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Review Article

Updates in the management of malignant pleural effusion: a clinical practice review

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Abstract: The presence of a malignant pleural effusion (MPE) confers a poor prognosis, with a high burden of disabling symptoms due to altered respiratory mechanics and abnormal diaphragm function. Management is often palliative in nature, with the emphasis on preventing fluid re-accumulation. In the era of targeted therapies, pleural biopsies are often required for gene expression and receptor status profiling, for which local anaesthetic thoracoscopy provides the highest diagnostic yield. Interventions to achieve symptom control include thoracentesis, chest drain insertion, indwelling pleural catheters, medical thoracoscopy and surgery. The evidence base for these interventions has historically been lacking with a somewhat linear pathway, however, numerous well-designed, multicentre randomised controlled trials over the last decade using patient-centred outcomes have informed recent clinical practice guidelines. Several therapeutic options and combinations now exist to achieve optimal symptom control and pleurodesis, centred around patient choice and priorities, inpatient versus outpatient strategies and the presence of non-expandable lung. This review will explore the data that has shaped MPE management in the last decade, with the aim of providing a deeper understanding of the rationale behind current international guideline recommendations. It will also highlight areas where the evidence base is lacking, research currently in progress and potential future directions.

Keywords: Malignant pleural effusion (MPE); pleural disease; pleurodesis

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Introduction

Malignant pleural effusion (MPE) is a common condition that causes disabling breathlessness and has a significant impact on quality of life. It is thought to affect up to 15% of patients with cancer (1) and accounts for 0.35% of all hospital admissions in the USA (2). The condition encompasses a heterogenous population of patients, however, it constitutes a hallmark of metastatic disease with a poor prognosis, with median survival between 3–12 months (1).

Interventions for MPE have traditionally resulted in significant lengths of stay in hospital. The last decade has seen an advancement in ambulatory strategies and the accumulation of high-quality randomised trials. The objective of this clinical practice review is to summarise recent literature, with a particular emphasis on randomised trials that have shaped the current landscape of MPE management. This will allow clinicians to better understand the comparative outcomes of interventional procedures

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utilised for MPE, to support decision-making with an evidence-based approach focusing on patient-centred outcomes.

Pathophysiology of symptoms in MPE

For many years, the pathophysiology of breathlessness with pleural effusions was poorly understood. Recent evidence implicates altered respiratory mechanics and the associated increased work of breathing as the culprit, rather than hypoxaemia or reduced lung volumes.

The Pleural Effusion and Symptom Evaluation (PLEASE) study and the subsequent PLEASE-2 study recruited 145 and 20 patients respectively, with symptomatic pleural effusions present (3,4). Measurements of breathlessness and ultrasound measurements of diaphragm excursion, shape and movement were undertaken pre- and post-drainage. Abnormal ipsilateral hemidiaphragm shape and movement were independently associated with relief of breathlessness following thoracentesis [odds ratio (OR) 4.37] (3). Furthermore, they witnessed compensatory contralateral hemidiaphragm hyperactivity, which resolved following thoracentesis. Interestingly, despite symptomatic improvement, there was no change in post-drainage oxygen saturations and a minimal increase in forced expiratory volume in 1 s (FEV1) of 0.22 L [95% confidence interval (CI): 0.18–0.27]. The benefits of thoracocentesis were similar in patients with and without non-expandable lung (NEL).

Investigation of MPE

The diagnosis of MPE is often multi-modality, with a combination of radiology, cytology and histopathology, the latter becoming increasingly important in the evolving era of molecular profiling and targeted immunotherapies.

Computed tomography (CT)

Contrast-enhanced CT imaging is an important initial investigation for suspected pleural malignancy. In addition to detecting pleural thickening and effusions, it can identify extra-pleural primary malignancies which may alter the diagnostic pathway. Features supportive of pleural malignancy include mediastinal, circumferential or nodular pleural thickening in addition to pleural thickening >1 cm (5).

Several factors influence the accuracy of CT imaging in pleural malignancy. Tsim *et al.* performed a retrospective review of 345 patients comparing the performance of CT pulmonary angiography (CTPA), which utilises early arterial phase-contrast enhancement, with delayed venous phase contrast CT in the diagnosis of pleural malignancy. They demonstrated a sensitivity of 27% (95% CI: 9–53%) for CTPA and 61% (95% CI: 53–68%) for venous phase CT (P=0.0056). Furthermore, reporting of CT scans by specialist thoracic radiologists resulted in a statistically significant improvement in sensitivity. Mean specificity (80%) did not differ significantly between groups (6).

With a positive and negative predictive value of 83% and 54% respectively (6), CT imaging cannot be relied upon for the exclusion of pleural malignancy. However, a CT diagnosis of pleural malignancy may be adequate to plan definitive management of MPE.

Other imaging modalities

Positron emission tomography fused CT (PET-CT) utilising ^{18}F-fluorodeoxyglucose (^{18}F-FDG), highlights areas of high metabolic activity, seen in a range of pathologies including infection, inflammation and malignancy (7). Unsurprisingly, the accuracy of PET-CT in diagnosing malignant pleural disease differs significantly between studies, reflecting the heterogenous population of patients and interpretation techniques (7,8). However, pooled data from studies including patients with suspected MPE, demonstrated a sensitivity and specificity of 89% and 92% respectively (8). Despite this, the role of PET-CT in MPE remains unclear and it rarely utilised. British Thoracic Society (BTS) guidelines advise considering its use where a high suspicion of pleural malignancy remains despite negative histology (8).

There is limited evidence to suggest magnetic resonance imaging (MRI) has a comparable, if not superior, diagnostic accuracy when compared with CT. Additionally, MRI may be able to better detect early chest wall and diaphragmatic infiltration (9). It is rarely used in clinical practice but is a developing research area particularly in the context of malignant pleural mesothelioma.

Use of thoracic ultrasound (TUS)

The widespread adoption of TUS has led to a reduction in adverse events from pleural interventions (10). In the early 2000's the role of ultrasound for chest drain insertion was recognised, but not advocated in United Kingdom (UK) guidelines (11). Following a number of adverse events associated with Seldinger chest drain insertion (12), the use

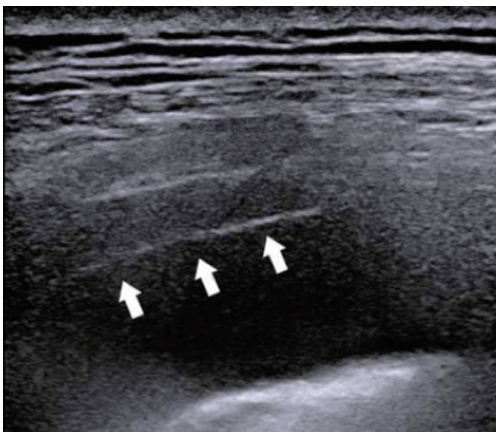

Figure 1 Transthoracic ultrasound demonstrating parietal pleural thickening (white arrows).

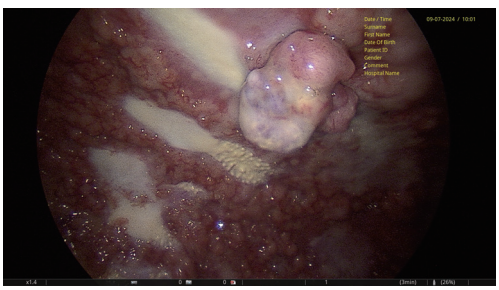

Figure 2 Malignant invasion of the parietal pleura with nodular thickening, visualised during local anaesthetic thoracoscopy.

of TUS was recommended for pleural interventions in the UK, and is recommended in international guidelines (8,13).

Whilst TUS was largely utilised for image-guided intervention, it is increasingly used in the initial assessment of MPE. TUS can identify thickening and nodularity of the diaphragm and parietal pleura (*Figures 1*,*2*), which are highly suggestive of malignancy (8), furthermore, septations are better visualised. These findings can guide the clinician on the most appropriate next steps in the diagnostic and therapeutic pathway. The ability to identify these abnormalities has become a core aspect of TUS training standards in the UK (14).

Cytology and tissue diagnosis

Cytological examination of pleural fluid is a core investigation in suspected MPE. It is imperative that clinicians recognise factors that influence cytology yields. These include sample size, tumour type and burden, sample quality and cytological tests performed, with a combined smear and cytospin/cell block preparation advised (1,8). There is significant variation in the reported yield of pleural fluid cytology, with pooled data suggesting a mean sensitivity between 49% and 91% (1) though recent UK-based prospective data suggests an overall sensitivity of 46% (95% CI: 42–58%) (15).

Submitting larger samples of pleural fluid for cytological examination can increase diagnostic yield. Large retrospective reviews have demonstrated diagnostic yields increasing in a linear fashion with fluid volume up to 50–75 mL (16,17). Volumes beyond this do not increase the diagnostic yield, though they do result in fewer nondiagnostic and atypical results. A smaller prospective study of 44 patients found 100% concordance between results obtained from the first 50 mL and subsequent large-volume aspirate (mean 890 mL), for both positive and negative results (18). Based on these studies, BTS guidelines recommend sending 50 mL of pleural fluid (8). Where MPE is suspected, a repeat aspiration may increase the yield by up to 27%, but only by 5% on the third attempt (19).

The tumour type significantly influences the likelihood of positive pleural fluid cytology, emphasising the need for a carefully considered approach. Positive results (>50% yield) are most likely from breast, lung adenocarcinoma and ovarian cancers, with much lower diagnostic rates in mesothelioma and haematological malignancies (15,16).

Further diagnostic samples may not be required in patients with MPE, particularly where a poor performance status precludes systemic or surgical treatment, or where tissue has already been obtained from a primary tumour site. For those who are fit for treatment, the complex nature of modern-day systemic anti-cancer treatments has resulted in a need for gene expression and receptor status profiling, therefore, pleural biopsy is often necessary (1). If the suspected malignancy is considered to be of low yield, such as mesothelioma, a direct-to-tissue biopsy approach may be considered rather than awaiting cytology results, which may add to delays in the diagnostic pathways (20).

The last decade has seen an expansion in the availability of physician-led and radiologically guided procedures to obtain a tissue diagnosis, including local anaesthetic thoracoscopy (LAT) (*Figure 2*), CT- and ultrasound-guided pleural biopsies. This has seen a shift away from surgical biopsies. The most recent BTS guidelines summarised 4 randomised studies which demonstrated a definitive diagnosis rate of 92.1% (SD ±6.5%) for thoracoscopy versus 84.4% (SD ±5.9%) for US- or CT-guided biopsy, which was

statistically significant. There was no significant difference between CT- and US-guided methods (8).

Risk stratification

Several prognostic scores have been developed to guide decision-making in MPE. The LENT score was developed following the study of 14 variables and their prognostic value (21). The score utilises pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance score (PS), neutrophil-to-lymphocyte ratio and tumour type, to estimate median survival. The score stratifies patients into low, moderate and high-risk groups with a median survival of 319 days [interquartile range (IQR), 228–549 days], 130 days (IQR, 47–467 days) and 44 days (IQR, 22–77 days), respectively.

Psallidas *et al.* (22) investigated a range of clinical and biochemical markers to create the PROMISE score, a prospectively validated tool that predicts 3-month mortality. They discovered several pleural fluid biomarkers that correlated with survival, including gelsolin, macrophage migration inhibitory factor, versican and tissue inhibitor of metalloproteinases 1 (TIMP1). The latter, TIMP1, was incorporated into the PROMISE score alongside serological and clinical parameters, though a mortality prediction can still be obtained without TIMP1 levels.

There are several specific prognostic scores for malignant pleural mesothelioma, which are beyond the scope of this review.

Management

MPEs carry a significant symptom burden and represents an incurable condition for most patients, where the primary aim of management is to relieve symptoms with minimal intervention and fewer days spent in hospital (23). Traditionally, practice has varied greatly between centres and individual physicians, with a lack of robust evidence and guidelines to support decision-making. Whilst interventions used in current practice are not new advances, there has been a wealth of evidence gathered in the form of large multicentre randomised controlled trials (RCT), which have provided clarity for clinicians to support decision-making.

Initial management of MPE

To guide intervention, the following questions should be considered:

(I) Is the patient symptomatic?
(II) What factors are most important to the patient?
(III) Will the patient benefit from definitive intervention?
(IV) Is the lung expandable?

Most patients with MPE are symptomatic, with breathlessness most commonly reported. Patients with the highest burden of symptoms are most likely to benefit from intervention (3). However, up to 25% of patients remain asymptomatic, in whom interventions should generally be avoided, instead a period of observation is preferable (13,24). There is some interesting ongoing research as to whether the presence of a pleural effusion in itself may drive tumour proliferation and cancer progression, and hence aggressive drainage may be a future treatment direction.

Large volume thoracocentesis

Initial large-volume thoracocentesis remains a key intervention for symptomatic MPE (8,13), which involves aspirating 500 to 1,500 mL of pleural fluid (25). This will confirm symptomatic benefit from intervention, as around 25% patients do not improve symptomatically. Furthermore, it will identify the presence of NEL, which occurs in around 30% of MPEs (24).

For the majority of patients, definitive intervention should be planned due to the high frequency of recurrence (1). A retrospective study of 23,431 patients revealed 55% of patients with MPE undergoing thoracocentesis required repeat pleural intervention. The median time to re-intervention was only 9 days (IQR, 3–32 days), demonstrating the propensity for rapid reaccumulation (26). International guidelines advocate definitive intervention in MPE, in preference to repeat thoracentesis (1,8,13). However, repeat thoracentesis may be suitable for some based on patient preference, limited life expectancy or patient fitness (8).

Results are awaited from the REPEAT prospective observational cohort study (27) to create a clinical score to predict the rate of reaccumulation. The study aims to recruit 200 patients with MPE in the UK, with data collected on clinical parameters and rate of reaccumulation, to help develop a clinical score, which they aim to validate on 40 patients. It is hoped this will lead to a reduction in unplanned admissions due to rapidly returning symptoms and avoid unnecessary intervention for slowly reaccumulating effusions.

Definitive intervention in MPE

Clinicians may utilise indwelling pleural catheters (IPCs),

chemical pleurodesis, surgery or a combination of procedures to achieve symptom control.

IPCs

Following Food and Drug Administration (FDA) approval in 1997, IPCs have revolutionised the management of MPE (28), achieving long-term control of breathlessness and improvements in quality of life (1). One systematic review, which included 1,370 patients from 19 studies, demonstrated symptomatic improvement in 95.6% of patients with IPCs, with a low rate of complications. Adverse events include empyema (2.8%), pneumothorax (5.9%), blocked catheters (3.7%) and cellulitis (3.4%) (28). Fysh *et al.* (29) performed a multi-centre retrospective review of 1,021 patients with IPCs for MPE. Fifty patients (4.9%) developed IPC-related pleural infection, with almost half of these patients requiring IPC removal. The planned AMPLE-4 trial will aim to determine if the use of topical mupirocin reduces IPC infection rates (30).

Despite this evidence, there is a concerning lack of data on the psychological impact of IPC use. It is recognised that IPCs can serve as a constant reminder of a life-limiting diagnosis, with 63% of patients reporting this in one study (31). Despite this, there remains an absence of studies addressing psychological impact as a primary outcome (32). Zhang *et al.* hope to address this with MY-IPC, a qualitative study utilising semi-structured interviews following IPC insertion. Interim analysis revealed highly variable experiences in the first 2 weeks, with positive and negative impacts in domains including anxiety, altered relationships, changes in independence and control, engagement in activities, and expectations. Analysis of the 6–8 week data is awaited (33).

Traditionally, IPCs have been utilised for long-term control of symptoms in MPE, however, research has increasingly focused on improving pleurodesis rates and the potential for IPC removal. AMPLE-2 demonstrated that aggressive, daily drainage resulted in 37% of patients obtaining spontaneous pleurodesis in the first 60 days, versus 11% of patients in the symptom-guided drainage arm (34). Patient-reported quality of life scores were higher in the daily drainage arm, however, the was no significant difference in breathlessness or pain scores, length of stay in hospital or mortality. The ASAP trial also supports an aggressive daily drainage strategy. When compared to alternate-day drainage, there were significantly higher rates of pleurodesis (47% *vs.* 24%) with no significant difference in adverse events (35). Whilst these results are encouraging, daily drainage may not be achievable due to limited resources, particularly where patients are not trained to perform it themselves.

IPCs with a silver-nitrate coating have been investigated as a strategy to improve pleurodesis rates, by eluting silver nitrate into the pleural space over 3–5 days. Results from the SWIFT randomised trial were disappointing, with no improvement in pleurodesis rates over 90 days when compared with standard IPCs (36). Furthermore, there was a higher frequency of loculations in the silver nitrate group. The results of SWIFT were surprising given the phase I SEAL-MPE trial had demonstrated pleurodesis rates of 89% after a median duration of 4 days (37). However, this was in only 9 participants who were undergoing daily IPC drainage over the first 14 days, which is not consistent with routine practice.

Digital drainage devices for IPCs are a more recent development, which patients can use at home. The Passio IPC drainage system (Bearpac Medical) has been trialled in a small number of patients with MPE with variable results (38). These devices allow a controlled flow rate, lower than that seen in vacuum drainage systems, which can reduce pain experienced by some patients during aspiration. A small pilot trial involving 8 patients demonstrated a high rate of complications, with 25% of patients experiencing valve failure which led to re-admission and IPC blockage occurring in 25% of cases. A follow-up study in 27 patients, of which 5 received the Passio device, found no complications and improvements in pain scores when compared with vacuum bottle drainage (39). A randomised-controlled, crossover study is in progress which will randomise patients with MPE to receive either the Passio device or standard IPC, with crossover at 2 weeks. The aim is to assess the safety, tolerability and patient experience (40).

Chemical pleurodesis

Multiple studies have confirmed the superiority of talc as a pleurodesis agent. Dipper *et al.* (41) performed a network meta-analysis of 80 randomised trials, with 5,507 participants included. This demonstrated a lower pleurodesis failure rate with talc slurry via chest drain compared with bleomycin and doxycycline.

In terms of chest drain size for pleurodesis, the TIME-1 trial demonstrated higher rates of pleurodesis with wide-bore chest drains. The trial demonstrated a 30% failure rate in the 12F arm versus a 24% failure rate in the 24F arm, in patients undergoing talc slurry pleurodesis. There

were, however, increased pain scores in patients receiving 24F drains. The trial additionally reported no significant difference in pleurodesis rates following non-steroidal anti-inflammatory drug (NSAID) administration. Whilst higher pleurodesis rates with large bore chest drains have been acknowledged in international guidelines, there are no specific recommendations (1,8). The authors would routinely use an 18F chest tube to balance pleurodesis efficacy with patient comfort.

Removal of the chest drain should take place when pleurodesis has been achieved. Current BTS guidelines suggest removal of chest drain when output has fallen to 200–250 mL over 24 hours (25). The SIMPLE trial demonstrated the use of ultrasound to predict successful pleurodesis and guide drain removal, resulting in a small but statistically significant reduction in the median length of hospital stay. A daily 9-point TUS assessment was used in the intervention group to evaluate the absence of lung sliding as a surrogate for successful pleurodesis (2).

Pleurodesis may also be achieved by the insufflation of talc during thoracoscopy. The TAPPS trial (42) compared local anaesthetic thoracoscopy and talc poudrage with intercostal drain and talc slurry to manage MPE in 330 patients. No significant difference in pleurodesis failure rates was observed between the treatment groups at 90 days, with 22% in the poudrage group and 24% in the slurry group. There was also no significant difference in patient-reported symptoms, number of nights spent in hospital, or mortality. Participants recruited were deemed fit enough to undergo local anaesthetic thoracoscopy, which limits the applicability to frailer patients where talc slurry would be the best option for chemical pleurodesis. The results from TAPPS mirror earlier data from Dresler *et al.* (43) who found no difference in 30-day pleurodesis rates after randomising to either talc slurry via chest drain or talc insufflation during thoracoscopy under general anaesthetic.

Whilst LAT should generally be reserved for patients requiring a tissue diagnosis, rather than a therapeutic option in MPE, talc poudrage may be considered at the time of a diagnostic thoracoscopy where the operator feels the macroscopic appearances suggest malignant pleural disease and the underlying lung is unlikely to be trapped.

IPC versus chemical pleurodesis

Based on USA data, talc pleurodesis remains the most popular definitive intervention for MPE (2). However, when comparing IPCs with chemical pleurodesis, evidence suggests both are effective options for control of symptoms associated with MPE.

The 2010 BTS guidelines recommended talc pleurodesis as the first-line definitive treatment in MPE, however, the results of the TIME2 trial challenged this (24,44). The trial randomised 106 patients with MPE to IPC or talc pleurodesis via 12F chest drain. The IPCs were drained 3 times weekly or as required for symptom relief. Both groups achieved good symptom control, with over 75% of patients achieving clinically significant improvements in visual analogue scale (VAS) scores, with no significant difference between groups at 42 days. There was, however, a statistically significant improvement in dyspnoea at 6 months in the IPC group versus talc pleurodesis. There was no difference in reported quality of life or pain scores. Patients undergoing IPC insertion had a significantly shorter length of stay in hospital. Furthermore, 57% of the IPC group were able to have their IPC removed. The risk of re-intervention was 22% in the talc pleurodesis arm compared with 6% in the IPC group. This trial helped shape more recent guidelines for management of MPE, with both the 2018 American Thoracic Society (ATS) guidelines and 2023 BTS guidelines now recommending either IPC or talc pleurodesis as first-line definitive treatment, with patient choice a strong deciding factor (8,13). Similar results were obtained by Boshuizen *et al.* (45) who randomised 94 patients with MPE to either talc pleurodesis or IPC insertion. There were similar improvements in breathlessness symptoms, however, the IPC arm had a median of 0 days in hospital versus 5 days for talc pleurodesis, with fewer patients in the IPC arm requiring further intervention.

Days spent in the hospital are an important aspect for patients when discussing treatment options, given the poor prognosis of MPE. The aforementioned trials have demonstrated fewer days spent in hospital with IPC insertion versus talc pleurodesis. Arguably, of equal importance is how many days are spent in hospital following discharge. The AMPLE trial assessed the total days spent in hospital from procedure to death or 12 months, after randomisation to IPC or talc slurry via chest drain. IPC patients had a small but statistically significant reduction in days spent in hospital, with a median of 10 days versus 12 in the talc slurry group. The IPC group had fewer effusion-related hospital inpatient days, but a similar number for non-effusion-related causes. Similar to the TIME2 trial, they demonstrated a reduction in re-intervention rates in the IPC group, but no significant difference in dyspnoea or

quality of life scores between groups (23,44). The results of the AMPLE trial may suggest that whilst IPC allows day case management and fewer initial days spent in hospital, there may be a convergence between groups over time.

Whilst re-intervention rates are an important patient-centred outcome, it is important to consider what constitutes an 'intervention' for the patient. From a physician's perspective IPCs reduce the need for further invasive procedures, however, from a patient's perspective draining the IPC multiple times a week is an intervention for them. Unless trained to perform at home, this may mean being unable to leave the house multiple times a week whilst awaiting community teams to visit, which can be burdensome for patients. Qualitative data is lacking in this area, but studies are in progress to understand this (33).

Adverse events are another important consideration when discussing management options with patients. Both AMPLE and TIME2 demonstrated a higher frequency of adverse events in IPC patients compared with talc pleurodesis (30% *vs.* 18% and 40% *vs.* 13% respectively), however, there was no statistically significant difference in serious adverse events (23,44).

The impact on quality of life and patient experience with IPC and talc pleurodesis was assessed in the OPTIMUM trial. Participants (n=142) were randomised to either IPC insertion as a day case procedure with the option of talc pleurodesis or chest drain and talc pleurodesis as an inpatient. Despite a median inpatient stay of 4 days in the chest drain arm, patients had comparable improvements in quality of life, pain and breathlessness scores at 30, 60 and 90 days compared with the IPC group (46). This may suggest hospital admissions alone do not have a long-lasting impact on perceived quality of life, further demonstrating the need to explore patient's wishes and priorities.

In short, both IPCs and chemical pleurodesis are effective interventions to manage symptomatic MPE with expandable lung, patient choice is the most important aspect in decision making and the pros and cons of each intervention should be communicated to the patient.

Surgical management of MPE

Surgical options for MPE include pleurectomy (partial or total) and decortication, with subsequent pleurodesis either via abrasion or chemical agents, i.e., talc (1). Previous case series have demonstrated effective control of MPEs in surgically treated patients with a low rate of recurrence (47-49), however, these studies were undertaken at a time prior to the widespread use of IPCs. Furthermore, important patient-centred outcomes such as dyspnoea and quality of life were not adequately assessed.

The role of surgery in the management of MPE remains poorly defined, with an absence of high-quality data. However, it is worth noting that international guidelines still acknowledge the role of surgical pleurodesis in select cases (1,8,13), particularly those with a better prognosis and good functional status.

Surgical versus medical management of MPE

There is a lack of high-quality evidence to compare medical and surgical interventions in MPE.

A retrospective comparison of LAT and video-assisted thoracoscopic surgery (VATS), both with talc poudrage, for the management of MPE in 231 patients demonstrated similar pleurodesis rates. However, the non-intubated procedures (LAT) had shorter operating room time, shorter hospital stays, lower perioperative mortality and reduced costs (50). This supports the use of LAT in the diagnosis and management of MPE. It is worth noting the intubated patients received only talc poudrage during VATS, which doesn't adequately reflect the range of surgical interventions performed during VATS in day-to-day practice.

Walker *et al.* (51) compared quality of life and participant satisfaction in 104 patients receiving four treatment options: IPC, VATS plus IPC, chest drain with talc slurry and VATS talc poudrage. All interventions provided improvements in patient satisfaction, dyspnoea and quality of life scores. There was no statistically significant difference between groups, however, there was a trend towards higher satisfaction scores in the VATS poudrage group at 6 weeks.

The MesoVATS trial (52) recruited individuals with any subtype of confirmed or suspected mesothelioma with pleural effusion. In total, 196 patients were randomly assigned to either VATS partial pleurectomy (VAT-PP) or talc pleurodesis (either talc slurry or poudrage). The trial failed to achieve the primary outcome of improved survival, with the VAT-PP group having a higher rate of complications, increased healthcare costs and longer hospital stays, with a median of 7 days in the VAT-PP group versus 3 days in the talc pleurodesis group. Given that the trial only included patients with malignant mesothelioma, it is unclear if this extrapolates to all causes of MPE.

AMPLE-3, a multi-centre, open-labelled randomised trial of patients with symptomatic MPE, is underway. Patients with an expected survival of ≥6 months and good

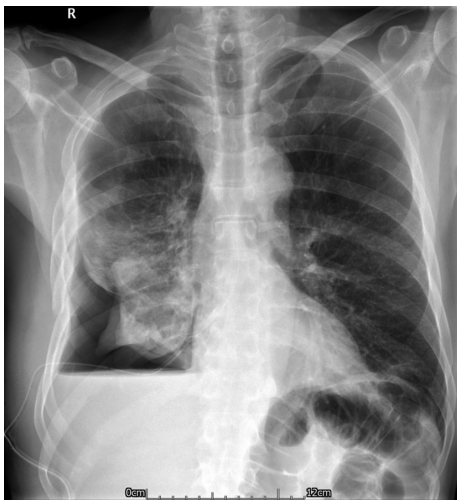

Figure 3 Right sided malignant pleural effusion with indwelling pleural catheter *in situ*, non-expandable lung visible following drainage of pleural fluid.

performance status will be randomised to either IPC or VATS pleurodesis, with the need for further ipsilateral pleural interventions over 12 months or until death, if sooner, as the primary outcome (53).

Management of MPE with NEL

At least 30% of patients with MPE have NEL (13), often referred to as trapped lung or lung entrapment (8). This results in incomplete apposition of the parietal and visceral pleurae which hinders effective pleurodesis (*Figure 3*). There is significant variability when defining non-expandable lung with intra-observer variation and no agreed definition. A definition of >25% of lungs not apposed to the chest wall has been used in a trial setting (8,54).

One area of research interest is the use of pleural manometry to predict the presence of NEL. A study of 65 patients suggested high pleural elastance predicted failure of pleurodesis (55). However, no prospective studies have been able to demonstrate a role in MPE management, and no recommendation is made in international guidelines (1,8,13). Furthermore, it has not been adopted amongst physicians in day-to-day practice (56). A feasibility trial of elastance-directed intervention has been published, with patients allocated either to IPC or chest drain pleurodesis depending upon elastance measurements- a proposed surrogate for the presence of trapped lung (known as the EDIT protocol) (57). A phase 3 study was proposed following this, though it is unclear if this is planned. Further data suggests a poor correlation between pleural elastance and radiological diagnosis of trapped lung (58), therefore further research is needed in this area.

Small retrospective studies such as Cardillo *et al.* (n=29) have assessed the role of surgery in NEL including limited decortication, demonstrating high success rates of up to 96% in controlling reaccumulation (49). However, this was a non-comparative study likely prone to significant selection bias, hence this practice has not been adopted into international guidelines, furthermore, many patients with MPE are unlikely to be suitable surgical candidates. MesoTRAP—a pilot randomised controlled trial, is underway in the UK assessing IPC versus VATS partial pleurectomy/decortication for patients with trapped lung associated with malignant mesothelioma, the results of which are awaited (59).

Pleuroperitoneal shunt placement during thoracoscopy/VATS has previously been deployed in the management of NEL, however, these have fallen out of favour owing to high complication rates (60,61).

More recently, IPCs have become widely adopted as the definitive intervention in NEL (8,59), with evidence suggesting effective control of symptoms, albeit based on small cohorts without randomisation (43). This is largely due to the high failure rates with chemical pleurodesis (43) and the potential to develop symptomatic loculations (24). Results from AMPLE-2 suggest that aggressive daily drainage of IPCs may be beneficial in NEL. At 6 months, 50% of patients with NEL had achieved spontaneous pleurodesis in the daily drainage group, compared with only 7.1% in the symptom-guided drainage group (34). Whilst there remains no consensus on the best way to manage NEL in MPE, owing to a lack of RCTs, guidelines state a very low evidence recommendation for the use of IPCs (13,14).

Combined procedures

Given the absence of technological advances in the management of MPE, research has focused on combining procedures to streamline patient treatment pathways and optimise success rates.

IPC-PLUS was a randomised, placebo-controlled trial that recruited 154 patients with MPE in whom a decision for IPC insertion had been made prior to recruitment (54). Clinical and radiological review was performed at day 10, participants with expandable lung were randomised to receive talc slurry or placebo via their IPC, to which the

patient was blinded. There was a significantly higher pleurodesis rate at day 35 in the talc group of 43% versus 23% in the placebo group (hazard ratio, 2.20; 95% CI, 1.23 to 3.92; P=0.008). This increased to 51% in the talc group and 27% in the placebo group at day 70 (hazard ratio, 2.24; 95% CI, 1.31 to 3.85; P=0.003). It is important to note that these rates from an enriched cohort where patients with NEL were actively excluded are dwarfed by the 75–80% pleurodesis rates quoted from studies of conventional inpatient talc slurry pleurodesis or poudrage (42). There were small but statistically significant improvements in quality of life and chest pain scores in the talc group compared with placebo. There was a statistically significant improvement in dyspnoea scores favouring the talc group at day 56, though the mean scores over the trial period did not meet statistical significance on post hoc analysis.

Participants in IPC-PLUS had their IPCs drained at least 4 times in the first 10 days, following this at least twice per week, which could be accommodated in most pleural centres, unlike the daily drainage regime seen in the AMPLE-2 trial (34,54). The results provide a further viable option for patients where admission avoidance and removal of a long-term catheter are important, though pleurodesis success rates are lower than those observed with talc slurry (41).

There is evidence to suggest that combining thoracoscopic talc poudrage (TTP) with IPC insertion increases pleurodesis success rates. Reddy *et al.* (62) and Boujaoude *et al.* (63) both reported pleurodesis success rates of 92% from their observational studies, with IPC removal at a median of 7.54 and 6 days, respectively. The cohorts were small (30 patients in each) and the lack of randomisation means results should be interpreted with caution. Despite these studies being published in 2011 and 2015 respectively, there is still a lack of high-quality data to evaluate these interventions. The TACTIC trial is a prospective multi-centre RCT in the UK that aims to answer this question, having recently completed recruitment, results should be available imminently. Participants with MPE were randomised to TTP (standard care) or combined TTP and IPC insertion. The primary outcomes are breathlessness scores and length of stay in hospital. Importantly, qualitative data will be obtained from patients and carers to explore patient experience and quality of life.

Septated effusions

Fibrinous adhesions are common in MPE, resulting in septations, which can result in incomplete drainage following chest drain or IPC insertion (64). The proportion of MPEs with septations is not known but Bielsa *et al.* found significant adhesions (defined as obstruction of one-third or more of the vision on thoracoscopy) in 40% of patients (65). The presence of septations is thought to be related to the tumour burden and confers a poor prognosis (66).

The management of septated MPEs can be challenging. The role of surgery is unclear, whilst this does allow the removal of pleural adhesions, the presence of NEL can make this undertaking futile in preventing fluid reaccumulation (1).

Intrapleural fibrinolytics have been utilised in septated MPEs for over 20 years, with previous evidence suggesting good radiological and symptomatic improvement (67-70). More recently, the TIME3 trial (64) randomised 71 patients with a non-draining MPE between three doses of 100,000 IU intrapleural urokinase or placebo. In line with previous studies, there was a radiological improvement in effusion size. However, there was no significant difference in dyspnoea scores, quality of life, or pleurodesis rates following talc slurry.

The trial reported a small, but statistically significant reduction in hospital stay of 1.6 days, and improved survival (69 *vs.* 48 days). However, there were imbalances between the groups in underlying diagnosis therefore, caution should be applied in interpreting these secondary outcomes. The authors emphasised the importance of exploring other palliative measures to control symptoms, given the poor prognosis in this subgroup of patients (64).

The mixed results for fibrinolytics in the management of MPE suggest clinicians should reserve this for the most symptomatic patients where other options are unavailable, patients should be aware of the risks, such as bleeding and pain. Other palliative options should also be explored to control dyspnoea symptoms (64,67).

Novel approaches

Other methods for controlling MPE, particularly in the setting of failed pleurodesis, have been explored. Astoul *et al.* (71) trialed a novel pleural-bladder pump system in 2 patients, after successful application in animal models. The system relies upon a subcutaneously implanted battery-powered device and is based on other commercially available systems for the control of ascitic fluid. For the two patients involved, results were mixed. One patient had successful control of their MPE with 33.5 L of fluid removed over a 1-year period, however, both patients experienced catheter

blockage. Overall, this is a very invasive procedure with higher risks than established interventions, which may limit the ability to obtain larger-scale data.

Conclusions

A patient-centred management plan is vital in achieving optimal outcomes in MPE, which requires careful consideration of patients wishes and their own goals. The last decade has seen an expansion of high-quality evidence to clarify outcomes from interventions in MPE to guide clinicians and ultimately provide optimal care to patients with a significant burden of symptoms.

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