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ERS/EACTS Statement on the management of malignant pleural effusions

Anna C Bibby[1,2], Patrick Dorn[3], Ioannis Psallidas[4], Jose M Porcel[5], Julius Janssen[6], Marios Froudarakis[7], Dragan Subotic[8], Phillippe Astoul[9], Peter Licht[10], Ralph Schmid[3], Arnaud Scherpereel[11], Najib M Rahman[4,12], Giuseppe Cardillo[13,14] & Nick A Maskell[1,2,14]

Affiliations

1. Academic Respiratory Unit, Translation Health Sciences, University of Bristol, Bristol UK
2. North Bristol Lung Centre, North Bristol NHS Trust, Bristol UK
3. Division of Thoracic Surgery, University Hospital Bern, Bern, Switzerland
4. Oxford Respiratory Trials Unit, University of Oxford, Oxford, UK
5. Pleural Medicine Unit, Biomedical Research Institute of Lleida, Lleida, Spain
6. Dept of Pulmonary Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
7. Department of Respiratory Medicine, Medical School of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece
8. Clinic for Thoracic Surgery, Clinical Center of Serbia, Belgrade, Serbia
9. Dept of Thoracic Oncology, Pleural Diseases and Interventional Pulmonology, Hospital North Aix-Marseille University,Marseille, France
10. Department of Cardiothoracic Surgery, Odense University Hospital, Denmark
11. Pulmonary and Thoracic Oncology Department, Hospital of the University (CHU) of Lille, Lille, France
12. Oxford Centre for Respiratory Medicine, University Hospitals, NHS Foundation Trust, Oxford, UK
13. Dept of Thoracic Surgery, Carlo Forlanini Hospital, Azienda Ospedaliera San Camillo, Forlanini, Rome, Italy
14. Taskforce Chairperson

Conflicts of Interest

All authors completed a conflict of interest form prior to embarking on the taskforce statement. No conflicts of interest were declared.

Abstract

Malignant pleural effusions (MPE) are a common pathology, treated by respiratory physicians and thoracic surgeon 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 multi-disciplinary 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 are effective at managing 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) Consequently 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 Taskforce 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 Taskforce was created based on the recommendations of the ERS Scientific Committee and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines Committee and included 9 Respiratory Physicians and 5 Thoracic Surgeons from 9 different European countries (see Appendix A). The aim of the Taskforce 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 Taskforce. Six clinical questions were chosen to be covered by the statement. They included the optimum management of MPEs, the management of trapped lung and loculated MPE, factors predicting prognosis, whether oncological therapy should precede definitive fluid management in treatment-sensitive tumours and whether histological diagnosis is always required. Certain topics had been covered in previous guidelines and statements (i.e. questions 1, 3 and 4), and the intention of the Taskforce was to present an updated summary of the literature, whilst other topics had not been specifically reviewed before (i.e. questions 2, 5 and 6). Each question, except the question on prognosis, were structured using the PICO (Patients, Intervention, Comparison and Outcomes) format. The PICO criteria for each question are presented in Appendix B.

The literature search was undertaken in January 2017 by an Information Scientist at the University of York, with guidance from a Taskforce 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 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 taskforce members (ACB and NAM). Articles were included or excluded based on pre-specified eligibility criteria for each clinical question (see Appendix D). Each reviewer screened abstracts independently before results were compared. Any disagreements were resolved by discussion, with involvement from the Taskforce Chairs if necessary.

Six sub-groups were formed, with each comprising a combination of physicians and surgeons with a range of expertise. Each sub-group reviewed the full-text articles of the reference material and further excluded any articles that did not match the eligibility criteria. The PRISMA diagram for each clinical question is shown in Appendix E.
Sub-groups prepared drafts summarising the relevant literature for their clinical question. These drafts were reviewed by the Taskforce at a meeting during the 2017 ERS congress in Milan. Comments and suggestions were made, following which sub-groups revised their drafts and submitted to the writing committee (ACB & NAM). The writing committee collated the drafts into a complete statement that was circulated to all Taskforce members. Feedback was incorporated into a revised second draft that was disseminated to the Taskforce. 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 Taskforce.

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 (ERJ) and the European Journal of Cardio-Thoracic Surgery (EJCTC).

Question 1 - What is the best definitive treatment for patients with symptomatic MPE?

MPE are usually associated with significant symptoms. Since 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 conducted a best evidence review of silver nitrate as pleurodesis agent, in which 42 papers were identified and 8 included.(6) 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 who failed talc pleurodesis, 89% of whom subsequently achieved pleurodesis with silver nitrate.(8)

Tan et al conducted a systematic review and meta-analysis of randomised trials and included 46 studies of 2053 patients in total.(9) 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 conducted a network meta-analysis of MPE pleurodesis strategies.(1) 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 in order to allow clinicians to understand patients' preferences and formulate individualised management plans.

Talc slurry versus talc poudrage

Three systematic reviews addressed bed-side talc slurry versus thoracoscopic talc poudrage (via surgical VATS or medical thoracoscopy). Tan et al demonstrated that poudrage was associated with less recurrence than slurry (RR 0.21, 95% CI 0.05-0.93) based on two studies.(9) 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 conducted a systematic review and meta-analysis of talc poudrage versus slurry.(10) Of 28 studies identified, 4 were included as high quality. No overall difference in successful pleurodesis was found (RR 1.06, 95 % CI 0.99-1.14), but poudrage was associated with a higher risk of respiratory complications (RR 1.91, 95% CI= 1.24-2.93). The increased complication rate was driven entirely by a single study by Dresler et al, the largest in the literature. In that trial, 501 patients were randomised to talc poudrage or slurry (250 vs 251 patients) using non-graded talc.(11) The primary outcome was radiographic absence of effusion at 30 days, in those that survived and in whom initial lung expansion was >90%. There was no difference overall (78% vs 71%), but in a post-hoc, subgroup analysis of breast and lung cancer patients, poudrage appeared superior (82% vs 67%). There was an excess of adverse events in the talc poudrage group (14% vs 6% for respiratory complications, and 8% vs 4% for respiratory failure) including 11 deaths.

Yim et al randomised 57 MPE patients with expandable lungs to talc slurry or poudrage, showing no difference in any outcome including complications.(12) Similarly, Terra et al 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.(13)

Four non-randomised studies compared talc slurry to poudrage. 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 vs 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 randomised patients to small bore catheter (10F) or large bore tube (24F) for tetracycline pleurodesis.(35) 18 patients were randomised, and no significant difference in pleurodesis rates was demonstrated. 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 conducted a 2 x 2 factorial randomised trial assessing opiate versus NSAIDs and small (12F) versus large (24F) chest tubes in 320 patients with MPE undergoing talc pleurodesis.(4) 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% vs 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 randomised 20 patients to either rotation or bed rest in the supine position following administration of radio-labelled talc.(36) No difference in distribution was found between the two arms, and thus rotation does not increase the likelihood of pleurodesis success.

Pleurodesis is recognised to be a highly painful procedure in some patients, and most physicians use opiate analgesia for the procedure. Although non-steroidal anti-inflammatory drugs are effective analgesics for acute pain, they have historically been avoided during pleurodesis due to fears that their anti-inflammatory effect may reduce pleurodesis success. Rahman et al randomised 320 patients to high dose ibuprofen (800mg tds) or opiate during pleurodesis for MPE and demonstrated no significant difference in pleurodesis success or pain using a non-inferiority design.(4) These results suggest non-steroidals 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 with successful pleurodesis following talc poudrage 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 randomised breast cancer MPE patients to thoracoscopic abrasion or bedside talc slurry (5g) and analysed radiological outcomes stratified by pleural pH levels.(45) Pleurodesis success rates were not significantly different in effusions with pH>7.3 and pH<7.3 (92% vs 91%). Hospital stay was shorter in the surgical group (5.5 days vs 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 rise in inflammatory cytokines (although non-significant) and better patient-reported outcomes.(46)

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

In the largest randomised trial of its type, Rintoul et al compared fluid control rates in 196 mesothelioma patients randomised to VATS pleurectomy or talc pleurodesis using poudrage or slurry.(5) 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 were therefore at risk of selection bias.

Indwelling Pleural Catheters

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) Systematic review of 19 case series, totalling 1370 patients treated with IPC, reported symptomatic improvement in 96%, with removal due to complications required in 8.5%.(56)

There are 4 randomised controlled trials comparing IPCs with chemical pleurodesis.(3, 57-59) Putnam et al randomised 144 MPE patients to IPC or doxycycline pleurodesis in a 2:1 ratio, demonstrating comparable improvement in symptoms in both groups.(57) However, the IPC group spent less time in hospital (1 day vs 6.5 days), and had 46% pleurodesis rate at 27 days.

In the TIME2 trial, Davies et al 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.(3) 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 vs 4 days) and requirement for further procedures (6% vs 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 undergo IPC insertion or talc slurry pleurodesis via a chest drain.(58) Patients who received an IPC had shorter hospital stays (10 vs 12 days, p=0.03) and required fewer subsequent pleural interventions (3 vs 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% vs 18%), but there was only one serious adverse event compared with 3 in the chest tube arm.

Demmy et al 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.(59) Recruitment target was not met, and a secondary endpoint of survival with effusion control was added retrospectively. However, IPCs were more successful for the primary outcome (62% versus 46%, p=0.064) and secondary outcome (82% vs. 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 clinically applicability of the primary outcome.

Three non-randomised studies compared IPCs with poudrage,(60) talc slurry,(61) and VATS pleurodesis/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 study 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 (47% vs 24% pleurodesis rate, p=0.003).(64) 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 end-point, 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, as 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 increasing 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 to 3 days) and removal of catheters after successful pleurodesis within around 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.

Therefore, 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 suggests that thoracoscopic talc poudrage (via surgical VATS or medical thoracoscopy) may be slightly more effective than slurry for MPE pleurodesis, and an on-going 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 RCT evidence 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 (i.e 24F) are associated with higher pleurodesis success rates in talc pleurodesis than smaller drains (i.e. 12F), with non-steroidals an effective analgesia option that do 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 MPE with trapped lung?

Trapped lung describes the situation where 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) However 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. Additionally 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 investigating trapped lung specifically, 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 may determine the choice of intervention for trapped lung, introducing additional bias.

A single systematic review focussing on the optimal approach to MPE concluded that IPCs are indicated in trapped lung.(79) This conclusion was based on 2 studies out of 14 included in the review. The first, by Pien et al, was a retrospective review of 11 patients with trapped lung, who underwent IPC insertion and home drainage.(80) All but one patient described symptomatic benefit, and 12/13 catheters placed remained in situ until the patient died. Serious adverse events, namely empyema, IPC blockage and catheter fracture, occurred in 3 patients.

Additional information regarding IPC in trapped lung is available from Demmy et al's randomised trial of talc pleurodesis versus IPCs in MPE.(59) The sub-group of 9 patients with trapped lung had higher effusion control rates at 30 days in the IPC arm compared with talc pleurodesis, alongside 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 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 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 over 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, hence 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 fibrinolytics. Pleuroperitoneal (PP) shunts have been used historically 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 reported "good outcomes" in 7 patients with trapped lung who underwent VATS decortication.(88) 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 investigated the use of 100,000 IU urokinase via IPCs in surgically inoperable patients with trapped lung or loculated effusions.(89) 3 out of 12 trapped lung patients demonstrated "excellent"

radiographic improvement following treatment, which persisted until death in 2/3. No adverse events were reported. However, the relevance of radiographic resolution, specifically its inconsistent relationship with symptoms make 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 fibrinolytics.

Question 3 – How should septated and loculated MPE 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, where 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 may become loculated over time, but the presence of septations in MPE does not necessarily prevent free flow of fluid within an effusion. In contrast, loculation may prevent complete drainage of the pleural space and limit lung re-expansion, thus 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 2/3 or more of the thoracoscopic view in 84 (15%).(91) The extent of pleural adhesions correlated with a greater pleural tumour burden and shorter median survival.(91) 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.(92) In contrast, two series of 142 and 117 patients reported sensitivities of 81% and 88% respectively, alongside 96% and 83% specificity for ultrasound identification of septations prior to thoracic surgery.(93, 94) 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).(95)

TUS has a role in loculated effusions, and has been shown to reduce complications and increase yield when used to guide interventions in loculated collections.(96, 97) However, the utility of TUS is limited in the presence of mediastinal loculations or loculations involving the fissures, as the overlying lung prevents imaging of the fluid beneath it. In these situations, computed tomography (CT) is of greater value, with a high sensitivity for identifying loculations.(97, 98)

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,(99, 100) however in patients with MPE multiple procedures are not ideal. Additionally, if the underlying lung is non-expandable, pleurodesis will be ineffective and therefore this approach will not result in definitive fluid control.

Intra-pleural fibrinolytic agents have been shown to improve fluid drainage in loculated pleural infection,(101) and uncontrolled small case series have reported their use in symptomatic loculated MPE with incomplete initial drainage.(102-109) Intra-pleural fibrinolytics increased fluid drainage in all cases, and improved symptoms and radiological appearances in 60%,(109) 86%,(108) and, in most studies, 100% of patients.(102-107) Different drugs, including streptokinase,(102-106, 109) urokinase,(108) and tissue plasminogen activator (t-PA),(107, 109) were employed at varying dosages.

Four controlled studies, three of which were randomized, investigated the role of intra-pleural fibrinolysis for the treatment of loculated MPE.(89, 110-112) 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 reduction in radiological effusion size of greater than two-thirds in 26 (72.2%) patients. All 26 subsequently received minocycline pleurodesis, with life-long 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 fibrinolytics.

The second study randomized 47 patients with symptomatic MPE to receive intra-pleural streptokinase (250,000 IU twice daily for 3 doses) or pleural drainage only.(110) No information was provided regarding the existence of pleural adhesions. 96% of patients in the fibrinolytic group achieved radiological lung expansion and were subsequently able to receive talc slurry, compared with 75% in controls (p=0.035). However, pleurodesis success at 1 month was similar in both groups (74% vs 56%, p=0.28).

The third study randomly allocated 40 patients with loculated MPE on CT to receive intra-pleural streptokinase (4 separate doses of 250,000 U) or placebo (saline) administered through a 20F tube, after which talc slurry pleurodesis was performed.(111) 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 greater than 40% (85% vs 35%, p=0.001). Fibrinolytic therapy was also associated with reduced requirements for supplementary oxygen (10% vs 45%) and lower rates of pleurodesis failure at 1 month (11% vs 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 hours) or placebo, followed by talc slurry pleurodesis after 24 hours.(112) There was no difference in dyspnoea scores on visual analogue scale over the first month or pleurodesis failure rates at 1 year in the fibrinolysis group compared with placebo. However, urokinase performed better than placebo for secondary outcome measures, including a 18% greater reduction in pleural opacity on chest radiograph 2 days post-randomization, shorter length of hospital stay (6.2 vs 8.7 days) and improved survival (48 vs 69 days; all p<0.05). Notably, 48% of the study population died within 1 month of randomization, highlighting the extremely poor prognosis of patients with this problem.

The use of fibrinolytics in patients with IPCs and loculated MPE has been studied in one multi-centre retrospective review.(113) 66 patients (64 with an MPE) who developed symptomatic loculations with IPCs in situ were treated with intra-pleural fibrinolytics. Most patients received a single dose (range 1-6) of either t-PA (n=52), urokinase (n=12) or streptokinase (n=2). Following therapy, the volume of pleural fluid drained increased in 93.3% and dyspnoea improved in 83%. The area of pleural opacity on chest radiograph decreased from 52% to 31% of the hemithorax in 13 evaluable patients. However, symptomatic loculations recurred in 27 (41%) patients and of 10 patients who received repeated fibrinolytic therapy only 1 had a sustained improvement in drainage and symptoms.

In summary
Intra-pleural fibrinolytics 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 who are not suitable for surgery.

Question 4 - What factors predict prognosis in MPE?

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, 114-120) Staging systems exist for each tumour that formally describe disease extent and prognosis.(121) Usually MPE signifies metastatic disease, higher stage and shorter survival, although mesothelioma is an exception to this rule.(121, 122) Finally, PS is a global evaluation of function that predicts outcome in cancer, including as a tool to assess patients' suitability for oncological treatment.(116, 117, 120, 123-128)

Prognosticating in MPE

Specific MPE-related prognostic factors include effusion size. Massive MPE, defined as fluid occupying the entire hemi-thorax, was associated with significantly worse survival in one large, prospective study.(129) This finding was replicated in a subsequent retrospective study, although the definition of massive effusion differed.(118)

Pleural fluid pH may also predict survival - an early study demonstrated worse prognosis in patients with pleural fluid pH<7.2.(130) However, whilst several subsequent studies replicated the original finding, albeit using lower pH cut-offs,(31, 118, 128) others found no relationship between pH and survival.(41, 125) Patient-level data from these studies was pooled in a meta-analysis that confirmed pH≤7.28 was associated with shorter survival.(115) 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, 118, 125, 128)

Other potentially prognostic pleural fluid variables include LDH, which correlated with survival in multiple observational series.(118, 128, 130) Haemorrhagic fluid was also associated with reduced survival times in patients with lung cancer,(118) and was a poor prognostic factor in patients with MPE undergoing thoracoscopy.(131) Positive pleural fluid cytology does not predict survival,(117, 131) although detection of specific receptors or mutations e.g. EGFR, in fluid can have treatment and prognostic implications.(132, 133) Interestingly, high serum levels of Vascular Endothelial Growth Factor (VEGF) did not predict response to bevacizumab (a VEGF antagonist) in mesothelioma.(134) However, high serum and pleural fluid VEGF levels are associated with worse outcomes in MPE,(135, 136) as are the downstream effects of inflammation, angiogenesis and tumour necrosis.(137, 138)

Inflammation and cancer are closely related, and serum inflammatory markers can predict prognosis.(139-142) The Glasgow Prognostic Score (GPS) combines C-reactive protein (CRP) with serum albumin and has been validated to predict survival in several tumour types.(143-145) Another inflammation-based prognostic score is the serum neutrophil-lymphocyte ratio (NLR), high values of which reflect raised neutrophils, low lymphocytes, or both. Raised neutrophils are an adverse prognostic marker in non-small cell lung cancer, melanoma, renal cell carcinoma and others.(146-149) Lymphocytes, however, are fundamental to immune-mediated cancer control and low counts result in less effective tumour destruction and worse survival.(150-152) The NLR combines these two variables to provide a simple prognostic value that has been shown to be accurate in many cancers.(41, 144, 153-159)

Chronic inflammation causes catabolism and cachexia, which has further negative implications in MPE.(140-142) 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.(143, 144, 160-162)

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 3 international centres.(155) Baseline factors were analysed for prognostic value and those with the strongest predictive ability included in the predictive model (see 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.(163-170) The forthcoming ERS Taskforce 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, namely gender, age, epithelioid differentiation, PS, and tumour stage.(116, 156, 163-169, 171-180) The relationship between survival and other factors such as quantification of asbestos exposure and presenting symptoms are less clear.(162, 164, 167, 172, 181-183) Multiple inflammatory markers correlate with survival, including white cell count,(120, 144, 156, 161, 165, 167-169) platelet count,(156, 163, 165, 168, 169, 171, 176) CRP,(156, 163, 165, 168, 169, 171, 176) platelet to lymphocyte ratio,(144) and lymphocyte to monocyte ratio.(161) Local inflammation also affects prognosis, with lymphocytic infiltration of tumours and tumour stroma associated with longer survival following surgery.(152, 157) Much work has been done investigating potential prognostic biomarkers, including mesothelin, osteopontin and megakaryocyte potentiating factor (MPF). However, heterogeneity in thresholds and sampling intervals mean that these tests are not yet sufficiently reliable to be employed in standard care.(158, 184-186)

Numerous unvalidated prognostic indices exist in the literature,(137, 156, 169, 170, 181, 182, 187-190) but only 3 have been externally validated.(168, 182, 191) Of the validated scores, two used pooled data from clinical trials and consequently have limited generalisability to the overall mesothelioma population.(168, 182) In contrast, Brims et al used an unselected cohort of 482 sequential mesothelioma patients to develop their prognostic tree, which was then validated in a separate consecutive cohort, creating a more representative and clinically useful tool.(191) 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 (see 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 MPE and cancer that is sensitive to oncological treatment (e.g. chemotherapy, immunotherapy, targeted therapy) receive treatment prior to definitive management of their MPE? If so which cancers?

To date, no international guidelines recommend the use of anti-tumour 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 anti-tumour 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%).(192) In contrast, another series of 30 patients with MPE due to SCLC reported increased myelosuppression following chemotherapy compared with 30 matched patients without MPE.(193) Whilst association should not be mistaken for causality, this observation supports the hypothesis that chemotherapy may accumulate in undrained effusions leading to increased toxicity.(192-194) 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 effective treatment for MPE,(195, 196), 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.(197) 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.(198-200) Finally a single case report describes complete resolution of MPE following initiation of chemotherapy in a patient with metastatic ovarian cancer.(201)

Molecular targeted therapy has been investigated in patients with MPE and NSCLC.(202-204) A case report described disappearance of MPE secondary to lung adenocarcinoma following treatment with bevacizumab, carboplatin and paclitaxel.(204) In a single-arm prospective study, 76 patients with MPE and epithelial growth factor receptor (EGFR) mutations were treated with oral gefitinib (an EGFR tyrosine kinase inhibitor, TKI) until disease progression, toxicity or withdrawal.(202) MPE were assessed with CT scans every three months. 70 patients (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 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.(203) PFS was longer in the bevacizumab/EGFR-TKI/chemotherapy group (6.3 vs 4.8 months, p=0.048), and longer still in patients with acquired T790M mutations treated with the triple regimen (6.9 vs 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 (mAb) in MPE.(205, 206) Safety profiles were variable and numbers were too small to comment on efficacy. Two randomised phase II studies have investigated the anti-VEGF mAb, bevacizumab, intra-pleurally in patients with NSCLC and MPE.(207, 208) 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.(207) 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.(208) Better MPE response rates (85.7% versus 56.6%) were seen with the addition of bevacizumab. Another, single-arm phase II study used intra-venous bevacizumab alongside systemic carboplatin-pemetrexed chemotherapy and demonstrated MPE control in 21 out of 23 patients (91.3%).(209) 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 anti-tumour treatment in MPE management. Since 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 MPE, 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.(210-220) Cytology has the highest diagnostic yield for adenocarcinoma, compared with mesothelioma, for which sensitivity is generally accepted to be around 30%, but may fall as low as 16%.(214-216) 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.(221) The yield of cytological diagnosis in epithelioid mesothelioma is higher in the presence of visceral pleural invasion.(222)

Analysing larger volumes of pleural fluid may improve diagnostic sensitivity in MPE, although there appears to be a threshold. Several studies confirmed that submitting more than 75mL of pleural fluid for cytological examination does not improve the yield when using direct smear method.(223-225) However, if both direct smear/cytospin and cellblock preparations are utilised, up to 150mL is recommended.(226) This combined method has been shown to offer additional value compared to smear slides alone.(227, 228)

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, further evaluation is required to determine their origin, i.e. primary pleural malignancy versus metastatic disease. Disease-specific immunochemical markers are summarized in Table 2.(229-233)

Flow cytometry may be an additional useful adjunct in the differentiation of lymphoma in pleural fluid.(234, 235) 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%.(236-238) Further innovative approaches may advance this technique in future.(239)

Where mesothelioma is suspected, specific tests are frequently required due to the complexities associated with making this diagnosis. Sarcomatoid mesothelioma is particularly difficult to diagnose, as 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.(240) Loss of BAP1 expression and homozygous deletion of p16 detected at fluorescent in-situ hybridisation (FISH) are highly specific indicators for mesothelioma, but negative results do not exclude the diagnosis.(241-244) 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.(242-244) Consequently, although some laboratories are confident making definitive cytological diagnoses,(217, 245) the International Mesothelioma Interest Group recommends that the diagnosis should always be based on biopsy.(231) Evaluation of biopsy tissue can also provide prognostic information in mesothelioma, as certain histological features, such as nuclear atypia and mitotic index are

correlated with prognosis in epithelioid disease.(246-249)

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.(250) 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.(250-253) Consequently pleural biopsy is usually necessary to provide sufficient tissue for analysis. Thoracoscopic pleural biopsies have a diagnostic sensitivity of over 92% for malignancy, and consistently outperform cytological examination, even when cell block preparation is performed.(254-256)

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 non-specific pleuritis found that up to 15% were subsequently diagnosed with pleural malignancy, most frequently mesothelioma.(257-261) The decision 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 (ctDNA/cfDNA), tumour RNA especially microRNAs (miRNAs) and circulating tumour cells (CTCs) from patients' blood samples.(262, 263) These "liquid biopsy" methods have proven useful in lung cancer patients in the detection of baseline EGFR mutations,(264, 265) and identification of mutations conferring resistance to targeted therapy, e.g. T790M EGFR mutation.(266, 267) 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.(268-270)

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 taskforce statement aimed to review the literature relating to the management of MPE, focussing 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 talc pleurodesis (via slurry or poudrage) and indwelling pleural catheters are both highly effective, and significantly improve symptoms. It is still unclear whether talc poudrage is more effective than talc slurry, and while indwelling catheters 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.

In conclusion, 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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REFERENCES

1. Clive AOJ, H. E.; Bhatnagar, R.; Preston, N. J.; Maskell, N. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev. 2016(5):CD010529.

2. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):ii32-ii40.

3. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012;307(22):2383-9.

4. Rahman NM, Pepperell J, Rehal S, Saba T, Tang A, Ali N, et al. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. JAMA. 2015;314(24):2641-53.

5. Rintoul RCR, A. J.; Edwards, J.; Waller, D. A.; Coonar, A.; Lovato, E.; Bennett, M.; Matthews, C.; Hughes, V.; Fox-Rushby, J.; Sharples, L. D. Mesovats: A multi-centre randomised controlled trial of video assisted thoracoscopic pleurectomy versus talc pleurodesis in malignant pleural mesothelioma. Journal of thoracic oncology. 2013;8:S2-S3.

6. Bucknor AH-P, K.; Davies, T.; Toufektzian, L. Is silver nitrate an effective means of pleurodesis? Interactive Cardiovascular and Thoracic Surgery. 2015;21(4):521-5.

7. da Silveira Paschoalini M, Vargas FS, Marchi E, Pereira JR, Jatene FB, Antonangelo L, et al. Prospective randomized trial of silver nitrate vs talc slurry in pleurodesis for symptomatic malignant pleural effusions. Chest. 2005;128(2):684-9.

8. Menna CA, Claudio; Ibrahim, Mohsen; Maurizi, Giulio; Poggi, Camilla; Barile, Rocco; Cassiano, Francesco; Rendina, Erino A. The effect of silver nitrate pleurodesis after a failed thoracoscopic talc poudrage. Biomed Res Int. 2013;2013:295890.

9. Tan CS, Artyom; Browne, John; Swift, Simon; Treasure, Tom. The evidence on the effectiveness of management for malignant pleural effusion: a systematic review. European Journal of Cardio-Thoracic Surgery. 2006;29(5):829-38.

10. Mummadi SK, A.; Hahn, P. Y. Malignant pleural effusions and the role of talc poudrage and talc slurry: A systematic review and meta-analysis. F1000Research. 1000;3(no pagination).

11. Dresler CMO, Jemi; Herndon, James E., 2nd; Richards, William G.; Scalzetti, Ernest; Fleishman, Stewart B.; Kernstine, Kemp H.; Demmy, Todd; Jablons, David M.; Kohman, Leslie; Daniel, Thomas M.; Haasler, George B.; Sugarbaker, David J.; Cooperative Groups, Cancer; Leukemia Group, B.; Eastern Cooperative Oncology, Group; North Central Cooperative Oncology, Group; Radiation Therapy Oncology, Group. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest. 2005;127(3):909-15.

12. Yim APC, A. T.; Lee, T. W.; Wan, I. Y.; Ho, J. K. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Annals of Thoracic Surgery. 1996;62(6):1655-8.

13. Terra RMJ, Jader Joel Machado; Teixeira, Lisete Ribeiro; Vargas, Francisco Suso; Pego-Fernandes, Paulo Manuel; Jatene, Fabio Biscegli. Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis? Chest. 2009;136(2):361-8.

14. Benko IM, T. F.; Horvath, O. P. Palliative treatment of malignant pleural effusions by video-assisted thoracoscopic surgery. Acta Chirurgica Hungarica. 1999;38(2):131-3.

15. Debeljak AK, P.; Triller, N.; Letonja, S.; Kern, I.; Debevec, L.; Rozman, A. Talc pleurodesis: comparison of talc slurry instillation with thoracoscopic talc insufflation for malignant pleural effusions. Journal of BUOn. 2006;11(4):463-7.

16. Stefani AN, Pamela; Casali, Christian; Morandi, Uliano. Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study. European Journal of Cardio-Thoracic Surgery. 2006;30(6):827-32.

17. Luh SPC, C. Y.; Tzao, C. Y. Malignant pleural effusion treatment outcomes: pleurodesis via video-assisted thoracic surgery (VATS) versus tube thoracostomy. Thoracic & Cardiovascular Surgeon. 2006;54(5):332-6.

18. Jancovici RL-L, L.; Pons, F.; Cador, L.; Dujon, A.; Dahan, M.; Azorin, J. Complications of video-assisted thoracic surgery: A five-year experience. Annals of Thoracic Surgery. 1996;61(2):533-7.

19. Cardillo GF, F.; Carbone, L.; Regal, M.; Corzani, F.; Ricci, A.; Di Martino, M.; Martelli, M. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. European Journal of Cardio-Thoracic Surgery. 2002;21(2):302-5; discussion 5-6.

20. Canto AG, R.; Arnau, A.; Galbis, J.; Martorell, M.; Garcia Aguado, R. Videothoracoscopy in the diagnosis and treatment of malignant pleural mesothelioma with associated pleural effusions. Thoracic & Cardiovascular Surgeon. 1997;45(1):16-9.

21. Steger VM, Ute; Toomes, Heikki; Walker, Tobias; Engel, Corinna; Kyriss, Thomas; Ziemer, Gerhard; Friedel, Godehard. Who gains most? A 10-year experience with 611 thoracoscopic talc pleurodeses. Annals of Thoracic Surgery. 2007;83(6):1940-5.

22. Janssen JPC, Gareth; Astoul, Phillippe; Tassi, Gian Franco; Noppen, Marc; Rodriguez-Panadero, Francisco; Loddenkemper, Robert; Herth, Felix J. F.; Gasparini, Stefano; Marquette, Charles H.; Becke, Birgit; Froudarakis, Marios E.; Driesen, Peter; Bolliger, Chris T.; Tschopp, Jean-Marie. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet. 2007;369(9572):1535-9.

23. de Campos JRV, F. S.; de Campos Werebe, E.; Cardoso, P.; Teixeira, L. R.; Jatene, F. B.; Light, R. W. Thoracoscopy talc poudrage : a 15-year experience. Chest. 2001;119(3):801-6.

24. Barbetakis NA, Christos; Papadopoulou, Fani; Samanidis, Georgios; Paliouras, Dimitrios; Kleontas, Athanassios; Lyriti, Konstantina; Katsikas, Ioannis; Tsilikas, Christodoulos. Early and late morbidity and mortality and life expectancy following thoracoscopic talc insufflation for control of malignant pleural effusions: a review of 400 cases. J Cardiothorac Surg. 2010;5:27.

25. Viallat JRR, F.; Astoul, P.; Boutin, C. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. Chest. 1996;110(6):1387-93.

26. Koledin MD, D.; Milovancev, A.; Bijelovic, M.; Baros, B. Pleural effusions of malignant etiology: Diagnostics, treatment and quality of life. Archive of Oncology. 2001;9(1):3-7.

27. Agrawal AT, Rajeev; Singh, Lalit; Chawla, Aakanksha. Clinico- pathological profile and course of malignant pleural effusion in a tertiary care teaching hospital in western U.P. with special reference to lung cancer. Lung India. 2015;32(4):326-30.

28. Arapis KC, R.; Stern, J. B.; Girard, P.; Debrosse, D.; Gossot, D. Thoracoscopic palliative treatment of malignant pleural effusions: results in 273 patients. Surgical Endoscopy. 2006;20(6):919-23.

29. Bal SH, S. S. Thoracoscopic management of malignant pleural effusion. International Surgery. 1993;78(4):324-7.

30. Trotter DA, Ahmad; Siu, Lyndon; Knight, Simon. Video-assisted thoracoscopic (VATS) pleurodesis for malignant effusion: an Australian teaching hospital's experience. Heart, Lung & Circulation. 2005;14(2):93-7.

31. Sanchez-Armengol A, Rodriguez-Panadero F. Survival and Talc Pleurodesis in Metastatic Pleural Carcinoma, Revisited. Chest. 1993;104(5):1482-5.

32. Schniewind BR, Tobias; Woltmann, Nikolas; Walter, Jessica; Becker, Thomas; Dohrmann, Peter; Kuchler, Thomas; Kurdow, Roland. Clinical outcomes and health-related quality of life after thoracoscopic talc pleurodesis. Journal of Palliative Medicine. 2012;15(1):37-42.

33. Kolschmann SB, Arndt; Gillissen, Adrian. Clinical efficacy and safety of thoracoscopic talc pleurodesis in malignant pleural effusions. Chest. 2005;128(3):1431-5.

34. Schulze M, Boehle AS, Kurdow R, Dohrmann P, Henne-Bruns D. Effective treatment of malignant pleural effusion by minimal invasive thoracic surgery: thoracoscopic talc pleurodesis and pleuroperitoneal shunts in 101 patients. The Annals of thoracic surgery. 2001;71(6):1809-12.

35. Clementsen PE, T.; Grode, G.; Hansen, M.; Krag Jacobsen, G.; Faurschou, P. Treatment of malignant pleural effusion: Pleurodesis using a small percutaneous catheter. A prospective randomized study. Respiratory Medicine. 1998;92(3):593-6.

36. Mager H-JM, Boudewijn; Verzijlbergen, Fred; Schramel, Franz. Distribution of talc suspension during treatment of malignant pleural effusion with talc pleurodesis. Lung Cancer. 2002;36(1):77-81.

37. Arellano-Orden ER-F, Auxiliadora; Juan, Jose Martin; Ocana Jurado, Manuel; Rodriguez-Panadero, Francisco; Montes-Worboys, Ana. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. Respiration. 2013;86(3):201-9.

38. Habal PO, Nedal; Jankovicova, Karolina; Krejsek, Jan; Mandak, Jiri. Predictive value of systemic and local inflammation parameters in talc pleurodesis assessment. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic. 2015;159(2):234-41.

39. Rodriguez-Panadero FS, A.; Martin Juan, J.; Ayerbe, R.; Torres Garcia, I.; Castillo, J. Failure of talc pleurodesis is associated with increased pleural fibrinolysis. American Journal of Respiratory & Critical Care Medicine. 1995;151(3 Pt 1):785-90.

40. Korsic MB, S.; Cucevic, B.; Janevski, Z. Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. Wiener Klinische Wochenschrift. 2015;127(23-24):963-9.

41. Yoon DW, Cho JH, Choi YS, Kim J, Kim HK, Zo JI, et al. Predictors of survival in patients who underwent video-assisted thoracic surgery talc pleurodesis for malignant pleural effusion. Thoracic Cancer. 2016;7(4):393-8.

42. Friedel GL, A.; Toomes, H. Video-assisted thoracoscopic pleurectomy as therapy for recurring malignant pleural effusion. Minimally Invasive Therapy. 1994;3(3):169-72.

43. Waller DAM, G. N.; Forty, J. Video-assisted thoracoscopic pleurectomy in the management of malignant pleural effusion. Chest. 1995;107(5):1454-6.

44. Ohta YO, M.; Shimizu, J.; Watanabe, G. Multimodality treatment including parietal pleurectomy as a possible therapeutic procedure for malignant pleural effusion. Surg Technol Int. 2007;16:184-9.

45. Crnjac AS, M.; Kamenik, M. Impact of pleural effusion pH on the efficacy of thoracoscopic mechanical pleurodesis in patients with breast carcinoma. European Journal of Cardio-Thoracic Surgery. 2004;26(2):432-6.

46. Hojski AL, M.; Crnjac, A. Release of growth factors after mechanical and chemical pleurodesis for treatment of malignant pleural effusion: A randomized control study. Radiology and Oncology. 2015;49(4):386-94.

47. Gu LJW, W. J. [Comparative study of video-assisted thoracoscopic surgery vs thoracic tube drainage in synthetic therapy for malignant pleural effusion secondary to non-small cell lung cancer]. Nan Fang Yi Ke Da Xue Xue Bao. 2006;26(7):1023-6.

48. Bernard AdD, Regis Bernard; Hagry, Olivier; Favre, Jean Pierre. Early and late mortality after pleurodesis for malignant pleural effusion. Annals of Thoracic Surgery. 2002;74(1):213-7.

49. Mineo TCS, Francesco; Tacconi, Federico; Ambrogi, Vincenzo. Quality of life and outcomes after nonintubated versus intubated video-thoracoscopic pleurodesis for malignant pleural effusion: comparison by a case-matched study. Journal of Palliative Medicine. 2014;17(7):761-8.

50. Ost DEJ, C. A.; Lei, X.; Cantor, S. B.; Grosu, H. B.; Lazarus, D. R.; Faiz, S. A.; Bashoura, L.; Shannon, V. R.; Balachandran, D.; Noor, L.; Hashmi, Y. B.; Casal, R. F.; Morice, R. C.; Eapen, G. A. Quality-adjusted survival following treatment of malignant pleural effusions with indwelling pleural catheters. Chest. 2014;145(6):1347-56.

51. Warren WH, Kalimi R, Khodadadian LM, Kim AW. Management of malignant pleural effusions using the Pleur x catheter. The Annals of thoracic surgery. 2008;85(3):1049-55.

52. Tremblay AM, G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest. 2006;129(2):362-8.

53. Sabur NFC, A.; Stather, D. R.; Maceachern, P.; Amjadi, K.; Hergott, C. A.; Dumoulin, E.; Gonzalez, A. V.; Tremblay, A. The impact of tunneled pleural catheters on the quality of life of patients with malignant pleural effusions. Respiration. 2013;85(1):36-42.

54. Gilbert CRL, H. J.; Skalski, J. H.; Maldonado, F.; Wahidi, M.; Choi, P. J.; Bessich, J.; Sterman, D.; Argento, A. C.; Shojaee, S.; Gorden, J. A.; Wilshire, C. L.; Feller-Kopman, D.; Ortiz, R.; Nonyane, B. A.; Yarmus, L. The Use of Indwelling Tunneled Pleural Catheters for Recurrent Pleural Effusions in Patients With Hematologic Malignancies: A Multicenter Study. Chest. 2015;148(3):752-8.

55. Bazerbashi S, Villaquiran J, Awan MY, Unsworth-White MJ, Rahamim J, Marchbank A. Ambulatory intercostal drainage for the management of malignant pleural effusion: a single center experience. Annals of Surgical Oncology. 2009;16(12):3482-7.

56. Van Meter MEM, McKee KY, Kohlwes RJ. Efficacy and Safety of Tunneled Pleural Catheters in Adults with Malignant Pleural Effusions: A Systematic Review. Journal of General Internal Medicine. 2011;26(1):70-6.

57. Putnam JB, Jr.; Light, R. W.; Rodriguez, R. M.; Ponn, R.; Olak, J.; Pollak, J. S.; Lee, R. B.; Payne, D. K.; Graeber, G.; Kovitz, K. L. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. Cancer. 1999;86(10):1992-9.

58. Thomas R, Fysh EH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The ample randomized clinical trial. JAMA. 2017;318(19):1903-12.

59. Demmy TL, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). Journal of the National Comprehensive Cancer Network. 2012;10(8):975-82.

60. Hunt BMF, Alexander S.; Vallieres, Eric; Louie, Brian E.; Aye, Ralph W.; Flores, Eva E.; Gorden, Jed A. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Annals of Thoracic Surgery. 2012;94(4):1053-7; discussion 7-9.

61. Fysh ETHW, G. W.; Kendall, P. A.; Bremner, P. R.; Dina, S.; Geelhoed, E.; McCarney, K.; Morey, S.; Millward, M.; Musk, A. W.; Lee, Y. C. G. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. Chest. 2012;142(2):394-400.

62. Bell DW, Gavin. A retrospective review of the palliative surgical management of malignant pleural effusions. 2013.

63. Walker SZ, Marijana; Massey, Christine; Shargall, Yaron; Bedard, Eric; Darling, Gail. A prospective study of patient-centred outcomes in the management of malignant pleural effusions. International Journal of Palliative Nursing. 2016;22(7):351-8.

64. Wahidi MM, Reddy C, Yarmus L, Feller-Kopman D, Musani A, Shepherd RW, et al. Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions. The ASAP Trial. American Journal of Respiratory and Critical Care Medicine. 2017;195(8):1050-7.

65. Schneider T, Reimer P, Storz K, Klopp M, Pfannschmidt J, Dienemann H, et al. Recurrent pleural effusion: who benefits from a tunneled pleural catheter? Thoracic & Cardiovascular Surgeon. 2009;57(1):42-6.

66. Boujaoude ZB, Thaddeus; Abboud, Mariam; Pratter, Melvin; Abouzgheib, Wissam. Pleuroscopic Pleurodesis Combined With Tunneled Pleural Catheter for Management of Malignant Pleural Effusion: A Prospective Observational Study. Journal of Bronchology & Interventional Pulmonology. 2015;22(3):237-43.

67. Reddy CE, Armin; Lamb, Carla; Feller-Kopman, David. Rapid pleurodesis for malignant pleural effusions: a pilot study. Chest. 2011;139(6):1419-23.

68. Freeman RKA, Anthony J.; Mahidhara, Raja S. A propensity-matched comparison of pleurodesis or tunneled pleural catheter in patients undergoing diagnostic thoracoscopy for malignancy. Annals of Thoracic Surgery. 2013;96(1):259-63: discussion 63-4.

69. Bhatnagar RL-S, Magda; Piotrowska, Hania E. G.; Kahan, Brennan C.; Hooper, Clare E.; Davies, Helen E.; Harvey, John E.; Miller, Robert F.; Rahman, Najib M.; Maskell, Nick A. Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. BMJ Open. 2014;4(11):e007045.

70. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 2014;384(9948):1118-27.

71. Huggins JT, Doelken P, Sahn SA. The unexpandable lung. F1000 Medicine Reports. 2010;2:77.

72. Doelken P. Clinical Implications of Unexpandable Lung Due to Pleural Disease. The American Journal of the Medical Sciences. 2008;335(1):21-5.

73. Lan R-S, Lo SK, Chuang M-L, Yang C-T, Tsao TC-Y, Lee C-H. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. Annals of internal medicine. 1997;126(10):768-74.

74. Huggins JT, Doelken P. Pleural manometry. Clin Chest Med. 2006;27(2):229-40.

75. Feller-Kopman D. Therapeutic thoracentesis: the role of ultrasound and pleural manometry. Curr Opin Pulm Med. 2007;13(4):312-8.

76. Boshuizen RC, Sinaasappel M, Vincent AD, Goldfinger V, Farag S, van den Heuvel MM. Pleural pressure swing and lung expansion after malignant pleural effusion drainage: the benefits of high-temporal resolution pleural manometry. Journal of bronchology & interventional pulmonology. 2013;20(3):200-5.

77. Feller-Kopman D, Walkey A, Berkowitz D, Ernst A. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. CHEST Journal. 2006;129(6):1556-60.

78. Salamonsen MR, Lo AK, Ng AC, Bashirzadeh F, Wang WY, Fielding DI. Novel use of pleural ultrasound can identify malignant entrapped lung prior to effusion drainage. Chest. 2014;146(5):1286-93.

79. Zahid I, Routledge T, Bille A, Scarci M. What is the best treatment for malignant pleural effusions? Interactive Cardiovascular & Thoracic Surgery. 2011;12(5):818-23.

80. Pien GW, Gant MJ, Washam CL, Sterman DH. Use of an implantable pleural catheter for trapped lung syndrome in patients with malignant pleural effusion. Chest. 2001;119(6):1641-6.

81. Ohm C, Park D, Vogen M, Bendick P, Welsh R, Pursel S, et al. Use of an indwelling pleural catheter compared with thorascopic talc pleurodesis in the management of malignant pleural effusions. Am Surg. 2003;69(3):198-202; discussion

82. Qureshi RA, Collinson SL, Powell RJ, Froeschle PO, Berrisford RG. Management of malignant pleural effusion associated with trapped lung syndrome. Asian Cardiovascular & Thoracic Annals. 2008;16(2):120-3.

83. van den Toorn LM, Schaap E, Surmont VF, Pouw EM, van der Rijt KC, van Klaveren RJ. Management of recurrent malignant pleural effusions with a chronic indwelling pleural catheter. Lung Cancer. 2005;50(1):123-7.

84. Burgers JA, Olijve A, Baas P. [Chronic indwelling pleural catheter for malignant pleural effusion in 25 patients]. Nederlands Tijdschrift voor Geneeskunde. 2006;150(29):1618-23.

85. Efthymiou CA, Masudi T, Thorpe JAC, Papagiannopoulos K. Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. Interactive Cardiovascular & Thoracic Surgery. 2009;9(6):961-4.

86. Petrou M, Kaplan D, Goldstraw P. Management of recurrent malignant pleural effusions: The complementary role of talc pleurodesis and pleuroperitoneal shunting. Cancer. 1995;75(3):801-5.

87. Genc O, Petrou M, Ladas G, Goldstraw P. The long-term morbidity of pleuroperitoneal shunts in the management of recurrent malignant effusions. European Journal of Cardio-Thoracic Surgery. 2000;18(2):143-6.

88. Yim AP, Ho JK, Lee TW, Chung SS. Thoracoscopic management of pleural effusions revisited. Aust N Z J Surg. 1995;65(5):308-11.

89. Hsu LH, Soong TC, Feng AC, Liu MC. Intrapleural urokinase for the treatment of loculated malignant pleural effusions and trapped lungs in medically inoperable cancer patients. J Thorac Oncol. 2006;1(5):460-7.

90. Chung C-L, Chen C-H, Sheu J-R, Chen Y-C, Chang S-C. Proinflammatory Cytokines, Transforming Growth Factor-β1, and Fibrinolytic Enzymes in Loculated and Free-Flowing Pleural Exudates. Chest. 2005;128(2):690-7.

91. Bielsa S, Martin-Juan J, Porcel JM, Rodriguez-Panadero F. Diagnostic and prognostic implications of pleural adhesions in malignant effusions. J Thorac Oncol. 2008;3(11):1251-6.

92. Mason AC, Miller BH, Krasna MJ, White CS. Accuracy of CT for the Detection of Pleural Adhesions: Correlation With Video-Assisted Thoracoscopic Surgery. Chest. 1999;115(2):423-7.

93. Cassanelli N, Caroli G, Dolci G, Dell'Amore A, Luciano G, Bini A, et al. Accuracy of transthoracic ultrasound for the detection of pleural adhesions. European Journal of Cardio-Thoracic Surgery. 2012;42(5):813-8.

94. Wei B, Wang T, Jiang F, Wang H. Use of transthoracic ultrasound to predict pleural adhesions: a prospective blinded study. The Thoracic and cardiovascular surgeon. 2012;60(02):101-4.

95. Medford AR, Agrawal S, Bennett JA, Free CM, Entwisle JJ. Thoracic ultrasound prior to medical thoracoscopy improves pleural access and predicts fibrous septation. Respirology. 2010;15(5):804-8.

96. Kohan JM, Poe RH, Israel RH, Kennedy JD, Benazzi RB, Kallay MC, et al. Value of chest ultrasonography versus decubitus roentgenography for thoracentesis. The American review of respiratory disease. 1986;133(6):1124-6.

97. Havelock T, Teoh R, Laws D, Gleeson F. Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):i61-i76.

98. Silverman SG, Mueller PR, Saini S, Hahn PF, Simeone JF, Forman BH, et al. Thoracic empyema: management with image-guided catheter drainage. Radiology. 1988;169(1):5-9.

99. Davies HE, Davies RJ, Davies CW. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):ii41-ii53.

100. VanSonnenberg E, Nakamoto S, Mueller P, Casola G, Neff C, Friedman P, et al. CT-and ultrasound-guided catheter drainage of empyemas after chest-tube failure. Radiology. 1984;151(2):349-53.

101. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. New England Journal of Medicine. 2011;365(6):518-26.

102. Balamugesh T, Christopher DJ, Rajesh T, Prince J. Fibrinolysis of loculated pleural effusion in malignant mesothelioma. Singapore Med J. 2004;45(12):594-5.

103. Dixit R, Dixit K, Bansal R. Intrapleural streptokinase in multiloculated malignant pleural effusion. Indian J Chest Dis Allied Sci. 2004;46(1):59-62.

104. Maskell NA, Gleeson FV. Images in clinical medicine. Effect of intrapleural streptokinase on a loculated malignant pleural effusion. New England Journal of Medicine. 2003;348(14):e4.

105. Jerjes-Sanchez C, Ramirez-Rivera A, Elizalde JJ, Delgado R, Cicero R, Ibarra-Perez C, et al. Intrapleural Fibrinolysis With Streptokinase as an Adjunctive Treatment in Hemothorax and Empyema: A Multicenter Trial. Chest. 1996;109(6):1514-9.

106. Davies CW, Traill ZC, Gleeson FV, Davies RJ. Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. CHEST Journal. 1999;115(3):729-33.

107. Ben-Or S, Feins RH, Veeramachaneni NK, Haithcock BE. Effectiveness and Risks Associated With Intrapleural Alteplase by Means of Tube Thoracostomy. The Annals of Thoracic Surgery. 2011;91(3):860-4.

108. Gilkeson RC, Silverman P, Haaga JR. Using urokinase to treat malignant pleural effusions. American Journal of Roentgenology. 1999;173(3):781-3.

109. Abu-Daff S, Maziak DE, Alshehab D, Threader J, Ivanovic J, Deslaurier V, et al. Intrapleural fibrinolytic therapy (IPFT) in loculated pleural effusions—analysis of predictors for failure of therapy and bleeding: a cohort study. BMJ Open. 2013;3(2):e001887.

110. Okur E, Baysungur V, Tezel C, Ergene G, Okur HK, Halezeroglu S. Streptokinase for malignant pleural effusions: a randomized controlled study. Asian Cardiovascular and Thoracic Annals. 2011;19(3-4):238-43.

111. Saydam O, Karapinar K, Gokce M, Kilic L, Metin M, Oz II, et al. The palliative treatment with intrapleural streptokinase in patients with multiloculated malignant pleural effusion: a double-blind, placebo-controlled, randomized study. Medical Oncology. 2015;32(6):179.

112. Mishra DEK, Clive DAO, Wills MGH, Dr. Helen E Davies MD M, Stanton DAE, Al-Aloul DM, et al. Randomised Controlled Trial of Urokinase versus Placebo for Non-draining Malignant Pleural Effusion. American Journal of Respiratory and Critical Care Medicine. 2017;0(ja):null.

113. Thomas R, Piccolo F, Miller D, MacEachern PR, Chee AC, Huseini T, et al. Intrapleural Fibrinolysis for the Treatment of Indwelling Pleural Catheter-Related Symptomatic Loculations: A Multicenter Observational Study. Chest. 2015;148(3):746-51.

114. Antony VB, Loddenkemper R, Astoul P, BOUTIN C, GOLDSTRAW P, HOTT J, et al. Management of Malignant Pleural Effusions. American Journal of Respiratory and Critical Care Medicine. 2000;162(5):1987-2001.

115. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. Chest. 2000;117(1):79-86.

116. Abakay A, Komek H, Abakay O, Palanci Y, Ekici F, Tekbas G, et al. Relationship between 18 FDG PET-CT findings and the survival of 177 patients with malignant pleural mesothelioma. European Review for Medical and Pharmacological Sciences. 2013;17(9):1233-41.

117. Zamboni MM, da Silva CT, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulmonary Medicine. 2015;15 (1):29.

118. Bielsa S, Salud A, Martínez M, Esquerda A, Martín A, Rodríguez-Panadero F, et al. Prognostic significance of pleural fluid data in patients with malignant effusion. European Journal of Internal Medicine. 2008;19(5):334-9.

119. Fentiman IS, Millis R, Sexton S, Hayward JL. Pleural effusion in breast cancer: a review of 105 cases. Cancer. 1981;47(8):2087-92.

120. Anevlavis S, Kouliatsis G, Sotiriou I, Koukourakis MI, Archontogeorgis K, Karpathiou G, et al. Prognostic factors in patients presenting with pleural effusion revealing malignancy. Respiration. 2014;87(4):311-6.

121. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. American joint committee on cancer staging manual. 7. New York: Springer; 2009.

122. Rusch VW, Chansky K, Kindler HL, Nowak AK, Pass HI, Rice DC, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. Journal of Thoracic Oncology. 2016;11(12):2112-9.

123. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996;32(7):1135-41.

124. Hwang SS, Scott CB, Chang VT, Cogswell J, Srinivas S, Kasimis B. Prediction of Survival for Advanced Cancer Patients by Recursive Partitioning Analysis: Role of Karnofsky Performance Status, Quality of Life, and Symptom Distress. Cancer Investigation. 2004;22(5):678-87.

125. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest. 2000;117(1):73-8.

126. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982;5(6):649-56.

127. Karnofsky DA. The clinical evaluation of chemotherapeutic agents in cancer. CM M, editor. New York: Columbia University Press; 1948.

128. Martinez-Moragon E, Aparicio J, Sanchis J, Menendez R, Cruz Rogado M, Sanchis F. Malignant pleural effusion: Prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. Respiration. 1998;65(2):108-13.

129. Jiménez D, Díaz G, Gil D, Cicero A, Pérez-Rodríguez E, Sueiro A, et al. Etiology and prognostic significance of massive pleural effusions. Respiratory Medicine. 2005;99(9):1183-7.

130. Sahn SA, Good JT. Pleural Fluid pH in Malignant Effusions Diagnostic, Prognostic, and Therapeutic Implications. Annals of Internal Medicine. 1988;108(3):345-9.

131. Sakr L, Maldonado F, Greillier L, Dutau H, Loundou A, Astoul P. Thoracoscopic assessment of pleural tumor burden in patients with malignant pleural effusion: Prognostic and therapeutic implications. Journal of Thoracic Oncology. 2011;6(3):592-7.

132. Wu S-G, Yu C-J, Tsai M-F, Liao W-Y, Yang C-H, Jan I-S, et al. Survival of lung adenocarcinoma patients with malignant pleural effusion. European Respiratory Journal. 2013;41(6):1409-18.

133. Soh J, Toyooka S, Aoe K, Asano H, Ichihara S, Katayama H, et al. Usefulness of EGFR mutation screening in pleural fluid to predict the clinical outcome of gefitinib treated patients with lung cancer. International Journal of Cancer. 2006;119(10):2353-8.

134. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2015;387:1405-14.

135. Gkiozos I, Tsagouli S, Charpidou A, Grapsa D, Kainis E, Gratziou C, et al. Levels of vascular endothelial growth factor in serum and pleural fluid are independent predictors of survival in advanced non-small cell lung cancer: Results of a prospective study. Anticancer Research. 2015;35(2):1129-37.

136. Hsu IL, Su WC, Yan JJ, Chang JM, Lai WW. Angiogenetic biomarkers in non-small cell lung cancer with malignant pleural effusion: Correlations with patient survival and pleural effusion control. Lung Cancer. 2009;65(3):371-6.

137. Edwards JG, Abrams KR, Leverment JN, Spyt TJ, Waller DA, O'Byrne KJ. Prognostic factors for malignant mesothelioma in 142 patients: Validation of CALGB and EORTC prognostic scoring systems. Thorax. 2000;55(9):731-5.

138. Edwards JG, Swinson DE, Jones JL, Muller S, Waller DA, O'Byrne KJ. Tumor necrosis correlates with angiogenesis and is a predictor of poor prognosis in malignant mesothelioma. Chest. 2003;124(5):1916-23.

139. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451-9.

140. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. Cell. 2010;140(6):883-99.

141. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.

142. Linton A, van Zandwijk N, Reid G, Clarke S, Cao C, Kao S. Inflammation in malignant mesothelioma - friend or foe? Annals of Cardiothoracic Surgery. 2012;1(4):516-22.

143. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treatment Reviews. 2013;39(5):534-40.

144. Pinato DJ, Mauri FA, Ramakrishnan R, Wahab L, Lloyd T, Sharma R. Inflammation-based prognostic indices in malignant pleural mesothelioma. J Thorac Oncol. 2012;7(3):587-94.

145. Forrest L, McMillan D, McArdle C, Angerson W, Dunlop D. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. British journal of cancer. 2003;89(6):1028.

146. Sculier J-P, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. Journal of Thoracic Oncology. 2008;3(5):457-66.

147. Paesmans M, Sculier J-P, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. J Clin Oncol. 1995;13(5):1221-30.

148. Schmidt H, Bastholt L, Geertsen P, Christensen IJ, Larsen S, Gehl J, et al. Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic model. British journal of cancer. 2005;93(3):273.

149. Atzpodien J, Royston P, Wandert T, Reitz M. Metastatic renal carcinoma comprehensive prognostic system. British Journal of Cancer. 2003;88(3):348.

150. Lissoni P, Brivio F, Fumagalli L, Messina G, Ghezzi V, Frontini L, et al. Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. The International journal of biological markers. 2003;19(2):135-40.

151. Anraku M, Cunningham KS, Yun Z, Tsao M-S, Zhang L, Keshavjee S, et al. Impact of tumor-infiltrating T cells on survival in patients with malignant pleural mesothelioma. The Journal of thoracic and cardiovascular surgery. 2008;135(4):823-9.

152. Yamada N, Oizumi S, Kikuchi E, Shinagawa N, Konishi-Sakakibara J, Ishimine A, et al. CD8+ tumor-infiltrating lymphocytes predict favorable prognosis in malignant pleural mesothelioma after resection. Cancer Immunology, Immunotherapy. 2010;59(10):1543-9.

153. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. JNCI: Journal of the National Cancer Institute. 2014;106(6):dju124-dju.

154. Kao SCH, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, et al. High Blood Neutrophil-to-Lymphocyte Ratio Is an Indicator of Poor Prognosis in Malignant Mesothelioma Patients Undergoing Systemic Therapy. Clin Cancer Res. 2010;16(23):5805-13.

155. Clive AO, Kahan BC, Hooper CE, Bhatnagar R, Morley AJ, Zahan-Evans N, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax. 2014;69(12):1098-104.

156. Linton A, Pavlakis N, O'Connell R, Soeberg M, Kao S, Clarke S, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. British Journal of Cancer. 2014;111(9):1860-9.

157. Suzuki K, Kadota K, Sima CS, Sadelain M, Rusch VW, Travis WD, et al. Chronic inflammation in tumor stroma is an independent predictor of prolonged survival in epithelioid malignant pleural mesothelioma patients. Cancer Immunology, Immunotherapy. 2011;60(12):1721-8.

158. Hooper CE, Lyburn ID, Searle J, Darby M, Hall T, Hall D, et al. The South West Area Mesothelioma and Pemetrexed trial: A multicentre prospective observational study evaluating novel markers of chemotherapy response and prognostication. British Journal of Cancer. 2015;112(7):1175-82.

159. Lee YS, Nam HS, Lim JH, Kim JS, Moon Y, Cho JH, et al. Prognostic impact of a new score using neutrophil-to-lymphocyte ratios in the serum and malignant pleural effusion in lung cancer patients. BMC Cancer. 2017;17(1):557.

160. Yao ZH, Tian GY, Yang SX, Wan YY, Kang YM, Liu QH, et al. Serum albumin as a significant prognostic factor in patients with malignant pleural mesothelioma. Tumor Biology. 2014;35(7):6839-45.

161. Yamagishi T, Fujimoto N, Nishi H, Miyamoto Y, Hara N, Asano M, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with malignant pleural mesothelioma. Lung Cancer. 2015;90(1):111-7.

162. Yao ZH, Tian GY, Wan YY, Kang YM, Guo HS, Liu QH, et al. Prognostic nutritional index predicts outcomes of malignant pleural mesothelioma. Journal of Cancer Research and Clinical Oncology. 2013;139(12):2117-23.

163. Borasio P, Berruti A, Bille A, Lausi P, Levra MG, Giardino R, et al. Malignant pleural mesothelioma: clinicopathologic and survival characteristics in a consecutive series of 394 patients. European Journal of Cardio-thoracic Surgery. 2008;33(2):307-13.

164. Christensen BC, Godleski JJ, Roelofs CR, Longacker JL, Bueno R, Sugarbaker DJ, et al. Asbestos burden predicts survival in pleural mesothelioma. Environmental Health Perspectives. 2008;116(6):723-6.

165. Wolf AS, Richards WG, Tilleman TR, Chirieac L, Hurwitz S, Bueno R, et al. Characteristics of malignant pleural mesothelioma in women. Annals of Thoracic Surgery. 2010;90(3):949-56.

166. Vigneswaran WT, Kircheva DY, Ananthanarayanan V, Watson S, Arif Q, Celauro AD, et al. Amount of Epithelioid Differentiation is a Predictor of Survival in Malignant Pleural Mesothelioma. Annals of Thoracic Surgery. 2016.

167. Baud M, Strano S, Dechartres A, Jouni R, Triponez F, Chouaid C, et al. Outcome and prognostic factors of pleural mesothelioma after surgical diagnosis and/or pleurodesis. Journal of Thoracic and Cardiovascular Surgery. 2013;145(5):1305-11.

168. Curran D, Sahmoud T, Therasse P, Meerbeeck Jv, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol. 1998;16(1):145-52.

169. Francart J, Vaes E, Henrard S, Legrand C, Baas P, Gaafar R, et al. A prognostic index for progression-free survival in malignant mesothelioma with application to the design of phase II trials: A combined analysis of 10 EORTC trials. Eur J Cancer. 2009;45(13):2304-11.

170. Kataoka Y, Yamamoto Y, Otsuki T, Kaku S, Maehashi-Wada N, Fukuma S, et al. External validation of prognostic indices for overall survival of malignant pleural mesothelioma. Lung Cancer.113:88-92.

171. Bille A, Krug LM, Woo KM, Rusch VW, Zauderer MG. Contemporary analysis of prognostic factors in patients with unresectable malignant pleural mesothelioma. Journal of Thoracic Oncology. 2016;11(2):249-55.

172. Flores RM, Zakowski M, Venkatraman E, Krug L, Rosenzweig K, Dycoco J, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. Journal of Thoracic Oncology. 2007;2(10):957-65.

173. Jennings CJ, Walsh PM, Deady S, Harvey BJ, Thomas W. Malignant pleural mesothelioma incidence and survival in the Republic of Ireland 1994-2009. Cancer Epidemiology. 2014;38(1):35-41.

174. Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E, et al. Survival of pleural malignant mesothelioma in Italy: A population-based study. International Journal of Cancer. 2009;124(1):201-7.

175. Taioli E, Wolf AS, Camacho-Rivera M, Kaufman A, Lee DS, Nicastri D, et al. Determinants of survival in malignant pleural mesothelioma: A surveillance, epidemiology, and end results (SEER) Study of 14,228 Patients. PLoS ONE. 2015;10 (12) (no pagination)(A922).

176. Rena O, Boldorini R, Papalia E, Mezzapelle R, Baietto G, Roncon A, et al. Persistent lung expansion after pleural talc poudrage in non-surgically resected malignant pleural mesothelioma. Annals of Thoracic Surgery. 2015;99(4):1177-83.

177. Adel AM, Abdel Hafeez ZM, El Sheikh ET, El Sharawy IA, Gobran NS. Malignant pleural mesothelioma: A retrospective analysis of clinicopathological and survival data. Thoracic Cancer. 2011;2(1):16-23.

178. Rahouma M, Aziz H, Ghaly G, Kamel M, Loai I, Mohamed A. Survival in Good Performance Malignant Pleural Mesothelioma Patients; Prognostic Factors and Predictors of Response. Asian Pac J Cancer Prev. 2017;18(8):2073-8.

179. Wang S, Ma K, Wang Q, Sun F, Shi Y, Zhan C, et al. The revised staging system for malignant pleural mesothelioma based on surveillance, epidemiology, and end results database. Int J Surg. 2017;48:92-8.

180. Zhang A, Cao S, Jin S, Cao J, Shen J, Pan B, et al. Elevated aspartate aminotransferase and monocyte counts predict unfavorable prognosis in patients with malignant pleural mesothelioma. Neoplasma. 2017;64(1):114-22.

181. Kataoka Y, Yamamoto Y, Otsuki T, Shinomiya M, Terada T, Fukuma S, et al. A new prognostic index for overall survival in malignant pleural mesothelioma: The rPHS (regimen, PS, histology or stage) index. Japanese Journal of Clinical Oncology. 2015;45(6):562-8.

182. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest. 1998;113(3):723-31.

183. Bottomley A, Coens C, Efficace F, Gaafar R, Manegold C, Burgers S, et al. Symptoms and patient-reported well-being: do they predict survival in malignant pleural mesothelioma? A prognostic factor analysis of EORTC-NCIC 08983: randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma. J Clin Oncol. 2007;25(36):5770-6.

184. Creaney J, Francis RJ, Dick IM, Musk AW, Robinson BW, Byrne MJ, et al. Serum soluble mesothelin concentrations in malignant pleural mesothelioma: relationship to tumor volume, clinical stage and changes in tumor burden. Clin Cancer Res. 2010:clincanres. 1929.2010.

185. Arnold DT, De Fonseka D, Hamilton FW, Rahman NM, Maskell NA. Prognostication and monitoring of mesothelioma using biomarkers: a systematic review. British Journal of Cancer. 2017;116(6):731-41.

186. Hollevoet K, Nackaerts K, Gosselin R, De Wever W, Bosquee L, De Vuyst P, et al. Soluble mesothelin, megakaryocyte potentiating factor, and osteopontin as markers of patient response and outcome in mesothelioma. Journal of Thoracic Oncology. 2011;6(11):1930-7.

187. Fennell DA, Parmar A, Shamash J, Evans MT, Sheaff MT, Sylvester R, et al. Statistical validation of the EORTC prognostic model for malignant pleural mesothelioma based on three consecutive phase II trials. J Clin Oncol. 2005;23(1):184-9.

188. Sandri A, Guerrera F, Roffinella M, Olivetti S, Costardi L, Oliaro A, et al. Validation of EORTC and CALGB prognostic models in surgical patients submitted to diagnostic, palliative or curative surgery for malignant pleural mesothelioma. J. 2016;8(8):2121-7.

189. Meniawy TM, Creaney J, Lake RA, Nowak AK. Existing models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma. British Journal of Cancer. 2013;109(7):1813-20.

190. Wang S, Ma K, Chen Z, Yang X, Sun F, Jin Y, et al. A Nomogram to Predict Prognosis in Malignant Pleural Mesothelioma. World J Surg. 2017;28:28.

191. Brims FJ, Meniawy TM, Duffus I, de Fonseka D, Segal A, Creaney J, et al. A Novel Clinical Prediction Model for Prognosis in Malignant Pleural Mesothelioma Using Decision Tree Analysis. J Thorac Oncol. 2016;11(4):573-82.

192. Niho S, Kubota K, Yoh K, Goto K, Ohmatsu H, Nihei K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with ipsilateral pleural effusion. J Thorac Oncol. 2008;3(7):723-7.

193. Herrstedt J, Clementsen P, Hansen OP. Increased myelosuppression during cytostatic treatment and pleural effusion in patients with small cell lung cancer. Eur J Cancer. 1992;28A(6-7):1070-3.

194. Light RW. Pleural diseases: Lippincott Williams & Wilkins; 2007.

195. Adiguzel C, Bozkurt SU, Kaygusuz I, Uzay A, Tecimer T, Bayik M. Human herpes virus 8-unrelated primary effusion lymphoma-like lymphoma: report of a rare case and review of the literature. Apmis. 2009;117(3):222-9.

196. Waddington TW, Aboulafia DM. Failure to eradicate AIDS-associated primary effusion lymphoma with high-dose chemotherapy and autologous stem cell reinfusion: case report and literature review. AIDS Patient Care STDS. 2004;18(2):67-73.

197. Dabaja BS, Ha CS, Thomas DA, Wilder RB, Gopal R, Cortes J, et al. The role of local radiation therapy for mediastinal disease in adults with T-cell lymphoblastic lymphoma. Cancer. 2002;94(10):2738-44.

198. Fujita A, Takabatake H, Tagaki S, Sekine K. Combination chemotherapy in patients with malignant pleural effusions from non-small cell lung cancer : cisplatin, ifosfamide, and irinotecan with recombinant human granulocyte colony-stimulating factor support. Chest. 2001;119(2):340-3.

199. Kitamura K, Kubota K, Ando M, Takahashi S, Nishijima N, Sugano T, et al. Bevacizumab plus chemotherapy for advanced non-squamous non-small-cell lung cancer with malignant pleural effusion. Cancer Chemother Pharmacol. 2013;71(2):457-61.

200. Masago K, Fujimoto D, Fujita S, Hata A, Kaji R, Ohtsuka K, et al. Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer. Mol. 2015;3(2):415-9.

201. Huang Z, Yan H, Chavan D, Yuan Z, Yang X, Zhang Y, et al. Effective treatment of a patient with stage IV ovarian cancer: A case report. Oncol. 2018;15(1):588-91.

202. Lin JB, Lai FC, Li X, Tu YR, Lin M, Qiu ML, et al. Sequential treatment strategy for malignant pleural effusion in non-small cell lung cancer with the activated epithelial grow factor receptor mutation. J Drug Target. 2016:1-22.

203. Jiang T, Li A, Su C, Li X, Zhao C, Ren S, et al. Addition of bevacizumab for malignant pleural effusion as the manifestation of acquired EGFR-TKI resistance in NSCLC patients. Oncotarget. 2017;09:09.

204. Mori R, Fujimoto D, Ito M, Tomii K. Bevacizumab for ramucirumab refractory malignant pleural effusion in non-small cell lung cancer: a case report and review of the literature. Oncotarget. 2017;8(29):48521-4.

205. Sebastian M, Kiewe P, Schuette W, Brust D, Peschel C, Schneller F, et al. Treatment of malignant pleural effusion with the trifunctional antibody catumaxomab (removab) (anti-EpCAMxanti-CD3): Results of a phase 1/2 study. Journal of Immunotherapy. 2009;32(2):195-202.

206. Shen J, Zhu Z. Catumaxomab, a rat/murine hybrid trifunctional bispecific monoclonal antibody for the treatment of cancer. Current opinion in molecular therapeutics. 2008;10(3):273-84.

207. Qi N, Li F, Li X, Kang H, Zhao H, Du N. Combination use of paclitaxel and avastin enhances treatment effect for the NSCLC patients with malignant pleural effusion. Medicine (Baltimore). 2016;95(47):e5392.

208. Du N, Li X, Li F, Zhao H, Fan Z, Ma J, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. Oncol Rep. 2013;29(6):2332-40.

209. Tamiya M, Tamiya A, Yamadori T, Nakao K, Asami K, Yasue T, et al. Phase2 study of bevacizumab with carboplatin-paclitaxel for non-small cell lung cancer with malignant pleural effusion. Medical Oncology. 2013;30(3):676.

210. Salyer WR, Eggleston JC, Erozan YS. Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasm involving the pleura. Chest. 1975;67(5):536-9.

211. Nance KV, Shermer RW, Askin FB. Diagnostic efficacy of pleural biopsy as compared with that of pleural fluid examination. Mod Pathol. 1991;4(3):320-4.

212. Prakash UB, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. Mayo Clin Proc. 1985;60(3):158-64.

213. Froudarakis ME, Plojoux J, Kaspi E, Anevlavis S, Laroumagne S, Karpathiou G, et al. Positive pleural cytology is an indicator for visceral pleural invasion in metastatic pleural effusions. Clin Respir J. 2017.

214. Renshaw AA, Dean BR, Antman KH, Sugarbaker DJ, Cibas ES. The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Chest. 1997;111(1):106-9.

215. Hooper C, Lee YC, Maskell N, Group BTSPG. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii4-17.

216. Henderson DW, Reid G, Kao SC, van Zandwijk N, Klebe S. Challenges and controversies in the diagnosis of mesothelioma: Part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol. 2013;66(10):847-53.

217. Segal A, Sterrett GF, Frost FA, Shilkin KB, Olsen NJ, Musk AW, et al. A diagnosis of malignant pleural mesothelioma can be made by effusion cytology: results of a 20 year audit. Pathology. 2013;45(1):44-8.

218. Rossi ED, Bizzarro T, Schmitt F, Longatto-Filho A. The role of liquid-based cytology and ancillary techniques in pleural and pericardic effusions: an institutional experience. Cancer Cytopathol. 2015;123(4):258-66.

219. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e65S.

220. Garcia LW, Ducatman BS, Wang HH. The value of multiple fluid specimens in the cytological diagnosis of malignancy. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc. 1994;7(6):665-8.

221. Rakha EA, Patil S, Abdulla K, Abdulkader M, Chaudry Z, Soomro IN. The sensitivity of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Diagnostic Cytopathology. 2010;38(12):874-9.

222. Pinelli V, Laroumagne S, Sakr L, Marchetti GP, Tassi GF, Astoul P. Pleural fluid cytological yield and visceral pleural invasion in patients with epithelioid malignant pleural mesothelioma. J Thorac Oncol. 2012;7(3):595-8.

223. Abouzgheib W, Bartter T, Dagher H, Pratter M, Klump W. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. Chest. 2009;135(4):999-1001.

224. Thomas SC, Davidson LR, McKean ME. An investigation of adequate volume for the diagnosis of malignancy in pleural fluids. Cytopathology. 2011;22(3):179-83.

225. Rooper LM, Ali SZ, Olson MT. A minimum fluid volume of 75 mL is needed to ensure adequacy in a pleural effusion: a retrospective analysis of 2540 cases. Cancer Cytopathol. 2014;122(9):657-65.

226. Swiderek J, Morcos S, Donthireddy V, Surapaneni R, Jackson-Thompson V, Schultz L, et al. Prospective study to determine the volume of pleural fluid required to diagnose malignancy. Chest. 2010;137(1):68-73.

227. Porcel JM, Quiros M, Gatius S, Bielsa S. Examination of cytological smears and cell blocks of pleural fluid: Complementary diagnostic value for malignant effusions. Rev Clin Esp. 2017;217(3):144-8.

228. Dekker A, Bupp PA. Cytology of serous effusions: An investigation into the usefulness of cell blocks versus smears. American journal of clinical pathology. 1978;70(6):855-60.

229. Galateau-Salle F, Churg A, Roggli V, Travis WD, World Health Organization Committee for Tumors of the P. The 2015 World Health Organization Classification of Tumors of the Pleura: Advances since the 2004 Classification. J Thorac Oncol. 2016;11(2):142-54.

230. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013;137(5):647-67.

231. Husain AN, Colby TV, Ordonez NG, Allen TC, Attanoos RL, Beasley MB, et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma: 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2017.

232. Karpathiou G, Stefanou D, Froudarakis ME. Pleural neoplastic pathology. Respir Med. 2015;109(8):931-43.

233. Yang Y, Liu YL, Shi HZ. Diagnostic accuracy of combinations of tumor markers for malignant pleural effusion: An updated meta-analysis. Respiration. 2017;94(1):62-9.

234. Katz RL, Raval P, Manning JT, McLaughlin P, Barlogie B. A morphologic, immunologic, and cytometric approach to the classification of non-Hodgkin's lymphoma in effusions. Diagn Cytopathol. 1987;3(2):91-101.

235. Simsir A, Fetsch P, Stetler-Stevenson M, Abati A. Immunophenotypic analysis of non-Hodgkin's lymphomas in cytologic specimens: a correlative study of immunocytochemical and flow cytometric techniques. Diagn Cytopathol. 1999;20(5):278-84.

236. Pillai V, Cibas ES, Dorfman DM. A simplified flow cytometric immunophenotyping procedure for the diagnosis of effusions caused by epithelial malignancies. Am J Clin Pathol. 2013;139(5):672-81.

237. Davidson B, Dong HP, Berner A, Christensen J, Nielsen S, Johansen P, et al. Detection of malignant epithelial cells in effusions using flow cytometric immunophenotyping: an analysis of 92 cases. Am J Clin Pathol. 2002;118(1):85-92.

238. Acosta M, Pereira J, Arroz M. Screening of carcinoma metastasis by flow cytometry: A study of 238 cases. Cytometry B Clin Cytom. 2016;90(3):289-94.

239. Tse HT, Gossett DR, Moon YS, Masaeli M, Sohsman M, Ying Y, et al. Quantitative diagnosis of malignant pleural effusions by single-cell mechanophenotyping. Sci Transl Med. 2013;5(212):212ra163.

240. Berg KB, Churg A. GATA3 Immunohistochemistry for Distinguishing Sarcomatoid and Desmoplastic Mesothelioma From Sarcomatoid Carcinoma of the Lung. Am J Surg Pathol. 2017;41(9):1221-5.

241. Churg A, Sheffield BS, Galateau-Salle F. New Markers for Separating Benign From Malignant Mesothelial Proliferations: Are We There Yet? Arch Pathol Lab Med. 2016;140(4):318-21.

242. Hwang HC, Sheffield BS, Rodriguez S, Thompson K, Tse CH, Gown AM, et al. Utility of BAP1 Immunohistochemistry and p16 (CDKN2A) FISH in the Diagnosis of Malignant Mesothelioma in Effusion Cytology Specimens. American Journal of Surgical Pathology. 2016;40(1):120-6.

243. Cigognetti M, Lonardi S, Fisogni S, Balzarini P, Pellegrini V, Tironi A, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. Mod Pathol. 2015;28(8):1043-57.

244. Hiroshima K, Wu D, Hasegawa M, Koh E, Sekine Y, Ozaki D, et al. Cytologic Differential Diagnosis of Malignant Mesothelioma and Reactive Mesothelial Cells With FISH Analysis of p16. Diagn Cytopathol. 2016;44(7):591-8.

245. Paintal A, Raparia K, Zakowski MF, Nayar R. The diagnosis of malignant mesothelioma in effusion cytology: a reappraisal and results of a multi-institution survey. Cancer Cytopathology. 2013;121(12):703-7.

246. Valente K, Blackham AU, Levine E, Russell G, Votanopoulos KI, Stewart JH, et al. A Histomorphologic Grading System That Predicts Overall Survival in Diffuse Malignant Peritoneal Mesothelioma With Epithelioid Subtype. Am J Surg Pathol. 2016;40(9):1243-8.

247. Habougit C, Trombert-Paviot B, Karpathiou G, Casteillo F, Bayle-Bleuez S, Fournel P, et al. Histopathologic features predict survival in diffuse pleural malignant mesothelioma on pleural biopsies. Virchows Arch. 2017;470(6):639-46.

248. Kadota K, Suzuki K, Colovos C, Sima CS, Rusch VW, Travis WD, et al. A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma. Mod Pathol. 2012;25(2):260-71.

249. Ghanim B, Klikovits T, Hoda MA, Lang G, Szirtes I, Setinek U, et al. Ki67 index is an independent prognostic factor in epithelioid but not in non-epithelioid malignant pleural mesothelioma: a multicenter study. Br J Cancer. 2015;112(5):783-92.

250. Hatoum H, Lourdes Y, Dhillon SS, Dy GK, Attwood K, Pokuri V, et al. Adequacy of malignant pleural effusion for epidermal growth factor receptor mutation analysis using the pyrosequencing method. Pleura. 2015;2(no pagination).

251. Carter J, Miller JA, Feller-Kopman D, Ettinger D, Sidransky D, Maleki Z. Molecular profiling of malignant pleural effusion in metastatic non-small-cell lung carcinoma the effect of preanalytical factors. Annals of the American Thoracic Society. 2017;14(7):1169-76.

252. Shin S, Kim J, Kim Y, Cho SM, Lee KA. Assessment of real-time PCR method for detection of EGFR mutation using both supernatant and cell pellet of malignant pleural effusion samples from non-small-cell lung cancer patients. Clinical Chemistry and Laboratory Medicine. 2017;55(12):1962-9.

253. Tang Y, Wang Z, Li Z, Kim J, Deng Y, Li Y, et al. High-throughput screening of rare metabolically active tumor cells in pleural effusion and peripheral blood of lung cancer patients. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(10):2544-9.

254. Rahman NM, Ali NJ, Brown G, Chapman SJ, Davies RJ, Downer NJ, et al. Local anaesthetic thoracoscopy: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):ii54-ii60.

255. Bibby AC, Maskell NA. Pleural biopsies in undiagnosed pleural effusions; Abrams vs image-guided vs thoracoscopic biopsies. Curr Opin Pulm Med. 2016;22(4):392-8.

256. Miyoshi S, Sasada S, Izumo T, Matsumoto Y, Tsuchida T. Diagnostic Utility of Pleural Fluid Cell Block versus Pleural Biopsy Collected by Flex-Rigid Pleuroscopy for Malignant Pleural Disease: A Single Center Retrospective Analysis. PLoS One. 2016;11(11):e0167186.

257. Davies HE, Nicholson JE, Rahman NM, Wilkinson EM, Davies RJ, Lee YC. Outcome of patients with nonspecific pleuritis/fibrosis on thoracoscopic pleural biopsies. Eur J Cardiothorac Surg. 2010;38(4):472-7.

258. Gunluoglu G, Olcmen A, Gunluoglu MZ, Dincer I, Sayar A, Camsari G, et al. Long-term Outcome of Patients With Undiagnosed Pleural Effusion. Arch Bronconeumol. 2015;51(12):632-6.

259. Venekamp LN, Velkeniers B, Noppen M. Does 'idiopathic pleuritis' exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration. 2005;72(1):74-8.

260. Janssen JP TF, Visser F. The long-term follow-up of exudative pleural effusion after nondiagnostic thoracoscopy. J Bronchol 2004(11):169-74.

261. Yang Y, Wu YB, Wang Z, Wang XJ, Xu LL, Tong ZH, et al. Long-term outcome of patients with nonspecific pleurisy at medical thoracoscopy. Respir Med. 2017;124:1-5.

262. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. Nat Rev Clin Oncol. 2017;14(9):531-48.

263. Cappellesso R, Galasso M, Nicole L, Dabrilli P, Volinia S, Fassina A. miR-130A as a diagnostic marker to differentiate malignant mesothelioma from lung adenocarcinoma in pleural effusion cytology. Cancer. 2017;125(8):635-43.

264. Karachaliou N, Mayo-de las Casas C, Queralt C, de Aguirre I, Melloni B, Cardenal F, et al. Association of EGFR L858R Mutation in Circulating Free DNA With Survival in the EURTAC Trial. JAMA Oncol. 2015;1(2):149-57.

265. Mok T, Wu YL, Lee JS, Yu CJ, Sriuranpong V, Sandoval-Tan J, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. Clin Cancer Res. 2015;21(14):3196-203.

266. Oxnard GR, Thress KS, Alden RS, Lawrance R, Paweletz CP, Cantarini M, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34(28):3375-82.

267. Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. 2016;2(8):1014-22.

268. Muraoka T, Soh J, Toyooka S, Aoe K, Fujimoto N, Hashida S, et al. The degree of microRNA-34b/c methylation in serum-circulating DNA is associated with malignant pleural mesothelioma. Lung Cancer. 2013;82(3):485-90.

269. Santarelli L, Staffolani S, Strafella E, Nocchi L, Manzella N, Grossi P, et al. Combined circulating epigenetic markers to improve mesothelin performance in the diagnosis of malignant mesothelioma. Lung Cancer. 2015;90(3):457-64.

270. Kirschner MB, Cheng YY, Badrian B, Kao SC, Creaney J, Edelman JJ, et al. Increased circulating miR-625-3p: a potential biomarker for patients with malignant pleural mesothelioma. J Thorac Oncol. 2012;7(7):1184-91.