# ERS/EACTS statement on the management of malignant pleural effusions

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**Management options for malignant pleural effusions have advanced over the past decade, with high-quality randomised trial evidence informing practice in many areas. However, uncertainties remain and further research is required** http://ow.ly/rNt730jOxOS

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ABSTRACT Malignant pleural effusions (MPE) are a common pathology, treated by respiratory physicians and thoracic surgeons alike. In recent years, several well-designed randomised clinical trials have been published that have changed the landscape of MPE management. The European Respiratory Society (ERS) and the European Association for Cardio-Thoracic Surgery (EACTS) established a multidisciplinary collaboration of clinicians with expertise in the management of MPE with the aim of producing a comprehensive review of the scientific literature.

Six areas of interest were identified, including the optimum management of symptomatic MPE, management of trapped lung in MPE, management of loculated MPE, prognostic factors in MPE, whether there is a role for oncological therapies prior to intervention for MPE and whether a histological diagnosis is always required in MPE.

The literature revealed that talc pleurodesis and indwelling pleural catheters effectively manage the symptoms of MPE. There was limited evidence regarding the management of trapped lung or loculated MPE. The LENT score was identified as a validated tool for predicting survival in MPE, with Brims' prognostic score demonstrating utility in mesothelioma prognostication. There was no evidence to support the use of oncological therapies as an alternative to MPE drainage, and the literature supported the use of tissue biopsy as the gold standard for diagnosis and treatment planning.

## Introduction

Malignant pleural effusions (MPE) are common, affecting up to 15% of all patients with cancer [1]. The incidence of MPE is likely to rise as global cancer incidence increases and overall survival improves. The majority of patients with MPE are symptomatic, with breathlessness the most common symptom [2]. The presence of MPE usually represents advanced or metastatic disease, and consequently survival is poor, ranging from a median of 3 months to 12 months depending on underlying patient and tumour factors [2]. The focus of treatment is inevitably palliative, and aimed at relieving symptoms.

Existing guidelines regarding the management of MPE were published over 7 years ago [2]. A number of high-quality trials have been published subsequently, many of which have changed practice [3–5]. Additionally, as increasing numbers of pleural interventions are being undertaken and experience with different management approaches has grown, new hurdles and issues have become apparent. This statement was written to summarise the evidence with regard to management of MPE in general, and in relation to specific questions that may be encountered by clinicians who manage MPE.

## Methods

The task force was assembled at the European Respiratory Society (ERS) Annual Congress in London 2016 with the goal of producing an expert statement on the management of MPE. The task force was created based on the recommendations of the ERS Scientific Committee and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines Committee and included nine respiratory physicians and five thoracic surgeons from nine different European countries (supplementary material: Appendix A). The aim of the task force was to develop a statement that represented a comprehensive, expert scientific review of the literature, identified by systematic searches with conclusions supported by accompanying references.

Topics to be covered by the statement were decided at the initial meeting of the task force. Six clinical questions were chosen to be covered by the statement. They comprised the optimum management of 1) symptomatic MPE, 2) MPE with trapped lung and 3) loculated MPE; 4) factors predicting prognosis; 5) whether oncological therapy should precede definitive fluid management in treatment-sensitive tumours; and 6) whether histological diagnosis is always required. Certain topics have been covered in previous guidelines and statements (*i.e.* questions 1, 3 and 4), and the intention of the task force was to present an updated summary of the literature, whilst other topics have not been specifically reviewed before (*i.e.* questions 2, 5 and 6). Each question, except the question on prognosis, was structured using the PICO (Patients, Intervention, Comparison and Outcomes) format. The PICO criteria for each question are presented in supplementary material: Appendix B.

The literature search was undertaken in January 2017 by an Information Scientist at the University of York, with guidance from a task force member (ACB). Three medical databases, Medline/PUBMED (National Library of Medicine, USA), EMBASE (Elsevier, the Netherlands) and Cochrane Library (UK), were searched using a combination of MeSH headings and keywords appropriate to the clinical question. Search results were limited to papers in English relating to adult patients. The full search strategy for each clinical question is shown in supplementary material: Appendix C. Once the search had been run, further potentially eligible articles were identified by snowballing, including reviewing the reference lists of identified papers. The search was repeated in January 2018 to identify recently published papers.

Abstracts were screened for inclusion by two task force members (ACB and NAM). Articles were included or excluded based on pre-specified eligibility criteria for each clinical question (supplementary material: Appendix D). Each reviewer screened abstracts independently before results were compared. Any disagreements were resolved by discussion, with involvement from the task force chairs if necessary.

Six subgroups were formed, with each comprising a combination of physicians and surgeons with a range of expertise. Each subgroup reviewed the full-text articles of the reference material and further excluded any articles that did not match the eligibility criteria. The Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) diagram for each clinical question is shown in supplementary material: Appendix E.

Subgroups prepared drafts summarising the relevant literature for their clinical question. These drafts were reviewed by the task force at a meeting during the 2017 ERS congress in Milan. Comments and suggestions were made, after which subgroups revised their drafts and submitted them to the writing

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committee (ACB, NAM). The writing committee collated the drafts into a complete statement that was circulated to all task force members. Feedback was incorporated into a revised second draft that was disseminated to the task force. Further revisions were discussed at a teleconference in November 2017, leading to production of the final draft. This was reviewed and approved by all members; hence, the final document represents a consensus statement of the entire task force.

The statement describes current practice regarding the management of MPEs, and summarises the evidence as it currently stands. The statement does not make recommendations for clinical practice. It has been endorsed by the ERS Scientific Committee and the EACTS Guideline Committee and peer-reviewed by expert reviewers on behalf of the *European Respiratory Journal* and the *European Journal of Cardio-Thoracic Surgery*.

## Question 1: what is the best definitive treatment for patients with symptomatic malignant pleural effusions?

MPE are usually associated with significant symptoms. Because the majority of patients with MPE will experience fluid re-accumulation after therapeutic aspiration, a definitive pleural intervention is recommended [2]. For the purposes of this document, "definitive" is regarded as a procedure intended to provide long-term relief from pleural effusion symptoms. Serial thoracentesis is not considered definitive and is therefore not included.

The literature covers many definitive pleural interventions for MPE, including pleurodesis using a chemical agent (*e.g.* tetracycline, doxycycline and bleomycin), talc pleurodesis *via* thoracoscopy (poudrage) or chest tube (slurry), mechanical pleurodesis at surgery, pleurectomy, and insertion of indwelling pleural catheters (IPC). This document will review the available evidence for the more common interventions.

### *Chemical pleurodesis*

Three systematic reviews assessed the efficacy of different pleurodesis agents. Bucknor *et al.* [6] conducted a best-evidence review of silver nitrate as a pleurodesis agent, in which 42 papers were identified and eight included. Half of these papers related to animal studies or non-malignant populations, but for the four studies undertaken in MPE, silver nitrate pleurodesis rates of 89–96% were reported. This compared favourably with pleurodesis rates of 84% with talc slurry in the only randomised trial included in the review [7]. Further support for silver nitrate was provided by a small case series of 17 patients in whom talc pleurodesis failed; 89% of these patients subsequently achieved pleurodesis with silver nitrate [8].

Tan *et al.* [9] conducted a systematic review and meta-analysis of randomised trials and included 46 studies with a total of 2053 patients. Pleural fluid recurred less frequently with talc (poudrage or slurry) compared with doxycycline or bleomycin. In the most recent and most thorough assessment in the literature, Clive *et al.* [1] conducted a network meta-analysis of MPE pleurodesis strategies. Talc poudrage was ranked highest in terms of fluid control, with clear benefit compared with bleomycin and tetracycline. Side effects were similar across the agents studied, although large-particle (graded) talc was recommended over mixed-particle size to reduce the risk of acute respiratory distress syndrome (ARDS). The authors noted a high or unclear risk of bias in all included studies, as well as high heterogeneity between trials. There was a lack of patient-reported outcomes and further work is required in this area to allow clinicians to understand patients' preferences and formulate individualised management plans.

### *Talc poudrage* versus *talc slurry*

Three systematic reviews addressed thoracoscopic talc poudrage (*via* surgical video-assisted thoracoscopic surgery (VATS) or medical thoracoscopy) *versus* bedside talc slurry. Tan *et al.* [9] demonstrated that poudrage was associated with less recurrence than slurry (relative risk 0.21, 95% CI 0.05–0.93) based on two studies. In a network meta-analysis, talc poudrage was ranked higher than slurry in terms of fluid control, accepting bias in the included studies [1]. Mummadi *et al.* [10] conducted a systematic review and meta-analysis of talc poudrage *versus* slurry. Of 28 studies identified, four were included as high quality. No overall difference in successful pleurodesis was found (relative risk 1.06, 95% CI 0.99–1.14), but poudrage was associated with a higher risk of respiratory complications (relative risk 1.91, 95% CI 1.24–2.93). The increased complication rate was driven entirely by a single study by Dresler *et al.* [11], the largest in the literature. In that trial, 501 patients were randomised to talc poudrage or slurry (250 *versus* 251 patients) using non-graded talc. The primary outcome was radiographic absence of effusion at 30 days in those who survived and in whom initial lung expansion was >90%. There was no difference overall (78% *versus* 71%), but in a *post hoc* subgroup analysis of breast and lung cancer patients, poudrage appeared superior (82% *versus* 67%). There was an excess of adverse events in the talc poudrage group

(14% *versus* 6% for respiratory complications, and 8% *versus* 4% for respiratory failure), including 11 deaths.

YIM *et al.* [12] randomised 57 MPE patients with expandable lungs to talc poudrage or slurry, showing no difference in any outcome including complications. Similarly, TERRA *et al.* [13] randomised 60 patients to talc poudrage or slurry, and demonstrated no difference in outcome, although a greater proportion of poudrage patients demonstrated complete lung expansion.

Four non-randomised studies compared talc poudrage to slurry. Two studies totalling 277 patients demonstrated no difference in pleurodesis outcomes [14, 15], whereas two others totalling 257 patients demonstrated higher pleurodesis success rates, shorter tube duration (9 days *versus* 6 days) and longer effusion-free survival with poudrage [16, 17].

There were 17 case series of >100 patients reporting the utility of talc poudrage in the literature, comprising 6347 patients. Varying doses of talc were used and definitions of pleurodesis success and complications differed. Success rates ranged from 77% to 98%, and complications from 2% to 17.2%, including mortality in some studies [18–34]. Important specific results in these studies included no incidences of ARDS in 558 patients undergoing talc poudrage with graded talc [22], lower pleurodesis success in patients with pleural pH <7.2 [31], and improved dyspnoea but deteriorating overall quality of life post-pleurodesis in MPE [32].

### *Chest tube size*

The majority of studies that demonstrated high pleurodesis rates with talc used large bore chest tubes (⩾24F). Numerous case series suggest reasonable pleurodesis rates using smaller bore catheters with a number of different agents.

Two randomised trials directly addressed chest tube size in pleurodesis. CLEMENTSEN *et al.* [35] randomised 18 patients to small bore catheter (10F) or large bore tube (24F) for tetracycline pleurodesis, and found no significant difference in pleurodesis rates. Although this was taken to indicate there was no difference in pleurodesis rates according to chest tube size in MPE, the study was underpowered for this outcome and was not designed as a non-inferiority trial. RAHMAN *et al.* [4] conducted a 2×2 factorial randomised trial assessing opiate *versus* nonsteroidal anti-inflammatory drugs and small (12F) *versus* large (24F) chest tubes in 320 patients with MPE undergoing talc pleurodesis. Pain comparisons were powered for superiority and pleurodesis for non-inferiority. Small bore tubes failed to meet the non-inferiority margin of 15%, demonstrating lower pleurodesis success (30% *versus* 24% pleurodesis failure).

### *Other issues regarding talc pleurodesis*

In the past, it has been assumed that adequate distribution of talc throughout the thoracic cavity was required to achieve successful pleurodesis. MAGER *et al.* [36] randomised 20 patients to either rotation or bed rest in the supine position following administration of radiolabelled talc. No difference in distribution was found between the two arms, and thus rotation does not increase the likelihood of pleurodesis success.

Pleurodesis is a highly painful procedure in some patients, and most physicians use opiate analgesia for the procedure. Although nonsteroidal anti-inflammatory drugs are effective analgesics for acute pain, they have historically been avoided during pleurodesis owing to fears that their anti-inflammatory effect may reduce pleurodesis success. RAHMAN *et al.* [4] randomised 320 patients to high-dose ibuprofen (800 mg three times daily) or opiate during pleurodesis for MPE and demonstrated no significant difference in pleurodesis success or pain using a non-inferiority design. These results suggest nonsteroidal drugs need not be avoided in patients undergoing pleurodesis for MPE.

Small-particle (or ungraded) talc is thought to be associated with significantly more side effects than large-particle (graded) talc, including ARDS and respiratory failure [11, 22]. Small-particle talc was associated with higher inflammatory cytokine responses in one small non-randomised comparative study [37]. Interestingly, higher inflammatory responses were seen in patients following talc poudrage with successful pleurodesis compared with non-successful pleurodesis in a case series [38]. Similarly, higher fibrinolytic activity in pleural fluid has been associated with pleurodesis failure [39].

Whilst pleurodesis aims to palliate symptoms rather than extend survival, one retrospective non-randomised study found talc poudrage pleurodesis was associated with longer survival compared with repeated thoracentesis [40]. However, the authors conflated correlation with causality, and ignored potential confounding by indication in the two treatment arms. Another series of 91 patients explored factors associated with poor survival after talc poudrage [41]. Poor performance status and prior use of

chemo/radiotherapy were adverse prognostic factors, and these clinical parameters may be helpful in triaging patients to treatments.

### *Surgical options*

Surgical options for MPE (aside from VATS talc poudrage which is covered in the section above) include pleurectomy and abrasion pleurodesis. Several cases series suggest partial and total pleurectomy are effective treatments for MPE [42–44].

Four randomised trials have compared surgical techniques with "medical" pleurodesis. Crnjac *et al.* [45] randomised breast cancer MPE patients to thoracoscopic abrasion or bedside talc slurry (5 g) and analysed radiological outcomes stratified by pleural pH levels. Pleurodesis success rates were not significantly different between effusions with pH >7.3 and with pH <7.3 (92% *versus* 91%). Hospital stay was shorter in the surgical group (5.5 days *versus* 7.5 days, p<0.05), and complication rate and mortality also favoured abrasion (16% *versus* 26% and 0% *versus* 9.5%, respectively). A smaller randomised trial compared the same interventions, using surrogate inflammatory outcomes. Surgical pleurodesis was associated with a greater increase in inflammatory cytokines (although nonsignificant) and better patient-reported outcomes [46].

Gu and Wang [47] randomised 53 non-small cell lung cancer (NSCLC) MPE patients to VATS pleurectomy or chest tube drainage, although it is unclear whether a pleurodesis agent was given in the chest drain arm. A significant improvement favouring VATS was seen in MPE response rates (92.3% *versus* 59.3%, p<0.05) and Karnofsky performance status (mean 33.5±11.3 and 24.07±10.5, p<0.05), but there were no differences in overall survival.

In the largest randomised trial of its type, Rintoul *et al.* [5] compared fluid control rates in 196 mesothelioma patients randomised to VATS pleurectomy or talc pleurodesis using poudrage or slurry. There was no significant difference in pleurodesis, and VATS was associated with higher expense and increased adverse events.

A non-randomised comparison of talc pleurodesis, abrasion and pleurectomy for MPE demonstrated longer hospital stays and worse mortality and morbidity following surgery [48]. Similarly, in another study, pleurodesis rates were lower in patients who underwent local anaesthetic thoracoscopy compared with VATS, but post-operative drainage, mortality, morbidity and costs were also lower in the medical thoracoscopy group [49]. Greater improvements in early physical health, global health and dyspnoea were seen with medical thoracoscopy, although this group comprised historic controls and was therefore at risk of selection bias.

### *Indwelling pleural catheters*

IPCs are an alternative to pleurodesis that offer long-term symptom control *via* regular home drainage of fluid. Multiple case series, totalling 1533 patients, have reported their utility in MPE management, specifically in terms of improving breathlessness and other symptoms, and quality of life [50–55]. A systematic review of 19 case series, totalling 1370 patients treated with IPC, reported symptomatic improvement in 96%, with removal owing to complications required in 8.5% [56].

There are four randomised controlled trials comparing IPCs with chemical pleurodesis [3, 57–59]. Putnam *et al.* [57] randomised 144 MPE patients to IPC or doxycycline pleurodesis in a 2:1 ratio, demonstrating comparable improvement in symptoms in both groups. However, the IPC group spent less time in hospital (1 day *versus* 6.5 days), and had a 46% pleurodesis rate at 27 days.

In the TIME2 trial, Davies *et al.* [3] randomised patients to IPC or inpatient talc slurry pleurodesis *via* a 12F intercostal drain, with a primary outcome measure of patient-reported breathlessness over 6 weeks.

No significant difference in dyspnoea scores was found between the groups, with a small difference in breathlessness favouring IPC at 6 months. IPCs were associated with reduced time in hospital (0 *versus* 4 days) and reduced requirement for further procedures (6% *versus* 22%), but also with increased adverse events (OR 4.70, 95% CI 1.75–12.60, p=0.002).

More recently, the AMPLE study randomised 146 patients with MPE to IPC insertion or talc slurry pleurodesis *via* a chest drain [58]. Patients who received an IPC had shorter hospital stays (10 *versus* 12 days, p=0.03) and required fewer subsequent pleural interventions (3 *versus* 16, p=0.001) than the pleurodesis group. Both arms reported sustained improvements in breathlessness and quality of life scores, with no difference between the two arms. Complication rates were higher in the IPC group (30% *versus* 18%), but there was only one serious adverse event compared with three in the chest tube arm.

Demmy *et al.* [59] randomised 57 patients to IPC placement with daily drainage or bedside talc pleurodesis, with a composite primary outcome of "success" based on reliable drainage, pleurodesis and 30-day survival. The recruitment target was not met, and a secondary endpoint of survival with effusion

control was added retrospectively. IPCs were more successful for the primary outcome (62% *versus* 46%, p=0.064) and secondary outcome (82% *versus* 52%, p=0.024). However, the results of this study should be interpreted with caution given the failure to recruit the target sample size, the potential bias introduced by adding outcomes *post hoc*, and the limited clinical applicability of the primary outcome.

Three non-randomised studies compared IPCs with poudrage [60], talc slurry [61] and VATS pleurodesis or decortication [62]. These studies reported reduced hospital stay and fewer repeat procedures for IPCs compared with slurry or poudrage [60, 61], but reduced survival compared with decortication [62]. However, all suffer from potential selection bias. One study assessed patient-reported outcome measures in MPE interventions, including patients having IPC, talc slurry pleurodesis and surgical VATS [63]. All patients demonstrated improved functional assessment and breathlessness scores, with no statistically significant difference between treatment groups.

Regarding IPC drainage regimens, the multi-centre, randomised ASAP trial [64] revealed that daily IPC drainage was more likely to result in auto-pleurodesis, either complete or partial, within 12 weeks compared with alternate day drainage (pleurodesis rate 47% *versus* 24%, p=0.003). Adverse event rates (and specifically infection rates) were similar in the two arms and although almost 30% of the 149 patients randomised died before the 12-week primary endpoint, deaths were evenly distributed between the two treatment regimens. Importantly, patients with trapped lung were excluded from the study, a pertinent consideration when applying this result to clinical care because aggressive drainage is likely to cause significant pain in this population. Careful evaluation of individual patients is therefore required before a daily drainage approach is followed.

#### *Combined procedures*

Given the growing evidence supporting IPCs, there is increasing interest in combining their use with other pleurodesis procedures. Three case series totalling 148 patients reported the use of IPCs during VATS [65] and combined with talc poudrage pleurodesis [66, 67]. The combination of poudrage and IPC was associated with short hospital stays (1–3 days) and removal of catheters after successful pleurodesis within ~7 days. A single non-randomised study used propensity matching to compare VATS poudrage with IPC placement at VATS in 60 patients [68]. The IPC group had shorter hospital stays and lower morbidity.

There is a lack of high-quality randomised evidence for the use of combined procedures in MPE, but this is a potential treatment direction for the future.

#### *In summary*

Talc is the most effective agent for chemical pleurodesis in MPE, and graded-particle talc appears safe. The data suggest that thoracoscopic talc poudrage (*via* surgical VATS or medical thoracoscopy) may be slightly more effective than slurry for MPE pleurodesis, and an ongoing randomised trial in the UK is aiming to answer this question [69]. Surgical pleurodesis procedures are no more effective than talc, especially in mesothelioma where evidence from a randomised controlled trial shows that VATS pleurectomy is associated with more complications and longer hospital stays, but no additional benefit in terms of pleurodesis success [70].

Large bore tubes (*e.g.* 24F) are associated with higher pleurodesis success rates in talc pleurodesis than smaller drains (*e.g.* 12F), with nonsteroidal drugs as an effective analgesia option that does not lower pleurodesis rates. IPCs appear to be as effective at relieving MPE symptoms as talc pleurodesis and are associated with reduced time in hospital, although adverse event rates appear to be higher than for talc.

### Question 2: what is the optimal management for malignant pleural effusion with trapped lung?

Trapped lung describes the situation in which the lung is unable to fully expand to fill the hemithorax, rendering the parietal and visceral pleura either partly or completely unopposed. Trapped lung can occur as a result of pleural thickening causing encasement of the lung, proximal endobronchial obstruction causing distal lung collapse or chronic atelectasis. Some authors differentiate between "lung entrapment", in which an active pleural process such as malignancy causes a visceral pleural peel to form, thus preventing lung expansion, and "trapped lung", in which the fibrous peel has arisen as a consequence of remote inflammation in the pleural space that is no longer active [71, 72]. For the purpose of this document, the term "trapped lung" will be used to cover both clinical entities.

Whether trapped lung can be predicted is an issue beyond the scope of this document. Pleural manometry, M-mode ultrasonography and patients' symptoms during aspiration have all been proposed as methods of predicting trapped lung [71, 73–78]. However, as yet none have been proven prospectively and further evidence is required before they can be adopted into routine clinical practice.

Regarding the management of trapped lung in MPE, there is little high-quality evidence. The literature is complicated by certain issues, including different definitions of the disease and the potential for variation in the degree of lung entrapment between individual patients and studies. In addition, several studies include patients with trapped lung, loculated effusions or previous failed pleurodesis, but do not clearly differentiate between patient groups when reporting outcomes. There are no randomised controlled trials specifically investigating trapped lung, and consequently the evidence must be interpreted with awareness of the risk of selection bias (in non-comparative studies) and confounding by indication (in non-randomised comparative studies). Furthermore, it is highly likely that institutional preference and expertise will determine the choice of intervention for trapped lung, introducing additional bias.

A single systematic review focusing on the optimal approach to MPE concluded that IPCs are indicated in trapped lung [79]. This conclusion was based on two studies out of 14 included in the review. The first, by Pien *et al.* [80], was a retrospective review of 11 patients with trapped lung who underwent IPC insertion and home drainage. All but one patient described symptomatic benefit, and 12 out of 13 catheters placed remained *in situ* until the patient died. Serious adverse events, *i.e.* empyema, IPC blockage and catheter fracture, occurred in three patients.

Additional information regarding IPC in trapped lung is available from the randomised trial of Demmy *et al.* [59] of talc pleurodesis *versus* IPCs in MPE. The subgroup of nine patients with trapped lung had higher effusion control rates at 30 days in the IPC arm compared with the talc pleurodesis arm, and better dyspnoea-free exercise scores (7.8 *versus* 4.5, p=0.02).

A non-randomised comparative study compared the use of poudrage pleurodesis at VATS to IPCs, with the intervention chosen according to whether trapped lung was present, suggesting successful treatment in trapped lung with IPCs [81].

There are several observational studies reporting the value of IPC in MPE with trapped lung, the results of which are summarised in table 1. It is worth noting that symptomatic outcomes were inconsistently defined across these studies, and whilst some studies reported the number of patients who experienced symptomatic relief, others subjectively graded the size of the response in individuals. Nonetheless, IPCs appear effective in trapped lung, with symptomatic improvement reported in >94% of patients in five studies totalling 133 patients [51, 80, 82–84], although a single study of 48 patients reported lower symptom relief rates of 48% [85]. Three of these studies included patients who had undergone VATS and been diagnosed with trapped lung intra-operatively, and so received an IPC at the end of the procedure [55, 82, 85]. In these studies, it is impossible to determine which procedure was responsible for which outcomes, both in terms of symptomatic benefit and adverse events, which were numerous. Length of stay was consistently shorter for trapped lung patients treated with IPCs than for comparator groups (usually comprising patients with non-trapped lung undergoing VATS talc poudrage) [81, 82].

Other approaches to managing malignant trapped lung include surgical decortication and intra-pleural fibrinolytic therapy. Pleuroperitoneal shunts have historically been used in trapped lung; however, the supporting evidence is of poor quality, complications rates are high and they are not currently used in routine clinical practice [34, 86, 87]. From a surgical perspective, Yim *et al.* [88] reported "good outcomes" in seven patients with trapped lung who underwent VATS decortication. A randomised controlled trial is underway in the UK assessing the role of surgical pleurectomy/decortication *versus* IPC in patients with mesothelioma and trapped lung (Meso-TRAP).

Hsu *et al.* [89] investigated the use of 100 000 IU urokinase *via* IPCs in surgically inoperable patients with trapped lung or loculated effusions. Three out of 12 patients with trapped lung demonstrated "excellent" radiographic improvement following treatment, which persisted until death in two out of the three. No adverse events were reported. However, the relevance of radiographic resolution, specifically its inconsistent relationship with symptoms, makes this finding difficult to interpret in a clinical context.

#### *In summary*

There is a lack of good-quality published evidence but IPCs appear to be an effective option in the management of MPE trapped lung. Dedicated prospective trials are needed to fully evaluate the utility of IPCs in trapped lung, and also to evaluate surgical interventions and the role of fibrinolytic therapy.

### Question 3: how should septated and loculated malignant pleural effusion be managed?

Loculated MPE are defined as MPE with multiple loci, *i.e.* there is more than one fluid collection, or the effusion is divided into multiple separate pockets of fluid. This is different to septated effusions, in which fibrinous strands have formed within an effusion, usually as a result of excessive fibrin formation due to inflammatory-mediated changes in procoagulant and fibrinolytic activity [90]. Septated effusions can

TABLE 1 Summary of observational studies that used IPCs for trapped lung

| Author | Year of publication | Total subjects | Subjects with trapped lung | Subjects reporting symptomatic improvement % | Time IPC *in situ* days | Median survival days | Pleurodesis rate % | Complications | Other outcomes/comments |
|---|---|---|---|---|---|---|---|---|---|
| **Warren [51]** | 2008 | 231 | 28 | 100 | 43.3 | NR | 54 | Infection (mainly cellulitis) 5<br>Catheter blockage 11<br>Skin reaction to dressing 1 | Combined results for all patients undergoing IPC insertion |
| **Bazerbashi [55]** | 2009 | 125 | NR | NR | 87 | 84.1 | 76 | Wound infection 7<br>Peri-catheter leak 2<br>Catheter blockage 2<br>Catheter displacement 2<br>Tumour seeding 1 | Combined results for patients with trapped lung and previous failed pleurodesis |
| **Ohm [81]** | 2003 | 41 | 34 | NR | NR | NR | NR | NR | Length of stay <2 days in 56% |
| **Pien [80]** | 2001 | 11 | 11 | 100 | 115 | NR | NR | Cellulitis 2<br>Pleural infection 2<br>Catheter occlusion 1 | |
| **Qureshi [82]** | 2008 | 127 | 52 | 94.2 | 93.8 | 126 | 42.3 | Surgical emphysema 2<br>Catheter blockage 2<br>Cellulitis 2<br>Fluid loculation 2 | |
| **van den Toorn [83]** | 2005 | 17 | 17 | 100 | 63 | NR | NR | Pleural Infection 1<br>Cellulitis 1<br>Catheter displacement 3<br>Hyponatraemia 1 | |
| **Efthymiou [85]** | 2009 | 48 | 48 | 48 | NR | NR | NR | Peri-catheter leakage 13%<br>Occlusion 4%<br>Catheter displacement 4% | 65% moderately or very satisfied with mobility improvement |
| **Sioris [91]** | 2009 | 51 | NR | NR | 120 | 91 | 21 | Early complications 4<br>Pleural infection 3<br>Catheter displacement 1<br>Catheter blockage 2<br>Cellulitis 1 | Combined results for patients with trapped lung, patients with high volume effusions and patients unsuitable for general anaesthetic |
| **Burgers [84]** | 2006 | 25 | NR | 100 | NR | 70 | 24 | Empyema 3<br>Haemoptysis 1 | |

Data presented as n, unless otherwise indicated. IPC: indwelling pleural catheters; NR: not reported.

become loculated over time, but the presence of septations in MPE does not necessarily prevent the free flow of fluid within an effusion. In contrast, loculation can prevent complete drainage of the pleural space and limit lung re-expansion, potentially contraindicating pleurodesis or resulting in insufficient symptomatic relief in patients with IPCs.

Septations are common in MPE. One retrospective analysis of 540 consecutive patients who underwent medical thoracoscopy for MPE found that 332 (60%) had some degree of adhesion (*i.e.* septation), which obstructed two thirds or more of the thoracoscopic view in 84 (15%) [92]. The extent of pleural adhesions correlated with a greater pleural tumour burden and shorter median survival [92]. Transthoracic ultrasonography (TUS) outperforms computed tomography (CT) in the identification of septations. In a prospective study of 64 patients undergoing VATS, pre-operative CT had 71% sensitivity and 72% specificity for detecting septations [93]. In contrast, two series of 142 and 117 patients reported sensitivities of 81% and 88%, respectively, and specificities of 96% and 83%, for TUS identification of septations prior to thoracic surgery [94, 95]. Another small observational study further supported the use of TUS over CT as an effective method for identifying thick pleural septations prior to thoracoscopy (sensitivities 100% and 12.5% respectively) [96].

TUS has a role in treating loculated effusions, and has been shown to reduce complications and increase yield when used to guide interventions in loculated collections [97, 98]. However, the utility of TUS is limited in the presence of mediastinal loculations or loculations involving the fissures, because the overlying lung prevents imaging of the fluid beneath it. In these situations, CT is of greater value, with a high sensitivity for identifying loculations [98, 99].

Septations can be broken up under direct vision at thoracoscopy (medical or surgical), whilst thoracic surgery is usually required to access multiple loculations, especially those positioned on the mediastinum. Multiple drains have been used to drain loculated effusions in the setting of pleural infection [100, 101]; however, multiple procedures are not ideal in patients with MPE. Additionally, if the underlying lung is non-expandable, pleurodesis will be ineffective and this approach will not result in definitive fluid control.

Intra-pleural fibrinolytic agents have been shown to improve fluid drainage in loculated pleural infection [102], and uncontrolled small case series have reported their use in symptomatic loculated MPE with incomplete initial drainage [103–110]. Intra-pleural fibrinolytic agents increased fluid drainage in all cases, and improved symptoms and radiological appearances in 60% [110], 86% [109] and, in most studies, 100% of patients [103–108]. Different drugs, including streptokinase [103–107, 110], urokinase [109] and tissue plasminogen activator [108, 110], were employed at varying dosages.

Four controlled studies, three of which were randomised, investigated the role of intra-pleural fibrinolysis for the treatment of loculated MPE [89, 111–113]. The first, which used a historical control group, prospectively evaluated 36 patients with symptomatic loculated MPE after drainage with an 8F catheter who were unsuitable for surgery [89]. The administration of intra-pleural urokinase (100 000 IU daily for 3 days) resulted in a greater than two-third reduction in radiological effusion size in 26 patients (72.2%). All 26 subsequently received minocycline pleurodesis, with lifelong fluid control in 21 (80.8%). Radiological lung expansion was significantly greater than in 40 retrospectively analysed historical controls with loculated MPE who did not receive fibrinolytic agents.

The second study randomised 47 patients with symptomatic MPE to receive intra-pleural streptokinase (250 000 IU twice daily for three doses) or pleural drainage only [111]. No information was provided regarding the existence of pleural adhesions. In the fibrinolytic group, 96% of patients achieved radiological lung expansion and were subsequently able to receive talc slurry, compared with 75% in the control group ($p=0.035$). However, pleurodesis success at 1 month was similar in both groups (74% *versus* 56%, $p=0.28$).

The third study randomly allocated 40 patients with loculated MPE on CT to receive intra-pleural streptokinase (four separate doses of 250 000 U) or placebo (saline) administered through a 20F tube, after which talc slurry pleurodesis was performed [112]. The fibrinolytic group had higher daily drainage volumes at all time points ($p<0.001$), with a greater proportion of patients showing CT improvements of >40% (85% *versus* 35%, $p=0.001$). Fibrinolytic therapy was also associated with reduced requirements for supplementary oxygen (10% *versus* 45%) and lower rates of pleurodesis failure at 1 month (11% *versus* 45%), although only the first result reached statistical significance.

Finally, in the TIME3 trial, 71 patients with non-draining MPE due to fibrinous adhesions received either urokinase (100 000 U, three doses over 36 h) or placebo, followed by talc slurry pleurodesis after 24 h [113]. There was no difference in dyspnoea scores on a visual analogue scale over the first month or pleurodesis failure rates at 1 year between the fibrinolysis and placebo groups. However, urokinase performed better than placebo for secondary outcome measures, including an 18% greater reduction in pleural opacity on

chest radiography 2 days post-randomisation, shorter length of hospital stay (6.2 *versus* 8.7 days) and improved survival (48 *versus* 69 days; all p<0.05). Notably, 48% of the study population died within 1 month of randomisation, highlighting the extremely poor prognosis of patients with this problem.

The use of fibrinolytic agents in patients with IPCs and loculated MPE has been studied in one multi-centre retrospective review [114]. A total of 66 patients (64 with an MPE) who developed symptomatic loculations with IPCs *in situ* were treated with intra-pleural fibrinolytic agents. Most patients received a single dose (range 1–6) of tissue plasminogen activator (n=52), urokinase (n=12) or streptokinase (n=2). Following therapy, the volume of pleural fluid drained increased in 93.3% of patients and dyspnoea improved in 83%. The area of pleural opacity on chest radiography decreased from 52% to 31% of the hemithorax in 13 evaluable patients. However, symptomatic loculations recurred in 27 patients (41%) and only one of the 10 patients who received repeated fibrinolytic therapy had sustained improvement in drainage and symptoms.

#### *In summary*

Intra-pleural fibrinolytic agents increase the volume of fluid drainage and improve the radiological appearance in loculated MPE. However, they have no effect on clinical outcomes, such as dyspnoea or pleurodesis success. Alternatives, however, are limited for patients with loculated MPE for whom surgery is not suitable.

### Question 4: what factors predict prognosis in malignant pleural effusion?

MPE management depends on prognosis. Patients with long survival require definitive interventions, whilst the aim for people with short life expectancy should be to maximise time at home [2].

Certain factors, *i.e.* tumour type, stage and performance status (PS), are accepted prognostic factors in malignancy, including MPE. In MPE, lung cancer carries the worst prognosis, whilst longer survival is seen in gynaecological tumours, predominantly due to the underlying tumour's sensitivity to treatment [2, 115–121]. Staging systems exist for each tumour that formally describe disease extent and prognosis [122]. Usually MPE signifies metastatic disease, higher stage and shorter survival, although mesothelioma is an exception to this rule [122, 123]. Finally, PS is a global evaluation of function that predicts outcome in cancer, as well as being used as a tool to assess patients' suitability for oncological treatment [117, 118, 121, 124–129].

#### *Prognosticating in malignant pleural effusion*

Specific MPE-related prognostic factors include effusion size. Massive MPE, defined as fluid occupying the entire hemithorax, was associated with significantly worse survival in one large prospective study [130]. This finding was replicated in a subsequent retrospective study, although the definition of massive effusion differed [119].

Pleural fluid pH may also predict survival: an early study demonstrated worse prognosis in patients with pleural fluid pH <7.2 [131]. However, whilst several subsequent studies replicated the original finding, albeit using lower pH cut-offs [31, 119, 129], others found no relationship between pH and survival [41, 126]. Patient-level data from these studies were pooled in a meta-analysis that confirmed pH ⩽7.28 was associated with shorter survival [116]. However, pH could not reliably predict 3-month survival and was therefore insufficiently accurate for clinical use. Pleural fluid glucose, which is closely related to pH, was similarly non-predictive [31, 41, 119, 126, 129].

Other potentially prognostic pleural fluid variables include lactate dehydrogenase, which correlated with survival in multiple observational series [119, 129, 131]. Haemorrhagic fluid was also associated with reduced survival times in patients with lung cancer [119], and was a poor prognostic factor in patients with MPE undergoing thoracoscopy [132]. Positive pleural fluid cytology does not predict survival [118, 132], although detection of specific receptors or mutations, *e.g.* of epidermal growth factor receptor (EGFR), in fluid can have treatment and prognostic implications [133, 134]. Interestingly, high serum levels of vascular endothelial growth factor (VEGF) did not predict response to bevacizumab (a VEGF antagonist) in mesothelioma [135]. However, high serum and pleural fluid VEGF levels are associated with worse outcomes in MPE [136, 137], as are the downstream effects of inflammation, angiogenesis and tumour necrosis [138, 139].

Inflammation and cancer are closely related, and serum inflammatory markers can predict prognosis [140–143]. The Glasgow Prognostic Score combines C-reactive protein with serum albumin and has been validated to predict survival in several tumour types [144–146]. Another inflammation-based prognostic score is the serum neutrophil to lymphocyte ratio (NLR), for which high values reflect raised neutrophil levels, low lymphocyte levels, or both. Raised neutrophil levels are an adverse prognostic marker in NSCLC, melanoma, renal cell carcinoma and others [147–150]. Lymphocytes, however, are fundamental to

| | Variable | Value | Score |
|---|---|---|---|
| **L** | Pleural fluid LDH level IU·L$^{-1}$ | <1500 | 0 |
| | | >1500 | 1 |
| **E** | ECOG PS | 0 | 0 |
| | | 1 | 1 |
| | | 2 | 2 |
| | | 3–4 | 3 |
| **N** | NLR | <9 | 0 |
| | | >9 | 1 |
| **T** | Tumour type | Mesothelioma<br>Haematological malignancy | 0 |
| | | Breast cancer<br>Gynaecological cancer<br>Renal cell cancer | 1 |
| | | Lung cancer<br>Other tumour types | 2 |

| Risk category | Total score |
|---|---|
| Low risk | 0–1 |
| Moderate risk | 2–4 |
| High risk | 5–7 |

FIGURE 1 The LENT score calculation and prognostic groups [45]. LDH: lactate dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group performance status; NLR: neutrophil lymphocyte ratio.

immune-mediated cancer control and low counts result in less effective tumour destruction and worse survival [151–153]. The NLR combines these two variables to provide a simple prognostic value that has been shown to be accurate in many cancers [41, 145, 154–160].

Chronic inflammation causes catabolism and cachexia, which have further negative implications in MPE [141–143]. Low albumin has been shown to be an independent prognostic factor, as well as predicting outcome as part of the Prognostic Nutritional Index, a validated predictor of survival in mesothelioma and other malignancies [144, 145, 161–163].

Many prognostic scoring systems have been suggested for MPE. However, only one has been externally validated. The LENT score was developed using data from 789 patients across three international centres [156]. Baseline factors were analysed for prognostic value and those with the strongest predictive ability were included in the predictive model (figure 1). Final scores separated patients into low-, moderate- or high-risk groups, with median survival of 319, 130 and 44 days respectively. Validation produced similar results, confirming that LENT is an accurate and robust tool for predicting MPE prognosis. The simplicity of the score makes it attractive for both clinical practice and research settings.

### *Prognostication in mesothelioma*

Multiple observational studies have reported prognostic factors in mesothelioma, although many were susceptible to selection bias, having been undertaken in selected populations [164–171]. The forthcoming ERS task force statement on mesothelioma contains information on prognostication, and therefore a full summary of the literature is not replicated here.

In brief, certain factors are consistently associated with survival in mesothelioma, *i.e.* sex, age, epithelioid differentiation, PS and tumour stage [117, 157, 164–170, 172–181]. However, for other factors, including presenting symptoms or quantification of asbestos exposure, the relationship with survival is less clear [163, 165, 168, 173, 182–184]. Multiple inflammatory markers correlate with survival, including white cell count [121, 145, 157, 162, 166, 168–170], platelet count [157, 164, 166, 169, 170, 172, 177], C-reactive protein [157, 164, 166, 169, 170, 172, 177], platelet to lymphocyte ratio [145] and lymphocyte to monocyte ratio [162]. Local inflammation also affects prognosis, with lymphocytic infiltration of tumours and tumour stroma associated with longer survival following surgery [153, 158]. Much work has been done investigating potential prognostic biomarkers, including mesothelin, osteopontin and megakaryocyte potentiating factor. However, heterogeneity in thresholds and sampling intervals mean that these tests are not yet sufficiently reliable to be employed in standard care [159, 185–187].

Numerous unvalidated prognostic indices exist in the literature [138, 157, 170, 171, 182, 183, 188–191], but only three have been externally validated [169, 183, 192]. Of the validated scores, two used pooled data from clinical trials and consequently have limited generalisability to the overall mesothelioma population [169, 183]. In contrast, Brims *et al.* [192] used an unselected cohort of 482 sequential mesothelioma

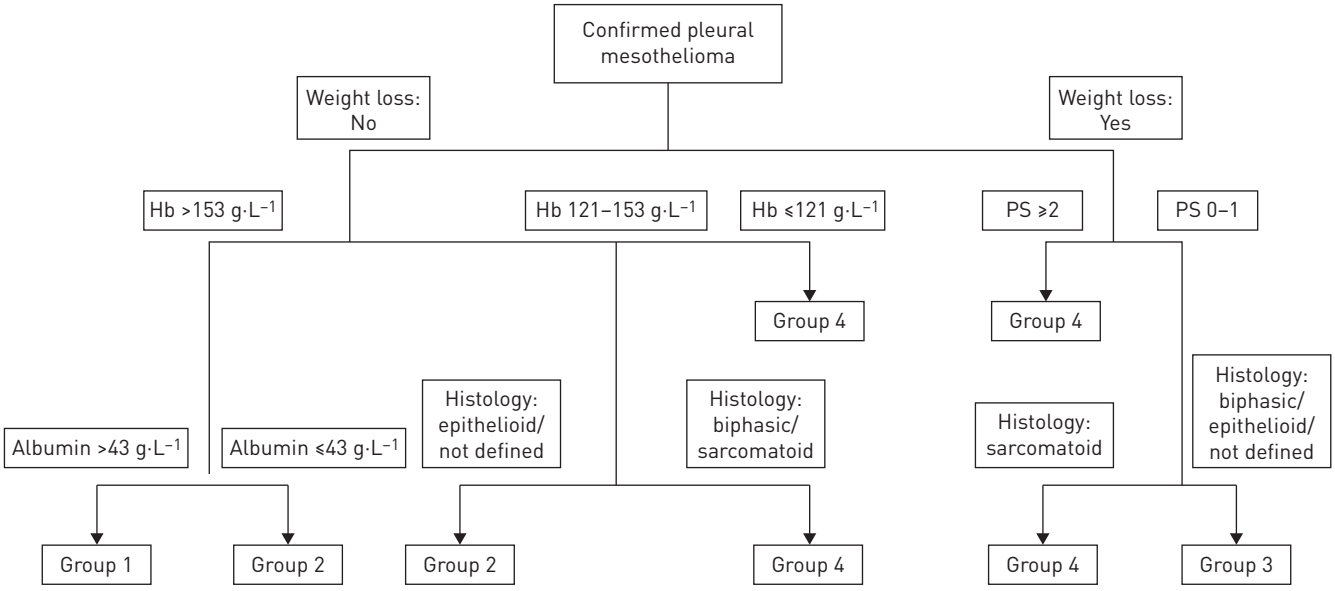


FIGURE 2 Brims' decision tree for predicting mesothelioma prognosis [192]. Hb: haemoglobin; PS: Eastern Cooperative Oncology Group performance status.

patients to develop their prognostic tree, which was then validated in a separate consecutive cohort, creating a more representative and clinically useful tool. The resultant decision tree separated patients into one of four prognostic groups, with survival falling from 34 months in Group 1 to 17.7, 12.0 and 7.4 months in subsequent groups (figure 2). The model showed reasonable accuracy for predicting death at 18 months, with 94.5% sensitivity and 76% positive predictive value.

***In summary***

Multiple baseline factors predict prognosis, including tumour type, stage, PS and inflammatory markers in blood and pleural fluid. Although multiple prognostic tools have been published, only the LENT score has been validated in MPE, and Brims' decision tree is the most clinically useful in mesothelioma.

## Question 5: should patients with malignant pleural effusion and cancer that is sensitive to oncological treatment (*e.g.* chemotherapy, immunotherapy, targeted therapy) receive treatment prior to definitive management of their malignant pleural effusion? If so, which cancers?

To date, no international guidelines recommend the use of antitumour medical treatment, *e.g.* chemotherapy, targeted therapy and/or immunotherapy, before standard palliative procedures for MPE management. Additionally, no randomised controlled trials were identified that compared palliative procedures for MPE with antitumour treatment.

However, observational studies suggest chemotherapy may be an effective first-line treatment in certain treatment-sensitive tumour types. For example, a retrospective study in small cell lung cancer (SCLC) demonstrated resolution of MPE following first-line chemotherapy in 34 of 62 patients (55%) [193]. In contrast, another series of 30 patients with MPE due to SCLC reported increased myelosuppression following chemotherapy compared with 30 matched patients without MPE [194]. Whilst association should not be mistaken for causality, this observation supports the hypothesis that chemotherapy may accumulate in undrained effusions, leading to increased toxicity [193–195]. Consequently, the authors recommend that effusions be drained prior to commencing systemic chemotherapy.

By contrast, in lymphoma, case reports have suggested systemic therapy may be an effective treatment for MPE [196, 197], whilst another retrospective study reported control of MPE in 20 patients with T-cell lymphoblastic lymphoma who were treated with various systemic agents and mediastinal radiotherapy [198]. In NSCLC, several retrospective studies have described the role of systemic chemotherapy in patients with MPE; however, the significant selection bias affecting these studies precludes meaningful clinical interpretation [199–201]. Finally, a single case report describes complete resolution of MPE following initiation of chemotherapy in a patient with metastatic ovarian cancer [202].

Molecular targeted therapy has been investigated in patients with MPE and NSCLC [203–205]. A case report described the disappearance of MPE secondary to lung adenocarcinoma following treatment with bevacizumab, carboplatin and paclitaxel [205]. In a single-arm prospective study, 76 patients with MPE and EGFR mutations were treated with oral gefitinib (an EGFR tyrosine kinase inhibitor (TKI)) until disease progression, toxicity or withdrawal [203]. MPE were assessed with CT scans every 3 months. Of the 76 patients, 70 (92%) had a reduction in MPE of >50% that lasted at least 3 months. However, 48 developed subsequent MPE recurrence and 33 went on to receive talc pleurodesis. Another study, retrospective and non-randomised, added the anti-VEGF monoclonal antibody bevacizumab to chemotherapy alone or to chemotherapy plus EGFR-TKI in 86 patients with MPE due to EGFR-positive NSCLC with acquired EGFR-TKI resistance [204]. Progression-free survival was longer in the bevacizumab/EGFR-TKI/chemotherapy group (6.3 *versus* 4.8 months, p=0.048), and longer still in patients with acquired T790M mutations treated with the triple regimen (6.9 *versus* 4.6 months, p=0.022). However, there was no difference in overall survival between the treatments. Selection bias is likely to have affected the results of both studies, and prospective randomised trials are needed to further clarify the role of targeted therapies in MPE with specific mutations.

A number of trials have investigated intra-pleural targeted therapies in MPE. Two phase I studies explored the safety of intravenous and intra-pleural chemotherapy alongside monoclonal antibodies in MPE [206, 207]. Safety profiles were variable and numbers were too small to comment on efficacy. Two randomised phase II studies have investigated intra-plural use of bevacizumab in patients with NSCLC and MPE [208, 209]. In one, a combination of bevacizumab and paclitaxel were administered intra-pleurally, leading to reduced pleural effusion size and improved symptoms in 78.6% of patients compared with 50% treated with intra-pleural paclitaxel alone [208]. The 1-year survival rate was higher in the bevacizumab arm (45.8% *versus* 20.8%), whilst adverse events were similar between the groups. The second phase II trial compared intra-pleural cisplatin with or without bevacizumab in 70 patients with MPE in non-squamous NSCLC [209]. Better MPE response rates (85.7% *versus* 56.6%) were seen with the addition of bevacizumab. A single-arm phase II study used intravenous bevacizumab alongside systemic carboplatin-pemetrexed chemotherapy and demonstrated MPE control in 21 out of 23 patients (91.3%) [210]. Again, further research is needed to determine the efficacy of this approach.

#### *In summary*

The current literature is limited, consisting mainly of small retrospective series or single-arm prospective studies. Thus no conclusions can be drawn on the value of antitumour treatment in MPE management. Because there is no strong evidence to suggest any detriment associated with standard interventional management of MPE, this is likely to remain the first line of treatment until evidence emerges to support alternative approaches. Further studies are needed, specifically to confirm the use of intra-pleural bevacizumab in NSCLC MPE and EGFR-TKI in patients with MPE due to NSCLC with mutated EGFR.

### Question 6: in order to determine treatment in malignant pleural effusion, is a histological diagnosis always required or is cytology sufficient?

The aim of cytological and histological investigations is twofold: to obtain a diagnosis and to determine therapeutic options. As cancer treatment options expand to include targeted therapies, immunotherapy and personalised treatments, the question of which investigation yields the most pathological information has become increasingly pertinent.

The diagnostic yield of pleural fluid cytology varies depending on tumour type, tumour load, sample quality, expertise of cytologist and availability of specific ancillary tests, *e.g.* gene expression. The mean diagnostic sensitivity of pleural fluid cytology for malignancy is between 49% and 91%, with maximal yield from two separate samples [211–221]. Cytology has the highest diagnostic yield for adenocarcinoma, compared with mesothelioma, for which sensitivity is generally accepted to be ∼30%, but may fall as low as 16% [215–217]. With respect to mesothelioma, cytological diagnosis is particularly challenging given that tissue invasion is not always present and histological subtypes can be difficult to differentiate [222]. The yield of cytological diagnosis in epithelioid mesothelioma is higher in the presence of visceral pleural invasion [223].

Analysing larger volumes of pleural fluid may improve diagnostic sensitivity in MPE, although there appears to be a threshold. Several studies confirmed that submitting >75 mL of pleural fluid for cytological examination does not improve the yield when using the direct smear method [224–226]. However, if both direct smear/cytospin and cellblock preparations are utilised, up to 150 mL is recommended [227]. This combined method has been shown to offer additional value compared to smear slides alone [228, 229].

Initial cytological evaluation of pleural fluid involves identifying cells and characterising them as benign/reactive or malignant based on morphological and immunohistochemical parameters. If malignant cells are seen,

TABLE 2 Immunohistochemical markers with high specificity for differentiating tumour types in malignant pleural effusion

| Mesothelial markers | Adenocarcinoma markers | Squamous-cell carcinoma markers | Organ-specific markers |
|---|---|---|---|
| Calretinin<br>CK5/6<br>D2-40 (podoplanin)<br>WT-1 | CEA<br>B27.3<br>Bg8<br>BerEP4<br>MOC-31 | P40<br>P63<br>CK5/6 | Lung: TTF-1, Napsin A<br>Prostate: PSA, PSMA<br>Kidney: PAX-2, PAX-8, RCC, CAIX<br>Pancreas: CA 19-9<br>Gastrointestinal: CDX-2, CK20<br>Gynaecological: PAX-8, WT1<br>Breast: Mammaglobin, GCDFP-15, ER, PR, GATA3 |

further evaluation is required to determine their origin, *i.e.* primary pleural malignancy *versus* metastatic disease. Disease-specific immunochemical markers are summarised in table 2 [230–234].

Flow cytometry may be a useful adjunct in the differentiation of lymphoma in pleural fluid [235, 236]. However, its role in the diagnosis of non-lymphoma MPE has not been fully established, with studies demonstrating variable sensitivities of between 50% and 94% [237–239]. Further innovative approaches may advance this technique in future [240].

Where mesothelioma is suspected, specific tests are frequently required owing to the complexities associated with making this diagnosis. Sarcomatoid mesothelioma is particularly difficult to diagnose because tests for mesothelial markers are often negative. Additionally, there are no specific antibodies that differentiate between sarcomatoid mesothelioma and other sarcoma-type tumours, although GATA3 has shown early promise in one small study [241]. Loss of BAP1 expression and homozygous deletion of p16 detected by fluorescent *in situ* hybridisation are highly specific indicators for mesothelioma, but negative results do not exclude the diagnosis [242–245]. These tests can be undertaken on both pleural fluid and biopsy samples, although sensitivity is reduced if no atypical mesothelial cells are present in effusion samples [243–245]. Consequently, although some laboratories are confident making definitive cytological diagnoses [218, 246], the International Mesothelioma Interest Group recommends that the diagnosis should always be based on biopsy [232]. Evaluation of biopsy tissue can also provide prognostic information in mesothelioma because certain histological features, such as nuclear atypia and mitotic index, correlate with prognosis in epithelioid disease [247–250].

Mesothelioma aside, the pauci-cellular nature of pleural fluid often results in insufficient cells on which to perform the necessary tests to confirm the diagnosis [251]. Additionally, tissue-specific gene expression and receptor status profiling may be required to assess suitability for therapeutic options such as molecular therapies, and pleural fluid alone is rarely sufficient for this. Whilst newer molecular profiling technologies such as high-throughput, next-generation and Sanger sequencing have shown promise in detecting genetic mutations on MPE cell blocks, they require further investigation before widespread adoption into clinical practice [251–254]. Consequently, pleural biopsy is usually necessary to provide sufficient tissue for analysis. Thoracoscopic pleural biopsies have a diagnostic sensitivity of >92% for malignancy, and consistently outperform cytological examination, even when cell block preparation is performed [255–257].

Even though pleural biopsy is the gold standard for diagnosing pleural malignancy, false negative results can occur. Observational follow-up studies of patients whose original biopsies showed nonspecific pleuritis found that up to 15% were subsequently diagnosed with pleural malignancy, most frequently mesothelioma [258–262]. The decision on whether to undertake repeat biopsies, possibly *via* a different approach, is usually made based on clinical suspicion and individual patient factors (*e.g.* suitability for surgery). Whatever pathway is chosen, many clinicians elect to undertake long-term radiological monitoring to ensure malignancy is not missed.

Recently, highly sensitive assays have been developed which allow the identification of circulating cell-free tumour DNA, tumour RNA (especially microRNAs) and circulating tumour cells from patients' blood samples [263, 264]. These "liquid biopsy" methods have proven useful in lung cancer patients in detecting baseline *EGFR* mutations [265, 266], and for identifying mutations conferring resistance to targeted therapy, *e.g.* T790M *EGFR* mutation [267, 268]. Whilst several of these assays have been approved by regulatory authorities for use in clinical care, they are not yet universally accessible. Furthermore, for some tumours, *e.g.* mesothelioma, no standardised approach has been developed and further studies are needed [269–271].

*In summary*

Cytology can provide useful diagnostic, prognostic and therapeutic information; however, low sensitivity remains an issue, especially in mesothelioma. Pleural biopsy remains the gold standard, although in cases where initial biopsies yield inflammation, repeat biopsy or extended follow-up is usually required. Newer technologies such as liquid biopsy may negate the need for biopsies in future, but further research is needed to ascertain their optimal role.

## Conclusions

This task force statement aimed to review the literature relating to the management of MPE, focusing specifically on issues that may be relevant to respiratory physicians, thoracic surgeons and oncologists in routine clinical practice.

The highest quality evidence for the optimal treatment of symptomatic MPE suggests that both talc pleurodesis (*via* slurry or poudrage) and IPCs are highly effective and significantly improve symptoms. It is still unclear whether talc poudrage is more effective than talc slurry, and whilst IPCs reduce time in hospital, they are associated with a modest increase in adverse events with long-term use.

In the context of trapped lung, evidence is lacking with regard to effective treatment options. IPCs often improve symptoms, but prospective randomised trials are required. Similarly, options are limited in loculated MPE, with little evidence to suggest that intra-pleural fibrinolysis has any sustained effect on patient symptoms and well-being.

Regarding prognostication, the LENT score is a simple, validated tool for predicting survival in MPE, whilst Brims' decision tree is most useful in mesothelioma. At present, there is no robust evidence to support the use of oncological therapies as an alternative to mechanical drainage, although further research is required. Currently, although cytological analysis can provide some diagnostic information in MPE, tissue biopsy remains the gold standard.

The management of MPE has advanced significantly since the most recent international guidelines were published, with several high-quality randomised controlled trials providing robust evidence to inform clinical practice. However, a number of unanswered questions remain, and ongoing research is required in order for clinicians to provide optimal care for this patient group.

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