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Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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epidemiology

incidence

Malignant pleural mesothelioma (MPM) is considered to be a relatively rare tumour. In Great Britain, the incidence in males is 3.4/100 000, in France it is 2.3/100 000 and in the Netherlands it is 3.2/100 000. In the last 10 years, the incidence of MPM has increased slightly, mainly due to the lag time of 30–50 years after exposure to asbestos and the banning of handling and importing this product in the late twentieth century. The World Health Organisation (WHO) estimates asbestos-related disease (ARD) accounts for 92 250 deaths per year globally [1]. Occupational exposure to asbestos accounts for more than 80% of the cases and makes MPM a preventable disease. Although the Western world is moving towards a levelling-off of ARD incidence, the continued use of asbestos in the developing world could lead to a global epidemic of MPM. Even though asbestos is banned in Europe, other developed countries have only controlled the import, but not abolished handling of asbestos products. Recently, a germline mutation in the BAP1 gene has been linked to predisposition in some cases of MPM [2]. Somatic mutations may also play a role in the development of MPM.

diagnosis

Patients typically present with complaints of shortness of breath, pain and weight loss. These symptoms can occur over a period of many months. During physical examination, unilateral effusions are often observed. It is of great importance that a detailed occupational history is obtained.

Standard work-up includes:

- Chest X-ray
- Computed tomography (CT) scan of chest and upper abdomen
- Thoracentesis, with examination of the pleural effusion
- General laboratory blood tests

Plain chest radiography lacks sufficient sensitivity for routine staging. Significant volumes of pleural effusions can mask pleural/chest lesions and make small malignant pleural effusions undetectable.

When an occupational history indicates considerable asbestos exposure, or the radiology is suggestive of mesothelioma, cytology can be used to detect malignant cells but histological specimens must often be obtained (see 'pathology' section).

A thoracoscopy is recommended to obtain adequate histology, to optimally stage, and to allow pleural fluid evacuation (with or without pleurodesis) [3, 4]. This can be performed as a pleuroscopy or as video-assisted thoracic surgery (VATS). MPM can be difficult to identify and it is therefore recommended to obtain biopsies from tissue of both abnormal and normal appearance. When a thoracoscopy is not feasible or contra-indicated, ultrasound-guided true-cut biopsies are a good alternative. Besides a clinical reason to obtain a diagnosis, there are medico-legal reasons to confirm the diagnosis of MPM. In Europe, the requirements for this vary between countries. To date, there are no studies that recommend screening of patients who have had any (occupational) history of asbestos exposure.

Circulating tumour markers have been tested to a great extent and only a few have been able to facilitate the diagnostic process: cyfra 21.1, Fibulin-3 and Mesothelin all lack specificity and should not be used as specific markers for mesothelioma [5, 6]. Carcinoembryonic antigen (CEA) is a negative marker and is not increased in MPM [7]. It can therefore be used to rule out MPM if cytological/histological analysis is inconclusive.

Recommendation 1
Diagnostic procedures in MPM should encompass at least

- *Occupational history with emphasis on asbestos exposure [II, A]*
- *CT scanning of the thorax [II, A]*
- *In all patients who have a unilateral pleural thickening, with or without fluid and/or calcified asbestos plaques, efforts should be made to obtain a pathological specimen, as there are no specific clinical features of MPM [II, A]*
- *There is no place for screening of persons exposed to asbestos [IV, B]*
- *Tumour markers cannot distinguish MPM [II, B]*

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pathology

The pathological diagnosis of MPM may be difficult for a number of reasons:

- MPMs are a heterogeneous group of tumours, with the ability to mimic almost any other form of malignant tumour.
- The three main subtypes (epithelioid, biphasic and sarcomatoid) have numerous variants, as described in the 2004 WHO classification [8].
- The pleura is a common site for metastatic disease and reactive changes in the pleura may be confused with MPM.
- There are other uncommon benign and malignant pleural tumours.

Samples for diagnosis may vary widely: pleural effusions, small (closed) pleural biopsies, image-guided needle core biopsies, larger open or VATS surgical biopsy samples or debulking specimens. Surgical resection (extrapleural pneumonectomy) is rarely performed. In some cases, samples may also be obtained through autopsy.

Significant sampling errors can occur in effusion cytology and small biopsy samples, but also with larger surgical samples (though less common). Blind biopsies are not recommended because of risk of complications and are no longer indicated since the introduction of thoracic ultrasonography.

Cytological features in effusions may permit a diagnosis of malignancy but reported sensitivities vary widely. When a biopsy is not possible, appropriate clinical and radiological features may assist in suggesting a diagnosis of MPM. Many mesotheliomas lack significant cytological atypia and it is impossible to distinguish between benign, reactive mesothelial proliferations and MPM. Cytology sample cells may show variable atypia (usually low grade) and exhibit a mesothelial immune phenotype, but malignancy cannot be confirmed. The term 'atypical mesothelial proliferation' is useful in this context, but is insufficient for a diagnosis of MPM. This does not confirm the diagnosis of MPM, but leaves the possibility open [see below for fluorescence *in situ* hybridisation (FISH) testing].

In the vast majority of cases, it is necessary to have adequate tissue biopsies and the use of appropriate immunohistochemistry (IHC) for definitive, primary diagnosis of MPM. Consequently, definitive diagnosis of mesothelioma by frozen section is not recommended.

Tissue biopsy samples the abnormal (mesothelial) cell population and permits micro-anatomical assessment of the location of these cells. This is crucial to identify the extent of invasion. IHC is pivotal in confirming the mesothelial nature of cells, but cannot confirm their biological potential (see below). The larger the tissue biopsy and the more targeted the sampling approach [radiological or surgical (VATS or open procedure)], the more reliable and definitive the diagnosis.

Invasion may be difficult to recognise, especially when tissue sampling is limited, but identification may be assisted by IHC (see below). Early invasive mesothelioma is particularly difficult, often disguised by cutting artefacts or the malorientation of sections, but may be suspected if there is nodular mesothelial cell proliferation. If definitive invasion cannot be recognised, the diagnosis of 'atypical mesothelial proliferation' is appropriate, and further sampling may be indicated. Distinguishing MPM from organising fibrinous exudates (fibrinous/fibrous pleurisy) requires a full-thickness biopsy sample, with correct orientation of histological sections, perpendicular to the pleural surface. Pathological details of these differential diagnoses are discussed elsewhere [9, 10].

The most commonly used mesothelial markers are calretinin, cytokeratin 5/6, WT1 and podoplanin (D240). For (adeno)carcinoma, the most useful markers are TTF1, CEA and EP4 [9, 10]. Some markers have been advocated for, due to their distinction of benign (desmin) versus malignant mesothelial cells (EMA, p53, GLUT1, IMP3), but these methods lack reliability and are generally not recommended. Other immunohistochemical markers may be appropriate, depending on the differential diagnosis in a particular case. It is worth noting that although pan-cytokeratin markers are not specific in any way for mesothelial cells, or malignancy, in the appropriate context, they can be extremely useful in the diagnosis of sarcomatoid mesothelioma, which often does not express the usual markers mentioned above.

The use of *in situ* hybridisation (e.g., FISH) to detect homozygous deletion of p16 is strongly associated with malignancy; it is not specific to MPM, but may aid diagnosis [11, 12]. The role of this technique has yet to be defined and established. Comprehensive analysis of the genomic landscape of mesothelioma has not yet been completely defined, however the Tumour Genome Atlas study is currently underway (www.cancergenome.nih.gov).

Recommendation 2

A. Definitive diagnosis of MPM on effusion cytology specimens

- *Effusion cytology for definitive diagnosis of MPM remains a controversial topic and is still generally not recommended [IV, C].*
- *If effusion cytology is frankly malignant, the diagnosis may be strongly suggested but confirmation by biopsy, if possible, is recommended [A, no level of evidence].*
- *IHC is invaluable to characterise the nature of atypical effusion cells and sample preparation to facilitate IHC should be carried out if at all possible [A, no level of evidence].*

B. Definitive diagnosis of MPM on tissue biopsy specimens

- *The recognition of tissue invasion is required for definitive diagnosis of MPM [IV, A].*
- *Larger and directly targeted biopsy samples facilitate definitive diagnosis. Surgical-type samples are preferred for diagnosis [IV, A].*
- *A major subtype diagnosis (epithelioid, biphasic, sarcomatoid) should be given in all cases of MPM [IV, A].*

C. IHC in the diagnosis of MPM

- *IHC is recommended for all primary diagnoses of MPM [IV, A].*
- *At least two 'mesothelial' markers and at least two '(adeno) carcinoma' markers should be used [V, A].*
- *Sarcomatoid MPM often does not express usual 'mesothelial' markers [IV, A].*

staging

Staging procedures are standard in all tumours. Staging not only describes the anatomical extent of a tumour, but it also correlates with prognosis and helps in treatment decision-making. At least five staging systems for MPM have been reported. The first

Table 1. TNM staging according to the International Mesothelioma Interest Group (IMIG)/Union for International Cancer Control (UICC) [14]

Stage	TNM	Comments
Ia	T1a N0 M0	Primary tumour limited to ipsilateral parietal pleura
Ib	T1b N0 M0	As stage Ia plus focal involvement of visceral pleura
II	T2 N0 M0	As stage Ia or Ib plus confluent involvement of diaphragm or visceral pleura or involvement of the lung
III	Any T3 M0	Locally advanced tumour
	Any N1 M0	Ipsilateral, bronchopulmonary or hilar lymph node involvement
	Any N2 M0	Subcarinal or ipsilateral mediastinal lymph node involvement
IV	Any T4	Locally advanced, technically unresectable tumour
	Any N3	Contralateral mediastinal, internal mammary, and ipsilateral or contralateral supraclavicular lymph node involvement
	Any M1	Distant metastases

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staging system was introduced by Butchart, consisted of four stages and was based on observations from only 29 patients [13]. This system was succeeded by others developed by Mattson, Boutin and Sugarbaker who based their system on their own experiences. Most of these staging systems had limitations, being based on small numbers of patients. The most recent system was developed in 1995; it was presented by the International Mesothelioma Interest Group (IMIG) and is approved by the Union for International Cancer Control (UICC) (Table 1) [14]. The limitation of most classifications is their inaccuracy in describing tumour (T-) and node (N-)extent. Most staging systems are based on surgical interventions, as current imaging techniques have limited resolution. The IMIG is currently validating a new tumour-node-metastases (TNM) staging system, using a large retrospective dataset obtained from centres all over the world.

Although the IMIG staging system could predict prognosis [15], it failed to be an independent prognostic factor when analysed in the clinical setting using multivariate analysis [16]. After the first analysis of an IMIG/International Association for the Study of Lung Cancer (IASLC) database with data from 3101 patients with MPM, several areas of the current staging system have been defined as requiring modification [17]. Multivariable analyses showed significant differences in overall survival (OS) for most T stages, but not for T2 versus T1. Although a negative node status was of prognostic importance, no difference between N1 and N2 was noted.

Disease stage according to the TNM system, when assessed by surgical staging, is an important predictor of prognosis in patients with mesothelioma, and the TNM system is therefore the preferred system.

For decision-making, magnetic resonance imaging (MRI), using gadolinium, may improve delineation of the tumour with regard to the surrounding tissues, especially when surgical resection is considered to be a part of the treatment plan. This will also help to visualise foci that may be present in the diaphragm, pericardium or chest wall [18].

The use of positron emission tomography (PET) scanning is still under debate because MPM tends to only grow locally and metastases occur solely in patients with advanced disease. Discrimination of involved lymph nodes is difficult, due to anatomy and the limited spatial resolution of current PET scans [19]. PET scanning can be used in the diagnostic work-up when PET-avid sites in the thoracic cavity need to be identified to obtain representative tissue. Some studies use repeated PET scanning as a response criterion in addition to the CT scan. However, no randomised prospective studies have yet been published on this. One of the caveats in the evaluation of PET scanning is the false-positive outcome after pleurodesis. This can result in high activity for a period of more than 6 months after pleurodesis.

Recommendation 3
Staging for every patient with a confirmed diagnosis of MPM

- *In the absence of a uniform, robust and validated staging system, experts advocate the use of the most recent TNM-based IMIG/UICC classification [III, B].*
- *The use of MRI is only recommended in special situations when tumour delineation is necessary [II, B].*
- *The use of PET scanning is limited and can be used for localisation of tumour sites, distant metastases or early response to treatment, as part of a study protocol [III, B].*

front-line therapy for mesothelioma

Front-line chemotherapy improves survival of patients with unresectable MPM. Combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a longer survival compared with cisplatin alone in randomised phase III trials [20, 21]. Carboplatin is an acceptable alternative to cisplatin and may be better tolerated in the elderly population [22, 23].

Several phase II clinical trials are investigating the addition of novel agents to pemetrexed/cisplatin therapy. To date, no agent has demonstrated superior efficacy. Although the agent CBP501 (a G2 checkpoint abrogator) met its primary end point, it was not considered to improve upon the efficacy of standard chemotherapy. Trials of anti-angiogenic agents such as bevacizumab or sunitinib [24, 25] have so far failed to demonstrate improvement over standard treatment.

maintenance therapy for mesothelioma

The use of continuation or switch maintenance therapy with pemetrexed monotherapy has changed practice in the management of non-small-cell lung cancer, but is yet to be evaluated in

the mesothelioma setting. However, a phase II trial addressing this question [NCT01085630], led by the Cancer and Leukemia Group B (CALGB), is currently underway. Switch maintenance, with the focal adhesion kinase inhibitor defactinib (VS6063) versus placebo, is currently under evaluation in the COMMAND trial [NCT01870609]. Another phase III, switch maintenance, study of gemcitabine versus observation is currently on-going in the Netherlands (NVALT 19). A recent phase III study evaluating switch maintenance to thalidomide was negative [26].

second-line therapy for mesothelioma

There is currently no second-line standard of care. Phase III evaluation of pemetrexed monotherapy in previously treated patients was not associated with longer survival when compared with best supportive care (BSC). Post-study chemotherapy has been shown to be associated with significantly longer survival, with an adjusted hazard ratio of 0.56 [27]. Single agent vinorelbine has shown useful activity in phase II trials [28, 29], demonstrating a trend towards longer survival as was seen in the first-line study (MSO1) [30].

There are promising developments in the novel agent arena, for example, anti-mesothelin immunotoxin [31]. Immunotherapy targeting CTLA4 with tremelimumab [32] is under evaluation in a large global phase III trial [NCT01843374]. Recent data suggest that the PDL1, a putative biomarker for PD1/PDL1 therapy, is significantly expressed in mesotheliomas, particularly the sarcomatoid subtype. In the absence of standard second-line or further-line therapy, it is recommended that patients are enrolled into clinical trials.

personalised medicine

Individual patient meta-analyses have shown that response to chemotherapy or progression-free survival (PFS) [33] is correlated with a longer survival. Personalised therapy is therefore warranted, although currently it is in its infancy.

Mesotheliomas harbouring epigenetically silenced argininosuccinate synthase (AS) are sensitive to arginine-degrading enzymes pre-clinically. Open label, randomised clinical evaluation of ADI-PEG 30, in AS-negative patients, has confirmed efficacy with increased PFS compared with BSC alone. A study to evaluate ADI-PEG20, in combination with chemotherapy, in AS-negative mesothelioma [NCT02029690] is underway. Mutation of NF2 occurs in around 50% of mesotheliomas, sensitising inhibition of FAK [34–36]. Accordingly, this trial is stratifying patients by Merlin expression.

Recommendation 4
The first- and second-line treatment of unresectable mesothelioma

- *Anti-folate/platinum doublet is the only approved standard of care [I, A].*
- *Maintenance therapy (switch or continuation) has not yet improved the OS and patients should be included in these studies [II, A].*
- *Patients in good condition should be recommended to join studies in second line [II, A].*

radiotherapy

Radiotherapy (RT) can be used for different indications in mesothelioma: as palliation, as preventive treatment and as part of a multimodality treatment.

For patients suffering from pain (e.g., by chest wall invasion), RT, prescribing usually short course regimens, can be considered although the systematic review by Macleod et al. [37, 38] suggested that no high-quality evidence currently exists to support RT in treating pain in MPM.

In the case of palliation, the aim of RT is to relieve pain and it is recommended in cases of infiltration of the chest wall or permeation nodules by MPM. The treatment is usually given in short courses such as 1×10 or 3×8 Gy.

There is much debate whether a scar after thoracoscopy and/or drainage procedures should be irradiated prophylactically in order to reduce the likelihood of seeding metastases. It is probably best to recommend refraining from this procedure unless in the setting of a clinical trial [39], such as the United Kingdom 'PIT' study (ClinicalTrials.gov Identifier NCT01604005).

One randomised trial compared immediate drain site RT (21 Gy in three fractions) to observation in 61 patients treated between 1998 and 2004 [40]. The authors concluded that prophylactic drain site RT in MPM did not reduce the incidence of tumour seeding, as indicated by previous studies conducted in the 1990s. Quality control of RT, the use of first-line therapy and patient selection can probably explain the discrepancy of these results. Puncture points or thoracoscopy scars should be identified and checked for early irradiation as soon as the diagnosis of MPM is confirmed (expert advice). A randomised study of post-intervention radiation of the tract is accruing in the UK (PIT trial).

pre- and postoperative RT

Data from the literature are limited and come from retrospective studies only. In general, it is not recommended that RT is administered pre- or postoperatively with large fields (hemi-thoracic RT) outside the setting of a clinical trial. The results are poor, in terms of local control, because of the complex growth patterns in the diaphragmal gutters and in the lobar fissures. The field size and neighbouring vital organs contribute considerably to toxicity. Radiation-induced lung toxicity is especially high when the lung remains *in situ* after decortication. Improved 3D planning and the introduction of intensity-modulated RT (IMRT) seem to overcome most of these issues and allow the remaining tumour tissue to be properly irradiated. Currently, the 'SMART' study is investigating a short accelerated course of high-dose hemithoracic IMRT followed by extrapleural pneumonectomy (EPP) [41].

In the absence of phase III randomised trials, the establishment of a prospective controlled study evaluating the efficacy and tolerability of adjuvant RT post-EPP is recommended. In this study, a minimum recommended dose of 50 Gy, with a daily fraction size of 1.8–2 Gy should be given. In one study, hemithoracic irradiation (54 Gy) was given as adjuvant therapy after EPP [42]. The local recurrence rate was 13%, with a 4% local-only recurrence rate. In two other studies, hemithoracic irradiation, in lower doses, was given as part of a trimodality

therapy [43, 44]. The local recurrence rate was 50%–60%, with the highest rate within 12 months after completion of treatment. One paper addressed the pattern of failure after trimodality treatment with 3D conformal RT (3DCRT) and highly conformal RT (HCRT) in 39 patients. It was concluded that HCRT was superior to 3DCRT and in-field recurrences occurred only in those treated with 3DCRT (16%). It remains unclear whether technical issues of surgery, the irradiation or other issues (such as patient selection) are the reason for this observation. Higher doses of radiation have resulted in better local control [45]. It is therefore recommended that this is carried out only in specialised centres (expert advice).

choice of radiation type after EPP

Preliminary results of IMRT in the adjuvant setting after EPP seemed particularly promising. IMRT may provide good local control and protect at risk organs such as the heart or liver. Even after removal of one entire lung, fatal pulmonary toxicity remained a problem, with six out of 13 patients developing fatal pneumonitis [46]. To predict the risk of pneumonitis, the pulmonary dosimetric values V20, V5 and mean lung dose (MLD) should be specified: V20 [volume of both lungs minus the planning target volume (PTV)] should be less than 15% and MLD should be less than 10 Gy. These dosimetric constraints can also be used for conformal RT; dose–volume histograms of all target volumes [clinical target volumes (CTV) and PTV] and of all critical organs (contralateral lung, cardiac volume, spinal cord, oesophagus, liver, right and left kidney) should be clearly stated. With more dosimetric constraints on the residual contralateral lung, the risk of pneumonitis could be reduced to a minimum after EPP.

Further studies are needed to better establish the role of RT. Recent studies have underlined the importance of RT technique, both in terms of local control and toxicity. It is therefore recommended that RT is delivered in specialised centres (expert advice).

Recommendation 5
RT can be considered in the following cases

- *For palliation of pain related to tumour growth, RT can be considered [II, A].*
- *The use of RT to prevent growth in drainage tracts is not proved to be useful [III, A].*
- *RT can be given in an adjuvant setting after surgery or chemo-surgery to reduce the local failure rate. However, no evidence is available for its use as a standard treatment [II, A].*
- *When postoperative RT is applied, strict constraints must be adhered to in order to avoid toxicity to neighbouring organs, and special, tissue sparing, techniques should be used [II, A].*

surgery

Surgery is used for staging procedures or with palliative or curative intent. Using VATS or thoracoscopy, large biopsy samples can be obtained for proper pathological, molecular and IHC analyses. During this procedure, the local extent of the tumour can be examined. Pleural effusions can be drained and, if required, a decortication or pleurodesis can be carried out.

surgery for staging and palliation

As most of the staging systems involve the extension of the tumour on the pleural lining and invasion of muscle layers, thoracoscopic inspection of the pleural cavity is required. Besides this intervention, the staging procedure can also be used to control pleural effusion; perform a talc poudrage or even decortication in the case of a captured lung. One study compared VATS (partial) pleurectomy versus standard talc poudrage in 196 patients [47]. OS did not improve in the experimental arm, but control of pleural effusion and quality of life were significantly better at 6 and 12 months.

surgery with radical intent

Due to the intricate location and relation to other normal tissues, it is virtually impossible to obtain free resection margins. Therefore, the aim of this procedure is to obtain a macroscopic resection by removing as much visible tumour as possible, using different surgical procedures.

Initially, terms like 'radical' pleurectomy and decortication were used without proper description, making comparison between reported studies difficult. The IASLC established a working group to recommend uniform definitions for surgical procedures dealing with mesothelioma [48]. Currently, a clear distinction is made between EPP and pleurectomy/decortication (P/D) with different subcategories:

- *EPP* implies a complete en bloc removal of the involved parietal and visceral pleura including the whole ipsilateral lung. If required, the diaphragm and pericardium can also be resected.
- *Extended P/D* is the same procedure but the lung is left *in situ*: macroscopic complete resection is still the goal.
- *P/D* refers to removal of all gross tumour, without resection of the diaphragm or the pericardium.
- A partial pleurectomy entails partial removal of parietal and/or visceral pleura leaving gross tumour behind.

In a retrospective analysis of data from three large institutions, 663 patients who underwent an EPP or P/D were examined for survival outcome and toxicity [49]. The operative mortality was slightly higher (7%) for EPP compared with P/D (4%), with a higher OS of 16 months for P/D versus 12 months for EPP.

Some studies reported on a trimodality approach in order to obtain cure. Different combined-modality regimens have been investigated. Similar to locally advanced lung cancer, induction chemotherapy was considered to increase the complete resection rate of early-stage mesothelioma.

A Swiss multicentre trial reported on the additive effect of radiation therapy after a combination of three cycles of cisplatin and gemcitabine as induction therapy followed by EPP in patients with resectable MPM [50]. Macroscopic complete resection was obtained in 37/61 (61%) patients and 36 patients received postoperative RT. The 90-day mortality was 3.2%, but 62% of patients experienced one or more complications [empyema (16%) and bronchopleural fistula (9.5%)].

Table 2. Summary of recommendations

Diagnosis	**Recommendation 1** **Diagnostic procedures in MPM should encompass at least** • *Occupational history with emphasis on asbestos exposure [II, A]* • *CT scanning of the thorax [II, A]* • *In all patients who have a unilateral pleural thickening, with or without fluid and/or calcified asbestos plaques, efforts should be made to obtain a pathological specimen, as there are no specific clinical features of MPM [II, A]* • *There is no place for screening of persons exposed to asbestos [IV, B]* • *Tumour markers cannot distinguish MPM [II, B]*
Pathology	**Recommendation 2** **A. Definitive diagnosis of MPM on effusion cytology specimens** • *Effusion cytology for definitive diagnosis of MPM remains a controversial topic and is still generally not recommended [IV, C]* • *If effusion cytology is frankly malignant, the diagnosis may be strongly suggested but confirmation by biopsy, if possible, is recommended [A, no level of evidence]* • *IHC is invaluable to characterise the nature of atypical effusion cells and sample preparation to facilitate IHC should be carried out if at all possible [A, no level of evidence]* **B. Definitive diagnosis of MPM on tissue biopsy specimens** • *The recognition of tissue invasion is required for definitive diagnosis of MPM [IV, A]* • *Larger and directly targeted biopsy samples facilitate definitive diagnosis. Surgical-type samples are preferred for diagnosis [IV, A]* • *A major subtype diagnosis (epithelioid, biphasic, sarcomatoid) should be given in all cases of MPM [IV, A]* **C. IHC in the diagnosis of MPM** • *IHC is recommended for all primary diagnoses of MPM [IV, A]* • *At least two 'mesothelial' markers and at least two '(adeno)carcinoma' markers should be used [V, A]* • *Sarcomatoid MPM often does not express usual 'mesothelial' markers [IV, A]*
Staging	**Recommendation 3** **Staging for every patient with a confirmed diagnosis of MPM** • *In the absence of a uniform, robust and validated staging system, experts advocate the use of the most recent TNM-based IMIG/UICC classification [III, B]* • *The use of MRI is only recommended in special situations when tumour delineation is necessary [II, B]* • *The use of PET scanning is limited and can be used for localisation of tumour sites, distant metastases or early response to treatment, as part of a study protocol [III, B]*
Personalised medicine	**Recommendation 4** **The first- and second-line treatment of unresectable mesothelioma** • *Anti-folate/platinum doublet is the only approved standard of care [I, A]* • *Maintenance therapy (switch or continuation) has not yet improved the OS and patients should be included in these studies [II, A]* • *Patients in good condition should be recommended to join studies in second line [II, A]*
Radiotherapy	**Recommendation 5** **RT can be considered in the following cases** • *For palliation of pain related to tumour growth, RT can be considered [II, A]* • *The use of RT to prevent growth in drainage tracts is not proved to be useful [III, A]* • *RT can be given in an adjuvant setting after surgery or chemo-surgery to reduce the local failure rate. However, no evidence is available for its use as a standard treatment [II, A]* • *When postoperative RT is applied, strict constraints must be adhered to in order to avoid toxicity to neighbouring organs and special, tissue sparing, techniques should be used [II, A]*
Surgery	**Recommendation 6** **The indications for surgery are** • *For palliation of pleural effusions when chest tube drainage is not successful [II, A]* • *To obtain diagnostic samples of tumour tissue and to stage the patient [II, A]* • *To be part of a multimodality treatment, preferably as part of a study [II, A]* • *To perform a macroscopic complete resection by means of P/D or EPP [III, C]*

MPM, malignant pleural mesothelioma; CT, computed tomography; IHC, immunohistochemistry; TNM, tumour-node-metastasis; IMIG, International Mesothelioma Interest Group; UICC, Union for International Cancer Control; MRI, magnetic resonance imaging; PET, positron emission tomography; OS, overall survival; RT, radiotherapy; P/D, pleurectomy/decortication; EPP, extrapleural pneumonectomy.

For the patients undergoing EPP, an encouraging median survival time of 23 months was obtained.

In another retrospective study of trimodality therapy, 60 patients underwent induction chemotherapy (cisplatin/antifolate in 30 patients), followed by EPP and postoperative RT to 50 Gy [51]. The full treatment protocol could be applied in half of the patients.

The European Organisation for Research and Treatment of Cancer (EORTC) studied the feasibility of trimodality therapy in a phase II trial (EORTC 08031) with clearly defined timelines [52]. Patients with pathologically proven mesothelioma (up to stage cT3N1M0) received induction chemotherapy (cisplatin and pemetrexed × 3) followed by EPP within 21–56 days after the last dose of chemotherapy, in the absence of progressive disease and unacceptable toxicity.

A 'success of treatment' was defined as a patient who had received the full protocol and was alive after 90 days without progressive disease and without grade 3 or 4 toxicity. Of the 57 patients included, 42 had EPP (73.7%) after induction therapy. The 90-day mortality was 6.5%, with an OS of 18.4 months and progression-free median survival of 13.9 months. Only 24 patients (42.1%) met the definition of success, and therefore the primary end point was not reached.

A similar phase II trial in the USA, but without predefined time limits, included 77 patients from nine institutions. The operative mortality was 7% and median OS was 16.8 months [53].

Although trimodal therapy seemed feasible in selected patients with promising results, this concept was tested in the UK with the Mesothelioma and Radical Surgery 1 (MARS 1) trial. MARS 1 was designed as a randomised trial between EPP and no EPP after induction chemotherapy. In the feasibility study, 112 patients were entered in 11 centres, during a 3-year period. Only 50 patients (45%) could be randomised after induction therapy and 16 patients were randomly assigned to receive EPP. In this small group, there were three case fatalities, giving a mortality rate of 18.8% [54]. The median OS for patients undergoing EPP was 14 months, compared with 19 months for those not having EPP. It was concluded by the authors that trimodality therapy offers no benefit and in fact may harm patients. Therefore, a further study, MARS 2, was designed to assess the feasibility of randomisation into P/D and not EPP.

In a systematic review of EPP for mesothelioma, carried out in 2010, 34 studies from 26 institutions were evaluated [55]. Median OS after EPP varied from 9.4 to 27.5 months, with a 5-year survival rate from 0% to 24%. Overall mortality ranged from 0% to 11.8% and morbidity from 22% to 82%. The conclusion of this systematic review was that selected patients might benefit from EPP, especially when combined with induction or adjuvant therapy.

The safety and efficacy of trimodality treatment was assessed in a systematic review encompassing 16 studies (including 5 prospective trials). The median OS ranged from 12.8 to 46.9 months with perioperative mortality from 0% to 12.5% [56]. The authors concluded that trimodality therapy may offer acceptable perioperative outcomes and long-term survival in selected patients treated in specialised centres.

A multidisciplinary team with sufficient experience should provide recommendations on the suitability of patients for trimodality therapy.

Recommendation 6
The indications for surgery are

- *For palliation of pleural effusions when chest tube drainage is not successful [II, A].*
- *To obtain diagnostic samples of tumour tissue and to stage the patient [II, A].*
- *To be part of a multimodality treatment, preferably as part of a study [II, A].*
- *To perform a macroscopic complete resection by means of P/D or EPP [III, C].*

response evaluation and follow-up

It is advised that response evaluation is performed with CT scanning and the examinations performed at presentation. The follow-up of a patient will depend on the local recommendations or as dictated by the protocol in case of study participation.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 2. Levels of evidence and grades of recommendation have

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [57].

been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer-review process.

conflict of interest

PB has reported: consultant for Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer and Verastem; research funding from Bristol-Myers Squibb, Merck Sharp & Dohme. DF has reported: honoraria and advisory board for Lilly; research funding and advisory board for Pierre Fabre. SP has reported: consultancy, advisory boards and/or lectures for F. Hoffmann-La Roche Ltd, Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, Merck Sharp & Dohme, Amgen, Clovis, Astellas and Tesaro. The other authors have reported no potential conflicts of interest.

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