PAPER

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Malignant pleural mesothelioma

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ABSTRACT Malignant mesothelioma is a rare tumour that arises from the mesothelial surfaces of the pleura, peritoneum, pericardium, or the tunica vaginalis, with the pleura the most commonly affected site. By 2015, mesothelioma is expected to result in approximately 2,000 deaths per annum in the UK. In the US, there are approximately 3,000 cases of malignant mesothelioma diagnosed yearly. Mesothelioma historically carried a dismal prognosis but, with the advent of new treatment options and translational research, progress is being made. This article will address pleural mesothelioma.

KEYWORDS Biphasic, cordectomy, EPP, IMRT, MARS, Pemetrexed

LIST OF ABBREVIATIONS Active symptom control (ASC), computed tomography (CT), epidermal growth fact receptor (EGFR), extrapleural pneumonectomy (EPP), International Mesothelioma Interest Group (IMIG), intensity modulated radiation therapy (IMRT), magnetic resonance (MR), malignant pleural mesothelioma (MPM), mitomycin C, vinblastine, cisplatin (MVP), pemetrexed plus cisplatin (PC), radiation therapy (RT), serum mesothelin-related peptide (SMR), Simian vacuolating virus 40 (SV40)

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INTRODUCTION

Malignant mesothelioma is a rare tumour that arises from the mesothelial surfaces of the pleura, peritoneum, pericardium, or tunica vaginalis, with the pleura the most commonly affected site. Mesothelioma has an approximate incidence of 7 per 100,000 among British male adults.[1] By 2015, mesothelioma is expected to result in approximately 2,000 deaths per annum in the UK.[2] In the US, there are approximately 3,000 cases of malignant mesothelioma diagnosed yearly.[3] Asbestos has been found to be the predominant cause of mesothelioma.

PATHOGENESIS

The pathogenesis of mesothelioma is a poorly understood sequence of events that leads to the malignant transformation of mesothelial cells. When inhaled, asbestos causes an inflammatory phagocytic response. The longer amphibole asbestos fibres are too large for phagocytosis, and arrive at the pleural surface directly or through the lymphatic system. Once in the pleura, asbestos may promote malignant transformation of mesothelial cells by several mechanisms. Asbestos induces DNA damage by the indirect action of reactive oxygen produced by the inflammatory response. Asbestos also influences the normal activity of genes that regulate the cell cycle and that are often altered in other human cancers. Stimulation of the autophosphorylation of EGFR by asbestos triggers a cascade leading to cell mitosis and apoptosis. Asbestos also interferes with mitotic segregation, thereby altering chromosomal morphology.[4]

Genetic predisposition and additional environmental factors may also contribute to pathogenesis. For example, it has been hypothesised that SV40 and ionising radiation may be potential causative agents.[4,5] Smoking is not a risk factor in mesothelioma.[6] Patients who smoke and have asbestos exposure have a higher risk of developing lung cancer.[7]

PRESENTATION

The average age of onset of MPM is 50–60 years.[3] The latency period, from exposure to asbestos to presentation with malignant disease, has been reported to be between 20 and 60 years, with a mean of 32 years.[8] The most frequently reported symptoms at time of presentation include dyspnoea, non-pleuritic chest pain, and weight loss.[6]

PATHOLOGY

There are three histological subtypes. Epithelioid mesothelioma is the most common type, constituting 50–70% of all malignant mesothelioma. The individual cells are relatively uniform, shaped like cubes or multi-sided boxes, with a distinct cell nucleus; they may assemble in a tubular or papillary pattern. Sarcomatoid

mesothelioma is the least common type of mesothelioma (10–15%). These cells typically have an oval, irregular shape and the nucleus of each cell is not as distinct as in epithelioid mesothelioma. A further 20–40% of mesothelioma cancer cells are classified as 'biphasic', a combination of the sarcomatoid and epithelioid types.[9,10] Patients with sarcomatoid or biphasic mesothelioma have shorter survival times than those with epithelial disease – the median time of survival with supportive care has been reported as six months for this subtype.[11]

PATHOLOGICAL CONFIRMATION OF DIAGNOSIS

A tissue biopsy is necessary to confirm the diagnosis of mesothelioma and to differentiate between the three subtypes. Epithelial mesotheliomas can be difficult to distinguish grossly and histologically from metastatic adenocarcinoma of the pleura. Possible primary sources include lung, breast, stomach, kidney, ovary, and prostate. Sarcoma (e.g. fibrosarcoma) and malignant fibrous histiocytoma can present with invasion of pleura, lung, and chest wall, like sarcomatous mesotheliomas. The biphasic type of mesothelioma can resemble sarcomatoid carcinoma and synovial sarcoma histologically.[12]

Confirmatory stains for mesothelioma include calretinin, cytokeratin 5/6, and thrombomodulin. No one single immunostain is entirely conclusive either for mesothelioma or metastatic carcinoma, hence the need for experienced interpretation of a panel of such markers in all cases.[13–16]

Tumour markers

There are no currently accepted tumour markers for diagnosis of management of patients with malignant mesothelioma. Serum markers under clinical investigation include SMR and osteopontin.

In a study on the mesothelin family of proteins, it has been found that patients with malignant mesothelioma have higher levels of SMR than healthy controls (both asbestos- exposed and non-exposed). Patients with lung adenocarcinoma, metastatic pleural tumours, and non-mesotheliomatous pleural effusions do not show raised levels. Validation studies are being conducted at multiple centres.[17–20]

RADIOLOGY

Chest X-ray can reveal pleural effusion which is confined to either the right (60%) or left (40%) lung. On occasion, a mass may be seen. Signs of prior non-cancerous asbestos disease, such as pleural plaques, pleural calcification, or scarring due to asbestosis may also be noted. Lobulated pleural thickening may also be seen on chest X-ray.[21]

COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

Ninety-five patients at a single institution were enrolled in a prospective staging protocol based on the IMIG staging system (see Table 1). Sixty-five patients underwent CT and MR imaging and a surgical procedure (excluding percutaneous needle biopsy) to stage and resect the tumour. Computed tomography and MR imaging were of nearly equivalent diagnostic accuracy in staging malignant pleural mesothelioma. Magnetic resonance imaging was superior to CT in revealing solitary foci of chest wall invasion and endothoracic fascia involvement, and in showing diaphragmatic muscle invasion; however, this advantage did not affect surgical treatment. For cost reasons, CT should be considered the standard diagnostic study before therapy.[22]

STAGING

Staging is based on the IMIG Staging System as shown in Table 1.

SURGERY

Surgery for MPM can be diagnostic, palliative, or, rarely, curative in intent.

Extrapleural pneumonectomy is a radical surgical procedure involving complete removal of the ipsilateral lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm. EPP achieves the greatest degree of cytoreduction, and allows higher radiation doses to be delivered to the ipsilateral hemithorax because the lung has been removed; it is the only procedure possible when a thick tumour rind obliterates the pleural space.[6]

It is difficult to assess the impact of surgical resection on survival. There have been no randomised trials to date of EPP.[23] Extrapleural pneumonectomy carries a greater morbidity than pleurectomy and the major complication rate ranges from 20 to 40%.[6] The MARS trial is currently enrolling patients to EPP vs a non-EPP contol arm. In this trial, EPP is sandwiched between induction chemotherapy and radical radiotherapy, as that is the setting in which the best survival rates have been achieved. The control arm offers full active trimodality therapy, in which every treatment is available to the patient, short of EPP. Specifically, those randomised not to have EPP will receive the same induction chemotherapy, are eligible for any palliative or debulking surgery considered appropriate, and radiotherapy should be given to any port sites or drain sites. Thereafter full supportive care will be given in both arms, including any chemotherapy and/or radiotherapy deemed clinically appropriate.[24]

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Primary tumour (T)	
T1a	Tumour limited to the ipsilateral parietal pleura including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura.
T1b	Tumour involving the ipsilateral parietal pleura including mediastinal and diaphragmatic pleura, scattered foci of tumour also involving the visceral pleura.
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: involvement of diaphragmatic muscle; confluent visceral pleural tumour (including the fissures) or extension of tumour from visceral pleura into the underlying pulmonary parenchyma.
T3	Describes locally advanced but potentially resectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall, non transmural involvement of the pericardium.
T4	Describes locally advanced technically unresectable tumour; tumour 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 tumour in the chest wall with or without associated rib destruction; direct transdiaphragmatic extension of tumour to the peritoneum; direct extension of tumour to the contralateral pleura; direct extension of tumour to one or more mediastinal organs; direct extension of tumour into the spine: tumour extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium.
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 the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes.
Metastases (M)	
Mx	Presence of distant metastases cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis present.
Staging	
Stage Ia	T1a N0 M0
Stage Ib	T1b N0 M0
Stage II	T2 N0 M0
Stage III	Any T3 M0, any N1 M0, any N2 M0
Stage IV	Any T4, any N3, any M1

TABLE I

CME

In the most recent report of a large series of patients at a single institution, major and minor morbidity of 24% and 41%, respectively, was reported. Current perioperative mortality rates are significant, with a single institution reporting on the largest series of patients having an incidence of 6% and a mortality of 3·8%.[25] Trimodality treatment, surgery, chemotherapy, and radiation therapy, for MPM is associated with prolonged survival for a post-operatively selected subset of early-stage tumours at the cost of a minor increase in the treatment-related mortality rate. A confirmatory multicentre phase II trial of neo-adjuvant PC followed by EPP and radiation for MPM is currently underway in the US.

Radical surgery remains the subject of much debate in the management of patients with early MPM. Most investigators feel surgery should be considered for fit patients with Stage I or II disease even though cures are rare.

Pleurectomy

Pleurectomy involves the complete resection of both visceral and parietal pleura and can include both pericardial and diaphragmatic resection, as well as resection of additional lung nodules. The parietal pleura is first dissected off the chest wall and then the mediastinum. The pleura is then opened and the visceral pleura removed.[26]

J R Coll Physicians Edinb 2007; **37:**232–237

In debilitated patients, the procedure can be done using the thoracoscope.[27] With either procedure, it is not generally possible to attain complete macroscopic debulking of the tumour. Pleurectomy is more successful than talc pleurodesis in reducing the recurrence of pleural effusion in mesothelioma.

Radiation

Adjuvant RT has also been used in an effort to improve the results following definitive surgery. Multimodality approaches commonly include adjuvant external beam radiation following extrapleural pneumonectomy, although there are no randomised trials that demonstrate its efficacy. Recently, attention has focused on IMRT, which may 'shape' the field of radiation to better conform to the curved pleural surface at risk of recurrence.[28–30]

Chemotherapy

Single agent chemotherapy has demonstrated response rates of 10–20%, and median survival times are similar to those seen following single-modality surgery, or radiation therapy, or no therapy. Combination chemotherapy utilising anthracyclines, platinum compounds, and alkylating agents report response rates ranging from 0–44%.[31] A meta-analysis of 83 studies reported a response rate of 23% for cisplatin alone and 28·5 % ($p<0·001$) for the combination of cisplatin and doxorubicin.[32] Recently, a multicentre phase III trial of pemetrexed plus cisplatin vs cisplatin alone in chemo-naïve pleural mesothelioma patients reported a 41·3% response rate and median overall survival of 12·1 months for the combination arm, significantly longer than the control arm.[33]

In the UK, the British Thoracic Society has recently completed the pilot phase of a randomised trial of chemotherapy for patients with MPM. Following completion of the pilot study, the trial has been granted full support from Cancer Research UK and the National Cancer Research Network and is designated 'MSO1'. This three-arm phase III trial aims to randomise 840 patients with MPM into one of three arms: ASC, without chemotherapy; ASC with vinorelbine chemotherapy; and ASC with mytomycin C, vinblastine and cisplatin (MVP) chemotherapy. The main end-points of MSO1 are overall survival, symptom palliation, quality of life, toxicity, response, and recurrence.[34]

PATIENT EVALUATION AND MANAGEMENT

Early stage patients

For those patients with stage I tumours of epithelial type and good performance status, EPP combined with chemotherapy and radiotherapy provides the best chance of prolonged survival. Trials are currently underway to determine which agents should be used and the type of radiotherapy. Negative prognostic factors in considering EPP or pleurectomy have been reported as tumour volume of >100 ml, biphasic histology, male sex, and elevated platelet count.[35] Controversy exists as to whether an extrapleural pneumonectomy vs pleurectomy affords greater survival.[23] For those patents deemed suitable surgical candidates referral to a clinical trial is appropriate.

Stage II–IV

For those patients not deemed surgical candidates existing data suggest that pemetrexed in combination with cisplatin should be considered as front-line therapy.[33, 36]

MANAGING DISEASE COMPLICATIONS

Dyspnoea

Patients must be carefully evaluated for the underlying cause. The most common causes are anaemia, pneumonia, diaphragmatic involvement, and pleural effusions.

Morphine is the medication of choice for palliation of dyspnoea. Morphine works by improving the quality of breathing and decreases both dyspnoea and the anxiety that accompanies it. Nebulised morphine is considered by some to be more effective than oral or injected (parenteral) morphine, but has the potential to cause bronchospasm. If a patient no longer attains relief taking the strongest oral or intravenous analgesic medications, then a solution containing local anaesthetics and opioid analgesics delivered epidurally might be considered. In addition to controlling pain, the epidural implant reduces the need for in-hospital pain care.

Effusions

Both pleural and peritoneal effusions represent major symptomatic problems for at least two-thirds of patients.[37] Symptomatic treatment of effusions includes drainage of effusions, chest tube pleurodesis, or thoracoscopic pleurodesis. An in-dwelling pleural catheter is a suitable alternative to pleurodesis when the patient is debilitated, has lung entrapment by tumour, or has a short predicted survival.

Severe chest pain

Severe chest pain is common in mesothelioma. Percutaneous cervical cordotomy, which interrupts the spinothalamic tract at the C1/C2 level causing contralateral loss of pain sensation, is particularly appropriate in mesothelioma as the tumour is unilateral and systemic analgesia may be ineffective and is limited by harmful side-effects.

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For those patients who do not experience relief of their pain by narcotics, radiation therapy in moderate doses of 4,000 to 5,000 cGy can be successful in palliating pain associated with involvement of the chest wall.[28, 29, 38] It is important to note that chemotherapy has demonstrated the ability to improve symptom control.[39] It should be considered an important component of palliative care.

KEYPOINTS

- Acute coronary syndrome
- Patients with pleural effusions and a history of asbestos exposure need to be evaluated for mesothelioma and lung cancer.
- Diagnosis should not be made on the basis of cytology alone.
- Fit patients with Stage I disease should be evaluated by a surgical oncologist.
- Patients who are not deemed fit for surgery should be considered for chemotherapy.
- Molecular biology will continue to be an important area of research into understanding this disease.

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