and daily drainage should be considered. If, however, reducing medical interactions is preferred, symptom-guided drainage is reasonable. Finally, IPC has been shown to be cost-effective in those with a shorter lifespan and, as a minimally invasive procedure, has very few exclusion criteria [118–120].

FIGURE 5 Indwelling pleural catheter *in situ*. The catheter is kept covered by a dressing in between drainages.

With these advantages comes the risk of IPC-specific complications as highlighted in table 1, necessitating a balanced discussion and individualised management, bearing in mind that patients with IPC *in situ* will require ongoing clinic appointments and home drainages. On average, a patient with an IPC for MPE *in situ* will self-drain three times per week [137].

IPC complications include pain on insertion/drainage, symptomatic loculation (failure of fluid drainage due to formation of adhesions), infection (soft tissue, tract and pleural infection), catheter tract metastases and dislodgement [121]. Most complications can be managed conservatively and rarely require IPC removal [138]. Intrapleural fibrinolytic therapy can be administered for the symptomatic loculations that occur in up to 14% of IPC patients, the most commonly used agents being a single dose of alteplase (4–10 mg) or urokinase (100 000 IU) administered *via* the IPC [126, 139]. IPC infection is usually manageable with antibiotics alone [128]. If refractory loculated infection occurs, the IPC can be used as a conduit for administration of tissue plasminogen activator and DNase according to the MIST-2 protocol (Second Multicentre Intrapleural Sepsis Trial; alteplase 2.5–10 mg and dornase alpha 5 mg *via* the IPC 12-hourly, up to six doses) [127, 140]. Catheter tract metastases, more common in MPM than MPE, can be managed safely with targeted radiotherapy [141].

Video-assisted thoracoscopic surgery

VATS remains commonplace in the management of MPE worldwide [142], but evidence for its benefits and its reported success rates of 68–100% are largely supported by retrospective or single-centre series [143–146]. Three randomised studies comparing VATS to chest tube and talc pleurodesis did not demonstrate any significant benefits with VATS [104, 147, 148]. Complications of VATS include fever, pneumonia, prolonged air leak and post-VATS neuralgia, which can affect 25% of patients [104, 149–152]. No prospective studies have compared VATS *versus* IPC to date, but retrospective data suggest a reduced re-intervention rate and fewer hospital days with IPC [143]. The currently recruiting Australasian Malignant PLeural Effusion (AMPLE)-3 trial will provide urgently needed evidence to assist with the decision between VATS and IPC [153].

Challenges in management

Non-expandable lung

NEL arises following formation of a fibrous visceral pleural peel, malignant visceral pleural thickening or numerous visceral metastatic nodules, preventing full lung re-expansion and apposition of the visceral and

TABLE 1 Summary of indwelling pleural catheter (IPC)-associated complications

	Management notes	Incidence	References
Common complications			
Pain	Pre-procedural local anaesthetic instillation Pre-emptive use of analgesia Optimise rate of drainage (shearing force on pleura secondary to negative pressure can occur with accelerated drainage) Rarely leads to need for IPC removal (0.4%) Investigate as necessary for other complications including infection, bleeding, tumour progression or invasion of chest wall	3–10% (mild) 0.4% (severe)	[105, 109, 121–125]
Loculation	Can occur by nature of MPE disease process or as complication of infection Use of intrapleural fibrinolysis is safe and effective	5–14%	[126]
Infection	Include pleural infection, empyema, wound site or skin tract infection Assess for systemic signs of infection Pleural fluid for culture (note bacterial colonisation is common), skin/wound swab Biochemical fluid markers are not overly helpful as malignant fluid may exhibit low pH, low glucose and/or high LDH levels with or without infection but change from baseline may be indicative Broad-spectrum antimicrobial cover Adequate fluid drainage (may require inpatient admission and attachment to underwater seal) Removal is usually unnecessary with above measures Intrapleural tPA/DNase *via* the IPC is safe and improves drainage in loculated IPC-related pleural infection	0.4–1.3%	[127, 128]
Blockage	Sterile saline flushes to ensure patency Consider use of fibrinolytics	1.5–3.7%	[122, 129]
Fluid leakage	Can occur secondary to rapid fluid accumulation and/or poor wound healing Limit tract size during insertion and avoid cuff placement near exit site to minimise risk Optimise adequate drainage and wound healing (appropriate dressings, dietary intake, *etc*.)	0.6%	[122, 129, 130]
Catheter tract metastasis	Outgrowth of the pleural tumour to the subcutaneous tissue can occur subsequent to IPC insertion Regular monitoring of symptoms and IPC site inspection is recommended Benefit from analgesia and targeted radiotherapy as required	14–42% (mesothelioma) 0.4–4.6% (other)	[121, 131, 132]
Less common complications			
Dislodgement	Can be associated with poor tract healing and cuff location Consider re-imaging and repositioning as appropriate	1.2–18%	[130, 133, 134]
Fractured drain and retained cuffs	IPCs have adhesive cuff to anchor the catheter subcutaneously Fracture of the IPC and/or retained cuffs can occur on removing IPC No significant long-term complications in patients who had retained fractions of IPC (no surgical intervention necessary in most cases)	9.8–23.5%	[126, 135, 136]

MPE: malignant pleural effusion; LDH: lactate dehydrogenase; tPA: tissue plasminogen activator.

parietal pleura (figure 6) [154]. NEL affects >30% of MPE patients [104], significantly limiting potential for long-lasting effusion control with conventional pleurodesis methods [155].

NEL frequently becomes apparent only after fluid drainage. Thoracentesis with concurrent pleural manometry can identify NEL [156]. Decreased lung compliance in the presence of NEL leads to more pronounced changes in pleural pressure with increased pleural elastance [157]. The superiority of manometry over clinical assessment for NEL (chest tightness during drainage, post-procedure radiograph) and utility of identifying NEL mid-procedure is debatable. Studies have failed to demonstrate lower rates of RPO or chest pain with concurrent use of pleural manometry during thoracentesis [158, 159].

Conversely, identifying NEL prior to definitive intervention would be of benefit as first-line IPC is the optimal choice in these cases. Noninvasive techniques that can forecast its probability include TUS identification of an absent sinusoid sign (a dynamic sonographic M-mode finding indicating motion of atelectatic lung during respiration within pleural fluid) and reduced motion of the atelectatic lung [160–162].

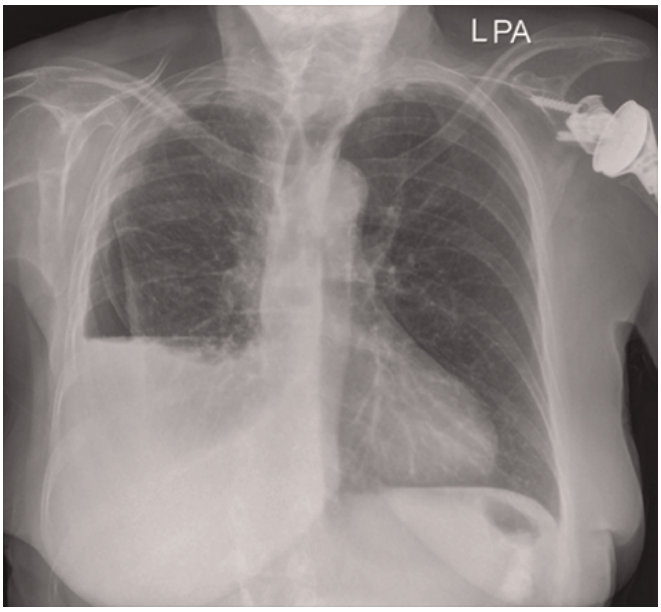

FIGURE 6 Non-expandable lung on chest radiography with re-accumulation of pleural fluid post-drainage leading to air–fluid level in the pleural space.

IPCs are now the mainstay of treatment in this group [3, 52]. Almost 30% of patients with NEL in the AMPLE-2 trial achieved spontaneous pleurodesis at 6 months after IPC insertion, with higher rates seen in the daily-drainage arm *versus* symptom-guided [115].

In select patients, there may be a role for surgical management. VATS pleurectomy and decortication allows surgical excision of the visceral pleural rind with reported success [163]. However, surgical attempts made to free the lung at thoracoscopy come at the cost of significantly increased procedure duration and high likelihood of persistent air leak post-operatively [146, 150].

Septated MPE

Septations within an MPE can impair drainage *via* chest tube or IPC. The residual fluid in the pleural cavity can cause persistent breathlessness and limits opportunities for achieving pleurodesis by preventing visceral and parietal pleural apposition. Adhesiolysis can be performed at thoracoscopy but, as discussed, MPE patients are frequently frail and comorbid, and surgery may be overly invasive. Intrapleural fibrinolytics alone have been unsuccessful in the management of pleural infection but have shown some benefit in improving drain output in MPE.

Although the largest RCT to date did not identify a statistically significant improvement in any outcome (breathlessness, re-intervention rates or pleurodesis success), intrapleural fibrinolytics (urokinase) in patients with residual septated effusion did reduce hospital days [164]. When combining these data with two previous smaller RCTs [165, 166], a recent meta-analysis in the British Thoracic Society guidelines demonstrated some improvement in each of these measurements with intrapleural fibrinolytics [167]. Intrapleural fibrinolytics improve drainage and may improve breathlessness in septated effusions with IPC *in situ* [126].

Systemic treatment

Systemic therapy (chemotherapy, immunotherapy and targeted therapy, or a combination) treatment decisions in advanced cancer should be based on patient suitability, histology, molecular profile and biomarkers.

Chemotherapy

Systemic chemotherapy for MPE depends on patient performance status, tolerability and overall suitability. Cisplatin is a potent anticancer drug used to treat a broad spectrum of malignancies and acts primarily by interfering with DNA replication. In advanced lung cancer, cisplatin is generally combined with a

third-generation cytotoxic agent such as pemetrexed or paclitaxel, depending on the histological subtyping [168]. Cisplatin exerts its effect on MPE by inhibiting primary focal tumour, metastasis and fluid accumulation within the pleura *via* circulation through pleural vasculature [169].

Immunotherapy

Immunotherapy targets checkpoint receptors expressed by immune cells that act on the tumour microenvironment and improve T-cell functionality. Programmed cell death protein-1 (PD-1) and its primary ligand (PD-L1) are expressed on T-cells, and on tumour cells and tumour-infiltrating myeloid cells, respectively [170]. Immune checkpoint inhibitors (ICIs) that target PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) are the two best understood pathways. The inhibition of these pathways by ICIs amplifies the anti-tumour effects of cytotoxic T-cells. Over the last decade, the innovation of these therapies has revolutionised the treatment of lung cancer, producing durable long-term responses not previously seen in advanced stage disease.

The KEYNOTE-189 phase III RCT demonstrated that the addition of pembrolizumab, a monoclonal antibody to PD-1, to standard-of-care chemotherapy improved overall survival and progression-free survival in patients without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations [171]. The level of PD-L1 expression reflects the likely degree of therapeutic benefit from PD-1/PD-L1 checkpoint inhibitors, with high expressors being eligible for single agent ICI without the addition of chemotherapy [172]. Correlation of PD-L1 expression in histological specimens of primary tumour in nonsmall cell lung cancer (NSCLC) and matched pleural fluid samples is high [173]; however, a number of studies have suggested that the response to ICIs is reduced in the presence of MPE [174, 175]. Utilisation of other anti-PD-1 agents and combinations is under evaluation across a number of clinical trials.

Anti-angiogenic therapy

Preliminary data suggest that bevacizumab, a VEGF-targeted recombinant monoclonal antibody that has an impact on tumour angiogenesis and further proliferation, in combination with carboplatin and pemetrexed chemotherapy, is likely to be efficacious in selected cases with MPE, with improved overall survival and progression-free survival reported [176, 177].

Ramucirumab, a VEGF receptor-2 antibody that inhibits tumour angiogenesis, has demonstrated activity in lung cancer patients and a phase II trial combined with docetaxel chemotherapy is currently recruiting patients with MPE [178].

Endostatin is a broad-spectrum anti-angiogenic therapy with reported therapeutic benefits, including tumour hypoxia when combined with chemotherapy in MPE patients, although further validation through prospective RCTs is required [169, 179–182].

Targeted therapy

Given the reported success of combination chemotherapy and ICI or anti-angiogenic regimens, a variety of trials have demonstrated improved survival for targeted therapies of recognised mutations, including EGFR tyrosine kinase inhibitors (such as osimertinib), ALK inhibitors (alectinib and lorlatinib) and ROS1 inhibitors (lorlatinib) [183, 184]. However, most patients with EGFR mutations will eventually develop resistance to therapy. Obtaining further pleural fluid is useful for molecularly profiling tumours, mandating change in therapy [185]. Newer oncogenic drivers have been identified, including the KRAS12C mutation, targeted by sotorasib and adagrasib, both recently approved by the United States Food and Drug Administration for treatment in patients who have progressed on at least one prior line of systemic treatment [186, 187].

Intrapleural agents

Intrapleural chemotherapy or alternate systemic therapy may offer localised cytotoxic effect, thus minimising systemic absorption and insult. A meta-analysis of intrapleural bevacizumab in addition to chemotherapy compared to intrapleural chemotherapy alone demonstrated improved rates of complete remission in the experimental (bevacizumab) arm, with only minor increased risk of adverse events [188]. An RCT comparing intrapleural *versus* intravenous bevacizumab in NSCLC with MPE demonstrated an increased rate of complete response, partial response and duration of response in the intrapleural arm, with lower rates of adverse events, although the positive results were not statistically significant [189]. The addition of intrapleural endostatin to standard chemotherapy has shown improved overall response in MPE patients [190]. Preliminary phase I and II trials with intrapleural chemotherapy have shown short-term partial or full response of MPE [191–196]. However, these options have not yet to our knowledge been directly compared to standard therapy and further randomised trials are needed.

Mesothelioma treatment

Molecular biomarkers BRCA-associated protein-1 (BAP1) or cyclin-dependent kinase inhibitor 2A (CDKN2A) may aid diagnosis and management strategies in MPM; however, validation is required [197–200]. Systemic chemotherapy has a proven survival benefit in MPM, with the combination of cisplatin and pemetrexed increasing median overall survival by 2.8 months when compared to cisplatin single therapy [201]. The CheckMate 743 RCT has demonstrated the ICI combination of nivolumab and ipilimumab improves response rates and overall survival compared to chemotherapy and is now the standard of care for patients with advanced mesothelioma [202].

Surgical management of MPM is advocated by some groups but neither of the main surgical procedures (extrapleural pneumonectomy and lung parenchyma preserving pleurectomy/decortication) has been shown to offer survival benefit in a prospective RCT [203]. In fact, both are associated with substantial morbidity and mortality rates, as high as 31% in extrapleural pneumonectomy [204]. Surgery as a standalone treatment, therefore, cannot be recommended in MPM, but novel approaches using multimodality intervention (surgery, radiotherapy, chemotherapy and immunotherapy) remain under investigation [205].

Multidisciplinary approach

Non-interventional adjunct therapies are being explored to improve symptom palliation of MPE patients [206]. Baseline nutritional status and body composition in MPM are associated with reduced activity levels and poorer QoL [207]. Utilising dietary interventions to improve outcomes is an untapped resource. MPM patients lose muscle mass over time, a finding associated with reduced activity levels and poorer survival [208]. Exercise has shown great promise in improving QoL but remains under-utilised and studies have been heterogeneous [209, 210]. QoL questionnaires and visual analogue scales for pain and breathlessness are inherently subjective. Objective functional assessment with actigraphy, using a tri-axial accelerometer worn at regular intervals, has been shown to be well tolerated by MPE patients and is an exciting development in the assessment of outcomes post-intervention [211, 212].

Key points

- MPE affects an estimated 1 million people globally per year.
- Minimising patient symptoms, optimising QoL and reducing hospital days are key aspects to personalised management strategies.
- Diagnostic work-up should include full clinical history, examination, radiological investigation and pleural fluid analysis, with or without pleural biopsy.
- Management plans include both procedural (pleurodesis, IPC and VATS) and systemic options (chemotherapy and immunotherapy).
- Considerations when choosing a management plan are probability of response to cancer-directed therapy, performance status, home supports, dexterity, comorbidities and available resources.

Self-evaluation questions

1. A 62-year-old smoker, with Eastern Cooperative Oncology Group performance score 3, is diagnosed with PD-L1-positive NSCLC on pleural fluid cytology. Her respiratory symptoms improved after drainage of 1 L. CT is performed after initial drainage (figure 7). 2 days later the patient describes worsening shortness of breath and chest radiography confirms re-accumulation of right-sided MPE. What is the most appropriate management for symptomatic relief?
    a) Repeat therapeutic thoracentesis
    b) Insert 12-F chest tube and administer talc slurry
    c) Start pembrolizumab
    d) Insert IPC
    e) Perform VATS decortication
2. Is the following statement true or false? Negative pleural fluid cytology definitively excludes a diagnosis of MPE.
3. Which of the following patient factors are important when considering appropriate management of MPD?
    a) Performance status
    b) Patient preference
    c) Probability of response to cancer-directed therapy
    d) Overall prognosis
    e) All the above
4. Which of the following statements regarding MPM is not true?
    a) Cytological sensitivity for mesothelioma has been reported as high as 60%
    b) Global incidence of MPM continues to rise worldwide
    c) Systemic therapy is the only modality that has proven survival benefit in MPM
    d) Incidence of catheter tract metastases is higher in mesothelioma than other cancers

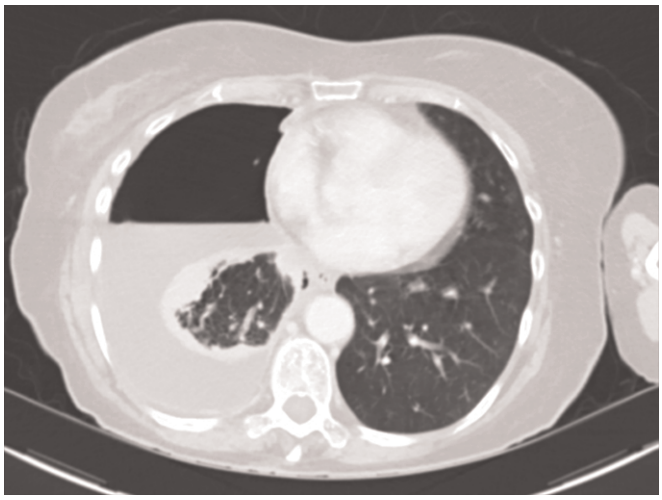

FIGURE 7 Computed tomography image to accompany self-evaluation question 1.

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Suggested answers

1. d.
2. False.
3. e.
4. a.