BTS Guideline for the investigation and management of malignant pleural mesothelioma

On behalf of the BTS Mesothelioma Guideline Development Group

Post public consultation draft
For final approval by BTS Standards of Care Committee (SOCC)

Block yellow shows GDG response to public consultation

Light blue show GDG response to SOCC comments in June

Contact:

British Thoracic Society, 17 Doughty St, London WC1N 2PL

sally.welham@brit-thoracic.org.uk

louise.preston@brit-thoracic.org.uk

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Disclaimer:

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Glossary and abbreviations

ADC	Apparent diffusion coefficient
AJCC	American Joint Committee on Cancer
ASC	Active symptom control
AUC	Area under the curve
CI	Confidence interval
CT	Computed tomography
CRP	C-reactive protein level
DWI-MRI	Diffusion-weighted magnetic resonance imaging
EORTC	European Organisation for the Treatment of Cancer
EPD	Extended pleurectomy decortication
EPP	Extra-pleural pneumonectomy
GDG	Guideline Development Group
GPP	Good practice point
HA	Hyaluronic acid
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
IHC	Immunohistochemistry
IPC	Indwelling pleural catheter
IQR	Interquartile range
LDH	Lactate dehydrogenase
MDTs	Multi-disciplinary teams
MPF	Megakaryocyte potentiating factor
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
NCAT	National Cancer Action Team
NICE	National Institute for Health and Care Excellence
NLR	Neutrophil-to-lymphocyte ratio
OPN	Osteopontin
OS	Overall survival
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PICOT	Patient, Intervention, Comparison, Outcome and Time
PLR	Platelet-to-lymphocyte ratio
PP	Partial pleurectomy
PS	Performance status
PTM	Procedure-tract metastases
RCT	Randomised controlled trial
RT	Radiotherapy
SMRP	Soluble mesothelin related peptides
SOCC	Standards of Care Committee (British Thoracic Society)
SUV	Standardised uptake values
UICC	Union for International Cancer Control
US	Ultrasound
VAT	Video assisted thoracoscopy
WBC	Total white blood count

SECTION 1: INTRODUCTION

1.1 Aim of the Guideline

The key aim of this Guideline is to provide detailed, evidence-based guidance for the investigation of suspected malignant pleural mesothelioma (MPM) and the subsequent care and management of individuals with proven MPM. MPM is a rare cancer where the malignancy affects the pleura, a thin membrane of lubricating cells that lines the lungs and chest wall. The focus of this guideline is MPM as it is far more common than mesothelioma occurring in the abdomen. ~~There is approximately 1 case of peritoneal mesothelioma to every 12 cases of MPM (http://www.mesothelioma.uk.com/).~~ The 2016 Mesothelioma Audit data reported that in the UK in 2014 pleural mesothelioma accounted for 2179 cases (97%), with 70 peritoneal cases (approx. 3%) [1].

In 2007 the BTS statement on mesothelioma was published in response to a request from the National Health Executive in England [2]. The BTS has reviewed this statement and is of the opinion that the publication is no longer fit for purpose as an up to date reference guide for health care professionals. The 2007 statement did not attempt to provide a comprehensive review of all relevant published literature and since the publication of the statement the BTS has achieved NICE accreditation for its guideline production process. The Standards of Care Committee of the British Thoracic Society established a guideline development working group, chaired by Professor Nick Maskell and Dr Ian Woolhouse in 2014.

The main cause of mesothelioma is breathing in asbestos dust – approximately 85% of all male mesotheliomas are attributable to occupational asbestos exposures. The use of products containing asbestos was banned in the UK in 1999. The latency period between first exposure and development of the disease is very long, typically 30-40 years.

Cases of mesothelioma were recorded systematically from the late 1960s. The incidence of mesothelioma has been increasing steadily since then, and current predictions suggest there will continue to be approximately 2,500 deaths per year for the rest of this decade, before numbers begin to fall. (HSE http://www.hse.gov.uk/Statistics/causdis/mesothelioma/mesothelioma.pdf).

The largest dataset of MPM in the UK comes from the National Lung Cancer Audit report which described 8740 cases seen in hospitals in England and Wales between 2008 and 2012 [3]. Eighty three percent of patients were male and the median age at diagnosis was 73 years. Sixty seven per cent of patients received active anti-cancer treatment (chemotherapy, radiotherapy and surgery) and overall median survival was 9.5 months, with one year and three year survival rates of 41% and 12%, respectively. The report identified significant variation in treatment and outcomes across the UK which further highlights this need for an evidence-based guideline to facilitate the highest standards of care for all mesothelioma patients in the UK.

1.2 Intended users of the guideline and target patient populations

The Guideline will be primarily of interest to healthcare professionals working within the NHS, but the aim was to make the Guideline as applicable to international practice as possible so that it may be used across Europe and America as appropriate. Given the nature of MPM, the majority of the guideline will be relevant to secondary care-based specialists; however symptom recognition, management and follow up are all relevant to community based specialities.

Intended users:

- Primary care – GPs and practice nurses
- Hospital specialist teams in respiratory medicine, oncology, thoracic surgery and palliative care.
- Hospices / community teams
- Specialist nurses (including lung cancer and palliative care)
- Radiologists
- Pathologists

1.3 Areas covered by the guideline

Inclusion

- The epidemiology and incidence of mesothelioma in the UK and worldwide
- The preferred investigation pathway of suspected cases of MPM
- Consider special situations including:
    - Imaging
    - Histology /Cytology
    - Frail patient not fit for invasive tests
- Biomarkers
- Role of Mesothelioma MDTs
- Outline best practice in oncological management:
- Role of chemotherapy
- Place for radiotherapy
- Role of surgery
- Guidance on palliation in MPM
- Guidance on providing patients with relevant disease specific information, including medicolegal/compensation issues
- Summary of future therapeutic agents that might be available within next 5 years
- Summary of major MPM recommendations

1.4 Areas not covered by the guideline

Non pleural mesothelioma is excluded from this Guideline.

1.5 Limitations of the guideline

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations cited here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

1.6 Members of the guideline development group

The GDG was chaired by two respiratory consultants – Dr Ian Woolhouse and Professor Nick Maskell. The GDG had a wide membership with representation from respiratory medicine, thoracic surgery, medical oncology, radiotherapy, pathology and primary care. A patient representative was on the group for the duration of the process. Those on the group were not required to be BTS members. A full list of members can be seen at Appendix 1.

1.7 Representation

Professor Dean Fennell and Dr Jeremy Steel represented the Association of Cancer Physicians. Dr Anthony Edey represented the British Society of Thoracic Imaging. Professor Corinne Faivre-Finn represented the British Thoracic Oncology Group. Professor Keith Kerr represented the Royal College of Pathologists. Dr Ian Woolhouse represented the Royal College of Physicians. Mr John Edwards and Mr Apostolos Nakas represented the Society of Cardiothoracic Surgeons. Dr Corinne-Faivre-Finn and Dr Anthony Edey represented the Royal College of Radiologists. Dr Tim Peel represented the Association for Palliative Medicine. Dr Steve Holmes represented the Primary Care Respiratory Society UK. Ms Liz Darlison represented the Royal College of Nursing (RCN). Dr Graham Abbott, Mr Paul Astle and Mr John Gillies were the patient representatives on the group.

SECTION 2: METHODOLOGY OF GUIDELINE PRODUCTION

2.1 Establishment of guideline development group

The Guideline Development Group (GDG) was convened in June 2014, with the first meeting taking place in October 2014. The full GDG met six times during the development of the guideline and kept in close contact by teleconference and email throughout the process.

2.2 Methodology

This guideline is based on the best available evidence and follows the NICE accredited BTS guideline production process. The methodology used to write the guideline adheres strictly to the criteria as set by the AGREE II collaboration, which is available online www.agreetrust.org/resource-centre/agree-ii/ . The British Thoracic Society Standards of Care Committee guideline production manual is available at: https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/

2.3 Summary of key questions and literature search

Clinical questions were gathered in the PICOT (Patient, Intervention, Comparison, Outcome and Time) format. The key questions are summarised below.

- Which clinical features predict the presence of MPM?
- In patients with suspected MPM (post CXR) which imaging modality is best for diagnosis/staging and what technical factors are important?
- Should biomarkers (serum/fluid) be measured in MPM?
- Is there a staging system for MPM that determines management and predicts outcome?
- What factors determine prognosis and timing of treatment in MPM?
- What are the appropriate cyto-pathological approaches which allow diagnosis and sub-typing of MPM?
- Is the care of patients with suspected/proven MPM improved by discussion at a specialist MDT?
- Where histological confirmation is either not possible or not definite, what are criteria for a clinical diagnosis of MPM

- What is the optimum strategy for the management of pleural fluid in MPM?
- Is there a role for surgery in the management and treatment of patients with MPM?
- Is there a role for systemic anti-cancer treatment in MPM?
- Is there a role for radiotherapy in MPM?
- What treatment/interventions are effective for symptom control in MPM?
- What are the nursing care and information needs for patients with suspected and proven MPM?
- What is the most effective follow up strategy of patients with MPM?

The PICOT framework was used to define the scope of the guideline and formed the basis of the literature search. The literature search was conducted in December 2014 by York University. Systematic electronic database searches were conducted in order to identify all papers which may potentially be included in the guideline. For each question, the following databases were searched: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE In-Process, EMBASE and PUBMED.

The search was limited to papers published in English. The searches identified a total of 6173 abstracts. The full list of abstracts was retained and is kept in an archive. A second search was completed in July 2016 to search for relevant papers published between 2014 and 2016, yielding a further 1038 potentially relevant references. Additional references were included from personal collections as appropriate.

2.4 Appraisal of the evidence

An initial screen was completed to remove letters, conference papers, and news articles. Dr Woolhouse and Professor Maskell read the remaining abstracts (5129), marked those considered relevant to the scope of the Guideline and allocated each relevant abstract to a clinical question(s). 950 abstracts were allocated to clinical question(s). For the second search, the initial screen reduced the abstracts to 582. These were all read by Dr Woolhouse and Professor Maskell and 44 were allocated to clinical question(s). GDG members were allocated to work on the questions in small groups.

Each abstract was read and at least two members agreed whether the paper was relevant to the particular guideline section. Papers were excluded if the following applied:

- If the paper did not answer the clinical question concerned
- If it was a case report of less than 20 patients – however, this was not an absolute cut off. Professional judgment was applied and some smaller case reports were considered, and indeed some case reports of more than 20 patients were excluded.
- If the language of the full paper was not English.

Full papers were obtained for all relevant, or possibly relevant, abstracts.

At least two members of each small group independently appraised each paper using the SIGN critical appraisal checklists. An evidence level was assigned to each study using the SIGN methodology (Table 1).

Table 1: SIGN Levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

328

329 **Table 2: SIGN Grades of recommendations**

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+

330 *Good practice points (GPPs)*

√	Recommended best practice based on the clinical experience of the guideline development group

331

332 Each relevant paper was read in full by at least 2 members of the GDG and an evidence table entry
333 was completed for each paper used to support a recommendation/good practice point. The full
334 GDG reviewed each section during the regular meetings and consensus was reached. Evidence
335 tables are available to view online.

336 From the outset, it was acknowledged that there would be little high quality evidence for some of
337 the clinical questions identified. In this instance, low grade evidence was considered, along with
338 expert opinion via consensus at the meetings.

339 The following parameters were used by the GDG to appraise the evidence:

- How applicable the obtained evidence was in making recommendations for the defined target audience of this guideline.
- Whether the evidence was generalizable and relevant to the target population for the guideline.
- Whether there was a clear consistency in the evidence obtained to support recommendations.
- What the implications of recommendations would be on clinical practice in terms of resources and skilled expertise.

Cost-effectiveness was not considered in detail as in-depth economic analysis of recommendations falls outside of the BTS guideline production process. However, the GDG were asked to be mindful of any barriers to implementing the recommendations and GPPs.

Recommendations were graded from A to D as indicated by the strength of the evidence as shown in Table 2. In line with SIGN guidance, "minus" evidence was considered where necessary, but only in such instances when there were no published "plus" papers. In this context, any recommendation based on this evidence was made Grade D. GPP were included where research evidence was lacking, but the GDG felt it was important to highlight practical points which could improve the care of patients. Research recommendations were also highlighted and passed to the Chair of the SOCC on publication of the guideline.

2.5 Planned review and updating of the guideline

In line with BTS policy, this guideline will be reviewed by the SOCC within 5 years of publication and will then be marked clearly on the BTS website as "Valid", "Under review" or "Superseded".

2.6 Declarations of interest

BTS Declarations of Interest forms have been completed by all members for each year they were part of the GDG. Details of these forms can be obtained from BTS Head Office. Declarations of Interest was a standing item at each GDG meeting.

2.7 Stakeholders

Stakeholders were identified at the start of the process and where appropriate societies and organisations were contacted and asked to nominate a specific person to join the GDG. All stakeholder organisations were notified when the guideline was available for public consultation.

SECTION 3: CLINICAL FEATURES WHICH PREDICT THE PRESENCE OF MESOTHELIOMA

There is a paucity of evidence exploring clinical features specific for malignant pleural mesothelioma (MPM). Many of the studies are retrospective questionnaire-based case series which possess a major inherent recall bias in the diagnosed group making interpretation difficult.

There is consistency in the following risk factors and clinical features:

- Male preponderance is in keeping with occupational exposure[4].
- ~~High risk occupations are consistently, 'manufacture of non-metallic products'~~ High risk occupations ~~are those concerned with the manufacture or non-metallic products which~~ include production of asbestos sheets, brake and clutch linings, construction/demolition work, dock and ship yard workers, electricians, plumbers and launderers[5].
- The predicted life time risk of mesothelioma for British men born in the 1940s who did more than 10 years of work in the following categories, before the age 30 is as below: 5.9% for

carpenters, 2% for plumbers, electricians and painters, and 0.8% for other construction workers[6].

- Non-occupational routes of exposure involves: para exposure via a relative or partner ~~spouse~~, living in the vicinity of an asbestos factory and environmental exposure (low level)[4]. There is a higher risk of developing MPM from exposure to amphiboles (brown and blue asbestos) rather than chrysotile (white asbestos, the most commonly used form) [7]. The mean latency between asbestos exposure and developing the disease is 40 years for pleural and 46 years for peritoneal mesothelioma[4].
- There are rare familial cases linked to mutation of the breast cancer associated protein 1(BAP-1) gene[8].

Symptoms:

Chest pain and dyspnoea are the most common presenting symptoms but the relative frequency of these symptoms is not consistent in different studies. Other symptoms include weight loss, fevers and sweats [4 9 10]. See Table 3.

Clinical Signs:

Pleural effusion is often present. Other signs are variable (eg palpable lymph nodes)[10]. Right side predominance of the disease in the order of 1.6:1. might partially reflect the increased pleural surface area of the right hemithorax[4].

Table 3: Symptoms at initial presentation in 90 evaluable cases of MPM[10].

Symptom	No. of cases	%
Pain	62	69
Non-pleuritic	56	
Pleuritic	6	
Shortness of breath	53	59
Fever, chills or sweats	30	33
Weakness, fatigue or malaise	30	33
Cough	24	27
Weight loss	22	24
Anorexia	10	11
Sensation of heaviness or fullness in chest	6	7
Hoarseness	3	3
Early satiety	2	2
Myalgias	2	2
Others*	1 each	1

* other symptoms included aphonia and dysphagia, abdominal distension, sensation of pressure in right upper quadrant, nausea, bad taste in mouth, perceived tachycardia, and headache.

Usually the first investigation in patients with suspected mesothelioma will be a chest x-ray. The NICE Guideline on Investigation and Referral for Suspected Cancer gives guidance on when a chest x-ray should be offered in suspected MPM (Figure 1).

~~Figure 1 provides a summary from the NICE Guideline, outlining where chest X –rays should be offered.~~

Figure 1 :NICE NG 12. Referral criteria for suspected malignant pleural mesothelioma [11].

Offer an urgent chest X-ray (to be performed within 2 weeks) to assess for mesothelioma in people aged 40 and over if:

- **they have 2 or more of the following unexplained symptoms, or**
- **they have 1 or more of the following unexplained symptoms and have ever smoked, or**
- **they have 1 or more of the following unexplained symptoms and have been exposed to asbestos:**
  - **cough**
  - **fatigue**
  - **shortness of breath**
  - **chest pain**
  - **weight loss**
  - **appetite loss. [new 2015]**

Consider an urgent chest X-ray (to be performed within 2 weeks) to assess for mesothelioma in people aged 40 and over with either:

- **finger clubbing or**
- **chest signs compatible with pleural disease. [new 2015]**

Evidence statements:

Occupational exposure to asbestos is recalled in the majority of patients with MPM. High-risk occupations are ship building and construction / demolition work (including boiler repair, and working as a carpenter or electrician). **Level: 2-**

Symptoms are not specific to MPM. Common symptoms at presentation include chest pain and breathlessness. Less common symptoms at presentation include weight loss, fatigue, fever, and cough. **Level: 2-**

The commonest examination finding at presentation is a pleural effusion (with less than 1 in 10 presenting with lymphadenopathy or clubbing). **Level: 2-**

Recommendations:

- Do not rule out a diagnosis of MPM on the basis of symptoms and examination findings alone. **Grade D**.
- Offer an urgent chest x-ray to patients with symptoms and signs as outlined in NICE GL12 **Grade D.**
- Refer all patients with a chest x-ray suggestive of MPM urgently (via the 2 week wait suspected cancer pathway in England and Wales). Consider referral for further investigation in patients with persistent symptoms and history of asbestos exposure despite normal chest x-ray. **Grade D**.
- A thorough occupational history should be taken to cover all occupations throughout life. It is important to elicit para exposure by exploring details of relative and/or ~~spousal~~ partner occupations. **Grade D**.

~~**SECTION 4: OBTAINING A HISTOLOGICAL DIAGNOSIS**~~

~~Where ever possible a histological biopsy is required to confirm the diagnosis of mesothelioma. The best method for obtaining pleural tissue is already covered in the current BTS pleural disease guidelines. For this reason this topic was not covered in the PICO questions used in our initial mesothelioma literature search. The BTS Pleural Disease guideline can be downloaded at the following website: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/~~

~~In summary these BTS pleural guidelines state:~~

~~1. In patients with a symptomatic exudative pleural effusion where a diagnostic pleural aspiration is negative or inconclusive, thoracoscopy (either by local anaesthetic thoracoscopy or video assisted thoracic surgery (VATS)) is suggested as the next choice investigation since the procedure is relatively uncomplicated and pleurodesis can be performed at the same time if indicated.~~

~~2. If a contrast-enhanced thoracic CT scan of a patient shows a focal area of abnormal pleura (with or without a pleural effusion) an image-guided cutting needle biopsy has a high yield and low complication rates. This technique is particularly useful in patients who are unsuitable for thoracoscopy.~~

SECTION 4: STAGING SYSTEMS

~~The recommendations of the International Mesothelioma Interest Group (IMIG) [12] were adopted in the current (7th 8th Edition) of the AJCC/UICC Staging Manual (see figure 2). This staging system was originally derived following expert consensus, rather than from data. Data from surgical series around the world were combined following International Association for the Study of Lung Cancer (IASLC) Staging Committee initiatives from 2007 onwards. The IASLC Staging and Prognostic Factors Committee then established the Mesothelioma Staging Project (MSP) in 2011. This is an international initiative analysing comprehensive data. Initial analysis of retrospective data from 3101 cases has been reported [13]. Data have now been entered into a second phase of the MSP and analyses are awaited.~~

~~The vast majority of cases entered into the MSP, as summarised in 2012, were surgical (all but 84 of 3101). Even so, it was accepted that there are inadequacies of current staging, especially differentiating T1 vs T2, Stages I vs II and the groups of N staging. Greater detail of T and N descriptors was incorporated into the second phase of data collection within the IASLC MSP. It is expected that the 8th edition of the AJCC/UICC staging manual will be include a greater number of non-surgical cases.~~

In 2016 The International Association for the Study of Lung Cancer (IASLC) International Staging Committee published proposals for the revisions of the T, N and M descriptors for the eighth edition of the TNM classification of MPM [14]. This was an international, multi-institutional cohort study. The study population was patients with newly diagnosed (cytologically or histologically) MPM. Information was collected on the extent of disease, demographic characteristics, comorbidities, treatment, and survival. The dataset included data on 1987 patients with pathologically confirmed MPM from 29 centres on four continents. These comprised of 509 cases with only clinical staging information, 836 cases with only pathological staging information (i.e. surgical staging), and 642 cases with both clinical and pathological information available. Survival was examined for T, N and M categories according to the seventh edition staging system. Categories were then modified where appropriate to improve prognostic performance. Clinical and pathological T1a and T1b were combined into a single T1 classification. Clinical and pN1 and pN2 categories were collapsed into a

single N category comprising ipsilateral, intrathoracic nodal metastases (N1). Nodes previously categorized as N3 were reclassified as N2. M category remained unchanged (see figure 2). The proposed TNM groupings are shown in figure 3. Figure 4 shows the survival curves for each of the new TNM stage groupings. The prognostic performance comparisons for each stage demonstrated statistically significant hazard ratios for stage IB versus IA, stage IIIA versus II, and stage IV versus IIIB.

The Brigham and Women's Hospital Group proposed an alternative system to the AJCC/UICC staging system [15]. The alternative system is based on patients undergoing extrapleural pneumonectomy, but this has not been accepted widely nor proposals from it included in AJCC/UICC staging group.

The 2016 National Mesothelioma Audit reported that only 42% of MPM patients diagnosed in 2014 had stage recorded [1].

497 Figure 2: 8 ~~7~~th edition AJCC/UICC staging for malignant pleural mesothelioma

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
	T1a No involvement of the visceral pleura
	T1b Tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, and diaphragmatic, and visceral)
	Involvement of diaphragmatic muscle
	Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumor; tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features:
	Involvement of the endothoracic fascia
	Extension of tumor into mediastinal fat
	Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
	Nontransmural involvement of the pericardium
T4	Locally advanced technically unresectable tumor; tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features:
	Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
	Direct transdiaphragmatic extension of tumor to the peritoneum
	Direct extension of tumor to the contralateral pleura
	Direct extension of tumor to mediastinal organs
	Direct extension of tumor into the spine
	Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary and peridiaphragmatic nodes
N3	Metastases in contralateral mediastinal, contralateral internal mammary, and ipsilateral or contralateral supraclavicular lymph nodes

Distant metastasis (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

Stage groupings

Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

From Edge SP, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

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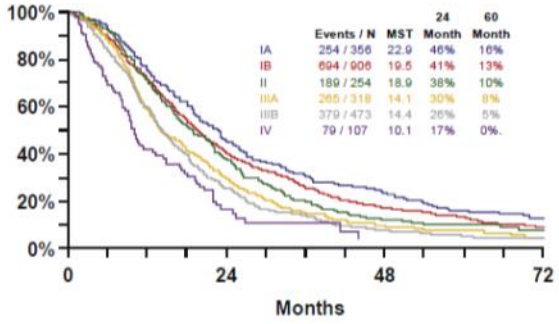
Figure ? : Overall survival accoding to best stage (proposed eighth edition).



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Evidence statements:

The proposed eighth edition of the IASLC TNM staging system predicts survival in surgically and non-surgically treated MPM patients. **Level 3**

~~The role of TNM staging in non-surgical patients is unclear.~~ ~~**Level 3**~~

Recommendation:

- Record staging of MPM according to the version 8 of the IASCL staging proposals**. Grade D.**
- ~~Consider staging MPM according to the latest version of the AJCC/UICC staging manual to aid stratification for clinical trials and to allow comparison of outcomes with the literature.~~ ~~**Grade D.**~~

SECTION 5: IMAGING MODALITIES FOR DIAGNOSING AND STAGING

The literature search revealed a large volume of evidence assessing the role of several imaging modalities in the diagnosis and staging of Malignant Pleural Mesothelioma (MPM). The use of ultrasound, computed tomography (CT), positron emission tomography (PET) and positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) were all included in the literature review.

A large number of the studies were conducted in mainland Europe or North America. Only a small number of studies were from the UK. The imaging characteristics of MPM are likely to be similar across the world and the demographic profile of patients included is similar to that of patients in the UK (male predominance, mean age >50years). Therefore the evidence was considered applicable to the UK population.

Evidence on diagnostic imaging

The majority of diagnostic evidence evaluates the role of imaging in differentiating benign from malignant pleural disease in general, rather than from MPM specifically. Numerous studies have demonstrated the utility of CT, PET-CT and MRI in the assessment of patients with suspected pleural malignancy [16]. These studies provide clear guidance on standard morphological characteristics of pleural malignancy using CT and MRI [17-20] and are summarised in Table 4 along with reported sensitivities and specificities [21-25].

Pleural malignancy is typically unilateral. Bilateral involvement is rare, accounting for as few as 3% of cases [18]. In 94% of cases of pleural malignancy there is a pleural effusion on the affected side. However, differentiation between MPM and metastatic pleural malignancy can be challenging. The presence of lung parenchymal involvement or mediastinal or hilar lymph node enlargement may help point towards metastatic pleural disease [24]. While the presence of pleural plaques is an indicator of prior asbestos exposure it is not a marker of malignancy *per se* and effusions can be found in this context as a result of benign asbestos-related pleural effusion.

Table 4: Diagnostic accuracy of different imaging modalities for diagnosing malignant vs benign pleural disease.

Morphology	Imaging Modality	Sensitivity (%)	Specificity (%)
Pleural thickening >1cm	CT US	35 – 47 42 (95% CI 26 – 61%)	64 – 94 95 (95% CI 74 – 99%)
Pleural nodularity	CT MRI US	37 – 48 48 42 (95% CI 26 – 61%)	86 – 97 86 100 (95% CI 82 – 100%)
Infiltration of the chest wall and/or diaphragm	CT MRI	17 – 29 44	100 100
Mediastinal pleural involvement	CT MRI	70 – 74 77	83 – 93 93
Interlobar fissure nodularity	CT	10	100

PET-CT can be used to provide useful functional information additional to morphology. Typically, areas of abnormal malignant pleural thickening have elevated maximal standardised uptake values (SUVmax) [26 27]. Thus, using a SUVmax threshold of >2.0 has been found to accurately differentiate malignant from benign pleural disease with a sensitivity of 88 – 100% and specificity of 88 – 92% [28-30]. In a meta-analysis of 11 PET-CT studies this technique had a pooled sensitivity of 95% (95% CI 92 – 97%) and specificity 82% (95% CI 76 – 88%) for differentiation of malignant from benign pleural disease [31]. Causes of false negatives include: small volume tumours and those with a low proliferative index, for instance early stage epithelioid mesothelioma. In addition, false positives may result from inflammatory diseases, tuberculous pleurisy, parapneumonic effusions and prior talc pleurodesis. One study, which included patients with prior talc pleurodesis, reported significantly lower specificity in comparison to other studies (specificity 35.3%), as a result of the high number of false positives in this group [32].

Studies using MRI have highlighted its potential in distinguishing benign from malignant pleural disease. Malignant pleural thickening tends to show inhomogenous hyperintensity on proton-density T2-weighted images and enhancement on T1-weighted images following gadolinium injection, in contradistinction to benign disease that is of low signal on both sequences. When these signal characteristics are combined with morphology and a pleural thickening >1cm the accuracy of MRI is very high for differentiation of benign from malignant disease with sensitivity of 100% and specificity of 95% in one study (95% confidence intervals not reported) [33]. More recent studies have highlighted potential utility for diffusion-weighted MR imaging (DWI-MRI) in differentiating pleural malignancy from benign pleural disease, with lower Apparent Diffusion Coefficient (ADC) values being demonstrated in pleural malignancy [34 35]. Coolen et al also performed DWI-MRI in a study of pleural malignancy and reported that inhomogeneous restriction in diffusion of the thickened pleura differentiates malignant from benign pleural disease with a sensitivity of 92.5% (95% CI 84-97% ~~83.7 – 96.8%~~) and specificity of 79% (95% CI 62-89% ~~62.2 – 89.3%~~) [36]. Gill et al

demonstrated that patients with epithelioid MPM have a significantly higher ADC value than those with non-epithelioid MPM and an ADC threshold of 1.1 could differentiate epithelioid MPM from sarcomatoid MPM with a sensitivity of 60% and specificity of 94% (95% confidence intervals not reported) [35]. These MRI data appear promising but are yet to be validated prospectively and importantly their added value in disease with atypical or equivocal CT signs is unclear.

Evidence on staging

Seventeen [28 37-52] studies were identified that evaluated the role of various imaging modalities when staging MPM. One systematic review [53] and 1 meta-analysis [54] were also identified in the literature. To a degree all imaging modalities are limited in accuracy of staging compared with the gold standard of post-operative histological staging and mediastinoscopic sampling of lymph nodes. However, assessment of limitations is made difficult by the relative infrequency of surgical resection and the use of comparator imaging techniques as the reference point in many of the studies.
Despite the overall benefits of CT scanning when initially assessing patients with suspected mesothelioma, CT performs poorly when compared against other modalities for staging of MPM. CT is particularly poor at assessing T4 stage where assessment of invasion through soft tissue such as diaphragm and chest wall is required. CT also performs poorly at lymph node staging, particularly when detecting involved N2 and N3 nodes. In one study, 37% of the patients were upstaged following a PET scan [38].

The role of MRI is limited in staging MPM [37 39 40 42 44 45 51]. However, MRI does perform better than CT, where tumour-soft tissue delineation is required. For example, MRI has a sensitivity and specificity of 87.5% and 87.5% for stage II disease, and 91% and 100% for stage III disease due to its superiority in detecting invasion into or through chest wall, endothoracic fascia, diaphragmatic muscle and mediastinal fat [39]. Table 5 provides a brief summary.

Table 5: Showing the sensitivity and specificity of CT, MRI and PET-CT in mesothelioma staging [39]

Imaging Modality	Stage II		Stage III	
	Sensitivity	Specificity	Sensitivity	Specificity
CT	100%	69.20%	75%	100%
MRI	87.50%	87.50%	91%	100%
PET-CT	100%	100%	100%	100%

It should also be noted that although Plathow et al [39] showed an accuracy of 100% and low inter-observer variability when staging MPM patients with PET-CT, compared to CT and MRI, the results of other smaller studies are mixed.

Evidence statements:

Overall reported diagnostic accuracy of CT in the detection of pleural malignancy is 68 - 97%, with specificity of 78-89%. **Level: 3.**

CT and ultrasound features of malignant pleural disease include pleural thickening >1cm, nodular pleural thickening, mediastinal pleural thickening and interlobar fissural nodularity. **Level: 3**.

Features favouring MPM over metastatic pleural malignancy are the presence of pleural plaques, involvement of the interlobar fissure and the absence of lung parenchymal involvement. **Level: 3**.

Overall reported diagnostic accuracy of PET-CT in the detection of pleural malignancy – sensitivity 88-95%, specificity 35-100%. **Level: 2+.**

False positives at PET-CT are common in TB pleuritis, inflammatory disorders of the pleura and previous talc pleurodesis. **Level: 3**.

Overall reported diagnostic accuracy of MRI in the detection of pleural malignancy – sensitivity 60-100%, specificity 73-95%. **Level: 2-.**

CT has limited accuracy for staging MPM using current staging systems. **Level: 3.**

MRI is better than CT at detecting invasion through diaphragm and T3 disease (invasion through muscle, bone, mediastinal fat) but has limited sensitivity in nodal staging. **Level: 3.**

Integrated PET-CT has the highest accuracy for staging MPM. It has better sensitivity across all three criteria T, N and M compared to CT and MRI. **Level: 2+.**

Recommendations:

- Offer ~~staging~~ CT thorax with contrast (optimised for pleural evaluation) as the initial cross-sectional imaging modality in the evaluation of patients with suspected MPM. **Grade D.**

- Use of PET-CT for aiding diagnosis of MPM is not recommended in patients who have had prior talc pleurodesis and caution should be employed in populations with a high prevalence of TB. **Grade D**.

- In patients where differentiating T stage will change management consider MRI. **Grade D.**

- In patients where excluding distant metastases will change management, offer PET-CT. **Grade D.**

SECTION 7: PATHOLOGICAL DIAGNOSIS

A diagnosis of MPM can be challenging because the tumour has a wide range of morphological appearances and may mimic many other epithelial or sarcomatoid malignancies. The best method for obtaining pleural tissue is already covered in the current BTS pleural disease guidelines. For this reason this topic was not covered in the PICOT questions used in our initial mesothelioma literature search. The BTS Pleural Disease guideline can be downloaded at the following website: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/

In summary the~~se~~ BTS pleural guideline~~s~~ states:

1. In patients with a symptomatic exudative pleural effusion where a diagnostic pleural aspiration is negative or inconclusive, thoracoscopy (either by local anaesthetic thoracoscopy or video assisted ~~thoracic~~ thoracoscopic surgery (VATS)) is suggested as the next choice investigation since the procedure is relatively uncomplicated and pleurodesis can be performed at the same time if indicated.

2. If a contrast-enhanced thoracic CT scan of a patient shows a focal area of abnormal pleura (with or without a pleural effusion) an image-guided cutting needle biopsy has a high yield and low complication rates. This technique is particularly useful in patients who are unsuitable for thoracoscopy.

The morphological features of MPM are well described elsewhere in the WHO classification of pleural tumours[55], and the guidelines of the International Mesothelioma panel [56],and are beyond the scope of this guideline. The importance of histological subtyping of MPM is highlighted in the national mesothelioma audit report which demonstrates that non-epithelioid histology was associated with significantly shorter overall survival in this cohort [1]. Table 6 highlights the main subtypes of mesothelioma and the differentce morphological features that might be present within each group.

Table 6: Mesothelioma subtypes

Epithelioid	Bisphasic	Sarcomatoid
Tubulopapillary	Any combination	Cellular storiform
Clear cell		Desmoplastic
Adenomatoid		Leiomyoid
Solid		Chondroid
Small cell		Lymphohistiocytoid
Pleomorphic		

The literature search identified 176 papers related to the use of ancillary techniques to improve the diagnosis of malignant mesothelioma (see Appendix 2 for full list of pathology papers). Several were rejected due to study age, the applicability of the diagnostic tests, small numbers of cases, or an inability to extract data, resulting in 70 papers being selected for review. All were retrospective case series. Case numbers varied greatly, from 23 up to 596 cases, and were often very heterogeneous case mixtures. Immunohistochemistry (IHC) was by far the most frequently considered ancillary diagnostic technique. Other approaches used included electron microscopy, chromosomal analysis, microRNA expression, DNA methylation, mRNA expression array, fluid chemistry assay, cytofluorimetry, flow cytometry, and insitu hybridization.

The quality of the evidence reviewed was highly variable. Some of the papers were unique descriptions of unusual diagnostic approaches without comparators. In some studies the origin of the tumour tissue was not clear and others used autopsy material. Many of the older studies, especially those published prior to 1990, use clones of primary antibody or other immunohistochemical techniques that are no longer used or available. More recent studies typically used contemporary reagents that are available and applicable in the UK.

Summary of individual immunohistochemistry evidence

A large number of IHC markers have been reviewed and are summarised in ~~the~~ Table 7 below, with sensitivity and specificity values where available. It should be noted that the sensitivity and specificity of many of these markers are reduced in sarcomatoid MPM, which frequently does not express any of the typical 'mesothelial' markers. In this scenario, expression of keratins may be the only demonstrable feature, which is helpful but non-specific. Additionally, discriminating malignant from benign mesothelial proliferations is not reliable using IHC markers.

Table 7: Summary of IHC markers

Marker	Immunoreactivity for mesothelioma	Specimen	Sensitivity (%)	Specificity (%)
Calretinin	Positive staining	Histological	89 – 100 (Refs[57],[58-72]	61 – 95 (Refs [57-72]
Thrombomodulin	Positive staining	Histological	52 – 100 (Refs [57-59 61-63 65 69 73-81]	56 – 98 (Refs [57-59 61-63 65 69 73-81] 36 – 47.5

		Cytological	67 – 86 (Refs [77 78]	(Refs [77 78]
CK5/6	Positive staining	Histological	89 – 100 (Refs [57-60 62 65 82]	58 – 97 (Refs [57-60 62 65 82]
MOC31	Negative staining	Histological Cytological	89 – 94 (Refs [57 60 66 83] 88 (Ref [84]	86 – 90 (Refs [57 60 66 83] 76 (Ref [84]
BerEp4	Negative staining	Histological Cytological	84 – 97 (Refs [57 61 62 66 67 76 79 83 85] 71 – 84 (Refs [77 84 86 87]	65 – 100 (Refs [57 61 62 66 67 76 79 83 85] 83 – 100 (Refs [77 84 86 87]
CEA	Negative staining	Histological Cytological	90 – 100 (Refs [57 58 61-63 66-68 74 76 83 85 88 89] 71 – 100 (Refs [77 84 86 87]	53 – 97 (Refs [57 58 61-63 66-68 74 76 83 85 88 89] 42 – 100 (Refs [77 84 86 87]
TTF-1	Negative staining	Histological	93 – 100 (Refs [58 62 66 68 90 91]	53 – 77 (Refs [58 62 66 68 90 91]
CAM 5.2	Positive staining	Histological	97 – 100 (refs [58 66 67 71 76 85]	0 – 1.5 (refs [58 66 67 71 76 85]
EMA	Positive staining (cell membrane)	Histological Cytological	74.5 – 90 (Refs [58 61 62 64 66 76 85 92] 58 – 78 (Refs [77 86 87]	7 – 87 (Refs [58 61 62 64 66 76 85 92] 8 – 99 (Refs [77 86 87]
Leu-M1	Negative staining	Histological Cytological	94 – 100 (Refs [67 74 85] 86 (Refs [84 86]	53 – 77 (Refs [67 74 85] 65 (Refs [84 86]
Vimentin	Positive staining	Histological Cytological	60 – 85 (Refs [61 74 76 85 88] 79 – 84 (Refs [77 86]	64 – 98 (Refs [61 74 76 85 88] 38 – 50 (Refs [77 86]
HBME-1	Positive staining	Histological Cytological	59 – 100 (Refs [58 61 63 67 73 76 79 81 83 93] 71 – 89 (Refs [77 78]	28 – 76 (Refs [58 61 63 67 73 76 79 81 83 93] 36 – 52 (Refs [77 78]
WT-1	Positive staining	Histological	72 – 91 (Refs [58-60 66	88 – 100 (Refs [58-60 66

			94]	94]
CD15	Negative staining	Histological	68 – 95 (Refs [58 60-63 76]	73 – 100 (Refs [58 60-63 76]
B72.3	Negative staining	Histological	90 – 100 (Refs [58 62 74 79 83 85]	4.2 – 90 (Refs [58 62 74 79 83 85]
BG8	Negative staining	Histological	83 – 94 (Refs [58 94]	88.5 – 98 (Refs [58 94]
Desmin	Positive staining	Histological	45 – 90 (Refs [85 92]	85 – 100 (Refs [85 92]
p53	Positive staining	Histological	45 – 95 (Refs [64 92 95]	47 – 100 (Refs [64 92 95]
GLUT-1	Positive staining	Histological	58 – 100 (Refs [96 97]	100 (Refs [96 97]
CD90	Positive staining	Histological	73 (Ref [98]	82 (Refs [98]
Claudin-4	Negative staining	Histological	100 (Ref[99]	99 (Ref[99]
D-240	Positive staining	Histological	72.5 (Ref [100]	93.5 (Ref [100]

Additional Techniques

Wu et al [101] examined p16 FISH to discriminate reactive from malignant mesothelium in 60 patients. Hemi or homozygous deletion of p16 was not seen in fibrous pleurisy (FP) but was detected in 66.7% of epithelioid MPM, 87.5% of biphasic MPM and 100% of sarcomatoid cases, highlighting potential utility in the differentiation of MPM from fibr~~in~~ous pleurisy. Hida et al [102] performed BAP1 and p16FISH in 40 cases of MPM and 20 cases of inflammatory pleuritis. All inflammatory cases and only 3 mesothelioma cases were negative for both. The presence of BAP1 and or p16FISH ~~can~~ may therefore be helpful in differentiating MPM from benign mesothelial proliferation.

Diagnosis in Cytology

This remains a controversial subject. The reliability of an MPM diagnosis on effusion cytology is highly variable, (sensitivity ranging from 16-73%, Walters 2011[103], Segal 2013 [104]) and is very much dependent upon cytologist experience. Some centres will send ~~slot~~ clot/cell block sections for the homozygous deletion of the 9p21 band (p16) which can increase diagnostic certainty.

Evidence statements:

Glut1 immunohistochemistry and p16FISH have potential for discriminating benign from malignant mesothelium. **Level 3.**

The sensitivity of pleural fluid cytology for the diagnosis of MPM is highly variable and is dependent on the cytologist's experience. **Level 3.**

Positive immunohistochemistry markers for MPM include calretinin, thrombomodulin, CK5/6, CAM5.2, EMA, Vimentin, GLUT-1, HBME-1, WT-1, P53. Overall sensitivity is 45 – 100%. **Level 3.**

Negative immunohistochemistry markers for MPM include Ber-Ep4, MOC-31, CEA, Leu-1, CD15, TTF-1, B72.3. Overall specificity is 53 – 100%. **Level 3**.

A combination of 2 positive mesothelial markers and 2 negative adenocarcinoma markers increases diagnostic accuracy. **Level 3**.

Diagnostic accuracy of immunohistochemistry markers is reduced in sarcomatoid MPM. **Level 3.**

Accurate subtyping of immunochemistry markers is reduced in sarcomatoid MPM. **Level 3.**

~~Glut1 immunohistochemistry and p16 FISH have potential for discriminating benign from malignant mesothelium. **Level 3**.~~

~~The sensitivity of pleural fluid cytology for the diagnosis of MPM is highly variable and is dependent on the cytologist's experience. **Level 3**.~~

Recommendations:

- Immunohistochemistry is recommended for the differential diagnosis of MPM in both biopsy and cytology type specimens. **Grade D**.
- A combination of at least two positive mesothelial (Calretinin, Cytokeratin 5/6, Wilms Tumour 1, D-240) and at least two negative adenocarcinoma immunohistochemical markers (TTF1, CEA, Ber-EP4) should be used in the differential diagnosis of MPM. (*Markers listed in likely order of value).* **Grade D**.
- Do not rely on cytology alone to make a diagnosis of MPM unless biopsy is not possible or not required to determine treatment due to patient wishes or poor performance status. **Grade D**.
- Pathologists should report the histological subtype of MPM in all cases. **Grade D.**

Good Practice Points:

- ✓ Biopsies from patients with suspected MPM should be reviewed by a pathologist experienced in the diagnosis of MPM and a second opinion should be sought if there is uncertainty over the diagnosis.

SECTION 7: USE OF BIOMARKERS

The literature search revealed a large volume of evidence, exploring different biomarkers that may have a role in MPM. Literature on at least 20 markers tested in serum, plasma, pleural fluid and exhaled breath were reviewed. A number of markers were assessed in exploratory studies with no further validation, and such markers have not been considered further given the lack of validation studies.

Several markers such as Mesothelin, Fibulin-3, Osteopontin and Megakaryocyte potentiating factor (MPF) have been extensively studied internationally. Individual studies and controlled meta-analyses specifically looking at these markers were identified and reviewed. Significant heterogeneity was noted between study populations. In particular, there was wide variability in comparator groups and disease prevalence. For example, comparator groups include normal controls, asbestos exposed well individuals, patients with benign effusions, and patients with non-mesothelioma malignant effusions. In some areas, the prevalence of mesothelioma in the sampled population was above 30%, in others less than 5%. The cut off value for markers varied in most studies.

Although most studies included sarcomatoid mesothelioma, this made up only a small proportion of the overall cohort ~~or~~ of any single study.

Evidence on diagnostic markers:

The most robust body of evidence at present for diagnosis of MPM is for Soluble Mesothelin Related Peptides (SMRP) and Osteopontin, as summarised below:

- A meta-analysis by Cui et al [105] reviewed 28 publications totalling 7550 patients (1562 MPM and 5988 non-MPM patients) which confirmed serum SMRP to have an overall sensitivity of 60% and a specificity of 81%, with an AUC of 0.734.
- The same review also demonstrated that pleural fluid SMRP has an overall sensitivity of 75%, specificity 76% and AUC 0.809 (Total number of patients 1506; 460 MPM and 1046 non-MPM)
- Summary sensitivities and specificities for SMRP and Osteopontin - from 2 meta-analyses by Hu et al [106], reviewing 6 publications with a total of 906 patients, and Lin et al [107] reviewing 7 publications with a total of 1096 patients, are shown in ~~the~~ Table 8 ~~below~~.

Table 8: Summary sensitivities and specificities for SMRP and Osteopontin

		sensitivity	specificity	AUC
SMRP	serum	60 (CI 56-64)	81 (CI 78-83)	0.734
	pleural fluid	75 (CI 69-80)	76 (CI 71-82)	0.809
OPN	serum + plasma	65 (CI 60-70)	81 (78-85)	0.83
	Serum + Plasma	57 (CI 52-61)	81 (79-84)	0.85

There were a number of studies on Fibulin-3, representing a smaller body of evidence than that above for SMRP and OPN. These are summarised in Table 9 ~~below~~:

Table 9: Summary sensitivities and specificities for Fibulin-3

		Sensitivity	Specificity	AUC	Cut off (ng/ml)
Pass et al [108]	Plasma	100	100	1	~~32.9~~ 33*
	Plasma	~~94.6~~ 95	~~95.7~~ 96	0.99	~~52.8~~ 53†
	Pleural fluid	~~83.8~~ 84	92~~.4~~	0.93	346~~.01~~
Agha et al [109]	Serum	88	81.8	0.776	~~66.5~~ 67
	Pleural fluid	72~~.3~~	80	0.878	150
Elgazzar et al [110]	Serum	100	~~96.7~~ 97	0.98	54~~.3~~
	Pleural fluid	90	~~96.7~~ 97	0.94	520
Creaney et al [111]	Plasma	22	95	n/a	52
	Plasma	48	71	0.671	29
	Pleural fluid	59	52	0.588	346
Kirschner [112]	Plasma	~~13.5~~ 14 ~~12.7~~ 13	~~96.6~~ 97 ~~87.5~~ 88‡‡		29‡

*Detroit cohort † New York cohort

‡ Sydney cohort ‡‡Vienna cohort

Markers for disease monitoring and assessment of progression

Sixteen [112-127] papers were reviewed in relation to above. Again, SMRP is the most widely studied marker but other biomarkers such as Fibulin-3, Osteopontin, Megakaryocyte potentiating factor (MPF) and Hyaluronic acid (HA) were also assessed. Study populations are heterogeneous with regards to their management. Disease progression/stability in these studies has in general been assessed by the use of the modified response evaluation criteria in solid tumours (RECIST).

Overall:

- SMRP shows a positive correlation with tumour bulk [113].
- In patients who had Extra Pleural Pneumonectomy there was a significant drop in SMRP levels (on average 54%). Despite the relationship with tumour bulk, there is no significant correlation with increasing disease stage.
- Mean and median SMRP levels for those with progressive disease showed a significant difference compared to patients with partial/complete response and stable disease [113].
- A falling SMRP level between baseline and 2 cycles of chemotherapy was associated with a longer 'time to progression' of disease. Fibulin 3 failed to show a similar relationship [126].
- Low Fibulin 3 at diagnosis is associated with a prolonged survival [112].

Outcome prediction

Four studies [122 123 125 126] assessed the independent predictive value of biomarkers on overall survival in MPM, accounting for the recognised prognostic indicators of histological subtype, age and performance status. These demonstrate:

- The modified Glasgow Prognostic Score (~~mGPS =~~ serum, c-reactive protein (CRP) and albumin level at baseline) and ~~the~~ blood neutrophil to lymphocyte ratio (NLR) are independent predictors of overall survival (HR 2.6 and 2.0 respectively) [122]
- Pleural fluid hyaluronic acid (HA) level (<225mg/L) is independently associated with overall survival – RR 0.63 [123]
- Resection specimen staining for smoothened (SMO) transmembrane receptor (HR 1.06) was an independent predictor of overall survival. [125]

A fall in SMRP between baseline and an interval of 6-8 weeks (post 2 cycles of chemotherapy) is predictive of radiographic stability of disease. A falling SMRP level at completion of chemotherapy is strongly associated with a longer survival [126]. Baseline SMRP was unable to predict survival. Apart from SMRP in the SWAMP study [126], none of the other markers have been prospectively validated.

Biomarkers for screening

Five studies [128-132] explored the potential role of biomarkers in screening for MPM. All 5 studies looked at SMRP but 2 studies also looked at Osteopontin, CA-125 and cytokeratin fragment 19 [105 126]. Studies were heterogeneous particularly with regards to the cut off value of SMRP, duration of follow-up and the patient populations (other cancers/control groups). Despite these differences, SMRP tended to be higher in those with asbestos-related disorders such as asbestosis or diffuse pleural thickening, and in renal impairment. One study found SMRP levels are also elevated in other

cancers such as lung, ovarian, pancreatic and endometrial cancer but the populations of patients with these cancers were small.

Evidence statements:

Diagnosis:

There is no diagnostic biomarker which is able to consistently diagnose MPM with a sensitivity and specificity above 90%. **Level 2+.**

The diagnostic value of biomarkers in sarcomatoid mesothelioma is lower than that for epithelioid, but small numbers mean that accuracy of sensitivity and specificity are difficult to derive. **Level 2-.**

Serum SMRP has a relatively high specificity in the diagnosis of MPM across a large number of studies (81%). **Level 2+.**

Serum and pleural fluid Osteopontin has a relatively high specificity in the diagnosis of mesothelioma across a modest number of studies (81%). **Level 2++.**

Fibulin-3 shows variable performance in diagnosis of MPM (sensitivity range 22-100%). **Level 2+**

Disease response:

SMRP level is correlated with tumour bulk and falls post extra pleural pneumonectomy but baseline level does not predict pathological stage in mesothelioma. **Level 2+.**

In assessing response to therapy, SMRP levels are higher in those with progressive disease compared to those with partial response, complete response or disease stability. **Level 3.**

During chemotherapy, a falling level of SMRP from baseline to interval, or a falling level at completion of palliative chemotherapy is associated with a longer survival. **Level 3.**

Outcome Prediction:

There is no prospectively validated biomarker which independently predicts overall survival in MPM. **Level 2-.**

Markers of inflammation, pleural fluid HA and cell staining patterns may predict survival but further studies are required to validate this. **Level 2-.**

Recommendations:

- Do not offer biomarkers in isolation as a diagnostic test in MPM. **Grade B.**
- Consider biomarker testing in patients with suspicious cytology who are not fit enough for more invasive diagnostic tests. **Grade B.**
- Do not routinely offer biomarker testing to predict treatment response or survival. **Grade B.**
- Do not offer biomarker testing to screen for MPM. **Grade C.**

Research Recommendation:

Further research is required to identify biomarkers that reliably predict treatment response within clinical practice

SECTION 8: FACTORS DETERMINING PROGNOSIS AND TIMING OF TREATMENT

There is a large body of evidence on this topic in the literature. The great majority of it is of poor quality, being retrospective case series. Some of these are taken from patients enrolled into clinical trials, where the consistency and quality of the data collected is higher.

A large number of baseline patient variables have been studied seeking prognostic factors. These include demographic factors (age, sex, race), disease features (histological sub-type and grade, site of disease, disease stage using various staging systems), Eastern Co-operative Oncology Group performance status (PS) or Karnofski performance score (KPS), symptoms (particularly chest pain and weight loss, usually not further defined), markers of inflammation (total white blood count (WBC), platelet count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein level (CRP)), and blood test markers of systemic disease such as haemoglobin level, haemoglobin difference from a population ideal value (160 g/L in men, 140 g/L in women), serum albumin.

Several prognostic scores have been developed for mesothelioma, combining groups of prognostic variables derived from derivation cohorts of mesothelioma patients and subsequently validated in different, test cohorts. The following scores are described in more detail below; the EORTC prognostic score (EPS), the CALGB score [133-138], the modified Glasgow prognostic score (mGPS) have been studied retrospectively in a cohort of mesothelioma patients [122],the LENT prognostic score [139], and a prognostic model using decision-tree analysis was published by Brims and others in 2016 [140].

Evidence from very large studies

Three retrospective studies were identified, which included more than 5,000 patients from population-level registries [141-143]. These consistently demonstrate that increasing age, male sex, advanced stage and non-epithelioid histology are prognostic of worse overall survival. Although this evidence is of low quality, being retrospective, the size of the datasets studied and the absence of any contradictory evidence increases the confidence in these findings.

Findings from the National Lung Cancer Audit

In 2015 Beckett and others published data from 8740 mesothelioma cases included in the National Lung Cancer Audit [3]. This is the largest prospectively collected case series in the literature. It has the advantage of reflecting the characteristics of unselected incident cases. In this respect it differs from the populations of clinical trial recruits who have been used to derive, for example, the EORTC and CALGB prognostic scores (see below). Poorer performance status and non-epithelioid histology were associated with shorter overall survival in this cohort. Survival by sex is not reported.

The EORTC Prognostic Score

This was derived by Curran and others in 1998 [134] based on maximum-likelihood parameter estimates of the prognostic factors retained in a multivariate model derived from a population of 204 patients (89% male) entered into clinical trials of chemotherapy in Europe. All patients were PS 0-2. More detail on the score can be found at Appendix 2.

CALGB prognostic groups

Herndon et al studied prognostic factors in a group of 337 patients with MPM not previously treated with chemotherapy who were entered into phase 2 trials of chemotherapy [138]. Cox survival and exponential regression trees were used to determine prognostic importance of pre-treatment patient characteristics. Terminal nodes were amalgamated to form 6 distinct prognostic sub-groups.

The derived prognostic groups are complex, and continuous variables are dichotomised differently for different sub-groups (for example, Hb and WBC).The full score can be seen at Appendix 2.

Edwards and others validated the CALGB groups in a retrospective study conducted in a UK population [137].

Meniawy and others have validated the CALGB prognostic group method in a recent, large study in Western Australia, in a population of patients where 62% received chemotherapy. This is considerably higher than the proportion of patients currently receiving chemotherapy for mesothelioma in the UK and therefore the median survival estimates derived from the validation study are likely to be considerably better than those observed in the UK.

The Neutrophil-to-Lymphocyte ratio (NLR)

5 studies have considered the NLR in mesothelioma. The evidence on the prognostic utility of NLR was reviewed by Meniawy et al [136]. They concluded that the cut-off value chosen for NLR is variable, the independent predictive effect inconsistent and the NLR has not been validated in a prospective study. More information about the studies can be found at Appendix 2.

The Modified Glasgow Prognostic Score (mGPS)

The mGPS stratifies cancer patients according to c-reactive protein and serum albumin (see Appendix 2). This was found to be an independent predictor of overall survival in MPM in one study [122] (HR 2.6, 95% CI 1.6-4.2, p<0.001) but has not been the subject of prospective validation.

Prognostic model using decision tree analysis

Brims and others derived a prognostic model using classification and regression tree analysis from an unselected population of 482 patients newly diagnosed with MPM in Western Australia, of whom 274 were collected retrospectively and 208 prospectively [140]. Unlike the cohorts used to derive the CALGB and EORTC models, which were of participants in chemotherapy trials, this paper included all patients with a confirmed diagnosis of MPM within the inclusion period. The model was validated in a cohort of 177 MPM patients prospectively collected in Bristol, UK. The validation cohort is likely to be highly representative of typical new patients with MPM presenting in the UK. The model was used to predict death at 18 months. The variable with the greatest influence upon survival in the derivation cohort was weight loss, defined as any weight loss considered significant by the medical team. The decision tree for classifying patients into prognostic groups in this study is shown in Table 10 ~~below~~. The variables having an influence on prognosis within this model are histological subtype, weight loss, PS, Hb and serum albumin. The C-statistic for the derivation cohort was 0.76 and the sensitivity 94.5% (95% CI 91.4-96.7%) and the specificity 38.2% (95% CI 30.6 – 46.3%). The positive predictive value for death at 18 months was 76% (95% CI 71.5% - 80.1%). The C-statistic for model performance in the validation cohort was 0.68 (95% CI 0.60-0.75).

The model can be found at Appendix 2.

Table 10: Brim decision tree classification

Prognostic group	Median survival (IQR), months, derivation cohort	Median survival (IQR), months, validation cohort
1	34.0 (22.9 – 47.0)	N/A
2	17.7 (11.6 – 25.9)	11.93 (8.53-18.56)
3	12.0 (6.0 – 20.6)	9.89 (4.84 – 17.81)
4	7.4 (3.3 – 11.1)	5.68 (3.12-10.84)

The LENT score

Clive and others derived the LENT score, for predicting survival in patients presenting with malignant pleural effusion (MPE) [139]. The LENT score uses pleural fluid LDH (>1500) IU/L, ECOG PS, NLR and tumour type to calculate a prognostic score (see Appendix 3 for a full description of the scoring

system). Data from three large international cohorts of patients were used to study the effect of the malignant cell-type on survival. A more detailed analysis of individual prognostic factors was then undertaken in two prospectively collected UK cohorts of patients presenting with MPE. One cohort was used to derive a prognostic score and the second to validate it. 14 pre-defined variables, recorded at presentation, were studied to ascertain their influence on survival using a multivariable Cox proportional hazard method. A prognostic score was then developed using the results of the international cohort for cell type and the UK cohort multivariable analysis.

Table 11: Summary of LENT score and median survival

LENT score and median survival		
Risk categories	**Total score**	**Median (IQR) survival**
Low risk	0-1	319 days (IQR 228-549 days)
Moderate risk	2-4	130 days (47-467 days)
High risk	5-7	44 days (22-77 days)

Patients with moderate-risk and high-risk LENT scores had hazard ratios (95% CI) for mortality of 1.49 (1.03-2.15) and 5.97 (3.58-9.97) compared with those with low-risk LENT scores. The relation between LENT score and median survival is shown in ~~the~~ Table 11 ~~above~~.

Symptoms

Chest wall pain and weight loss have been studied as prognostic variables [133 136 138]. In retrospective case series, chest pain was independently associated with poorer OS in all three studies but has not been subjected to prospective validation. The findings with respect to weight loss are inconsistent. Weight loss was independently predictive of survival in two studies [136 138] but not in the third [133].

Evidence statements:

Increasing age, male sex, non-epithelioid histology, advanced stage, and poorer performance status independently predict poorer survival in MPM. **Level 2+**

The LENT prognostic score provides an approximate estimate of median survival, at presentation, in patients presenting with a pleural effusion due to MPM. **Level 2+**

The EPS and CALGB prognostic groups reliably separate patients into groups with better and worse overall survival but they have been studied only retrospectively, in patients with better performance status and treated with chemotherapy in the majority. **Level 2+**

Markers of inflammation including WBC, platelet count, CRP, serum albumin, PLR and NLR may predict survival but further studies are required, particularly prospectively, to validate this. **Level 3**

The decision-tree model separated unselected UK patients newly diagnosed with MPM into groups with differing median survival using variables that are routinely collected in almost all patients. **Level 2+**

Recommendations:

- Consider calculating a prognostic score in MPM patients at diagnosis~~, particularly when entering patients into clinical trials~~. **Grade D**

- Prognostic scores can provide useful survival information for patients and doctors but should not be used in treatment decision-making. **Grade D**

- When calculating a prognostic score use one of the following:

a. The EORTC prognostic score
b. The CALGB score
c. The modified Glasgow Prognostic Score
d. The LENT score if a pleural effusion is present
e. The decision tree analysis

The decision tree analysis scoring systems is likely to be the most useful in routine clinical practice.**Grade D**

SECTION 9: PLEURAL FLUID MANAGEMENT

There is poor consistency in the literature concerning the outcome of "pleurodesis success" as it is variably defined according to time point, radiology only, combined radiology and need for further pleural drainage and by patient reported outcome measures.

There is also substantial lack of consistency in the analysis of time to event data, with many studies reporting proportion of "success" at a given time point in those patients assessable at the time – i.e. patients who have died or are unable to attend follow up are discounted, leading to increasing rates of pleurodesis success over time in some studies.

Rintoul et al directly compared video assisted thoracoscopic (VATS) partial pleurectomy to talc (poudrage or slurry). Although early pleurodesis success, as assessed by chest x-ray reporting, appeared high in the VATS partial pleurectomy group, this was not sustained over the study follow up period (37% talc vs 59% VATS PP at 1 month, 60% at 3 months in both, 57% talc vs 77% VATS PP at 6 months, but 77% talc vs 70% VATS PP at 12 months) [144]. VATS pleurectomy was not associated with survival benefit (primary outcome) nor benefits to lung function. VATS partial pleurectomy patients had a significantly higher complication rate (31% vs 14%) and longer hospital stay (7 days versus 3 days). VATS was associated with slight improvement in quality of life but only from the 6 month follow up point onwards and not in all quality of life domains.

Davies et al undertook an RCT comparing indwelling pleural catheter (IPC) insertion with talc slurry in patients with symptomatic malignant pleural effusions and found no difference in pleurodesis success or patient measured breathlessness [145]. ~~There was a shorter hospital stay with IPC, with minimisation by mesothelioma, but only small numbers of MPM cases.~~
Fysh et al undertook a large retrospective case series which demonstrated no difference in surgical versus "medical" pleurodesis in MPM (28.2% vs 29.7% complete success, 39.7% vs 38.8% partial success) [146]. In another retrospective series, Bielsa et al demonstrated worse pleurodesis success in mesothelioma (66%) and lung (63%) versus breast (77%) and other (74%). ~~Failure of mesothelioma versus metastatic pleural cancer was 2.7~~ [147].

Two other studies specific to MPM evaluated VATS pleurodesis in non-comparative case series, reporting pleurodesis success rates of 81%-98%, but were retrospective, and suffer from selection bias and used different pleurodesis definitions [148 149]. Non-MPM specific studies reported pleurodesis success rates of 80-86% and did not differentiate mesothelioma from other MPE. One of these studies reported performance status rather than pleurodesis success [150-152].

Evidence statements:

Pleural effusion due to MPM may have a lower pleurodesis success rate than other malignant effusions. **Level 2-.**

No single fluid control technique (Surgical including pleurectomy and VATS, thoracoscopic talc poudrage, talc slurry or IPC) has been shown to be superior in terms of patient symptoms or pleurodesis success in MPM. **Level 1-.**

VATS partial pleurectomy has been shown to be more expensive, associated with greater complications and longer hospital stay than talc slurry pleurodesis. **Level 1+.**

VATS partial pleurectomy is associated with minor improvement in quality of life versus talc slurry in those patients who survive more than 6 months. **Level 1-.**

Indwelling pleural catheters and talc slurry pleurodesis have similar patient related outcomes in malignant effusion and MPM. **Level 1++.**

Recommendations:

- Offer either talc (via slurry or poudrage) or indwelling pleural catheters for symptomatic pleural effusion in MPM, informed by patient choice. **Grade A.**
- Talc slurry or thoracoscopic talc poudrage pleurodesis should be offered to patients with MPM in preference to a VATS partial pleurectomy surgical approach for fluid control in MPM. **Grade A.**

SECTION 10: THE ROLE OF SURGERY

Surgical resection has been offered to a highly selected subgroup of patients with MPM since the 1950's, although its role remains controversial. Surgery can be offered with palliative intent, where the aim is debulking of the tumour mass with the aim of controlling pleural fluid, reducing pulmonary restriction, or by attempting to achieve a complete macroscopic resection, with the aim of improving length and/or quality of life. The International Association for the Study of Lung Cancer's Staging and Prognostic Factors Committee has proposed definitions for surgery, which have been adopted for this guidance [153]

1. Partial pleurectomy (PP): partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumour behind. This may be performed by VAT or with thoracotomy.

2. Pleurectomy/Decortication (PD ~~P/D~~): parietal and visceral pleurectomy to remove all gross tumour without resection of the diaphragm or pericardium.

3. Extended Pleurectomy/Decortication (EPD): parietal and visceral pleurectomy, with the goal of complete macroscopic resection, with resection of the diaphragm and/or pericardium as required.

4. Extrapleural pneumonectomy (EPP): en-bloc resection of the parietal pleura, pericardium, diaphragm, lung and visceral pleura

Evidence Review

95 papers were identified and reviewed, of which 12 were considered in detail [134 144 154-163]. There were 2 randomised controlled trials, 4 systematic reviews, 4 prospective observational studies and 2 retrospective studies.

Pleurectomy

A systematic review has been performed of thirty-four studies involving 1916 patients who underwent pleurectomy [161]. These included 12 studies on extended PD ~~P/D~~, 8 studies on PD ~~P/D~~ and 14 studies on PP. All the studies were observational with high risk of selection bias. Perioperative mortality ranged from 0% to 11% and perioperative morbidity ranged from 13% to 43%. Median overall survival ranged from 7.1 to 31.7 months and disease-free survival ranged from 6 to 16 months.

The MesoVATS trial randomised 196 patients with suspected or confirmed mesothelioma (of whom 175 had mesothelioma) between talc pleurodesis or VATS PP [144]. The primary outcome was survival at 1 year, which was 52% (95% CI 41–62) in the VAT-PP group and 57% (46–66) in the talc pleurodesis group (hazard ratio 1·04 [95% CI 0·76–1·42]; p=0·81). Surgical complications were significantly more common after VAT-PP than after talc pleurodesis, occurring in 24 (31%) of 78 patients who completed VAT-PP versus ten (14%) of 73 patients who completed talc pleurodesis (p=0·019), ~~as were respiratory complications (19 [24%] vs 11 [15%]; p=0·22)~~. Median hospital stay was longer at 7 days (IQR 5–11) in patients who received VAT-PP compared with 3 days (2–5) for those who received talc pleurodesis (p<0·0001).

Extended pleurectomy Decortication and Extra-pleural pneumonectomy

The Mesothelioma and Radical Surgery (MARS) feasibility study assessed EPP versus no EPP for patients with MPM [154]. Patients with pathologically confirmed mesothelioma deemed fit enough to undergo trimodal therapy were included. All patients underwent induction platinum-based chemotherapy followed by clinical review. After further consent, patients were randomly assigned to EPP followed by postoperative hemithorax irradiation or to no EPP. Of 112 patients registered 50 were subsequently randomly assigned: 24 to EPP and 26 to no EPP. EPP was completed satisfactorily in 16 of 24 patients assigned to EPP. Two patients in the EPP group died within 30 days and a further patient died without leaving hospital. One patient in the no EPP group died perioperatively after receiving EPP off trial in a non-MARS centre. The hazard ratio [HR] for overall survival between the EPP and no EPP groups was 1·90 (95% CI 0·92–3·93; exact p=0·082), and after adjustment for sex, histological subtype, stage, and age the HR was 2·75 (1·21–6·26; p=0·016). Median survival was 14·4 months (5·3–18·7) for the EPP group and 19·5 months (13·4 to time not yet reached) for the no EPP group. Of the 49 randomly assigned patients who consented to quality of life assessment (EPP n=23; no EPP n=26), 12 patients in the EPP group and 19 in the no EPP group completed the quality of life questionnaires. Although median quality of life scores were lower in the EPP group than the no EPP group, no significant differences between groups were reported in the quality of life analyses.

There has been much discussion around the validity of the MARS trial results. In particular, criticism that the study was not powered to detect a survival advantage attributable to EPP and that the operative mortality was higher than that of other contemporary series. The MARS trial authors have subsequently responded that the EPP mortality in MARS (2 of 19; 10.5%; 95% confidence limits 1.3%–33.1%) lies within the range reported in a systematic review of 34 studies, including 2320

patients, where 30-day mortality ranged from 0% to 11.8% [164]. Furthermore, the authors note that the median survival of patients in the EPP arm of MARS of 14.4 months from randomization is in keeping with major series in the literature which report median survival times of 10 to 14 months.

Cao et al [159] performed a systemic review of 34 studies with 2462 patients who underwent EPP for MPM. All the studies were observational and subject to high risk of selection bias. The median overall survival varied from 9.4 to 27.5 months, and 1-, 2-, and 5-year survival rates ranged from 36 to 83%, 5 to 59%, and 0 to 24%, respectively. Overall perioperative mortality rates ranged from 0 to 11.8%, and the perioperative morbidity rates ranged from 22 to 82%. Quality of life assessments from three studies reported improvements in nearly all domains at 3 months postoperatively. Patients who underwent trimodality therapy involving EPP and adjuvant chemoradiotherapy had a median overall survival of 13 to 23.9 months.

Two meta-analyses have been performed comparing outcomes following either PD or EPP. All the studies included in the analyses were observational with high risk of selection bias. The meta-analysis by Taioli et al[165] included 1512 patients treated by PD and 1391 treated with EPP . There was a significantly higher proportion of short-term deaths in the EPP group versus the PD ~~P/D~~ group (percent mortality meta estimate; 4.5% vs 1.7%; $p < 0.05$). There was no statistically significant difference in 2-year mortality between the 2 groups, but there was significant heterogeneity. The meta-analysis by Cao et al 2014 included 632 patients who underwent EPP and 513 patients who underwent EPD [162]. All-cause perioperative mortality was found to be significantly lower after EPD compared to EPP (2.9% vs 6.8%; RR, 0.53; 95% confidence interval [CI], 0.31–0.91; $p = 0.02$; $I2 = 0\%$). Perioperative morbidity was also found to be significantly lower after EPD compared to EPP (27.9% vs 62.0%; RR, 0.44; 95% CI, 0.30–0.63; $p < 0.0001$; $I2 = 44\%$). There were insufficient data for this meta-analysis to compare the overall survival outcomes between the two treatment arms.

The effects of PD on lung function and quality of life have been assessed in a number of small cohort studies. None of these studies compared changes in outcomes with patients who were not selected to undergo surgery and so the results must be interpreted with caution. Mollberg et al found that quality of life scores did not deteriorate in 28 patients with good performance status (0-1) who underwent PD [155]. Bölükbas et al found that the mean forced vital capacity improved from 55% of predicted to 69% of predicted ($p<0.01$) in 16 patients who underwent radical pleurectomy [156]. Ploenes et al retrospectively reviewed the outcomes of 25 patients who underwent EPP and 23 who had PD [158]. Pulmonary function was not significantly reduced in the PD group postoperatively. In the EPP group, the median vital capacity fell from 78% of predicted to 48% predicted ($p<0.001$). Burkholder et al assessed quality of life in 36 patients undergoing PD [157]. Global quality of life scores were unchanged in the 17 patients with performance status of 0 and improved in the 19 patients with performance status of 1 or 2.

A feasibility multi-centre randomised trial comparing extended Pleurectomy/Decortication to no surgery (MARS-2 trial) is currently recruiting in the UK [163]. Results from this surgical trial are awaited with interest.

Evidence statements:

VAT Partial Pleurectomy has no effect on overall survival and results in increased complications and longer hospital stay than talc pleurodesis **Level 1+** ~~**1++**~~

Extra-Pleural Pneumonectomy ~~is potentially harmful to patients~~ does not improve survival when added to treatment with chemo-radiotherapy **Level 1+**

Extended Pleurectomy / Decortication may result in lower perioperative mortality than Extra-pleural pneumonectomy. **Level 1-**

Quality of life and lung function may not deteriorate in patients selected to undergo pleurectomy decortication**. Level 2-**

Recommendations:

- Do not offer VATS Partial Pleurectomy over talc pleurodesis in MPM **Grade A**
- Do not offer Extra-Pleural Pneumonectomy in MPM **Grade B**
- Do not offer extended pleurectomy decortication outside of a clinical trial **Grade D**

Research recommendation:

The role of VATS-PP and EPD in good prognosis patients should be examined further in clinical trials, which should include robust measurement of quality of life.

SECTION 11: SYSTEMIC ANTI-CANCER TREATMENT

Evidence

The literature search revealed a large volume of evidence assessing the role of systemic treatment. Over two hundred articles were obtained from a search. Of these, 69 were not relevant to the question. Papers were excluded if they involved tri-modality therapy or radiotherapy as major features in the trial design. This included papers looking at the role of neo-adjuvant or adjuvant chemotherapy in the setting of surgery. Papers were excluded if they involved intrapleural chemotherapy and photodynamic therapy during as part of surgical therapy.

Evidence on first-line systemic therapy

Almost all the first-line studies identified were non-randomised phase II trials. Four large phase III randomised trials comparing novel systemic therapy to 'standard' therapy were identified. Two of the large randomised trials used a control arm of single-agent cisplatin and one used a control arm of active symptom control (ASC). Table 12 summarises phase III trial data.

Table 12: Randomised phase III trials in first-line treatment of MPM

Trial	Year of publication	Treatment arms	OS (months)	P-value
Vogelzang [166]	2003	P/C v C	12.1 vs 9.3	P=0.020
Van Meerbeeck [167]	2005	R/C v C	11.4 vs 8.8	P=0.048
Muers [168]	2008	ASC + ctx v ASC	8.5 vs 7.6	P=0.290
Zalcman [169]	2015	P/C/B v P/C	18.8 vs 16.1	P=0.017

P= pemetrexed; R=ralitrexed; C =cisplatin; ASC= active symptom control; B= bevcizumab; ctx= chemotherapy: OS=overall survival

The first large randomised trial (known as EMPHASIS) to be published in patients with MPM compared three-weekly intravenous chemotherapy with the anti-folate drug pemetrexed at a dose of 500mg/m^2 and cisplatin at a dose of 75mg/m^2 with a control arm of cisplatin at a dose of 75mg/m^2 [166] .The primary outcome was survival. Secondary outcomes were time to progressive disease, time to treatment failure, tumour response rate, and duration of response. 226 patients were randomised to pemetrexed/cisplatin, and 222 to cisplatin alone. The median survival time for pemetrexed/cisplatin-treated patients was longer than for patients receiving cisplatin alone: 12.1 months versus 9.3 months, representing a statistically significant difference (p=0.020). The median time to progressive disease was significantly longer for patients who received pemetrexed and cisplatin as compared with patients who received cisplatin alone (5.7 months v 3.9 months; p = 0.001). The median time to treatment failure was also significantly longer in the pemetrexed/cisplatin arm than in the control arm. The response rates were 41% for pemetrexed/cisplatin patients versus 17% in the control group.

Whilst this trial was recruiting the investigators became aware of excessive bone marrow toxicity likely due to folate depletion probably caused by pemetrexed. They decided to give all patients, both in the trial arm and the control arm, vitamin B12 (by intramuscular injection) and folic acid (by tablet) supplementation. Bone marrow toxicity was reduced and vitamin supplementation is now standard for all patients treated with pemetrexed. The incidence of nausea, vomiting, fatigue, diarrhoea, dehydration, and stomatitis were significantly higher in the pemetrexed/cisplatin arm.

In 2005 a broadly similar randomised controlled trial was published by the European Organisation for the Research and Treatment of Cancer (EORTC) [167]. The experimental arm was the antifolate drug raltitrexed combined with cisplatin (arm B), with a control group of single-agent cisplatin (arm A). Raltitrexed is comparable to pemetrexed in that its main mechanism of action is by inhibiting thymidylate synthase thereby preventing the formation of precursor pyrimidine nucleotides. Endpoints were overall survival, response rates and quality of life. Patients had to have good performance status (WHO 0-2) and adequate haematological, renal and hepatic function. Two hundred and fifty patients were randomised: 80% were male and the median age was 58. The main grade 3 or 4 toxicities observed were neutropenia and emesis, reported twice as often in the combination arm. Among 213 patients with measurable disease, the response rate was 13.6% (arm A) versus 23.6% (arm B; P = 0.056). Median overall and 1-year survival in arms A and B were 8.8 (95% CI, 7.8 to 10.8) v 11.4 months (95% CI, 10.1 to 15), respectively, and 40% v 46%, respectively (P = 0.048).

A large cooperative group based in the UK led by Muers organised a large three-arm randomised clinical trial known as MS01[168]. Patients were randomised into 3 groups. Group 1: active symptom control (ASC). The essential elements of ASC were defined as regular follow-up in a specialist clinic; structured physical, psychological, and social assessments at every clinic visit; rapid involvement of additional specialists; and parallel nursing support. Patients could receive, as required, steroids, analgesic drugs, appetite stimulants, bronchodilators, or palliative radiotherapy, Group 2: ASC plus mitomycin, cisplatin and vinblastine chemotherapy (MVP), or Group 3: ASC plus vinorelbine chemotherapy. A total of 840 patients (280 in each group) were needed to detect an improvement of 3 months survival, however due to slow accrual the trial design changed to a two-group comparison by combining the two chemotherapy groups. The two-group design needed a total of 420 patients (140 ASC, 280 ASC plus chemotherapy) to reliably detect an improvement from 9 months median survival with ASC alone to 12 months with ASC plus chemotherapy. Four hundred and nine patients with malignant pleural mesothelioma, from 76 centres in the UK and two in Australia, were randomly assigned to ASC alone [n=136]; to ASC plus MVP (four cycles of mitomycin 6 mg/m^2, vinblastine 6 mg/m^2, and cisplatin 50 mg/m^2 every 3 weeks [n=137]); or to ASC plus

vinorelbine (one injection of vinorelbine 30 mg/m^2 every week for 12 weeks [n=136]). The results showed that, compared with ASC alone, there was no significant survival benefit for ASC plus chemotherapy (hazard ratio [HR] 0.89 [95% CI 0.72-1.10]; p = 0.29). Median survival was 7.6 months in the ASC alone group and 8.5 months in the ASC plus chemotherapy group. There were no between-group differences in four predefined quality-of-life subscales (physical functioning, pain, dyspnoea, and global health status) at any of the assessments in the first six months. The trial attracted some criticism for the decision to combine the two different chemotherapy arms, thus reducing the power to detect a significant difference for the separate regimens [170].

A more recent trial reported by Zalcman et al presented data on the addition of bevacizumab to pemetrexed and cisplatin chemotherapy for patients with newly diagnosed MPM [169]. The trial, called MAPS (Mesothelioma Avastin Cisplatin Pemetrexed Study) was a randomised, controlled, open-label, phase 3 trial. Patients aged 18-75 years with unresectable MPM who had not received previous chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0–2, had no substantial cardiovascular comorbidity, were not amenable to curative surgery, had at least one evaluable (pleural effusion) or measurable (pleural tumour solid thickening) lesion with CT, and a life expectancy of >12 weeks from 73 hospitals in France. Patients were stratified by histology [epithelioid vs sarcomatoid or mixed histology subtypes], performance status score [0–1 vs 2], study centre, or smoking status [never smokers vs smokers]) to receive intravenously 500 mg/m² pemetrexed plus 75 mg/m² cisplatin with (PCB) or without (PC) 15 mg/kg bevacizumab in 21 day cycles for up to six cycles, until progression or toxic effects. The primary outcome was overall survival (OS) in the intention-to treat population. 448 patients were randomised to treatment (223 to PCB and 225 to PC). Overall survival was significantly longer with PCB (median 18·8 months [95% CI 15·9–22·6]) than with PC (16·1 months [14·0–17·9]; hazard ratio 0·77 [0·62–0·95]; p=0·0167). Overall, 158 (71%) of 222 patients given PCB and 139 (62%) of 224 patients given PC had grade 3–4 adverse events. More grade 3 events, higher rates of hypertension and more thrombotic events were noted with PCB compared with PC. Bevacizumab treatment is not currently ~~available~~ licensed for use in the UK and is not available in the NHS.

An International Expanded Access Program (EAP) led by Santoro followed more than 3000 mesothelioma patients treated with single-agent pemetrexed or pemetrexed in combination with cisplatin or carboplatin [171]. Patients with histologically confirmed MPM, not amenable to curative surgery, received pemetrexed 500 mg/m2 in combination with either cisplatin 75 mg/m2 or carboplatin AUC 5, once every 21 days with standard premedication. A total of 1704 chemonaïve patients received pemetrexed plus cisplatin (n = 843) or pemetrexed plus carboplatin (n = 861) and were evaluated for safety. The efficacy evaluable population consisted of 745 patients in the pemetrexed plus cisplatin group and 752 patients in the pemetrexed plus carboplatin group for whom physician-reported tumour response was available. The pemetrexed plus cisplatin group demonstrated a response rate of 26.3% compared with 21.7% for the pemetrexed plus carboplatin group, with similar 1-year survival rates (63.1% versus 64.0%) and median time to progressive disease (7 months versus 6.9 months). Based on these data pemetrexed plus ~~and~~ carboplatin is generally considered an acceptable alternative two-drug first line option especially for patients deemed unfit for cisplatin, although the data on which this practice is based are not from a randomised controlled trial.

Second line systemic treatments in MPM

Buikhuisen et al undertook a systematic review of 10 studies reporting on 1251 patients treated with second-line chemotherapy in MPM [172]. The majority of studies were phase II with only two phase III randomised trials. The authors concluded that only a limited number of randomised studies with

combination therapy had been conducted. The authors suggested the following as second line treatment options for patients with MPM: 'single agent vinorelbine or pemetrexed are acceptable second line agents for patients relapsing after a first line platinum combination regardless of whether or not pemetrexed was used in the first line setting'. They also stated that the 'low reported activity of the drugs in second line warrants referral of fit patients to participate in clinical trials'.

Jassem et al compared the efficacy and safety of pemetrexed and best supportive care in patients with MPM after first-line chemotherapy (excluding pemetrexed) [173]. Of the 243 patients included, 18.7% of the 143 patients receiving pemetrexed showed a partial response but the median overall survival was not significantly different between the two groups.

The VANTAGE-014 study compared vorinostat, an oral histone deacetylase inhibitor, with placebo in 661 MPM patients who had previously received one or two systemic regimens [174]. Median overall survival for vorinostat was 30·7 weeks (95% CI 26·7–36·1) versus 27·1 weeks (23·1–31·9) for placebo (hazard ratio 0·98, 95% CI 0·83–1·17, p=0·86).

Anti-PD1 immune checkpoint therapy ~~may have~~ has potential for the treatment of mesothelioma. Approximately 40 percent of tumours ~~of patients~~ express PDL1, which is associated with non-epithelioid histology and worse outcome for high expressing tumours [175]. Keynote 28 is the first phase Ib trial to report on the activity of pembrolizumab in patients with pleural mesothelioma and enrolled 25 patients ~~with~~ harbouring PDL1 positive tumours [176]. This study showed a 20% response rate with durability lasting on average 12 months. Stable disease was 52% giving a disease control rate (DCR) of 72%. Median overall survival was 18 months. In summary, emerging data suggest~~s~~ anti-PD1 or PDL1 immunotherapy, exhibits efficacy in mesothelioma, however randomised trials will be needed to confirm the incremental benefit and value. In this regard, the CRUK CONFIRM phase III trial is currently randomising patients 2:1 to nivolumab versus placebo [NCT03063450]

Evidence statements

For patients with MPM with good performance status first-line therapy with cisplatin and pemetrexed and bevacizumab leads to longer survival than cisplatin and pemetrexed alone. However, bevacizumab is not licensed for this use in the UK. **Evidence level 1 + +**

For patients with MPM with good performance status first-line chemotherapy with cisplatin and pemetrexed leads to longer survival than cisplatin alone. **Evidence level 1 + +**

For patients with MPM with good performance status first-line chemotherapy with cisplatin and raltitrexed leads to longer survival than cisplatin alone. **Evidence level 1 + +**

The combination of mitomycin, cisplatin and vinblastine or single agent vinorelbine did not demonstrate survival benefit over active symptom control. **Evidence level 1 +**

Carboplatin in combination with pemetrexed is a safe and effective alternative to cisplatin in combination with pemetrexed. **Evidence level 3**

Second line pemetrexed does not improve survival in patients previously treated with first line chemotherapy regimens that did not include pemetrexed. **Evidence level 1+**

Second line vorinostat does not improve survival in patients previously treated with one or two cycles of chemotherapy. **Evidence level 1+**

Recommendations

- Offer patients with MPM with good performance status (0-1) first-line therapy with cisplatin, pemetrexed. Raltitrexed is an alternative to permetrexed. ~~and bevacizumab~~. **Grade A**

- ~~If bevacizumab is unavailable, offer patients with MPM with good performance status (0-1) first-line chemotherapy with cisplatin and pemetrexed. Raltitrexed is an alternative to pemetrexed. **Grade A** If~~ the manufacturers seek a UK license for bevacizumab, consider its use in addition to cisplatin and pemetrexed as first line therapy for patients with MPM with good performance status (0-1).

- Do not offer pemetrexed or vorinostat as second line treatment for patients with MPM. **Grade A.**

Good practice points

- ✓ Where cisplatin is contraindicated, or has adverse risk, offer ~~C~~carboplatin in combination with pemetrexed.

- ✓ First line clinical trials are an appropriate option for patients with good performance status and are recommended above any other option for second-line treatment, providing the patient is of adequate performance status.

Research Recommendations

Randomised controlled trials of immunotherapy in MPM.
Randomised controlled trials of second line therapy in MPM.

~~Further research as highlighted by the James Lind Alliance is needed in the following areas;~~
~~Immune boosting therapy (eg. anti PD1 and anti PDL1 checkpoint inhibition)~~
~~Further comprehensive genomic profiling of mesothelioma leading to individualised therapy~~
~~The role of second line chemotherapy~~

~~**Future therapies: Summary of ongoing trials into potential treatments using PD1 inhibitors/anti PDL1 in mesothelioma.**~~

~~Pembrolizumab is an antibody based therapeutic agent that is targeted at the immune inhibitory protein programmed death 1 (PD1). This protein engages with, and inhibits T cell mediated immunity against cancers, which express foreign antigens by virtue of their mutations which ultimately causes of the cancer. By interacting with PD1, pembrolizumab reactivates the immune system by essentially removing its camouflage. This leads to the immune system attacking the cancer. This approach has been successful across a wide range of cancers and has been heralded as a new paradigm in cancer therapeutics. For example, approval internationally has been granted for the use of pembrolizumab for the treatment of melanoma, non-small lung cancer, bladder cancers with many other studies ongoing, showing promising results.~~

~~The Keynote 28 study investigators (study NCT 02054806) presented clinical trial data at the 2015 American Association for Cancer Research (AACR). This study showed that pembrolizumab has significant activity in patients with mesothelioma associated with a 28% response rate and 76% disease control rate. Critically, the expression of the PDL1 (programmed death 1 ligand), a potential predictive biomarker for pembrolizumab, was not shown to be associated with efficacy, implying that patients could benefit irrespective of the biomarker.~~

~~The European Thoracic Oncology platform (ETOP) are planning a study randomizing pembrolizumab against chemotherapy shortly. Another study, Keynote 158 is currently recruiting at a single UK centre enrolling patients who will receive single agent pembrolizumab as part of a biomarker analysis.~~

~~Nivolumab is being evaluated in a single arm trial in the Netherlands, and Cancer research UK is supporting the CONFIRM trial, a placebo controlled double blind phase III trial of nivolumab in relapsed mesothelioma due to open in 2017. Another CRUK study is evaluating combination FAK/PD1 inhibition in mesothelioma.~~

~~The anti PDL1 agent avelumab is being evaluated in mesothelioma (JAVELIN basket study), and the basket study PEMBIB is evaluating pembrolizumab with nintedinib.~~

~~Combination immunotherapy studies with anti-CTLA4 and anti-PD1 immunotherapy has been initiated (NBIT01) Finally, Checkmate 743 will evaluate nivolumab/ipilumumab combination in a randomised phase III in the front line setting.~~

SECTION 12: RADIOTHERAPY

12.1 Prophylactic radiotherapy to procedure tracts

Subcutaneous tumour nodules, seeded up the tract of previous needle or tube insertions, surgical or other invasive procedures, are sometimes observed in MPM patients. Prophylactic radiotherapy to these sites may have a role in preventing the development of tumour tract nodules ~~from developing~~.

Evidence review

Four randomised controlled trials comparing prophylactic radiotherapy to procedure tracts to no radiotherapy, and a systematic review (written before the 2016 RCT was published) are evaluated [177-181]. The Boutin study was conducted in the era before chemotherapy was routinely offered to MPM patients fit enough to receive it [177]. All patients had had both an Abrams biopsy and a thoracoscopy before randomization. The incidence of metastatic nodules in the control group was high (40%) and has not been replicated in any other observational studies. The Bydder and O'Rourke studies excluded patients who had received prior chemotherapy [178 179]. Information regarding subsequent chemotherapy treatment was not available. The incidence of chest wall nodules in the control groups were lower and the differences in the incidence of nodules between treatment groups not significantly different. It has been questioned whether these studies were adequately powered [181].

The SMART Trial was a randomised, multi-centre, phase III trial evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases after surgical and large bore pleural procedures [180]. Eligible patients were recruited from 22 UK hospitals and randomised (1:1) to immediate radiotherapy (21 Gray in three fractions over three working days), or deferred radiotherapy (same dose given if a procedure tract metastasis (PTM) developed). 203 patients were randomised (102 to immediate radiotherapy, 101 to deferred radiotherapy). No statistically significant difference was identified in the PTM rates of the immediate and deferred radiotherapy

groups (9/102 (8·8%) vs 16/101 (15·8%) respectively; OR 0·51 (0·19, 1·32); p=0·14). There was no difference identified in quality-of-life, chest pain, analgesia requirements or survival of the two groups.

A Phase III Randomised Trial of Prophylactic Irradiation of Tracts in Patients with Malignant Pleural Mesothelioma Following Invasive Chest Wall Intervention (the PIT trial) was due to complete recruitment in June 2016 and results are expected in 2017 [182]. Table 13 provides a summary of trails comparing prophylactic and procedure tracts to no radiotherapy.

Table 13: Summary of trials comparing prophylactic radiotherapy to procedure tracts to no radiotherapy

Study	Patients	Treatments	Nodules in treatment group	Nodules in control group	Significance	Notes
Boutin 1995 [177]	40	21Gy in 3 12.5-15MeV	0/20	8/20	P<.001	Pre-Chemotherapy Era
Bydder 2004 [178]	43 (58 sites)	10Gy in 1 9MeV	2/28	3/30	N.S	Chemotherapy patients excluded
O'Rouke 2007 [179]	61	21Gy in 3 250kV photons or 9-12MeV	4/31	3/30	N.S	Chemotherapy patients excluded
Clive 2016 [180]	203	21Gy in 3 fractions	9/102	16/101	N.S	Chemotherapy included

Evidence statement

Three out of four randomised controlled trials did not show a reduction in procedure tract metastases with prophylactic radiotherapy to chest wall procedure tracts **Level 1+**

Prophylactic radiotherapy to chest wall procedure tract has not been shown to improve quality-of-life, chest pain, analgesia requirements or survival **Level 1+**

Recommendation

- Do not offer prophylactic radiotherapy to chest wall procedure tracts routinely. **Grade A**

12.2 Radiotherapy as part of multi-modality treatment

The role of radiotherapy as part of the multimodality treatment of MPM is controversial. Radiotherapy can be delivered either as the sole local treatment modality after chemotherapy or as an adjuvant/neoadjuvant treatment in the context of a surgical approach. However, as MPM typically involves large areas of the pleura, the delivery of radical doses of radiotherapy are limited by the surrounding organs at risk such as normal lung, liver, heart and spinal cord.

A number of important remarks should be made with regards to the interpretation of the available literature. Firstly, the majority of studies identified evaluated multimodality treatment and very few investigated specifically the role of pre/postoperative RT or RT alone. Secondly, the majority of the studies identified evaluated RT in the context of extra-pleural pneumonectomy which is now very rarely performed in the UK. Lastly, none of the studies reviewed included surgical or radiotherapy quality assurance. Specifically, the majority of the studies reviewed had no built-in radiation dose constraints for organs at risk.

Evidence review

Twenty one studies were identified which included radiotherapy as part of the multimodality treatment [154 183-202]. One evaluated pre-operative radiotherapy (in the context of EPP) [183], two hemithoracic radiotherapy alone [184 185] and 17 post-operative radiotherapy (4 in the context of pleurectomy decortication and 13 in the context of EPP).

Four studies were retrospective cohort series, and 16 were prospective studies, of which only four are multicentre and two are randomised controlled trials (RCT).

Studies evaluating postoperative radiotherapy either after EPP or PD have shown that RT in the context of multimodality treatment is feasible, but some severe toxicities, particularly pneumonitis have been reported [154 186-201]. The rate of grade 5 radiation pneumonitis ranges from 0-46% in the studies that have reported RT-related toxicity and a lung dose-volume effect was identified in patients who developed grade 3+ radiation pneumonitis [186 191 193-195].

Only one RCT specifically evaluated the role of post-op radiotherapy and showed no benefit for this treatment [201]. The Swiss Group for Clinical Cancer Research (SAKK) trial is a 2-part multicentre randomised phase 2 study, analysed on intention to treat. It included patients with pathologically confirmed MPM, resectable TNM stages T1–3 N0–2, M0, WHO performance status 0–1 and age <70 years. In part 1 of the study, patients were given three cycles of neoadjuvant chemotherapy followed by EPP; the primary endpoint was complete macroscopic resection (R0–1). In part 2, patients with complete macroscopic resection were randomly assigned to receive adjuvant radiotherapy or not (3D conformal radiotherapy or intensity-modulated radiotherapy was permitted with dose ranging from 55.9 to 57.6 Gy, using a boost technique).The primary endpoint was locoregional relapse free survival. 151 patients were evaluable after neoadjuvant chemotherapy, of whom 75% had EPP and 64% complete macroscopic resection. 54 patients were enrolled in part 2. Median locoregional relapse-free survival from surgery was 7.6 months (95% CI 4.5–10.7) in the no radiotherapy group and 9.4 months (6.5–11.9) in the RT group. Median overall survival calculated from registration for patients in part 2 was 20·8 months (95% CI 14·4–27·8) in the no RT group and 19·3 months (11·5–21·8) in the RT group. One patient died of grade 5 radiation pneumonitis. However, it should be noted the trial was terminated earlier than planned due to slow accrual (at 73% of the accrual).

Evidence statements:

Post-operative radiotherapy after chemotherapy and extra-pleural pneumonectomy has not been shown to improve survival. **Level 1+.**

Post-operative radiotherapy after chemotherapy and pleurectomy decortication has not been shown to improve survival. **Level 2-.**

Pre-operative radiotherapy has not been shown to improve survival. **Level 2-.**

Radical radiotherapy used in isolation has not been shown to improve survival. **Level 2-.**

Recommendation:

- Do not offer pre or post-operative radiotherapy in MPM. **Grade A.**

Research recommendation:

Prospective clinical trials of preoperative radiotherapy, post-operative radiotherapy after pleurectomy decortication and definitive radiotherapy after chemotherapy in MPM are required.

12.3 Radiotherapy for symptom palliation

Symptoms in MPM include pain, breathlessness and cough. Palliative radiotherapy has been used in an attempt to control these symptoms, as well as for other indications.

Evidence review

There are six studies, of which two explore whole hemi-thorax irradiation [184 203] and four of localised treatment to areas of disease and/or symptoms [204-207]. There ~~is one~~ are two systematic reviews addressing the role of radiotherapy for symptom palliation ~~which includes these studies~~ [208 209].

Of the **hemi-thorax studies**: A retrospective case series described no change in chest pain or performance status in 47 patients treated with 40Gy in 20 fractions [184]. The other was a prospective phase II study without controls, including 19 patients treated with 30Gy in 10 fractions [203]. It reported an improvement in pain control in 68% at one month, but this was not maintained (1). Toxicity was not reported in this study.

The **localised treatment studies** showed variable response rates (in terms of pain improvement). The dose and duration of response were also variable in these uncontrolled reports. The results are summarised in ~~the~~ Table 14.

Table 14: Summary of studies exploring localised hemi-thorax irradiation

Study	Type Of Study	Patients	Dose; number of fractions (#)	Pain Improvement %	Duration of Response
Macleod [204]	Prospective phase II No control	40	20 Gy ; 5 #	47	5 weeks
Davis [205]	Retrospective	111	<20Gy* >40Gy*	60 57	No data
Graaf-Strukowska [206]	Retrospective	189	<4Gy; 1 # 36Gy; 9#	40 50	98 days 69 days

Jenkins [207]	Retrospective	54	36 Gy; 12#	57	2 weeks

*** Fractionation not specified**

A randomised phase II study opened to recruitment in the UK in August 2016 aiming to establish optimal dose/fractionation for symptom control in MPM (SYSTEMS2 SRCTN12698107.)

Evidence statements:

Hemi-thorax radiotherapy has not been shown to have a consistent impact on chest pain or performance status in MPM. **Level 3**.

Localised radiotherapy can improve pain control in MPM although the effect is variable and is short lived. **Level 3.**

Radiation dose fractionation utilised in studies of localized radiotherapy for pain control in MPM are variable. The optimal dose is not known. **Level 3.**

Recommendations:

- Do not offer hemi-thorax radiotherapy for MPM. **Grade D**
- Consider palliative radiotherapy for localised pain in MPM where the pain distribution matches areas of underlying disease. **Grade D.**

Research recommendation:

Further prospective randomised clinical trials are required to determine the role of radiotherapy for symptom control in MPM and the optimal dose fractionation.

SECTION 13: SYMPTOM CONTROL

Review of the literature revealed that there are no randomised controlled studies of symptom control in patients with MPM only.

There is one published case series of 53 patients with pain from MPM managed with cervical cordotomy [210]. This was a retrospective case note review and although the majority of patients appeared to have a reduction in pain following the procedure this study is subject to considerable selection and recall bias.

Evidence statement

There are no studies of symptom control that specifically relate to MPM.

Good practice point

- ✓ Symptoms in MPM should be managed as per current guidelines for cancer in general (see Table 15) and early involvement of palliative care specialists is recommended.

Table 15: Summary of current cancer related symptom management guidelines in relation to common symptoms seen in MPM

Symptom	Management	Reference literature
Breathlessness	Pleural fluid control Sustained release morphine Breathing control and use of fans	See Section 9 Ref [211], [212] Ref [213-216]
Pain	Opioids ~~Amitryptilline~~ Amitriptyline, duloxetine, gabapentin or pregabalin for neuropathic pain Radiotherapy for refractory localised pain	Ref [217] [218] Ref [219] [220] See Section 12
Fatigue	Aerobic exercise	Ref [221]
Anorexia	Megestrol Acetate	Ref [222]

SECTION 14: CARE AND MANAGEMENT

14.1 Care in multi-disciplinary teams

Multidisciplinary Team (MDT) meetings are an established feature in cancer services. Widespread adoption and development, despite very little supporting evidence, has been seen across all tumour types over the last two decades. There is a suggestion that MDT working improves recruitment to clinical trials [223] and that patients find MDT working reassuring and improves their experience of care [224 225].

To support the development of MDTs ~~MDT's~~ the National Cancer Action Team published Guidelines on Characteristics of an Effective MDT (NCAT 2010) although given the Mesothelioma incidence the option of virtual MDT working should be considered [226]. NHS England have outlined their commissioning expectations for Mesothelioma requesting the establishment of specialist Mesothelioma MDTs and recommending they manage a minimum of 25 patients per year (NHS England 2013).

Bibby et al (2016) recently published a retrospective evaluation of their specialist regional mesothelioma MDT based in the south-west of England [227]. Of the 210 cases that were reviewed by the specialist MDT, 10% had their diagnoses overturned and 20% were enrolled into a clinical trial.

Evidence statement:
Specialist MPM multidisciplinary meetings may improve diagnostic accuracy and recruitment to clinical trials. **Evidence Level 3**

Recommendation:

- ➢ Consider referring MPM cases to a regional mesothelioma MDT. **Grade D**

Good Practice Points

- ✓ All Mesothelioma cases should be discussed in a timely fashion by a MDT that reviews a sufficient number of cases to maintain expertise and competence in the diagnosis and treatment of MPM.
- ✓ The MDT membership should fulfil the requirements set by national cancer peer review (to include a named clinical nurse specialist for MPM).
- ✓ The MDT should maintain an up to date portfolio of mesothelioma trials and offer recruitment to all eligible patients.

14.2 Information needs of patients

Patients undergoing investigation and treatment for mesothelioma may have unmet psychosocial and information needs. A clear understanding is essential for patients and their carers to make informed choices about the options for management. They may need professional support when interpreting information. The NICE guideline on the management of lung cancer (CG121) made detailed recommendations on the information and support needs of patients, some of which will be applicable to MPM [228] . The National Lung Cancer Forum for Nurses has emphasised the key role of the lung clinical nurse specialist in providing information and support to patients and has produced specific guidance for managing patients with mesothelioma https://www.nlcfn.org.uk/. ~~In addition, the UK has~~ There are 14 mesothelioma specific clinical nurse specialists in the UK.

Evidence review

The search revealed 13 abstracts potentially relevant to this question. Eight studies were of sufficient quality and relevance to be included in the review, of which 4 included less than 30 patients, therefore the volume of evidence is limited. The studies can be grouped in those assessing emotional support, compensation and intervention.

Emotional support

Granieri et al (2013) collected quality of life data from 27 patients with MPM, 55 relatives and 40 healthy controls in Italy [229]. Patients with MPM had a greater belief that goals could not be reached or problems solved, while often claiming that they were more indecisive than the healthy controls. First-degree relatives reported lower opinions of others, a greater belief that goals cannot be reached or problems solved, support for the notion that they are indecisive, and were more likely to suffer from fear that significantly inhibited normal activities than were healthy controls. Arber (2013) interviewed 10 patients with MPM from 2 hospitals in the South of England [230]. All participants reported high levels of uncertainty and feelings of a lack of control leading to psychosocial distress since receiving their diagnosis. All the participants found it difficult to cope with their diagnosis because of all the negative information and 'bad news' around MPM, and this led to feelings of despair. Clayson et al (2005) interviewed 15 patients in the North of England [231]. Four main themes emerged: coping with symptoms, the burden of medical interventions, finding out about mesothelioma and psychosocial issues. Dyspnoea was the commonest symptom and the unpredictability and often speed of onset caused great distress. All patients acknowledged asbestos as the cause of their disease.

A systematic literature review [232] comparing psychological care needs of mesothelioma patients and those with advanced lung cancer found ~~there to be~~ similarities between the two populations but recommend developing separate assessment and care pathways so that distinct differences (hopelessness, legal and financial matters, attribution of blame) can be addressed.

Intervention

Moore et al (2008) evaluated a hospital-based mesothelioma support group in London. Six responses were received from twenty one attendees[233] . All of those that responded found the group useful in terms of sharing experiences and gaining information.

Compensation

Chamming et al. (2013) performed a linked database study in 2407 patients in France and determined that 30% of patients with MPM did not claim occupational disease compensation [234]. Claims were lower in older patients, women and white collar workers. A similar study by Cree et al (2009) of 568 MPM patients in Canada demonstrated that only 42% filed a claim [235]. A retrospective case note review (Kuschner et al. 2012) performed in North America identified 16 patients with mesothelioma treated at 3 Department of Veteran Affairs hospitals of whom only 1 had documented advice on compensation [236].

Every serious illness creates extra costs for patients and their families and mesothelioma is no exception. Mesothelioma is usually ~~almost always~~ caused by exposure to asbestos. The industrial nature of mesothelioma means patients often have complex benefit and compensation claims. ~~This information is correct at time of going to press xxxx2017. For all civil claims there is a three year time limit from the first date the patient became aware that there is evidence of a compensatable asbestos related disease.~~

There are two main ways to get additional financial support when someone is diagnosed with mesothelioma in the UK:

A] State benefits

B] Pursuing a civil compensation claim

For all civil claims there is a three year time limit from the first date the patient became aware that there is evidence of a compensatable asbestos related disease.

State benefits

The Department for Work and Pensions recognises the seriousness of mesothelioma and does not normally require a medical examination. Patients under the age of 65 are eligible for the Personal Independent Payment [PIP], and Attendance Allowance [AA] if the patient is over 65. PIP provides financial assistance for patients who need help with daily living including personal care and mobility. For patients who have been given a terminal diagnosis they can claim under the Special Rules meaning they will be given priority in the claim being dealt with. Under the Special Rules patients can receive the allowance at the highest rate. An award of these benefits does not affect an individual's right to apply for other means tested benefits.

Industrial injuries disablement benefit (IIDB)

This is a non means tested allowance which patients can claim if on the balance of probability they were exposed to asbestos at work. It is not necessary for a person to have worked directly with asbestos to get this benefit. This benefit is paid via direct debit weekly, fortnightly or every 13 weeks. An award of IIDB will be treated as income and may affect other means tested benefits.

Pneumoconiosis (Workers Compensation) Act 1979

This government scheme is designed to compensate those patients exposed to asbestos through work. A lump sum payment under the Pneumoconiosis (Workers Compensation) Act 1979 [PWCA] can be applied for if on the balance of probability the asbestos exposure occurred during their time at work

Diffuse mesothelioma scheme 2008

If patients are unable to make a claim under the PWCA, and are not entitled to compensation from an MOD [Ministry of Defence] scheme a one off lump sum can be applied for. This is suitable where

exposure is from a secondary source, exposure was in the environment, for those who were self-employed or where exposure cannot be specified but occurred in the UK. The lump sum is assessed by the patient's age.

A claim can be made for the lump sum by the deceased's widow or widower, a child under 16, a partner who was living with the patient with mesothelioma at the time of death or any other relatives who were financially dependent on the patient at the time of death. The amount paid in posthumous claims is lower than in life time benefits.

War disablement pension

If a patient was exposed during their service in the armed forces prior to 1987 they are not able to make a claim from their employer because the crown has immunity. A claim can however be made from the Service Personnel and Veterans Agency. All veterans can make a choice between receiving a traditional war pension or a lump sum regardless of age at diagnosis.

Civil claim against a previous employer

If on the balance of probability exposure to asbestos was from an employer or a previous employer a civil claim can be pursued via a specialist solicitor who deals with asbestos claims. Claims are often made through the insurers of the company by establishing an employer's negligence or breach of statutory duty to protect the worker from the effects of asbestos dust and fibres. If a company or an insurer cannot be found, an application to The 2014 Diffuse Mesothelioma Payment scheme can be made.

As part of a civil claim the solicitor may be able to recover costs such as pain and suffering or hospice care. All cases are fast tracked with an aim that patients can receive compensation in their lifetime. The vast majority of cases are settled without going to court. Careful discussion from a specialist solicitor with the patient and family is required because some claims are worth more if the patient ~~is not alive~~ has died.

~~STATE BENEFITS~~

~~The Department for Work and Pensions recognises the seriousness of mesothelioma and does not normally require a medical examination.~~

~~Patients under the age of 65 are eligible for the Personal Independent Payment [PIP] and Attendance Allowance [AA] if the patient is over 65. PIP provides financial assistance for patients who need help with daily living including personal care and mobility. For patients who have been given a terminal diagnosis they can claim under the Special Rules meaning they will be given priority in the claim being dealt with. Under the Special Rules patients can receive the allowance at the highest rate. An award of these benefits does not affect an individual's right to apply for other means tested benefits.~~

~~INDUSTRIAL INJURIES DISABLEMENT BENEFIT [IIDB]~~

~~This is a non means tested allowance which patients can claim if on the balance of probability they were exposed to asbestos at work or as an apprentice. It isn't necessary for a person to have worked directly with asbestos to get this benefit. This benefit cannot be claimed if you were self-employed in the work that led to the asbestos exposure. This benefit is paid via direct debit weekly, fortnightly or every 13 weeks. An award of IIDB will be treated as income and may affect other means tested benefits.~~

~~Pneumoconiosis (Workers Compensation) Act 1979~~

~~This government scheme is designed to compensate those patients exposed to asbestos through work but who cannot make a successful civil compensation claim. A lump sum payment under the Pneumoconiosis (Workers Compensation) Act 1979 [PWCA] can be applied for if on the balance of probability the asbestos exposure occurred during their time at work~~

~~2008 DIFFUSE MESOTHELIOMA SCHEME~~

~~If patients are unable to make a claim under the PWCA, have not received payment in respect of the disease from an employer, a civil claim or elsewhere and are not entitled to compensation from an MOD [Ministry of Defence]scheme a one off lump sum can be applied for. This is suitable where exposure is from a secondary source, exposure was in the environment, for those who were self-employed or where exposure cannot be specified but occurred in the UK. The lump sum is assessed by the patient's age.~~

~~A claim can be made for the lump sum by the deceased's' widow or widower, a child under 16, a partner who was living with the patient with Mesothelioma at the time of death or any other relative who were financially dependent on the patient at the time of death. The amount paid in posthumous claims is lower than in life time benefits.~~

~~WAR DISABLEMENT PENSION~~

~~If a patient was exposed during their service in the armed forces prior to 1987 they are not able to make a claim from their employer because the crown has immunity. A claim can however be made from the Service Personnel and Veterans Agency. All veterans can make a choice between receiving a traditional war pension or a lump sum regardless of age at diagnosis.~~

~~CIVIL CLAIM AGAINST A PREVIOUS EMPLOYER~~

~~If on the balance of probability exposure to asbestos was from an employer or a previous employer a civil claim can be pursued via a specialist solicitor who deals with asbestos claims. Claims are often made through the insurers of the company by establishing an employer's negligence or breach of statutory duty to protect the worker from the effects of asbestos dust and fibres. If a company or an insurer cannot be found an application to The 2014 Diffuse Mesothelioma Payment scheme can be made.~~

~~As part of a civil claim the solicitor may be able to recover costs such as pain and suffering or hospice care. All cases are fast tracked with an aim that patients can receive compensation in their lifetime. The vast majority of cases are settled without going to court. Careful discussion from a specialist solicitor with the patient and family is required because some claims are worth more if the patient is not alive.~~

~~*Intervention*~~

~~Moore et al (2008) evaluated a hospital-based mesothelioma support group in London [233]. Six responses were received from 21 attendees. All of those that responded found the group useful in terms of sharing experiences and gaining information.~~

Evidence statement

Patients with MPM and their relatives have reduced quality of life compared to healthy controls. **Level: 2+**

A diagnosis of MPM causes high levels of psychosocial distress. **Level: Qualitative**

Documentation of compensation advice and subsequent claims are variable. **Level: 3**

Recommendations

- Offer accurate and understandable information to patients and carers about compensation for MPM. **Grade D**

- Offer patients with MPM and their carers the opportunity to discuss concerns regarding their disease. **Grade D**

15.3 Follow-up strategies

The literature search did not reveal any evidence pertaining to who and how MPM patients should be followed-up. The search identified 12 papers that were thought to be relevant to the imaging component of this question. Following review of the 12 abstracts 9 papers [237-245] were fully critiqued to answer the question regarding the best form of imaging when following up patients with MPM.

None of the papers reviewed were from the UK but a large number were from within the European region. The rest from Australia, USA and Turkey. Given the patient populations are generally similar this evidence is broadly applicable to the UK population. Most of the studies are from the pre-pemetrexed cisplatin chemotherapy era but for the purpose of answering the specific question here about follow-up, the results are generally acceptable.

The papers reviewed were consistent in their findings that a bi-dimensional method of assessing tumour volume is inadequate in MPM[245]. A number of the studies compared Response Evaluation Criteria In Solid Tumors (RECIST) with mRECIST CT criteria. Modified RECIST, despite having its limitations, remains the best method of assessing tumour response when followed up over a period of time [246 247].

One study demonstrated using mRECIST criteria in MRI can be better at soft tissue/tumour delineation and pleural effusion identification, ~~but~~ when compared with mRECIST criteria in CT [248].

Three studies explored the role of volumetric assessment (using Cavalieri principle) of the tumour on CT [246 249 250]. No significant intraclass or interobserver variability noted, but this method is a time consuming and onerous way of measuring tumour in MPM therefore limiting its clinical utility.

Evidence Statements:

CT scanning using modified response evaluation criteria in solid tumours (RECIST) for interpretation gives the best assessment of tumour response to chemotherapy. **Level 3.**

Recommendation:

- In MPM patients where accurate determination of radiological progression is required, consider CT with modified RECIST measurement **Grade D.**

Good practice point

- ✓ A personalised care approach should be considered for each patient:

Patients should be offered 3-4 monthly follow-up appointments with an oncologist, respiratory physician or specialist nurse according to their current treatment plan. If patients wish to be seen less frequently, offer regular telephone follow-up with specialist nurse with an option to attend~~ing~~ clinic ~~if~~ in the event of clinical deterioration.

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Appendix 1
Full list of Guideline Group Members

Professor Nick Maskell

Dr Ian Woolhouse

Dr Lesley Bishop

Ms Liz Darlison

Dr Duneesha de Fonseka

Dr Anthony Edey

Mr John Edwards

Professor Corinne Faivre-Finn

Professor Dean Fennell

Dr Steve Holmes

Professor Keith Kerr

Mr Apostolos Nakas

Dr Tim Peel

Professor Najib Rahman

Dr Mark Slade

Dr Jeremy Steele

Dr Selina Tsim

Contributors:

The lay representatives on the group were Dr Graham Abbott, Mr Paul Astle and Mr John Gillies.

Additional nursing contributors to the Guideline Development Group were Ms Sarah Smith (March 2015-Oct 2015) and Ms Gerry Slade (until March 2015).

Appendix 2: Prognostic Scores

The EORTC Prognostic Score

The score is:

EPS = 0.55 (if WBC>8.3 x 109/L) + 0.6 (if PS=1 or 2) + 0.52 (if histological diagnosis probable or possible) + 0.67 (if histology=sarcomatoid) + 0.6 (if male)

The patient has a good prognosis if EPS <= 1.27 and a poor prognosis if EPS > 1.27.

Information about the CALGB Prognostic groups

Derivation and validation studies of the CALGB prognostic groups			
Prognostic group number	Derivation study, Herndon 1998, median survival (mo), 1yr, 2yr	Validation study Edwards et al 2005, median survival (mo), 1yr, 2yr	Validation study, Meniawy 2013, median survival (mo)
1	13.9, 63%, 38% n=36	14.8, 55.9%, 16.8% n=22	16.5 n=56
2	9.5, 41%, 21% n=36	6.4 n=2	
3	9.2, 30%, 10% n=146	6.6, 29%, 5.3% n=55	14.2 n=131
4	6.5, 25%, 6% n=33	8.1, 40%, 0% n=5	
5	4.4, 7%, 0% n=73	3.4, 3.5%, 0% n=30	9.4 n=80
6	1.4, 0%, 0% n=13	1.1, 0%, 0% n=9	

The Neutrophil-to-Lymphocyte ratio (NLR):

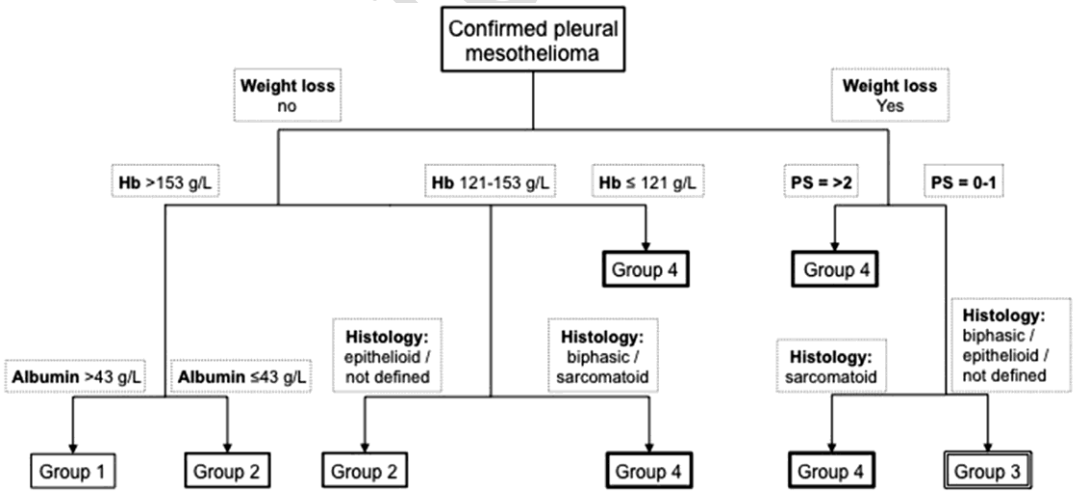
Permission to reproduce the Published multivariate analysis of neutrophil to lymphocyte ratio in malignant mesothelioma will be sought

Table 4. Published multivariate analyses of neutrophil-to-lymphocyte ratio in malignant mesothelioma

	Kao *et al* (2010)	Kao *et al* (2011)	Pinato *et al* (2012)	Kao *et al* (2013)	Meniawy *et al* (this study)
Total no. of study patients	173	85	171	148	274
No. in multivariate model	NR	NR	NR	130	274
No. with NLR available	168 (97%)	84 (99%)	159 (94%)	79 (53%)	274 (100%)
Treatments received	Chemotherapy First line (69%) Second line (31%)	Extrapleural pneumonectomy (EPP)	Chemotherapy (41%) Supportive care (42%) Unknown (17%)	Chemotherapy (53%) Radiotherapy (34%) EPP (5%)	Chemotherapy (62%) Supportive care (38%) EPP (1%)
Median baseline NLR	NR	3	NR	3.5	3.5
Cutoff used in analysis	<5 *vs* ⩾5	<3 *vs* ⩾3	<5 *vs* ⩾5	<3 *vs* ⩾3	<5 *vs* ⩾5
Prognostic variables entered into final multivariate model					
Age		NS		NS	+
Gender	NS	NS	NS	NS	NS
Nonepithelioid histology	+	NS	NS	+	+
Sarcomatous histology					+
Stage				+	NS
Performance status			NS		+
Weight loss					+
Chest pain					+
Hb level				+	NS
White cell count	NS		NS	NS	NS
Platelet count	NS			NS	+
Baseline NLR	+	+	+	+	NS
Calretinin score		+			
mGPS			+		
Albumin, EPS, CRP, PLR			NS		
Treatments received	NS			+	

Abbreviations: CRP = C-reactive protein; EPS = european organization for the research and treatment of cancer prognostic score; Hb = haemoglobin; mGPS = modified glasgow prognostic score; NLR = neutrophil-to-lymphocyte ratio; NR = not reported; NS = nonsignificant; PLR = platelet-to-lymphocyte ratio; + = significant ($P<0.05$).

Prognostic model using decision tree analysis



The LENT scoring system

Mnemonic	Variable	Score
L	Pleural fluid LDH (IU/L)	
	<1500	0
	>1500	1
E	ECOG Performance Status	
	0	0
	1	1
	2	2
	3-4	3
N	NLR	
	<9	0
	>9	1
T	Tumour type	
	Low risk (mesothelioma, haematological malignancy)	0
	Moderate risk (breast, renal, gynaecological cancer)	1
	High risk (lung cancer, other tumour types)	2