REVIEW SERIES

Lung cancer • 8: Management of malignant mesothelioma

C Parker, E Neville

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Malignant mesothelioma is a relatively common malignant tumour which is associated with prior exposure to asbestos. The diagnosis, histology, prognosis, and management of this disease are reviewed. The disappointing outcome of most curative treatment strategies is discussed and improved palliation is highlighted.

Malignant mesothelioma is a challenging disease that understandably causes considerable distress and anxiety to patients, relatives, and clinicians. The incidence of mesothelioma has been steadily increasing over the past 30 years, and is expected to continue until 2020 with a projected 1300 cases each year. The 1940s male birth cohort is particularly affected, mesothelioma accounting for approximately 1% of all deaths.[1–3] The incidence increases with age and is approximately 10 times higher in men aged 60–64 years than in those aged 30–34.

There is an association with the inhalation of asbestos fibres, which frequently has occurred years previously and sometimes in a seemingly low dose. Mesothelioma is rare in patients without any direct occupational exposure or indirect paraoccupational or environmental exposure.[4] Current estimates suggest an occupational history is obtained in over 90% of patients.[5] There is no evidence to suggest a safe or threshold level of exposure, but the risk is low where exposure is of low intensity. Few populations are exposed only to one type of asbestos fibre. The first description of an association between malignant mesothelioma and asbestos exposure was by Wagner in patients exposed to crocidolite in South African mines.[6] All types of asbestos fibre can cause mesothelioma, although crocidolite is considered a higher risk. Chrysotile, crocidolite, and amosite have been the most commonly used in industry, accounting for 95%, 3%, and 1%, respectively, of the world's production of asbestos. Necroscopic studies have led to the determination of asbestos fibre load and the demonstration of a dose related effect,[7] thus making improbable the argument that mesothelioma only requires one fibre of asbestos for initiation of the malignancy.

The presence of asbestos fibres in the lungs of the general population suggests that exposure may occur unknowingly and there appears to be a substantial variation in fibre accumulation within areas of the lung.[8 9] The average latency period following exposure and development of disease or death is very long—usually a minimum of 20 years—although the range is wide. Cases developing within 15 years of exposure are rare.[10 11] Since the early 1970s, legislation has decreased contamination of the environment by asbestos followed by a later ban on asbestos usage. The importance and relevance of the latency period is reflected by the still increasing incidence of mesothelioma.

As the disease remains refractory to standard antitumour treatment, there has been rampant therapeutic nihilism among attending clinicians. Indeed, curative treatment remains an elusive goal. Nevertheless, active and aggressive palliation is showing increasing benefit.

See end of article for authors' affiliations

Correspondence to:
Dr E Neville, Respiratory Centre, St Mary's Hospital, Portsmouth PO3 6AD, Hants, UK;
edmund.neville@smail01.porthosp.swest.nhs.uk

DIAGNOSIS

Clinical features

Mesothelioma typically presents with chest pain or breathlessness, and constitutional symptoms may be present.[12 13] The chest pain may be pleuritic, lateralised, dull, or diffuse, typically progressing relentlessly during the course of the illness and often proving difficult to control. The pain may have neuropathic components due to entrapment of intercostal thoracic, autonomic, or brachial plexus nerves.

Dyspnoea is multifactorial, caused by accumulation of pleural fluid, pleural thickening, thoracic restriction, and lung encasement, as well as problems of co-morbidity such as airflow obstruction and cardiac dysfunction. Other symptoms and signs depend on the site and extent of the disease.

The disease tends to progress locally rather than by haematogenous spread, although distant metastases are seen. At necropsy it is reported that up to 50% have evidence of subclinical metastatic spread. Bilateral disease may occur in 5% of patients.[14] Some patients appear to have a period of prolonged clinical stability while others have rapidly progressive disease.

Peritoneal mesothelioma is relatively uncommon, although the incidence has been steadily rising. The age distribution is similar to pleural disease but there is less male predominance.[15 16] The ratio of pleural to peritoneal disease in the asbestos exposed population has been of the order of 12:1, but is slowly rising.[17] Peritoneal mesothelioma presents with progressively severe non-specific abdominal pain and/or ascites. Later features include bowel obstruction.[18 19]

Staging

Accurate staging is essential if the possibility of inclusion in a clinical trial of treatment is being considered, although staging was initially developed to assess operability and, in patients subsequently deemed inoperable, to offer prognostic information.

Table 1 Histological type of pleural mesothelioma and survival

No of cases	Median survival (months)				Reference
	All types	Epithelioid	Sarcomatoid	Mixed (biphasic)	
248	14.0	16.2	10.1	14.7	Yates *et al*[5]
153	10	11	5	10	Hillerdahl[13]
83	8.1	8.4	6.9	6.3	Van Gelder *et al*[24]

There are three staging classifications of pleural mesothelioma. The staging system proposed by Butchart involves classification of the tumour into one of four groups. Stage 1 was defined as potentially operable disease with tumour simply confined to the ipsilateral pleura, pericardium and diaphragm.[20] The International Mesothelioma Interest Group (IMIG)[21] has implemented a more detailed staging system based on the TNM system and is largely based on CT findings. Sugarbaker *et al*[22 23] further staged patients at operation.

Diagnostic imaging

Standard plain chest radiographs may show a pleural effusion or irregular pleural thickening, often with evidence of pleural plaques. In the presence of a supportive exposure history these appearances should suggest mesothelioma.

Ultrasound and CT scanning are helpful in distinguishing pleural thickening from fluid collections, and in guiding aspiration or biopsy to obtain appropriate pathological samples.[24–26] CT and MRI scans can be used to assess suitability for surgical consideration in patients presenting with stage 1 disease.[27 28]

Pleural fluid cytology

Cytological yield in suspected mesothelioma is poor with a sensitivity of only 32%,[29] and should be interpreted only with appropriate clinical detail, radiology, and histological samples.

Pleural biopsies

Histological samples are key to establishing a diagnosis. Blind percutaneous needle biopsy (Abrams biopsy) provides diagnostic material in under 50% of cases.[30] Radiological guided biopsies are more accurate, particularly where disease is localised.[31]

Thoracoscopy

Where available, medical thoracoscopy has a dual role. Biopsies taken under direct vision are of larger size and better quality.[32 33] Thoracoscopy also affords the opportunity to perform effective pleurodesis and is safely performed under local anaesthesia and light sedation. In the study by Boutin[32] the overall diagnostic sensitivity was as high as 90%, sensitivity for malignancy was 88%, and specificity 96%. Morbidity is low (<1%) and is related to the development of pleural empyema, pleurocutaneous fistulae, and transcutaneous tumour seeding. Even after exhausting these diagnostic modalities the diagnosis may prove elusive. Some patients still require a formal surgical biopsy because the tumour may evoke a marked local fibrous response and malignant tissue may be missed on small biopsy samples. Other cases are diagnosed only at necroscopic examination.

HISTOLOGY

There are three histological types—epithelioid, sarcomatoid (or fibrous), and biphasic (or mixed)—the latter being easiest to diagnose and containing elements of both types. Epithelioid mesothelioma is the most common and may be confused with metastatic adenocarcinoma.

Box 1 Classification of pleural cancer treatment

Curative intent

- Surgery
- Chemotherapy
  - Systemic
  - Intracavitary
- Radiotherapy
- Multimodality therapy

Active symptom control

- Breathlessness
- Analgesic measures for chest pain
  - Pharmacological
  - Non-pharmacological
- Tumour seeding in the chest wall
- Miscellaneous

PROGNOSIS

Despite major developments in assessment and treatment, the prognosis in mesothelioma remains poor (range 2–86 months). Various series have reported survival data which remain generally disappointing,[10 34–36] but in most series there are a small number of unexpected long term survivors.

Various prognostic factors permit a degree of refinement of survival prediction. Advancing age, extensive disease, and sarcomatoid or biphasic histological subtypes are independent adverse risk factors.[34] Long term survivors tend to be almost exclusively from the epithelioid group (table 1).

MANAGEMENT

When considering the management of patients with any cancer, it is important to classify treatments broadly into those studied with a "curative" intent and those measures considered for active symptom control and palliation (box 1). Effective management should be organised through a multidisciplinary team, as is routine with lung cancer.

Curative intent

Surgery

Patients potentially suitable for radical surgery have epithelioid tumours of low volume and are otherwise fit for major surgery. Estimates have suggested that 1–5% of all patients with mesothelioma might be suitable for surgery.[37] There are no randomised controlled trials to establish the role of radical surgery in this disease. Evidence is based on large series such as those described by Butchart and Sugarbaker.[20 27 38]

Extrapleural pneumonectomy (EPP) and pleurectomy are the surgical procedures most extensively investigated. Early experiences with EPP reported a high operative mortality and a significant number of early disease recurrences. This highlights the importance of strict patient selection and the still limited role of surgery. EPP carries a higher operative mortality than pleurectomy (5–31% *v* 1–5.4%), depending on surgical experience and patient selection, and significant morbidity (25%). Common complications include cardiac arrhythmias (25–40%), respiratory failure, pneumonia, and

bronchial air leaks.[39 40] However, in the Lung Cancer Study group series reported in 1991, the local recurrence rate following EPP was 10% compared with 52% following pleurectomy.[41]

Neither EPP alone nor pleurectomy has been shown to improve survival; EPP is limited by operative deaths, residual tumour, local recurrence, and metastatic disease. Multimodality therapy is therefore being developed, using surgery to reduce the tumour burden before adjunctive therapy.

Chemotherapy

Despite protean chemotherapy trials, no single agent has so far been shown to be consistently effective. Objective response rates with either single or multiple drugs seldom exceed 25%. Doxorubicin has been most extensively studied but the overall response rates are poor.[42 43] Similar results have been found with other chemotherapeutic drugs. Combination regimens have also shown poor response rates, with increasing toxicity and no additional survival benefit.[39 40 44] Such trials are frequently small and non-randomised, with varying measures of subjective and objective response. A summary of the main chemotherapy trials has been published by Baas *et al*.[45]

Intracavitary chemotherapy should deliver high peak levels of drugs directly adjacent to tumour tissue, but penetration into the tumour is shallow and the results have been poor.[46 47] No trials to date have compared the effects of chemotherapy and best supportive care on symptoms and quality of life. End points of trials should include tumour response as assessed by serial CT scans and appropriate quality of life measures as well as survival.

Radiotherapy

Radiotherapy with curative intent would irradiate large volumes of the thorax and is limited by unacceptable pulmonary toxicity. In vitro studies suggest that mesothelioma cells are at best only partially radiosensitive.[48–50] Radiotherapy alone has no impact on survival,[51 52] and there is no evidence to support its role as single modality treatment. When available, modern radiotherapy techniques to irradiate the pleura selectively, sparing the lung parenchyma, would be an important area for study. Radiotherapy has a more important role in symptom palliation and in the prophylaxis of tumour seeding. It also forms part of multimodality therapy.

Multimodality therapy

As single therapy has proved uniformly ineffective, various combinations of treatment have been developed. Multimodality therapy involves surgical debulking of tumour burden, radiotherapy or photodynamic therapy for residual local disease, and systemic chemotherapy targeting distant spread. This concept has been pioneered by Sugarbaker.[27 38 53] Initial results appeared promising, although the patients were highly selected and not representative of the overall mesothelioma population. Only patients with Butchart stage 1 disease, good performance status, good cardiovascular status (ejection fraction >45%), sufficient respiratory reserve, and no significant co-morbidity were deemed eligible, and some of these patients were re-staged at thoracotomy. With increasing surgical experience, 30 day mortality from EPP can be reduced to 4%, although the morbidity remains significant. The results of trimodality therapy with less aggressive surgery are less promising.[52 54 55]

Only 1–2% of patients are likely to be eligible for consideration of multimodality therapy. At presentation less than 20% have stage 1 disease.[56] Many have co-morbidity with reduced cardiac or respiratory function that precludes aggressive surgery.

Multivariate analyses suggest that patients with epithelioid tumours, no extrapleural lymphadenopathy, and negative resection margins have the best prognosis, hence projections of benefit of this treatment are disappointing.[57] It is highly unlikely that this form of treatment will impact significantly on the current management crisis for the majority of patients with malignant mesothelioma.

Although Sugarbaker presents some prospect of survival in an otherwise bleak environment, his results must be interpreted on a background of a selection policy that may exclude 98–99% of patients, and where 1–2% of all patients may survive more than 5 years without any active treatment.

Active symptom control (palliation)

Dyspnoea

Where dyspnoea is primarily related to the presence of a pleural effusion, an early definitive pleural procedure is important. Over 95% of patients will develop a pleural effusion with symptomatic dyspnoea. Co-morbid diseases should be treated simultaneously.

There are no trials reporting specifically on the management of pleural effusions in malignant mesothelioma. Details are reported in studies of malignant pleural effusions of differing aetiology.[58–60] Generally, early intervention with effective pleural drainage via medical thoracoscopy and poudrage is preferable, being a highly effective procedure but unfortunately not yet widely available. Alternatives include the use of a chest tube and chemical pleurodesis with talc slurry or tetracycline.[61–67] Achieving complete visceral and parietal pleural apposition improves the success rate of pleurodesis, which may necessitate low pressure thoracic suction. Complications of chemical pleurodesis include pain, fever, pleural sepsis, and well documented but fortunately rare cases of adult respiratory distress syndrome with talc pleurodesis.[68]

Small drains are as effective as large ones and are more comfortable for the patient.[69–72] They are well tolerated and are accompanied by minimal complications. The duration of drainage is determined clinically.

Where the patient is frail, fluid re-accumulation slow, and pleurodesis has failed, repeated aspirations can be performed as a temporising measure on an outpatient basis. Recurrent procedures and indwelling pleural catheters, however, significantly increase the risk of tumour seeding in the chest wall. With advancing disease, where the tumour involves the visceral pleura, the underlying lung may become trapped. In this circumstance attempts at pleurodesis will be unsuccessful. Pleuroperitoneal shunts and long term indwelling pleural catheters can be considered, particularly in the case of trapped lung.[73 74] Both, however, have a reasonably high failure rate due to blockage of the tubes. Other complications include local skin erosion and infection, tube breakage, and potential tumour seeding.[75]

Other surgical procedures may have a role in the management of recurrent pleural effusions. Open pleurectomy and decortication are effective but invasive procedures. Video assisted thoracoscopic surgery is available with lower morbidity and mortality permitting partial pleurectomy, but is difficult after previously attempted pleurodesis.[76]

Surgery should be reserved for patients who have failed chemical pleurodesis or who have trapped lung with an expected survival of >6 months. Breathlessness is not eased by radiotherapy.

Effective analgesia for chest pain

Pharmacological

Chest pain is a frequent and disabling symptom, worsening as the disease relentlessly progresses. A syndrome referred to as the "costopleural syndrome" is recognised in pleural mesothelioma, causing severe intractable pain.

Standard management follows the WHO analgesic ladder. Analgesia should be given regularly and titrated against need but, as the pain from chest wall involvement has a variable response to opiates because of added inflammatory and neuropathic components, rapidly escalating doses are usually

required. Where neuropathic pain predominates, tricyclic antidepressants or anticonvulsants may be tried. However, although analgesics are widely used in chronic pain syndromes, few trials have shown them to be effective.[77 78]

The role of chemotherapy in pain management is less clear but, in an uncontrolled study of mitomycin C, vinblastine and cisplatin, Middleton *et al*[79] reported objective benefit for some months with eight of 39 patients achieving a partial response and a median duration of benefit of 9 months. This clearly requires further evaluation.[80]

Non-pharmacological

Percutaneous cervical cordotomy has proved particularly beneficial in patients with the costopleural syndrome.[81–83] This procedure interrupts the spinothalamic tract at C1/2, causing a contralateral loss of pain perception below the level of the lesion.[84] This is a highly skilled procedure which is currently only available in three UK centres. In Portsmouth it is current practice to refer patients for cordotomy on the same day as opiates are first prescribed.[81] The complications of cordotomy include thermoanaesthesia, troublesome dysaesthesia, and persisting motor weakness. No patient in the series reported by Jackson *et al*[81] experienced hemiplegia or the inability to walk due to motor weakness and there was no reported sphincter disturbance. Pain was significantly reduced in 83% and 20/52 (38%) were able to stop opiate medication completely. Published mortality 1 week after cordotomy for malignant disease is 6%[81 85] and reflects patient selection. There is no evidence of respiratory depression postoperatively.[86]

Radiotherapy plays an important role in patients in whom chest pain is secondary to bone erosion or secondary cutaneous tumour nodules.[87] It is less effective for diffuse pain. The benefit may be short lived with no dose response effect. Two retrospective studies showed a favourable response in approximately 60% of patients[88 89] with the first courses of palliative radiotherapy being more effective than subsequent courses.

Tumour seeding in the chest wall

It is well recognised that mesothelioma can seed along the tracks of aspiration, biopsy, or chest drain sites, and can result in a painful chest wall mass. This risk of tumour seeding can be reduced from 40% to zero by prophylactic radiotherapy,[90] although this study only included 40 patients. Radiotherapy was delivered in fractions over 3 days. A similar study reported no recurrences in 20 patients.[91] However, where treatment was delayed for 2 months following an invasive procedure, tumour nodules developed[92] which are less responsive to local radiotherapy.

There are no randomised controlled studies on the role of prophylactic radiotherapy, particularly regarding appropriate scheduling or dosage. This remains an integral part of ongoing studies.

Miscellaneous

A persistent cough is common in mesothelioma, although the mechanism of its production is obscure. Symptomatic use of opiate linctuses, oral steroids, and nebulised local anaesthetics can be considered.

Anorexia, weight loss, and fatigue are common in late stages of disease. Treatment is unsatisfactory but gastric prokinetic agents and steroids can be tried.[93 94]

Many patients also require psychological support and appropriate advice regarding compensation issues and benefit entitlements. This emphasises the importance of a coordinated multidisciplinary team approach. Patients' families should also be sympathetically counselled regarding the legal requirement for a post-mortem examination.

Authors' affiliations

C Parker, E Neville, Respiratory Centre, St Mary's Hospital, Portsmouth PO3 6AD, Hants, UK

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Summary points

- Malignant mesothelioma is a relatively common malignant tumour of increasing incidence, associated with prior asbestos exposure.
- Diagnosis may be difficult but should be established early.
- Survival with supportive care alone varies between 2 and 86 months, including occasional long term survivors.
- Most patients require symptom palliation from the time of initial diagnosis.
- No treatment has so far conclusively improved survival significantly beyond supportive care.
- The main emphasis of treatment should be on symptom control, organised through a multidisciplinary team.
- Patients should be counselled regarding their right to compensation and appropriate assistance afforded.
- Patients and/or their families should be informed of the legal requirement to report all deaths of asbestos related disease including mesothelioma to the coroner (or procurator fiscal) for a post-mortem examination.

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