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BTS guideline for the investigation and management of malignant pleural mesothelioma

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ABSTRACT

The full guideline for the investigation and management of malignant pleural mesothelioma is published in *Thorax*. The following is a summary of the recommendations and good practice points. The sections referred to in the summary refer to the full guideline.

INTRODUCTION

The full guideline for the investigation and management of malignant pleural mesothelioma is published in *Thorax*.[1] The key features of the guideline are highlighted in a short article published to accompany the full guideline.[2] The following is a summary of the recommendations and good practice points. The sections referred to in the summary refer to the full guideline.

BACKGROUND

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. The main cause of mesothelioma is breathing in asbestos dust—approximately 85% of all male mesotheliomas are attributable to occupational asbestos exposure. Products containing asbestos were banned in the UK in 1999. The latency between first exposure and development of the disease is typically 30–40 years. Only two-thirds of patients in England and Wales receive active anticancer treatment (chemotherapy, radiotherapy and surgery) for MPM and overall median survival is poor at 9.5 months, with 1-year and 3-year survival rates of only 41% and 12%, respectively. The poor survival rates, taken together with the significant variation in treatment and outcomes across the UK, highlight the need for an evidence-based guideline to facilitate the highest standards of care for all patients with mesothelioma in the UK.[3]

Target audience for the guideline

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 include primary care general practitioners (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.

Areas covered by the guideline include (1) the epidemiology and incidence of mesothelioma in the UK and worldwide, (2) the preferred investigation pathway of suspected cases of MPM, (3) consider special situations including:

- Imaging
- Histology/cytology
- Frail patient not fit for invasive tests

(4) biomarkers, (5) role of mesothelioma MDTs, (6) outline best practice in oncological management, (7) role of chemotherapy, (8) place for radiotherapy, (9) role of surgery, (10) guidance on palliation in MPM, (11) guidance on providing patients with relevant disease-specific information, including medicolegal/compensation issues, (12) summary of future therapeutic agents that might be available within the next 5 years and (13) summary of major MPM recommendations.

Non-pleural mesothelioma is excluded from this guideline.

METHODOLOGY

This guideline is based on the best available evidence. The methodology used to write the guideline adheres strictly to the criteria as set

Table 1 Key to evidence statements

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

RCT, randomised controlled trial.

by the Appraisal of Guidelines, Research and Evaluation (AGREE) 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 http://www.brit-thoracic.org.uk/guidelines-and-quality-standards/).

Clinical questions, literature search and appraisal of the literature

Clinical questions were structured in the Patient, Intervention, Control, Outcome format (see online appendix 1 in the full guideline),[1] to define the scope of the guideline and inform the literature search. The first search was conducted in December 2014 and was updated in July 2016. Appraisal was performed in line with the AGREE II criteria. Further details are available in the full guideline.

Considered judgement and grading of evidence

The Guideline Development Group (GDG) used evidence tables (see online appendix 2 in the full guideline)[1] to assess the body of evidence for each clinical question. Guideline group members worked in small groups to appraise the literature and at least two members of each group independently appraised each paper using the SIGN critical appraisal checklists. An evidence level was assigned to each relevant study using the SIGN methodology (see table 1).

From the outset, it was acknowledged that there would be little high-quality evidence for some of the clinical questions. Where this was the case, low-grade evidence was considered, along with expert opinion via consensus at the meetings of the GDG. Parameters were set by the GDG when appraising the evidence:

- How applicable the obtained evidence was in making recommendations for the defined target audience.
- Whether the evidence was generalisable and relevant to the target population.
- Whether there was a clear consistency in the evidence used to support recommendations.
- What the implications 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 British Thoracic Society (BTS) guideline production process. However, the GDG were asked to be mindful of any barriers to implementing the recommendations and GPPs.

Recommendations were graded A to D as indicated 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. GPPs were included where research evidence was lacking, as the GDG felt it was important to highlight practical points that could improve the care of patients. Research recommendations were also highlighted.

DRAFTING THE GUIDELINE

The GDG was convened in June 2014, with the first meeting taking place in October 2014. The group met a total of six times and kept in close contact by email and teleconferenced throughout the process. The BTS Standards of Care Committee (SOCC) reviewed the draft guideline in November 2016. The draft guideline was made available online from 22 March 2017 until 24 April 2017 for public consultation and circulated to all relevant stakeholders. The BTS SOCC reviewed the revised draft in June 2017, and final SOCC approval was granted in September 2017.

SUMMARY OF RECOMMENDATIONS AND GOOD PRACTICE POINTS

Section 3: Clinical features that predict the presence of mesothelioma

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 symp-

Table 2 Grades of recommendations

Grade	Type of evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or*
	A systematic review of RCTs 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+
√	Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasise these as Good Practice Points.

RCT, randomised controlled trial.

toms 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 partner occupations. **Grade D**.

Section 4: Staging systems

Recommendation

- Record staging of MPM according to the version 8 of the International Association for the Study of Lung Cancer (IASLC) staging proposals**. Grade D.**

Section 5: Imaging modalities for diagnosing and staging

Recommendations

- Offer 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 tuberculosis. **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 6: Pathological diagnosis

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

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

Recommendations

- Consider calculating a prognostic score in patients with MPM at diagnosis. **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

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 video-assisted thoracoscopic surgery partial pleurectomy (VATS-PP) surgical approach for fluid control in MPM. **Grade A.**

Section 10: The role of surgery

Recommendations

- Do not offer VATS-PP over talc pleurodesis in MPM. **Grade A.**
- Do not offer extra-pleural pneumonectomy (EPP) in MPM. **Grade B.**
- Do not offer extended pleurectomy decortication (EPD) 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 anticancer treatment

Recommendations

- Offer patients with MPM with good performance status (WHO 0–1) first-line therapy with cisplatin and pemetrexed. Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to pemetrexed. **Grade A.**
- 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 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

The role of immunotherapy in MPM should be further assessed in large phase III randomised controlled trials.

Further randomised controlled trials of second-line therapy on MPM are required.

Section 12: Radiotherapy

Recommendations

- Do not offer prophylactic radiotherapy to chest wall procedure tracts routinely. **Grade A.**
- Do not offer preoperative or postoperative radiotherapy in MPM. **Grade A.**
- Do not offer hemithorax 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

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

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

Good practice point

- ✔ Symptoms in MPM should be managed as per current guidelines for cancer in general (see section 13: symptom control in the full guideline) and early involvement of palliative care specialists is recommended.

Section 14: Care and management

Recommendation

- Consider referring MPM cases to a regional mesothelioma MDT. **Grade D.**
- 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.**
- In patients with MPM where accurate determination of radiological progression is required, consider CT with modified Response Evaluation Criteria in Solid Tumours (mRECIST) measurement. **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.
- ✔ 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 clinic in the event of clinical deterioration.

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 presented 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.

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