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Malignant pleural effusion: from bench to bedside

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ABSTRACT Malignant pleural effusion (MPE) is a common but serious condition that is related with poor quality of life, morbidity and mortality. Its incidence and associated healthcare costs are rising and its management remains palliative, with median survival ranging from 3 to 12 months. During the last decade there has been significant progress in unravelling the pathophysiology of MPE, as well as its diagnostics, imaging, and management. Nowadays, formerly bed-ridden patients are genotyped, phenotyped, and treated on an ambulatory basis. This article attempts to provide a comprehensive overview of current advances in MPE from bench to bedside. In addition, it highlights unanswered questions in current clinical practice and suggests future directions for basic and clinical research in the field.

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This review provides up to date knowledge for malignant pleural effusion covering aspects from bench to bedside http://ow.ly/10w7vN

Introduction

Malignant pleural effusion (MPE) is defined as the accumulation of a significant amount of exudate in the pleural space, accompanied by the presence of malignant cells or tumour tissue. MPE presents a severe medical condition which can result in breathlessness, pain, cachexia and reduced physical activity.

Epidemiological information is limited, but an estimated 50 000 new diagnoses of MPE are made in the UK each year [1]. The incidence and associated healthcare costs of MPE are expected to rise due to an increase in the global cancer rate and advances in systemic therapy, the latter of which allow many patients to live longer [2].

The majority of MPE is caused by metastatic disease: most commonly lung cancer in men and breast cancer in women. These two cancers combined account for 50–65% of all MPE [3]. Mesothelioma is the most common type of primary pleural tumour and is associated with MPE in more than 90% of cases [4]. Despite the progress in cancer treatment, the management of MPE remains palliative, with median survival ranging from 3 to 12 months [5]. Patients' prognosis is highly variable and depends on several factors (primary cancer, stage, performance status and pleural fluid proteins). To this end, the LENT (pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group performance score, neutrophil-to-lymphocyte ratio and tumour type) prognostic score was recently proposed as a tool for the accurate prediction of survival [6]. Although LENT has the potential to aid in the assessment of patients with MPE, it requires prospective validation.

During the last decade, there has been significant progress in unravelling the pathophysiology of MPE, as well as its diagnostics, imaging and management. Expanding interest in this area has resulted in an increasing number of cutting-edge laboratory studies that have developed experimental models of MPE which shed light on the pathogenesis of the phenomenon and tested novel biological agents as potential treatment options [7]. Advances in high-throughput techniques (proteomics, genomics) have triggered developments in the discovery of biomarkers for the disease. The use of thoracic ultrasound (TUS) in everyday practice has enhanced the diagnosis of MPE and assisted in the refinement of pleural procedures [8]. Additionally, clinical research in MPE has progressed and high-quality, suitably powered, randomised controlled trials have begun to provide a more robust evidence base for some of the treatment approaches in the field [9, 10]. This article attempts to provide a comprehensive overview of current advances in MPE from bench to bedside. In addition, it highlights unanswered questions haunting current clinical practice and defines some future directions for basic and clinical research in the field.

Pathophysiology of MPE
Pleural localisation and propagation of malignant disease
Autopsy studies indicate that tumour cells metastasise to the pleura mainly through the blood-stream and initially invade the visceral pleura [11, 12]. Most lung carcinomas translocate to the ipsilateral visceral pleura *via* the pulmonary vessels [11]. Thereafter, secondary dissemination to the parietal pleural occurs by tumour seeding along adhesions or by exfoliated tumour cells floating in the effusion. The pleura may also be invaded through lymphangitic spread or even through direct extension of tumours infiltrating adjacent structures (*i.e.* lung, chest wall, mediastinum or diaphragm).

For the establishment of viable tumour foci on pleural surface, cancer cells contained in the fluid need to adhere to the mesothelium, escape local anti-tumour immune responses, invade the pleural tissue and obtain access to nutrients and growth stimuli. Tumour-mesothelial cell interactions and cancerous invasion of the pleura implicate adhesion molecules and proteolyic enzymes, although these processes are poorly investigated [13]. Mesothelial cells have been found to limit tumour cell proliferation, whereas the impact of cancerous cells on mesothelial cell growth is controversial. Co-culture studies demonstrated that they either stimulate proliferation or induce apoptosis of mesothelial cells, while *in vivo* observations suggest that mesothelial cells in MPEs had lower proliferation compared with those in benign effusions [14–16]. Cytokines that possess immune-inhibitory properties and are abundant in the malignancy-affected pleural cavity, as well as local accumulation of immunosuppressive and protumour CD4+ lymphocytes, contribute to immune evasion and facilitate tumour growth [17–21]. Relative to this, MPE is characterised by defective recruitment, activation and the cytotoxic potential of CD8+ cells [22, 23]. Macrophages from malignant effusions not only display reduced cytotoxic activity against autologous tumour cells but they also inhibit tumour cell apoptosis [24, 25].

After their detachment from a pleural tumour, cancer cells are deprived of the nutrients provided by the tumour vasculature and of the supportive cell–cell and cell–matrix interactions, thus becoming amenable to apoptosis [26]. However, floating tumour cells not only survive, but are still capable of forming secondary foci in other sites of the pleural cavity denoting that they either dramatically change their metabolic needs or use alternative sources of energy and growth factors. It is therefore possible, though still speculative, that pleural fluid that contains both nutrients and mitogenic/survival stimulators might support cancer cells from the time they exfoliate from a pleural tumour mass until they form secondary implantations that invade the subpleural tissues and obtain access to the host vasculature.

Formation of MPE: general aspects
Pleural fluid accumulates when its production overwhelms removal. The reason why some tumours cause effusions while others do not is unclear. *Post mortem* studies demonstrate that mediastinal lymph node

invasion, but not the extent of pleural involvement, predicts the presence of an effusion [11]. In addition, it has long been believed that pleural fluid clearance occurs through the lymphatics that originate from the stomata of the parietal pleura and drains through the mediastinal nodes. Based on the above, it was initially assumed that impaired pleural fluid drainage, secondary to tumour invasion of the drainage system, is the primary mechanism of MPE formation. However, this notion was challenged by the following: 1) the rate of MPE accumulation is commonly higher than that expected if it is merely due to clearance of the fluid occurring secondary to lymphatic blockage; 2) in the majority of MPE, the protein content is higher than that in normal pleural fluid, suggesting the presence of plasma leakage; and 3) MPE occurs even in patients without parietal pleura involvement. It is therefore currently believed that a combination of increased fluid production due to fluid extravasation from hyper-permeable parietal or visceral pleural and/or tumour vessels and impaired lymphatic outflow underlie the development of MPE [7].

Cell and molecular biology of MPE

Since pleural fluid overproduction has been recognised as a key event in MPE formation, considerable effort has been invested in unravelling the molecular mechanisms of pleural tumour-driven fluid extravasation. Evidence from *in vivo* studies indicates that MPE formation is dictated by a complex tumour–host interplay which through paracrine and autocrine effects stimulates pleural inflammation, tumour angiogenesis and vascular hyperpermeability [7]. To trigger these events, tumour cells execute pro-inflammatory and pro-angiogenic transcriptional programmes which are controlled, at least in part, by transcription factors nuclear factor (NF)-κB [27] and signal transducer and activator of transcription (STAT) 3 [28, 29]. Autocrine tumour necrosis factor (TNF), interleukin (IL)-6 and osteopontin (OPN) participate in positive feedback loops regulating tumour NF-κB/STAT3 activation to promote MPE [29–31]. In addition, tumour-derived mediators, including vascular endothelial growth factor (VEGF), C-C-motif chemokine ligand (CCL) 2 and TNF, directly stimulate inflammatory cell influx and/or vascular changes [31–34]. Finally, host mediators perpetuate this malicious interplay by amplifying inflammatory and angiogenic signalling loops. To this end, host IL-5 promotes MPE by facilitating the pleural influx of eosinophils and tumour-promoting myeloid suppressor cells [35]. In addition, tumour-expressed OPN protects tumour cells from pro-apoptotic stimuli and host-secreted OPN promotes pleural inflammation and angiogenesis, while the cytokine from both origins provokes vascular leakage [30]. Recently, it has been proved that mast cells are required for MPE formation and by releasing tryptase AB1 and IL-1β they induce pleural vasculature leakiness and trigger NF-κB activation thereby fostering fluid accumation and tumour growth [34]. This novel concept on MPE pathogenesis was exploited in preclinical studies that demonstrated that a variety of pharmacological agents including VEGF, sulindac derivative, TNF and angiopoietin inhibitors, zolendronic acid, a dual VEGF receptor/sTie2 antagonist, bortezomib and endostatin curtail experimental MPE, and may now warrant clinical testing [33, 36–40].

Diagnosis
Imaging

The role of imaging techniques is firmly established in the diagnostic workup of patients with suspected MPE. Nowadays, TUS is routinely used by respiratory physicians mainly for the guidance of pleural interventions to minimise complications [41]. The utility of the technique is strongly recommended by national and international guidelines [42]. Evidence also shows that TUS could provide important information on the diagnostic pathway of pleural effusion. Pleural or diaphragmatic thickening and nodularity on TUS are highly specific for malignancy and may therefore help to expedite timely investigation in those with these high-risk features [8, 43].

Contrast-enhanced thoracic computed tomography is the current gold-standard imaging modality for the pleura. It can also provide useful information on the pleural cavity as a whole as well as on the primary tumour site and stage. LEUNG *et al.* [44] suggested that the presence of nodular thickening, mediastinal, parietal and circumferential pleural thickening to have high specificity (88–94%) but low sensitivity (36–51%) in identifying malignancy. However, this modality is not perfect and data from a recent retrospective series suggest that approximately one in three patients with pleural malignancy may not demonstrate clear features of cancer on computed tomography [45]. Therefore, invasive investigation and careful follow-up are often warranted even if specific malignant characteristics are not identified in initial imaging studies. The role of positron emission tomography using 18-fluorodeoxyglucose for diagnosing MPE is still not well established. According to a recent meta-analysis of 14 studies including a total of 639 patients, the moderate accuracy of the technique precludes its everyday use to differentiate malignant from benign pleural effusions (table 1) [46].

Cytology–pathology

The methods used to definitively diagnose MPE have also evolved in recent years. Cytology is a well-established initial test with a mean sensitivity of 60%, but this depends on the underlying primary tumour, sample preparation and experience of the cytologist [47]. The diagnostic yield of pleural fluid

	Qualitative or visual PET readings	Semi-quantitative (SUV) PET readings	Qualitative or visual readings using PET systems	Qualitative readings using integrated PET-CT systems	Semi-quantitative (SUV) readings using integrated PET-CT systems
TABLE 1 Diagnostic accuracy of FDG-PET in the identification of malignant pleural effusions					
Studies n	11	7	6	5	6
Sensitivity %	91	82	96	89	81
Specificity %	67	74	75	61	74
Positive LR	2.83	3.24	4.09	2.32	3.22
Negative LR	0.14	0.25	0.06	0.19	0.26

FDG: fluorodeoxyglucose; PET: positron emission tomography; SUV: standardised uptake value; CT: computed tomography; LR: likelihood ratio. Data from [46].

cytology for mesothelioma is even lower and most international guidelines advocate the use of pleural biopsy as a preferred diagnostic method over fluid cytology, though the latter is sometimes sufficient in some experienced laboratories [48–51]. In conjunction with the above limitations of cytology, the expanding use of cancer therapies targeted to tissue-specific gene expression or receptor status which necessitates the acquisition of ample tumour tissue for immunohistochemistry and/or genotyping, has led to an increasing requirement for adequately-sized pleural biopsies [52].

Pleural biopsies can be obtained by different techniques: blind, radiologically-guided or through direct visualisation of the pleura. Based on the results of a randomised trial, blind pleural biopsies are no longer advocated given their lower diagnostic yield [53]. Over the recent years, medical thoracoscopy has been increasingly used by respiratory physicians for the investigation of suspected malignant pleural effusions with negative fluid cytology. Medical thoracoscopy has the advantage of a high diagnostic yield and is well established as a key diagnostic test in the investigation of an exudative pleural effusion of unknown cause. The technique can be performed under local anaesthesia with either rigid or semi-rigid scopes and yields a sensitivity of more than 90% for MPE [54]. Medical thoracoscopy has a favourable safety profile and is considered an overall safe procedure. The BTS reported 16 cases of death in 4736 cases across 47 studies, a mortality rate of 0.3% [1]. Another advance in pleural sampling is the development of physician-based ultrasound-guided pleural biopsies. Evidence suggests that on frail patients with tethered lungs who may be unfit for medical thoracoscopy, ultrasound-guided pleural biopsy is a valid alternative with a diagnostic yield of 94% [55].

Biomarkers

During the previous decade, research has mainly focused on pleural fluid proteins as biomarkers in order to obtain information on patients' diagnosis, prognosis or treatment outcomes. More recently, the development of high-throughput techniques has boosted the characterisation of nucleic acids in MPE. A plethora of different biomarkers have been measured and these include proteins expressed by cancer cells (*e.g.* mesothelin, CEA, CA15-3, CA125, CYFRA 21-1), surface receptors on immune cells (*e.g.* CD163+ on macrophages), extracellular matrix proteins (*e.g.* OPN, fibulin-3) and RNA/DNA levels and sequence [56–60]. Although the majority of nucleic acid biomarkers have not yet gained acceptance in clinical practice, analysis of epidermal growth factor receptor (EGFR), EML4-ALK and KRAS mutations have a valid role for the targeted treatment of patients with lung cancer. Interestingly, evidence indicates that EGFR mutations are abundant in patients with MPE compared to primary tumour samples [61].

The clinical implication of diagnostic biomarkers is limited due to the inadequacy of the validation of the results by subsequent studies. Mesothelin, first published as a useful biomarker in 2003, has however since been confirmed as a useful biomarker in serum in at multiple independent studies with very similar sensitivity and specificity levels, and its elevation in pleural fluid is also a useful guide to the presence of malignancy, including in initially cytology negative effusions [42, 62, 63].

There have been many, often contradictory, biomarker studies with varying specificity and sensitivity, mainly related to the differentiation of malignant from benign effusions [64]. The different results may be ascribed to variations in study populations, measurement techniques (*i.e.* different ELISA kits for the same cytokine), sample preparation (*i.e.* measurements in pleural fluid serum *versus* plasma), failure to include enough control samples in the initial studies or methodological inconsistencies that introduce systematic errors [65]. Promising biomarkers are emerging, but further research with larger studies and prospective validation is required before clinical application. Currently, there are at least two clinical studies pursuing that goal through the prospective collection of samples from patients with MPE (The efficacy of sonographic and

biological pleurodesis indicators of malignant pleural effusion-SIMPLE; www.isrctn.com ISRCTN16441661) and mesothelioma (Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma-DIAPHRAGM; www.isrctn.com ISRCTN10079972) using a standardised approach on the timing and testing of biomarkers.

Management

Although the first randomised trials in MPE were performed in 1977, the optimum management of the disease still remains under debate and research [66]. While the majority of patients with MPE will experience symptoms affecting their quality of life, some remain relatively asymptomatic and can be observed. For those that do develop symptoms, dyspnoea is the most common complaint, followed by chest discomfort and cough [67]. Prior to considering any definitive therapeutic intervention, all patients with MPE should undergo a therapeutic aspiration to assess symptomatic improvement and rate of fluid re-accumulation. Once it is determined that MPE is present, symptomatic and warrants intervention, several options are available.

During the past two decades there has been a change in direction in MPE research and management. Historically, studies were focused on halting pleural fluid accumulation and often employed aggressive surgical methods (pleurectomy); and most clinical trials aimed at identifying the best agent that would achieve obliteration of the pleural space (pleurodesis). The most common end-point of these early studies was radiological improvement at 1–3 months post-pleurodesis, without consideration of the patients' symptoms [68]. Currently, the treatment approach for patients with MPE predominantly aims at alleviating patients' symptoms and improving patient-reported outcome measures, with the latter having gained recognition as a key goal of management [9]. In addition, more aggressive procedures done by thoracic surgeons have been gradually replaced with minimally invasive strategies performed by respiratory physicians. As a result, the ambulatory management of patients with MPE is now more feasible than ever, with indwelling pleural catheters (IPC) and many innovative technologies currently being tested in trials.

Therapeutic aspiration

In general, selection of the most appropriate treatment approach should be individualised, while also considering patient preference. Patients with poor performance status, minimal life expectancy, and an underlying chemotherapy-sensitive malignancy (*e.g.*, lymphoma or small cell lung cancer) can be managed with therapeutic aspiration [4]. Thoracentesis is generally safe, especially if it is performed under TUS guidance. Re-expansion pulmonary oedema can occur infrequently after the removal of more than 1.5 L of fluid (<0.5% risk in large series) [69]. Although fluid drainage does not improve survival, it can substantially improve symptoms and avoid hospitalisation. The drawback of this approach is that over time the effusion is likely to recur, leading to repeated uncomfortable procedures and relative frequent hospital visits.

Pleurodesis

Pleurodesis is defined as parietal-to-visceral pleural fusion with concomitant obliteration of the pleural space. It can be accomplished *via* a variety of chemical or mechanical means, after complete drainage of the effusion that allows parietal-to-visceral pleural apposition. Instillation of the sclerosing agent is thereafter followed by a profound inflammatory response between the layers, which, in turn, result in fibrin accumulation and pleural fibrosis. A variety of different chemicals (talc, bleomycin, tetracycline, iodopovide and others) and bacterial products (from *Corynobactum parvum*, *Streptococcus pyogenes*, *Staphylococcus aureus* and others) have been used in clinical studies to achieve pleurodesis [70–73]. The profound inflammatory response they cause may result in adverse events such as pain and fever but it is believed that the level of inflammation correlates with the likelihood of successful pleurodesis [74].

The type of sclerosant, the method of administration and the method of selection of patients that will be treated with pleurodesis are still unclear. Talc is the most commonly used pleurodesis agent and a meta-analysis supports its use as the sclerosant of choice [4, 75]. Even within the context of large randomised trials, pleurodesis success rates remain under 80% and are almost certainly lower in everyday practice [9, 10, 76, 77]. It has been proven that graded preparations (as opposed to small particle talc) should be used to minimise systemic talc particle dissemination and the risk of acute respiratory distress syndrome [78, 79]. Talc can be administrated either as a slurry through the chest drain or as poudrage during medical thoracoscopy. Even though it was historically believed that talc poudrage was more effective than slurry, this has changed in light of three randomised studies [76, 80–82]. Results from the largest randomised trial in MPE revealed that the success rates of talc slurry and talc poudrage are not significantly different. A subgroup analysis of patients with lung and breast cancer suggested a better success rate for talc poudrage [76]. On the contrary, a recent metanalysis demonstrated that talc poudrage was superior to talc slurry in pleurodesis success [83]. It is expected that the results of TAPPS trial, which is a suitably powered

multicentre, open-label, randomised controlled trial designed to compare the pleurodesis success rate of talc poudrage with talc slurry, will provide evidence on the most efficient way of pleurodesis [84].

Studies report a median length of hospital stay of 4–7 days for inpatient talc pleurodesis, which for patients with poorer survival represents a significant proportion of their remaining lives. Even today, no consensus exists about the optimal size of the chest drain and the time of removal of the tube post-pleurodesis. National guidelines advocate the use of small bore (<14 F) chest drains, but this is now challenged by the results of the largest study to specifically address tube size for MPE in terms of pleurodesis success [10]. Specifically, the TIME1 study showed that smaller chest tubes might be inferior to larger ones in terms of pleurodesis success [10]. The results need validation by future randomised trials powered to address the optimum size of chest drain for pleurodesis.

Indwelling pleural catheters

IPCs have gained popularity during the last decade as they offer ambulatory management, thereby minimising hospital stay and healthcare costs [2, 74]. An IPC is a silicone tube placed in the pleural cavity and tunnelled subcutaneously. The proximal end of the exposed tube has a one-way valve which connects to drainage bottles. Drainage is guided by symptoms and is patient-driven, offering a sense of control to most patients. The optimal schedule of MPE drainage through an IPC is still not clear. Two actively recruiting randomised studies (www.clinicaltrials.gov NCT00978939 and NCT00761618) are under way to address this question (aggressive daily *versus* three times weekly drainage).

Guidelines have advocated the use of IPCs in those patients with MPE that have failed pleurodesis or in those with trapped lung (unsuitable for pleurodesis) [4]. A meta-analysis of 1348 patients with MPE treated with IPCs revealed that 95.6% had symptomatic improvement and 45.6% achieved spontaneous pleurodesis after a median of 52 days [85]. In addition, the TIME2 randomised controlled trial showed that IPCs achieved control of breathlessness and quality of life comparable to talc pleurodesis, but significantly shortened the length of hospital stay [9]. Recent data also provided reassurance on the safety of IPC use, with a risk of death from pleural infection below 0.3% [86]. IPC-related pleural infection occurred in <5% of patients enrolled in another multicentre study and was well-controlled with antibiotics. Moreover, patients with an IPC who develop an associated pleural infection appear to have high rates of post-infectious pleurodesis and also prolonged survival times, as suggested by a recent observational study [87]. There is ongoing research on possible combinations of IPC with sclerosant agents in order to enhance pleurodesis success [88]. As IPC offer long-term access to the pleural cavity, they represent ideal potential portals for local drug delivery. In addition to IPC-delivered bacterial moieties that have been evaluated as potential immunomodulators against MPE, IPC will hopefully facilitate further research in this field [82].

Ambulatory management

Pleural-specific services and technologies are expanding, and this has led to a greater drive towards ambulatory management [89]. The traditional approach of admitting patients with MPE for talc pleurodesis is now outdated. Recent advances in IPC and medical thoracoscopy have created the potential for an attractive "one-stop" approach to diagnosis and management. Combinations of medical thoracoscopy with IPC at the end of the procedure to assure drainage of fluid or sclerosant delivery through IPC could streamline patients' pathways for the limitation of hospitalisation. Clinical trials are currently under way to establish the use and benefit of combined treatment methods.

Future directions

In vitro assays and animal models of MPE have aided clinicians significantly in better understanding the biology of the condition, and, most likely, have subconsciously contributed to current less invasive ambulatory treatment approaches [7]. These experimental tools should be expanded and improved to accurately reflect the diverse origins and phenotypes of human MPE. It is expected that in future experimental models will be an asset on understanding the cellular origin and components of MPE and will probably result in advancing current treatment options.

Future endeavours in the field of clinical MPE research and management should strive toward individualised and targeted approaches (collectively coined precision medicine), since the disease likely represents a syndrome rather than a robust entity and heterogeneity exists even within different pleural tumour cells from the same patient [90]. In this regard, experimental evidence and clinical observation dictate that MPE development most probably rests on cancer hallmarks and molecular culprits that are distinct from those of tumour metastasis to other organs [7]. Hence, patients with MPE from different primary neoplasms should likely be stratified separately in clinical trials to ensure definitive study outcomes. Even more so, patients with MPE should most certainly be studied alone in clinical trials, and should not be grouped together with patients with other metastatic forms of cancer. To this end, a completely separate stage assigned to MPE in

the forthcoming revisions of tumour/node/metastases staging systems for lung, breast and other tumours would tremendously augment research in this area.

Whole genome, transcriptome and proteome studies of patients with pleural neoplasms are becoming more feasible every day. Exploitation of these techniques with well-designed experimental setups will likely lead to the identification of the molecular signatures that cause MPE and may also establish malignant effusions as vectors for the liquid molecular biopsy of lung and pleural tumours. In this direction, analyses at single-cell resolution will contribute the most towards identifying the signature of tumour clones that are causative of effusion formation and towards understanding the clonal evolution of pleural cancer dissemination. Novel techniques, such as massive parallel whole transcriptome sequencing of single cells captured within lipid droplets (drop-SEQ), are likely going to revolutionise our capacity to look at the global cancer genome and transcriptome of an unprecedented multitude of single cells from patients with MPE [91].

The implementation of newer management techniques for patients with MPE, such as IPC, should be optimised and will likely constitute a powerful, first-line clinical and research tool in this patient population. It is conceivable that a multitude of longitudinal measurements will be facilitated by wide-spread use of IPC [92]. It is also conceivable that IPC are expected to provide a powerful valuable tool for local therapies against MPE [74].

However, the insights gained into the origins and mechanisms of malignant pleural disease from cell, animal and human studies described will be wasted if they are not directly converted into improvements in patient management and outcome. To this end, better understanding of the molecular culprits of effusion development, as well as the underlying neoplasms, should foster clinical studies of targeted therapies against MPE in the near future [93]. As these molecular alterations are expected to be different in subgroups or even in each individual patient with MPE, targeted therapies will need to be individualised. Parallel co-clinical trials of patient-derived xenografts in humanised mice may direct clinical decisions and help optimise treatment, predict early response, and identify emergent resistance. At the same time that biology is introduced to the clinical field of MPE and palliative treatment is refined, the survival of ambulatory patients with malignant pleural disease is anticipated to change dramatically. Hence, in addition to clinical and molecular assessment, novel prognosticators, such as the LENT score mentioned above, will need to be adjusted to identify sub-phenotypes of MPE with different physical histories. Clinical end-points will also need to be refined during this process. In addition to symptom relief and fluid production, both overall and quality of life-adjusted survival may very well be a meaningful end-point in the near future [94].

Conclusions

In summary, MPE management and research have made tremendous progress over the last few years. Formerly bed-ridden patients are nowadays genotyped, phenotyped, and treated on an ambulatory basis, and TUS together with IPC have significantly contributed to this change. Medical thoracoscopy is well established as a key diagnostic test in the investigation of MPE. Combined with these powerful clinical tools, adaptations in staging, study end-points and design, as well as application of novel high-throughput research tools to patients with MPE will likely result in etiologic therapy of the condition in the near future.

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