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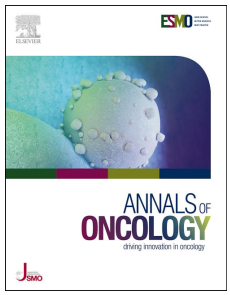

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Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Popat[1,2], P. Baas[3,4], C. Faivre-Finn[5], N. Girard[6], A.G. Nicholson[2,7], A.K. Nowak[8,9], I. Opitz[10], A. Scherpereel[11], M. Reck[12], on behalf of the ESMO Guidelines Committee*

[1]Royal Marsden Hospital NHS Foundation Trust, Section of Clinical Studies, Institute of Cancer Research, London; [2]National Centre for Mesothelioma Research, National Heart & Lung Institute, Imperial College London, London, UK; [3]Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam; [4]Leiden University Medical Center, Leiden, The Netherlands; [5]Department of Clinical Oncology, The Christie NHS Foundation Trust and University of Manchester, Manchester, UK; [6]Thorax Institute Curie Montsouris, Institut Curie, Paris, France; [7]Department of Histopathology, Royal Brompton & Harefield Hospitals, London; [8]National Centre for Asbestos Related Diseases, Centre for Respiratory Health, University of Western Australia, Nedlands; [9]Medical School, University of Western Australia, Nedlands, Australia; [10]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland; [11]Department of Pulmonary and Thoracic Oncology, University of Lille, CHU Lille, INSERM U1189, OncoThAI, Lille, France; [12]Department of Thoracic Oncology, LungenClinic Airway Research Center North (ARCN), German Center for Lung Research, Grosshansdorf, Germany.

Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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Highlights:

- This ESMO Clinical Practice Guideline provides key recommendations for managing malignant pleural mesothelioma.
- The optimal diagnostic methods, pathological evaluation and staging are described.
- The authors make recommendations on the role of surgery and macroscopic complete resection as part of multimodality therapy.
- The authors discuss optimal first-line, maintenance and salvage systemic therapies and immune checkpoint inhibitors.
- The authors discuss the role of prophylactic, radical and palliative radiotherapy and optimal supportive care.

INCIDENCE AND EPIDEMIOLOGY

Incidence

Incidence of malignant pleural mesothelioma (MPM) is generally higher in males than females and is attributed to historical differences in exposures with world-standardised incidence rates per 100,000 persons of 0.7 and 0.3 in the USA and 1.7 and 0.4 for Europe (for males and females, respectively). Incidence is highest in countries with greatest previous asbestos use such as the Netherlands, UK and Australia.[1] Due to a lag time of around 40 years between exposure and presentation, alongside relatively recent usage bans, incidence continues to rise in many countries. In Europe, rates of mesothelioma were rising sharply in the early 2000s, although there is longer term uncertainty on incidence given the high usage of asbestos domestically. Moreover, in the developing world, asbestos use continues to rise.[2] Several studies have reported better survival for females compared with males.[3]

Epidemiology

MPM is a relatively rare tumour classified by the World Health Organization (WHO) as directly attributable to all types of asbestos exposure and is therefore both an industrial and preventable disease. Asbestos use is currently banned in 67 countries[4] but continues to be high in Central Asia compared with Europe, with several countries, including the USA, having no ban but only usage restrictions. Mesothelioma is a disease of the elderly, being rare below the age of 50, with a sharp rise in incidence thereafter and a median age at diagnosis of 76.[5]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Patients typically present with one or more of dyspnoea, chest pain and weight loss. Symptoms may occur over many months. During physical examination, unilateral effusions are typical. It is important that a detailed occupational history is obtained for potential legal compensation.

Standard work-up (Table 1) includes:

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

Plain chest radiography lacks sufficient sensitivity and specificity for diagnosis and staging. Significant volumes of pleural effusions can mask pleural/chest lesions and make small, malignant pleural lesions undetectable. When an occupational history indicates significant asbestos exposure, or radiology is suggestive of mesothelioma, cytology can be used to detect malignant cells (but may yield false negatives), and immunohistochemical confirmation should be undertaken (see the Pathology and molecular biology subsection). Thoracoscopy is recommended to obtain adequate histology, to stage optimally and to allow pleural fluid evacuation (with or without pleurodesis).[6, 7] This can be carried out by pleuroscopy or by video-assisted thoracic surgery (VATS). MPM can be difficult to identify and therefore deep biopsies from ideally three sites are recommended. When thoracoscopy is not feasible or contraindicated, CT scan or ultrasound-guided biopsies are a good alternative. Other than obtaining a diagnosis, there are medico-legal reasons to confirm a MPM diagnosis. To date, there are no studies that recommend screening of patients who have had any (occupational) history of asbestos exposure.

Potential circulating tumour markers have been extensively tested; however, 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.[8] Carcinoembryonic antigen (CEA) is a negative marker and is not increased in MPM. It may be useful to rule out MPM when tissue analysis is inconclusive.

Pathology and molecular biology

Classification of mesothelioma has been updated in 2021 by the WHO.[9] Nearly all pleural mesotheliomas are diffuse, although very rarely tumours are localised,

defined by a single circumscribed mass with no clinical or histological evidence of spread.[10] There are three histological subtypes: epithelioid, sarcomatoid and biphasic. There is increased recognition, however, of the importance of architectural patterns and both cytological and stromal features.[9, 11] Also, following several independent, retrospective cohort studies, grading of epithelioid mesotheliomas is recommended for epithelioid subtypes.[9, 11, 12]

The diversity of histological features in mesotheliomas, combined with the pleura being a common site for metastatic disease and reactive changes showing significant atypia, makes diagnosis on morphology alone problematic and use of immunohistochemistry (IHC) is recommended. For epithelioid mesotheliomas, diagnosis can usually be made by using a combination of two 'mesothelioma-associated' markers [e.g. calretinin, Wilms tumour-1 (WT-1), cytokeratin 5/6] and two '(adeno)carcinoma-associated' markers [e.g. CEA, Ber-EP4, MOC-31], supplemented by other markers dependent on possibility of known, suspected or occult malignancies.[13] These other markers are far less specific and sensitive in sarcomatoid malignancies, although broad spectrum cytokeratins are positive in the majority of sarcomatoid mesotheliomas, while most sarcomas are negative.[13] There are also numerous other antibodies that may be of value to a greater or lesser extent, reviewed elsewhere, and pathologists should consider these as appropriate.[13] Exclusion of mesothelioma by identifying tumour molecular variants specific to certain sarcomas (e.g. primary pleural synovial sarcoma and t(x:18) may also be valuable.[13] Diffuse and localised mesotheliomas also need to be distinguished from the much rarer well-differentiated papillary mesothelial tumour (WDPMT) and adenomatoid tumour, both of mesothelial origin but with far more indolent behaviour.[9]

Samples used for diagnosis of pleural mesothelioma range from pleural effusion cytology, blind or image-guided needle core biopsies, open or VATS surgical biopsies samples to macroscopic complete resection (MCR), extended pleural decortication (EPD) and extrapleural pneumonectomy (EPP) samples. Opinions differ on the accuracy of cytological diagnosis and most will require a minimum of IHC on cell blocks to confirm mesothelial phenotype.[13, 14] In most cases, tissue biopsies that allow identification of subpleural invasion and its extent are required.

Thoracocentesis for the sole purpose of cytological diagnosis should be avoided as biopsy is more likely to provide a definitive diagnosis, to minimise the risk of permeation metastasis along thoracocentesis tracts. Definitive diagnosis can be made on single samples of any size but an expert consensus document recently proposed that sampling of at least three sites, if feasible, should be undertaken to increase the likelihood of robust subtyping and grading, with subsequent supporting evidence in a retrospective cohort.[11, 15] Expert consensus also proposed that imaging might be useful in targeting biopsies to specific areas of interest.[11]

In relation to the differential diagnoses of the epithelioid subtype versus mesothelial hyperplasia and sarcomatoid subtype versus reactive fibrous pleuritis, recent studies have identified that mesotheliomas often show loss of *BAP1* (more common in epithelioid subtype) and/or loss of *CDKN2A* (more common in sarcomatoid subtype). Loss of *BAP1* can be identified through IHC. Loss of *CDKN2A* requires molecular analysis, although loss of methylthioadenosine phosphorylase (MTAP) staining can act as a surrogate(with 96% specificity but 78% sensitivity[16]), as *MTAP* is located very close to *CDKN2A* at 9p21.3. It is recommended, however, that any laboratories using these antibodies or molecular assays have validated testing protocols.[9] Molecular testing should not be used in isolation of other findings as the field is far from fully understood. For example, the significance of focal loss of *MTAP* remains uncertain.

The 2021 WHO classification also recognises mesothelioma *in situ* (MIS).[9, 17] Until recently, such a diagnosis was not possible due to the morphological overlap between reactive and neoplastic atypia in mesothelial cells, although advances in molecular pathology have allowed MIS to be diagnosed through a combination of clinical, imaging and morphologic data, together with loss of BAP1 staining and/or loss of MTAP staining and/or homozygous deletion of *CDKN2A*.[9] The 2021 WHO classification also recommends grading of epithelioid mesotheliomas into a two-tier system of high- and low-grade, applicable to resections and biopsies.

Recommendations

Diagnostic procedures

- Diagnostic procedures should encompass at least occupational history with emphasis on asbestos exposure [II, A] and contrast-enhanced CT of the thorax and upper abdomen [II, A].
- In all patients who have a unilateral pleural thickening, with or without fluid and/or pleural plaques, efforts should be made to obtain a pathological specimen [II, A]. Thoracoscopy is preferred [III, B].
- The role of screening of persons exposed to asbestos for early MPM diagnosis is uncertain [IV, E].
- Circulating tumour markers cannot adequately distinguish MPM [II, D].

Pathological sampling

- Effusion cytology for MPM definitive diagnosis remains controversial and biopsy is recommended especially for histological subtyping and if clinical trial participation is considered [IV, B].
- Biopsy sampling of at least three distant sites when feasible, with possible targeting of areas of interest via thoracoscopic imaging, is recommended for robust subtyping and grading [IV, B].

Pathological classification

- Mesotheliomas should be classified using the current WHO criteria, including major subtype and documentation of architectural patterns, grading of epithelioid subtypes and stromal and cytologic features that refine prognostication [IV, A].
- Epithelioid mesotheliomas should be graded as low or high grade [IV, B], with this stratification used in ongoing and future trials and research [V, C].
- A diagnosis of mesothelioma *in situ* can be made in a multidisciplinary (clinical, imaging, morphological and molecular) setting, with molecular tests undertaken in validated laboratories [IV, A].

Use of IHC

- IHC is recommended for all primary diagnoses of MPM [IV, A].
- For epithelioid subtype, at least two ‘mesothelial’ markers and at least two ‘(adeno)carcinoma’ markers should be used [V, A].
- For sarcomatoid subtype, cytokeratin staining should be used [V, A].

- Loss of *BAP1* and/or *MTAP* as surrogate for *CDKN2A* deletion aid the MPM diagnosis and are required as part of the multidisciplinary diagnosis of mesothelioma *in situ*, undertaken in a strictly validated setting [IV, A].

STAGING AND RISK ASSESSMENT

The current 8th revision of the Union for International Cancer Control (UICC) TNM staging system for mesothelioma is based on the updated International Association for the Study of Lung Cancer (IASLC) mesothelioma staging project, using prospective data on >3500 patients treated both surgically and non-surgically, and is presented in Supplementary Table S1 and S2.[18] Contrast-enhanced CT of the thorax and upper abdomen is the recommended baseline imaging for diagnosis and staging for all patients. Clinical staging for MPM is challenging because of the nature of the disease and growth pattern; additional staging investigations may be required for surgical candidates. Currently different imaging protocols are being explored for better T-staging, specifically for lung parenchyma, diaphragm and chest wall infiltration—critical points if considering resection. An important change with regard to N-staging is that no difference in survival between clinical stages N0, N1 and N2 was identified,[19] and contralateral nodes are now classified as N2. For surgical candidates, consideration of mediastinal staging by endobronchial ultrasound (EBUS) or mediastinoscopy should be given to exclude contralateral involvement. Mediastinoscopy is recommended in case of potential resectable disease and if EBUS is negative despite FDG-avid lymph nodes or very small lymph nodes with a low chance of diagnostic yield by EBUS. For M-stage, although rarely metastatic at diagnosis, in surgical candidates it is important to exclude metastases by e.g. positron emission tomography (PET)-CT, due to survival differences between single- versus multiple-site cM1 cases.[20] Interpretation of PET-CT may be limited if previous chemical pleurodesis was carried out, but remains useful to exclude occult distant metastatic disease, and because of prognostic utility of maximum standard uptake values.[21] MRI may be useful for specific surgical questions.[22] Brain imaging is not routine but should be considered in case of clinical suspicion, although central nervous system involvement in early-stage disease is very rare.

Pathological staging

For T-stage, because of a well-documented survival difference between pT3 and pT4 tumours,[23] clear marking of the surgical specimen is critical for accurate pathological staging, as is the resection of previous biopsy or incision sites,[24] which have prognostic importance, as does the resected tumour weight.[25] For N-stage, hilar and mediastinal nodes are now classified as N1 and contralateral or all extra-thoracic nodal metastases are categorised as N2.[19] The significance of lymph node metastases at other locations such as the mammary vessels, intercostal or peri-diaphragmatic lymph nodes remains unknown.

Staging investigations

Pretreatment staging investigations are important for patient allocation to active treatment or supportive care. The patient's age, performance status (PS) and physiological functioning should be evaluated before extensive staging to consider if active therapy [systemic therapy, radiotherapy (RT) or surgery] will be tolerated. More extensive staging is recommended for those considered suitable for surgical resection with multimodality therapy.[26] A summary of staging recommendations proportionate to planned treatments is presented in Figure 1.

Recommendations

Staging

- The 8th revision of the UICC TNM staging system should be used for clinical and pathological staging [I, A].
- Non-invasive staging for a patient fit to undergo active treatment should include contrast-enhanced CT of the chest including the upper abdomen [III, B].
- For patients considered for MCR, additional staging including PET-CT should be carried out [III, B].

Pathological staging

- Pathological staging should be limited to MCR specimens with smaller specimens being clinically staged [V, B].

MANAGEMENT OF MPM

Treatment of mesothelioma

The treatment strategy (Figures 2-4) should take into account factors such as staging, histology, age, PS, comorbidities and the patient's preferences. Treatment decisions should ideally be discussed within a multidisciplinary tumour board who are experienced in mesothelioma management.

Role of surgery

Surgery for staging and palliation. Surgery plays a role in mesothelioma diagnosis, treatment and palliation. For diagnosis and treatment allocation, an accurate diagnostic procedure is crucial. For this purpose, sufficient numbers of large and deep pleural biopsies (either by VATS or mini-thoracotomy) should be obtained to prove microscopic subpleural fat tissue invasion and to allow for adequate immunohistochemical analysis. Uniportal approach for VATS has the advantage of reducing the risk of port-site recurrence. Surgical procedures for palliation such as effusion control should be primarily minimally invasive whenever possible, to minimise morbidity. A randomised controlled trial (MesoVATS)[27] comparing VATS partial pleurectomy with talc pleurodesis with the primary outcome of overall survival (OS) at 1 year showed no differences between groups. Therefore, currently talc poudrage via thoracoscopy remains the first procedure of choice for pleurodesis. VATS partial pleurectomy is a valid therapy option for patients fit enough for surgery with non-expanded lungs and who therefore would not benefit from chemical pleurodesis. Indwelling pleural catheters (IPC), which can be inserted in an outpatient setting and are convenient for patients to handle independently, are a very good alternative for rapid palliation of recurring pleural effusions, even with an entrapped lung.[28] Whether VATS-pleurectomy/decortication is more effective than IPC for patients with entrapped lungs is currently being investigated in a multicentre randomised feasibility phase III trial (MesoTRAP).[29]

Cytoreductive surgery with radical intent. MCR, defined as a procedure to remove all visible and palpable tumour within the hemithorax may be suitable for selected patients in selected centres with such experience, as part of multimodality treatment. MCR can be achieved by EPP consisting of *en bloc* resection of lung, pleura, pericardium and diaphragm or EPD, where visceral and parietal pleura are

removed together with pericardium and diaphragm. Both techniques include systematic mediastinal lymph node dissection for optimal staging. Although EPP was traditionally the technique of choice, in a systematic review of 1145 patients comparing outcomes after EPD with EPP, perioperative mortality (2.9% versus 6.8%, $P = 0.02$) and morbidity (27.9% versus 62.0%, $P < 0.001$) were significantly lower with EPD than EPP, whereas OS was comparable.[30] These results were further confirmed in a meta-analysis of 2903 patients treated with EPD or EPP.[31] Therefore, lung-sparing EPD should be considered as the first-choice surgical procedure, whereas EPP may be offered in highly selected patients when carried out in high-volume centres.

The role of surgery over non-surgical therapy has been addressed in only one randomised controlled trial: the Mesothelioma and Radical Surgery (MARS) trial, a small trial that identified poorer survival for EPP.[32] This UK trial was not powered to assess OS and was designed to evaluate feasibility of randomisation for EPP over non-surgical therapy. Nevertheless, the adjusted hazard ratio (HR) for OS between EPP and no-EPP groups was 2.75 [95% confidence interval (CI) 1.21-6.26]; however, the 12-month survival rate was not significantly different. Currently, a multicentre, randomised trial comparing EPD to no surgery (MARS-2) is ongoing (NCT02040272). By contrast, a variety of retrospective and prospective cohort studies and population and cancer registries suggest a survival advantage for patients undergoing surgery,[33, 34] although selection bias obviously plays an important role. Factors suggestive for surgery not being beneficial include sarcomatoid histology, contralateral mediastinal or supraclavicular lymph node involvement, extrathoracic disease, multilevel chest wall infiltration or inadequate cardiopulmonary reserve. Currently, no single prognostic factor, but rather prognostic scores, may be considered for patient treatment allocation.

The combination and sequence of modalities used within multimodality treatments in combination with surgery is not standardised. Platinum–pemetrexed chemotherapy (ChT) is usually given in either neoadjuvant and/or adjuvant paradigms to surgery, and the question of timing is currently being explored (NCT02436733). The role of adjuvant or neoadjuvant immunotherapy is unknown. The potential role of high-dose perioperative RT is discussed below.

First-line systemic therapy

Patients not suitable for MCR, as defined in a multidisciplinary tumour board, are candidates for a non-surgical approach with first-line systemic therapy. Systemic therapy should be considered for all MPM patients with PS 0-2. Two randomised phase III trials of all MPM histological subtypes demonstrated an improved OS for pemetrexed[35] (68% epithelioid; 24% non-epithelioid) or raltitrexed[36] (61%-75% epithelioid; 18%-31% non-epithelioid) with cisplatin compared with cisplatin monotherapy. For cisplatin–pemetrexed, folic acid and vitamin B12 supplementation was essential to reduce the pemetrexed toxicities. Despite limited literature, consensus suggests that administration of first-line ChT should not be delayed after diagnosis and should be considered before functional clinical deterioration as pemetrexed-based ChT can improve dyspnoea and quality of life (QoL).[37] ChT should be continued for up to six cycles in non-progressing patients, without unacceptable toxicity. Based on several large phase II trials, the CheckMate 743 trial and the MPM pemetrexed International Expanded Access Program showing comparable efficacy of first-line cisplatin–pemetrexed and carboplatin–pemetrexed; this latter combination is a reasonable alternative.[38, 39]

Targeted therapies in combination with first-line ChT. The phase III MAPS trial demonstrated a significant OS benefit for the addition of bevacizumab (15mg/kg), to cisplatin–pemetrexed as first-line treatment (HR 0.77, 95% CI 0.62-0.95, *P* = 0.0167; median OS 16.1 versus 18.8 months) in MPM (81% epithelioid; 19% non-epithelioid), with only mild and manageable increased toxicities and no negative impact on QoL.[40, 41] This study therefore represents another standard of care for unresectable MPM patients having platinum-based ChT; however, to date, bevacizumab has not been submitted for regulatory approval. Despite multiple studies, no other anti-angiogenic drugs or tyrosine kinase inhibitors (TKIs) have demonstrated a significant OS gain in phase III trials,[42] with trials of other targets ongoing.

Immunotherapy, alone or combined with other systemic therapy, as first-line treatment for MPM. Immune checkpoint inhibitors (ICIs) and other immunotherapies were first tested as salvage treatment in relapsed MPM with encouraging results (see Systemic therapy for second line and beyond section). In parallel, ICIs are also

being evaluated in the first-line setting. The phase III CheckMate 743 trial randomised 605 unresectable, treatment-naive, PS 0-1 MPM patients (75%-76% epithelioid; 24%-25% non-epithelioid) to combination nivolumab (3 mg/kg once every 2 weeks) plus low-dose ipilimumab (1 mg/kg once every 6 weeks) for up to 2 years (or until progression or unacceptable toxicity) versus cisplatin–pemetrexed or carboplatin–pemetrexed combination for up to six cycles.[39] OS was significantly increased with nivolumab–ipilimumab over ChT (HR 0.74, 95% CI 0.61-0.89, *P* = 0.002). Importantly, at 3 years of follow-up, 23% of patients treated by immunotherapy were alive versus only 15% with ChT. This OS gain was observed in the trial as a whole. In an exploratory analysis, immunotherapy demonstrated similar efficacy across both epithelioid and non-epithelioid histologies, but there was differential ChT efficacy by histology, translating to a larger immunotherapy OS benefit in non-epithelioid subtypes than epithelioid (HR 0.46, 95% CI 0.31-0.68 and HR 0.86, 95% CI 0.69-1.08, respectively). No significant improvement in progression-free survival (PFS) was observed between ICI and ChT arms (6.8 versus 7.2 months median, respectively; HR 1.00, 95% CI 0.82-1.21) or for objective response rates (ORRs) (39.6% versus 42.7%, respectively), with PFS initially inferior over the first 7 months. At 3 years of follow-up, however, 14% of patients treated by immunotherapy were alive and progression-free versus 1% with ChT. [43] There were no unexpected toxicities with ICIs and rates of grade 3-4 treatment-related adverse events were reported at similar rates between both arms. Any grade treatment-related adverse events led to discontinuation in 23.0% and 15.8% of patients, respectively. Thus, the balance of efficacy against toxicities was more favourable in non-epithelioid MPM patients than in epithelioid cases. Interestingly, patient-reported outcomes (PROs) data from this trial seemed to favour the immunotherapy arm in terms of QoL and of symptoms deterioration.[44] Taken together, these data suggest that nivolumab–ipilimumab is a new first-line option for unresectable MPM, more so for non-epithelioid disease, and is now approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), without histology or biomarker subtype restriction.

Several other experimental immunotherapy combinations are being explored in phase III trials, including the PrE0506/DREAM3R trial (NCT04334759) evaluating cisplatin–pemetrexed–durvalumab with maintenance durvalumab versus cisplatin–

pemetrexed, the ETOP 13-18/BEAT-meso trial (NCT03762018) comparing carboplatin–pemetrexed–bevacizumab followed by bevacizumab maintenance with carboplatin–pemetrexed–bevacizumab–atezolizumab followed by atezolizumab–bevacizumab maintenance, the CCTG IND227/IFCT-1901 trial (NCT02784171) comparing cisplatin–pemetrexed and carboplatin–pemetrexed with or without pembrolizumab for six cycles, followed by pembrolizumab maintenance. Other immunotherapy strategies have also been tested but, with discordant or negative results.[45] Dendritic cell vaccination was found to be promising in small trials, providing rationale for the randomised phase II-III trial DENIM (NCT03610360). In conclusion, nivolumab–ipilimumab represents a new standard-of-care option for inoperable first-line MPM patients alongside cisplatin–pemetrexed or carboplatin–pemetrexed and platinum–pemetrexed–bevacizumab. More studies are needed to firmly establish immunotherapy for all settings of MPM patients, however, either alone or in combination with standard treatment or targeted therapies, and to validate predictive biomarkers for patient selection.

Maintenance systemic therapy

There are no strong data in the literature suggesting a benefit for maintenance treatment after standard first-line ChT by platinum–pemetrexed. A recent randomised phase II trial, which closed prematurely due to poor recruitment, assessed pemetrexed continuation maintenance versus observation after four to six cycles of first-line platinum–pemetrexed. No improvement in PFS or OS was observed.[46] A randomised phase II trial (NVALT19; NTR4132) tested a switch to maintenance gemcitabine versus best supportive care (BSC) after four to six cycles of platinum–pemetrexed. PFS was significantly longer with gemcitabine, but there was no OS benefit.[47] Switch to maintenance defactinib [a focal adhesion kinase (FAK) inhibitor] versus placebo was also evaluated after first-line therapy,[48] but no OS benefit was observed regardless of biomarker (merlin) expression. While the addition of bevacizumab to first-line cisplatin–pemetrexed ChT is now considered a standard as discussed above, this trial was not designed to assess the contribution of bevacizumab maintenance.

Systemic therapy for second line and beyond

There is a limited evidence-base for active post-ChT second-line cytotoxic ChTs, evidenced by the VIM and PROMISE-meso trials, randomising against symptom control and pembrolizumab, respectively.[49, 50] Most other efforts in the second-line setting have focussed on signal-seeking trials, rather than large, randomised trials to definitively demonstrate benefits of second or subsequent-line treatment.

Role of ICIs. A number of trials of ICIs have been conducted in second or subsequent-line settings. These used *CTLA-4*, *PD-1* and *PD-L1* targeting agents. The DETERMINE study compared tremelimumab with placebo, and showed no OS benefit.[51] Subsequently, clinical trials of single-agent programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibition have shown modest activity, with ORRs ranging from 10% to 29% and highly variable PFS and OS.[52–56] The MAPS2 phase II trial randomised 125 second- and third-line MPM patients to nivolumab or nivolumab plus ipilimumab. Both arms reached their primary endpoint of a centrally reviewed response rate of over 40%, with an encouraging OS of 11.9 and 15.9 months, respectively.[57] The PROMISE-meso randomised phase III clinical trial compared pembrolizumab with second-line vinorelbine or gemcitabine monotherapy, and demonstrated no OS benefit for pembrolizumab despite a higher response rate; notably, 63% of patients on ChT crossed-over to receive pembrolizumab.[50] Discrepancies between PROMISE-meso and MAPS2 trials, beyond different designs could also be the consequence of different patient selection, as more MAPS2 patients may have had relatively indolent disease, not immediately progressing after first line. Indeed, in that trial a stratification factor was time of progression/relapse after first-line completion (>/<3 months), and rapidly progressive MAPS2 patients had the shortest OS, comparable with the OS of the pembrolizumab arm patients from the PROMISE-meso trial. Results of the CONFIRM study, a randomised phase III trial comparing nivolumab with placebo in the second- or third-line setting, demonstrated a significant OS (HR 0.72, 95% CI 0.55-0.94, P = 0.02) and PFS benefit, with greater benefit in epithelioid subtypes and no predictive utility of PD-L1 expression[58], but the recent OS benefit for first-line nivolumab–ipilimumab will reduce the relevance of results of ICI therapy in ICI pretreated patients.

Role of other systemic therapies. There is some evidence for retreatment with platinum–pemetrexed doublet. A recent meta-analysis suggested that reintroduction of platinum–pemetrexed or pemetrexed alone was amongst the most active options in the second-line setting.[59] Vinorelbine or gemcitabine monotherapy are used in practice and, while they demonstrate modest ORRs, there is no evidence of improved survival for vinorelbine over placebo/BSC from the randomised VIM trial[49] or for vinorelbine or gemcitabine over single-agent pembrolizumab from the randomised PROMISE-meso trial.[50] In a small randomised phase II trial (RAMES), combination gemcitabine–ramucirumab demonstrated an encouraging OS benefit over gemcitabine–placebo.[60]

Role of systemic therapy beyond second line

The CONFIRM study is the only clinical trial that provided randomised evidence in the third-line setting, versus placebo, in ICI-naive patients. At the moment, use of treatment beyond the second line remains speculative.

Personalised therapy

Predictors for standard-of-care therapies. A variety of biomarkers have been evaluated to predict benefit from bevacizumab[40] or nintedanib,[42] none with proven predictive utility.

PD-L1 is expressed in 40%-60% of MPM tumour cells, strongly in sarcomatoid cases.[61] This association may explain the reported worse outcomes in PD-L1 positive MPM.[61] In several studies, PD-L1 expression was loosely correlated with response to ICIs, alone or in combination with CTLA-4 inhibitors,[51, 53, 54, 56, 57, 62, 63] including exploratory analysis of CheckMate 743 where OS with ICIs was improved over ChT in PD-L1-positive MPM (≥1% of tumour cells, HR 0.69, 95% CI 0.55-0.87) but not in PD-L1-negative cases (HR 0.94, 95% CI 0.62-1.40),[39] although the optimal testing method and cut-off remain unknown. Tumour mutational burden (TMB) is low in MPM[64] and microsatellite instability is rare with only one of 74 cases in The Cancer Genome Atlas (TCGA) being hypermutated.[64]

Genomic alterations for precision medicine. In MPM, activating mutations are rare and genomic losses/alterations are more widespread. Mutations occur most frequently in *BAP1* (25%-60% of cases), *CDKN2A/B* (40%-45% of cases) and *NF2* genes (20%-50% of cases)[64]; these mutations are observed across all MPM histologies with some variability in frequency. Somatic *BAP1* losses/inactivating mutations occur in up to 60% of MPMs and support a classical two-hit tumour suppressor mechanism. Somatic *BAP1* mutations may have germline counterparts that define the *BAP1* hereditary cancer syndrome;[65] these mutations are observed in less than 5% of MPM patients. In patients with a family history of mesothelioma or cancers consistent with the *BAP1* hereditary cancer syndrome, referral to a clinical genetics service is recommended for germline *BAP1* mutation screening. *NF2* mutations were reported preclinically to predict the efficacy of mTOR inhibition, but clinical data have been disappointing to date. *NF2* mutations may lead, through altered merlin function to FAK inhibitor-induced synthetic lethality, and experimental approaches are ongoing, including the potential for YAP/TEAD inhibitors for tumours with dysregulation of the Hippo pathway. *CDKN2A/B* regulates the Rb and MDM2-TP53 tumour suppressor pathways; *CDKN2A* mutations may predict the efficacy of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with trials ongoing. Preclinical evidence and some series suggest that sensitivity to chemotherapeutic agents may be *BAP1*-driven and this has been observed also in MPM patients.[66, 67] *BAP1* loss has been evaluated as a possible biomarker of poly(ADP-ribose) polymerase (PARP) inhibitor efficacy. In a phase II trial of rucaparib in *BAP1*- or *BRCA1*-deficient patients (MiST1) rucaparib met the primary endpoint of disease control at 12 weeks (58%) [68] Other alterations that may be potentially actionable in MPM include *PTCH1* mutations (5% of cases) and loss of argininosuccinyl synthetase, amongst others. Clinical trials are ongoing, but the absence of selection of patients based on genotyping may hamper the identification of any signal of clinical efficacy; the Mesothelioma Stratified Therapy trial (NCT03654833) is investigating such selection of patients based on molecular characterisation. Mesothelin-directed agents have been, and continue to be, under intensive investigation in MPM.

Role of RT

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

Palliative RT for symptom control. For patients with pain (e.g. chest wall invasion or other thoracic structures), RT can be considered, although limited high-quality evidence currently exists to support RT for pain control.[69] Palliative RT is typically given in short courses of 1-10 fractions. A prospective, multicentre, single-arm study investigated 20 Gy in five fractions to painful areas and demonstrated that RT is effective in controlling pain five weeks after treatment completion.[70] A follow-on study is ongoing comparing this regime to a higher RT dose using advanced techniques (ISRCTN126981070). No prospective studies have specifically investigated the role of RT for palliation of cough or breathlessness.

Prophylactic RT of instrumentation tracts. For decades, the role of prophylactic irradiation of tracts after diagnostic or therapeutic pleural procedures to reduce the risk of subcutaneous metastasis was heavily debated. Three small randomised, controlled trials carried out in the pre-ChT era reported contradictory results. However, since the publication of the previous version of this ESMO Clinical Practice Guideline (CPG) in 2015, two large, randomised, multicentre studies were published, neither of them demonstrating a benefit to prophylactic tract irradiation. In both studies, the majority of patients received ChT. The first study (SMART trial) compared immediate RT (21 Gy in three fractions within 42 days of large-bore pleural interventions) with deferred RT.[71] No significant difference between the two arms in terms of tract metastases rate, chest pain, analgesia requirements, QoL and OS was demonstrated. A suggestion of benefit, however, was identified in subgroups i.e. epithelioid histology and those untreated with ChT (predefined analysis), and in those with RT protocol deviations. Nevertheless, the applicability of these results is limited by small numbers in each subgroup. The second study [Prophylactic Irradiation of Tracts, (PIT)] compared prophylactic RT of tracts (21 Gy in three fractions within 42 days of pleural intervention) with no RT. [72] No significant difference in incidence of chest wall metastases at 6 and 12 months was reported between the two groups, including when controlling for stratification factors (epithelioid histology versus others and ChT intention), although the cumulative incidence was higher at later timepoints in both trials e.g. month 24 in PIT. Skin

toxicity from RT was mild. Furthermore, contrary to a commonly held belief, PIT demonstrated that more than half of the patients who developed chest wall metastases did not report increased pain scores. Despite some differences in participants recruited, RT techniques and endpoints between the SMART and PIT trials, both studies conducted in the ChT era came to the same conclusion: that prophylactic irradiation of tracts is not justified in routine practice, although some have commented on statistical design and potential late benefit of post-operative RT (PORT). [73]

High-dose RT

Pre- and post-operative RT. The delivery of perioperative RT is challenging due to complex volumes of irradiation related to the growth patterns of the disease in the diaphragmal gutters and in the lobar fissures. Field sizes and dose delivered to neighbouring organs at risk (OAR) contribute considerably to toxicity. Radiation-induced lung toxicity is especially high when the lung remains *in situ* after decortication but improved 3-dimensional RT planning and the introduction of intensity-modulated RT (IMRT) have led to improved conformality of the high-dose radiation volumes and decreased toxicity. Strict dosimetric constraints should be implemented for target volumes and critical organs (contralateral lung, cardiac volume, spinal cord, oesophagus, liver, right and left kidney). Studies have underlined the importance of RT techniques, both in terms of local control and toxicity. It is therefore recommended that such RT be delivered in specialised centres.

Studies evaluating perioperative RT either before or after surgery (EPP or EPD) have shown that RT is feasible in the multimodality setting. Severe toxicities have been reported, however, particularly radiation pneumonitis in up to 46% of patients.[74] In patients who develop ≥3 grade radiation pneumonitis, a normal lung dose-volume effect was established,[75, 76] and strict dose constraints applied to the contralateral lung have resulted in reduction in severe pneumonitis.

Most of the studies evaluating RT in the multimodality setting were carried out in the context of EPP, which is no longer a standard surgical procedure. Since the last ESMO CPG, a randomised controlled trial in the post-operative setting was

published. The SAKK trial randomised 54 patients after EPP to either observation or adjuvant hemithoracic RT (3-dimensional conformal RT or IMRT; median dose 55.9 Gy).[77] The trial closed early due to poor accrual and was therefore underpowered. The primary endpoint was locoregional relapse-free survival with no significant difference observed between the two arms (9.4 months versus 7.6 months). Two prospective studies demonstrated that hemithoracic pleural IMRT for MPM is feasible, and has an acceptable toxicity profile after EPD with median survival up to 26 months.[78, 79] An important finding is that heart-dose correlates with symptomatic radiation pneumonitis; therefore, the dose to both lung and heart must be taken into consideration in order to reduce lung toxicity[80] and randomised trials are required to establish the role of hemithoracic IMRT after routine EPD. Preoperatively, the delivery of a short, accelerated course of high-dose IMRT (25 Gy in five fractions to the entire hemithorax with concomitant 5 Gy boost to areas at risk) followed by EPP within a week is possible. In a single centre phase II study of 96 patients. median OS was 24.4 months but 49% developed grade 3-4 complications within 30 days of EPP, significantly exceeding the 35% threshold set for feasibility (P = 0.0018). [81] One patient died of grade 5 pneumonia. Further confirmatory multicentre studies are needed.

There are limited data on the role of stereotactic ablative body RT (SABR) in patients with oligorecurrent MPM after multimodality treatment.[82]

Proton therapy. Proton therapy is an attractive alternative to standard photon RT due to its physical properties. They result in improved sparing of normal tissues (including contralateral lung, heart, stomach and kidneys and liver) when irradiating the pleura, compared with standard photons.[83] Several challenges, however, should be considered when treating with protons including range uncertainty, treating moving targets with significant tissue heterogeneity and requirements for adaptive treatment due to changes in anatomy during treatment course. Furthermore, to date, prospective studies on proton treatment in this setting are limited to mostly small and single centre studies.[84, 85] Data is particularly needed on the impact of proton therapy on a patient's QoL given its promise to reduce toxicity to OAR.

Recommendations

Role of surgery

- Surgery is recommended to obtain diagnostic samples of tumour tissue and to stage the patient [II, A], for palliation of pleural effusions when chest tube drainage is not successful [II, A] and to obtain diagnostic samples of tumour tissue and to stage the patient [II, A].
- Talc poudrage via thoracoscopy remains the first surgical procedure of choice for pleurodesis over VATS partial pleurectomy [I, A].
- MCR in combination to other modalities is recommended in selected MPM patients, to be carried out at experienced centres and to be discussed with a multidisciplinary team involving thoracic surgeons, pulmonologists, medical and radiation oncologists [III, C].
- EPD is a lung-preserving procedure and is preferred over EPP [III, B].

First-line systemic therapy

- Pemetrexed combined with cisplatin [I, A; ESMO-Magnitude of Clinical Benefit (ESMO-MCBS) v1.1 score: 3] (or alternatively carboplatin), and vitamin supplementation, up to six cycles is recommended as a first-line systemic therapy option [I, A].
- Combination of bevacizumab with platinum–pemetrexed is recommended as first-line systemic therapy option [I, A].
- Nivolumab plus ipilimumab, given up to 2 years equivalent dosing, is recommended as a first-line systemic therapy option regardless of histologies or PD-L1 status for unresectable MPM [I, A; ESMO-MCBS v1.1 score: 3].
- Maintenance gemcitabine is not routinely recommended in patients with non-progressive MPM but may prolong PFS and can be considered when the benefits of deferring progression outweigh the inconveniences and toxicities of ongoing treatment [II, C].
- Maintenance pemetrexed is not recommended in patients with non-progressive MPM after first-line platinum–pemetrexed ChT [II, E].

Systemic therapy for second line and beyond

- Single-agent pembrolizumab in immunotherapy-naive patients as second-line therapy has similar outcomes to single-agent ChT and is a treatment option [II, C].

- Single-agent nivolumab is superior to BSC in pretreated immunotherapy-naive patients and is a treatment option [I, A].
- Combination nivolumab–ipilimumab can be considered in immunotherapy-naive patients as a second- or third-line treatment option [II, C].
- Reintroduction of platinum–pemetrexed or pemetrexed ChT has second-line activity in selected circumstances, as suggested by ORRs [II, C].
- Single-agent gemcitabine or vinorelbine [II, B] have limited second-line activity, as suggested by ORRs or OS, with encouraging activity for gemcitabine–ramucirumab combination [III, C].
- There is no evidence basis for routine third-line therapy in MPM. Clinical trial participation should be considered [V, C].

Personalised therapy

- PD-L1 expression, immune micro-environment analyses, or TMB should not be used to select patients for treatment with ICIs [I, D].
- No current treatment options warrant routine molecular testing of MPM [III, D].
- Screening of *BAP1*-deficient MPM patients for germline mutation is not recommended in the absence of family history suspicious for a *BAP1* syndrome [V, D].

Role of RT

- RT can be considered for palliation of pain related to local infiltration of thoracic structures [III, B].
- The use of prophylactic RT of tracts after diagnostic or therapeutic pleural procedures to prevent chest wall metastases is not recommended [I, D].
- RT can be considered in an adjuvant setting after MCR to reduce the local failure rate; however, no evidence is available for its use as a standard treatment [II, D].
- When PORT is applied, strict thoracic critical organs dose constraints must be adhered to in order to avoid toxicity to OAR [II, A].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Supportive care

As systemic treatment for mesothelioma is not considered curative, maintaining palliative and supportive care is paramount to ensuring adequate QoL. Such measures should be cross-referenced with the ESMO CPGs on supportive and palliative care.[86] These guidelines are relevant for issues commonly occurring in MPM, including cancer-related fatigue, cancer pain, dyspnoea and advanced care planning. The above sections on RT and surgery also include guidance on the palliative use of these modalities. Night sweats are common but there is no consensus on management. While early parallel referral to palliative care services may be considered, a large, randomised trial has demonstrated that early (peridiagnostic) referral to specialist palliative care services does not improve health-related QoL.[87] Hence, specialist palliative care referrals can be reserved until clinically needed, at least in MPM patients who are cared for in centres with good access to supportive and palliative care. Nevertheless, despite an adequate PS at diagnosis, there remains a high symptom burden. Recurrent pleural effusion may be problematic for some patients and early pleurodesis is appropriate; however, if the lung is trapped, an indwelling catheter may promote pleurodesis and provide good symptom relief. There is no additional benefit for aggressive daily drainage over symptom-driven pleural draining in breathlessness control.[88]

People with mesothelioma have high rates of presarcopenia and malnutrition, which impact on QoL and physical activity,[89] and general guidance from the ESMO CPG on cancer cachexia in adult patients should be followed.[90]

Response evaluation and follow-up

It is advised that response evaluation is carried out with contrast-enhanced CT scanning and examinations carried out at presentation. The follow-up of a patient will depend on the local institutional recommendations. For clinical trial evaluation, the modified for mesothelioma RECISTv1.1 criteria are recommended.[91]

Recommendations

Palliative and supportive care

- Early access to specialist palliative care at the time of diagnosis does not improve QoL [I, D].
- Pleurodesis is useful in preventing recurrent effusions [I, A].

- For recurrent pleural effusions, an indwelling pleural catheter can provide good clinical benefit [I, B].
- For patients with indwelling pleural catheters, aggressive draining is not superior in breathlessness control to symptomatic drainage [I, E].

Surveillance

- Response evaluation imaging is best carried out with contrast-enhanced CT scanning [III, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPGs development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in Supplementary Table S3. ESMO-MCBS v1.1[92] was used to calculate scores for new therapies/indications approved by the EMA and/or the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA approval status of new therapies/indications is correct at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4.[93] Statements without grading were considered justified standard clinical practice by the authors.

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FIGURE LEGENDS

Figure 1: A staging summary for MPM.

Red: surgery; white: other aspects of management.

CT, computed tomography; EBUS, endobronchial ultrasound, EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; VATS, video-assisted thoracic surgery.

Modified from Optiz et al.[26] with permission.

Figure 2: Therapeutic strategy by treatment intent.

Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

Figure 3: Treatment algorithm for multimodality management of MPM.

Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments.

ChT, chemotherapy; MPM, malignant pleural mesothelioma; VATS, video-assisted thoracic surgery.

[a] Extended pleurectomy/decortication is the favoured approach.

[b] Current data supports multi-modality systemic therapy with platinum–pemetrexed.

Figure 4: Treatment algorithm for patients unsuitable for multimodality management (inoperable) of MPM.

Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

ICI, immune checkpoint inhibitor; MPM, malignant pleural mesothelioma; PS, performance status.

[a] ESMO-MCBS v1.1[92] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[b] For patients not previously exposed to ICI therapy.

Table 1: Table of diagnostic work-up

Initial presentation	**Diagnostic phase**
Occupational history	CT scan
Chest X-ray	Pleural fluid sampling (cytology)
General blood tests	Thoracoscopy or CT/US guided histological biopsy[a]

CT, computed tomography; US, ultrasound.

[a] Thoracoscopy with confirmatory biopsy is preferred.