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ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma

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ABSTRACT The European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/ European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) task force brought together experts to update previous 2009 ERS/ESTS guidelines on management of malignant pleural mesothelioma (MPM), a rare cancer with globally poor outcome, after a systematic review of the 2009–2018 literature. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach. The evidence syntheses were discussed and recommendations formulated by this multidisciplinary group of experts. Diagnosis: pleural biopsies remain the gold standard to confirm the diagnosis, usually obtained by thoracoscopy but occasionally *via* image-guided percutaneous needle biopsy in cases of pleural symphysis or poor performance status. Pathology: standard staining procedures are insufficient in ∼10% of cases, justifying the use of specific markers, including *BAP-1* and *CDKN2A* (*p16*) for the separation of atypical mesothelial proliferation from MPM. Staging: in the absence of a uniform, robust and validated staging system, we advise using the most recent 2016 8th TNM (tumour, node, metastasis) classification, with an algorithm for pre-therapeutic assessment. Monitoring: patient's performance status, histological subtype and tumour volume are the main prognostic factors of clinical importance in routine MPM management. Other potential parameters should be recorded at baseline and reported in clinical trials. Treatment: (chemo)therapy has limited efficacy in MPM patients and only selected patients are candidates for radical surgery. New promising targeted therapies, immunotherapies and strategies have been reviewed. Because of limited data on the best combination treatment, we emphasise that patients who are considered candidates for a multimodal approach, including radical surgery, should be treated as part of clinical trials in MPM-dedicated centres.

Introduction

Malignant pleural mesothelioma (MPM) is a rare tumour that has become a world health issue due to its poor prognosis and its increasing incidence, largely due to prior asbestos exposure. However, there has been a remarkable improvement of the knowledge of MPM pathogenesis in recent years, leading to new potential drugs and strategies [1, 2]. Moreover, recent results from trials with multimodal treatment or innovative drugs such as targeted therapies or immunotherapies have brought new hope for MPM patients [3].

Optimal treatment in MPM has not previously been well defined and recent informative guidelines from the British Thoracic Society [4], the American Society of Clinical Oncology [5], the National Comprehensive Cancer Network (NCCN) [6] and the European Society for Medical Oncology [7] have reviewed similar published evidence and came to different conclusions and recommendations. This task force was conducted by the European Respiratory Society (ERS) in collaboration with the European Society of Thoracic Surgeons (ESTS), the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society for Radiotherapy and Oncology (ESTRO). It brought together experts on mesothelioma from different scientific societies to update the previous recommendations [8], with the aim of providing clinicians with a clear, concise and up-to-date statement on MPM management.

Methods

The purpose of these guidelines is to update the previous ERS/ESTS clinical practice guidelines for the management of MPM [8] and provide evidence-based recommendations for specialist care clinicians who want to offer patients a therapeutic approach based on radiotherapy, surgery, (chemo)therapy (first-line and salvage) or a combination of these modalities. Epidemiology, aetiology, biomarkers and screening of asbestos-exposed populations, clinical and pathological diagnosis and staging as well as treatment allocation have been summarised narratively and research priorities have been issued.

This current joint ERS/ESTS/EACTS/ESTRO task force was co-chaired by AS, IO, PMP and GC and included 28 clinicians with experience in several disciplines of MPM management and research and one European Lung Foundation representative (JB). One methodologist (DR) ensured that all the methodological requirements were met. The co-chairs and task force members discussed the evidence and formulated the recommendations; the methodologist did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest.

A first literature search was performed in November 2016 using the Ovid MEDLINE system. This research was performed by a scientific librarian (VD), experienced in searching for medical and scientific publications, and by physicians, experts in the treatment of thoracic neoplasms and trained in

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evidence-based medicine. The Ovid MEDLINE database was searched using the OvidSP interface. The "Population, Intervention, Comparison, Outcome" (PICO) questions model for clinical questions was used to identify the concepts included in the questions, as shown in the supplementary material [9]. The corresponding search criteria were translated into Medical Subject Headings (MeSH) terms, free-text keywords and name of substances or interventions (supplementary material). Results were limited to articles published from 2009 to the present. It was a search strategy decision to limit the start of the search to 2009, after the previous ERS/ESTS guidelines, to restrict it to pertinent citations, as a systematic search of the literature up to 2008 was conducted by the previous task force. Citations were exported from MEDLINE into reference manager databases (EndNote) to allow the removal of duplicates and to facilitate the selection process performed by reviewers. All articles retrieved by the librarian were selected for their eligibility by two authors based on the title and abstract, and the final selection was performed by reading the full publication and its inclusion was decided by consensus. This search was supplemented by screening the references of the selected articles and other literature known to the experts.

An update of the literature was performed on January 2019 in order to capture randomised clinical trials relevant to the clinical questions. Supplementary figure S1 shows a flow chart of the literature search.

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to appraise the quality of evidence and to formulate, write and grade most recommendations. GRADEpro Guideline Development Tool software (McMaster University, 2015; developed by Evidence Prime, Hamilton, ON, Canada) was used to develop evidence profiles that summarised the findings for each outcome and the rationale for the quality of evidence appraisal [9].

The evidence profiles were sent to the task force members for review. Using an iterative consensus process conducted face to face, *via* teleconference and *via* email, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention, the quality of evidence, acceptability and feasibility.

A strong recommendation for an intervention indicates that most well-informed patients would choose the intervention, whereas a conditional recommendation for an intervention indicates that well-informed patients may make different choices.

Thus, based on an extensive search of the literature (2009–2019) on MPM, the authors answered several questions on this cancer, to update previous European guidelines [8], including the following PICO questions:

Surgery
  Should partial pleurectomy, compared to talc pleurodesis, be used as a palliative procedure in patients with symptomatic MPM?
  Should "radical surgery" (including extrapleural pneumonectomy or pleurectomy/decortication) be used in patients with MPM?

Radiotherapy
  Should radiotherapy be used for pain relief in patients with MPM?
  Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?
  Should adjuvant postoperative radiotherapy be used in patients with MPM?

Medical treatment
  Should first-line (chemo)therapy consisting of platinum alone or in combination with pemetrexed be used in patients with MPM?
  Should bevacizumab be added to first-line standard (chemo)therapy in patients with MPM?
  Should targeted therapies be added to first-line standard (chemo)therapy in patients with MPM?
  Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard (chemo)therapy?

Multimodality
  Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, (chemo)therapy, radiation therapy) compared to (chemo)therapy alone be used in patients with MPM?

Epidemiology of mesothelioma
Incidence trend and predictions
From publications investigating the incidence trend at the world level, it appears that there is a lack of data regarding mesothelioma incidence and/or mortality for a large part of the world population [10–12] and especially for countries still using asbestos, such as in Eastern Europe, Asia, South America and most of Africa [13]. From available data, large disparities in mesothelioma incidence/mortality rates and trends are noticeable from country to country (supplementary table S1) [10–12, 14–43].

The pattern of mesothelioma incidence is highly correlated with the pattern of asbestos importation and use [14, 44] with a delay of ~40 years due to the long latency period. It has been estimated that the incidence peak in Western Europe will be reached around 2020, and epidemiological data support these predictions [45]. Lower incidence rates in some parts of Asia and Central or Eastern European countries may be related to a poorer quality of data regarding diagnostic certification and registration [46] and a higher mortality from other causes. Besides, due to the long latency period, the epidemic of mesothelioma in those countries is likely to be at its beginning [13, 14].

The task force experts consider essential that all countries set up permanent epidemiological surveillance systems based on the exhaustive registration of mesothelioma cases at a national level.

Mesothelioma aetiology
Asbestos exposure
Asbestos is the principal aetiological agent of MPM. The term asbestos refers to six silicate minerals which are able to form very thin fibres, divided between the serpentine group (chrysotile) and the amphibole group of minerals (crocidolite, amosite, anthophyllite, tremolite and actinolite). Chrysotile is less biopersistent in the lungs than amphiboles. Chrysotile, amosite and crocidolite have all been widely used for industrial purposes.

To date, there are no new data questioning the previous guidelines [8]: 1) a dose–response relationship between asbestos exposure and mesothelioma occurrence has been demonstrated [47]; 2) however, it is still impossible to define a threshold of cumulative exposure below which there is no increased risk, implying that all exposed individuals are constituting a population at risk; and 3) the mean (range) latency of MPM following asbestos exposure is 40 (15–67) years [48].

Occupational asbestos exposure accounts for >80% of cases in males (supplementary table S2) [49–52] and the differences in attributable risk between males and females is probably due to household [53, 54] or environmental exposure (supplementary table S3) [51, 52, 55–74].

Exposure to other elongated mineral particles
Other elongated mineral particles such as erionite or fluoro-edenite may be involved in the aetiology of malignant mesothelioma (supplementary table S4) [75–94], with potential environmental exposure in various countries, such as Turkey, USA and Mexico [95–97].

From the available literature, occupational exposure to refractory ceramic fibres does not seem to be associated with the occurrence of MPM [88, 89]. However, some studies have raised the hypothesis of a synergistic effect between co-exposure to asbestos and other synthetic fibres, namely refractory ceramic fibres or mineral wool fibres [51, 98–100].

In 2014, in the absence of human data, multiwalled carbon nanotubes (MWCNT)-7 was classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (group 2B), while other sorts of carbon nanotubes were not classifiable as to their carcinogenicity to humans (group 3) [90, 94]. Recent experimental studies demonstrated the induction of MPM following intratracheal instillation of MWCNT into rat lungs [101, 102].

Genetic predisposition
Studies of familial aggregation of mesothelioma cases have reported an increased risk for subjects having parents and siblings diagnosed with mesothelioma [103–105]. Those observations led to the identification of a genetic component involved in the increased risk of mesothelioma in those families [106–112], namely a germline mutation of the BRCA1-associated protein (BAP)-1 gene, a tumour suppressor gene involved in the modulation of transcription and DNA repair. Other studies have attempted to identify new loci that might be associated with mesothelioma [111, 113–120].

A significant proportion of patients with malignant mesothelioma carry germline mutations in cancer susceptibility genes, especially those with peritoneal mesothelioma, minimal asbestos exposure, young age and a second cancer diagnosis [121, 122].

These data support clinical germline genetic testing for selected patients with malignant mesothelioma and provide a rationale for additional investigation of genetic pathways in malignant mesothelioma.

Other risk factors
Ionising radiation (mainly therapeutic radiation) is a risk factor for mesothelioma [123, 124], although it accounts for a small proportion of mesothelioma cases relative to asbestos exposure [13].

There were some controversies regarding the implication of the simian virus 40 (SV40) in MPM pathogenesis. In 2014, the IARC considered that SV40 could not be classified as carcinogenic to humans (group 3) [125]. It should be noted that tobacco smoking is not a risk factor for MPM.

The task force experts consider that national and international authorities must take an active role to achieve a complete and definitive ban of asbestos use worldwide, and to promote a close watch of other potential risk factors for MPM.

Biomarkers and screening in asbestos-exposed populations

Screening for MPM would raise many issues about the target population, the most efficient tool(s) to use, and, primarily, the rationale of such screening for a quite rare cancer.

Pleural plaques and MPM

Based on several consensus statements of an increased prevalence of pleural plaques among mesothelioma cases compared to non-mesothelioma subjects, the hypothesis of an association between pleural plaques and MPM has been raised [126–128]. However, since pleural plaques are considered a marker of asbestos exposure, it is not surprising to find such association and it is challenging to estimate the independent association between pleural plaques and MPM, considering that asbestos exposure is a strong confounder in this relationship. While most studies were based on chest radiograph detection of pleural plaques, recently, a positive and significant association between pleural plaques and MPM was found, detected using computed tomography (CT) scanning, while accounting for occupational asbestos exposure [129]. However, some authors have suggested that it cannot be ruled out that pleural plaques are only a marker of asbestos exposure [128].

Pleural plaques are likely to be a simple marker of previous asbestos exposure; the task force experts consider that no invasive diagnostic procedure is justified due to their presence. However, CT scans could detect (benign) asbestos-related lung diseases in exposed subjects, which may justify compensation according to national rules, but which may also be a marker of increased risk of MPM.

Research priority: the relationship between pleural plaques and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT screening in the asbestos-exposed population should be determined in well-designed clinical trials.

(Diagnostic) biomarkers

Several blood biomarkers have been proposed for MPM screening, diagnosis, prognosis or follow-up during treatment. Results of biomarkers applied in populations for diagnosis purposes are summarised in supplementary table S5 [130–152]. The performance of these markers tested alone or in combination have been evaluated and reviews published [153–157]. A meta-analysis on the diagnostic value of soluble mesothelin in >4000 patients estimated sensitivity and specificity at 47% and 95%, respectively [135]. A few prospective studies conducted in subjects previously exposed to asbestos (supplementary tables S6 and S7) failed to demonstrate any value of serum mesothelin as a screening tool in these populations [158–164]. Simulations of real-life use of biomarkers (supplementary table S8) found a very high number of false-positive cases, even in populations highly exposed to asbestos. The role of mesothelin and other biomarkers for monitoring the response to antitumour treatment are currently being evaluated in a number of centres.

Research priority: routine determination of previously proposed biomarkers in MPM have no current validated role in diagnosis, prognosis or clinical follow-up (disease monitoring). Thus, further research into the role of biomarkers in these goals is required and highly encouraged.

Methods of assessing asbestos exposure

No significant change was found since the 2009 ERS/ESTS guidelines [8].

MPM compensation

As occupational asbestos exposure is strongly associated with the occurrence of mesothelioma, some countries have set up compensation programmes, *i.e.* recognition of MPM as an occupational disease [18, 165–167] and/or compensation from asbestos victims' funds [167]. An analysis of the literature [18, 165–167] suggests undercompensation for MPM cases.

The task force experts consider that the dissemination of information to clinicians and patients regarding the right to compensation for MPM should be reinforced according to the specific rules applying in each country.

Diagnosis of MPM
Clinical manifestations
The following recommendations from the 2009 ERS/ESTS guidelines are still valid in 2019 without any change according to the 2009–2017 literature [8].

The clinical manifestations of MPM are usually nonspecific and insidious and should not be used alone as diagnostic criteria, even in cases of previous asbestos exposure.

Chest radiography usually shows a unilateral pleural effusion and/or thickening. Chest radiography alone should not be used for the diagnosis of MPM. In addition, chest CT scan is unsuitable for definitive diagnosis of MPM, but diffuse or nodular pleural thickening is suggestive of the disease, especially involving mediastinal pleura. Chest CT scans with intravenous contrast agent (optimised for pleural evaluation) is the modality of choice for initial evaluation of patients with suspected MPM. Positron emission tomography (PET)–CT can be used to provide useful functional information on pleural lesions, if prior talc pleurodesis has not been performed, even if it not specific enough to diagnose MPM routinely. Functional magnetic resonance imaging (MRI) may be considered in these situations and other difficult diagnostic cases. MRI data appear promising, but are yet to be validated prospectively. The imaging modalities are the cornerstone of determining the correct biopsy site.

What is the best pleural biopsy method in suspected cases of mesothelioma?
Thoracoscopic biopsies (performed under local or general anaesthesia) are the gold standard for investigating an undiagnosed pleural effusion where the differential diagnosis includes mesothelioma. However, other biopsy methods are less invasive and may be more appropriate in selected cases. Thus, image-guided cutting-needle biopsies have high diagnostic rates and are particularly useful in patients with pleural thickening without associated pleural effusion, or in frail patients not fit enough for thoracoscopy. In particular, thoracic ultrasonography (TUS) allows the physician and radiologist to perform pleural biopsies more accurately and safely without any radiation exposure.

Blind closed-needle biopsies
The sensitivity of Abrams biopsies for malignancy is between 27% and 60% [168–172], being much lower for mesothelioma diagnosis. In the largest review of 2893 Abrams samples, diagnostic yield was only 57% for malignant disease [171]. Because of its poor yield, its use is diminishing in most developed countries and it cannot be recommended as a first-line investigation in this setting.

Image-guided pleural biopsy
The sensitivity of image-guided biopsy has been reported in a number of observational series, with both ultrasound- and CT-guided biopsies being superior to blind pleural biopsy [173, 174]. A prospective randomised trial comparing CT-guided cutting-needle biopsies with Abrams biopsy demonstrated that cutting-needle biopsies were 40% more sensitive at diagnosing malignancy [175]. The yield from CT-guided biopsy was 87%, compared with 47% for Abrams biopsies (p=0.02), with the added benefit of fewer passes of the needle in the image-guided group. This is important in cases of suspected mesothelioma where tumour seeding can occur along biopsy tracks.

A recent publication suggests that physician-led, ultrasound-guided pleural biopsy is effective, both as a planned procedure in patients not suitable for thoracoscopy, and as a secondary "on-the-table" option if thoracoscopy fails [176]. Diagnoses were obtained in 47 (94%) out of 50 patients. Out of 15 patients with a final diagnosis of malignancy, ultrasound-guided biopsy provided diagnostic material in 13 (87%).

Video-assisted thoracic surgery and medical thoracoscopy
Video-assisted thoracic surgery (VATS) and medical thoracoscopy plays an important role in the diagnosis of MPM. As well as securing a pathological diagnosis [177], it also allows evacuation of symptomatic pleural effusion and pleurodesis using talc poudrage [178]. In addition, it permits the assessment of the pleural cavity for staging purposes, in particular the assessment of visceral pleural and diaphragmatic pleural invasion, which are important prognostic factors [179].

Local-anaesthetic thoracoscopy or medical thoracoscopy
The diagnostic yield of medical thoracoscopy for pleural malignancy is high. Pooled results from 1369 patients in 22 case series showed an overall diagnostic sensitivity of 92% [180]. Medical thoracoscopy has been shown to be more successful at diagnosing malignancy than blind or image-guided Abrams biopsies [181–183], and had a higher diagnostic yield than CT-guided cutting-needle biopsies in one small randomised trial [184]. The complication rates are very low, with analysis of 47 studies including 4756

patients reporting a mortality rate of 0.34%, major complications in 1.8% and minor complications in 7.8% of cases [180].

VATS

VATS pleural biopsies carry a sensitivity of 95%, specificity of 100% and negative predictive value of 94%. This is similar to medical thoracoscopy, although no randomised trial has directly compared the two procedures. VATS offers the additional benefit of allowing the performance of more invasive surgical interventions, such as lung resection and tumour debulking, at the same time as the diagnostic procedure. It is important to note that VATS can be performed under local anaesthesia on nonintubated patients [185].

Tumour spread at resected previous chest tracts and scars is common and was identified as a negative prognosticator for long-term survival [186, 187]. Therefore, VATS (or medical thoracoscopy) incisions should be generally in line with possible forthcoming thoracotomy incisions [188]. This allows the resection of VATS (or medical thoracoscopy) tracts at the time of future surgery to avoid tumour recurrence in these areas [189, 190].

Open pleural biopsy

Sometimes, due to an obliterated pleural space secondary to locally advanced disease, VATS is not possible. In such cases, a small muscle-sparing incision within an intercostal space (with and without associated partial rib resection) allows for open pleural biopsy. CT- or TUS-guided cutting-needle biopsy is another option in this setting. Therefore, thoracotomy is usually not necessary for the accurate diagnosis of MPM.

Pathology

The diagnosis of mesothelioma is purely histological, based on an adequate tissue specimen and on international evidence-based comprehensive classification agreed by experts throughout the world. The World Health Organization (WHO) histological classification was updated in 2015 [191]. The development of recommendations for MPM pathology was not considered in the scope of these guidelines, because the European task force experts considered that the recommendations from the International Collaboration on Cancer Reporting and the recent update of the International Mesothelioma Interest Group consensus statement are applicable in this context [192, 193].

Clinical information is required for an accurate diagnosis by the pathologist, because it can influence the initial hypothesis, the processing of the specimen, the procedure of sampling and the ancillary analysis to be performed (immunohistochemistry (IHC), the choice of antibodies, fluorescence *in situ* hybridisation (FISH) analysis, RNA sequencing, comparative genomic hybridisation array, *etc.*).

Histopathological specimen examination according to MPM clinical presentation

As pleural effusion is usually the first clinical sign of MPM, cytology is often the first diagnostic procedure to be performed. However, most effusions are caused by the epithelioid type, since sarcomatoid mesothelioma does not usually shed cells into the serosal cavity [194]. Distinction from benign pleural lesions can be impossible on cytology alone, because subpleural fat tissue invasion, which is the most important criterion for malignancy, is lacking. However, recent tests based on molecular abnormalities can be valuable tools. Cytological suspicion of mesothelioma should be followed by tissue confirmation.

The International Mesothelioma Panel recommended that disease recurrence and metastases can be ascertained on cytology alone [193]. However, according to these latest guidelines, in patients unable to benefit from pleural tissue biopsies, a diagnosis of MPM could be ascertained on pleural effusion cytology alone when using specific ancillary techniques, and be as reliable as tissue biopsy, even if the sensitivity remains lower (30–75%). Thus, although cytology of pleural effusion is not recommended for obtaining an initial firm diagnosis of MPM, it may be very useful for differentiating MPM from other, more common malignancies, *e.g.* lung carcinoma. Cytology is more reliable if pleural exudate is preserved in cytoblocks and if ancillary tests (IHC or genetic testing, *e.g.* p16 deletion in FISH) can be performed [193, 195].

Therefore, as the production of cytoblocks is not a routine procedure in all institutions, the experts would like to highlight the necessity of preparing cytoblocks from pleural effusion samples.

Diagnosis of mesothelioma from fine-needle biopsies is associated with the same diagnostic constraints as pleural cytology, with a low sensitivity (30%) [196, 197]. A conclusive diagnosis can only be made if the material is representative of the tumour with sufficient quantity to allow IHC and FISH analysis characterisation in the context of appropriate clinical, radiological and/or surgical findings [198].

Macroscopy

The macroscopic aspect of mesothelioma varies during the natural history of the tumour. Therefore, the topography of the tumour is an important component for pathological staging. A diagnosis of diffuse MPM is more suggestive when the mesothelioma progresses and forms a rind of tumour encasing the lung. Nevertheless, other secondary or primary tumours may have a misleading pseudomesotheliomatous gross characteristic. The type of biopsy may affect the accurate typing and subtyping of diffuse MPM. In addition, it is important to know if the lesion is localised or diffuse, principally because (rare) localised MPM might benefit from surgical resection [194].

Microscopy

The task force experts consider the 2015 WHO classification reasonable, because it provides a comparative basis for diagnosis, prognosis and therapeutic management of the patient. However, it is well known that some epithelioid mesothelioma subtypes have a better prognosis (papillary, acinar, trabecular), while others have a worse prognosis (solid). Moreover, the presence of particular stromal responses (with abundant myxoid stroma or the rare lymphohistiocytoid variant) also has prognostic value. Some cytological features are associated with a poor outcome (pleomorphic and transitional). The current definition of biphasic mesothelioma requires that ⩾10% of both epithelioid and sarcomatoid components be present. There is a consensus agreement that if the percentage of sarcomatoid component is <80% in the diagnosis of biphasic mesothelioma, it is correlated with a better prognosis. The evaluation of the percentage of the sarcomatoid component is restricted to resected tumours (large surgical specimens) and should not be evaluated on smaller samples [199].

Role of IHC

IHC enables the separation of different MPM subtypes from other malignancies or pleural metastases, using various sets of antibodies, with a relatively high diagnostic accuracy (supplementary tables S9–S11). In addition to these markers, claudin 4 has recently emerged as one of the most useful markers to separate mesothelioma (claudin 4-negative) from adenocarcinomas (claudin 4-positive) such as breast cancer metastases [193]. Furthermore, sarcomatoid mesothelioma may be cytokeratin-negative in 5% of cases and in 10% if heterologous elements are present; in this situation the diagnosis should only be made in the context of appropriate clinical, radiological and/or surgical findings [194].

The three well-defined genetic alterations in diffuse MPM are loss of *neurofibromatosis 2* (*Nf2*) by mutation or heterozygous or homozygous deletion, observed in 45–50% of cases; the homozygous deletion of the gene *CDKN2A* (*p16*) located on the 9p21 locus, reported in nearly 100% of sarcomatoid mesothelioma [200]; and loss (absence of nuclear staining when a positive internal control is present on the slide) of BAP-1 (a tumour suppressor gene located on 3p21 locus) by mutation, biallelic deletion or deletion/insertion, detected in 45–100% of diffuse MPM, mostly epithelioid subtype. While the loss of Nf2 has not proven to be useful in the IHC diagnostic routine [201], BAP-1 loss is a reliable marker on paraffin-embedded tissue and cytoblock section and is associated with a better prognosis. Loss of CDKN2A (p16) detected on formalin-fixed, paraffin-embedded sections as well as on cytoblocks using FISH is associated with a worse prognosis and observed with a sensitivity up to 50%, being higher in sarcomatoid mesothelioma. The presence of homozygous deletion of the CDKN2A (p16) by FISH analysis is extremely useful, specifically when subpleural fat tissue or lung parenchyma invasion are missing, and favours the diagnosis of malignancy if there is a strong clinical context and radiological evidence of a pleural tumoural process. However, it should be taken into account that BAP-1 loss and p16 are not 100% specific for mesothelioma.

The loss of BAP-1 expression and/or CDKN2A (p16) homozygous deletion may allow the discrimination of MPM from benign pleural lesions. Given the prognostic and therapeutic significance of BAP-1 loss, BAP-1 may be assessed first by IHC.

Electron microscopy is time- and resource-consuming, and is no more useful with IHC and FISH assays. Finally, freezing pleural tumour tissue is not required routinely, but it may be highly valuable for academic and translational research projects. If so, quality control of the specimen should be performed, and informed consent is needed for ethical biobanking.

Staging and prognosis assessment
8th TNM revision

The International Association for the Study of Lung Cancer (IASLC) mesothelioma staging project experts have updated their initial findings [202] using prospective data on >3500 patients treated both surgically and nonsurgically [203]. Their recommendations [204, 205] will inform the 8th revision of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system for mesothelioma, summarised here.

Clinical staging
T stage
T1a (parietal pleura) and T1b (visceral pleura) have been combined into one T1 classification with tumours involving the ipsilateral parietal or visceral pleura only. The T2 classification was used most often due to lung invasion or involvement of fissures. T4 stage was usually due to diffuse chest wall, diaphragm or transmural pericardial invasion. The most common deficiency of clinical staging was the failure to identify occult chest wall or pericardial invasion. In these cases, upstaging was demonstrated subsequently following surgery.

Exploratory analysis suggests that absolute measurement of pleural tumour thickness correlates with survival. When measurements of maximal thickness at upper (apex to inferior margin of aortic arch), middle (between upper and lower) and lower (inferior to left atrium) zones were taken, both the maximum thickness at any level or the sum of the thickness were prognostic. Pleural thickness (maximum or sum) correlated with T stage and nodal positivity [204].

Research priority: prospective data collection about the measurement of tumour thickness or volume is to be encouraged.

N stage
The IASLC staging project found no difference in survival between clinical stages N0, N1 and N2 [206]. Clinical staging underestimated N status, subsequently found at surgery, in 33% of cases and overestimated it in 6%. Nodal size and the likelihood of malignant involvement have not been found to be correlated [207]. Nodal stage may be predicted from tumour volume. Patients with tumour maximal thickness of <5.1 mm had a 14% risk of nodal metastases, whereas this risk rose to 38% in patients with tumours of maximal thickness >5.1 mm (p<0.0001) [204].

Invasive mediastinal nodal staging with endobronchial ultrasound (EBUS) or mediastinoscopy can aid clinical staging, but clinicians should be aware that it may not be possible to access all nodal disease, extramediastinal areas (*i.e.* internal mammary), peridiaphragmatic or intercostal areas.

Task force experts consider that the use of noninvasive imaging is inaccurate in the assessment of nodal metastasis, and even direct biopsy may not exclude occult nodal disease. Therefore, clinicians should be aware of the implications of these staging limitations when discussing pretreatment prognosis.

M stage
The IASLC project evaluated only 84 cM cases, which nevertheless had sufficiently poorer prognosis than cT4 cases to be considered as the only descriptor in the stage IV classification. Exploratory analyses suggested a possible difference in survival for single- *versus* multiple-site cM1 cases [205].

Task force experts consider that it is important to exclude occult distant metastases if radical therapy is considered due to poor prognosis associated with stage IV.

Pathological staging
T stage
There appear to be no survival differences between pT1, pT2 and pT3, but there was between pT3 and pT4 (hazard ratio (HR) 1.34, p<0.0005) [204]. The classification of pT3 was most often due to partial-thickness pericardial invasion, and pT4 was most commonly due to diffuse chest wall involvement. Other variables that may have prognostic significance include tumour involvement of previous biopsy or incision sites [186, 208] and the weight of tumour resected [209].

Clearly marked anatomical structures (pericardium, chest wall biopsy sites) on resection allow accurate pathological orientation and staging, particularly in lung-sparing operations. Any previous biopsy site should always be excised and submitted for histology.

N stage
The pattern of lymphatic drainage of the pleura does not follow the same pathway as for the lung parenchyma; mediastinal nodes may be the initial site of metastases before the lung parenchyma is involved. Traditional pN2 may therefore precede pN1.

The IASLC staging project reported no survival difference between pN1 and pN2. Therefore, clinical and pathological N1 and N2 are combined into a single N1 category including all ipsilateral, intrathoracic nodal metastases. Contralateral or all extrathoracic nodal metastases are then categorised as N2 [206].

The importance of extramediastinal nodal metastases in the intercostal and peridiaphragmatic groups remains unknown due to paucity of data. The proportion of involved *versus* normal lymph nodes has been found to be more prognostic than anatomical location [210].

Pretreatment staging investigations

The stage of the disease determines whether the direction of intervention is cancer-directed (in order to prolong cancer-specific survival) or merely palliation of symptoms. This decision of how extensive the staging measures are will be determined by an initial assessment of the patient's fitness for either surgery or (chemo)therapy. Other factors include the underlying cell type of the tumours (epithelioid *versus* non-epithelioid) and the TNM staging.

Noninvasive staging

A summary of noninvasive staging is presented in figure 1.

Semiautomated tumour volume calculations on chest CT scan have correlated volume with pTN stages and overall survival [211].

Fludeoxyglucose (FDG)-PET is limited in the assessment of nodal stage due to the close proximity of diseased pleura, masking uptake. Moreover, previous chemical pleurodesis might affect FDG uptake and maximum standard uptake value (SUV_{max}) measurement. However, it may be useful in the identification of occult distant metastatic disease. PET-CT had low sensitivity for stage N1 (38%) and T4 (67%) disease [177]. PET-CT had a higher specificity for stage II (77% *versus* 100%, p<0.01) and stage III (75% *versus* 100%, p<0.01) disease compared to CT alone [212]. SUV_{max} may be of prognostic significance, even in unresectable disease [213].

MRI may be useful at the margins of the disease: the apex around the subclavian vessels, inferiorly around the diaphragm in order to demonstrate unresectable, multifocal chest wall invasion [177]. Although MRI is superior for detection of brain metastases and bone invasion, this technique was not superior to CT in terms of detection of lymph node metastases (p=0.85) and visceral pleural tumour (p=0.64). PET-MRI may be at least as accurate as PET-CT in staging [214], whereby radiologists felt significantly more confident staging PET-MRI compared to PET-CT using dedicated sequences. Further applications of functional MRI remain research areas only at present [215].

Invasive staging

A concurrent mediastinal nodal biopsy technique by mediastinoscopy has been described [216].

While extramediastinal nodes are anatomically inaccessible, there may be some benefit in excluding those with positive upper mediastinal nodes, as they carried a worse prognosis than lower or extramediastinal areas [208].

EBUS has been found to have superior sensitivity and negative predictive value to mediastinoscopy for nodal disease in MPM. However, values were both <60% for EBUS [217]. The theoretical additional yield
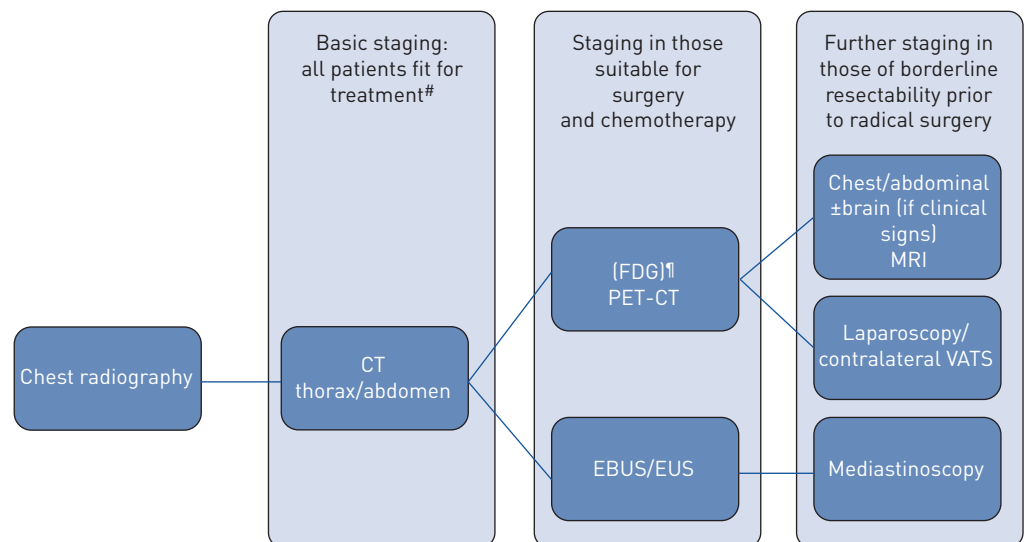
FIGURE 1 A summary of staging algorithm for patients with malignant pleural mesothelioma. #: patients unfit for any treatment could derive some benefit from basic computed tomography (CT) scan in terms of palliative therapy (pleurodesis) or reparation; ¶: after talcage, positron emission tomography (PET)–CT is less accurate than functional magnetic resonance imaging (MRI). FDG: fludeoxyglucose; EBUS: endobronchial ultrasound; EUS: endoscopic ultrasound; VATS: video-assisted thoracic surgery.

from EBUS in stations not accessible to mediastinoscopy was 26%, with a mean survival not significantly worse than those within range of mediastinoscopy. Those with only extramediastinal lymph node metastases had a significantly better survival than either of the above groups [218].

EBUS/endoscopic ultrasound (EUS) followed by simultaneous transcervical extended mediastinal lymphadenectomy and laparoscopy/peritoneal lavage revealed only a small number of undetected nodal metastases that were not found by EBUS/EUS, and the majority of those with positive laparoscopy also had positive mediastinal nodes. This algorithm did not include PET-CT [219].

More invasive techniques including contralateral thoracoscopy and laparoscopy have been infrequently used and are difficult to appraise [220]. They have been shown to help identifying occult stage IV disease not seen on PET-CT.

The task force experts consider that the algorithm proposed in figure 1 is a reasonable approach for pretreatment staging investigations. However, it is not intended as a recommendation for clinical practice.

Research priority: the prospective use of volumetric assessment software should be encouraged.

Which other prognostic factors are of importance?

There is consistent evidence that cell type of MPM is of prognostic significance with epithelioid tumours offering superior survival to non-epithelioid subtypes.

Several nonanatomical prognostic variables can be used to influence the selection of treatment including chest pain, weight loss and dyspnoea, leading to poor performance status, anaemia, leukocytosis and thrombocytosis [221]. Composite prognostic scoring indices have been derived by several organisations including the European Organisation for Research and Treatment of Cancer (EORTC) [222] and Cancer and Leukemia Group B (CALGB) [223] to categorise patients and guide treatment decisions. Specific prognostic scores for surgically resected disease have also been calculated using similar variables: tumour volume pre-(chemo)therapy, C-reactive protein (CRP) level, nonepithelioid histology and progressive disease according to modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria after induction (chemo)therapy [224].

Another simple, clinically relevant model, called the Brims score [225], was proposed to evaluate patients' prognosis using routinely available parameters at the time of diagnosis. This model defined four risk groups with significant different outcomes (p<0.0001). The strongest predictive variable was the presence of weight loss. Risk group 1 included the patients with the best survival at 18 months (86.7% alive, median overall survival (overall survival) of 34.0 months); these patients had no weight loss, a haemoglobin level >153 g·L^{-1}, and a serum albumin level >43 g·L^{-1}. Risk group 4d had the worst outcome (0% alive, median survival 7.5 months); these patients had weight loss, a performance score 0 or 1, and sarcomatoid histological MPM subtype.

Finally, the PROMISE score was proposed recently as a prognostic score in cohorts of patients with malignant pleural effusion in which a number of patients had mesothelioma [226].

The task force experts consider that prognostic factors and scoring systems may help in the decision process, but cannot usually be applied *per se* on an individual basis outside clinical trials, as they were not validated for this purpose.

Research priority: the routine use of the Brims score is encouraged, and combined with other scores as part of clinical trials for prospective validation.

In the future, patient-reported outcome measures may potentially improve the management of MPM based on a recent literature survey [227]. There is also a need to derive predictive factors of (chemo)therapy.

Treatment of MPM
Surgery for MPM patients
Should partial pleurectomy compared to talc pleurodesis be used as palliative procedure in patients with symptomatic MPM?

Our systematic review identified one randomised controlled trial (MesoVATS trial) [228] that compared partial pleurectomy (PP) by VATS *versus* talc pleurodesis in patients with MPM. The MesoVATS trial was an open-label randomised controlled trial conducted in 12 centres in the UK. The primary outcome was overall survival at 1 year. There were no differences between groups in the overall survival at 1 year (HR 1.04, 95% CI 0.76–1.42) nor at 6 months follow-up. Surgical complications were significantly more common after VATS-PP than after talc pleurodesis, occurring in 24 (31%) out of 78 patients who completed VATS-PP *versus* 10 (14%) out of 73 patients who completed talc pleurodesis (p=0.019). Median (interquartile range) hospital stay was longer at 7 (5–11) days in patients who received VATS-PP compared with 3 (2–5) days for

those who received talc pleurodesis (p<0.0001). However, the proportion of patients with resolved pleural effusion was significantly higher in the PP group than in the talc pleurodesis group at 1 month (37% *versus* 59%), but not at 3 months (60% *versus* 60%) or 12 months (77% *versus* 70%), although these numbers were based on surviving patients and heavily influenced by the attrition of follow-up (supplementary table S14). Furthermore, the benefits of VATS-PP (better quality of life, less short-term pleural effusion) do not balance the inconveniences (more leaks and cost). These data do not support a change of practice.

Recommendation: we recommend talc poudrage *via* thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence).

We suggest palliative VATS-PP to obtain pleural effusion control in symptomatic patients fit enough to undergo surgery who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence).

Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM?

Radical surgery in MPM is defined as macroscopic complete resection, which can be achieved by extrapleural pneumonectomy (EPP) consisting of *en bloc* resection of pleura, lung, pericardium and diaphragm combined with systematic mediastinal lymph node dissection, or (extended) pleurectomy/ decortication (P/D) and systematic mediastinal lymph node dissection. P/D is a resection of the total parietal and visceral pleurectomy, sparing the pericardium and the hemidiaphragm, while extended pleurectomy/decortication (EP/D) includes the resection of the pericardium and the hemidiaphragm, when required, and in order to remove all the macroscopic disease [229].

Whereas population and cancer registries consistently report a better outcome for surgically treated patients, they do not correct for prognostic factors, or do so incompletely, and are hence subject to patient selection and recall bias [230–235].

Our systematic review identified one randomised controlled trial (Mesothelioma and Radical Surgery (MARS) trial) [236] and two observational studies [237, 238] that compared surgical to nonsurgical therapeutic approaches in patients with MPM. The MARS trial was designed as a feasibility study and underpowered to assess any benefit (or absence thereof) of EPP. The low number of patients and the number of registered events was very limited; these features decreased the panel's confidence in the estimated effects to low. The study showed that the adjusted HR for overall survival between the EPP and no-EPP groups was 2.75 (95% CI 1.21–6.26). At a median follow-up of 24.7 months from randomisation, 30 out of 50 patients had died (EPP n=17; no EPP n=13); thus, the analysis of survival included only 30 deaths. The 12-month recurrence-free survival in the EPP group was 34.8% (95% CI 16.6–53.7%) compared to 42.3% (95% CI 23.5–60.0%) in the no EPP group, although the difference was not statistically significant. There were no statistically significant differences in those patients who completed the quality-of-life assessment (EPP n=12; no EPP n=19), although the median quality-of-life scores seemed to be lower for the EPP group than the no-EPP group. 12 serious adverse events were reported during the study period: 10 in the EPP group and two in the no-EPP group. Further critical problems are that the total number of patients achieving the trimodality approach was very low, and a relevant number of no-EPP patients received EPP (supplementary table S15).

These results differ from a large retrospective cohort of 1365 consecutive patients with MPM, suggesting that patients with good prognostic factors (*i.e.* age <70 years, epithelioid histology) have similar survival, whether they receive medical therapy only, P/D or EPP [237] (supplementary table S16).

Another retrospective study in 150 patients showed a nonsignificant trend to better overall survival and disease-free survival in those patients undergoing surgical resection (P/D or EPP) [238].

One bias of retrospective studies is that the choice of P/D or EPP depends largely on the institutions' experience, because of a huge variability of outcomes reporting regarding morbidity, mortality, quality of life and overall and disease-free survival. Therefore, due to the low overall confidence and the conflicting results between studies, the panel did not consider issuing a recommendation until more consistent data become available. A multicentre randomised trial comparing extended P/D to no surgery (MARS-2 trial) is currently recruiting in the UK [239]. Results from this surgical trial are awaited with interest.

Research priority: patients considered for radical surgery should be either included in prospective randomised controlled clinical trials or in national/international surgical registries.

Remark: surgery may be appropriate for carefully and highly selected MPM patients. This would usually be EP/D rather than EPP, because of its lower comparative respiratory postoperative morbidity and

preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid-predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery other than in the context of research. However, as no single prognostic factor influences treatment allocation, prognostic scores encompassing several prognostic factors should be preferred (see sections on staging and allocation).

Radiotherapy of MPM

Should radiotherapy be used for pain relief in patients with MPM?

Evidence from randomised controlled trials is not available for palliative radiotherapy in MPM. A prospective multicentre single-arm study [240] investigating 20 Gy in five fractions to painful areas in 40 patients demonstrated that radiotherapy can be effective in treating pain in selected mesothelioma patients (number needed to treat=2). Despite very limited data in the setting of MPM, the role of radiotherapy in pain control for other solid tumours has been demonstrated and is accepted in clinical routine [241–243].

Recommendation: we suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (moderate recommendation, low quality of evidence).

Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?

Randomised controlled trials investigating prophylactic drain site radiotherapy in MPM have shown contradictory results. BOUTIN *et al.* [244] previously showed that an irradiation with 21 Gy in three fractions for three consecutive days in the 4 weeks following drainage or thoracoscopy prevents subcutaneous metastasis developing along drainage channels or thoracentesis tracts. However, a subsequent randomised trial was published comparing immediate drain site radiotherapy 21 Gy in three fractions to no radiotherapy in 61 patients treated between 1998 and 2004, with no difference in terms of tract metastatic recurrence between the two arms [245, 246]. O'ROURKE *et al.* [245] concluded that prophylactic drain site radiotherapy in MPM did not reduce the incidence of tumour seeding as indicated in previous studies [247, 248].

Since the last guideline, two further randomised studies were not able to demonstrate a benefit with prophylactic tract irradiation. A multicentre phase III trial [249] compared immediate radiotherapy (21 Gy in three fractions within 42 days of the pleural intervention) with deferred radiotherapy (same dose given within 35 days of diagnosis of procedure-tract metastases (PTM)); 203 patients were randomised. There was no significant difference in terms of PTM rate, chest pain, quality of life, analgesia requirements or survival. However, there was a suggestion of a benefit in two predefined subgroup analyses, *i.e.* patients with epithelioid-only histology and those who did not receive (chemo)therapy (supplementary table S17).

The applicability of these findings is limited by the small numbers, thus further studies in these specific subgroups may be warranted. A further multicentre phase III randomised trial randomised 375 patients to prophylactic irradiation of tracts (21 Gy in three fractions within 42 days of the pleural intervention) or not. At 12 months, the rate of tract recurrence was 8.1% *versus* 10.1%, respectively (p=0.59) [250]. Prophylactic radiotherapy did not have a statistically significant reduction on the risk of procedure site recurrence, with a pooled relative risk of 0.64 (95% CI 0.27–1.51).

While the results of these two large randomised controlled trials can be considered contradictory to older and smaller trials of the pre(chemo)therapy era, the limited effects of radiotherapy to the prophylactic drain sites observed in these UK phase III trials do not justify this procedure in routine practice.

Recommendation: we do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality of evidence).

Should adjuvant postoperative radiotherapy be used in patients with MPM?

The 17/04 SAKK trial (Neo-adjuvant Chemotherapy and Extrapleural Pneumonectomy of MPM With or Without Hemithoracic Radiotherapy) randomised 54 patients post-EPP to observation *versus* adjuvant (minimum dose of 50 Gy with daily fraction size of 1.8–2 Gy) [251]. The trial closed earlier than planned due to poor accrual. Radiotherapy was associated with slightly better median locoregional relapse-free survival (9.4 months *versus* 7.6 months); however, this was not statistically significant (supplementary table S18).

A phase I/II trial has demonstrated that a short accelerated course of high-dose hemithoracic intensity-modulated radiation therapy (IMRT) followed by EPP is feasible [252]. Patients received 25 Gy in five daily fractions over 1 week to the entire ipsilateral hemithorax with concomitant 5 Gy boost to areas at risk followed by EPP within 1 week of completing neoadjuvant IMRT. Patients with epithelioid histological subtypes had a

3-year survival of 84% after a median follow-up of 23 months. While these results are encouraging and warrant further investigation, this approach is considered experimental at this point. Radiation therapy after lung-sparing surgery might be another approach, resulting in promising survival data [253].

A phase II study [254] demonstrated that hemithoracic pleural IMRT for MPM is safe and has an acceptable rate of side-effects. Its incorporation with (chemo)therapy and P/D forms a new lung-sparing treatment paradigm for patients with locally advanced MPM, but randomised trials are needed to potentially establish this in clinical routine.

Research priority: radiotherapy after pleurectomy±decortication or after EPP should only be considered within the context of clinical trials and/or included in national/international surgical registries.

Medical treatment of MPM
Some phase II and III trials have been completed in first-line and salvage therapy since the 2009 ERS/ESTS guidelines [255]. They are presented in supplementary tables S12 [256–274] and S13 [256, 259, 260, 275–290].

Should first-line (chemo)therapy consisting of platinum in combination with pemetrexed be used in patients with MPM?
No innovative drug has been validated in MPM since 2009 [255].

Recommendations (unchanged after the previous guidelines [8]): we recommend first-line combination (chemo)therapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for (chemo)therapy (good performance status, ECOG performance status 0–2, no contraindications) (strong recommendation, low quality of evidence).

Remarks: the administration of (chemo)therapy should not be delayed and should be considered before the appearance of functional clinical signs (or clinical deterioration). Chemotherapy should be stopped in the event of progressive disease, grade 3–4 toxicities or cumulative toxic doses, but should be continued up to six cycles in patients who respond or are stable.

Research priority: patients demonstrating prolonged symptomatic and objective response with first-line pemetrexed-based (chemo)therapy may be treated again with the same regimen in the event of recurrence. In the remainder of cases, inclusion of the patients in clinical trials is highly encouraged.

Should bevacizumab or other targeted therapies be added to first-line standard (chemo)therapy in patients with MPM?
In 2009, the guidelines task force concluded that immunomodulating agents, targeted therapies and vaccines should not be used in the treatment of MPM outside clinical trials. Many targeted therapies have been assessed in MPM since this time (reviewed in [2, 3]), including mainly antiangiogenic drugs and other growth factor inhibitors.

A large (n=448), phase III trial (Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS)) showed benefit in adding bevacizumab to cisplatin (cis)/pemetrexed (pem) doublet as first-line treatment [271] with significantly longer survival (primary end-point) (HR 0.67, 95% CI 0.61–0.94; p= 0.015) and a 2-month increase in progression-free survival (PFS) (HR 0.61, 95% CI 0.50–0.75; p<0.0001) favouring the bevacizumab arm, with only a mild and manageable increase of toxicity and no negative impact on quality of life. This study suggested a new standard of care for unresectable MPM patients, as validated by some US (NCCN) and French guidelines. However, to date, bevacizumab has not received US Food and Drug Administration or European Medicines Agency approvals in MPM because the French Cooperative Thoracic Intergroup MAPS trial was an academic trial, not initially designed for registration purposes (supplementary table S20).

No other antiangiogenic drug or tyrosine kinase inhibitors has yet demonstrated significant efficacy in a randomised phase III trial [3]. Thus, nintedanib, a drug targeting vascular endothelial growth factor receptor 1–3, platelet-derived growth factor receptor-α/-β and fibroblast growth factor receptor 1–3 failed to show any value in the phase III LUME-Meso trial [291] despite previous promising results in a randomised phase II trial versus placebo in conjunction with first-line cis/pem [292] with significant improvement in median PFS (HR 0.54) and in median overall survival (HR 0.77) (supplementary table S21).

Other main targeted drugs evaluated in MPM included vorinostat, an inhibitor of histone deacetylases, which failed to show any survival advantage versus placebo as second- or third-line treatment in a large phase III trial [284]. The phase II COMMAND trial (NCT01870609), assessing the focal adhesion kinase inhibitor VS-6063/defactinib versus placebo as maintenance treatment after first-line cis/pem, did not meet its primary goals (median PFS and median overall survival) [293]. Other promising drugs include pegylated arginine deaminase (ADI-PEG 20), in combination with cis/pem, targeting arginosuccinate

synthetase-1-deficient tumours such as biphasic (mixed) or sarcomatoid MPM [294]; the loss of BAP-1 may induce the sensitivity of MPM cells to therapies targeting the EZH2 pathway.

Recommendation: we suggest that bevacizumab, if available, be proposed in combination with cisplatin/ pemetrexed as first-line treatment in patients fit for bevazucimab and cisplatin, but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).

Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard (chemo)therapy?

Since 2009, new immunotherapies have been tested in MPM, in particular immune checkpoint inhibitors such as anti-CTLA-4 (ipilimumab, tremelimumab), anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (durvalumab, avelumab). Tremelimumab failed to show any survival improvement *versus* placebo as second-line treatment in a phase III trial [289] (supplementary table S22). In preliminary data from small nonrandomised trials, anti-PD-1 or anti-PD-L1 antibodies seemed to induce increased overall response rate and overall survival compared to historical second- or third-line chemotherapies [3, 295]. PROMISE MESO (NCT02991482), a phase III trial comparing pembrolizumab *versus* either vinorelbine or gemcitabine, has completed enrolment. CONFIRM (NCT03063450), a phase III double-blind randomised trial evaluating nivolumab *versus* placebo is ongoing [3, 296]. Moreover, in the same setting, nivolumab alone or combination of nivolumab plus ipilimumab significantly increased the disease control rate after 12 weeks of treatment and overall survival in a randomised phase II trial [297]. This combination was also efficient in another mono-arm phase II trial as second- or third-line treatment for MPM [298]. Durvalumab and tremelimumab combination may also have a therapeutic value in MPM patients, based on a first report [299]. Finally, preliminary reports of first-line (chemo)therapy plus anti-PD-1 or anti-PD-L1 are promising [300].

Several other trials are ongoing [301], assessing immunotherapies, alone or combined with (chemo) therapy and/or targeted therapies (anti-angiogenic, epigenetic drugs), as first-line or salvage therapies. Interestingly, cell therapy (with dendritic cells, chimeric antigen receptor (CAR) T-cells) or gene therapy trials are also currently recruiting MPM patients.

Research priority: novel insights in immunotherapy are promising, but need further development and results from ongoing or planned phase III trials before any definitive recommendations can be made for their use in the clinical routine. Inclusion of patients in these trials is highly recommended.

What assessment criteria should be used to determine the efficacy of systemic treatment in MPM?

No specific significant data have been published since the previous guidelines [255]. The activity of a treatment can be assessed on clinical criteria (symptoms control and quality of life), imaging criteria (CT scan, PET scan) and survival criteria (time to progression, overall survival).

Overall survival is not the only valuable parameter to assess the effectiveness of medical treatment in clinical trials. It is recommended that quality of life and symptom control be taken into account, to evaluate the clinical benefit (efficacy/tolerance) in diseases with poor prognosis and for which the survival impact of the treatment is not clearly demonstrated or is marginal. No particular score to assess quality of life is recommended specifically, except the modified version of the Lung Cancer Symptom Scale adapted to patients presenting with malignant mesothelioma.

For clinicians MPM is characterised by obstacles in tumour measurement and response assessment. To help them in routine practice as well as in the conduct, interpretation and reporting of clinical trials, the modified RECIST was proposed in 2004. However, the practical application of these criteria was tricky, leading to misinterpretation and inconsistencies in tumour response assessment. Therefore, the modified RECIST 1.1 for mesothelioma [302] were proposed recently to provide updated response assessment guidelines improving previous criteria but also aiming at better defining crucial concepts for MPM, such as minimally measurable disease, measurable lesions, acceptable measurement location or nonmeasurable pleural disease. In addition, they may help to better evaluate nonpleural disease, pathological lymph nodes and bilateral MPM and to establish progressive disease.

Even if they have not been prospectively validated, the task force experts consider the updated modified RECIST 1.1 guidelines the preferred method of choice for measuring tumour lesions and response to treatment on CT scans. If a patient has had pleurodesis, it has been strongly suggested that a chest CT scan should be repeated before the start of (chemo)therapy in order to better evaluate the response to treatment. In fact, pleural lesions may be better described after removal of pleural effusion, favouring a correct assessment of patient outcome. PET scan and biological markers are still under investigation for the evaluation of treatment response in MPM.

Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, (chemo)therapy, radiation therapy) compared to (chemo)therapy alone be used in patients with MPM?

In order to address the role of multimodality therapy in MPM, the following clinical questions were raised. Is multimodality treatment better than (chemo)therapy alone? What is the optimal regimen within each modality? What is the optimal sequence of interventions within a combined modality approach? However, since 2009, our systematic review of the literature, as well as two other recent reviews [303, 304] only identified two randomised clinical trials on the topic: MARS and SAKK 17/04 [236, 251]. Both trials have been considered in other sections of these guidelines (radical surgery and postoperative radiotherapy), without mentioning that they were assessing multimodality options, leading the task force to only issue research priorities. These two trials had many weaknesses. For example, the MARS study was a feasibility trial that did not reach the prespecified sample size [236]; multimodality treatment was compared to continued oncological management, which could include (chemo)therapy and palliative radiotherapy [236], or (chemo)therapy and surgery [251]. Median overall survival observed in both studies was less than expected when compared with observational data; this result might partly be explained by the inclusion of patients with worse prognosis. Globally, these trials involved limited number of patients and events, and wide 95% confidence intervals that included appreciable harm or benefit (supplementary tables S15 and S18).

Thus, as emphasised by other recent reviews [303, 304] or guidelines [4–6], the literature remains biased for multimodal management of MPM patients, without high quality of evidence in favour of a specific therapeutic combination or scheme. Multimodal treatment consisting of at least macroscopic complete resection and (chemo)therapy (platinum/pemetrexed doublet), was superior to either single modality in selected patients with regard to survival, but at the cost of increased treatment-related morbidity and mortality [304]. Given the added cost of multimodality strategies, the possible increase in risk of adverse effects and the lack of evidence of their effectiveness, the Cochrane review authors also concluded that these interventions should not be proposed in routine clinical practice.

Research priority: we still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centres in order to be included in a prospective (randomised) clinical trial and/or registered in a large institutional database.

Treatment allocation

This question, as well as the global management of MPM patients, is summarised by the algorithm presented in figure 2. Counselling patients for the most appropriate and promising treatment, balancing life expectancy with quality of life remains a difficult issue, despite the development of a more detailed TNM staging [200, 305, 306], progress in staging tools and improved knowledge of tumour biology. In contrast to most other malignancies, the discrepancy in reliability between clinical and pathological staging leads quite frequently to an unsatisfactory patient selection for multimodality treatment including radical surgery. When radical surgery (usually P/D) is considered, clinical and functional assessment should be undertaken as described above, including at least spirometry, diffusion capacity of the lung for carbon monoxide, and cardiovascular assessment. CT, PET-CT and/or MRI are used to exclude distant metastasis and evaluate resectability. Thus, the decision whether radical surgery is recommended should be based on a number of different aspects. It has been shown in various studies [211] that tumour volume, measured preoperatively on CT scans, predicts pT/pN and overall survival. Other single factors such as mediastinal nodal involvement or histology available preoperatively (see staging section) predict overall survival. Despite an increasing knowledge about molecular markers and their diagnostic and prognostic value, they are not yet used for treatment allocation. Not surprisingly, single factors are insufficient for proper treatment allocation, and prognostic scores have been developed. The EORTC and the CALGB [222, 223] scores were developed for better identification of patients receiving (chemo)therapy. Prognostically relevant "CORE" covariates (stage, sex, age, histology and type of surgery) were evaluated for patient selection [221]. A multimodality prognostic score based on tumour volume, histology, CRP at diagnosis, nodal status and response to (chemo)therapy allows the identification of patients with very poor prognosis despite multimodality therapy [224]. In conclusion, several prognostic scores have been proposed for treatment allocation of MPM patients. But to date, no single parameter or score has been widely validated for routine use for this purpose.

Research priority: current and future scores suggested for patient treatment allocation, always decided by an MPM expert multidisciplinary board, require prospective validation by multicentre studies.

Palliative care

The control of malignant pleural effusion (MPE) is not detailed in these guidelines, as it is fully explained in the new ERS/EACTS guidelines on MPE management [307].
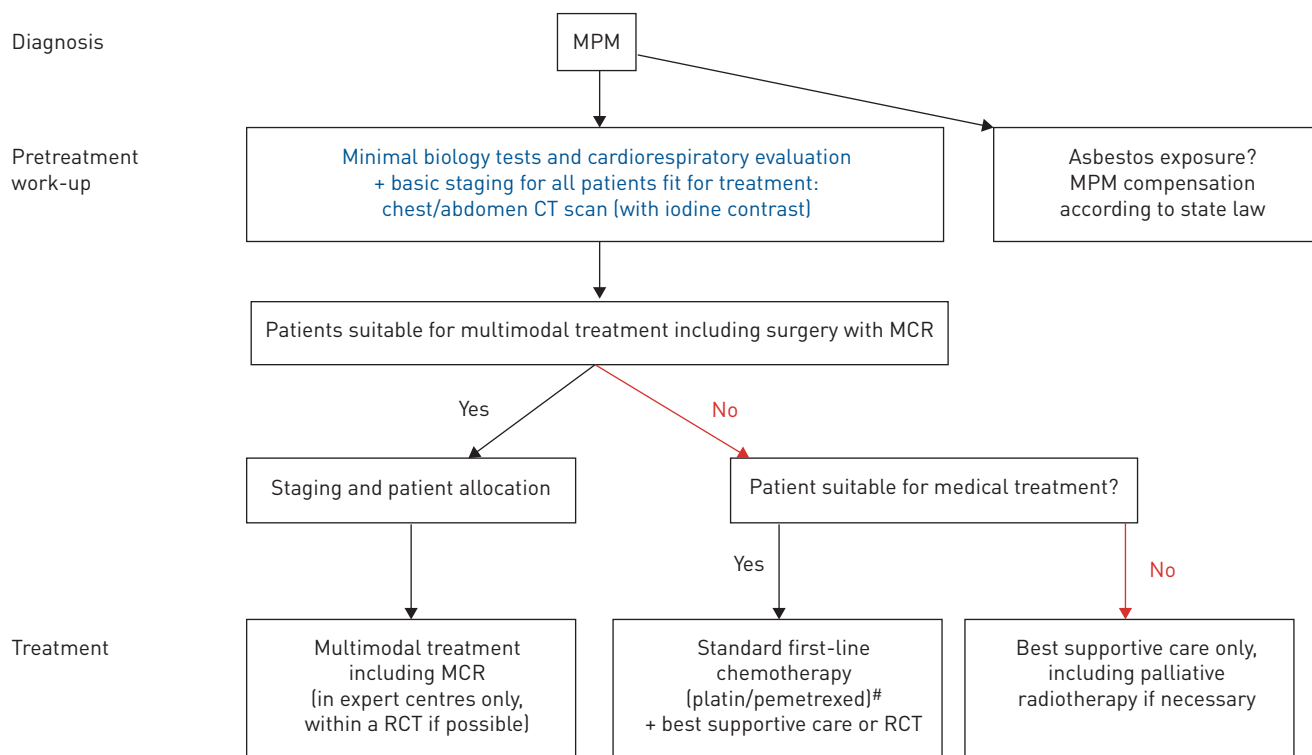
FIGURE 2 A simplified algorithm for the management of patients with malignant pleural mesothelioma (MPM). RCT: randomised controlled trial; MCR: macroscopic complete resection. #: ±bevacizumab if available and no contraindication.

Good-quality palliative care is vital for MPM patients, the majority of whom will require symptom control at some stage in the course of their disease. Currently there are no published large randomised controlled studies of symptom control in patients with MPM only. A small prospective randomised (1:1) phase II trial assessed the use of early *versus* delayed (chemo)therapy at time of symptomatic progression after best supportive care (BSC) only in 43 patients, presenting with stable symptoms after control of pleural effusion [308]. The early use of (chemo)therapy provided an extended median time to symptomatic progression *versus* the delayed (chemo)therapy group (25 *versus* 11 weeks, p=0.1), and a trend to survival advantage (median overall survival of 14 months *versus* 10 months, p=0.1).

There are a two relatively unique problems experienced by a proportion of mesothelioma patients. 1) Excessive sweating: no RCT studies have been published in this field, but it remains a common problem in a proportion of mesothelioma patients. Although there are no good-quality data, oral prednisolone can be very effective in helping to reduce this disabling symptom; 2) severe unilateral thoracic pain: a case series of 53 patients with MPM and associated persistent pain despite oral analgesia were managed with cervical cordotomy [309]. The majority of patients had a reduction in pain following the procedure; however, further, more robust studies are required to confirm this finding.

A review of the numerous palliative care intervention for patients with MPM was out of the scope of this guideline. Therefore, the task force experts encourage following existing national palliative care guidelines for guidance on pain control in cancer patients.

The task force experts emphasise that it is recognised that mesothelioma is associated with high psychological burden, and although quantitative evidence is sparse, there are qualitative papers and systematic reviews that demonstrate this [310].

Follow-up after active treatment
There are no evidence-based recommendations regarding the follow-up in mesothelioma patients undergoing a dedicated treatment mainly based on (chemo)therapy. Although (chemo)therapy has been shown to benefit patients, there are no consistent data allowing us to answer the question of the optimal duration of (chemo)therapy and the design of patients' survey after cessation of the treatment. Therefore, symptoms such as breathlessness, chest pain or both indicate re-evaluation by CT scan to search for progressive disease [308, 311, 312]. Other main symptoms consist of cough (frequently due to pleural effusion), anorexia, weight loss, fatigue, sweating, dysphagia and psychological distress. There are no data

showing the place of PET and MRI in the follow-up for MPM. The development of targeted therapies and immunotherapy in a near future would probably lead clinicians to adapt the modalities of follow-up for mesothelioma patients [313]. To date, there is no sufficient evidence for routine use of biomarkers such as blood mesothelin or other markers for follow-up of MPM patients, either to predict the response to treatment or patient outcomes.

Research priority: the role of periodic follow-up with imaging (chest/abdominal CT scan, MRI or PET) should be assessed in clinical trials.

Remarks: monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow-up. However, in addition to clinical follow-up, and pending further evidence from clinical trials, the task force group suggests a chest/abdominal CT scan every 3–6 months after active treatment of MPM patients.

The outlook for MPM

After a decade during which systemic therapy for mesothelioma has languished at a therapeutic plateau [314], recent advances have demonstrated that improvement in efficacy can be associated with the addition of novel agents in the context of randomised phase III trials, e.g. bevacizumab [271], but not nintedanib with a negative phase III trial (NCT01907100) despite positive randomised phase II trial results [292]. The role of aggressive local control in the form of extended pleurectomy/decortication will become clearer in the next few years, but positive result of current trials may promote further discussion regarding the radicality of a surgical approach.

Despite these recent advances and awaited results from ongoing surgical clinical trials such as MARS2 (NCT02040272), a major challenge remains in the relapsed setting, where there is currently no approved standard.

Accordingly, translational and clinical research in this setting has the potential to significantly improve survival outcomes. Despite the failure of CTLA-4 checkpoint targeted immunotherapy in relapsed mesothelioma [289], the emerging signals of activity for anti-PD-1 monotherapy [295] and combination PD-1 (or PD-L1)/CTLA-4 targeted therapy [297], indicate some potential for these approaches in the relapsed and potentially frontline settings [296], as demonstrated in other cancers such as melanoma [2, 3]. However, the MAPS-2 trial reported a higher incidence of grade 3 or 4 adverse events (26.2% versus 12.7%), and even three toxic deaths, with the combination nivolumab/ipilimumab versus nivolumab alone, respectively [315]. This toxicity issue and the choice of inadequate surrogate end-points such as PFS instead of overall survival must be taken into account when assessing the value of new drugs in MPM [316].

Thus, a major challenge for the field as a whole, will be how best to predict the efficacy of both monotherapy and combination immune checkpoint inhibition. This is particularly important from a health economic standpoint to ensure that advances are ultimately affordable, as well as driving up the efficacy of therapy through enrichment of those likely to respond. Meeting this challenge will require assessment of established predictive biomarkers such as PD-L1, but also the role of other potential predictors including tumour infiltrating lymphocytes [317], cytokine expression [318] and tumour mutation burden [319, 320], ideally in the context of phase III clinical trials. Exploitation of the abscopal effect could also enhance the efficacy of immunotherapy and warrants exploration [321].

Studies are currently under development in the context of combination with both (chemo)therapy and novel agents [301] (e.g. focal adhesion kinase [322], bevacizumab [323]). Future advances in next-generation combination immunotherapy, e.g. indoleamine 2,3-dioxygenase [324]/T-cell immunoglobulin mucin-3 inhibitors [325]/vaccines, etc. may emerge from the rapid pace of development in basic and translational science and advances in other cancers, as well as tailoring of therapeutic hypotheses based on specific mesothelioma biology, including gene-driven metabolic reprogramming.

Genomic stratification of systemic therapy has revolutionised treatment in other areas including lung and breast cancers. Mesothelioma is lagging behind, partly due to a lack of druggable oncogenic mutations [2]. However, recent advances demonstrate potential opportunities. Arginine auxotrophy, arising from the loss of the citrulline-to-arginine converting enzyme argininosuccinyl synthetase, has recently been shown to be a druggable target [294, 326, 327] with a phase III trial now enrolling in the front-line setting. Other novel metabolic vulnerabilities may be identified from interrogation of recently available large-scale genomic data that could underpin the development of new synthetic lethal strategies.

Tumour suppressor losses are common in mesothelioma and may have implications for targeted therapy. For example, the discovery that inactivation of the BAP1 tumour suppressor is associated with upregulation of EZH2 [328] or defective homologous DNA repair [329] has led to the development of phase II trials to test this hypothesis. Other preclinical evidence suggests how sensitivity to

BOX 1 Summary of questions and recommendations

Questions	Recommendations and research priorities
Epidemiology	
MPM screening	Research priority: the relationship between pleural plaques and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT screening in the asbestos-exposed population should be determined in well-designed clinical trials.
Biomarkers for MPM	Research priority: routine determination of previously proposed biomarkers in MPM have no current validated role in diagnosis, prognosis or clinical follow-up (disease monitoring). Thus, further research into the role of biomarkers in these goals is required and highly encouraged.
Staging	
Clinical staging	Research priority: prospective data collection about the measurement of tumour thickness or volume is to be encouraged.
Pre-treatment staging investigations	Research priority: the prospective use of volumetric assessment software should be encouraged.
Which other prognostic factors are of importance?	Research priority: the routine use of the Brims score is encouraged, and combined with other scores as part of clinical trials for prospective validation.
Surgery (PICO)	
Should partial pleurectomy compared to talc pleurodesis be used as a palliative procedure in patients with symptomatic MPM?	Recommendation: we recommend talc poudrage via thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence). We suggest palliative VATS-PP to obtain pleural effusion control in symptomatic patients fit enough to undergo surgery who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence).
Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM?	Research priority: patients considered for radical surgery should be either included in prospective randomised controlled clinical trials or in national/international surgical registries. Remark: surgery may be appropriate for carefully and highly selected MPM patients. This would usually be EP/D rather than EPP, because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid-predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery other than in the context of research. However, as no single prognostic factor influences treatment allocation, prognostic scores encompassing several prognostic factors should be preferred (see sections on staging and allocation).
Radiotherapy (PICO)	
Should radiotherapy be used for pain relief in patients with MPM?	Recommendation: we suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (moderate recommendation, low quality of evidence).
Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?	Recommendation: we do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality of evidence).
Should adjuvant post-operative radiotherapy be used in patients with MPM?	Research priority: radiotherapy after pleurectomy±decortication or after EPP should only be considered within the context of clinical trials and/or included in national/international surgical registries.
Medical treatment (PICO)	
Should first line chemotherapy consisting of platinum in combination with pemetrexed be used in patients with MPM?	We recommend first-line combination (chemo)therapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for (chemo)therapy (good performance status, ECOG performance status 0–2, no contraindications) (strong recommendation, low quality of evidence). Research priority: patients demonstrating prolonged symptomatic and objective response with first-line pemetrexed-based (chemo)therapy may be treated again with the same regimen in the event of recurrence. In the remainder of cases, inclusion of the patients in clinical trials is highly encouraged.
Should targeted therapies be added to first line standard chemotherapy in patients with MPM? Should bevacizumab be added to first line standard chemotherapy in patients with MPM?	Recommendation: we suggest that bevacizumab, if available, be proposed in combination with cisplatin/pemetrexed as first-line treatment in patients fit for bevazucimab and cisplatin, but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).

BOX 1 Continued

Questions	Recommendations and research priorities
Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard chemotherapy?	Research priority: novel insights in immunotherapy are promising, but need further development and results from ongoing or planned phase III trials before any definitive recommendations can be made for their use in the clinical routine. Inclusion of patients in these trials is highly recommended.
Multimodal treatment (PICO)	
Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with MPM?	Research priority: we still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centres in order to be included in a prospective (randomised) clinical trial or registered in a large institutional database.
Treatment allocation of MPM	Research priority: current and future scores suggested for patient treatment allocation, always decided by an MPM expert multidisciplinary board, would require prospective validation by multicentre studies.
Follow-up of MPM patients	
What should be the follow-up of a patient after active treatment of MPM?	Research priority: the role of periodic follow-up with imaging (chest/abdominal CT scan, MRI or PET) should be assessed in clinical trials. Remarks: monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow-up. However, in addition to clinical follow-up, and pending further evidence from clinical trials, the task force group suggests a chest/abdominal CT scan every 3–6 months after active treatment of MPM patients.

chemotherapeutic agents can be BAP1-driven and prompt a future patient stratification to improve the efficacy of standard treatments [330]. Emerging insights into other synthetic lethal interactions with CDKN2A and NF2 have significant translational potential.

Micro-RNAs (MiRs) broadly regulate the transcriptome of mesothelioma and may contribute to the drug-resistant and aggressive phenotype. Recently, MiR16 has been identified as a potential tumour suppressor that can be targeted using so-called targoMiRs. VAN ZANDWIJK et al. [331] reported that MiR-directed targoMiR can be delivered in the clinical setting and can induce responses in relapsed mesothelioma, suggesting that this approach could have therapeutic potential in the future.

The apparently unique treatment-resistant profile of mesothelioma prompts a need for in-depth preclinical research to gain an increased understanding of mesothelioma biology. Potential areas of focus for research include microenvironment–tumour interaction, gene-driven metabolism [329, 332] and elucidation of the mechanisms behind cell death. Preclinical research should use accurate models such as organoids, patient-derived xenografts, primary cells and fresh tissues, and humanised mouse models to study immune response. Ultimately, randomised clinical trials for prospective therapies should use strong primary end-points such as overall survival comparing outcomes to the current standard therapies. At the clinical level, patients should be stratified based on strong data from genetic and cell biological preclinical analysis of mesothelioma cells.

The awareness of these gaps along with the increasing pace of knowledge regarding genomics and biology of mesothelioma will allow to multiply our chances of achieving a real improvement of the clinical outcomes for patients.

This document was endorsed by the European Respiratory Society (ERS) on November 10, 2019, by the European Society of Thoracic Surgeons (ESTS) on November 7, 2019, by the European Association for Cardio-Thoracic Surgery (EACTS) on November 4, 2019 and by the European Society for Radiotherapy and Oncology (ESTRO) on February 17, 2020.

The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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